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Essays on the Economics of Drug Prescribing and Utilization

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Essays on the Economics of Drug Prescribing and Utilization

by

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Professor Enrico Moretti, Chair
Professor David Card
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Professor William Dow

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Abstract

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Consumers do not purchase prescription drugs in a standard marketplace setting; instead, they rely on physicians to select an appropriate drug on their behalf. This potential agency problem is amplified by the fact that different consumers pay different prices for the same drug, depending on the copayments required by their insurance plan. There is a prevalent public concern that physicians are overly influenced by pharmaceutical company promotion, but little is actually known about how they choose which drugs to prescribe.

This dissertation investigates the extent to which agency and information problems affect prescribing, and consequently, patient outcomes. I use individual-level data on prescription drug purchases by employees and retirees in twenty-nine Fortune 500 firms from 2003-2007 to construct a sample of patients receiving first-time prescriptions for chronic drugs. In the first two chapters, I estimate how initial prescriptions respond to three factors of patient utility: the copays set by individual health plans, large-scale copay shocks induced by patent expirations, and the predicted price-sensitivity of an individual patient. In the third chapter, a smaller sample with physician identifiers is used to measure the range of physician prescribing (number of drugs used) within a class, and its impact on patient outcomes.

In Chapter 1, I study the responses of physicians and patients to variation in the cost of drugs, and assess the welfare and health consequences of asymmetric and imperfect information in the prescription drug market. I focus on statins (cholesterol-lowering drugs) which are currently the most prescribed category of prescription drugs in the United States. Demand for drugs that treat chronic conditions depends on the initial prescriptions written by a physician, and on the subsequent decisions of patients to continue the prescription or stop. I show that the continuation decision is relatively sensitive to co-payment prices. Initial prescriptions, by comparison, are relatively insensitive to co-payment prices, suggesting that physicians either don't know the prices their patients are paying, or fail to take prices into consideration. I use the event of the highly publicized expiration of the patent for Zocor (simvastatin) to test between these explanations. Insurance plans have much lower co-pays for off-patent drugs: my analysis suggests that physicians are aware of this fact, and substantially increased prescriptions for Zocor and its generic equivalents following the patent

expiration. Interestingly, the increases were larger for lower-income and healthier patients, suggesting that physicians correctly perceive the adherence elasticity of their patients and adjust their initial prescriptions accordingly, but only in response to a large and universal price change.

In Chapter 2, I study the prescribing responses to ten patent expirations occurring between 2004 and 2007 in four drug classes: antidepressants, statins, calcium channel blockers, and beta blockers. Four of the patent-losing drugs (including Zocor) experienced significant increases in prescribing rates, while three experienced statistically significant decreases. Understanding what drives this variation can inform how pharmaceutical advertising, health plans, and patient costs affect physician decisions. I identify two factors that explain much of the variation in these responses: the size of the copay drop upon expiration (i.e. the difference in copays of the brand and generic versions of the drug), and the current prevalence of generic prescribing in the drug class. Results suggest that physicians are more likely to increase their prescribing of a drug, after it becomes available as a generic, if it previously had a higher copay, on average. However, there is a baseline tendency to reduce prescribing of a patent-losing drug, likely driven by the cessation of its advertising, and this tendency grows stronger with the existing rate of generic prescribing in a class.

In Chapter 3, which is coauthored with Geoffrey Joyce and Neeraj Sood, we measure the range of physician prescribing within the ten most prevalent therapeutic classes, the factors affecting the broadness of this range, and its impact on patient outcomes. We find that physicians prescribe more broadly than commonly perceived. In 8 of 10 classes, the median physician prescribes at least 3 different drugs despite the small number of initial prescriptions observed per doctor (median=7). Physicians treating patients with a greater range of comorbid conditions and varied formulary designs prescribe a broader range of drugs within a class. Though narrow prescribers are more likely to prescribe highly advertised drugs, few physicians prescribe these drugs exclusively. Narrow prescribing has modest effects on medication adherence and out of pocket costs in some drug classes.

To Justin.

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Chapter 1

The Role of Patient Copayments in Prescribing and Refill Decisions

Consumers do not purchase prescription drugs in a standard marketplace setting; instead, they rely on physicians to select an appropriate drug on their behalf. This potential agency problem is amplified by the fact that different consumers pay different prices for the same drug, depending on the co-payments required by their insurance plan. In this paper I use individual level data on prescription drug purchases by employees and retirees in a group of Fortune 500 firms to study the responses of physicians and patients to variation in the cost of drugs, and assess the welfare and health consequences of asymmetric and imperfect information in the prescription drug market. I focus on statins (cholesterol-lowering drugs) which are currently the most prescribed category of prescription drugs in the United States. Demand for drugs that treat chronic conditions depends on the initial prescriptions written by a physician, and on the subsequent decisions of patients to continue the prescription or stop. I show that the continuation decision is relatively sensitive to co-payment prices. Initial prescriptions, by comparison, are relatively insensitive to co-payment prices, suggesting that physicians either don't know the prices their patients are paying, or fail to take prices into consideration. I use the event of the highly publicized expiration of the patent for Zocor (simvastatin) to test between these explanations. Insurance plans have much lower co-pays for off-patent drugs: my analysis suggests that physicians are aware of this fact, and substantially increased prescriptions for Zocor and its generic equivalents following the patent expiration. Interestingly, the increases were larger for lower-income and healthier patients, suggesting that physicians correctly perceive the adherence elasticity of their patients and adjust their initial prescriptions accordingly, but only in response to a large and universal price change.

1.1 Introduction

Over the past decade, insurers have sought to rein in rising drug costs by increasing patient cost-sharing and adopting incentive-based benefit structures. Tiered formularies, which use multiple copay levels ("tiers") to encourage choice of less costly drugs, have become nearly ubiquitous in both employer-sponsored and Medicare Part D plans.[1]

Relative to simpler benefit structures with a fixed copay (out-of-pocket cost) for all drugs, tiered formularies have been found to reduce overall drug expenditures, but raise patient costs in the process.[2] An important concern has thus arisen: If they lead utilization rates of chronic medications to suffer, then tiered formularies – and high copays, more generally – may reduce drug expenditures today at the expense of medical costs tomorrow. This concern is intensified by the fact that we cannot expect insurers' incentives to be aligned with socially efficient use of long-term medications. The high degree of turnover in the commercial health insurance market– and the existence of Medicare– reduce their expected gains from costly investments in preventive care ([10]).

Little attention has been paid to the role of physicians, who have the power to mitigate the effects of cost-sharing through cost-sensitive prescribing. Tiered formularies operate on the assumption that cost-sensitive patients can choose low-tier drugs, but prescription drugs cannot, by definition, be purchased at will. Instead, physicians prescribe drugs for their patients, and they may not observe nor respond sufficiently to their patients' copays.

This paper answers three questions that are critical to evaluating the efficiency of current pharmaceutical benefit structures: First, how does the copay of a first prescription affect a patient's continuation of treatment? Second, do physicians consider patient copays when choosing which drug to prescribe?[3] Third, how does the difficulty of observing plan-specific copays affect physicians' ability to respond to them? Beyond their direct relevance to health policy, these questions are important for understanding physician agency. Despite mounting public concern over payments and interactions between pharmaceutical firms and physicians, very little is known about how physicians choose which drugs to prescribe. Do physicians value patients' monetary savings, or only health gains? Do they monitor their patients sufficiently to learn the effects of patient costs on medication adherence? Do they accurately observe patient costs, when they vary across plans? Do they take into account patient heterogeneity in dimensions beyond medical status, such as price sensitivity? These questions are all addressed within my empirical framework.

I model the prescribing of a chronic drug as a simple two-stage dynamic game. The physician prescribes a drug, and after the first period of use, the patient decides whether

[1] Benefit designs with 3 or more tiers currently apply to 78 percent of privately insured workers and over 85 percent of Medicare Part D beneficiaries. Sources: Kaiser Family Foundation [2010], Hargrave et al. [2010].

[2] See [25] for a review of this literature.

[3] I use the term "copay" loosely, to represent any out of pocket cost paid by a patient. In some plans, a *coinsurance* (fixed share of billed price) rather than a *copayment* (fixed dollar amount) applies.

to continue or quit.[4] If the physician is a fully-informed perfect agent for the patient, his prescription will respond to the patient's copay in two ways. First, indirectly, through the expected effect of a drug on a patient's health. This expected effect depends on the probability that the patient continues treatment, since the health effect of a chronic, preventative drug requires consistent long-term use. If patients vary in the degree to which copays affect their continuation decisions, physicians will correspondingly vary the weight they place on copays when prescribing.

Second, patient costs enter the physician decision in the traditional way: a perfect agent seeks to maximize patient utility, taking into account the implicit trade-off between health and consumption. Even a patient who will continue treatment regardless of the drug chosen – because her utility from any drug exceeds the utility of no treatment – may not obtain maximal utility from the highest quality drug; its added benefit to her may not exceed its added cost.[5] Note that the patient cannot on her own determine which drug maximizes her utility, since she cannot predict the comparative efficacy of different drugs for her specific condition.

Perfect physician agency is unlikely for a number of reasons, including information costs, the unobservability of patients' utility functions, and the possible presence of other incentives on the part of the physician. For example, it is possible that some physicians value their patients' consumer surplus less than their health *per se*, or not at all.[6] Some physicians may act as "health maximizers," always choosing the highest quality drug for a patient they expect to continue treatment. Nevertheless, if their prescribing is indeed aimed to maximize patient health, these physicians will still respond to copays when they expect them to affect adherence.

The assumption of full information regarding costs is also unrealistic. Surveys find that despite a widespread reported desire to take patient costs into account, 60-70% of physicians "never or rarely" know a patient's pharmacy benefit structure or copayments for different drugs ([45, 36]). If a physician lacks information on a patient's copays, he will also lack information on her likely continuation, which depends on drug copays. In this case, I assume that the physician estimates patient costs and the likelihood of continuation using an unbiased prior based on drug patent status.[7]

I focus on statins (HMG-CoA reductase inhibitors), the most prescribed class of drugs in the U.S. since 2006. Statins reduce blood cholesterol levels, and have been found effective in

[4]The welfare costs of suboptimal initial prescribing would be trivial if it were easy for patients to re-optimize quickly, but there are large switching costs in the prescription drug market. Patients are far more likely to discontinue treatment after one prescription (27%) than to switch drugs on their second prescription (3%). While 75 % of discontinuing statin patients return to the class over the next 2.5 years, their median lost treatment time is over one year.

[5]I use "he" for the physician and "she" for the patient.

[6]Potential reasons include malpractice liability concerns and risk aversion. Also, if physicians face external incentives to prescribe certain drugs, they may be less willing to trade patient health than patient surplus for such "rewards."

[7]Off-patent status indicates availability as a generic, and generic drugs are associated with lower copays.

reducing the risk of coronary heart disease and heart attacks.[8] They have been the largest therapeutic class in U.S. sales for most of the last decade ($19.6 billion in 2006 alone).[9] The statin class is particularly well-suited for this study for four reasons. First, it is a self-contained and well-defined drug class; there exist neither sub-types of statins nor prominent competing drug classes treating the same conditions. Second, unlike antidepressants, which have high heterogeneity in their patient-specific effects, the efficacy ranking of statins is largely consistent across patients.[10] Third, statins are expensive. The copay for a month's supply of a statin ranges from $0 to $105 in my sample, with an average of $22 for brand drugs and $9 for generic drugs. The average yearly cost for an adherent statin user in my sample is $216, but only 49% of starting patients are adherent over the first year. Fourth, the patent of a major statin (Zocor (simvastatin)) expired on June 23, 2006. I exploit this highly publicized event to estimate the effects of a change in physicians' copay priors.

I use a rich dataset of pharmaceutical and medical claims from 15 self-insured Fortune 500 firms offering over 100 plans. I use variation in formularies across plans and over time to obtain precise estimates of the copay elasticity of the continuation decision, among patients starting statin therapy. On average, a $10 (or 44%) copay increase reduces the probability of continuation by 3.6 percentage points (4.7% of the average continuation rate). However, there is important heterogeneity. Healthy, retired patients with incomes below $50,000 have probability reductions of 6 percentage points (7.5%), while an employed, healthy patient with income above $50,000 has a reduction of only 1.5 percentage points (2%). Diagnosed chronic conditions and treatment by a specialist also reduce the copay elasticity. From these estimates, I obtain a predicted continuation probability for each patient and each drug. Due to variation in drug quality and cost-sensitivity, the least expensive drug is not always the one with the highest predicted continuation probability. For example, Lipitor, the most commonly prescribed drug prior to Zocor's patent expiration, yields the highest predicted continuation probability (conditional on copays) for 77% of patients in the period prior to Zocor's patent expiration, and for 34% of patients in the period afterwards.[11]

Next, I use a conditional logit framework and variation across plan formularies to estimate the effects of drug copays and predicted continuation probabilities on the choice of initial drug. Copay effects on prescribing are modest in the period prior to Zocor's patent expiration: a $10 increase in relative copay reduces a drug's choice probability by 2.7 percentage points. The effect increases to 5 percentage points, however, when the period surrounding Zocor's patent expiration is included. In addition, for every copay-associated percentage

[8] [28] review recent long-term trials and their implications for recommended treatment guidelines.

[9] Spending began to decrease in 2007, with the patent expiration of two brand statins. 2009 was the first year in which another class, Antipsychotics, passed statins in spending. Source: IMS Health Prescription Audit PLUS.

[10] Efficacy is measured as expected percent reduction of lower density lipoprotein (LDL). At a 20 mg dose, this measure varies from 21% (fluvastatin) to 48% (rosuvastatin).

[11] The patients for whom Lipitor yielded highest continuation probabilities after Zocor's patent expiration faced relatively low copays for Lipitor: on average $15 per month versus $11.50 for generic Zocor.

point increase in an individual's predicted continuation probability (based on her copay and personal characteristics), a drug's choice probability increases by an additional 1.1 percentage points.

I find that the prescribing response to continuation probability is entirely driven by the change in physicians' copay priors upon Zocor's patent expiration. Prescriptions for this molecule increase significantly following generic entry, but the rate of increase in different plans does not appear related to plan-level variation in the magnitude of the molecule's copay change upon generic entry.[12] Instead, within each plan, the increase in its prescribing strongly favors patients with low salaries and better health, those whose adherence to statin therapy is most likely to be copay-elastic.

The empirical findings of this paper are consistent with the hypothesis that physicians aim to take into account patients' costs, particularly when they may affect adherence. They also indicate that physicians do not observe patient costs perfectly, and use patent status as an indicator of costs. Once a drug class contains prominent generic drugs, new patients can be sorted among on-patent and off-patent drugs based on their estimated adherence elasticities. Interestingly, I find that in another chronic drug class already containing prominent off-patent drugs (beta blockers), the patent expiration of an additional major drug has no effect on initial prescribing. This suggests that predicted adherence is a primary factor in the physician's initial prescription decision.

While patient copays and predicted adherence have significant effects on prescribing, much of the variation in the physician prescribing decision remains unexplained. Only 40% of patients receive an initial fill for the drug that yields their highest predicted probability of continuation.[13] The average continuation rate would increase by 3.9% if all patients were prescribed the drug maximizing their continuation probabilities, with an increase of 5.9% among patients earning less than $50,000 per year. Patients would pay, on average, $5.57 less per monthly prescription. However, a simulation finds that providing physicians with perfect information on patient copays would not significantly improve prescribing: the drug selected would only change in 6.6% of initial prescriptions. The fact that among healthy patients, those with higher salaries are less likely to start on simvastatin, raises the possibility that physicians are price-discriminating on behalf of pharmaceutical firms. Alternatively, physicians may believe that the benefits of more potent statins exceed their added cost relative to simvastatin, even for healthy patients with less purported need for them.

This paper proceeds as follows. Section 2 discusses the institutional setting and relevant literatures. Section 3 describes the two-stage model of initial prescribing and patient continuation. Section 4 describes the data. Section 6 contains the empirical framework and results. Section 7 discusses results in another drug class. Section 8 concludes.

[12] I use the term "molecule" to refer to all versions of a drug, i.e. both the brand and generic versions of a multi-source drug.

[13] I use the term "fill" to describe a purchased drug, emphasizing that I only observe filled prescriptions.

1.2 Background and Literature

In this section, I summarize the roles and incentives of each player in the prescribing and dispensing of prescription drugs, and relevant research on their behavior. Since my data consist of *filled* (purchased) rather than *written* prescriptions, what I call the "physician prescribing decision" is the net output of a series of action that begin and end with the physician. It is worth emphasizing, however, that the physician must approve any prescription switch suggested by any of the others. Thus, pharmacist or patient requests can be understood as a mechanism through which the physician learns about the copays, copay sensitivity, and drug preferences of a given patient.

I then briefly describe the statin drug class and the patent expiration of Zocor (simvastatin) and Pravachol (pravastatin) in 2006.

1.2.1 The Prescribing and Dispensing of Prescription Drugs

The Health Plan and Formulary

In setting patient costs and procedures for obtaining prescription drugs, health plans play an important role in determining their beneficiaries' usage rates. While facing double-digit annual growth of drug expenditures from 1995 to 2004, insurers began aggressively pursuing cost-cutting strategies. The share of employer-insured individuals covered by tiered benefit plans (as opposed to fixed copay or coinsurance plans) rose from 26% in 2000 to 78% in 2009 [14]. This rapid shift has drawn substantial research attention to the effects of patient cost-sharing, with most studies finding that cost-sharing in general, and tiered formularies in particular, reduce drug expenditures and utilization.[15] A 10% increase in the price faced by the patient reduces drug spending by 2% to 6%, depending on drug class and patient health conditions, and the utilization change is largely driven by adherence rather than starting and stopping rates ([25]).

This literature has raised the concern that tiered formularies– and high copays, more generally– are reducing current drug expenditures at the expense of future medical costs (see Goldman, Joyce and Zheng (2007) for a review). After all, the rise in pharmaceutical spending that drove insurers to increase patient costs was driven in large part by the expansion of use of new, superior treatments for common chronic conditions ([37]).

If high copays induce non-adherence in patients who *should* be taking antidiabetic, antihypertensive, or other important chronic medications, one may question whether health insurers are being short-sighted, or if they face low incentives for covering preventive health care. Since chronic prescription drugs are an expensive investment in long-term patient health, insurers may not pursue efficient levels of their use if another insurer– or Medicare– is likely to reap the gains of the health improvements. [10] find that inefficient investment

[14] Kaiser Family Foundation, 2010

[15] These studies are reviewed by Goldman, Joyce and Zheng (2007)

in preventive care may result from search frictions (for employers) and frequent turnover (of patients and employers) in the commercial health insurance market. This potential misalignment of incentives highlights the importance of understanding how copays affect both prescribing and patient adherence, since we cannot assume profit-maximizing insurers are designing formularies aimed towards socially efficient use of chronic drugs. [16]

The Physician

A prescription must indicate a specific drug molecule, either by brand name or molecular (generic) name. For this reason, physicians have the "first move" in the process determining an individual's first fill.

While physicians who work exclusively for one managed care organization (for example, for Kaiser in California) may face pressure or incentives from their employer to prescribe cost-effectively, no such incentives are present in the typical physician practice. Nonetheless, the vast majority of physicians agree, in surveys, that "When choosing between equally effective and safe medications, it is important to prescribe the drug that minimizes patients' out-of-pocket costs" ([45, 36]).

On the other hand, there is evidence that pharmaceutical marketing to physicians affects prescribing (e.g., [26, 49]) and significant debate about whether such marketing is harmful to patients.[17] [27] find evidence in the U.K. that physicians are sensitive to pharmaceutical detailing, shifting their prescribing towards other on-patent drugs when a major antidepressant (Prozac) loses its patent. In the U.K., however, an off-patent molecule offers no cost savings to patients, who pay a flat copay for all drugs.

Some studies find results suggestive of imperfect physician information on patient copays. [50] find evidence of spillovers of Medicaid Preferred Drug Lists (PDLs) on non-Medicaid patients.[18] [35] finds that a move to tiered copays hurts adherence more than an across-the-board increase in copays with the same change to average copays– suggesting that either there is low substitutability of drugs within a class, nonlinearities in the response to copays, or that copays do not shape prescribing.

[16] Very large firms, however, are typically self-insured, and often continue to cover their employees as retirees ([20]). The firms in my study fall into this category. Their stronger incentives to promote adherence to chronic drugs may explain why many plans in my sample offer more generous pharmaceutical benefits than commercially insured plans on average.

[17] It may be beneficial through keeping busy physicians informed of new advances in pharmaceutical treatments and details regarding their use. It may be harmful for the obvious reason that marketers do not disseminate unbiased information, and thus, may bias physicians' beliefs of the costs and benefits of potentially risky and expensive drugs.

[18] It is important to note that Medicaid PDLs are the strictest kind of formulary, in which non-preferred drugs are not merely offered at higher copays, but not covered at all.

The Pharmacist

Most individuals in my sample (77%) fill their first statin prescription at a retail pharmacy, while the others purchase by mail. Surveys reveal that it is usually at the pharmacy that a patient first learns her monetary cost (copay) for the drug prescribed ([44]). Physicians and pharmacists alike view part of the pharmacist's role as reviewing a patient's plan formulary for cost-saving alternatives, before filling a prescription for a non-formulary or high-tier drug.[19]. The pharmacist must contact the physician's office to request approval for any switch, however.[20] This is referred to as *therapeutic interchange*: interchanging prescriptions for therapeutically-similar, but not molecularly identical, drugs.

If a plan imposes restrictive policies on the coverage of certain drugs, for example, requiring that a patient try an existing generic drug in the class before a brand drug is covered ("step therapy"), or requiring the physician to document a patient's need for a particular brand drug ("prior authorization"), this will usually be discovered at the pharmacy. The pharmacist, again, acts as an intermediary in contacting the physician and informing him of the policy.

In contrast, *generic substitution* (supplying a generic version of a prescribed drug molecule) does not require contacting the prescribing physician. In all 50 states, pharmacists are either mandated or allowed tos dispense generic versions of a *multi-source* drug molecule, as long as the prescriber has not explicitly prohibited it. [21] While low rates of generic substitution were a policy concern a few decades ago, these have increased dramatically with the state-level mandates. Two other factors have also contributed. First, most plan formularies now require patients to pay the highest levels of cost-sharing for brand versions of multi-source molecules, sometimes the full retail price difference between the brand and generic versions. Second, dispensing fees (paid to the pharmacy by insurers and pharmacy benefit managers, per drug fill) give pharmacists higher profit margins on generic drugs.[22] In addition to virtually guaranteeing generic substitution, this incentive may also lead pharmacists to suggest therapeutic interchange to patients.

[19]Only 25 percent of physicians believe that it is their responsibility to prescribe preferred drugs, while 68 percent believe it is the pharmacists' responsibility to check a drug's formulary status. The same physicians report that about 20 percent of their prescriptions result in a pharmacist's call about nonformulary status, and that in 53 percent of these cases, they approve prescription changes (Shrank et al. [2006])

[20]The very few exceptions include prescriptions written by hospital doctors and filled in hospital pharmacies, and other cases in which doctors belonging to a closed network may be contractually obligated to give *ex ante* approval for pharmacists to interchange prescriptions within certain drug classes.

[21]*Multi-source* refers to multiple manufacturers producing and selling the same drug molecule; this can only occur when a drug is no longer protected by a patent.

[22]Citation forthcoming.

1.2.2 The Statin Drug Class

Statins are the first-line recommended drug treatment for high blood cholesterol. Today, they are the class of drugs most frequently filled in the United States, with 210.5 million dispensed prescriptions in 2009.[23] The spread in their use from the mid-1990s to today has been driven by a series of long-term studies demonstrating their efficacy in preventing cardiac events (e.g. heart attacks) among patients with coronary heart disease, and in preventing the emergence of heart disease itself.

At the start of my study period, 2005, there was one existing generic statin (lovastatin) which was not very commonly prescribed (6.7% of initial fills in my sample). The most commonly prescribed statin, *Lipitor*, was and remains the drug with highest U.S. sales ($7.5 billion in 2007). 46% of initial fills in my sample were for Lipitor, in 2005.

During my sample period, two statins faced patent expiration. Zocor (simvastatin) was the second most prescribed statin at the time of its patent expiration (15.8% of initial fills in my sample), while Pravachol (pravastatin) was much less common (4.5%).

The range of expected percentage LDL lowering for the highest does of each statin is shown below. The two newest statins, Lipitor and Crestor, are both more potent than Zocor. Vytorin is a combination of simvastatin with ezetimbe, another cholesterol-lowering agent. Thus, it is also more potent than simvastatin alone.[24] Pravachol and two other statins available at the time are less potent than Zocor.

Table 1.1: Doses of Available Statins Required to Attain an Approximate 30% to 40% Reduction of LDL-C Levels and Patent Status in 2005

Drug	Dose, mg	LDL Reduction	Patent Status (2006)
Lipitor (atorvastatin)	10	39%	On-patent
Mevacor (lovastatin)	40	31%	Off-patent since 2001
Pravachol (pravastatin)	40	34%	Expired on April 20, 2006
Zocor (simvastatin)	20 - 40	35% - 41%	Expired on June 23, 2006
Lescol (fluvastatin)	40 - 80	25% - 35%	On-patent
Crestor (rosuvastatin)	5 - 10	39% - 45%	On-patent

Source: Grudy et al. and NCEP (2004)

Recommended guidelines for statin treatment are disseminated by the National Cholesterol Education Program (NCEP) and updated every few years. These are quite detailed. They provide algorithms to determine patient risk based on several chronic conditions and personal characteristics considered "risk factors" (e.g. diabetes, cardiac disease, smoking), and they provide tables with "goal" cholesterol levels for each type of patient. Thus, there is

[23]Including *Zetia* (ezetimbe) which is not a statin. Source: IMS National Prescription Audit PLUS

[24]I refer to Vytorin as a different molecule since it is impossible to unbundle the two active ingredients, simvastatin and ezetimbe.

clear variation in the need for cholesterol reduction across patients. Though I cannot observe some of the factors relevant to this assessment (e.g. measured cholesterol level, smoking), I can observe some of the most important ones: diabetes, heart disease, recent heart attack, and "high cholesterol" diagnosis. These characteristics will allow me to control rather well for patient type when estimating both adherence and prescribing decisions.

1.2.3 Patent Expiration

New drugs approved by the Food and Drug Administration are eligible for patent protection, which typically lasts 11-12 years after the drug's launch. The Hatch-Waxman Act (1984) instituted a reward of 180-day generic exclusivity to the manufacturer of the first-approved generic version of any drug, as an incentive for rapid entry following a patent's expiration. As a result, the market price of an off-patent drug molecule usually drops gradually at first, and more precipitously after the first 180 days. Copays, however, are affected immediately, since they are predicated on generic status rather than the actual price of a drug. The following table compares the average copays in 2- and 3-tier employer plans nationwide, or years 2005-2007, and in the present sample.

As mentioned in section 1.2.1, generic substitution is extremely common once a generic version of a drug is available, regardless of whether the physician has written the brand or generic name of a molecule.[25] As Figure 1.1 shows, for the two drugs whose patents expire during my sample period, generic versions rapidly overtook the full share of initial prescriptions for their respective molecules.

[Figure 1.1 about here]

There is typically some media attention surrounding the patent loss of major drugs, and more so when they occur in drug classes in which the majority of prescribing is for patented drugs. This was the case of Zocor's patent expiration. Zocor was, at the time, Merck's largest drug, and its generic entry threatened the profits of Lipitor, the highest selling drug in the United States. Consequently, this was a high-profile patent expiration, anticipated to reshape statin prescribing. [26]

Patent expiration may also shape prescribing through the cessation of drug company advertising for the patent-losing drug. Due to their large market, statin manufacturers do a significant amount of promotion, both direct to physicians (detailing, free samples) and direct to consumers (e.g. television advertisements). Promotion has been found to significantly affect both physician and patient preferences for drugs ([26, 49]). However, without data on promotional interactions between physicians and pharmaceutical firms, I cannot directly explore this phenomenon. I can only assert that the overall shift of prescribing toward the Zocor molecule, upon its patent expiration, is likely mitigated by the reactions of physicians

[25] With the exception of when a physician writes "Do not substitute."

[26] In Section 1.6, I extend my analysis to patent expirations in other classes, in which prominent generic drugs already existed at the time. I find very different prescribing responses, but the differences are consistent with the explanation that physicians seek to maximize the adherence of cost-sensitive patients.

who respond to pharmaceutical firm influences to prescribe on-patent drugs (as found in [27].

1.2.4 Medicare Part D

While Medicare Part D came into effect in 2006, during the sample period, this reform did not directly affect the plans covered in this sample.

1.3 Model of Prescribing and First Refill

In this section I present a simple model of chronic drug prescribing and adherence as a two-stage dynamic game. My approach is similar to that of []ellickson. In the first stage, the physician chooses a drug molecule[27] as an initial prescription for patient i, among the set of N_c drugs in therapeutic class c. The factors that enter this decision are: the expected health effects of each drug j on patient i (ω_{ij}), the cost of each drug to patient i (p_{ij}), and potentially, external incentives to prescribe certain on-patent drugs (t_j). In the second stage, after using the drug for one period, the patient decides whether to continue treatment in the drug class. This decision takes into account her perceived health benefit from the drug she was prescribed (v_{ij}) and its copay (p_{ij}). The effect of the copay is heterogenous and possibly correlated with income, current health, and other characteristics (x_i).

