Pharmaceuticals, Incremental Innovation and Market Exclusivity

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JOB MARKET PAPER

May 12, 2013

Abstract

This paper assesses the welfare gains from incremental innovation in pharmaceuticals. Such innovation can yield consumer gains through improved quality, but the additional market exclusivity granted to innovators may also delay generic entry, a practice referred to as "evergreening", and reduce consumer surplus. Quantifying this tradeo is vital in determining the optimal patent policy and regulatory treatment of incremental innovation. To shed light on this problem, I focus on incremental innovations in selective serotonin reuptake inhibitor (SSRI) anti-depressant drugs, including the pediatric use of existing drugs, which has been granted a six-month exclusivity extension over existing patents, and two new formulations of existing branded drugs (Lexapro and Paxil CR), which have been granted new patents. I estimate the patients' demands for antidepressants with a random coecient logit model, based on individual-level prescription drug data. I then recover the marginal cost for the branded and generic firms based on the Bertrand Nash model. Before calculating the welfare change from status quo to counterfactual scenarios, I estimate counterfactual equilibrium prices from firms' profit maximizing models, given the simulated demands over counterfactual alternative choice sets (for example, incremental innovation products might be removed, or the generic entry might occur one year earlier due to the withdrawal of market exclusivity). Consumer surplus change is measured using the compensating variation between two scenarios. By comparing scenarios of either withdrawing or allowing market exclusivity for incremental innovations with scenarios of withdrawing or retaining incremental innovations, I found

that the consumer benefits from incremental innovation are overwhelmed by the consumer surplus loss due to market exclusivity when considering a single incremental innovation, whereas the consumer benefits from innovation outweigh the consumer losses from exclusivity when considering the counterfactual of withdrawal of all incremental innovations and market exclusivities. This result suggests that innovation benefits are primarily driven not by the quality improvements of products but by the competition e□ect of the introduction of several incremental innovation products in the market.

Keywords: pharmaceuticals, incremental innovation, market exclusivity, patents.
JEL Codes: I18, K11, L65, L10.

1 Introduction

"Incremental Innovations are not small achievements. Heat stable version of anti-retroviral drugs may not be critically important to HIV patients in large cities where there is easy access to electricity and refrigeration, but they are surely important to people in rural areas."

Greg Kalbaugh, Director of US-India Business Council[1]

"Over the next few years, a number of blockbuster drugs face patent expiration. ... it is estimated that by 2012, brands with more than $30 billion in sales will face new competition from generics. As more brands face patent expiration, many manufacturers will face the dilemma of how to grow revenue and minimize operational cutbacks as reliance on the new drug pipeline is unrealistic. One tactic is to develop an extended release formulation of an existing brand. Whether you call it extended release (ER, XR), long-acting (LA), or extra-long (XL), the modified formulation is intended to simplify dosing, improve compliance and ***extend the life of the patent****. (emphasis added)"*

Kelly Renfro, Marketing Manager for McKesson Patient Relationship Solutions[2]

Innovation drives growth, but competition may undermine the incentives for innovation due to the nonrivalrous nature of ideas. Market exclusivity, provided by intellectual property rights and data exclusivity provisions, aims to incentivize innovation by allowing firms recoup their R&D expenditures and extract the returns to investments in the marketplace. These policies are controversial: How can we minimize dead-weight loss due to monopoly pricing without undermining incentives to innovate? This paper examine the welfare e□ects of incremental innovation and delayed generic entry that results from granting additional market exclusivity periods to incremental pharmaceutical innovations.

"Incremental innovation" in pharmaceuticals, in contrast to the radical innovation of a new molecule to treat diseases, involves improvements over existing drugs such as the discovery of a new therapeutic use, new formulation, additional pediatric use, or improved e□cacy and safety. The Hatch-Waxman Act (1984) grants innovators additional market exclusivity for incremental innovations (details in Section 2). Although incremental innovation may generate social benefits, additional market exclusivity may impose social costs. Market exclusivity implies an extension of monopoly, which hurts consumer surplus: budget-constrained patients are may be unable to purchase a treatment at all, or too little; this may in turn a□ect health status measures. I measure the value of incremental innovation from an economic perspective. I estimate demand based on individual prescription-level data for antidepressant use, and then calculate welfare under various counterfactual policy scenarios. Specifically, I am interested in determining whether the value of incremental innovation to patients exceeds the costs of extending market exclusivity.

This study contributes to policy debates in the regulation of pharmaceuticals, healthcare, and intellectual property. Many have accused the pharmaceutical industry of "evergreening, " or extending patent protection through the introduction of new products that represent minor advances over older drugs. An oft-cited example

[1] http://www.thaindian.com/newsportal/health1/allow-patents-for-incremental-innovation-of-medicines-study_100238527.html

[2] http://www.pharmaphorum.com/2011/03/18/battling-patent-expiration-by-building-brand-loyalty/

is the case of Prilosec, a best-selling prescription heartburn drug. Just before the expiration of Prilosec's patent in April 2002, the producer of Prilosec, AstraZeneca got approval for another drug, Nexium, in February 2001 and marketed it from March 2002. Nexium is one-half of the Prilosec molecule. Most clinical studies found no increase in e□cacy. However, AstraZeneca obtained another patent that will expire in November 2018. But others point to examples of incremental innovation with important benefits. The anti-retroviral drug Norvir, a first-line treatment of HIV/AIDS, was approved by FDA in 1996 but requires refrigeration. In 2010, a heat-stable version of Norvir was introduced. While this incremental advance may not be important for developed country patients, it may make treatment far more accessible in countries without widespread refrigeration.