I consider prescribing under two scenarios, (i) the physician assumes a patient will adhere (or does not expect the cost of the medication to influence their adherence), and (ii) the physician considers the patient's likely adherence response to each possible drug.

The physician may use backward induction to predict and respond to a patient's probability of adherence to each possible drug (q_{ij}), since a non-adherent patient gains no therapeutic benefit. The physician's estimate of the probability of adherence is based on observable patient characteristics and his estimate of the patient's copay: $\widehat{q}_{ij}(x_i, E[p_{ij}])$.

Four assumptions are key to the setup of this model. I begin by briefly explaining these assumptions, and I refer to the Appendix for their empirical justification. I then model each of the two stages of this game, working backwards from the patient's continuation decision.

1.3.1 Underlying Assumptions and Definitions

Definition 1. An *initial fill* is a patient's first observed purchase of a statin following at least one year of coverage in the data.

Definition 2. A *timely second fill* is a refill *or* fill of another statin that occurs no later than 60 days following the last day of medication supplied by the initial fill.

[27] I emphasize that the physician chooses a molecule rather than a specific version of a multi-source (off-patent) molecule, because as described in Section 1.2.1, the generic substitution decision rests with the patient and pharmacist, assuming the physician has not prohibited generic substition.

Assumption 1. *A patient without a timely second fill has discontinued statin treatment for the year. I refer to such patients as* discontinuers*, and correspondingly, to the occurrence of a timely second fill as* continuing*.*

In the data I use, 26% of statin patients who start in the first half of 2005 have no timely second fill. Among these, one-third have no other statin fills at all in 2005-2007, and among the two-thirds who have a "late" second fill, the median lost treatment time is 376 days.

Assumption 2. *Patients whose second fill is for a different statin would continue on the first statin if switching were not possible.*

This assumption is consistent with a notion of patients deciding to continue statin treatment prior to deciding whether to stay on drug j or switch to another statin. It is worthwhile to note that less than 3% of patients with a timely second fill switch to a different statin at this time, suggesting that switching costs are high.[28] If switching costs are inversely correlated with a patient's average therapeutic value from statin treatment (e.g. a patient with a strong need for treatment is also likely to visit or contact her doctor more frequently), then this assumption is reasonable. The assumption allows me to describe all patients with a timely second fill (of any statin) with the same inequality (Equation 1.3), based on their valuation of the drug initially prescribed and the utility of no treatment. This simplifies both the model and estimation, and is consistent with the data: While the copay of the drug initially filled affects continuation, the copays of other drugs– even when a much less expensive one is available– have no effect.

Definition 3. I use a common medical definition of *full adherence* – filling enough prescriptions to maintain a supply of medication covering at least 80% of the days in a certain period, for example, one year following the initial prescription.

Assumption 3. *A timely second fill is a strong predictor of adherence over the next year.*

Among patients with a timely second fill, 62.9% achieve full adherence over one year. Among the others, only 4.7% achieve the same. Thus, although continuing after the first prescription is not sufficient to guarantee full adherence, it is an easily measured intermediate outcome that makes year-long full adherence far more likely.

Assumption 4. *Patients do not selectively choose whether to fill their first prescriptions.*

While it is possible that some patients never fill their initial prescriptions, this decision is beyond the scope of my analysis (I only observe filled prescriptions). My analysis presumes that all patients prescribed a statin by their doctor will purchase a first supply of *a* statin (in section 1.2.1 I describe the possibility that a patient or pharmacist contacts the physician

[28] Among other factors, these may include the time and effort necessary to contact the doctor, the psychic cost of expressing concern over monetary costs, and procrastination between doctor visits.

to request therapeutic interchange). If prescriptions for high cost drugs lead patients to walk away instead of requesting therapeutic interchange, my results will underestimate the effect of copays on adherence and overestimate physicians' responsiveness to copays. In the Appendix, I evaluate this possibility and find no evidence supporting it.

1.3.2 Stage 2: The Patient's Continuation Decision

Let Y_i be a binary variable that equals 1 if patient i continues after her first fill (a timely second fill of any statin is considered continuing). By assumption 2, this decision takes the drug of the initial fill (j) as given, and does not depend on the characteristics of other drugs available. Patient i's utility depends on her perception of drug j's expected therapeutic effect and its out-of-pocket cost. The therapeutic benefit of statins lies in their long-term preventative effects, rather than in any discernible effect on present-day symptoms. Thus, I assume that patients' perception of a drug's therapeutic effect comes from their doctors' assessment, the potential influence of direct-to-consumer advertising of statin drugs, and the potential ability to monitor the reduction of their cholesterol levels at future doctor visits. [48] model statin adherence as partly based on a decaying function of time since they first learned of their health risks, representing the drop in salience of the initial "scare." For this reason, I do not require equality between the patient's perception of a drug's therapeutic effect, when deciding whether to continue, and the doctor's potentially more accurate perception, though they are likely to be related.

I model a patient's utility from drug j, at the time of the continuation decision, as follows.

$$\begin{aligned} U_{ij} &= c_i + v_{ij} - \alpha_i p_{ijt} && (1.1) \\ &= C(x_i) + V_j(x_i) - \alpha(x_i) \cdot p_{ijt} + \eta_{ij} && (1.2) \end{aligned}$$

where c_i is the perceived therapeutic benefit – net of any inconvenience associated with filling a prescription – that is shared across all statins (i.e. the value of the cholesterol-reduction provided by the least-powerful statin, and general risk of side effects) and v_{ij} is the value of the additional therapeutic benefit offered by better/stronger statins. $C(x_i)$, $V_j(x_i)$, and $\alpha(x_i)$ are means conditional on patient characteristics, and η_{ij} is a Type I extreme value error capturing idiosyncratic variation across patients in all of these values.

p_{ijt} is patient i's plan-determined copay for drug j at time t. The therapeutic effect patient i expects to gain from drug j over the next period, $C(x_i) + V_j(x_i) + \eta_{ij}$, includes the disutility of any side effects and the present discounted value of expected long-term health benefits to accrue over this period.[29]

The patient continues if $U_{ij} \geq U_0$, where U_0 is the utility of no statin treatment. I denote the probability that a patient continues, conditional on x_i and p_{ij}, as q_{ij}. This probability

[29]The set of observable covariates x_i includes age, employment status, dummies for relevant chronic conditions, the number of comorbid conditions, recent heart attack, and high salary (see Data Appendix for a list of included conditions).

takes the familiar logit form:

$$q_{ij} = \text{Prob}\{Y_i = 1\} = \text{Prob}\{U_{ij} > U_0\} \quad (1.3)$$

$$= \frac{\exp(C(x_i) + V_j(x_i) - E[\alpha_i|x_i]p_{ijt})}{1 + \exp(C(x_i) + V_j(x_i) - E[\alpha_i|x_i]p_{ijt})} \quad (1.4)$$

The goals in estimating this equation are twofold. The first goal is to characterize how copays affect continuation past the first prescription – an immediate indicator of drug adherence – through the estimate of $\frac{dq_{ij}}{dp_{ij}}$, overall, and for specific types of patients, $E[\frac{dq_{ij}}{dp_{ij}}|x_i]$. Second, the model of the doctor's prescribing decision may take $E[\frac{dq_{ij}}{dp_{ij}}|x_i]$ and $E[q_{ij}|x_i]$ as inputs.

Note that a low estimate of $E[\frac{dq_{ij}}{dp_{ij}}|x_i]$ for some set of observables x_i indicates either a low $E[\alpha_i|x_i]$ or a high $E[c_i + v_{ij}|x_i]$. A patient who has dire need for cholesterol-reduction (high c_i) is less likely to discontinue statin treatment, regardless of the drug she starts on. If she has a large α_i, she may be more likely to switch to a cheaper statin in the second fill, or later on (see Assumption 2). For example, patients who have worse health conditions are less sensitive to copays in their continuation decisions, but this does not necessarily indicate that they have negligible values of α_i. It simply means that if they start and stay on a drug whose additional benefit (v_{ij}) does not exceed its added cost ($\alpha(p_{ij} - \underline{p})$, where $\underline{p}$ is the copay of the statin with no added benefit beyond c_i), they lose substantial consumer surplus over time.

Variation in p_{ij} comes from cross-sectional variation in plan copays and changes in each plan's copays over time. For estimates of $E[\alpha|x_i]$ to be unbiased, three assumptions must be satisfied. I discuss these below. A remaining source of endogeneity is physician selection of patients on unobservables: if a physician sees a signal that the researcher does not see – for example, a specific request from a patient for a certain drug – then patients who start on a drug *despite* a high copay may have unobservable preferences for this drug. This will bias my copay elasticity estimates towards zero.

Assumption 5. *A patient's perceived therapeutic effect from drug molecule j does not depend on a drug's patent status.*

This assumption is supported by the data; the change in continuation probability when *Zocor* goes off-patent is largely consistent with the predicted change based on the copay drop.

Assumption 6. *For all pairs of drugs j and k in a class, the distribution of $\eta_{ij} - \eta_{ik}$ across individuals is independent of $p_{ij} - p_{ik}$.*

This assumption does not prevent the possibility that all plans preferentially price drugs that are more efficacious on average. At the cross-sectional level, this assumption prohibits

that health plans preferentially price specific drugs that are uniquely suited to *unobservable* preferences of their beneficiaries. Given that my data comes directly from the health plans' records, this seems unlikely, since the plan designers are unlikely to have additional exploitable information. Furthermore, since I require a patient to be covered by a plan for one year prior to an initial prescription, it is similarly unlikely that patients select into plans based on preferences over drugs in drug classes that they do not currently use. When plan fixed effects are included, this assumption becomes even less restrictive, simply prohibiting that patients strategically time their first prescriptions with temporal changes in the plan's copay structure.

Assumption 7. *For all pairs of drugs j and k in a class, the distribution of $\alpha_i - E[\alpha|x_i]$ across individuals is independent of $p_{ij} - p_{ik}$.*

Since α_i is unobserved, I will only be able to estimate an average value conditional on observables: $\bar{\alpha}_i(x_i)$. Thus, $(\alpha_i - \bar{\alpha}_i(x_i)) * p_{ij}$ will fall into the error term, and for consistent estimation of $\bar{\alpha}(x_i)$, this assumption is required. A stricter assumption, which would also suffice, is that the distribution of α_i is the same in each plan. However, if there is variation in the average α_i by plan, which I denote $\bar{\alpha}_{ip}$, then plans with particularly price-sensitive patients may be more likely to preferentially price certain drugs, or to choose tier copay levels that are smaller in magnitude and closer together.

When plan fixed effects are included, this assumption can be relaxed somewhat. Then, $\bar{\alpha}_{ip}$ may be correlated with the overall benefit structure of a plan, as long as the distribution of α_{ip} does not change between starters in period t and starters in period $t+1$ in a way that is correlated with changes in the relative copays of any two drugs in the class.

1.3.3 Stage 1: The Physician's Prescribing Decision

Upon evaluating patient i, prescribing doctor d forms estimates of the therapeutic effects of each drug for this patient: $\omega_{ijd}, j \in J$. Note that these represent the therapeutic effects under full adherence, though we will soon account for the possibility of non-adherence.

I assume that the doctor's estimate is unbiased,[30] with error equal to μ_{ijd}, and that the difference between ω_{ijd} and $V_j(x_i)$ (which is the sum of the individual heterogeneity term η_{ij} and the doctor's predictive error μ_{ijd}), is distributed by the Type I extreme value distribution.

[30] In reality, a doctor might have biased views of the efficacy of a certain drug, either for all patients or for patients of some (observed or unobserved) type. The doctor's views may be influenced by pharmaceutical detailers. Alternatively, he may be risk-averse and prefer to prescribe an older drug, or one with which he has more experience. However, by incorporating variation in doctor beliefs in the form of state-dependence in doctor prescribing, I show in the empirical analysis that this does not change my results.

$$\begin{aligned} \omega_{ijd} &= c_i + v_{ij} + \mu_{ijd} && (1.5)\\ &= C(x_i) + V_j(x_i) + \eta_{ij} + \mu_{ijd} && (1.6)\\ &= C(x_i) + V_j(x_i) + \epsilon_{ij} && (1.7) \end{aligned}$$

Assumption 8. $E[\mu_{ijd}] = 0$

Assumption 9. $\epsilon_{ij} \sim EEV(1)$

Initial Prescription, With Full Information and Assumed Adherence

Let U_{dijt} represent the payoff to the physician of prescribing drug j to patient i in period t. If the physician is a fully-informed and perfect agent for the patient, then his payoff is limited to his perception of the patient's expected utility from a drug. He will take into account (i) the expected health benefit to the patient, ω_{ijd}, and (ii) the price paid by the patient, p_{ij}. First, I describe this decision in the case in which a physician assumes that a patient will adhere to the prescribed medication for the next year.

With full information on α_i and p_{ijt}, and perfect agency, doctor d will prescribe drug j if $U_{dijt} \geq U_{dikt}$ for all drugs k in the class, where:

$$\begin{aligned} U_{dijt} &= \omega_{ijd} - \gamma_i P_{ijt} && (1.8)\\ &= C(x_i) + V_j(x_i) - \gamma_i P_{ijt} + \epsilon_{ij} && (1.9) \end{aligned}$$

where P_{ijt} represents the expected discounted sum of copays for drug j over the next year, conditional on the current copay at time t, and γ_i is the discounted-equivalent weight the doctor places on this value.

Incorporating Adherence

From Assumptions 1 and 3, we take it as given that a patient who immediately discontinues will gain no treatment benefit from statins in the current year, while a patient who continues past the first prescription has some probability, around 2/3, of achieving full adherence. I assume that from the doctor's perspective, only a fully adherent patient gains the full therapeutic benefit of drug j, while a non-adherent patient gains zero therapeutic benefit.[31]

[31] This is not an unreasonable assumption. [43] found that statin fill rates of 80% or higher are associated with significantly greater mortality reduction, among post-heart attack patients, than statin fill rates of 40-80% and below 40%. Since statins work by reducing the amount of cholesterol produced in the body, which is otherwise produced on an ongoing basis, temporary usage for one month is not likely to have any lasting effect. However, the mechanics of the model do not change if the doctor bases treatment value on a more flexible measure of adherence, for example, a continuous measure of days of drug coverage.

This implies that a non-adherent patient gains negative utility from starting and stopping treatment, since she pays a cost to acquire one month's supply of a drug, but gains zero benefit from it.

If we denote as Π the probability of full adherence, conditional on continuation past the first prescription, then the physician's estimate of the expected therapeutic effect of drug j for patient i becomes: $\omega_{ij} \cdot E[q_{ij}|x_i, p_{ij}] \cdot \Pi$. Suppose for now that Π does not depend on the initial drug or copay, so we can drop it from the equations that follow. This implies that after the first decision to continue, subsequent continuation decisions are independent of the initial drug and its copay.[32]

Initial Prescription, under Full Information, Perfect Agency, and Endogenous Adherence

With full information on $E[\alpha_i|x_i]$ and p_{ijt}, and perfect agency, physician d will prescribe drug j if $U_{dijt} \geq U_{dikt}$ for all drugs k in the class, where:

$$U_{dijt} = \widehat{q}_{ij} * (\omega_{ijd} - \gamma_i P_{ijt}) - a_i p_{ijt} \tag{1.10}$$

where $\widehat{q}_{ij} = E[q_{ij}|x_i, p_{ij}] = \text{Prob}\{i\text{continues}|x_i, p_{ij}, \alpha_i, j\}$.

A few aspects of this equation are worth noting. First, as expected, the expected probability of continuation $\widehat{q}_{ij}$ increases the probability that a drug is chosen, by increasing the chance that a patient will receive the expected health benefit ω_{ijd}. Insofar as $\widehat{q}_{ij}$ depends on a drug's copay, this will make physicians more likely to prescribe drugs with lower copays.

Second, the patient's copay enters this equation in three places. First, through the cost of the first-time fill (at the end of the equation) which is paid by adherent and non-adherent patients alike. Second, through the cost of year-long adherence, if it is attained. This effect will appear as an interaction between $\widehat{q}_{ij}$ and p_{ij}. Third, through the predicted continuation rate $\widehat{q}_{ij}(x_i, p_{ij})$.

This equation, unfortunately, cannot be estimated without assuming specific values for ω_{ijd}, since it is not observed. However, a few assumptions yield an equation that is easier to estimate.

We can categorize patients into two types, following the reasoning described in 1.3.2. Assume some patients have characteristics x_i for which expected values of c_i and α_i satisfy:

$$C(x_i) \gg E[\alpha|x_i]\overline{p}$$

where $\overline{p}$ is the physician's perception of the maximum possible copay for a statin, for

[32]Since patients who continue have a reasonable chance of visiting their physician before subsequent refills, the switching costs are lowered, thus subsequent fill decisions are likely to be less affected by the initial drug. However, among statins, subsequent decisions are still negatively affected by initial drug copays, on average, so the elasticity of immediate continuation with respect to copay underestimates the effect of copays on adherence.

patient i.

These may be either patients with severe diagnosed conditions (high c_i) or with extremely low price parameters α_i. In either case, they are unlikely to discontinue their prescription for reasons related to its cost: $\frac{dq_{ij}}{dp_{ij}} \approx 0$. Thus, Equation 1.8 closely approximates the prescribing decision. Under the assumption of perfect agency, the physician takes costs into account even if they will not affect a patient's adherence, because they still reduce patient utility. Furthermore, the physician make take costs into account more strongly for a patient with a high $\widehat{q}_{ij}$ (even while $\frac{dq_{ij}}{dp_{ij}} \approx 0$, levels of $\widehat{q}_{ij}$ still vary with patient characteristics). Thus we add $\widehat{q}_{ij} * p_{ij}$ to Equation 1.8.

The other type of patient is one for whom:

$$C(x_i) < E[\alpha|x_i]\overline{p}$$

The physician does not expect this type of patient to adhere to all statins, and expects copays to affect the patient's decision. A simple test for the presence of patients of this type – and an assessment of whether doctors prescribe differently to these patients – is made possible by adding q_{ij} to equation 1.8:

$$\begin{aligned} U_{dijt} &= \omega_{ijd} + \theta\widehat{q}_{ij} - \gamma_i P_{ijt} && (1.11) \\ &= C(x_i) + V_j(x_i) + \theta\widehat{q}_{ij} - \gamma_i P_{ijt} + \epsilon_{ij} && (1.12) \end{aligned}$$

In Section 5, I estimate a composite of Equation 1.8, augmented with $\widehat{q}_{ij} * p_{ij}$, and Equation 1.11, obtaining:

$$\begin{aligned} U_{dijt} &= \omega_{ijd} + \theta\widehat{q}_{ij} - \gamma_i P_{ijt} - \xi\widehat{q}_{ij} P_{ijt} && (1.13) \\ &= C(x_i) + V_j(x_i) + \theta\widehat{q}_{ij} - \gamma_i P_{ijt} - \xi\widehat{q}_{ij} P_{ijt} + \epsilon_{ij} && (1.14) \end{aligned}$$

Among patients for whom $\frac{dq_{ij}}{dp_{ij}} \approx 0$, variation in $\widehat{q}_{ij}$ is only driven by drug-specific characteristics, which will be absorbed by alternative-specific constants that vary by type of patient. Among patients for whom $\frac{dq_{ij}}{dp_{ij}} < 0$, an effect on prescribing can be determined through a positive coefficient on $\widehat{q}_{ij}$. This will indicate that physicians place more weight on copays when prescribing to patients for whom copays may affect adherence.

1.3.4 With Imperfect Information on Copayments

The physician may not observe a patient's actual set of copays, which are determined by her health plan. I assume that wide publicity of Zocor's patent expiration in June 2006 made physicians aware of its changed patent status. This generates variation in the price perceived by physicians who do not observe each patient's own copays, since most health plans have

smaller copays for generic drugs. I test the extent to which physicians' prescriptions respond to the change in national average copays for the Zocor molecule, versus the individual-specific copay deviations from the national average. I do this by decomposing each copay p_{ijt} into $\bar{p}_{jt}$, the average national copay for molecule j at time t, and $p_{ijt} - \bar{p}_{jt}$, the individual-specific deviation. To the patient, only the true copay p_{ijt} is relevant, so we expect the coefficients on both terms of the decomposition to be equal under perfect information. I find strong evidence in section 1.5.3 that the response to the national change is larger, indicating that physicians don't perfectly observe copays, but their priors change in response to this patent expiration. The difference is even more striking between the effects of $\widehat{q}_{ij}(x_i, \bar{p}_{jt})$ and its individual-specific deviation. This indicates that doctors are quite sensitive to patient variation in adherence tendencies, and seek to maximize adherence for these patients by prescribing low-cost drugs.

1.4 Data

The data used in this paper are a subset of the full medical and pharmaceutical claims for over 150 distinct retiree and employee plans offered by 29 Fortune 500 firms from 2005-2007. These plans had full-year coverage of 1,440,020 primary beneficiaries and 3.0 million lives in 2006.

I restrict my sample to the 16 employers who report beneficiary salaries. I observe these salaries in \$10,000 bins from *Under \$50,000 including missing* to *Above 250,000*. These employers range in size from 3,639 to 111,145 primary beneficiaries with full-year coverage in 2006.[33]

The drug claims include detailed information on each drug fill, including NDC number (National Drug Code), days supplied, place of fill (mail or retail pharmacy, in- or out-of-network), date, and all amounts paid (copay or coinsurance paid by patient, amount paid by plan, deductibles and other non-covered amounts paid by patient). Drug fills were matched by NDC numbers to Thompson Redbook data, to obtain additional characteristics such as drug strength, generic status, and therapeutic class.

Through the corresponding medical claims, rich patient medical information is available for the length of each patients' tenure with a plan in the sample. I use diagnosed chronic conditions and number of annual doctor visits, as well as age, sex, and 3-digit zip code of residence.

Individual prescribers can be tracked through masked identifiers. However, a large number of prescribers appear in the data (496,882) with only a small number of prescriptions each (median = 6 across all drug classes, 99th percentile = 317). In my final sample of initial prescriptions for statin drugs, 55% have unique prescribers, and only 15% come from the 1217 prescribers with 10 or more observed initial fills. Thus, within-doctor analyses are not

[33]The identities of the firms are not known, and it is possible that some of them offer other plans to their employees that are not included in these data.

feasible without losing the majority of the sample, but I use doctor identifiers in other ways, for example, controlling for the last drug prescribed by a certain physician, to account for their habits.

Lacking information on physician areas of specialty, I calculate each prescriber's share of prescriptions for cardiovascular drugs (the therapeutic group containing statins, antihypertensives, and other drugs frequently prescribed by cardiologists). The distribution is bimodal (see Appendix Figure A.1), suggesting 0.6 as a natural breakpoint. I use this cutoff to define imputed "specialists" (prescribers with more than 60% of their prescriptions for cardiovascular drugs) and "generalists" (less than 60%).

1.4.1 Initial Prescriptions

I define an initial prescription as a patient's first fill after at least one year. I exclude repeat starts (i.e. if a patient quits, waits more than a year, and then starts again, only her first observed start is counted as "initial.") For patients observed as early as 2003 or 2004, I exclude those with any observed statin fill during that period. The goal is to focus as closely as possible on new statin starters, but because many plans are not included in the sample prior to 2005, my sample size drops by 40% if I strengthen the requirement to "first fill after at least two years."

Table 1.2 summarizes patient characteristics for patients with initial prescriptions for certain drugs, in the period prior to Zocor's patent expiration. The distribution is not very skewed at this time, since most of the drugs prescribed are on-patent drugs. In the period after its patent expiration, however, (1.3) Zocor (simvastatin) becomes significantly more targeted towards lower-income patients and patients without high cholesterol.

To test the change in Zocor prescribing more formally, Table 1.4 reports results from a conditional logit model including copays, plan fixed effects, and the interaction of the Zocor molecule with various patient characteristics. The baseline interactions report whether Zocor was more likely to be chosen in the period prior to its patent expiration, relative to other statins and conditional on their copay differences. There is only a mildly significant effect of age$>$ 60 on choice of the Zocor molecule. *Zocor*Post-entry* captures the overall post-expiration increase in Zocor prescribing (13%), beyond what was expected based on its copay change. Interactions of *Zocor*Post-entry* with various variables indicate variation in the magnitude of the increase of Zocor prescribing in each group. This magnitude was significantly smaller when one of three patient characteristics was present: high cholesterol, cardiac disease, or high salary.

1.4.2 Defining Plan Copays

While the claims data report exact copay or coinsurance amounts paid for each drug fill, these vary by type of fill (e.g. by mail or retail pharmacy, and number of days supplied). For the conditional logit analysis done below, we must know the prices faced by each patient

for options that were not chosen, and we must use a standard copay definition that does not depend on the place of fill, which is not known by the physician at the time of prescribing. I define as "standard" the most common type of fill: a 30-day prescription filled at an in-network retail pharmacy.[34]

Using plan identifiers, I empirically identify each plan's standard copay for each statin in each quarter within 2005-2007. I leave the standard copay undefined in plans for which there does not appear to be one dollar value that applied to the standard fill at least 90% of the time. While these plans are excluded from the *Verified Copay Sample* used in the conditional logit analysis, I include them in the analysis of copay effects on continuation to maximize power. Details on the process of defining and verifying standard plan copays are provided in the data appendix (forthcoming).

1.4.3 Prescribing and Copay Trends

Figure 1.2 illustrates the variation in copays across plans, as well as the change in the distribution of Zocor copays upon its patent expiration.

Figures 1.3 and 1.4 plot the average drug copays and initial prescribing shares of each statin in my sample from 2005-2007. The vertical line demonstrates the quarter in which generic simvastatin became available. It appears that the upward trend in Zocor molecule prescribing may have begun in the quarter prior to generic entry; this is in fact the national trend. Many insurers began reducing their copays for Zocor in an effort to steer prescribing there, in anticipation of its patent expiration. For the same reason, copays for Lipitor, the most commonly prescribed statin, began increasing prior to Zocor's patent expiration. A response to an upcoming cost reduction is also consistent with sophisticated prescribing: if doctors understand that switching costs are high and copay gains will begin in the next period, they will maximize patients' utility and adherence by shifting prescribing towards Zocor in anticipation of its patent expiration. Pravachol/pravastatin, a statin with a much smaller prescribing share, also faced patent expiration during my study period, in April 2006. No significant change in its prescribing trend occurred.

Given the large variation in plan copays and in the level of the copay change for the *Zocor* molecule when it became generic, a natural starting point for this analysis is to examine whether prescribing changes–towards simvastatin– were functions of the copay incentives put forth by plans. The left panel of Figure 1.5 shows the percentage increase in prescribing of this molecule per plan, by the dollar value of the copay change. For example, a plan with a Zocor copay of $25 in the pre-entry period, and $10 in the post-entry period, would be shown at -$10 on the x-axis. Strikingly, it appears that there is no relationship between the copay change in a given plan (each represented by a circle in Figure 1.5 and sorted on

[34]This specification overestimates the long-term copay differences between drugs, in dollars, since some patients will begin filling prescriptions in large quantities, by mail, once they are settled on a long-term drug. Copays can be 30-40% lower when filled by mail in 90-day quantities. However, in percentage terms, differences between different drugs' copays remain fairly constant within a plan.

the x-axis) and the increased share of Zocor prescriptions. We can similarly assess, by a difference-in-differences approach, the effect of initial copays on continuation rates. These are shown in the right panel of Figure 1.5. Even without controlling for variation in patient characteristics, copay-induced changes in continuation are noticeable; the pre-post increase in plan average continuation rates of Zocor starters is largest among plans that formerly had very high copays for Zocor.

However, Figure 1.6 hints toward the findings of this paper, by separating patients into high and low salary groups, within each plan. First, there is a distinct slope within each group, and it is steeper in the high-income group. Second, the increase in prescribing to low salary individuals is larger, within the same plan, than the increase in prescribing to high salary individuals. This suggests that differential prescribing to different types of patients may lead overall prescribing to appear less copay-driven than it is. It also suggests that prescribing to low salary patients responds primarily to the overall drop in copay, since there is not much variation in the size of the increase with the size of the copay change.

1.5 Empirical Specification and Results

This section presents my main empirical results. The first goal is to estimate how the copay of the first drug prescribed affects a patient's probability of continuing treatment in the class (Table 1.5), where continuing is defined as having a timely second fill of any statin. I allow this effect to vary based on several patient characteristics including income, employment, and health conditions. From the resulting estimates, I obtain each patient's probability of continuation $\widehat{q_{ij}}(p_{ij})$ for each drug molecule, given patient-specific copays for drug j, p_{ij}. I also estimate each patient's probability of continuation at another copay level, namely, the national average for brand or generic drug copays, which I denote $\bar{p}_{jt}$, since patent status of drug molecule j may change over time. Both of these predicted values will enter the second stage of estimation, the physician's prescribing decision.

The second goal of the empirical analysis is to estimate how the physician's choice of which molecule to prescribe responds to patient costs and to patients' cost sensitivity. I use a conditional logit framework to estimate how the probability a certain drug is prescribed responds to variation in its cost across patients. To test whether the response to copays is stronger when patient costs influence the continuation probability (when $\frac{dq_{ij}}{dp_{ij}} < 0$), I include $\widehat{q_{ij}}$, described above, as an additional covariate. I also include the interaction $\widehat{q_{ij}}p_{ij}$, which allows the weight placed on patient costs to vary with the probability that the patient will continue, and hence, pay this cost more than once.

The third goal is to estimate how imperfect copay knowledge influences the effects of p_{ij} and $\widehat{q_{ij}}$ on presribing. To this end, I exploit the patent expiration of Zocor as an event causing a large and observable copay change for the Zocor molecule. I use a decomposition of copay into the national average ($\bar{p}_{jt}$) and each patient's deviation, ($p_{ij} - \bar{p}_{jt}$), to determine the importance of a copay's observability. This approach relies on the assumption that brand

and generic versions of the Zocor molecule have equal therapeutic value, and do not differ in any factor entering the prescribing decision, other than their copays.

In Tables 1.6 and 1.7, I present results from the analysis of the physician prescribing decision. First, I show that in the pre-entry period (Table 1.6), in which no prominent generic drugs were available, the response to copays was small, and the response to predicted continuation probabilities was insignificant. In contrast, the effects are much larger in the full period, which includes Zocor's patent expiration. In Table 1.7, using the decomposition of copay into the national average ($\bar{p}_{jt}$) and the individual's deviation, ($p_{ij} - \bar{p}_{jt}$), I show that it is the response to Zocor's patent expiration that drives the large observed effects of $\widehat{q_{ij}}$. Physicians appear to have increased prescribing of the Zocor molecule specifically to patients predicted to be copay-sensitive, regardless of their actual copay levels.

1.5.1 Estimation of Patient Continuation Decision

I estimate a logit equation at the patient level for continuation past the first prescription using only observations in the pre-entry period.[35] [36] Recall that each individual only appears in the sample once, as these are first prescription fills observed after at least one year of observation in the sample, with no observed prior use of a statin.

The estimating equation is

$$Y_{ij} = \vec{\alpha_x} x_i p_{ijt} + f(x_i, j) + \epsilon_{ij} \tag{1.15}$$

where $Y_{ij} = 1$ represents a timely second fill (a second prescription for any statin within 60 days of the end of supply of the first prescription), and ϵ_{ij} is a Type 1 EEV error.

$f(x_i, j)$ represents controls for patient characteristics included in x_i (diagnosed health conditions and recent heart attack or stroke, employment status, gender, old age, treatment by a specialist, and low/high salary). In Columns 1 and 2 I assume these patient characteristics enter separately ($f(x_i, j) = \delta_j + \beta_1 x_{1i} + \beta_2 x_{2i} + ... + \beta_6 x_{6i}$), while in columns 3-4 I control for them more flexibly. I construct a definition of "type" of patient as a unique grouping of a subset of characteristics: old age, male, high salary, high cholesterol, and 3 or more comorbid conditions. While the remaining characteristics continue to enter linearly, I include a separate dummy for each type ($f(x_i, j) = \sum \beta_{jk}(\text{Type} = k, \text{Molecule} = j)$). In all specifications, I interact many characteristics with copay to determine how copay elasticities vary differently across individuals.

Results reported in Table 1.5 show that copay elasticity is strongest (most negative) for healthy, retired patients with incomes below $50,000 (15.6% of overall sample). For these

[35] I define continuation as a second fill for *any* statin drug within 60 days of the end of supply of the first prescription.

[36] I restrict the sample in this way for two reasons. First, because results in a later section demonstrate that selection on observables towards off-patent drugs intensifies significantly once Zocor is off-patent. Thus, selection on unobservables is more of a concern in the post-entry period. Second, this allows me to test the fit of the predicted values using out-of-sample observations from the post period.

patients, a $10 increase in initial copay corresponds to a 5.9-6.4 percentage point drop in the probability of continuing in the class (about a 7.5% drop). The last column shows my preferred specification, which I will use to estimate predicted refill probabilities per patient, per drug ($\widehat{q}_{ij}$). In this specification I include cross-interactions of the factors that significantly affect copay elasticity.

Figure 1.8 shows the distribution of estimated copay marginal effects on continuation. The modal value ($-.015$) is for young (under age 60), healthy (no diagnoses for high cholesterol or other chronic conditions), and high salary (above $50,000) males.

I denote the estimated marginal effect of copays on continuation probability as $\widehat{\alpha}_c$. I sort patients into quartiles of $\widehat{\alpha}_c$, which I will use to compare results on adherence and prescribing across patients with differing levels of cost-sensitivity. For example, Figure 1.9 gives a preview of the results to come: Initial prescribing of the Zocor molecule increases significantly more among patients with low (very negative) estimated price sensitivity.

1.5.2 Evaluating Fit

While the continuation decision is highly variable, the model estimated in Column 4 of Table 1.5 does a good job of matching out-of-sample trends in continuation rates. I evaluate the match of monthly means of predicted continuation to observed mean continuation rates for the Zocor molecule before and after patent expiration. Since the model is estimated only using the pre-period, the post period predicted values are based on the pre-period association between patient characteristics, copays, and continuation. Figures **??** and 1.7 show the predicted and actual continuation trends among Zocor molecule starters with low and high salaries. The model-based probabilities do a good job predicting the actual continuation of both groups.

I do the same analysis based on quartiles of $\widehat{\alpha}_c$, from the distribution shown in Figure 1.8. Lower predicted α implies more negative copay elasticity, thus we expect to see a larger increase in continuation rates in lower quantiles. Indeed, the differing trends in each quartile not only behave as expected, but match the predicted trend lines fairly well. As expected, we observe a larger increase in continuation rates (in response to Zocor generic entry) among the more copay sensitive patients, and no increase at all among patients in the 4th quartile.

To more test whether the patient continuation response to generic Zocor is equivalent to that predicted by its copay change, models equivalent to those of Table 1.5 are run over the full period, with a dummy variable for the Zocor molecule in the post-entry period. The results are shown in Appendix Table A.1. While there is a significant negative effect of the Zocor molecule in the post-entry period, relative to the effect of copays overall, it is not large. It appears that the majority of the change in its continuation rates is driven by its copay change.

1.5.3 Estimation of Initial Drug Selection

Tables 1.6 and 1.7 report results of a conditional logit model based on Equation 1.13. If physicians respond to patient copays, then $\hat{\lambda}$ will be negative. If physicians are more sensitive to copays when patients have continuation probabilities that are sensitive to copays, then the coefficient on $\hat{q}_{ij}$ will have a positive effect. (Note that among patients with continuation probabilities independent of copays, $\widehat{q}_{ij}$ will not vary significantly across drugs j, given that any drug-specific components of average continuation probability are absorbed in the drug-specific constants $\delta_j(x_i)$.)

$$V_{ijt} = \delta_j(x_i) + \lambda p_{ijt} + \theta \widehat{q}_{ij} + \xi p_{ijt} \cdot \widehat{q}_{ij} + \epsilon_{ij} \tag{1.16}$$

In this equation, $\widehat{q}_{ij}$ is the predicted probability that patient i continues in the class, given an initial prescription for drug j. Note that to correctly predict $\widehat{q}_{ij}$, a correct value of p_{ijt}, the patient's copay, is needed.

Since physicians may not accurately observe each patient's copays, I estimate a specification that corresponds to the above but replaces $\widehat{q}_{ij}$, p_{ijt}, and $p_{ijt} \cdot \widehat{q}_{ij}$ with decompositions based on the national mean copay for a drug molecule in a given time period, and the difference determined by the patient's own copay.

$$V_{ijt} = \delta_j(x_i) + \lambda_1 \bar{p}_{jt} + \lambda_2(p_{ijt} - \bar{p}_{jt}) + \theta_1 \widetilde{q}_{ij} + \theta_2(\widehat{q}_{ij} - \widetilde{q}_{ij}) + \xi_1 \bar{p}_{jt} \cdot \widetilde{q}_{ij} + \xi_2(p_{ijt} \cdot \widehat{q}_{ij} - \bar{p}_{jt} \cdot \widetilde{q}_{ij}) + \epsilon_{ij} \tag{1.17}$$

where $\widehat{q}_{ij} = E[q_{ij}|p_{ijt}]$ as before, and $\widetilde{q}_{ij} = E[q_{ij}|\bar{p}_{jt}]$.

Table 1.6 shows that the results are very different in the pre-entry period (prior to Zocor's patent expiration) versus the full period. This is because Zocor's patent expiration provides a large and salient change in copay of the Zocor molecule. Interestingly, the predicted continuation probability only plays a significant role in the full period, suggesting that when they cannot use patent status as a price indicator, physicians are not able to prescribe less expensive drugs to more cost-sensitive patients.

In the specification that assumes full adherence, I find that the effects all go in the expected directions and are significant. However, their magnitude increases substantially when decomposed into two parts, specifically because the response to the national copay is much stronger. In fact, the response to $\widetilde{q}_{ij}$ entirely drives the significance of $\widehat{q}_{ij}$ in the first column, since the difference $(\widehat{q}ij - \widetilde{q}ij)$ has no significant effect on prescribing. This holds even within plans (in the last column). This is not surprising, given the earlier finding that prescribing of generic Zocor was highly aimed towards low salary, relatively healthy patients, and the evidence in Figure 13 that Zocor molecule prescribing increased inversely with $E[\alpha_i]$ in general. Bootstrapped standard errors are in the process of being estimated. However, based on previous runs, I expect the standard errors to increase by a factor of 2-2.5. The effects of predicted continuation probability will likely remain significant at the 5% level.

1.5.4 Simulation of Prescribing and Adherence under Counterfactuals

Using the estimates of λ_1, θ_1, and ξ_1 from Equation 1.17, in Table 1.7, I simulate prescribing and continuation decisions under the case of perfect physician observation of p_{ij}. Indirect utilities are generated under the assumption that the true values of p_{ij} and $E[q_{ij}|p_{ij}]$ received the same weight in utility as the more easily observed national mean values. A set of Type I extreme value errors that rationalizes each prescription, given the indirect utilities, is generated by an Accept-Reject approach. I hold these generated errors constant in evaluating which alternative is chosen under the counterfactual.

Prescribing does not change dramatically. 5.6% of prescriptions in the pre-entry period, and 6.4% of prescriptions in the post-entry period, are different under this simulation. The average increase in continuation probability would be 7% among the patients who receive different prescriptions, which translates to a very small change overall, about half of a percentage point.

If there were a way to ensure that each patient was prescribed the drug that maximized her probability of continuation, however, the improvement in adherence would be larger. 40% of patients would receive different prescriptions, and average population continuation would improve by 2.5 percentage points. Further, patients would save on average $7 per monthly fill of their statin prescription, up to $84 per year.

1.6 Comparison: AnotherDrug Class

There is an alternate interpretation for the effects I attribute to "continuation probabilities." As was discussed in Section 1.3.2, there are two factors driving variation in continuation probabilities: c_i, a patient's valuation of statin treatment, and α_i, a patient's price elasticity. If the elasticity of the continuation decision is mostly driven by variation in α_i, then the estimated effect of $\widehat{q}_{ij}$ may simply be a response to the preferences of price-sensitive patients. In other words, the continuation probabilities reflect α_i, and physicians seek to maximize $V_j(x_i) - a_{\alpha_i} p_{ij}$ in their prescribing.[37] Under this interpretation, physicians are not directly concerned with the probability that patients may quit, but they indirectly mitigate quitting through maximizing each patient's predicted utility.

However, this explanation implies that when any popular drug loses its patent, its utility to price-sensitive patients increases through its drop in copay. We would expect to see prescribing shift towards any patent-losing drug, given that at least some cost-sensitive patients should have values of α_i, c_i, and v_{ij} such that $\alpha_i p_{ij,t} < c_i + v_{ij} < \alpha_i p_{ij,t-1}$, where $p_{ij,t}$ and $p_{ij,t-1}$ are the post- and pre-expiration copays of molecule j, respectively. While this interpretation is consistent with the reaction to the Zocor patent expiration, I can reject it by looking beyond statins at important patent expirations in other drug classes.

[37] a is the price parameter used in prescribing, and in the case of perfect agency, it is some function of α_i

A key difference between statins and other chronic drug classes is that there was no prominent generic statin available prior to Zocor's patent expiration. The only generic drug available at the time was lovastatin, the oldest and one of the least potent statins. With less than 7% of starting patients receiving lovastatin prescriptions at the time of Zocor's patent loss, the vast majority of starters were filling on-patent (single-source) drugs. Thus, there were strong gains to be captured in continuation probabilities from shifting prescribing towards the newly off-patent drug, particularly for cost-sensitive patients.

There is a remarkably different response to patent expiration in classes already containing generic drugs with large prescribing shares. Consider another major class of chronic cardiac drugs, beta blockers. Like statins, beta blockers have widely known effectiveness in preventing heart attacks among patients with cardiac disease, and they are a common treatment for hypertension. Unlike statins, many widely prescribed beta blockers were already off-patent in 2005, and available at low prices. However, the most widely prescribed drug (with 34% of initial prescriptions) was Toprol XL (metoprolol succinate), which faced patent expiration in November, 2006.[38] This drug is a once-daily dosage version of an earlier drug, metoprolol tartrate, which was already off-patent at the time. Given that 34% of patients in the pre-expiration period were willing to pay, on average, $9 more per month to obtain a once-daily formulation of Toprol XL instead of its twice-daily equivalent, we would expect its use to increase further in the post-expiration period when its copay drops to the same level as its twice-daily equivalent.

However, as shown in Figure 1.11, this is not the case. Prescribing of the Toprol XL molecule does not react at all to its patent expiration. As Appendix Table A.2 shows, patients were already being sorted between on-patent and off-patent drugs by their patient characteristics, in particular, diagnoses of chronic conditions, salary, and employment status. While not yet conclusive, the lack of a prescribing response to the patent expiration of the most popular beta blocker suggests that physicians are more concerned with maximizing patients' probability of staying on their chronic medications than in maximizing their overall expected utility from a drug.[39] When patients are already sorted efficiently between on-patent and off-patent drugs, with respect to their continuation rates, there are less gains to shifting prescribing towards a newly off-patent drug. In the following chapter, I expound this analysis by investigating ten patent expirations in four different drug classes.

[38]Only the 25MG formulation, accounting for about 20% of Toprol XL prescriptions, was available as a generic at first. In mid-2007, all formulations became available as generics.

[39]If plans and PBMs play a role in informing physicians about patent expirations, it is also possible that physicians are unaware of patent expirations that are "less important" to the plan or PBM. If a large share of patients are already on generic drugs, the plan and PBM have less to gain from spreading awareness of a new (and probably more expensive) off-patent drug.

1.7 Conclusion

In this paper, I measured the effect of variation in copayments for statins on (i) the continuation decision of a patient starting therapy, and (ii) the initial prescribing decision. While examining prescribing, I compared responses to two types of copay variation: plan-specific variation, and variation driven by the patent expiration of a drug and its resulting copay changes. I also tested whether physicians respond differently to copays when they perceive that costs may affect a patient's probability of continuing treatment.

Drugs that prevent and manage chronic illnesses are hugely cost-effective when used regularly as prescribed, but only 30-50% of starting patients achieve adequate levels of adherence.[40] I find that high copays are more likely to lead a cost-sensitive patient to quit treatment entirely than to switch to a less expensive drug, and I find meaningful heterogeneity in the effect of a drug's copay on a patient's probability of continuing treatment, along income and health dimensions.

I find mixed results regarding physicians' ability to mitigate the effects of cost-sharing. Initial fills are somewhat responsive to patient-specific copays, indicating that either physicians, patients, or pharmacists are paying attention to copays in a way that improves adherence and patient welfare. However, only 40% of patients start on the drug predicted to maximize their continuation probability. Thus, it appears that tiered formularies reduce expenditures both on the intensive margin, as desired, but also on the extensive margin.

My findings supports the hypothesis that physicians do not perfectly observe copays, but my simulation results suggest that prescribing would not be very different if they did. Thus, I cannot conclude that mechanisms making copays easier to observe, such as providing physicians with mobile devices linked to current plan formularies, would significantly change prescribing. However, it is possible that my estimation of prescribing response to perceived copay is an underestimate. This would be the case if physicians face external incentives to prescribe brand drugs, which cease when a drug loses its patent.

Since the remaining patented statins are more potent than simvastatin, it is understandable that patients with worse diagnoses (who are less cost-sensitive *and* more in need of a strong statin) are less likely to start on simvastatin than their healthier counterparts. However, the fact that among healthy patients, those with higher salaries are also less likely to start on simvastatin, raises the possibility that physicians are price-discriminating on behalf of pharmaceutical firms. Alternatively, physicians may believe that the benefits of more potent statins exceed their added cost relative to simvastatin, even for healthy patients with less purported need for it. In future work, I hope to disentangle these possible effects by exploring switching rates, conditional on continuation, and how these affect physicians' initial prescriptions.

Last, by briefly presenting evidence from another drug class, I demonstrate that the prescribing response to patent expiration can vary significantly. The results of this paper

[40] [46]

suggest that this variation is driven by whether a drug class already contains prominent off-patent products. This finding is not consistent with a model in which physicians do not directly consider adherence, but respond to patients' perceived price elasticities and valuation of different drugs. It is consistent, however, with a model in which the prescribing response to copays is augmented by the possibility of improving a patient's continuation probability.

To summarize, this paper makes four contributions. I estimate the elasticity of the choice of initial prescription with respect to copays, among employer-insured adults in the largest chronic drug class in the United States. This basic empirical objective has been surprisingly elusive in the health literature, due to the difficulty of observing, across a range of health plans, each patient's copays for all alternatives. Second, I improve on current estimates of the effect of copays on adherence, by demonstrating the importance of the first refill decision and allowing estimates to depend on individual characterists that significantly affect cost sensitivity. Third, I show that physician prescribing responds both to copays and to heterogeneity in copay sensitivity, but primarily in response to large and universal price changes. Fourth, I show that the selection of cost-sensitive patients towards generic drugs reduces the importance of new generic entry when prominent generic drugs are already available in a drug class. This selection may also lead to upward bias in the estimate of copay effects on adherence, which may help reconcile the wide variation found in previous studies of copay effects on adherence.

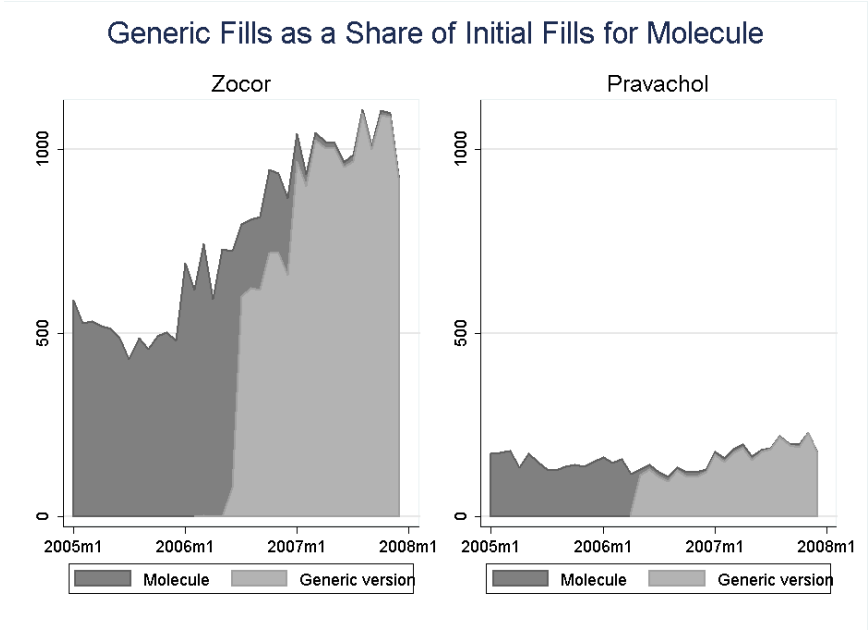

Figure 1.1: *Generic substitution rates, initial prescriptions.* The dark gray represents all fills of initial prescriptions for each molecule. The light gray shows the share of fills for generic versions in each period.

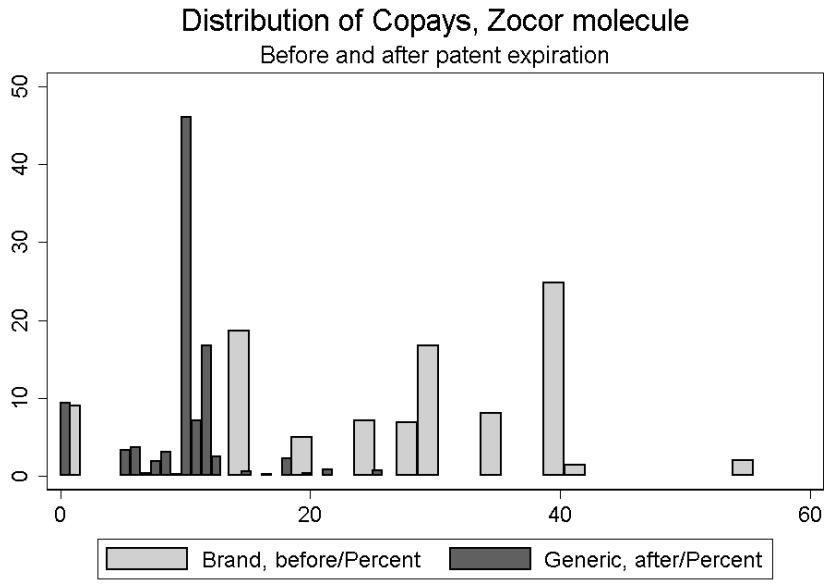

Figure 1.2: *Copay Distribution of Plans in Sample.*

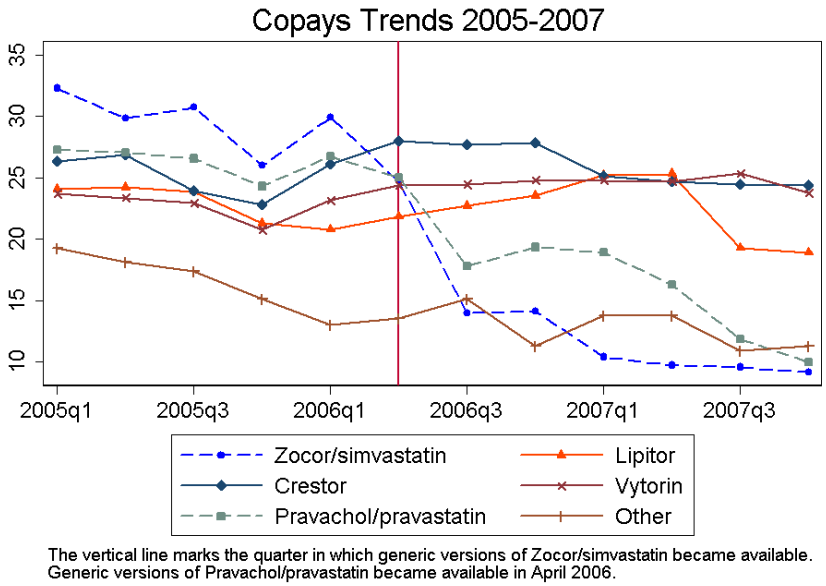

Figure 1.3: *Average copays by molecule, 2005-2007.* The two dashed lines represent the drugs that faced patent expiration in 2006.

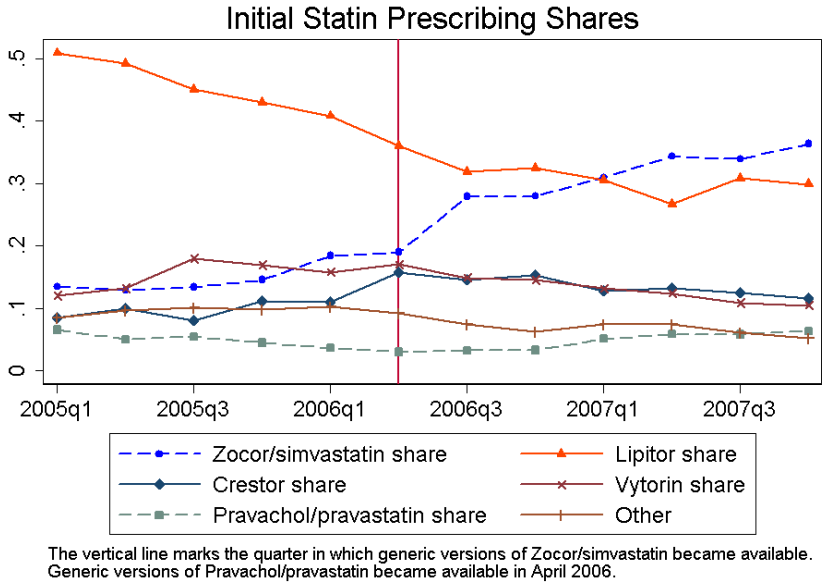

Figure 1.4: *Initial prescriptions by molecule, 2005-2007.*

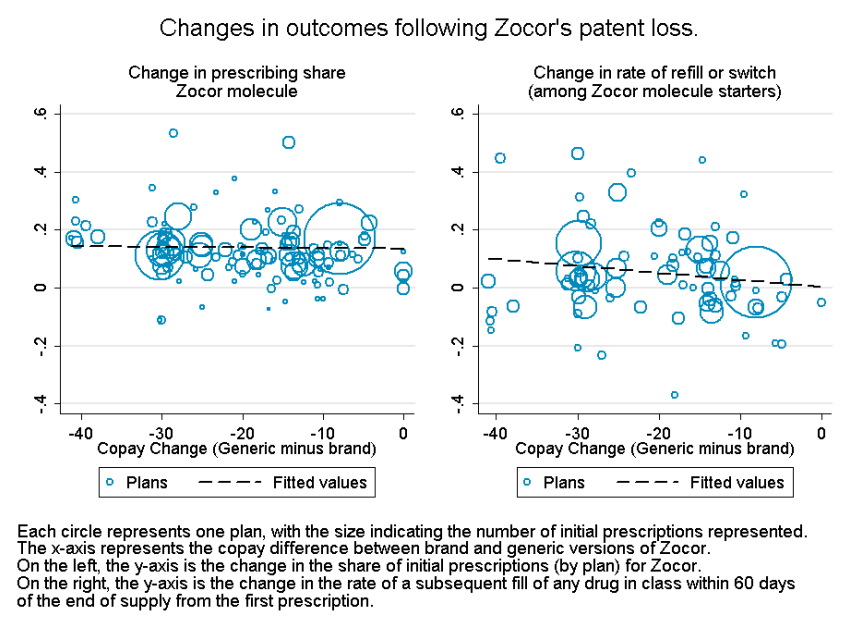

Figure 1.5: *Changes in Zocor Prescribing and Continuation, by plan.* This figure shows the wide variation across plans in their copay changes for Zocor upon its patent expiration, and resulting changes in prescribing and refill rates.

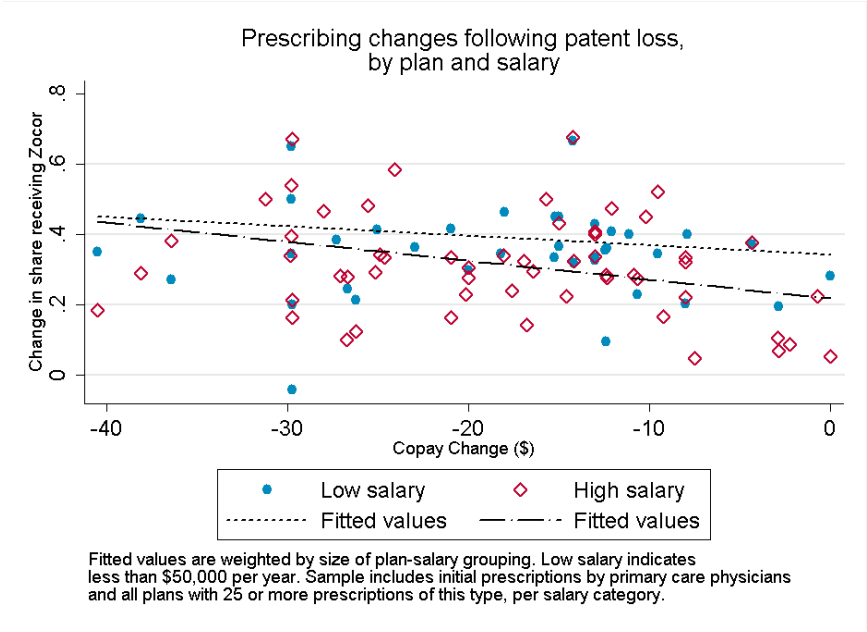

Figure 1.6: *Change in Zocor Prescribing, by plan and salary.* This figure corresponds to the left panel of Figure 1.5. Patients within a plan are separated into two groups: salaries above and below $50,000.