Even if incremental innovation yields real clinical benefits, the costs associated with extending a monopoly – either through new patents or through Hatch-Waxman exclusivity extensions – may be significant. Many developed countries are facing rising health care expenditure, a large portion of which is due to pharmaceuticals. Regulators use a variety of mechanisms to control pharmaceutical expenditure, including price controls and the promotion of generics. As Lichtenberg (2001) [20] has emphasized, the introduction of new drugs may reduce total health expenditure and create other benefits, such as fewer inpatient visits and lost workdays due to illness. A full examination of these trade-o□s is essential in assessing e□orts to balance cost, innovation and access. Market exclusivity extensions are another policy tool that allows regulators to balance incentives for incremental innovation that increases welfare against the static gains from earlier generic entry (Grabowski (2006, 2008) [14] [13]; Engelberg (2009) [11]).

In the intellectual property area, there is a debate about the standards of patentability, particularly whether incremental innovation satisfies the novelty and nonobviousness requirement of most patent systems. Some countries, including India, refuse to grant patents for some types of incremental innovation. Giving innovators the same period of patent protection on an incremental advance as on a new molecule may distort incentives. Although this study doesn't explicitly consider the shift between incremental innovation and radical innovation, it might shed light on the future research related to the substitution e□ects of these two types of innovation.

In this study, I focus on incremental innovations in selective serotonin reuptake inhibitor (SSRI) anti-depressant drugs, including the pediatric use of existing drugs, which has been granted a six-month exclusivity extension over existing patents, and two new formulations of existing branded drugs (Lexapro and Paxil CR), which have been granted new patents. I estimate the patients' demands for antidepressants with a random coe□cient logit model, based on individual-level prescription drug data. I then recover the marginal cost for the branded and generic firms based on the Bertrand Nash model. Before calculating the welfare change from status quo to counterfactual scenarios, I estimate counterfactual equilibrium prices from firms profit maximizing model, given the simulated demands over counterfactual alternative choice set (for example, incremental innovation products might be removed, or the generic entry might occur one year earlier due to the withdrawal of market exclusivity). Consumer surplus change is measured using the compensating variation between two scenarios.

By comparing scenarios of either withdrawing or allowing market exclusivity for incremental innovations with scenarios of withdrawing or retaining incremental in-

novations, I found that the consumer benefits from incremental innovation are overwhelmed by the consumer surplus loss due to market exclusivity when considering a single incremental innovation, whereas the consumer benefits from innovation outweigh the consumer losses from exclusivity when considering the counterfactual of withdrawal of all incremental innovations and market exclusivities. This result suggests that innovation benefits are primarily driven not by the quality improvements of products but by the competition effect of the introduction of several incremental innovation products in the market.

This paper is structured as following: sections 2 and 3 explain market exclusivity policies for pharmaceuticals and the antidepressant market, respectively. Section 4 details the estimation strategy. Section 5 describes the data, including data sources, sample choice, products and variables. Section 6 presents the estimation results, and I conclude section 7.

2 Background of Market Exclusivity

The pharmaceutical industry is innovation intensive, with firms investing a very high proportion of annual sales into R&D; Additionally, their profitability relies heavily on patent protection. This salient feature of the industry results from the characteristics of innovation and the production process of the pharmaceuticals. The development of a successful branded drug is highly risky. To get approval from government regulatory authorities such as FDA in the US, the median time duration from the start of clinical trials to NDA (New Drug Application) issuance was 98.9 months. In each phase, the attrition rate is surprisingly high (around 25%, 52%, 36% for phase I, II, III, respectively, see Scherer, 2000[30]), resulting in large costs for clinical trials.

In comparison, the cost to copy a branded drug is remarkably low, not only for production but also for approval from the government authority. According to the Hatch-Waxman Act passed in 1984, a generic producer could file an ANDA (Abbreviated New Drug Application) based only on proof of bio-equivalence to the branded drug as long as its data exclusivity has expired. Once generic drugs enter into the market, both the price and sales revenue of branded drugs tend to drop about 80% over the next year. In this way, the length of patent protection governs the profitability and effective life of pharmaceuticals.

Policy makers are continually trying to balance the need to develop new drugs and improving patients' access to existing drugs while maintaining affordable health expenditures. By allowing generic producers to easily get approvals and market share, patients have access to blockbuster drugs that otherwise might not be affordable. However, it greatly reduces the profits of innovators and therefore undermines the incentives for them to carry out R&D for a new generation of drugs. The objective of government regulator is to develop an optimal policy that maximizes total social welfare while taking into account all these considerations.