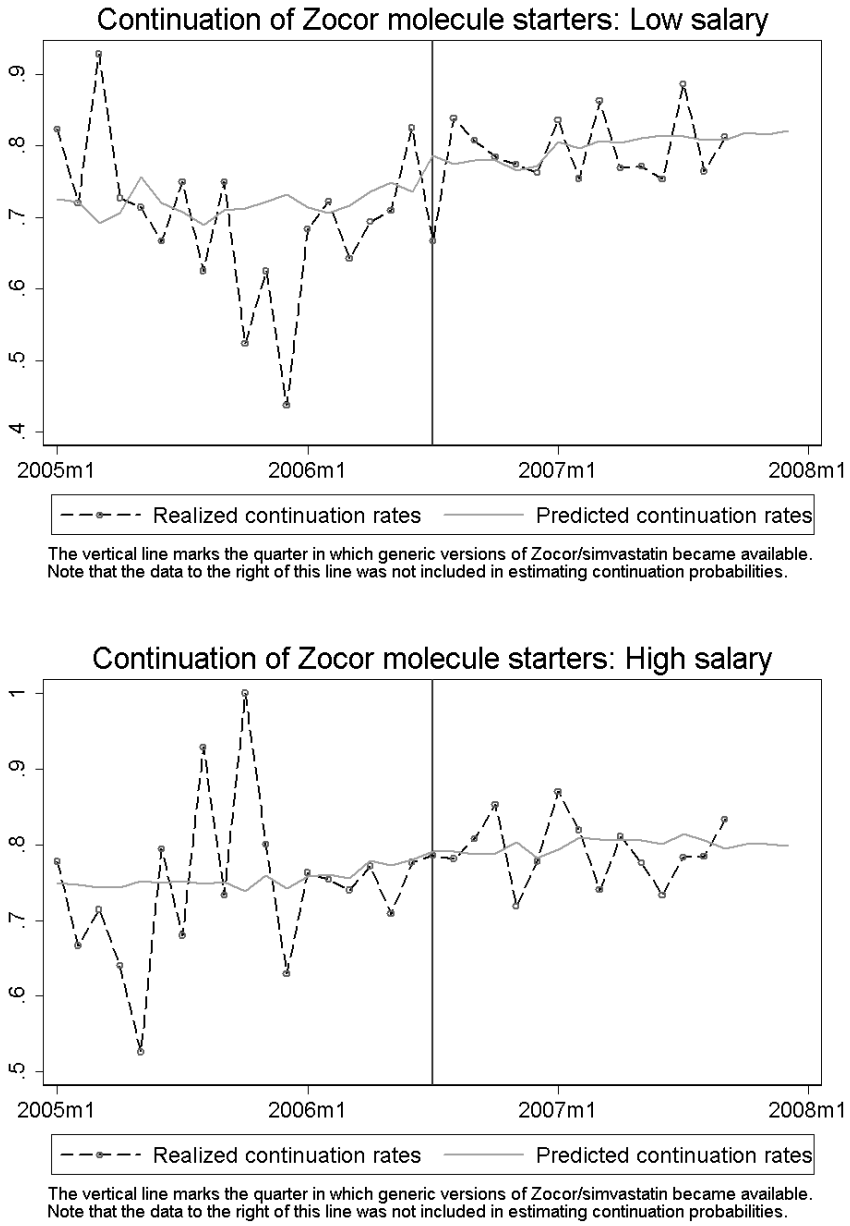

Figure 1.7: *Predicted and Actual Zocor Continuation Rates, by salary groups.* These figures compare the predicted values based on Table 1.5 to the observed continuation rates of patients initiating a Zocor prescription.

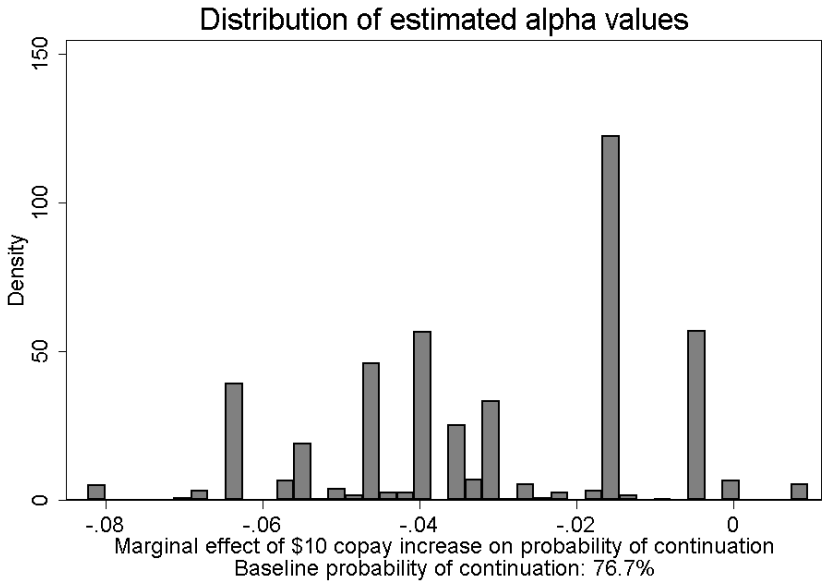

Figure 1.8: *Distribution of* $\widehat{\alpha_c}$. $\widehat{\alpha_c}$ is the estimate of an individual's predicted response to the copay of a first prescription, based on the individual's characteristics

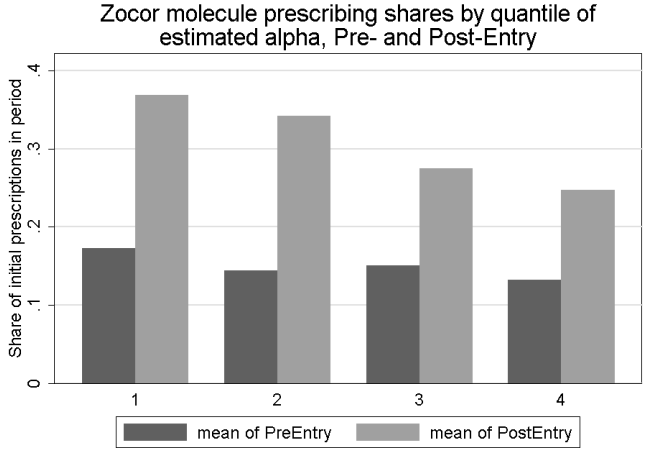

Figure 1.9: *Changes in Zocor Initial Prescribing Rates, by quartile of* $\widehat{\alpha_c}$. $\widehat{\alpha_c}$ is the estimate of an individual's predicted response to the copay of a first prescription.

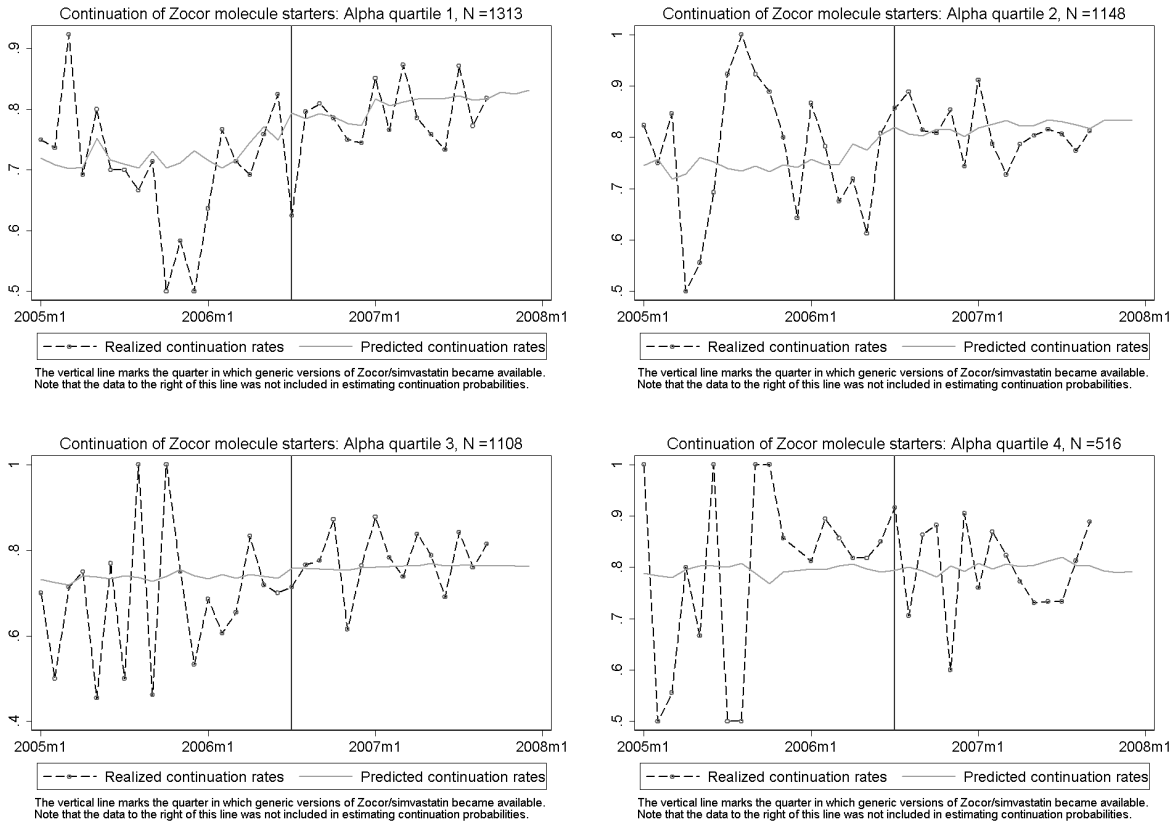

Figure 1.10: *Predicted and Actual Zocor Continuation Rates, by quartile of* $\widehat{\alpha}_c$.

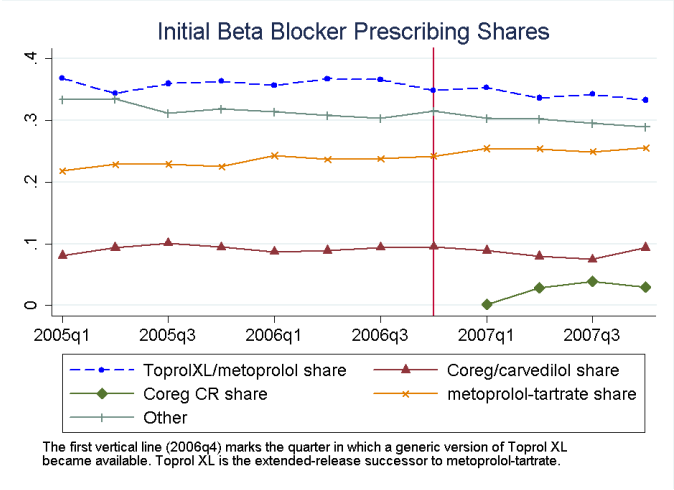

Figure 1.11: *Initial Prescriptions of Beta Blockers by Molecule.*

Table 1.2: Descriptive statistics by initial fill, pre-entry period

	(1)	(2)	(3)	(4)	(5)
	Total	Weaker Statin	Zocor	Lipitor	Stronger Statin
Demographics					
Salary above $50,000	0.68	0.68	0.65	0.68	0.69
Non-retired employee (%)	0.58	0.54	0.54	0.59	0.60
Age	58	59	59	58	57
Male (%)	0.54	0.52	0.55	0.53	0.55
Health conditions					
High cholesterol	0.18	0.16	0.17	0.17	0.22
Diabetes	0.13	0.15	0.15	0.12	0.13
Cardiac disease	0.13	0.09	0.16	0.14	0.11
Recent heart attack	0.09	0.07	0.10	0.09	0.07
Stroke	0.03	0.02	0.03	0.03	0.02
Prescription and outcomes					
Specialist	0.10	0.08	0.09	0.11	0.10
Copay	$23.49	$18.89	$28.68	$22.51	$24.43
Timely refill or switch	0.76	0.76	0.73	0.77	0.76
Adherence over 1 year	0.47	0.48	0.46	0.47	0.46
N	8,493	1,204	1,346	3,676	2,267
%	100%	14.8%	18.6%	43.3%	26.7%

Note: Sample includes initial fills from January 2005- June 2006, the period of the sample preceding Zocor's patent expiration. Weaker statins are Pravachol and lovastatin. Stronger statins are Crestor and Vytorin (which includes two active ingredients: simvastatin and ezetimbe). Health conditions are based on diagnoses in the medical claims, with the exception of *Recent heart attack* which is based on a claim for circulatory-related emergency room visit. A *timely refill or switch* must occur within 60 days of the end of supply of the first fill. Adherence is defined as filling enough prescriptions to cover at least 80% of the days in the first year.

Table 1.3: Descriptive statistics by initial fill, *post*-entry period

	(1)	(2)	(3)	(4)	(5)
	Total	Weaker Statin	Zocor	Lipitor	Stronger Statin
Demographics					
Salary above $50,000	0.65	0.62	0.60	0.71	0.66
Employee (%)	0.63	0.58	0.58	0.68	0.65
Age	56	57	58	55	55
Male (%)	0.54	0.53	0.53	0.56	0.52
Health conditions					
High cholesterol	0.18	0.16	0.15	0.18	0.23
Diabetes	0.13	0.15	0.15	0.10	0.12
Cardiac disease	0.11	0.10	0.11	0.13	0.11
Recent heart attack	0.08	0.07	0.08	0.08	0.07
Stroke	0.04	0.03	0.04	0.04	0.03
Prescription and outcomes					
Specialist	0.10	0.07	0.07	0.12	0.12
Copay	$18.86	$14.14	$11.28	$22.80	$25.37
Timely refill or switch	0.78	0.75	0.79	0.76	0.78
Adherence over 1 year	0.45	0.43	0.45	0.44	0.47
N	9,511	1,096	2989	2898	2528
%	100	11.5	31.4	30.5	26.6

Note: Sample includes initial fills from July 2006-December 2007, the period of the sample following Zocor's patent expiration. Weaker statins are pravastatin and lovastatin. Stronger statins are Crestor and Vytorin (which includes two active ingredients: simvastatin and ezetimbe). Health conditions are based on diagnoses in the medical claims, with the exception of *Recent heart attack* which is based on a claim for circulatory-related emergency room visit. A *timely refill or switch* must occur within 60 days of the end of supply of the first fill. Adherence is defined as filling enough prescriptions to cover at least 80% of the days in the first year.

Table 1.4: Individual characteristics correlated with choice of Zocor molecule

	(1)	(2)
Copay	-0.0038***	-0.0038***
	(0.0002)	(0.0003)
Post entry period	0.13***	0.13***
	(0.010)	(0.01)
Zocor x High salary	-0.011	0.0099
	(0.009)	(0.010)
Zocor x Post entry x High sal.	-0.091***	-0.084***
	(0.02)	(0.02)
Zocor x High cholesterol	-0.019	-0.017
	(0.01)	(0.01)
Zocor x Post entry x High chol.	-0.056**	-0.060**
	(0.02)	(0.02)
Zocor x Cardiac Disease	0.015	0.013
	(0.01)	(0.01)
Zocor x Post entry x Cardiac Disease	-0.054*	-0.057**
	(0.02)	(0.02)
Zocor x Age > 60	0.024**	0.00017
	(0.008)	(0.009)
Zocor x Post entry x Age > 60	0.018	0.023
	(0.02)	(0.02)
Plan f.e.	No	Yes
Observations	129370	129370

Note: Marginal effects on the probability of a Zocor molecule initial prescription from the conditional logit model described in Equation X. *High salary* is above $50,000. Comorbities include diagnosed chronic conditions. *Post entry* refers to the period starting the week of July 23, 2006, when generic Zocor (*simvastatin*) was launched.

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

Table 1.5: Copay effects on Continuation Decision (Pre-entry period)

	(1)	(2)	(3)	(4)
Copay	-0.036***	-0.064***	-0.059***	-0.061***
	(0.004)	(0.005)	(0.004)	(0.005)
Interacted with:				
High salary		0.026***	0.025***	0.036***
		(0.004)	(0.004)	(0.007)
Diagnosed condition		0.0077*	0.0090***	0.0090**
		(0.003)	(0.002)	(0.003)
Recent heart attack		-0.017**	-0.016**	-0.012
		(0.006)	(0.006)	(0.007)
Recent stroke		0.0036	0.0026	0.012
		(0.010)	(0.01)	(0.01)
Non-retired		0.023***	0.020***	0.023**
		(0.005)	(0.005)	(0.007)
Prescribed by specialist		0.013	0.013	0.021*
		(0.007)	(0.007)	(0.009)
Observations	14189	14189	14189	14189
Patient characteristics	Yes	Yes	Yes	Yes
Molecule f.e.	Yes	Yes	Yes	Yes
Type f.e.			Yes	Yes

Note: Average marginal effect of a $10 copay increase on the probability of *Continue past first fill*. *Continue past first fill* equals 0 if the patient has a gap of 60 days or more following the last day of coverage of the first prescription fill, and 1 if the patient fills a prescription for *any* drug in the class during that period. *High salary* is above $50,000. Patient characteristics include dummies for each related chronic illness, *Non-retired*, and *Prescription from a specialist*. Recent heart attack is in the last or current year. Stroke is based on current year diagnosis code. *Type* denotes unique groupings of *High cholesterol*, *3+ Comorbid conditions*, *High salary*, *Above age 60*, and *Male*. Column (4) adds triple-interactions, which are not shown. All models are estimated in the period prior to Zocor patent expiration. Standard errors are clustered by plan.

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

Table 1.6: Choice of initial prescription (Pre-entry and Full Period Comparison)

	Pre-entry Period		Full Period (2005-2007	
	(1)	(2)	(3)	(4)
Copay: p_{ijt}	-0.027***	-0.020*	-0.050***	-0.035***
	(0.004)	(0.008)	(0.002)	(0.005)
Continuation Probability: $\widehat{q_{ij}}(p_{ijt})$		0.0064		0.011***
		(0.004)		(0.002)
Interaction: $p_{ijt} \cdot \widehat{q_{ij}}(p_{ijt})$		-0.00096		-0.0018***
		(0.0005)		(0.0003)
N	8087	8087	17076	17076
Log. Lik.	-12695.1	-12693.4	-26870.3	-26852.3
Patient characteristics	Yes	Yes	Yes	Yes
Doctor's last prescription	Yes	Yes	Yes	Yes

Note: Continuation probability is the probability, conditional on a drug and its copay, that a patient will fill a second prescription for any statin within 60 days following the last day covered by the first prescription. Patient characteristics included for each alternative are dummies for each related chronic illness, *Non-retired*, *3+ Comorbid conditions*, *High salary*, and a dummy indicating if the patient's spouse used the same statin in the previous year. Prescriber controls included in each model are: *Specialist*, region dummies, and *Most recent molecule prescribed as an initial prescription.*

Marginal effects on drug choice; Standard errors in parentheses

Table 1.7: Choice of initial prescription: Full-period 2005-2007

	(1)	(2)	(3)	(4)	(5)
Copay:					
p_{ijt} (Actual copay)	-0.035***				
	(0.005)				
$\bar{p}_{jt}$ (National average, by patent status)		-0.087***	-0.052***	-0.056***	-0.054***
		(0.004)	(0.010)	(0.010)	(0.01)
$p_{ijt} - \bar{p}_{jt}$ (Difference)		-0.036***	-0.035***	-0.034***	-0.032***
		(0.002)	(0.006)	(0.006)	(0.007)
Continuation Probability:					
$\widehat{q_{ij}}(p_{ijt})$	0.011***				
	(0.002)				
$\widehat{q_{ij}}(\bar{p}_{jt})$			0.015***	0.014***	0.011**
			(0.004)	(0.004)	(0.004)
$\widehat{q_{ij}}(p_{ijt}) - \widehat{q_{ij}}(\bar{p}_{jt})$			0.0033	0.0039	0.0021
			(0.003)	(0.003)	(0.004)
Interacted:					
$p_{ijt} \cdot \widehat{q_{ij}}(p_{ijt})$	-0.0018***				
	(0.0003)				
$\bar{p}_{jt} \cdot \widehat{q_{ij}}(\bar{p}_{jt})$			-0.0010**	-0.0011**	-0.00028
			(0.0004)	(0.0004)	(0.0005)
Difference			-0.00086	-0.00094	-0.00020
			(0.0005)	(0.0005)	(0.0009)
N	17076	17076	17076	17076	17076
Log. Lik.	-26852.3	-26819.4	-26807.7	-26741.1	-26264.1
Patient characteristics	Yes	Yes	Yes	Yes	Yes
Doctor's last prescription	Yes	Yes	Yes	Yes	Yes
Type f.e.				Yes	Yes
Plan f.e.					Yes

Note: q_{ij} represents the predicted probability that patient i continues her prescription for drug j (see Table 1.5). q is calculated as a function of the true copay (actual q_{ij}) or as a copay-uninformed value, average national copay instead. p units are ten dollars, and q is in percentage points. Patient characteristics include dummies for each chronic illness, *Non-retired*, and a dummy indicating if the patient's spouse had used the same statin in the previous year. *Type* denotes unique groupings of *High cholesterol*, *3+ Comorbid conditions*, *High salary*, *Above age 60*, and *Male*. Prescriber controls included in each model are: *Specialist* and *Most recent molecule prescribed as an initial prescription*. Marginal effects on drug choice probability; Standard errors in parentheses.

Chapter 2

Prescribing Responses to Patent Expiration

2.1 Introduction

In Chapter 1, we saw that initial prescriptions for statins shifted significantly towards the Zocor molecule following its patent expiration. Prescribing changed most dramatically for patients predicted to be cost-sensitive in their adherence decisions, suggesting that physicians aim to reduce their patients' costs by prescribing generic drugs, when the potential gains are large. However, it is well known that patent expirations often reduce a molecule's aggregate demand; the case of Zocor's patent expiration has been described as "overturning conventional wisdom" in its large, immediate growth of prescribing (Aitken, Berndt and Cutler, 2010). Lakdawalla, Philipson, and Wang (2008) find that in almost 40% of 101 patent expirations between 1992 and 2002, there is a short-term drop in aggregate consumption of the drug molecule.[1]

Similarly, in Chapter 1 we saw that the patent expiration of the most commonly prescribed beta blocker in 2006 (Toprol XL) had no positive effect on its prescribing rate, despite its notable advantage (once-daily dosing) over an existing, prominent generic drug with the same active ingredient. A potential explanation discussed in Section 1.6 is the prevalence of generic beta blockers prior to Toprol XL's patent expiration. If physicians were already sorting their most price sensitive patients to generic beta blockers, then the potential gains of adjusting prescribing patterns in response to a new generic could be insufficient for overcoming inertia in prescribing habits. Zocor, in contrast, was the first powerful statin to become available at a lower price.

[1]The term "molecule" is used to refer collectively to both brand and generic manufactured versions of a single drug. Note that we are not discussing substitution from brand to generic versions of the off-patent molecule, which typically occurs by default due to state-level generic substitution laws. The type of substitution of interest is *between* molecules, i.e. from competing drugs in the same therapeutic class to the newly off-patent – and thus, suddenly less expensive – drug.

The constrast in the publicity and salience of these two patent expirations may also have contributed: Around the time of their patent expirations, Zocor appeared in the headline of 289 U.S. media articles with the words "generic" or "patent expiration," while Toprol only appeared in 34 headlines.[2] A third explanation is that the size of the copay change when Toprol XL became available as a generic was not as large as Zocor's copay change, since beta blockers are less costly than statins. For the same reason, brand-name statins are substantially more expensive for insurers, who may have put pressure on physicians to prescribe Zocor when it became available in generic form.

In this paper, I estimate prescribing responses to ten patent expirations in four chronic drug classes during 2004-2007 and test explanations for their heterogeneity. When a drug's patent expires, at least three factors in the prescribing decision are affected: the patient's copay amount, the price paid by the insurer, and the quantity of its advertising. While the changes in the copay and insurer cost are correlated (insurers select copays in an effort to align patient incentives with their own), they differ somewhat in their timing.[3] Health plans with a strong cost incentive may induce changes in prescribing by implementing policies such as *step-therapy* or *prior authorization*, requiring extra work from physicians who wish to prescribe non-generic drugs to new patients. Thus, their costs may indirectly influence observed prescribing rates, beyond the effect achieved through copays.

If it were the only changing factor, the reduction in the cost of a drug molecule would consistently cause *some* increase of demand for the patent-losing molecule, even in drug classes with low price elasticities of substitution.[4] The magnitude of the price change may explain variation in prescribing responses to different patent expirations within a drug class, since some drugs are particularly expensive (more likely to be classified as "Tier 3" drugs) towards the end of their patent period.[5] However, variation in the magnitude of price reductions cannot explain why some patent expirations lead to negative prescribing changes.

The third changing factor is the drug's advertising, which promptly drops by about 70% (Lakdawalla, Philipson, and Wang 2007). There are several types of pharmaceutical advertising targeting physicians, including medical journal advertisements (2.6% of promotional spending towards physicians), visits to physicians (29%), and the free provision of samples

[2]Author's calculations using Lexis-Nexis search.

[3]Most health plans have fixed copays for generic drugs, so the copay drop occurs as soon as the generic drug is available for purchase. The price of the drug faced by the insurer declines more gradually, since the Hatch-Waxman Act of 1984 awards a six-month exclusivity period to the first approved generic manufacturer of a drug.

[4]Note that we are not discussing substitution from brand to generic versions of the off-patent molecule, which typically occurs by default due to state-level generic substitution laws. The type of substitution of interest is *between* molecules, i.e. from competing drugs in the same therapeutic class to the newly off-patent – and thus, suddenly less expensive – drug.

[5]In some cases this is by design. Pharmaceutical companies often launch new "follow-up" drugs prior to their drugs' patent expirations, and adjust their prices with the aim of shifting demand towards their new drug, shielding their revenues from the patent expiration.

for them to dispense to patients (64%).[6] For some of these, the accumulated "stock" may transfer to the new generic version, as it gradually depletes. This would cause a continuous decline in desirability, or willingness-to-pay, for the patent-losing drug. Combined with the immediate copay change, this could result in a temporary uptick but eventual downturn of prescribing. Other types of promotion, for example, goodwill fostered between a physician and a pharmaceutical company, may be not be transferable to the generic version, and may instead lead a physician to prescribe other drugs with still-valid patents [27]. If the importance of non-transferable advertising is high, it may overcome price effects and lead to an immediate, unrecoverable reduction in prescribing. The same outcome could be observed if the stock of free samples depletes quickly once the patent expires, if samples are an important driver of a given drug's prescriptions.

Evaluating physician responses to patent expirations is important to understanding how pharmaceutical advertising, health plans, and patient costs affect physician decisions. I focus on chronic drug classes, as the welfare implications of costly drug choices loom larger when patients are expected to purchase them repeatedly.[7] In the case of chronic drugs, the effect of a patent expiration on aggregate consumption of drug molecule x depends on three factors: 1) whether patients currently using competing drugs switch to x, once it is cheaper, 2) whether new patients are increasingly likely to start with x versus other drugs, and 3) whether the refill rates of both continuing and new users of drug x are affected by its lower copays and generic status. In this paper, I focus on the second factor: Are *new* patients more likely to be prescribed a given drug after its patent expires? More so than refills and drug switches, initial prescriptions reflect a decision made by the prescribing physician. [8]

The first hypothesis, based simply on the notion of negative price elasticity, is that larger average reductions in copays will have a more positive effect on prescribing of the patent-losing drug. Following the results of the previous chapter, the second hypothesis is that average copay changes will have stronger effects than cross-sectional copay variation within the class, since the latter is difficult for physicians (or patients) to observe at the time of the first prescription. The third hypothesis is that the current share of generic prescribing in the class will be negatively related to the patent expiration's effect on prescribing. The fourth hypothesis is that changes in drug prices paid by insurers influence prescribing, through indirect measures they may take to reduce their costs.

I begin by measuring the short- and medium-term effects of each patent expiration on

[6] Source: 2001 data, IMS Health [30]

[7] First, the loss in consumer surplus multiplies, if a patient continually purchases a drug that is more expensive than an equally effective competitor. Second, there is a risk that the patient will discontinue the drug due its cost, which could have harmful health consequences if the physician is not informed.

[8] However, the physician's decision is likely to respond to his own expectations, or observations, or factors (1) and (3), as they indicate how patients value the new generic versions of drug molecule x. As shown in the model of prescribing developed in Chapter 1, if a physician includes patient utility (or simply health) in his objective function, the patient's probability of refilling a chronic drug prescription will factor into the physician's initial choice of drug.

initial prescribing rates within the relevant drug class. The short-term (three month) change in prescribing is significantly positive in four of ten cases (one in each of the four classes), and significantly negative in two of the ten. I show descriptive evidence that the short and medium-term prescribing changes are correlated with the relative drop in a drug's average copay, and with the corresponding drop in amount paid by insurers, though these two factors are highly correlated. It also appears that prescribing changes are negatively correlated with the generic share of prescribing prior to the new patent expiration, though patterns diverge at the tails.

A conditional logit model is used to predict the drug initially prescribed to each patient starting treatment in one of the four drug classes during 2004-2007. This model allows the inclusion of drug copays and plan payments at the level of the individual patient. However, consistent with the results of the previous chapter, I find that cross-sectional variation in copays affects prescribing much less than temporal variation in average copays of a drug.

To determine what factors drive variation in the prescribing effects of the ten patent expirations, I estimate several models with the different factors hypothesized to matter, and compare the predicted and actual short-term prescribing changes for each patent-losing drug.

Results indicate that the average copay change is the most important factor explaining variation in the impact of a patent expiration. I cannot measure the effect of advertising changes directly, without panel data of drug-specific advertising. Instead, while controlling for copay changes and other factors, I use a *post patent expiration* dummy variable to capture the average residual effect of the patent expiration on prescribing. As expected, this dummy has a negative effect, indicating that if copays did not change upon patent expiration, prescribing would decrease. At a copay change of about $6 (for a monthly prescription), the copay effect and advertising effect are equal, yielding a zero predicted change in prescribing. Including generic prescribing share reveals that the effect of loss of advertising of a brand drug increases towards the equivalent of a $16.86 copay increase, as the generic prescribing share approaches 1. The results are robust to several specifications accounting for possible confounding factors.

This paper contributes to three literatures. A number of studies aim to measure how accurately physicians perceive drug costs, primarily through surveying them on drug prices. Findings of this literature are summarized in [3]: only 31% of physician estimates are within 20-25% of the drug's actual cost, and they tend to overestimate the price of low cost drugs and underestimate the price of high cost drugs. Another group of studies aim to estimate the effect of different types of advertising on prescribing [41] [49] [50]. In particular, studies find that the distribution of free samples leads to lower prescribing rates of antihypertensives defined as "first-line" treatment, and leads physicians to use medications other than their preferred drug choice [8][12].

A separate set of studies focus on the effects of drug patent expirations. Lakdwalla, Philipson and Wang find that drugs that were not fully advertised prior to their patent expiration are more likely to have prescribing increase to a new, stable volume [38]. In contrast, drugs that were heavily advertised often face short-term decreases in prescibing.

Gonzalez and colleagues identify UK physicians who are sensitive to drug detailing, and find that the prescribing of these physicians shifts towards other patented antidepressants when the patent of Prozac, the pioneer of SSRI antidepressants, expires [27]. Jena and colleagues find that pioneer drugs (the first entrants to a new class of drugs) do not experience trend changes in demand upon their patent expirations, concluding that they are not viewed as close substitutes to later entrants to the drug class. [33]. They mention, however, that these later entrants (known as "me too" drugs) may be closer substitutes to one another, as would be the case, for example, "if each subsequent me-too drug offered incrementally less benefit than the prior" [33].

2.2 Theoretical Framework

I use a modified version of the model of physician choice presented in Section 1.3.3. In this version, there are three factors affecting the physician d's choice of drug for patient i: his estimate of the patient's therapeutic benefit from each drug (ω_{ijd}), the current stock of advertising for a drug (A_{jdt}), and the copay *perceived by the doctor* for patient i at time t ($\tilde{p_{ijdt}}$), which may or may not equal the patient's actual copay p_{ijt}.

I characterize the perceived copay $\tilde{p_{ijdt}}$ as a weighted average of the patient's true copay and the average copay for all patients, in the relevant quarter t: $\tilde{p_{ijdt}} = \lambda p_{ijt} + (1-\lambda)\bar{p}_{jt}$. λ can be interpreted as the total probability that either the physician observes a patient's actual copays at the time of prescribing or that the pharmacist contacts the physician to suggest a prescribing change based on the patient's copays (before the prescription is filled).

$$\begin{aligned} U_{dijt} &= \omega_{ijd} + aA_{jdt} - \gamma\tilde{p_{ijt}} && (2.1) \\ &= V_j(x_i) + aA_{jdt} - \lambda\gamma p_{ijt} - (1-\lambda)\gamma\bar{p}_{jt} + \epsilon_{ij} && (2.2) \end{aligned}$$

As explained in Section 1.3.3, I assume that the physician's prediction of ω_{ijd} differs from the true value for patient i (v_{ij}) by an amount that combines with the individual heterogeneity term conditional on patient characteristics x_i, $\eta_{ij} = v_{ij} - V_j(x_i)$, to yield the total error term ϵ_{ij}. I assume this term is distributed by the Type I extreme value distribution.

Without advertising data, A_{jt} is an unobserved variable, and a cannot be estimated. However, monthly expenditures on advertising are known to decline significantly in the few months following patent expiration, and I seek to estimate the average impact of this decline on prescribing [38].

2.2.1 Changes upon Patent Expiration

If drug j's patent expires at time $t = 1$, I assume that ω_{ijd} remains constant, but A_{jdt} and $\tilde{p_{ijt}}$ change. Thus the prescriber's choice utility for drug j changes as follows:

$$U_{dij1} - U_{dij0} = a(A_{jd1} - A_{jd0}) - \gamma(\lambda(p_{ij1} - p_{ij0}) + (1-\lambda)(\bar{p}_{j1} - \bar{p}_{j0})) \quad (2.3)$$

The first component, $a(A_{jd1} - A_{jd0})$ is negative, since $A_{jd1} < A_{jd0}$. The second component, however, is positive, since $p_{ij1} < p_{ij0}$ and $\bar{p}_{j1} < \bar{p}_{j0}$, and price affects utility negatively. Thus, whether prescribing increases or decreases following patent expiration depends on which component is larger, as well as on whether relevant characteristics of other drugs in the choice set are also affected.

2.2.2 Assumptions

Since advertising expenditures are not included in the data, some strong assumptions are needed to estimate an average effect of the advertising drop that accompanies patent expiration. This effect will be estimated as the average residual change in prescribing following patent expirations, while accounting for the effect of copay change.

Assumption 10. *Variation in the change in stock of advertising* $(A_{jd1} - A_{jd0})$ *is unrelated to the average copay change of a drug* $\bar{p}_{j1} < \bar{p}_{j0}$.

There are plausible reasons for this assumption to be violated in either direction, since pharmaceutical companies compete both through price and through promotion. An expensive drug class is likely to have higher promotional spending, on average, as it is likely to contain more innovative products whose benefits must be conveyed to physicians. Since promotion levels eventually approach 0 after patent expirations, this would imply a positive correlation between $(A_{jd1} - A_{jd0})$ and $\bar{p}_{j1} < \bar{p}_{j0}$ at the class level, which would lead both the estimates of γ (price elasticity) and the estimate of $a(A_{jd1} - A_{jd0})$ (advertising effect) to be biased towards zero. However, this can be addressed by estimating results separately for each drug class.

On the other hand, many drug companies respond strategically to upcoming patent expirations, by patenting and releasing a slightly different version of the drug, and using intensive marketing efforts to shift prescribing towards the new drug, with a longer patent life. One way of to shift prescribing is by offering rebates to insurers, who correspondingly put a preferential copay on the drug. As a result, the product nearing patent expiration is essentially abandoned by its manufacturer, left with both higher copays and lower advertising expenditures than other drugs facing patent expiration without "follow-up" drugs by their manufacturers.[9] This can be addressed by controlling for whether a patent-losing drug has a

[9]This also suggests a declining market share for the product prior to its patent expiration, which means

newly released version by the same manufacturer, which I do as a robustness check in section 2.4.3.

In the pooled conditional logit regressions, I estimate an average measure of γ across the four drug classes, weighted by their size in the sample. Price elasticity of prescribing reflects the substitutability of products within a class, and thus, there is no reason to believe it would be equal in any two different drug classes. Constraining it to be equal requires the assumption that variation in γ across the four drug classes is independent of class-level variation in $a(A_{jd1} - A_{jd0})$, the effect of loss of advertising upon patent expiration. As a robustness check, I estimate a model that allows γ to vary by drug class.

2.3 Data

The data for this study is drawn from the same dataset used in Chapters 1 and 3, which includes pharmaceutical and medical claims for employees and retirees of 29 Fortune 500 companies. For the present analysis, I identified the four largest chronic drug classes in which at least one major drug (with an ex-ante prescribing share of at least 20%) lost its patent in the 2004-2007 period. I then identified all other drugs which faced patent expirations during this period in each of the four classes, yielding a sample of ten patent expirations overall. Defining "initial" as the first prescription within a drug class after at least one year yields 748,125 initial prescriptions from 2004-2007 in the four drug classes: antidepressants (excluding TCAs), statins (including combination product Vytorin), calcium channel blockers, and beta blockers.

The data include plan identifiers and copays for each drug purchase, which allow for the empirical definition of the full set of plan copays within each quarter, in each plan. The amount paid by the health plan, for each drug fill, is reported. However, this is an upper bound of the plan's cost for brand drugs, since confidential rebate agreements are a common way for pharmaceutical companies to negotiate preferential treatment of their drugs, for example, placement on a "Preferred Brand" formulary tier.

Table 2.1 describes the patent-losing drugs in each class: their annual sales, average copays, and share of initial prescriptions in the class, prior to patent expiration, as well as any follow-up drug released by the same manufacturer prior to their patent expiration. A count of newspaper headlines reveals the wide range in media salience of each patent expiration.

Table 2.2 reports the changes in initial prescribing rates of each drug. To summarize variation in the relative positioning of each drug within the relevant class at the time of its prescribing, Figure 2.1 plots each patent expiration along two dimensions: its own share of initial prescriptions, prior to its patent expiration, and the generic share of prescribing prior to its patent expiration. Whether the marker for each drug is filled in represents whether

the estimated effect of the patent expiration will vary with the choice of comparison period prior to the patent expiration.

its prescribing significantly increased after patent expiration. For example, Toprol XL was a prominent brand drug in a generic-dominant class, but had no significant increase in prescribing, while Celexa was an infrequently prescribed antidepressant, but had a positive increase in prescribing.

Figures 2.2 to 2.5 show bivariate plots of the short- and medium-term prescribing changes with the factors hypothesized to affect them: the average copay change, the average plan payment change, and the generic prescribing rate in the drug class, prior to the patent expiration. All appear to have the expected sign of correlation. Figure 2.4 demonstrates that copays have a gradual effect; the drugs with the largest copay changes in the short-term have larger prescribing changes between the short- and medium-term, despite having smaller copay changes during this later period.

Appendix B includes graphs of prescribing rates of each product from 2004-2007 in each of the four classes.

2.4 Estimation and Results

2.4.1 Conditional Logit Estimation

Tables 2.3, 2.4, and 2.5 report results of a series of conditional logit models based on Equation 2.1, but with a dummy for *post patent expiration* in lieu of any direct measure of advertising. All models include drug-specific fixed effects (δ_j) for the top 5-7 drugs in each class, relative to the base category of "other brand drugs." The first model estimated includes only individual-specific copays (p_{ijt}) and the *post patent expiration* dummy variable ($post_{jt}$). The latter is meant to capture the effect of the advertising decrease that coincides with patent expiration.

$$V_{ijt} = \delta_j + \alpha p_{ijt} + post_{jt} + \epsilon_{ij} \tag{2.4}$$

Columns (1) and (2) estimate this equation over the full sample period and the period surrounding each patent expiration, respectively. $\widehat{\alpha}$ is negative and small, and $\widehat{post_{jt}}$ is positive. Given the hypothesis that physicians do not always observe patient costs ($\lambda < 1$ in equation 2.1), this is not surprising. The large-scale drop in copays associated with a patent expiration should be far more visible to physicians than cross-sectional variation in drug copays, and thus, is not captured by the copay variable but by $\widehat{post_{jt}}$ in this.

then $\bar{p}_{jt}$ will have no additional effect on prescribing when it is added. In fact, we see that it has a much larger effect than p_{ijt}, indicating that despite not being well able to discern a new patient's copay for a given drug, physicians do have a sense of which drugs generally have larger copays.

Columns (3) adds the average price change of patent-losing molecules to the estimation:

$$V_{ijt} = \delta_j + \alpha p_{ijt} + \beta \bar{p_{js}} + post_{jt} + \epsilon_{ij} \tag{2.5}$$

The subscript s on $\bar{p_{js}}$ indicates the patent status of drug j at time t. For observations in the six months prior to patent expiration, $\bar{p_{js}} = \bar{p_{j,brand}}$ is the average copay of the drug during this time, across all patients being prescribed any drug in the class during that time. For observations in the nine months following the patent expiration, $\bar{p_{js}} = \bar{p_{j,generic}}$ is the average copay of the generic version of the drug during this time. The goal is to see how much of the estimate $\widehat{post_{jt}}$, which was positive in columns (1) and (2), can be explained by the size of the price change of the varying patent-losing drugs. In fact, including $\bar{p_{js}}$ in the model turns $post_{jt}$ negative, as hypothesized, since it captures the effect of advertising cessation. $\hat{\beta}$ is strongly negative, and 3.4 times larger than $\hat{\alpha}$.

Copays of competing brand drugs may also be affected by the patent expiration. For example, many health plans raised their copays for Lipitor, the most popular statin, when competitor Zocor became available as a generic. This would lead Zocor to become comparatively even less expensive, but would not be captured by $\bar{p_{js}}$ as defined above. Thus in columns (4) and (5), I include the mean average copay, by quarter, for all drugs in the sample.[10] The estimates are nearly identical, though α decreases, since it now purely represents the effect of cross-sectional variation (within quarter) in drug copays.

Columns (5) adds the *ex-ante generic prescribing share* of each patent-losing molecule, interacted with the *post patent expiration* dummy, to the estimation.

$$V_{ijt} = \delta_j + \alpha p_{ijt} + \beta \bar{p_{js}} + post_{jt} + \epsilon_{ij} \tag{2.6}$$

The goal is to measure whether an early patent expiration, when there is not yet much generic prescribing in a drug class, has a larger effect on prescribing than a subsequent patent expiration. The effect is significant and negative, as predicted. Furthermore, including this variable makes the baseline estimate of $post_{jt}$ insignificantly different from zero. The interpretation is as follows. The first patent expiration in a drug class is a highly salient event offering large potential to improve the adherence of cost-sensitive patients. The first molecule will gain significant market share after its patent expiration, depending on the size of its copay change. Subsequent patent expirations, however, are increasingly less potent; the expected effects of their copay reductions are partially offset by the drop in advertising. A hypothetical explanation is that the only physicians still prescribing brand drugs, when prominent generic drugs are available, are those who are more sensitive to advertising.

Based on the magnitude of the estimates in column (5), in a drug class with a 50% generic prescribing rate, the effect of lost advertising is strong enough to negate the effect of an \$8.37 perceived copay decrease, and in a class with an 80% generic prescribing rate, the effect is large enough to overpower a \$13.43 perceived copay decrease.

A question left for further research is what drives this effect. There appears to be little substitution from existing generic products to new (patent-losing) generic products. The increase in prescribing share, even when large, is typically driven by substitution from competing brand products to the new generic. This can be seen in the plots of prescribing shares

[10] Mean average copay is calculated by a portion of a quarter during the quarter of the patent expiration

over time in Appendix B.

2.4.2 Evaluating Fit

Since the goal of this paper is to explain heterogeneity in responses to patent expirations, in this section I show how the models estimated above move progressively closer to "fitting" the prescribing effects of the ten patent expirations studied.

From each model, predictive probabilities are obtained for each observation (i.e. the probability that person i in period t is prescribed drug j given her copay p_{ijt}). From these, I use a two-group test of proportions to evaluate whether the share predicted to be prescribed drug j in the three months following drug j's patent expiration differs significantly from the share predicted to be prescribed drug j in the three months prior to its patent expiration. I also compare, in Figure 2.6, each drug's predicted share increase in percentage points against its actual increase in prescribing share. In each figure, the ten drugs are plotted with actual change on the horizontal axis and predicted change on the vertical axis. Thus, a perfect fit would correspond to a series of points along the 45° line. The plots show that the predictions of model (5), from estimating equation 2.6, align the points more closely than models excluding either the mean copay change or the generic prescribing share.

2.4.3 Robustness

To assess the robustness of the core results, I incorporate other possibly confounding variables in the models of Table 2.4.

In the first column, I include plan costs for drug prescriptions, to test whether insurers attempt to influence prescribing through channels other than the formulary, for example, by contacting high-volume physicians, or by implementing strict policies requiring patients to try a generic drug prior to receiving coverage for a brand drug. As this would happen at the individual plan level, we would not expect the average plan payment in a given quarter to have much of an effect (unless there are spillovers). The results suggest a potential mild effect of actual plan payment. The estimate of the effect of average plan payments, however, is positive.

In the second column of Table 2.4, I allow the copay elasticity to vary by drug class. I include interactions of the mean quarterly copay with indicators for the statin, beta blocker, and calcium channel blocker classes (antidepressants are the baseline category). The three other classes all appear more copay-elastic than the antidepressant class, which supports the view that antidepressants are the most heterogenous class, with varying side effects.

Lastly, I account for a possible source of endogeneity of copays. As discussed in Section 2.2.2, some drugs are "abandoned" by their manufacturers prior to patent expiration, in favor of newly released follow-up drugs. These drugs nearing patent expiration may be given higher prices (which translate to higher copays) and much lower advertising, which would bias my estimates of copay sensitivity as well as the post patent expiration (advertising) effect. In

the last column of Table 2.4, I allow the post patent expiration effect to differ for the four drugs whose manufacturers released follow-up versions. As expected, these molecules have a smaller (zero) baseline effect of patent expiration, since their advertising is changing much less upon patent expiration. However, the estimate of copay sensitivity remains negative and significant, as does the effect of generic share prior to patent expiration.

2.4.4 Subgroup analysis

In Table 2.5, I estimate equation 2.6 on some interesting subgroups of patients. The goal is to compare the estimates of γ (price sensitivity), λ (probability that true copay is observed), and the expected prescribing response to a patent expiration causing a \$10 average copay drop, in a class with 50% generic prescribing: Do the estimates shift in the expected directions based on the patient population? For example, if low income and low salary patients are more price-elastic, we expect to see a more negative estimate of γ, but not necessarily a larger estimate of λ, unless these patients are also better informed about their copays, or their physicians or pharmacists take more time to learn them. The evidence in columns (5)-(8) shows a small difference in price sensitive prescribing between areas of low and high median household income, and a much larger difference in this parameter between low- and high-salary employees: the coefficient for low-salary employees is 61.5% more negative. The interpretation of a more negative γ, in the absence of a larger λ, is that physicians respond more strongly to patent expirations (and other discernible trends in average copays), consistent with the findings of Chapter 1.

Since specialists are likely to see patient with more complex health conditions, for whom one drug may be substantially more appropriate than another, the hypothesis is that γ is closer to zero. However, if specialists are more familiar with the average copays of the drugs they frequently prescribe, this could have an effect in the opposite direction. Similarly, if specialists make a greater effort to choose a low tier drug, when appropriate, then the estimated λ will be higher. Results in columns (3) and (4) support both of these hypotheses.

Another hypothesis is that physicians treating patients from a smaller number of plans will likely be more familiar with the precise copays of these plans. Unfortunately, the data are not well-suited for testing this hypothesis, since they include a huge number of physicians and a large quantity of small plans: for physicians observed prescribing to at least 20 patients, the median number of patients seen per plan is 15. I do not find any evidence that λ differs along this dimension, though the estimate of γ (price sensitivity) appears more negative for plans with a larger number of patients per physician. Whether the plan is an HMO (managed care) or PPO, which is unobserved for most of the plans, is likely to be confounding this estimate.

2.5 Comment

This study has several limitations, many of which can be addressed in future work. First, there is measurement error in estimating average copays from the present sample, rather than a nationally representative sample. Future work will use the nationally representative Medical Expenditure Panel Survey to compute average copays for each drug in each time period. A more accurate estimate of the role of the accuracy of perceived copays (λ) will be achieved through a maximum likelihood model that allows price elasticity, but not λ, to vary across drug classes.

The primary limitation of this study is the lack of data on promotional expenditures on drugs. I plan to obtain access to panel data of promotional expenditures by type of advertising. The results of this paper will be complemented by estimates of the effects of non-price changes, specifically, changes in the stock and flow of detailing, samples, and journal advertisements.

Similarly, direct-to-consumer (DTC) advertising, which also ceases after patent expiration, may be a factor in patient preferences. I plan to estimate the response of adherence of new patients to patent expiration, as well as whether existing users of a heavily advertised drug have any change in their adherence or switch rates after its patent expiration. A comparison will reveal whether patients value a drug more, prior to its patent expiration, and whether this helps explain the variation in prescribing responses.

Lastly, it is clear from the changes in prescribing rates over time, shown graphically in Appendix B that prescribing responses are not immediate but gradual, reflecting either slow diffusion of the information that affects prescription decisions, or peer influences on prescribing. A dynamic model of prescribing could differentiate the immediate from the long-term effects of patent expirations under different circumstances.

2.6 Conclusion

Among ten drugs treating chronic conditions, with patent expirations occurring between 2004 and 2007, only four experienced large increases in prescribing rates, while three experienced statistically significant decreases. This paper identifies two factors that explain much of the variation in these responses: the size of the copay drop upon expiration (i.e. the difference in copays of the brand and generic versions of the drug), and the current prevalence of generic prescribing in the drug class. Results suggest that physicians are more likely to increase their prescribing of a drug, after it becomes available as a generic, if it previously had a higher copay, on average. However, there is a baseline tendency to reduce prescribing of a drug, after its patent expiration, and this tendency grows stronger with the existing rate of generic prescribing in a class.

The baseline tendency for a reduction in prescribing (aside from the copay effect) is likely driven by the cessation of advertising that accompanies patent expiration. Future work will

use data on promotional expenditures to yield precise estimates of the effects of different kinds of advertising on prescribing decisions.

This paper also provides a new estimate of the precision of a physician's estimate of a patient's copay.[11] I estimate that the response to individual-specific copay has a weight of about 20% in the physician's perceived copay, relative to the sample average copay of a drug at a given time. To be clear, it may be the case that the physician never observes an individual's own copay, but ends up changing an individual's first prescription, based on a call from a pharmacist, about 20% of the time. In either case, the implication is that an insurer's own formulary is only modestly able to "steer" initial prescriptions to certain drugs, despite a stronger response by physicians (or pharmacists) to large-scale copay changes.

2.7 Figures and Tables

[11] This estimate is calculated as the ratio of the prescribing response to cross-sectional variation in copay, relative to the sum of this response and the response of prescribing to variation in average copay of a drug over time.

Table 2.1: Drugs facing patent expirations in four chronic drug classes, 2004-2007

Brand name (generic)	Date of generic entry (Month $t = 0$)	Follow-up drug by same manufacturer	Share of initial Rx, $t = [-3, 0]$	Avg. copay $t = [-3, 0]$	Headlines $t = [-6, 6]$	Sales, calendar year before $t = 0$ (in $1,000)
Statins						
Pravachol (pravastatin)	4/24/2006	N/A	0.04	$25.16	120	1,315,013
Zocor (simvastatin)	6/23/2006	Vytorin (comb.)	0.21	$23.43	289	3,106,628
Antidepressants						
Celexa (citalopram)	10/28/2004	Lexapro	0.04	$20.78	27	1,260,303
Zoloft (sertraline)	7/26/2006	N/A	0.20	$20.02	44	2,561,069
Wellbutrin XL (bupropion)	12/14/2006	N/A	0.07	$32.86	76	1,326,323
Beta Blockers						
Toprol XL (metoprolol succ.)	11/22/2006	N/A	0.35	$15.40	34	1,294,098
Coreg (carvedilol)	9/4/2007	Coreg CR	0.06	$22.34	87	1,158,322
Calcium Channel Blockers						
Plendil (felodipine)	11/2/2004	N/A	0.01	$27.39	0	151,542
Norvasc (amlodipine)	3/27/2007	Caduet (comb.)	0.42	$16.87	177	2,149,017
Lotrel (amlodipine/benazepril)	5/23/2007	N/A	0.16	$21.46	59	1,292,863

Date of generic entry is identified as first appearance of more than 1 generic fill on the same day, in aggregate claims data, and generally coincide with the publicized date of patent expiration. Follow-up drugs: Lexapro is the "left-hand" side, or S-enantiomer of Celexa. Coreg CR is a once-daily dosage version of Coreg (just as Toprol XL and Wellbutrin XL are once-daily dosage version of their predecessors). Vytorin is a combination drug containing Zocor and Zetia (a non-statin cholesterol reducer), and Caduet is a combination of Norvasc and Lipitor (a statin), just as Lotrel is a combination of Norvasc and an ACE inhibitor. Share of initial prescriptions in the sample are reported for the 90 days prior to each drug's patent expiration. Headline mentions of each drug, along with articles containing the word "generic", are summed over the six months before and after each patent expiration (Lexis-Nexis search). Drug sales are reported for the last full calendar year ending prior to the year of the patent expiration (i.e. 2005 for Zocor). Source: drugs.com, using Verispan data.

Table 2.2: Medium-run outcomes of patent expiration by drug.

Brand name	Date of generic entry ($t = 0$)	Follow-up drug?	Class-level generic share, $t = [-3, 0]$	Share of initial prescriptions		Share change (%)
				$t = [-3, 0]$	$t = [6, 9]$	$t = [-3, 0]$ to $[6, 9]$
Statins						
Pravachol	4/24/2006	No	0.07	0.04	0.05	0.10
Zocor	6/23/2006	Yes	0.09	0.21	0.31	0.50
Antidepressants						
Celexa	10/28/2004	Yes	0.22	0.04	0.06	0.69
Zoloft	7/26/2006	No	0.32	0.20	0.20	-0.03
Wellbutrin XL	12/14/2006	No	0.53	0.07	0.05	-0.23
Beta Blockers						
Toprol XL	11/22/2006	No	0.52	0.35	0.34	-0.05
Coreg	9/4/2007	Yes	0.74	0.06	0.08	0.43
Calcium Channel Blockers						
Plendil	11/2/2004	No	0.25	0.01	0.02	0.19
Norvasc	3/27/2007	Yes	0.35	0.42	0.53	0.25
Lotrel	5/23/2007	No	0.57	0.16	0.10	-0.38

Entry dates and follow-up drugs are described in the previous table. t counts 30-day periods before and after patent expiration. Class-level generic share is calculated using all initial prescriptions in the class in the 90 days prior to the date of generic entry. Share of initial prescriptions in the sample are calculated within the drug class, among patients who have not purchased any drug for at least 365 days prior.