Market exclusivity is influenced by a complex interaction of several factors (Grabowski and Kyle, 2007 [15]). In short, it is determined by the complementary action of patents and data exclusivity. Patents granted by USPTO (The United States Patent and Trademark Office) protect drug innovations from pure price competition, enabling drug innovators to recover research and development expenditures and thereby encouraging further research investment. Data exclusivity approved by the FDA re-

stores the patent period loss during the regulatory review and clinical trial period, as well as protects clinical data from being utilized by generic competitor to file abbreviated new drug application (ANDAs)[3].

To illuminate the importance of data exclusivity, one should examine the sophisticated nature of pharmaceutical innovation and the market regulatory system. To ensure the safety and e□cacy of marketing drugs, the FDA sets a series of regulatory requirements throughout the whole development process from the moment a new chemical entity is synthesized until final FDA approval of a NDA. The process is divided into three main stages: preclinical research, clinical investigation, and NDA approval. It is well-known that the requirements are rigorous and demanding. However, the patent term for pharmaceuticals remains unchanged, allowing 20 years after the filing date for patents applied for after 1995; and 17 years after the issue date for patents applied for before 1995.

This means that the e□ective patent life of pharmaceuticals is substantially shorter due to the government requirements. When a firm discovers a promising new chemical compound, the first thing to do is to file for a patent. From that moment, the patents 20-year term is on the clock, well before knowing if the compound can be developed into a marketable medicine. The government then requires substantial chemical, animal and human testing, followed with FDA review process of a NDA. The testing and approval process usually takes about 7 to 13 years (Congress House Committee, 1980) [27]. Therefore, for pharmaceutical products, the 20-year patent term has become a legislative figment. In reality, the e□ective patent life for pharmaceuticals has been eroded, and on average has only 6.8 years. The incentives to invest in pharmaceutical R&D have been reduced substantially.

The Hatch-Waxman Act (1984) was enacted by Congress to alleviate this problem by restoring market exclusivity to pharmaceutical innovations. In this act, two seemingly contradictory goals have guided the federal government's legislation: encouraging pioneer companies to continue developing innovative technologies while also making inexpensive generic pharmaceuticals available to consumers.

According to Hatch-Waxman Act, the generic manufacturer is allowed to use the clinical data of the patented drug to prepare its own FDA application prior to expiration of the patent rights, thus providing an abbreviated process for FDA approval of generic drug applications. The generic manufacturers can file abbreviated new drug applications (ANDAs) without their own clinical trials data as long as they provide proof of bio-equivalence to the branded drug. This substantially facilitates the entry of generic drugs (from 3 or more years to a few months, see CBO, 1998[26]). On the other hand, the Act provides a partial restoration of the patent life of the research-based drug company (the "pioneer") by adding 5 years of data exclusivity without surpass the maximum e□ective patent life of 14 years. The 5-year exclusivity is the period in which generic firms are forbidden from filing any ANDAs based on pioneer's clinical trial data. Besides the NCE exclusivity, Hatch-Waxman Act also provides other terms of data exclusivity:

1. **Three years** of exclusivity granted for a change in an approved drug product. The changes include new indications, dosage strength, dosage form, route of administration, patient population, and conditions of use. The changes require

[3]Hutt (1982)[19] discusses the importance of patent term restoration to pharmaceutical innovation.

new clinical investigations and the exclusivity could prevent effective approval (but not submission) of ANDAs.

2. **Seven years** of orphan-drug exclusivity. A company that develop such a drug (to treat a rare medical condition which implies the condition affects fewer than 200, 000 people in the US) could be protected from competition for seven years.
3. **Six months** of pediatric exclusivity. Unlike other exclusivity, the pediatric exclusivity could be attached to existing periods of exclusivity and patent protection. It can be extended to all approved formulations, dosage forms and indications for products that contain the same active ingredient so long as they are protected by an exclusivity or patent. More than one period of pediatric exclusivity is possible, e.g., new indication.

Within these three exclusivity periods, generic firms could file ANDAs, but they cannot get approval from the FDA. Only after the expiration of the data exclusivity, their generic products could be approved. However, only when the patent expires, the approved generic ANDAs could be marketed.

In this sense, data exclusivity adds a new hurdle for the generic firms to enter the market. Generic firms could also file and get approval of new drug application based on their own safety and efficacy data, however, that implies they should carry out their own clinical trial, and it introduces an immense amount of costs and uncertainty.

For pharmaceutical manufacturers, whether innovator or generic, their objective is to exploit every market potential and extract maximum returns. For the innovator, they are protecting their product from competition, restoring their patent terms and obtaining as long a data exclusivity as possible. However, for the generic firm, they are trying every shot to challenge current patents, and apply for ANDAs as early as possible to capitalize on market share. According to the Act, the first-to-file ANDA generic can obtain a 180-day exclusivity in which FDA will not approve a subsequently filed ANDA for the same product. Therefore, the competition of the branded and the generic passed on to the arena of patent and data exclusivity. As quoted at the beginning of our paper, the incremental innovation is one of the important strategies for the innovator to win in this battle.

3 The Anti-depressant industry and SSRIs

In this paper, we focus on the antidepressant industry, more specifically, the Selective Serotonin Reuptake Inhibitor antidepressants (SSRIs). The reason to concentrate on this market lies in the following: molecules in this class are relatively homogeneous with individually idiosyncratic therapeutic responses and side effects. Therefore, it is a differentiated but mutually exclusive market. The products with patent protection, incremental innovations, and generic entry coexist. In this sense, the market structure forms the indispensable ingredients (incremental innovation, market exclusivity, consumer loss without generic entry) for answering our question. Market is competitive with balanced share across brands, which facilitates the demand estimation.

The antidepressant manufacturing industry is the largest prescription industry in the United States, with more than 200 million prescriptions dispensed annually for

2007-2011 (IMS Health).[4] Trends will likely continue upward with the rising diagnosis rates and increasing public awareness of the disease. In fact, the World Health Organization forecasts that unipolar major depression will displace heart disease as the heaviest disease burden by 2020. [22] Furthermore, anxiety disorders affect about 40 million American adults in any given year. They include panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, and phobias. For these anxiety disorders, antidepressants are standard treatment.

Antidepressants are almost equal in their successes in relieving depression. The differences determining patient choices, come down to safety, effectiveness, costs, side effects and the presence of other medical conditions that could affect the drug's safety and effectiveness. Among them, side effects are especially crucial considerations. Common antidepressant side effects are nausea, weight gain, sexual dysfunction, and anxiety. Moreover, antidepressants are addictive, and discontinuing use may cause withdrawal symptoms in patients. Reducing these side effects is a vital area of research for pharmaceutical companies.

The diagnosis of depression involves more subjective criteria than other common diseases such as arthritis, cancer, or diabetes. As a result, Direct-To-Consumer (DTC) advertising has historically played a large role in creating popular recognition of depressive symptoms, "growing market" and fostering a demand for specific medications. Studies show that only half of people with depression are treated.[33] Thus, the success of new antidepressant treatments hinges on the ability of manufacturers to effectively market their products to the public.

According to action mechanisms, the antidepressants can be categorized into several therapeutic subdivisions, [5] in which SSRIs are the most commonly used as the first-line treatment of depression because of their favorable side effect profile and low toxicity. SSRIs also amount to the top prescribed antidepressants in the US retail market in 2010.[6] They work by preventing the reuptake of serotonin by the presynaptic neuron, thus maintaining a higher level of serotonin in the synapse. This allows the brain to better transmit signals, thus improving mood.

Prozac was the first SSRI marketed by Eli Lilly with FDA approval in 1987, later followed with other SSRIs including Zoloft (1991), Paxil (1992), Celexa (1998), Lexapro (2002) and updated versions, such as Prozac Weekly, Paxil CR etc.. After the added six-month of data exclusivity for Prozac due to its pediatric studies expires in Aug. 2001, the generic competitors enter. Generic counterparts for Paxil, Celexa and Zoloft then entered into the market in 2003, 2004 and 2006. The most recent SSRI Lexapro also began to face its generic competitor after Mar. 2012.

Unlike most markets where consumers hold the full discretion in making choices, demand for pharmaceuticals relies not only on ultimate patients' tastes (the efficacy and side effects response, brand loyalty), but also on the behaviors of physicians who prescribe these drugs and pharmacists who dispense the prescriptions. Fortunately,

[4]See the Top-line Market Data "Top Therapeutic Classes by U.S. Dispensed Prescriptions" in www.imshealth.com.

[5]The antidepressants mainly include the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), and Serotonin-norepinephrine reuptake inhibitors (SNRIs).

[6]From the statistics in "2010 top 200 generic drugs by total prescriptions" and "2010 top 200 branded drugs by total prescriptions" provided by www.drugtopics.com.

unlike other therapeutic classes of drugs[7], anti-depressants leave little scope to physicians when they decide what to prescribe. The e□cacy and side-e□ect responses of anti-depressants are quite idiosyncratic across individuals. The traditional way to prescribe anti-depressants is to try one or two molecules to see which works with the fewest adverse reactions. According to patients' responses, doctors then write the prescription afterwards. In addition, people usually believe that physicians have incomplete or no information about relative prices (Ellison et al., 1997 [10]), however, for the treatment of chronic disease, exceptions happen (Caves et al. 1991[6]). Therefore, in our study, agency problems play little role in choice decisions, which justifies the rationale of applying discrete choice model in our problem.

4 Estimation Strategy

The existing empirical literature has generally focused either on costs of market exclusivity or the benefits of innovation. Several papers have examined the consequences of early generic entry through Paragraph IV challenges (Branstetter et al. 2011)[5]; others have estimated consumer losses that would result from market exclusivity (Chaudhuri et al., 2006). [7] There is also a large body of work on the benefits of innovations in healthcare. The representative studies include: Trajtenberg (1989) [32] evaluates the value of CT scanners; Cleanthous (2011) [8] quantifies the patient welfare benefits from innovation in the depression drugs class; Lucarelli and Nicholson (2009) [23] and Dunn (2010) [9] calculate quality adjusted price indexes for colorectal cancer drugs and anti-cholesterol drugs respectively, suggesting that the price increase in pharmaceuticals are coming from the quality innovation.[8] However, few analyses have considered both sides simultaneously to answer whether the benefits of incremental innovation exceed the consumer surplus loss from market exclusivity. Our study fills this gap by focusing on the e□ects of incremental innovations in pharmaceuticals. Our approach roots from BLP random coe□cient logit model. This method has been adopted by many people to study the value of new products in non-health related fields[9] or health-related area. This paper is closely related to Dunn (2010) [9] which applies BLP model with micro-level data in pharmaceutical industries.[10]

4.1 Demand Side Estimation

The patient choice decision of prescription drugs is complicated. Given the purchasing decision, it could be viewed as the joint choice of the patient, the physician and the insurer. The patient relies on his doctors to tell them which drug, if any, is best

[7]Such as several chemically distinct but similarly working H2 antagonists used to treat duodenal ulcers; Several ACE inhibitors used in the treatment of hypertension; And also numerous chemically distinct antibiotics.