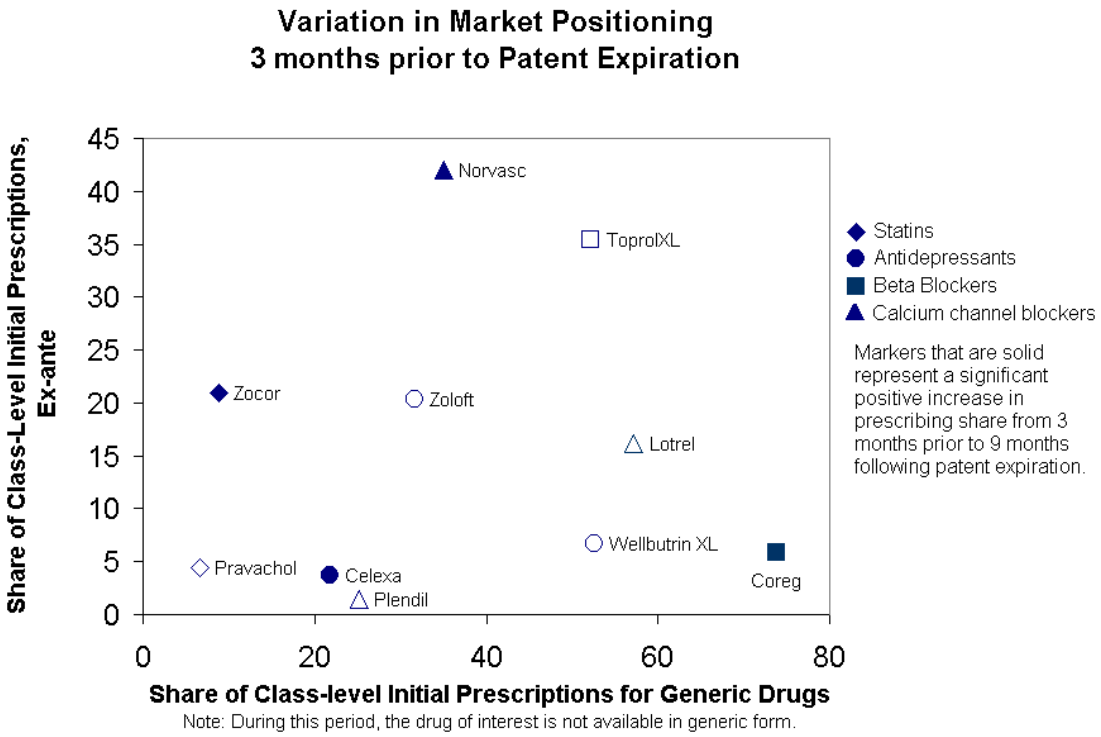

Figure 2.1: *Variation across patent-losing drugs in three dimensions.*

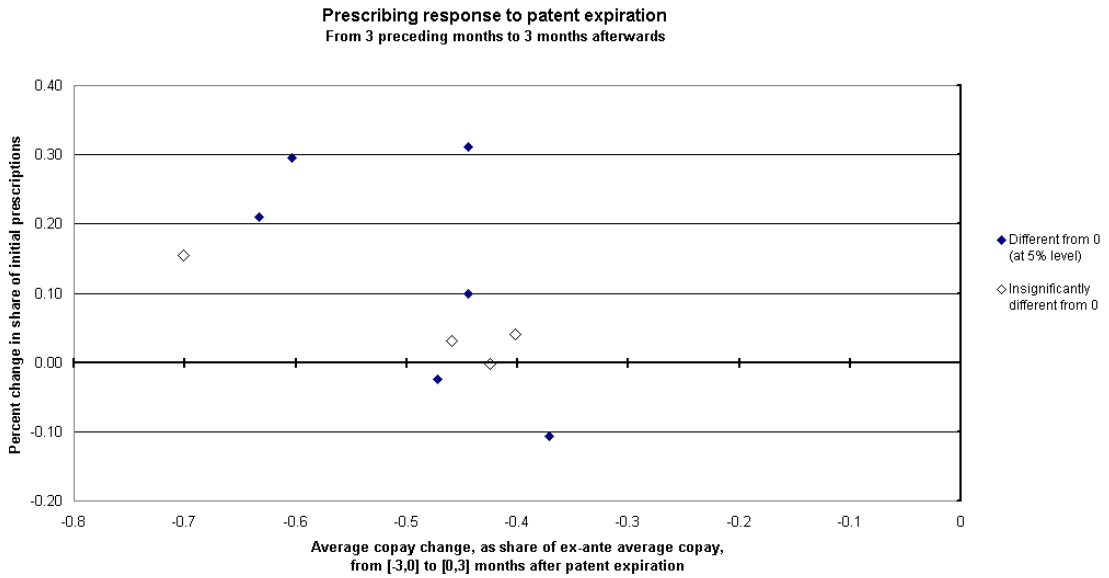

Figure 2.2: *Change in prescribing rate of patent-losing molecule, by size of immediate copay change.*

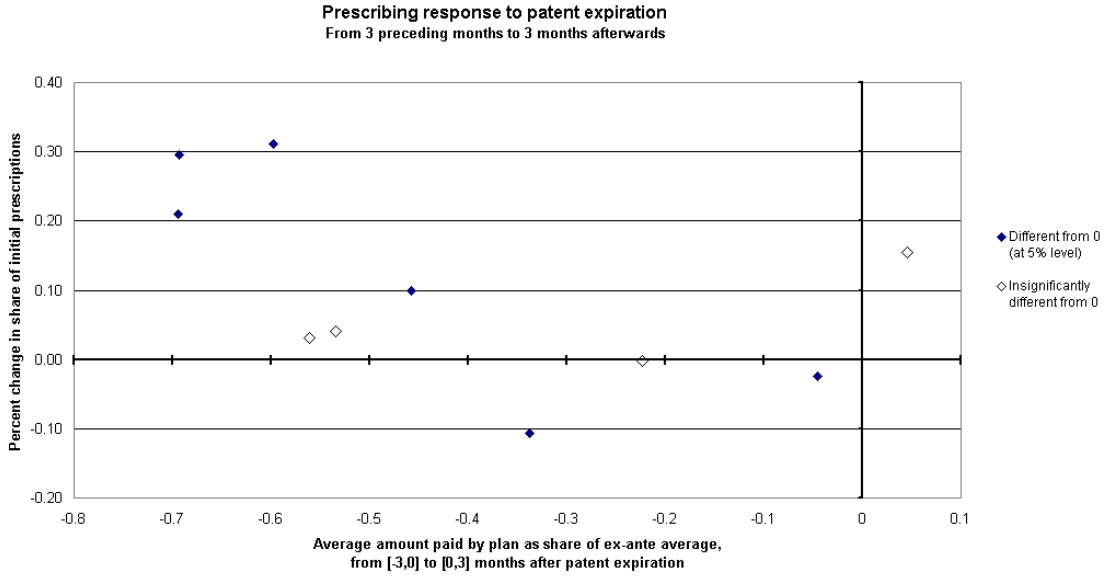

Figure 2.3: *Change in prescribing rate of patent-losing molecule, by size of immediate plan payment change.*

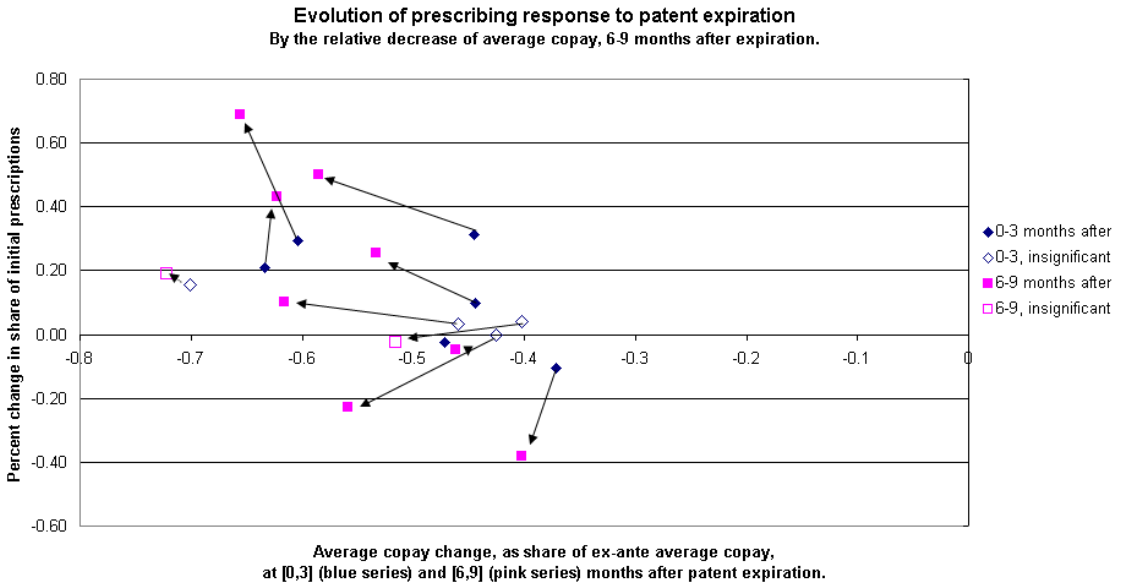

Figure 2.4: *Change in prescribing rate of patent-losing molecule, by size of medium-run copay change.*

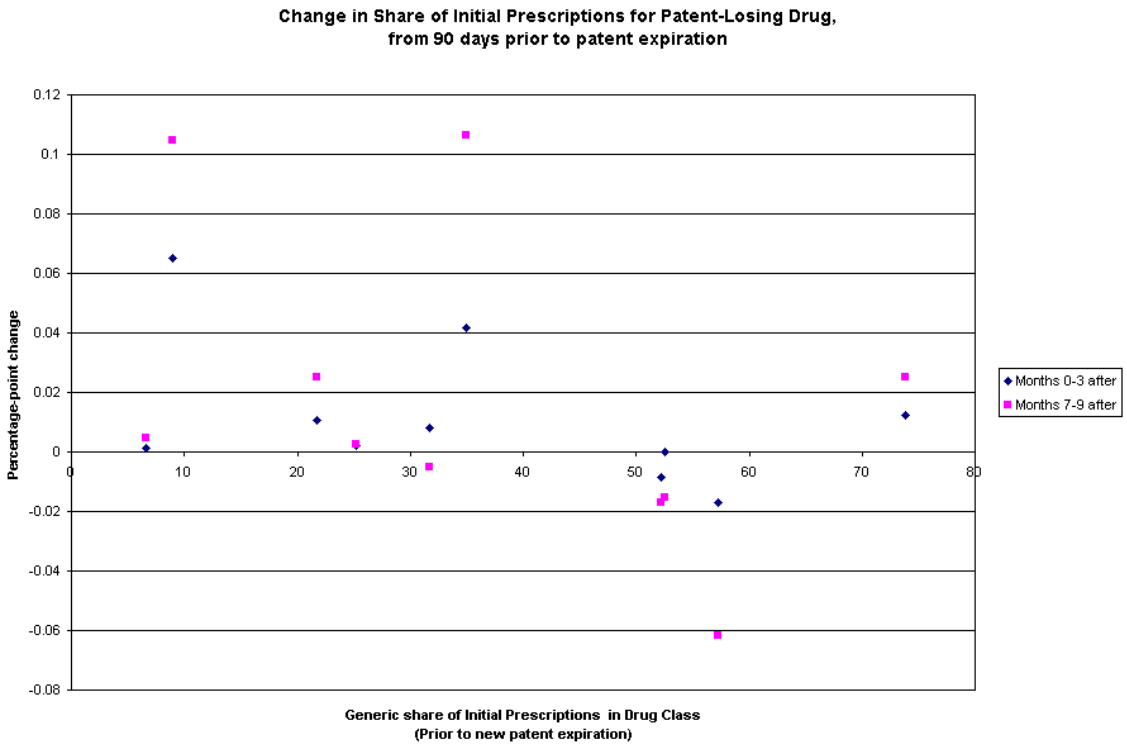

Figure 2.5: *Change in prescribing rate of patent-losing molecule, by ex-ante generic prescribing share.*

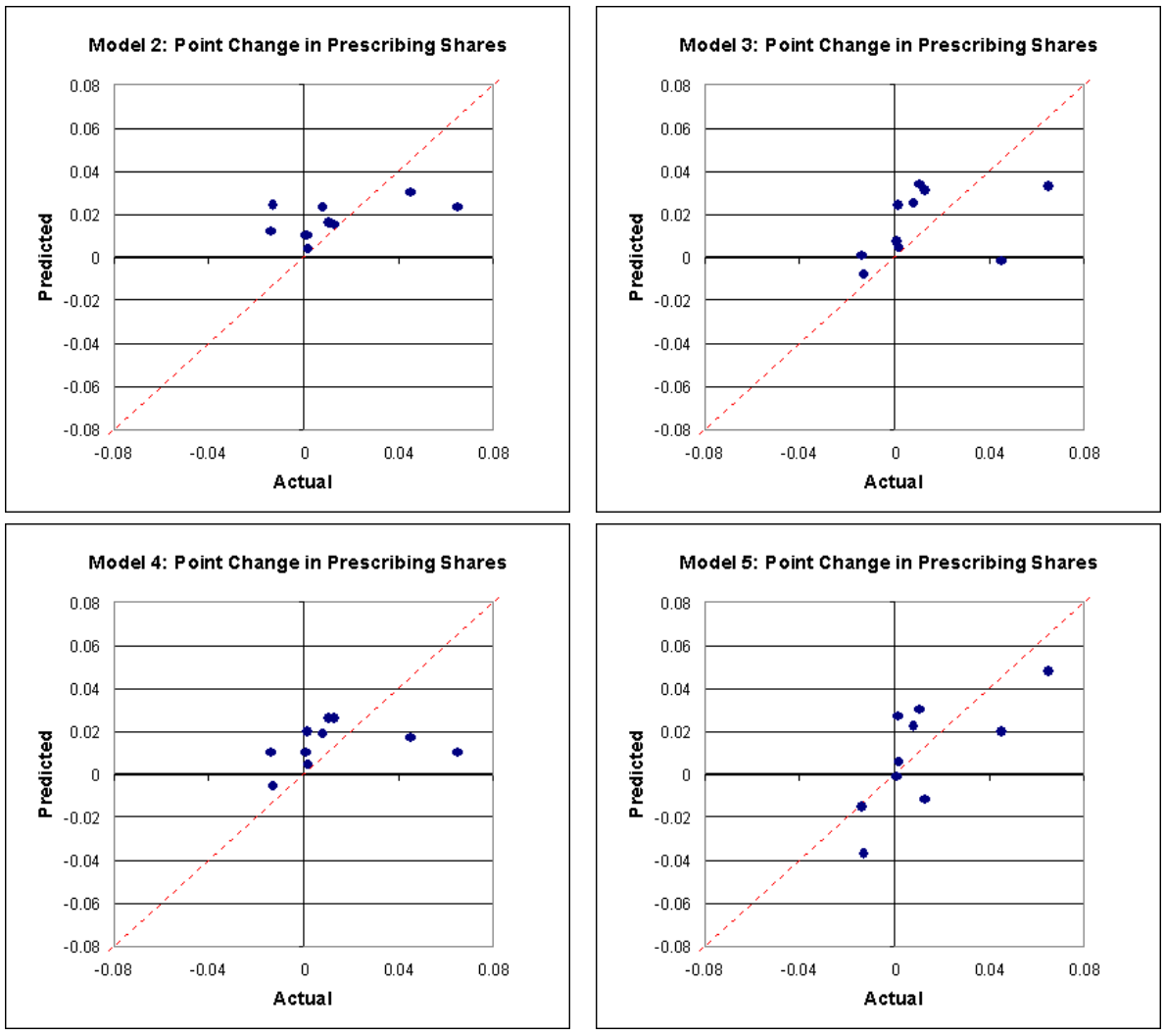

Figure 2.6: *Predicted and Actual Share Point Changes.*

Table 2.3: Copay effects on prescribing during patent expiration periods

	(1)	(2)	(3)	(4)	(5)
	Entire period, 2004-2007	From six months prior to nine months after each patent expiration			
Choice of initial prescription among drugs $j = 1, .., J$					
p_{ij} (Actual copay)	-0.016***	-0.015***	-0.014***	-0.011***	0.011***
	(0.0003)	(0.0003)	(0.0004)	(0.0004)	(0.0004)
$p_{\bar{ij},b}$ or $p_{\bar{ij},g}$ (Pre/post average copay)			-0.048***		
			(0.002)		
$p_{\bar{ijt}}$ (Quarterly average copay)				-0.046***	-0.040***
				(0.001)	(0.001)
Post patent expiration dummy	0.10***	0.023**	-0.33***	-0.34***	0.0032
	(0.006)	(0.008)	(0.02)	(0.01)	(0.02)
Interacted with:					
Generic share of initial prescriptions, 3 months prior to patent expiration					-0.86***
					(0.04)
N	702,683	370,347	370,347	370,347	370,347
Log. Lik.	-1224314.1	-672856.2	-672654.7	-672158.7	-671877.5

Conditional logit coefficients; Standard errors in parentheses.

Note: Four classes with ten patent expirations are pooled. Separate constants for each drug, in each class, are estimated but not shown. *Pre/post average copay* is defined as the average brand copay in the last six months prior to patent expiration or the average generic copay over the first nine months following patent expiration, depending on the period of the current observation. This variable represents the sample population's average copay change associated with a patent expiration, while *Quarterly average copay* also includes other temporal variation in copays, for all drugs in each class. *Post patent expiration dummy* is interacted with *Generic share of initial prescriptions (3 months prior)* to test whether "early" patent expirations in a drug class have a stronger effect due to their salience or to the larger potential gains in patient adherence.

Table 2.4: Copay, plan cost, and class-level interactions

	(1)	(2)	(3)
Choice of initial prescription among drugs $j = 1, .., J$			
p_{ij} (Actual copay)	-0.016***		-0.011***
	(0.0003)		(0.0003)
p_{jt}^{-} (Quarterly average copay)	-0.027***	-0.039***	-0.038***
	(0.001)	(0.001)	(0.001)
Interacted with:			
Statin		-0.011***	
		(0.001)	
Calcium channel blocker		-0.020***	
		(0.001)	
Beta blocker		-0.066***	
		(0.002)	
Paid by plan (actual)	-0.0061***		
	(0.0002)		
Paid by plan (quarterly average)	0.0044***		
	(0.0003)		
Post patent expiration dummy	0.11***	0.18***	-0.24***
	(0.01)	(0.01)	(0.02)
Interacted with:			
Generic share of initial prescriptions, 3 months prior to patent expiration	-0.95***	-1.35***	-0.47***
	(0.03)	(0.03)	(0.03)
Manufacturer released follow-up drug prior to patent expiration, dummy			0.43***
			(0.01)***
N	702,412	716,914	702,683
Log. Lik.	-1221174.1	-1245913.5	-1221319.8

Conditional logit coefficients; Standard errors in parentheses

Table 2.5: Subgroup comparisons of price coefficient (γ) and accuracy of perceived prices (λ)

	No. of patients, same prescriber and plan		Level of specialization in drug category		Median Area Household Income		Salary of employed primary earner	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	< 15	$>= 15$	Low	High	$< \$47,000$	$> \$47,000$	$< \$50{,}000$	$> \$50{,}000$
Choice of initial prescription								
p_{ij} (Actual copay)	-0.012***	-0.013***	-0.012***	-0.010***	-0.011***	-0.010***	-0.019***	-0.011***
	(0.0004)	(0.0005)	(0.0003)	(0.0008)	(0.0004)	(0.0004)	(0.001)	(0.001)
$\bar{p_{jt}}$ (Quarterly average copay)	-0.026***	-0.030***	-0.030***	-0.019***	-0.038***	-0.034***	-0.044***	-0.029***
	(0.001)	(0.002)	(0.001)	(0.003)	(0.001)	(0.001)	(0.004)	(0.004)
Post patent expiration dummy	0.17***	0.25***	0.28***	0.074	0.063**	0.23***	0.24***	0.26***
	(0.02)	(0.03)	(0.02)	(0.05)	(0.02)	(0.02)	(0.07)	(0.06)
Interacted with:								
Generic share, 3 mo. prior	-1.01***	-1.31***	-1.32***	-0.78***	-0.92***	-1.15***	-1.58***	-1.33***
	(0.05)	(0.05)	(0.04)	(0.08)	(0.04)	(0.04)	(0.1)	(0.1)
N	277174	236837	442135	76378	347956	353773	34907	43476
Log. Lik.	-479028.8	-414347.2	-780248.5	-128540.7	-606372.0	-613297.4	-63679.4	-76645.9
Implied γ	-0.037***	-0.044***	-0.043***	-0.029***	-0.050***	-0.044***	-0.063***	-0.039***
	(0.001)	(0.002)	(0.001)	(0.003)	(0.001)	(0.001)	(0.004)	(0.004)
Implied λ	.32***	.31***	.29***	.35***	.23***	.24***	.30***	.27***
	(0.0003)	(0.0002)	(0.0001)	(0.002)	(0.0001)	(0.0001)	(0.001)	(0.001)

Conditional logit coefficients; Standard errors in parentheses

Note: Number of patients with the same prescriber and health plan is calculated using all drug prescriptions in all drug classes, for physicians with at least 20 different patients observed. The hypothesis is that physicians with more than 15 (the observed median) patients are more likely to be familiar with the copays of the health plan, and thus, have larger estimated λ. Level of specialization is based on the share of a physician's observed prescriptions (in the entire sample) that fall within the therapeutic category containing the present drug class: for example, statins are a subset of cardiac drugs. The cutoff level used to impute "specialist" is 60 percent. Low income areas are below the sample median of median household income, based on 2000 Census and 3-digit zip code. Low salary patients have reported salaries below $50,000. Spouses and retirees are excluded from the salary-based comparison.

Chapter 3

Physician Prescribing Behavior and Its Impact on Patient Outcomes

Coauthored with Geoffrey F. Joyce and Neeraj Sood

Concerns over rising drug costs, medication errors and potential conflicts of interest have focused attention on physician prescribing behavior. Using pharmacy claims linked to prescriber information from 29 large employers and over 150 different health plans from 2005-2007, we measure the range of physician prescribing within the ten most prevalent therapeutic classes, the factors affecting the broadness of this range, and its impact on patient outcomes. Physicians prescribe more broadly than commonly perceived. In 8 of 10 classes, the median physician prescribes at least 3 different drugs despite the small number of initial prescriptions observed per doctor (median=7). Physicians treating patients with a greater range of comorbid conditions and varied formulary designs prescribe a broader range of drugs within a class. Though narrow prescribers are more likely to prescribe highly advertised drugs, few physicians prescribe these drugs exclusively. Narrow prescribing has modest effects on medication adherence and out of pocket costs in some drug classes.

3.1 Introduction

In 2004, pharmaceutical firms spent over $57 billion on marketing in the US, roughly twice their expenditures on research and development [1]. Most of this spending targeted physicians through sales representatives (detailing), sampling (provision of drugs at no cost), physician meetings and advertisements in medical journals [2]. For example, industry sponsored promotional events increased from 120,000 in 1998 to 371,000 events in 2004 [3]. There

has also been a significant increase in the frequency and size of federal and state penalties for illegal promotion of drugs and pricing irregularities [1].

These trends have raised concern that pharmaceutical companies might have undue influence on the prescribing behavior of physicians. In particular, there is concern that a significant fraction of physicians might be prescribing a narrow range of heavily promoted drugs or might be exclusively prescribing branded drugs to the detriment of patient welfare. However, empirical evidence on the prescribing behavior of physicians and its consequences for patients is limited. Some studies suggest that physicians prescribe narrowly, particularly general practitioners, but much of this evidence is decades old. [4]; [5]; [6]; [7]; [8]. More recent work finds that the prescribing patterns of physicians are substantially more concentrated than the aggregate market in each class, and that physicians differ in their preferred drug within a class [9]; [10].

The appropriateness of broad versus narrow prescribing is likely to depend on the composition of the drug class. Narrow prescribing may be optimal when one drug is clearly superior to the others, or if all the drugs in the class act in a similar way. For example, prescribing only a generic or low cost brand in a largely homogenous class may be beneficial given that lower patient cost-sharing is associated with improved adherence [11]; [12]; [13]. In addition, most generics are inherently safer than newer drugs because of their longer track record in clinical practice and known side-effects [14]; [15]. Alternatively, some classes are characterized by heterogeneous effects, where a specific drug provides therapeutic benefit to some patients and little to others, or has known side effects that are problematic for a subset of patients. If the heterogeneous benefits and side effects of these drugs are known ex-ante, a better informed physician will prescribe more broadly, taking into account the specific medical characteristics of each patient. Taub and colleagues find that psychiatrists prescribe more broadly than general practitioners within the atypical antipsychotic class, but they cannot determine how much of the difference is explained by variation in the case-mix of patients seen by psychiatrists versus non-specialists [9].

Beyond the challenge of predicting a drug's therapeutic value to a new patient, an unrelated factor further complicates the prescribing decision: plan formularies. Most drug classes today include an array of similar products that compete for essentially the same population of patients, and health plans typically choose a small subset of these products to offer at low cost-sharing rates. In addition, direct-to-consumer advertising has emboldened patients to request specific treatments [16]; [17]; [18]. How these factors have affected physicians' choice of drug therapies is uncertain.

In this paper, we examine the breadth of physician prescribing in ten large drug classes with several similar-acting agents. We measure the number and type (generic or brand) of different drugs prescribed as initial prescriptions by each physician and the factors that affect their choices. We then examine whether broad or narrow prescribing is associated with patient outcomes such as rates of medication adherence, therapeutic switching, and out-of-pocket drug spending. We know of no other study that examines the relationship between how broadly physicians prescribe and patient outcomes.

3.2 Methods

We use unique data matching prescriptions to prescribing physicians. The data include medical and pharmaceutical claims from 29 large employers in the United States from 2003 to 2007. The drug claims include information on the type of drug, drug name, national drug code, dosage, days supplied, and place of purchase (retail or mail order). Starting in 2005, all pharmacy claims identify the prescriber by masked DEA number. Thus from 2005-2007, we can observe prescriptions made by the same physician to different patients in different insurance plans. We do not have any additional information about the prescribers.

We define an initial prescription as the absence of any pharmacy claim in the same therapeutic class for at least twelve months. To be eligible for the sample, a patient must be at least 18 years old and continuously enrolled for at least one year before initiating therapy, and for at least six months afterwards.

3.2.1 Empirical Approach

After identifying physicians with a minimum of five *initial* prescriptions within a drug class, we calculate the number of distinct drugs prescribed by each individual physician. This serves as our measure of prescribing breadth or narrowness.

After describing the breadth of prescribing in ten prominent drug classes, we aim to answer two questions: First, what factors drive a physician to prescribe more narrowly (smaller number of drugs) or broadly (larger number)? Second, is broad or narrow prescribing more beneficial to patients? If broad prescribers put more effort into creating a "custom" treatment for each patient, and are more successful in matching their patients to therapeutically optimal drugs, we would expect their patients to be more likely to adhere to treatment, and less likely to switch to different drug. If broad prescribers are, instead, motivated to minimize their patients' costs by prescribing the least expensive drug based on their plan's formulary, then we would expect patient out-of-pocket spending to decrease with breadth of prescribing, though switching may increase. For these analyses, we focus on the five brand-dominated classes: PPIs, statins, SS/NRIs, calcium channel blockers, and antihistamines.

To assess what factors influence a physician's breadth of prescribing, we estimate a Poisson regression with *Number of different drugs prescribed* as the dependent variable. We control for the following factors, which are clearly related to this value, but are not our variables of interest:

- *Number of initial prescriptions observed,* which is an upper bound on the number of different drugs prescribed.
- *Number of patients with prior use in the class,* as they are more likely to receive a less commonly prescribed drug, having tried and discontinued treatment earlier.

- *Half years with a prescription observed,* since a physician writing prescriptions over a three year period is likely to prescribe a greater array of drugs than a physician with the same number of prescriptions observed within the same six month period.

The variables of interest are:

- *Combinations of chronic conditions,* for example, one patient with diabetes, one with diabetes and heart disease, and a third with only heart disease, count as three combinations. Specific health conditions may lead to broader prescribing for the purpose of tailoring the treatment to the particular disease.

- *Number of plans,* which may capture not only variation in formularies but also variation in unobserved insurer policies, for example, "step-therapy" (mandated generic drugs for first-time patients).

- *Different copay orderings,* to capture the degree to which formulary placement influences prescribing. Several health plans may have different copay values but the same copay *ranking* over drugs, which is what determines the lowest cost drug.

We also include the squares of several of these variables. Since the number of drugs prescribed is bounded by the number of drugs in the class, most of the explanatory factors have diminishing positive effects over the range that they are observed. Table 3.5 reports the results of the Poisson regression, which are described in section 3.4

The second goal is to assess whether broad or narrow prescribers are able to achieve better patient outcomes. To do so, we must characterize physicians' narrowness in a way that takes into account their mix of patients, as well as the other factors listed above. We use the Poisson regression of Table 3.5 to predict the number of drugs prescribed by each physician, given their set of patients. We then classify each physician as high, medium or low in degree of narrowness (concentration) based on the tertile of their residual. This is the classification that will be used to assess the impact of narrowness of prescribing on outcomes.

We use OLS and logit regressions to estimate the impact of "high" and "low" narrowness of prescribing on three patient-level outcomes: medication possession ratio (MPR) over the six months following the initial prescription, therapeutic switching (changing medications within the class), and out-of-pocket drug costs. The MPR is expressed as a percentage, defined as the number of days supply of a medication (i.e. possession) over the six months following the initial prescription, and patient out-of-pocket drug costs reflect the predicted cost of a one-year supply of medication, based on the amount paid thus far per day supplied.

The regressions of MPR and switching include age and its square, gender, median household income (by 3-digit zip code), dummies for high salary (>$50,000), missing salary information, and any previous use in the class. Since patients receiving prescriptions from specialists are more likely to adhere, we use a proxy for specialist: the share of all of a physician's observed prescriptions that are in the relevant category, for example, cardiac drugs.

We control for comorbid conditions related to the drug class using a set of disease indicators identified in the medical claims based on ICD-9 diagnoses. For example, we include binary indicators for hyperlipidemia, diabetes, hypertension, chronic heart failure, cardiac disease, vascular disease, and stroke for statin users. In addition, we control for the initial drug prescribed when estimating the impact of narrowness on switching, since there is high variation in switching rates across drugs, and narrow prescribers are more likely to prescribe certain drugs.

Since there is no reason for out-of-pocket costs to be affected by anything other than plan-level formulary values, and of course, the drug prescribed, we do not use the same set of controls. Due to the small number of patients per plan, we are not able to use plan fixed effects. Instead, we use two variables reflecting the plan formulary's generosity: the mean copay for brand drugs within the plan, and the difference between the mean brand copay and the mean generic copay.

Results are shown in Table 3.4 in the form of average predicted values for "high", "medium" (the omitted category in the regressions), and "low" narrowness. The full regression results are in Appendix C.

3.3 Data

3.3.1 Classification of Drugs

We use a common classification scheme-the 2007 Red Book published by Thomson-to associate each drug with a therapeutic class. Table 1 shows the 10 most common therapeutic classes (in terms of dollars spent) in our sample for 2005. These are cholesterol-reducing drugs, antidepressants, non- H2A stomach drugs, antihistamines, nonsteroidal anti-inflammatory drugs, opiates, beta blockers, calcium channel blockers, ACE inhibitors, and antidiabetic drugs excluding insulin. To further narrow down the classes, we focus on statins within cholesterol-reducing drugs (dropping ezetimbe, fibrates and others), on SSRIs and SNRIs within antidepressants (keeping bupropion formulations, dropping tricyclic antidepressants), and on proton pump inhibitors (PPIs) within non- H2A stomach drugs. In the antihistamine class, we drop promethazine which is prescribed primarily as an acute treatment and often used as a sedative or antiemetic rather than for allergy treatment.