[8]There are still a lot, such as Lichtenberg (2001, 2005) [20] [21] has studied the impact of the introduction of new chemical entities on the health status. Hsieh and Sloan (2008) [17] underline that the estimated benefits of adopting pharmaceutical innovation generally far exceed the costs.

[9]Based on BLP model, Petrin (2002) [28] studies the value of minivan introduction; Nevo (2003) [25] measure the welfare e□ect of new products and quality change in breakfast cereal industry.

[10] However, Dunns paper does not allow random coe□cients but uses a conditional logit model.

suited to treat his condition. At the same time, the third-party payers might restrict the choice set according to the patient's insurance plan or induce price sensitivity through the structure of the insurance plan. However, the most pivotal role in this choice making process is played by the patient's heterogeneous reactions to the drugs, especially in anti-depressant drugs where each individual responds very differently to the drugs, regardless of the efficacy or side-effects. Therefore, in our modeling, we will ignore the principal-agent relationship but regard the patient's demand as a black box determined simultaneously by individual characteristics and drug attributes.

Random coefficient model is a best fit to deal with this problem. In this model, consumer's utility is determined by the interaction of drug characteristics (including prices)with both observable and unobservable demographic characteristics, which allows for flexible substitution patterns. The patient choice in antidepressants is best suited to discrete choice model: patients consume only one anti-depressant at a time which is exactly an underlying assumption of the discrete choice model.[11].

Consider that a utility-maximizing patient i, where $i = 1,\ldots,I_t$, in a given time period t, where $t = 1,\ldots,T$, faces $J_t + 1$ alternatives: J_t different antidepressant drugs and the option of not purchasing any of the drugs, the outside option, $j = 0$. As in Berry, Levinsohn and Pakes (1995, 2004) [2] [3] and Nevo (2000) [24], the indirect utility of any patient i, in market t choosing drug j can be expressed as

$$u_{ijt} = \beta_{ipt} x_{jpt} + \sum_k x_{jkt}\beta_{ikt} + \xi_{jt} + \epsilon_{ijt}.$$

with

$$\beta_{ict} = \bar{\beta}_c + \sum_r z_{irt}\beta^o_{cr} + v_{ic},\ c = p,k.$$

The payoff of patient i purchasing drug j at date t depends on the drug price x_{jpt} and drug characteristics, including x_{jkt} (observable) and ξ_{jt} (unobservable). We allows patients to have heterogeneous preferences over observed drug attributes $x_{jct}, c = p,k$, [12] through the coefficients β_{ict}. The coefficients vary both with observable patient characteristics z_{irt}, indexed $r = 1, \ldots, R$ and unobservable household characteristics v_{ic}, indexed $c = 1, \ldots, K$.[13] We assume $v_{ic} \sim N(0,\Sigma)$, ϵ_{ijt} to be a zero-mean stochastic term.

For notation simplicity, in the following we will omit the market notation t. By grouping the drug-specific common term together, we get:

$$u_{ij} = \delta_j + \sum_{cr} x_{jc} z_{ir} \beta^o_{cr} + \sum_c x_{jc} v_{ic} + \epsilon_{ij}, \tag{1}$$

with $\delta_j = \sum_c x_{jc}\bar{\beta}_c + \xi_j$, we call it as the mean utility component of drug j, which is common to all patients in market t.

For the outside option, as in Grifith et al. (2010) [16], the individual utility takes the following form

$$u_{i0} = \delta_0 + \sum_r z_{ir}\beta_{1r} + \epsilon_{i01}.$$

[11] In our sample, we observe that some of the individuals may choose different drugs in different time, which is the evidence that patients are changing to a more suitable drug. Therefore, we will drop the former drug choice and only keep the latter one since it better reflects the patient's characteristics

[12] p denotes price, k denote other drug characteristics, c denotes all the drug attributes.

[13] It implies the unobservable individual preference specific to drug characteristics.

where z_{ir} for $r = 1, \quad , R$, is a vector of observable individual characteristics. We interact the payo provided by selecting the outside option with observable individual characteristics to allow for heterogeneity in choices to buy or not. The parameter δ_0 capture the baseline payo from the outside option and for each r, β_{1r} captures the variation in payos across individuals due to z_{ir}.

Individual i chooses drug j which gives him/her the highest payo, i.e., $u_{ij} > u_{il}, 8l \neq j, l$ 2 f0, $\quad , J$g. Then, by assuming the random utility component ϵ_{ij} to be independent and identically distributed across both drugs and patients and follows an extreme value distribution, we can write the probability of individual i choosing drug j as

$$Pr_i(j \mid z, v, x, \delta, \beta) = \frac{exp(\delta_j + \sum_{cr} x_{jc} z_{ir} \beta^o_{cr} + \sum_c x_{jc} v_{ic})}{\sum_{l=0}^{J} exp(\delta_l + \sum_{cr} x_{lc} z_{ir} \beta^o_{cr} + \sum_c x_{lc} v_{ic})}. \tag{2}$$

In the above formula, we can observe the patient's choice results (therefore, $Pr_i(j)$), the drug characteristics x_{lc}, and the individual characteristics z_{ir}. For the unobservable individual characteristics, by assumption, we have $v \quad N(0, \Sigma)$, [14] then after integrating out v,

$$Pr_i(j \mid z, x, \delta, \beta) = \int Pr_i(j \mid z, v, x, \delta, \beta) P_v(dv). \tag{3}$$

A general concern in demand estimation is that unobservable drug characteristics lead to correlation between the error term and price resulting in inconsistent estimates of the price coe cients. The traditional way to circumvent this problem in mixed logit model is to introduce the mean utility term δ_{jt} which encompasses the price and unobserved product characteristics (BLP, 1995, 2004 [2] [3]). Therefore, a consistent estimates of δ_{jt}, β^o_{cr} and Σ are implementable. And then we could deal with the endogeneity problem in linear model

$$\delta_j = \bar{\beta}_p x_{jp} + \sum_k x_{jk} \bar{\beta}_k + \xi_j. \tag{4}$$

by instrumental variable estimation. In this way, the model can be estimated in two stages: δ_j, β^o_{cr}, and Σ are estimated from (2) by simulated maximum likelihood estimation; And then based on the estimates of δ_j in the first stage, $\bar{\beta}_c$ and ξ_j are estimated from (4) by IV estimation.

4.2 Instrumental Variables

Finding relevant and valid instruments is always challenging in demand estimation. It should correlate with the drug price but be uncorrelated with unobserved drug characteristics ξ_{jt}. A usual way in the literature is to find the cost factors in other countries or the competitors which a ects the firms' pricing strategy but irrelevant to the product characteristics.

In our study, to exploit the detailed individual-level data, we adopt a di erent approach by Dunn (2010) [9] and adapt the demand predicts in the first stage logit estimates as IVs, but with drug prices and the unobserved product characteristics set

[14] Here, v is a coe cient vector which corresponds to the drug characteristics x_{lc}.

to zero. The intuition behind the IV strategy is to employ the demographic information in the patient-level data which is reflected in the first stage demand estimates since choices are a□ected by individual characteristics. The individual information is controlled in the logit model and it shouldn't enter the unobserved component of model, ξ_{jt}. Therefore individual demographics should not be correlated with the unobserved component of demand; but the aggregate preferences of individuals in the market should be correlated with the price. As the firm's price strategy in oligopolistic model depends on both the demand of the drug and the derivative of demand with respect to price, Dunn (2010) [9] provides a detailed proof regarding the use of aggregated demographics as instrumental variables in the context of a simple linear demand model. Graynor and Vogt (2003) [12] utilized the first-stage demand estimates from the logit maximum likelihood equation as an instrument for price. Similar to their methods, assume that firms choose price based on a mark-up term derived from an oligopoly pricing model that depends on both the demand for the product and the derivative of demand with respect to price, $markup = p_{jt} \quad mc_{jt} = \frac{D_{jt}}{\frac{\partial D_{jt}}{\partial p_{jt}}}$. Both the demand function and the derivative can be calculated by summing individual decisions and their responses to price. Specifically, the market demand for product j at date t is simply:

$$D_{jt}(j \mid z, x, \delta, \beta) = \sum_{i=1}^{I_t} Pr_{it}(j \mid z, x, \delta, \beta) \tag{5}$$

and the responsiveness to price is measured as:

$$\frac{\partial D_{jt}}{\partial p_{jt}} = \sum_{i=1}^{I_t} \frac{\partial Pr_{it}(j \mid z, x, \delta, \beta)}{\partial p_{jt}}. \tag{6}$$

The first-stage estimates may be used to construct these demand measures, but they are likely to be endogenous because the function $Pr_{it}(j \mid z, x, \delta, \beta)$ depends on the market price, p_{jt}, and the unobservable, ξ_{jt}. Therefore, in order to use the first-stage estimates, the terms containing price, p_{jt}, and the unobservable, ξ_{jt}, must be removed from the equation; so to construct the instruments all parameters interacted with price, $\bar{\beta}_p$, β^o_{pr}, v_{ip}, are set equal to zero, and the mean utility of product δ_{jt} is also equal to zero. That is, (5) and (6) are estimated at the point where $Pr_{it}(j \mid z, x, \delta = 0, \bar{\beta}_p = 0, \beta^o_{pr} = 0, v_{ip} = 0, \beta_{ic})$. Therefore, by representing all these price related parameters $\bar{\beta}_p$, β^o_{pr} and v_{ip} as β_p, we could construct the instruments as

$$D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k),$$
$$and \quad \frac{\partial D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k)}{\partial p_j}.$$