Since most plans assign lower copayments to generic drugs, and often charge the same copayment for all generics, narrow prescribing is most likely to impact average costs in classes where brand drugs are dominant. For this reason, some analyses focus on the five drug classes in which more than 50 percent of initial prescriptions are for brand drugs: statins, SSRI/SNRIs, PPIs, antihistamines, and calcium channel blockers. We call these the "brand-dominated" classes.

In three of these classes, one major drug became newly available as a generic during the study period: simvastatin (statin, starting June 2006), sertraline (SSRI, June 2006),

and fexofenadine (antihistamine, September 2005). In the calcium channel blocker class, two generics entered the market towards the end of our study period (2007): amlodipine in March and amlodipine/benazepreil in May. In measuring the number of drugs prescribed, we treat brand and generic formulations of a multisource product as different drugs. However, the results are not sensitive to this choice. We use the IMS Advertising Database to measure the degree of drug promotion for each product. The advertising data are reported quarterly and contain expenditures on direct-to-consumer and direct-to-physician advertising for each drug, including medical journal advertisements, promotional visits to physicians and drug samples.

3.3.2 Classification of Providers

We restrict the sample to physicians with at least five initial prescriptions within a class from 2005-2007. We focus on initial prescriptions since refills may reflect the prescribing decisions of other providers. This yields a sample of 74,163 initial statin prescriptions, prescribed by 8,923 unique providers. The corresponding prescription / provider counts for the other brand-dominant classes are PPIs (52,978 / 6,621), SS/NRI (46,040 / 5,866), antihistamines (39,644 / 4,788), and calcium channel blockers (13,633 / 1,975). We categorize providers within each class by the number of distinct drugs prescribed as initial prescriptions over the sample period (2005-2007). For example, a doctor with two initial prescriptions of escitalopram, three initial prescription of sertraline, and one initial prescription of duloxetine is categorized as prescribing three drugs in the SS/NRI class. We examine use of the top-selling and most heavily promoted drugs in the class, as well as rates of generic drugs by prescriber type (categorized as 1, 2, 3, 4 or 5+ drugs prescribed as initial prescriptions). We also calculate the share of a physician's observed prescriptions that are in the relevant therapeutic category (e.g. cardiovascular drugs for statin prescriptions) as a proxy for their degree of specialization.

Given that new drugs may enter the market and additional clinical evidence may emerge over the 3-year study period, we also categorize physicians based on the number of distinct drugs prescribed each year. This reduces our sample substantially as two-thirds to three-quarters (depending on the class) of physicians in the 3-year sample do not have five initial prescriptions within a calendar year. To facilitate comparison with other studies of prescribing concentration, we also calculate the share of prescriptions for each physician's "favorite" drug.

3.3.3 Plan Characteristics

A physician's ability to prescribe in accordance with a patient's formulary is complicated by the fact that on average, physicians manage patients from more than 13 different health plans [19]. We capture the complexity of formulary designs facing each physician in two ways. First, we count the number of observed health plans represented by the physician's

patients. Second, we characterize the relevant variation in pharmacy benefit designs facing each physician based on the number of different ordering of copayments for the most prescribed brand drug, the second most prescribed brand drug and the top generic drug in the class.

3.4 Results

Table 1 shows the distribution of brand and generic prescribing within each of the ten classes. The number of drug products in each class ranges from 7 (PPIs) to 116 (opiates), while the number of active ingredients ranges from 6 to 37. Generic versions are available for a majority of the active ingredients in 7 of the ten classes, and in 4 classes, the majority of initial prescriptions are for generic products.

Most doctors do not prescribe brand or generic medications exclusively, with some notable exceptions. Nearly half of the physicians prescribing ACE inhibitors and NSAIDS and 90 percent of physicians prescribing opiates prescribe only generic drugs in the class. By contrast, less than one percent of physicians prescribe only generic statins or PPIs. As the share of generic prescribing in the class increases, the proportion of physicians prescribing only generics increases and the share prescribing only brands decreases. In the five classes where the generic share is closest to one-half (38 to 61 percent), between 80 and 89 percent of physicians prescribe both brand and generic medications as initial prescriptions.

The distribution of the number of drugs prescribed per physician is shown in Table 2. To put these numbers in context, we also report the number of drugs that account for 75 percent of initial prescriptions in the class and the market share of the top-selling drug. Only a small fraction of physicians prescribe a single drug in the class, ranging from less than one percent for SSRI/SNRIs to 15 percent for ACE inhibitors. In eight of the ten classes, the median physician prescribes 3 or 4 different drugs. This reflects broad prescribing given that the median number of initial prescriptions per physician in our sample ranges from 6 to 8 in the 10 classes. The case of SSRI/SNRI antidepressants is particularly striking: 45% of doctors prescribe five or more different drugs in the class. Of the 1,659 doctors for whom we observe 8 to 12 initial prescriptions, 72 percent prescribe five or more different drugs and less than 2 percent prescribe one or two drugs.

Table 3 shows the distribution of physician prescribing in the five brand-dominated classes. Physicians prescribing one or two drugs are more likely to prescribe the leading drug in the class, which in most cases, is the most heavily promoted drug. For example, among physicians prescribing just 1 statin, 80 percent prescribe the market leader and most heavily promoted drug. The generic share increases with number of initial drugs prescribed in three of the five classes, while PPIs and antihistamines exhibit a different pattern.

In the PPI class, which had only one generic drug (omeprazole) during 2005-2007, the generic share decreases monotonically with the number of drugs prescribed (as does the share of the top brand drug), indicating that narrow prescribers in this class were split between

high prescribers of the top (brand) drug and high prescribers of generic omeprazole. Perhaps due to the degree of similarity between these two products (esomeprazole, the top brand and generic omeprazole), doctors generally prescribe one drug or the other. For example, among the 1,229 physicians prescribing just two drugs in the class, only 23 percent prescribed both esomeprazole and omeprazole, while 46.5 percent prescribed the leading brand and another brand drug and 20 percent prescribed generic omeprazole and another brand drug. By contrast, the leading brand and generic antihistamines have different active ingredients and most doctors prescribe both. Overall, as doctors prescribe more broadly, they move away from the most prescribed drug in the class towards generics and/or less common brands.

Physicians treating patients with different comorbidities prescribe more broadly. This pattern occurs in all five classes and is nearly monotonic (Table 3). Further, physicians treating patients from a larger number of health plans (and formularies) are more likely to prescribe broadly. These results are robust to multivariate models that control for detailed patient and plan characteristics (results not shown; see Appendix A).

If broad prescribers are better able to match a patient to their optimal drug, we might observe better adherence to medications and less switching within class. We find that broader prescribing is associated with modestly better adherence in two of the five classes (Table 4). Patients prescribed PPIs and antihistamines by a doctor in the broadest category of prescribing are 7 to 8 percent more likely to continue use for six months than a patient treated by a doctor who prescribes most narrowly. However, we find no statistically significant differences for SS/NRIs and CCBs, and a small opposite effect (lower adherence) for statins. Similarly, we find little evidence to suggest that broader prescribing significantly affects switch rates or the average out-of-pocket cost per 30-day prescription.

3.5 Comment

There is a widespread perception that physicians prescribe a narrow range of drugs within a therapeutic class. This is often attributed to two primary factors. The first is clinical experience, wherein physicians gain knowledge of a particular drug through experience and then prescribe it broadly to their other patients. The second factor is pharmaceutical marketing. Prior work has established that detailing has a significant effect on prescribing behavior and brand loyalty, particularly among physicians with limited access to colleagues [2].

Despite these perceptions, we find surprisingly broad prescribing across ten prominent classes. While 40 to 60 percent of their prescriptions are for one drug, the median physician in our sample prescribes at least 3 different drugs for incident users in 8 of the 10 classes. These results are even more striking considering the small number of initial prescriptions per physician (median=8) and the dominance of brand drugs in five of the ten classes studied. Physicians whose patients are covered by a wider array of health plans and formularies prescribe more broadly, as do physicians who treat patients with varying comorbidities. This suggests that attempts to match specific drugs to a patient's health condition and formulary

design are important factors in deviating from the their favorite drug. While physicians who prescribe narrowly are more likely to prescribe highly advertised drugs, few doctors prescribe these drugs exclusively.

Our results suggest that physician prescribing habits are less entrenched than commonly perceived. Why we observe these patterns is unclear. Broad prescribing may simply reflect the increasing number of drugs in a class, many of which act in a similar way and share common side effect profiles. Broad prescribing may also reflect the influence of pharmaceutical marketing, but with less pernicious effects. Surveys of physicians reveal that detailing is an important source of information for many providers, and that drug samples provide greater flexibility in prescribing to low-income patients [20]. The widespread availability and use of drug samples may provide the clinical experience physicians depend on to assess the efficacy and benefits of new products.

An alternative explanation for the observed breadth of prescribing is the influence of manufacturers, pharmacy benefit managers (PBMs) and third-party payers. Through explicit campaigns that promote switching to "featured" products or financial incentives inherent in the formulary design, physicians and patients may be steered towards a wider array of products than in the past [21]. These incentives may interact, as prior research suggests that advertising affects demand only for drugs that have preferential status on the patient's formulary [22].

There are several possible reasons why prescribing of antidepressants, in particular, is so diffuse. First, we categorized SNRIs, NRIs and SSRIs into a single class. More than one-third of doctors in the sample prescribe drugs from all three categories, 61% prescribe both SSRIs and SNRIs and only 17 percent prescribe SSRIs only. This suggests that doctors view these sub-classes distinctly and include more than the dominant SSRIs in their prescribing patterns. Further, there are 22 different drugs in the class by product name, but only 8 active ingredients. If we recalculate the number of drugs prescribed based on distinct active ingredients, we find that 32.8% of the doctors (versus 45%) prescribe 5 or more drugs. However, the share of physicians prescribing 1 or 2 drugs rises only from 6% to 8% and the median doctor still prescribes 4 drugs in the class.

Our findings suggest that the vast majority of physicians are not wedded to a "favorite" drug, nor reluctant to try new therapies as more clinical information becomes available or new products enter the market. This is an important finding given the potential social costs of habitual prescribing, where physicians make prescription decisions based on incomplete information [23]. Nonetheless, the use of a few drugs may be associated with high quality prescribing in some therapeutic classes [5]; [14].

Our analysis has several limitations. First, pharmacy claims do not solely reflect the choice of physicians, but also the preferences of patients and the input of the pharmacist and health plan. The actual prescribing patterns of physicians is likely to be narrower than observed in our analysis if patient preferences and formulary incentives lead to therapeutic substitutions at the pharmacy. While recent evidence suggests that patients have an impact on prescribing decisions, physician preferences dominate [24]; [25]. Second, we only observe a

subset of each physician's patients, specifically those enrolled in the set of employer-sponsored plans covered by our dataset. Thus, we may understate how many different drugs each doctor prescribes to incident users. Third, we examine physician prescribing over a three-year period to increase the number of physicians and initial prescriptions in our sample. However, additional drugs may enter the market and new clinical information may emerge over this period that would cause physicians to change their choice of drugs. Analyzing prescribing patterns over a one-year period reduces the average number of drugs prescribed in a class, but the median physician still prescribes 3 drugs or more in 7 of the ten classes. Fourth, we lack detailed demographic information on physicians. However, we estimate their degree of specialization by measuring the fraction of a physician's observed prescriptions in the relevant therapeutic category. Finally, some of the patients classified as incident users in our sample already had experience with a drug in the class beyond our 1-year "clean window", which may inform the doctor's current choice of medication. To test the extent of this error, we examined patients with a two-year clean window prior to their "initial" prescription. Although this reduced our sample size by more than half, it did not substantively change our results.

While we observe broad prescribing in one dimension, we cannot separate the independent effects of the physician from that of the patient and the formulary. The use of electronic prescribing will allow future studies to examine differences in what is prescribed by the physician and what is dispensed at the pharmacy. More detailed data is needed to understand how prescribing practices vary by physician age, gender, specialty, and practice setting. Future work also should explore the appropriateness and clinical effects of broad versus narrow prescribing, which is likely to vary across therapeutic classes. We find that broader prescribing has small and inconsistent effects on several patient outcomes, but more work in this area is needed.

3.6 Tables

Table 3.1: Distribution of Brand and Generic Prescribing in 10 Therapeutic Classes, Initial Prescriptions Only

		Percent of Prescribers		
Therapeutic Class	Generic Prescribing Share	Doctors Prescribing ONLY Generics	Doctors Prescribing ONLY Brands	Doctors Prescribing Brands and Generics
ACE Inhibitors	86.3	53.8	0.7	45.5
SSRI/SNRI	44.6	3.0	8.4	88.6
Antihistamines	37.8	2.1	14.0	84.0
Beta Blockers	57.1	11.5	3.0	85.5
Calcium Channel Blockers	40.3	2.7	9.7	87.6
Antidiabetics	61.3	15.9	3.9	80.2
NSAID	83.9	39.1	0.9	60.0
Opiates	98.6	89.7	0.0	10.3
PPIs	20.9	0.9	34.8	64.3
Statins	23.8	0.6	27.6	71.9

Table 3.2: Breadth of Physician Prescribing in Brand-dominant and Generic-dominant Classes

Percent of Prescribers

	Primarily Brand Drug Classes					Primarily Generic Drug Classes				
	Statins	PPIs	Calcium Channel Blockers	Antihistamines	SSRI/SNRI	Beta Blockers	Antidiabetic	ACE Inhibitors	NSAID	Opiates
Doctors Prescribing 1 Drug	2.6	3.9	2.6	6.5	0.6	3.6	9.8	15.4	8.7	15.0
Doctors Prescribing 2 Drugs	14.3	18.6	13.5	33.7	5.4	17.3	23.6	38.4	19.6	36.0
Doctors Prescribing 3 Drugs	31.4	37.6	28.9	42.9	19.5	34.6	28.6	29.0	27.8	29.6
Doctors Prescribing 4 Drugs	28.8	27.8	28.8	16.5	30.3	27.3	22.4	12.5	23.0	13.6
Doctors Prescribing 5+ Drugs	22.9	12.1	26.3	0.5	44.2	17.2	15.6	4.6	20.9	5.9
N (unique prescribers)	8,923	6,621	1,975	4,788	5,866	3,974	1,531	4,008	13,674	35,180
Average share of prescriptions for "favorite" drug, 2005-2007	51.4	54.4	50	61.3	41.7	53.8	60	69	59.2	70
Average share of prescriptions for "favorite" drug, 2007	60.4	60	48.9	73.2	47.7	54.3	64.1	74.2	68	73.2
Generic Prescribing Share	23.8	20.9	40.3	37.8	44.6	57.0	61.3	86.3	83.8	98.6
Market Share of Leading Drug in 2007	36.1	30.5	35.8	50.2	20.0	23.4	51.9	64.1	28.0	55.4
Number of drugs accounting for 75% of initial prescriptions in 2005-2007	4	4	6	2	7	4	4	3	7	3
Number of drugs accounting for 75% of initial prescriptions in 2007	4	3	6	2	5	4	4	2	6	3

In each column, the cell containing the median prescriber is boxed.

We define therapeutic classes by the Redbook 2007 classification. Antidiabetic does not include insulin. Antihistamines exclude those used for acute symptoms such as nausea. Antihistamines and NSAIDs exclude products available over the counter.

Table 3.3: Distribution of Physician Prescribing, by Type of Drug and Patient Characteristics

	a. Type of Drug Prescribed			b. Patient Heterogeneity within Doctor	
Statins	Generic	Top Drug in Class	Direct to Physician Promotional Expenditures	Number of Plans	Combinations of Chronic Conditions
Doctors Prescribing 1 Drug	2.8	79.9	$159,955	3.59	4.07
Doctors Prescribing 2 Drugs	17.2	53.6	$121,118	3.53	4.26
Doctors Prescribing 3 Drugs	21.8	38.9	$101,349	3.77	4.55
Doctors Prescribing 4 Drugs	25.3	30.8	$88,774	4.13	5.06
Doctors Prescribing 5+ Drugs	27.3	25.5	$79,845	4.95	6.42
Total	23.8	34.5	$93,882	4.10	5.07
N	74,163	74,163	73,872	8,923	8,923
PPIs	Generic	Top Drug in Class	Direct to Physician Promotional Expenditures	Number of Plans	Combinations of Chronic Conditions
Doctors Prescribing 1 Drug	24.1	46.3	$67,463	3.36	2.60
Doctors Prescribing 2 Drugs	23.4	39.8	$66,810	3.48	2.62
Doctors Prescribing 3 Drugs	22.1	34.0	$65,853	3.61	2.77
Doctors Prescribing 4 Drugs	20.3	29.6	$65,222	4.12	2.95
Doctors Prescribing 5+ Drugs	17.2	27.8	$64,800	5.21	3.48
Total	20.9	32.7	$65,644	3.91	2.87
N	52,978	52,978	52,585	6,621	6,621
SS/NRIs	Generic	Top Drug in Class	Direct to Physician Promotional Expenditures	Number of Plans	Combinations of Chronic Conditions
Doctors Prescribing 1 Drug	26.1	41.9	$73,763	3.70	3.81
Doctors Prescribing 2 Drugs	36.8	37.5	$63,081	3.33	3.63
Doctors Prescribing 3 Drugs	39.6	29.0	$56,487	3.46	3.76
Doctors Prescribing 4 Drugs	43.7	22.5	$50,626	3.52	3.88
Doctors Prescribing 5+ Drugs	47.0	17.1	$46,189	4.18	4.97
Total	44.6	21.1	$49,587	3.79	4.33
N	46,040	46,040	45,092	5,866	5,866
Antihistamines	Generic	Top Drug in Class	Direct to Physician Promotional Expenditures- All	Number of Plans	Combinations of Chronic Conditions
Doctors Prescribing 1 Drug	29.8	63.5	$21,458	3.61	2.40
Doctors Prescribing 2 Drugs	43.2	42.5	$18,571	3.97	2.57
Doctors Prescribing 3 Drugs	37.6	37.0	$22,704	4.43	2.74
Doctors Prescribing 4 Drugs	33.5	33.1	$23,999	5.53	3.15
Doctors Prescribing 5+ Drugs	30.6	25.0	$19,418	5.14	3.14
Total	37.8	38.9	$21,747	4.41	2.73
N	39,644	39,644	39,627	4,788	4,788
CCBs	Generic	Top Drug in Class	Direct to Physician Promotional Expenditures- All	Number of Plans	Combinations of Chronic Conditions
Doctors Prescribing 1 Drug	19.8	60.1	$10,122	2.96	3.90
Doctors Prescribing 2 Drugs	26.0	56.6	$12,582	3.23	4.19
Doctors Prescribing 3 Drugs	35.9	41.7	$11,896	3.23	4.38
Doctors Prescribing 4 Drugs	43.0	31.8	$10,705	3.27	4.60
Doctors Prescribing 5+ Drugs	48.2	25.5	$9,695	3.56	5.47
Total	40.3	35.8	$10,894	3.32	4.69
N	13,633	13,633	13,337	1,975	1,975

Table 3.4: Adherence, Out-of-Pocket Costs and Switching Rates, By Physician Prescribing

a. Predicted MPR within the class within six months of the initial prescription

Degree of narrow (concentrated) prescribing.	Statins	PPIs	SSRI/SNRI	Antihistamines	Calcium Channel Blockers
High	0.77	0.58***	0.66	0.35***	0.77
Medium	0.76	0.60	0.66	0.37	0.76
Low	0.75*	0.61	0.66	0.37	0.76
Total Average MPR	0.76	0.60	0.66	0.36	0.77
N	60,366	42,057	36,039	32,191	10,844

Notes: Dependent variable is calculated as total daily doses purchased within 180 days of initial prescription, divided by 180. Categories of narrowness are tertiles of the percent deviation of each doctor's *number of drugs prescribed* from *predicted number of drugs prescribed.*

Degree of narrow (concentrated) prescribing.

b. Predicted Annual Copay (Patient Cost of One Year's Supply) within the class

	Statins	PPIs	SSRI/SNRI	Antihistamines	Calcium Channel Blockers
High	$144.03***	$208.51	$146.94	$177.68*	$123.97**
Medium	$139.77	$208.51	$145.47	$170.72	$116.75
Low	$139.77	$214.86**	$141.17*	$179.467**	$108.85***
Mean Avg Annual Copay	$141.17	$210.61	$144.03	$175.91	$116.75
N	41,566	26,508	31,163	18,767	8,715

Notes: Dependent variable is calculated as the year-equivalent total copay amount, based on the average copay payment per daily dose in the six months following the initial prescription. To capture plan formulary characteristics, we control for the mean brand copay in the class for each patient's plan, as well as the mean copay difference between brand and generic drugs. We exclude plans in which these values could not be determined (see Appendix).

Degree of narrow (concentrated) prescribing.

c. Predicted Switching within the class during six months after the initial prescription

	Statins	PPIs	SSRI/SNRI	Antihistamines	Calcium Channel Blockers
High	0.10	0.19	0.20	0.15	0.19*
Medium	0.10	0.18	0.20	0.15	0.21
Low	0.12***	0.18	0.22**	0.14	0.20
Total Probability of Switching	0.11	0.18	0.21	0.15	0.20
N	41,621	19,930	20,436	6,585	7,594

Notes: Dependent variable is binary, equal to 1 if the patient is observed to fill a prescription for another drug in the class, written by the same prescriber as the initial prescription, within six months following the initial prescription. For this analysis, we exclude patients who discontinue therapy in the class within the first six months, and we control for the drug initially prescribed.

Table 3.5: Poisson regressions of narrowness of prescribing on characteristics of doctors and patients

	(1)	(2)	(3)	(4)	(5)
	Statin	PPI	SS/NRI	Antihistamines	Calcium Channel Blockers
Y = Number of drugs prescribed as initial prescriptions					
Combinations of chronic conditions	0.144***	0.179***	0.274***	0.0317	0.172*
	(0.0197)	(0.0543)	(0.0383)	(0.0471)	(0.0705)
Combinations of chronic conditions (squared)	-0.00691***	-0.0191*	-0.0225***	0.00174	-0.0114
	(0.00134)	(0.00799)	(0.00340)	(0.00679)	(0.00596)
Different copay orderings	-0.0106	0.0442*	0.0776***	0.123***	0.0901*
	(0.0170)	(0.0172)	(0.0217)	(0.0171)	(0.0399)
Number of plans	0.108***	0.0707***	0.0814**	0.00421	0.118
	(0.0177)	(0.0168)	(0.0295)	(0.0138)	(0.0768)
Number of plans (squared)	-0.00670***	-0.00315**	-0.00808**	0.0000271	-0.0198*
	(0.00136)	(0.00109)	(0.00252)	(0.000762)	(0.00907)
Initial prescriptions observed	0.122***	0.119***	0.265***	0.0231**	0.427***
	(0.00969)	(0.0148)	(0.0216)	(0.00716)	(0.0405)
Initial prescriptions (squared)	-0.00167***	-0.00168***	-0.00226***	-0.000399**	-0.0105***
	(0.000221)	(0.000411)	(0.000476)	(0.000140)	(0.00148)
Patients with prior use in class	0.0936***	0.0917***	0.131***	0.0822***	0.0134
	(0.0138)	(0.0177)	(0.0216)	(0.0128)	(0.0431)
Patients with prior use (squared)	-0.00166	-0.00701**	-0.00914**	-0.00216	0.00681
	(0.00145)	(0.00234)	(0.00281)	(0.00117)	(0.00674)
Half years with a prescription observed	0.159***	0.0793***	0.155***	0.137***	0.102**
	(0.0152)	(0.0166)	(0.0244)	(0.0148)	(0.0346)
Observations	8923	6621	5866	4788	1975
Log Likelihood	-15357.9	-10940.8	-10619.1	-7370.9	-3474.9
Log Likelihood, Constant only	-15906.1	-11174.1	-11293.6	-7465.4	-3589.9

Bibliography

[1] Murray Aitken, Ernst R. Berndt, and David M. Cutler. Prescription drug spending trends in the united states: Looking beyond the turning point. *Health Affairs*, 28(1):w151–w160, 2009.

[2] G. Caleb Alexander, Lawrence P. Casalino, and David O. Meltzer. Patient-Physician Communication About Out-of-Pocket Costs. *JAMA*, 290(7):953–958, 2003.

[3] G. Michael Allan, Joel Lexchin, and Natasha Wiebe. Physician awareness of drug cost: A systematic review. *PLoS Med*, 4(9):e283, 09 2007.

[4] Olivier Armantier and Soiliou Namoro. Prescription drug advertising and patient compliance: A physician agency approach. *Advances in Economic Analysis & Policy*, 6, 2006.

[5] J.S. Berkeley and I.M. Richardson. Drug usage in general practice. An analysis of the drugs prescribed by a sample of the doctors participating in the 1969-70 North-east Scotland work-load study. *J R Coll Gen Pract*, 23(128), 1973.

[6] Ernst R. Berndt and Murray L. Aitken. Brand loyalty, generic entry and price competition in pharmaceuticals in the quarter century after the 1984 waxman-hatch legislation. Working Paper 16431, National Bureau of Economic Research, October 2010.

[7] Jayanta Bhattacharya and William Vogt. A simple model of pharmaceutical price dynamics. *Journal of Law & Economics*, 46(2):599–626, 2003.

[8] J. Boltri, E. Gordon, and R. Vogel. Effect of antihypertensive samples on physician prescribing patterns. *Family Medicine*, 34, 2002.

[9] A. Buusman, J. Kragstrup, and M. Andersen. General practitioners choose within a narrow range of drugs when initiating new treatments: a cohort study of cardiovascular drug formularies. . *European Journal of Clinical Pharmacology*, 61(9), 2005.

[10] Randall D. Cebul, James Rebitzer, Lowell J. Taylor, and Mark Votruba. Unhealthy insurance markets: Search frictions and the cost and quality of health insurance. *American Economic Review*, forthcoming.

[11] Frances M. Chevarley. Intellectual Property and Marketing. *Statistical Brief*, (288), 4 2010.

[12] L. Chew, T. O'Young, T. Hazlet, K. Bradley, C. Maynard, and D. Lessier. A physician survey of the effect of drug sample availability on physicians' behavior. *Journal of General Internal Medicine*, 15, 2000.

[13] et al. Chinburapa, V. Physician prescribing decisions: the effects of situational involvement and task complexity on information acquisition and decision making. . *Soc Sci Med*, 36(11), 1993.

[14] Andrea Coscelli. The importance of doctors' and patients' preferences in the prescription decision. *Journal of Industrial Economics*, 48(3):349–69, September 2000.

[15] Andrea Coscelli and Matthew Shum. An empirical model of learning and patient spillovers in new drug entry. *Journal of Econometrics*, 122(2):213–246, October 2004.

[16] Gregory S. Crawford and Matthew Shum. Uncertainty and learning in pharmaceutical demand. *Econometrica*, 73(4):1137–1173, 07 2005.

[17] Paul Ellickson, Scott Stern, and Manuel Trajtenberg. Patient welfare and patient compliance – an empirical framework for measuring the benefits from pharmaceutical innovation. In *Medical Care Output and Productivity*, NBER Chapters, pages 539–564. National Bureau of Economic Research, Inc, 2001.

[18] William Encinosa, Didem Bernard, and Avi Dor. Does prescription drug adherence reduce hospitalizations and costs? NBER Working Papers 15691, National Bureau of Economic Research, Inc, January 2010.

[19] N Britten et al. Continued prescribing of inappropriate drugs in general practice. . *J Clin Pharm Ther*, 20(4), 1995.

[20] Kaiser Family Foundation. Employer health benefits: 2007 summary of findings. Technical report, The Kaiser Family Foundation and Health Research & Educational Trust, October 2007.

[21] Kaiser Family Foundation. Employer health benefits: 2010 summary of findings. Technical report, The Kaiser Family Foundation and Health Research & Educational Trust, October 2010.

[22] M.A. Gagnon and J. Lexchin. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLoS Medicine*, 5(1), 2008.

[23] Dana P. Goldman and Geoffrey F. Joyce. Medicare Part D: A Successful Start With Room for Improvement. *JAMA*, 299(16):1954–1955, 2008.

[24] Dana P. Goldman, Geoffrey F. Joyce, Jose J. Escarce, Jennifer E. Pace, Matthew D. Solomon, Marianne Laouri, Pamela B. Landsman, and Steven M. Teutsch. Pharmacy Benefits and the Use of Drugs by the Chronically Ill. *JAMA*, 291(19):2344–2350, 2004.

[25] Dana P. Goldman, Geoffrey F. Joyce, and Yuhui Zheng. Prescription Drug Cost Sharing: Associations With Medication and Medical Utilization and Spending and Health. *JAMA*, 298(1):61–69, 2007.

[26] Füsun F. Gönül, Franklin Carter, Elina Petrova, and Kannan Srinivasa. Physicians' prescribing responses to a restricted formulary: the impact of medicaid preferred drug lists in illinois and louisiana. *American Journal of Managed Care*, 2005.

[27] Jorge Gonzalez, Catarina Sismeiro, Shantanu Dutta, and Philip Stern. Can branded drugs benefit from generic entry? the role of detailing and price in switching to non-bioequivalent molecules. *International Journal of Research in Marketing*, 25(4):247 – 260, 2008.