For generic drugs, we could expect that the pricing behaviour of generic firms be di□erent from branded firms and the competition extent also di□erent. By allowing the instrument to be distinct from the branded drugs, we have the instruments for generics as:

$$generic_{jt} \quad D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k),$$
$$and \quad generic_{jt} \quad \frac{\partial D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k)}{\partial p_j}.$$

Another group of IVs have also been considered in our study. Adopting the instruments employed in Branstetter et al. (2011) [5], we generate three alternative instruments to perform the robustness check. The variables includes: the number of dosages in which a product is available; years after the first generic entry; and number of firms (branded and generics) selling the same molecule in the market. The relevance and validity of all these instruments will be discussed in section 5.

4.3 Supply Side Estimation

Counterfactual simulations concerning the effects of incremental innovation withdrawal and market exclusivity removal require knowledge of the marginal costs of SSRI anti-depressants in the market. Adopting the traditional approach in the literature, we assume that the marginal cost mc_{jt} is constant and the industry is an oligopoly engaging in Bertrand competition with differentiated products. Firms myopically maximize profits each period, and then the firms' first-order conditions can be derived and used to infer the marginal costs.

Following the literature, we assume the firms are profit maximizers. Based on the typical Bertrand-Nash model, assume firm f produces subset J_t of the J total products[15]. It's profit function is:

$$\Pi_f = \sum_{j \in J_f} (p_j - mc_j) D_j \tag{7}$$

$$F.O.C.: \; D_j + \sum_{l \in J_f} (p_l - mc_l) \frac{\partial D_l}{\partial p_j} = 0. \tag{8}$$

Rewrite it in matrix form, the mark-up can be calculated by:

$$p - mc = \Delta(p, X, \beta)^{-1} D(p, X, \beta), \tag{9}$$

where the (j, l) element of Δ is

$$\Delta_{j,l} = \begin{cases} \frac{\partial D_l}{\partial p_j} & \text{if } j \text{ and } l \text{ are produced by the same firm;} \\ 0 & \text{otherwise.} \end{cases}$$

However, there are some exceptions in our study due to our data limitation. Our individual-level data, while providing detailed individual characteristics and purchasing history, contained inaccurate records about the drug manufacturers, especially for generics[16]. We could identify the producer if the patient purchased the branded one since there is unique branded producers corresponding to each molecule.

[15] In our case, most of the firms have only one product except Forest Labs (producer of Celexa and Lexapro) and Glaxosmithkline (producer of Paxil and Paxil CR). Before the patent expiration of Celexa, Forest Labs developed a new transforms of Citalopram Hydrobromide (active ingredient of Celexa): Escitaloproam Oxalate. When pricing Celexa (Lexapro), Forest Labs should consider the substitive effects of Lexapro to Celexa.

[16] The NDC (national drug code) recorded in MEPS which is used to link the products to manufacturers are highly inaccurate and incomplete. We could only observe the drug name and strength for each purchasing record. For the a large number of generics which are highly homogeneous in trade name and strength, we were unable to identify their manufacturers.

For generics, it becomes a problem as there are dozens of pharmaceutical producers providing generics of the same molecule. Therefore, the only thing we can do is to treat all generics of one molecule as a single product although in fact they are provided by multiple competitors. In this case, the firm margins will be overestimated based on Bertrand-Nash model.

At the same time, there are two important phenomena in our market which illustrate us that simply assuming perfect competition or oligopoly market over all these years might be inappropriate. Phenomena 1: generic manufacturers enter the market sequentially following the patent expiration of the branded. Due to the Hatch-Waxman Act, the first generic entry could obtain 180 days of market exclusivity, which implies that within that period, the FDA cannot allow the second generics to enter and the first generics could enjoy a certain level of market power. While after the expiration of market exclusivity, generics firms flush into the market, for example (see Table 16), after Zoloft lost its patent protection, only Teva[17] entered in 2006, while in 2007, there were overall 16 generic producers entered. Phenomena 2: many generic firms simultaneously produce several product line. For example, Teva and Mylan (internationally well-known generic producers) produce four molecules. Phenomena 1 tells us that the market transition from oligopoly to perfect competition experiences a gradual process, it involves regulatory approval, entry into the market, and patient education about the availability of new drugs. Phenomena 2 implies that the firms also care about the substitution e□ects across generics with SSRI subclass when pricing. However, we can't capture this substitution e□ect based on our data.

Another issue we haven't tackled is the role of prescription drug copayment rates. According to Medicare Part D, the federal government started to subsidize the costs of prescription drugs for Medicare beneficiaries in the US from Jan. 2006. Several studies [18] have quantified the e□ects of Medicare Part D in overall drug utilization and generics use and illustrated that the assessment of Medicare Part D is complex due to its wide varieties of plans. There are rising concerns about pharmaceutical studies to recover price elasticity based on prices rather than copayment rate. [19] This is especially true with the introduction of Medicare Part D drug insurance.[20] Without taking into account the copayment rate, price elasticity tends to be overestimated, which induces underestimated firm margins. While due to our data limitation, treating all generic competitors as a single producer tends to overestimate firm margins. These two biases act in opposite directions, making our cost recovering di□cult and complicated. These issues remind us that the interpretation of Bertrand Nash model should be very careful. The method used to estimate the counterfactual prices with consideration of these issues will be discussed in the next section.