[28] Scott Grundy, James Cleeman, C. Noel Bairey Merz, H. Bryan Jr. Brewer, Luther Clark, Donald Hunninghake, Richard C. Pasternak, Sidney C. Jr Smith, and Neil Stone. Implications of recent clinical trials for the national cholesterol education program adult treatment panel iii guidelines. *Circulation*. For the Coordinating Committee of the National Cholesterol Education Program, Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association.

[29] Elizabeth Hargrave, Jack Hoadley, Laura Summer, and Katie Merrell. Medicare part d formularies, 2006-2010: A chartbook. Technical report, MedPac, October 2010.

[30] Barbara Henderson. IMS Study: U.S. Physicians Responsive to Patient Requests for Brand-Name Drugs. *Press Release*, 2002.

[31] S. Hensley and B. Martinez. To sell their drugs, companies increasingly rely on doctors. . *Wall Street Journal*, 2005.

[32] John Hsu, Vicki Fung, Mary Price, Jie Huang, Richard Brand, Rita Hui, Bruce Fireman, and Joseph P. Newhouse. Medicare Beneficiaries' Knowledge of Part D Prescription Drug Program Benefits and Responses to Drug Costs. *JAMA*, 299(16):1929–1936, 2008.

[33] A. Jena, J. Calfee, E. Manslee, and T. Philipson. 'Me-Too' Innovation in Pharmaceutical Markets. *Forum for Health Economics & Policy*, 12, 2009.

[34] Geoffrey F. Joyce, Jose J. Escarce, Matthew D. Solomon, and Dana P. Goldman. Employer Drug Benefit Plans and Spending on Prescription Drugs. *JAMA*, 288(14):1733–1739, 2002.

[35] Sachin Kamal-Bahl and Becky Briesacher. How do incentive-based formularies influence drug selection and spending for hypertension? *Health Affairs*, 23(1), 2004.

[36] S Khan, R Sylvester, D Scott, and B. Pitts. Physicians' opinions about responsibility for patient out-of-pocket costs and formulary prescribing in two midwestern states. *Journal of Managed Care Pharmacy*, 14(8):780–789, 2008.

[37] J.D. Kleinke. The Price Of Progress: Prescription Drugs In The Health Care Market. *Health Aff*, 20(5):43–60, 2001.

[38] Darius Lakdawalla, Tomas J. Philipson, and Y. Richard Wang. Intellectual Property and Marketing. *Reg-Markets Center Working Paper No. 07-20*, 2007.

[39] John C. LaRosa, Jiang He, and Suma Vupputuri. Effect of Statins on Risk of Coronary Disease: A Meta-analysis of Randomized Controlled Trials. *JAMA*, 282(24):2340–2346, 1999.

[40] Frank R. Lichtenberg and Tomas J. Philipson. The dual effects of intellectual property regulations: Within- and between- patent competition in the us pharmaceuticals industry. Working Paper 9303, National Bureau of Economic Research, November 2002.

[41] P. Manchanda and E. Honka. The effects and role of direct-to-physician marketing in the pharmaceutical industry: an integrative review. . *Yale Journal of Health Policy Law and Ethics*, 5(2), 2005.

[42] H. McGavock, K. Wilson-Davis, and J.P. Connolly. Repeat prescribing management–a cause for concern? *British Journal of General Practice*, 49(442), 1999.

[43] Jeppe N. Rasmussen, Alice Chong, and David A. Alter. Relationship Between Adherence to Evidence-Based Pharmacotherapy and Long-term Mortality After Acute Myocardial Infarction. *JAMA*, 297(2):177–186, 2007.

[44] William Shrank, Sarah Fox, Adele Kirk, Susan Ettner, Clairessa Cantrell, Peter Glassman, and Stephen Asch. The effect of pharmacy benefit design on patient-physician communication about costs. *Journal of General Internal Medicine*, 21(4):334–339, 2006.

[45] William Shrank, Henry Young, Susan Ettner, Peter Glassman, Stephen Asch, and Richard Kravitz. Do the incentives in 3-tier pharmaceutical benefit plans operate as intended? results from a physician leadership survey. *American Journal of Managed Care*, 11:16–22, 2005.

[46] Ross J. Jr Simpson. Challenges for Improving Medication Adherence. *JAMA*, 2006.

[47] Robyn Tamblyn, Rejean Laprise, James A. Hanley, Michael Abrahamowicz, Susan Scott, Nancy Mayo, Jerry Hurley, Roland Grad, Eric Latimer, Robert Perreault, Peter McLeod, Allen Huang, Pierre Larochelle, and Louise Mallet. Adverse Events Associated With Prescription Drug Cost-Sharing Among Poor and Elderly Persons. *JAMA*, 285(4):421–429, 2001.

[48] P. Thiebaud, B. V. Patel, and M. B. Nichol. The demand for statin: the effect of copay on utilization and compliance. *Health Economics*, 17:8397, 2008.

[49] Sriram Venkataraman and Stefan Stremersch. The debate on influencing doctors' decisions: Are drug characteristics the missing link? *ERIM Report Series Reference No. ERS-2007-056-MKT.*, 2007, 09.

[50] S Virabhak and JA Shinogle. Physicians' prescribing responses to a restricted formulary: the impact of medicaid preferred drug lists in illinois and louisiana. *American Journal of Managed Care*, 2005.

Appendix A

Additional material referenced in Chapter 1

Here, I discuss the assumptions presented in Section 1.3.1, which are based on stylized facts.

1. Patients who fail to fill their second prescription less than 60 days late have temporarily discontinued statin treatment.

   Figure A.2 plots the cumulative distribution function of the "lateness" of the second fill (the solid line). If patients take their statin daily, starting the day of their initial fill, they will run out of pills on the day marked zero on this figure. The upside-down L-shape reflects the fact that patients either refill less than 60 days late (74 % of starters), or they don't return for a very long time. I use this 60-day cut-off as a binary outcome of "continuing." Note that either refilling the same prescription or one for a different statin is counted as "continuing." Two-thirds of those who fail to refill by the 60 day cut-off do, in fact, return over the next 2.5 years, indicating that they are likely to be patients who *should* be taking statins. The remaining third (8% of starters) have no second fill during this time.

   [Figure A.2 about here]

2. Switching is highly uncommon among continuing patients.

   The dotted line in the figure above is the CDF of second fills of the same drug molecule (whereas the solid line includes drug switches). Prior to the 60 day cut-off, the difference between the lines is very small, indicating that among these second fills, the vast majority (97%) are for the same drug initially prescribed. Starting on a different drug molecule *after* having temporarily discontinued is much more common, close to fifty percent. Given that continuing patients almost exclusively fill the same drug, in the next section I model the patient's continuation decision as depending only on the therapeutic effect and copay of the drug initially prescribed.

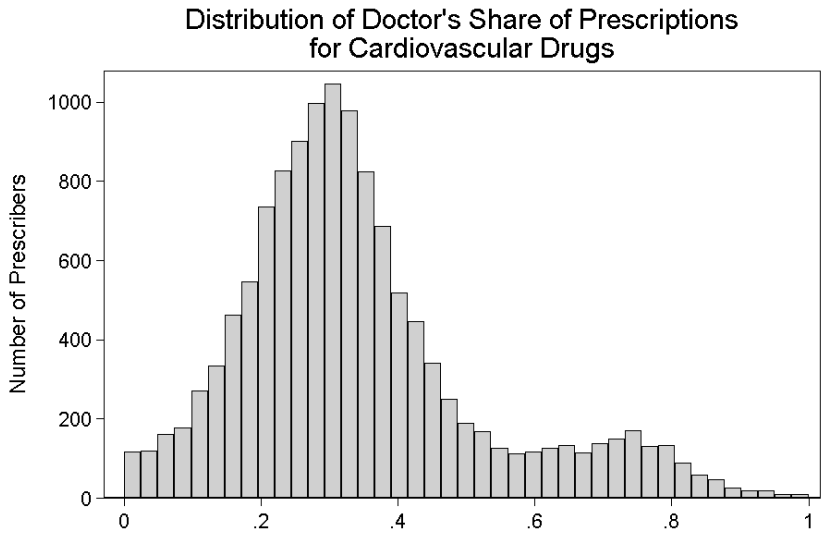

Figure A.1: *Distribution of physician's share of prescriptions for cardiovascular drugs.* I classify prescribers with shares above 0.60 as *specialists*.

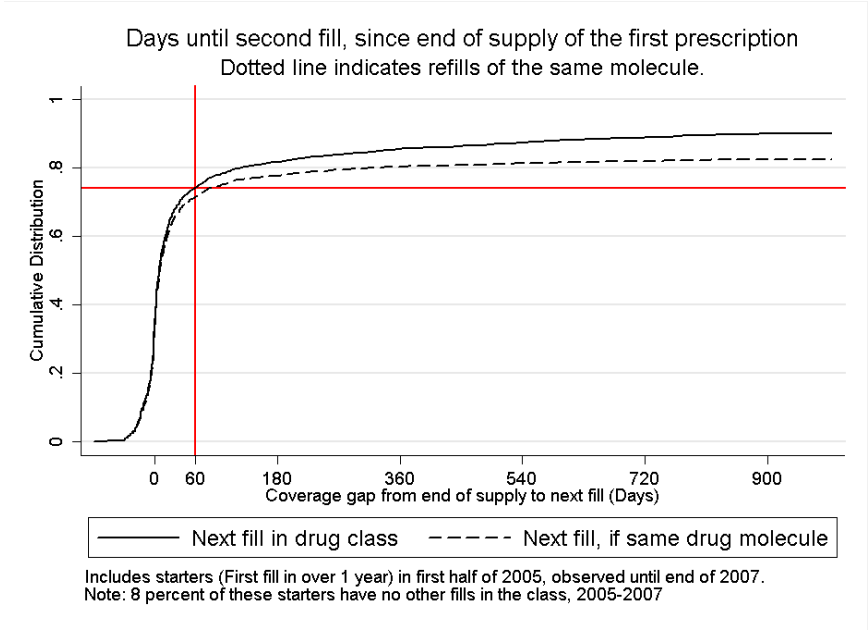

Figure A.2: *Days until second fill.*

3. Continuing after the first prescription, as I have defined it, is a strong predictor of adherence over the next year.

   I refer to the common measure of adherence as having a supply of medication covering at least 80% of the days in a certain period. Among patients who refill or switch within 60 days, 62.9% achieve adherence over one year. Among those who discontinue after the first prescription, only 4.7% are able to achieve the same. Thus, although continuing after the first prescription is not sufficient to guarantee full adherence, it is an easily observable and measurable intermediate measure that makes eventual adherence far more likely. For this reason, I use this measure of continuation as the outcome of interest that depends on initial copay (and drug) and may influence the prescribing decision.

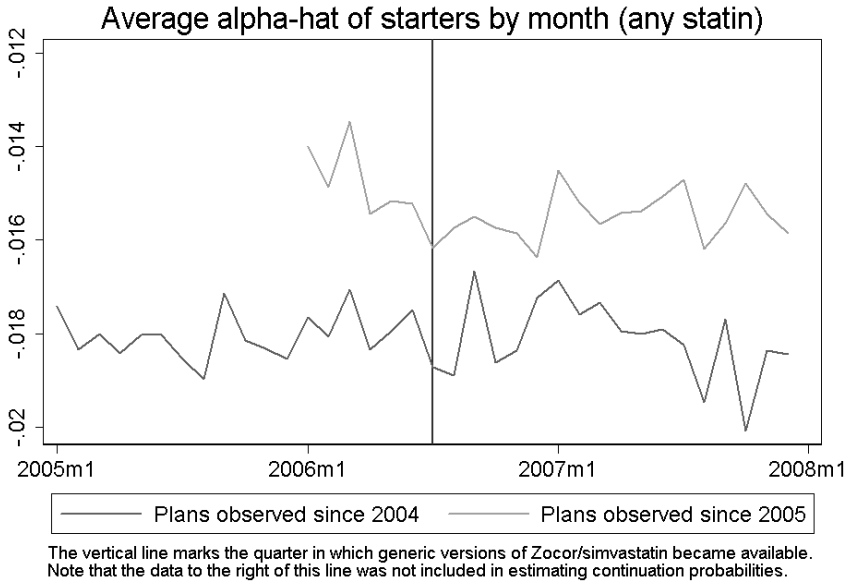

Figure A.3: *Trend in $\widehat{\alpha}_c$ over sample period.*

4. Patients do not selectively fill their initial prescriptions.

   I cannot observe patients who receive a prescription from their doctor yet do not purchase any fills of the drug. However, if patients were exhibiting "purchase noncompliance" in a way that reflected the price-sensitivity of their (subsequent) continuation decision, we would expect to see more price-sensitive patients filling first prescriptions in the period after Zocor's patent expiration. (Because, on average, patients are receiving prescriptions associated with lower copays.) I can assess this possibility by examining average values of estimated α_i, based on the observable characteristics of patients, such as income and health status. As Figure A.3 shows, there is no evidence that patients starting after Zocor's patent expiration are more price-sensitive. Thus, there is no evidence that purchase noncompliance is correlated with α_i.

Table A.1: Copay effects on Continuation Decision (Full period, 2005-2007)

	(1)	(2)	(3)	(4)
Copay	-0.030***	-0.045***	-0.044***	-0.047***
	(0.003)	(0.005)	(0.004)	(0.005)
Zocor*Post-entry	-0.29**	-0.28*	-0.25*	-0.24*
	(0.09)	(0.1)	(0.1)	(0.1)
Interacted with:				
High salary		0.014***	0.014***	0.022***
		(0.003)	(0.003)	(0.006)
Diagnosed condition		0.0016	0.0061**	0.0096***
		(0.003)	(0.002)	(0.002)
Recent heart attack		-0.0079*	-0.0054	-0.0046
		(0.004)	(0.004)	(0.005)
Recent stroke		0.014	0.012	0.016***
		(0.007)	(0.007)	(0.005)
Non-retired		0.0099*	0.0079	0.0090
		(0.005)	(0.004)	(0.006)
Prescribed by specialist		0.011**	0.011**	0.020***
		(0.004)	(0.004)	(0.006)
Observations	27947	27947	27947	27947
Patient characteristics	Yes	Yes	Yes	Yes
Molecule f.e.	Yes	Yes	Yes	Yes
Type f.e.			Yes	Yes

Note: Average marginal effect of a $10 copay increase on the probability of *Continue past first fill*. *Continue past first fill* equals 0 if the patient has a gap of 60 days or more following the last day of coverage of the first prescription fill, and 1 if the patient fills a prescription for *any* drug in the class during that period. *High salary* is above $50,000. Patient characteristics include dummies for each related chronic illness, *Non-retired*, and *Prescription from a specialist*. Recent heart attack is in the last or current year. Stroke is based on current year diagnosis code. *Type* denotes unique groupings of *High cholesterol*, *3+ Comorbid conditions*, *High salary*, *Above age 60*, and *Male*. All models are estimated in the period prior to Zocor patent expiration. Standard errors are clustered by plan. Model (4) includes three-way interaction terms such as High Salary X Diagnosed X copay, but these are not shown to conserve space.

Table A.2: Descriptive statistics: Initial Beta Blocker Fills, 2005-2007

	Total	Generic Drug	Brand Drug
Demographics			
Salary above $50,000	0.39	0.38	0.39
Non-retired (%)	0.34	0.35	0.31
High salary (retiree)	0.25	0.24	0.27
High salary (employed)	0.65	0.64	0.67
Age	64	64	65
Male (%)	0.54	0.53	0.55
Health conditions			
Hypertension	0.43	0.41	0.44
Cardiac disease	0.29	0.26	0.32
Recent heart attack	0.19	0.18	0.20
Congestive heart failure	0.07	0.04	0.09
Prescription and outcomes			
Specialist	0.26	0.19	0.31
Copay	$11.64	$5.56	$20.47
Timely refill or switch	0.79	0.76	0.82
Adherence over 1 year	0.56	0.51	0.60
N	19,254 (100%)	8,940 (46.4%)	10,314 (53.6%)

Appendix B

Additional material referenced in Chapter 2

The following figures show the prevalent products and evolution of prescribing rates from 2004-2007 in each of the four drug classes.

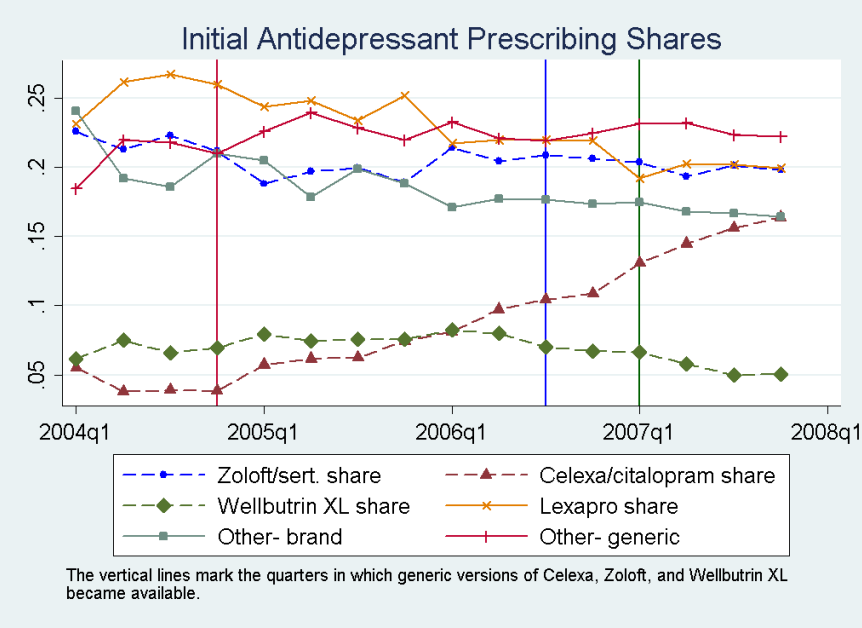

Figure B.1: *Initial prescriptions in the Antidepressant class, 2004-2007*

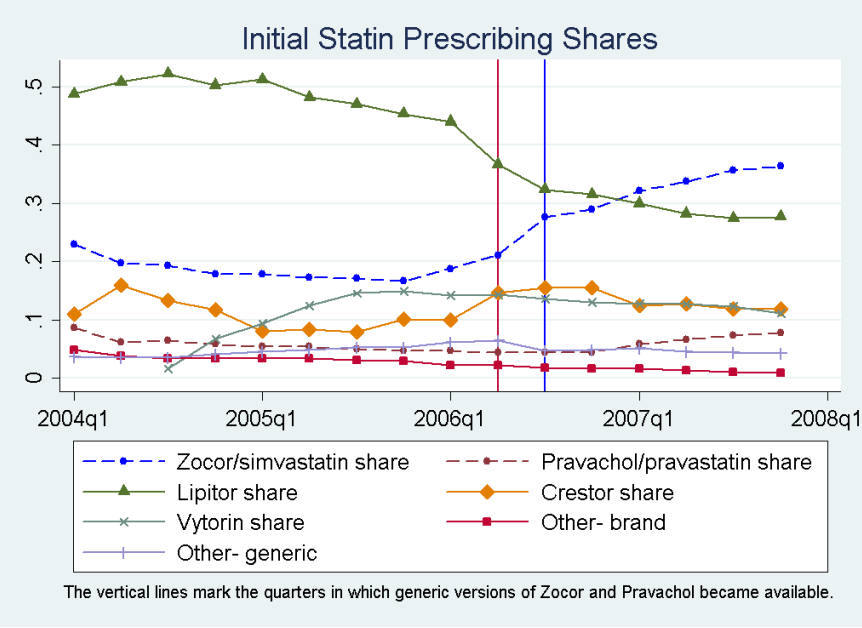

Figure B.2: *Initial prescriptions in the Statin class, 2004-2007*

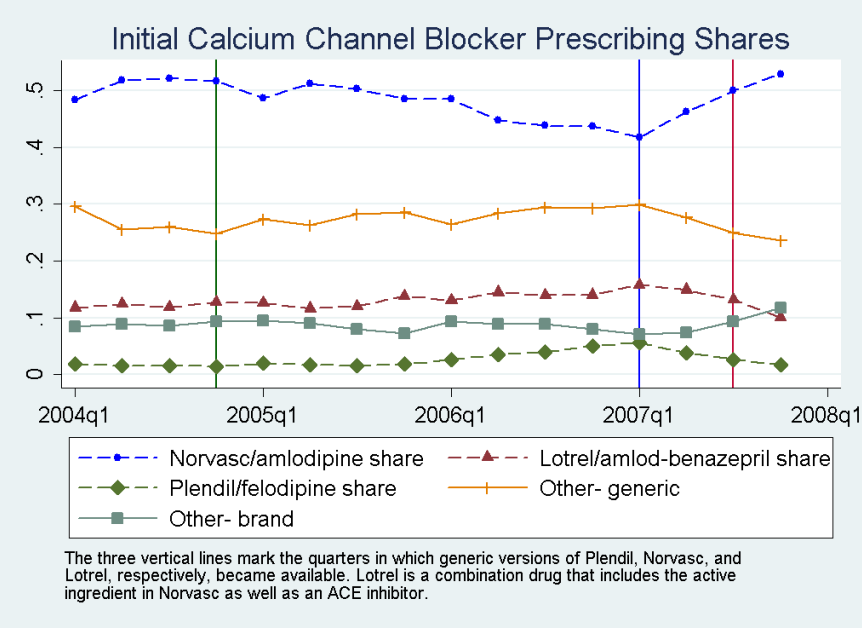

Figure B.3: *Initial prescriptions for Calcium Channel Blockers, 2004-2007*

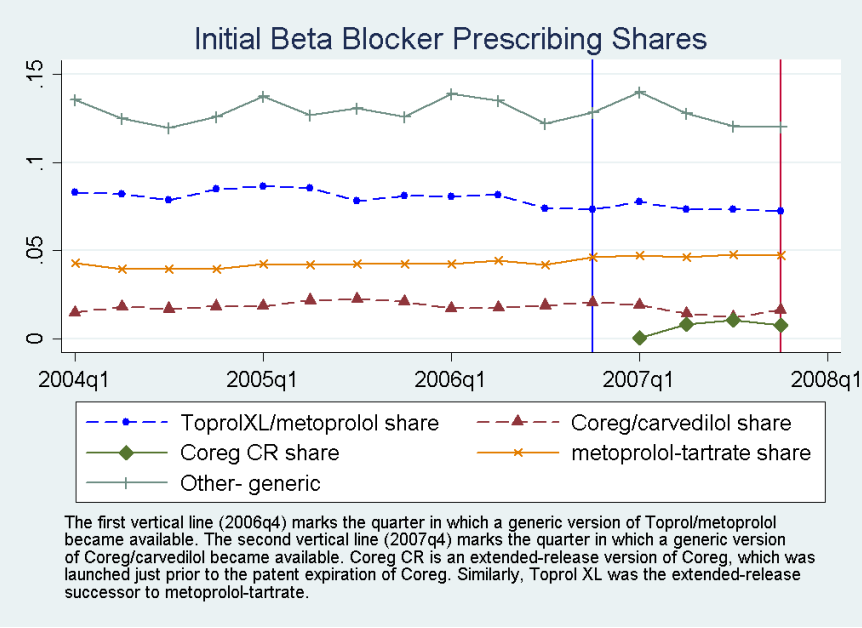

Figure B.4: *Initial prescriptions for Beta Blockers, 2004-2007*

Appendix C

Additional material referenced in Chapter 3

Table C.1: Narrow Prescribing Effects on Adherence

	(1)	(2)	(3)	(4)	(5)
Y = MPR over 6 month period					
	Statin	PPI	SS/NRI	Antihistamine	Calcium channel blocker
Degree of Narrow Prescribing, relative to predicted value					
High	0.006	-0.024***	-0.005	-0.0180***	0.016
	(0.004)	(0.005)	(0.005)	(0.005)	(0.009)
Low	-0.008*	0.006	-0.006	0.001	0.005
	(0.004)	(0.005)	(0.005)	(0.005)	(0.008)
Age	0.017***	0.014***	0.006***	0.005***	0.019***
	(0.001)	(0.001)	(0.0006)	(0.0006)	(0.002)
Age, sq.	-0.0001**	-0.00008***	-0.00004***	-0.00003***	-0.0001***
	(0.00001)	(0.00001)	(0.00001)	(0.00001)	(0.0000)
Male	0.027***	0.019***	-0.006	-0.008*	0.03***
	(0.003)	(0.003)	(0.004)	(0.003)	(0.006)
Median HHI	0.008***	-0.008***	0.008**	0.012***	-0.005
	(0.002)	(0.002)	(0.003)	(0.002)	(0.005)
Salary above $50,000	0.031***	0.057***	0.05***	0.025***	0.025*
	(0.004)	(0.006)	(0.006)	(0.0048)	(0.012)
Missing salary	0.030***	0.059***	0.046***	0.031***	0.012
	(0.003)	(0.004)	(0.005)	(0.005)	(0.007)
Proxy for specialist					
Category share	0.16**	0.05	0.04	-0.09*	1.03***
	(0.05)	(0.04)	(0.05)	(0.05)	(0.19)
Category share, sq.	-0.09	0.05	0.003	0.32***	-0.93***
	(0.052)	(0.051)	(0.047)	(0.054)	(0.17)
Previous use	-0.056***	0.016***	0.013**	0.056***	-0.028***
	(0.003)	(0.004)	(0.004)	(0.004)	(0.008)
Constant	0.0382	0.0744***	0.374***	0.120***	-0.161*
	(0.0280)	(0.0215)	(0.0212)	(0.0185)	(0.0629)
N	60366	42057	36039	32191	10844

Marginal effects; Standard errors in parentheses

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

Table C.2: Narrow Prescribing Effects on Patient Costs

	(1)	(2)	(3)	(4)	(5)
Y = Log Annual OOP					
	Statin	PPI	SS/NRI	Antihistamine	Calcium channel blocker
Degree of Narrow Prescribing, relative to predicted value					
High	0.0309***	0.000586	0.0142	0.0419*	0.0600**
	(0.00862)	(0.0134)	(0.0134)	(0.0184)	(0.0185)
Low	0.00133	0.0345**	-0.0317*	0.0460**	-0.0654***
	(0.00897)	(0.0117)	(0.0138)	(0.0160)	(0.0165)
Mean brand copay (plan)	0.0463***	0.0182***	0.0538***	0.0397***	0.0368***
	(0.000568)	(0.00100)	(0.00212)	(0.000936)	(0.00173)
Brand-generic copay difference (plan)	-0.0113***	0.0144***	-0.0320***	-0.0188***	-0.00279
	(0.000657)	(0.00144)	(0.00244)	(0.00118)	(0.00228)
Constant	4.093***	4.436***	4.252***	4.485***	4.143***
	(0.00910)	(0.0111)	(0.0197)	(0.0168)	(0.0179)
N	41566	26508	31163	18767	8715

Marginal effects; Standard errors in parentheses

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

Table C.3: Narrow Prescribing Effects on Switching Rates

	(1)	(2)	(3)	(4)	(5)
$Y = 1$ if patient tried another drug within the class during the first six months					
	Statin	PPI	SS/NRI	Antihistamine	Calcium channel blocker
Degree of Narrow Prescribing, relative to predicted value					
High	-0.001	0.007	-0.004	-0.007	-0.025*
	(0.003)	(0.007)	(0.007)	(0.010)	(0.010)
Low	0.014***	-0.004	0.020**	-0.015	-0.012
	(0.003)	(0.006)	(0.007)	(0.008)	(0.012)
Age	-0.000	-0.002	-0.001	-0.004**	-0.001
	(0.001)	(0.001)	(0.001)	(0.001)	(0.003)
Age, sq.	-0.00000	0.0000	-0.00000	0.00004**	0.00001
	(0.00001)	(0.00001)	(0.00001)	(0.00000)	(0.00000)
Male	-0.004	-0.03***	0.01	-0.01	0.01
	(0.003)	(0.01)	(0.01)	(0.01)	(0.01)
Median HHI, $10,000s	0.003*	0.005	-0.002	-0.009*	0.000
	(0.002)	(0.003)	(0.004)	(0.004)	(0.01)
Salary above $50,000	-0.006	-0.031***	-0.001	0.005	0.024
	(0.004)	(0.008)	(0.009)	(0.011)	(0.019)
Missing salary	-0.013***	-0.05***	-0.023***	-0.01	-0.012
	(0.003)	(0.006)	(0.007)	(0.010)	(0.010)
Proxy for specialist					
Category share	-0.04	0.14**	0.17*	0.12	-0.28
	(0.05)	(0.05)	(0.07)	(0.08)	(0.19)
Category share, sq.	0.09*	-0.18**	-0.08	-0.13	0.27
	(0.05)	(0.07)	(0.07)	(0.08)	(0.19)
Previous use	0.005	-0.013*	0.015*	0.017*	0.018
	(0.003)	(0.006)	(0.007)	(0.009)	(0.013)
N	41,621	19,930	20,436	6,585	7,594

Marginal effects; Standard errors in parentheses

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