[17] Teva and Ivax Sub Teva Pharms are all from the same group.

[18] See Yin et al. (2008) [34] and Zhang et al. (2008) etc.. [35]

[19] Arcidiacono et al. (2012)[1] build a pharmaceutical pricing model incorporating the insurance copayment rate and provide reasonable elasticity estimates. Brand et al. (2012)[4] also discusses the importance of copayments rather than prices in health care studies.

[20] Zhang et al.(2012) [36] has found that Medicare Part D coverage gap was associated with modest reductions in the use of antidepressants and those with generic drug coverage reduced their brand-name antidepressant prescriptions.

4.4 The Counter-factual Scenarios and New Equilibrium Prices

In assessing the effects of incremental innovation, we start by focusing on the most extreme case, in which incremental innovations are non-existent. Only the originals and their generics circulate in the market. Illustrating by Table 1, the product sets include only column 1 and 4. We use the results from the analysis of this case as a benchmark. In the next step, we consider withdrawal of each type of incremental innovation respectively. Therefore, in total, we have four cases:

- Withdrawal of all incremental innovations and the corresponding additional market exclusivity: remove column 2-3;
- Withdrawal of new formulated version of Celexa: Lexapro.
- Withdrawal of new formulated version of Paxil with safety improvement: Paxil CR;
- Withdrawal of pediatric usage for all products and the corresponding 6-month market exclusivity: drop column 3 and remove the pediatric usage for all the rest products;[21]

Although we have discussed several different types of data exclusivity granted to innovation in Section 2, the data exclusivity granted to incremental innovations in our market are only those for pediatric studies. Three years of data exclusivity granted to the firms for new indications were overlapped with patent protection and therefore they have played no role in extending market exclusivity.[22] However, the patent protection for the newly formulated products, such as Lexapro, create another barrier for generic competition. Therefore, in our counterfactual analysis, the market exclusivity we consider are the 6-month market exclusivity granted to Prozac, Paxil, and Zoloft for their pediatric studies[23] and the patent protection for Lexapro and Paxil CR.

As the above list suggests, we proceed from analyzing the effects of withdrawal of the entire incremental innovations to the analysis of eliminating a specific type of incremental innovation. This approach was motivated by the observations that market exclusivity extension, provided by Hatch-Waxman Act and intellectual property right, are specific to each type of incremental innovation. By considering separately the introduction of each incremental innovation and accompanied market exclusivity extension, the welfare effects could be evaluated and policy implications could be drawn.

Before carrying on the counter-factual analysis, the first step is to derive the new equilibrium prices under counter-factual scenarios. In deriving these prices, we start by assuming profit maximization pricing policy for the branded firms without generic entry. Such assumptions aim to be consistent with the price making assumptions in

[21] It implies that the following products will no longer have the pediatric usage indication: Prozac (2006), generic Prozac (2003), Prozac (2006), generic Prozac (2006), Zoloft (1991), Zoloft (2002), Zoloft (2003), Generic Zoloft (2006).

[22] The reason that we don't consider new indications in SSRIs also lies in the fact that there is almost no significant effects of new indication dummies over the mean utility of drugs from our estimates.

[23] Although the safety and efficacy of the medication for the treatment of Major Depressive Disorder has been built only for Prozac. The safety and efficacy of the treatment for Obsessive Compulsive Disorder has also been developed for Zoloft.

marginal cost estimation. Before generic entry, the branded firms re-optimize in response to the market change and set new prices, taking the prices of all other firms as given. However, after the generics flood the market, as we explained in section 4.3, the counterfactual prices estimated from biased marginal cost in new equilibrium might be misleading. As we already know, Bertrand Nash model overestimates the margin of firms in case of generic competition, therefore underestimates the marginal cost in case of generic competition. Upon underestimated marginal costs and overestimated margins in Bertrand Nash Model, the estimates of counterfactual prices are inaccurate and the direction of bias is unpredictable, not to mention the copayment rate issue.

Therefore, one way to deal with these issues, is to consider only the pre-2006 markets and calculate counterfactuals for the years before 2006. Another way to include all these years is to infer the counterfactual prices from the marketplace prices rather than from estimated marginal costs for the years after 2006. For example, consider the counterfactual of withdrawal of pediatric exclusivity of Prozac, the counterfactual price of Prozac in this scenario is set to be the marketplace price one year later (i.e., the generic competition come to the market one year earlier, which drop down the price one year earlier).

4.5 Measurement of Welfare Effect

The simulation of the new equilibrium under di□erent scenarios can provide important insights into how consumers and firms will respond to the removal of incremental innovations and additional market exclusivity (for example, which products consumers will substitute or which prices will decrease the most). To get a more precise idea of how patient's well-being will ultimately be a□ected by the policy removal (withdraw the additional market exclusivity granted to the incremental innovation), we compute, as the last step in our analysis, the welfare e□ects if the regulators no longer grant additional market exclusivity to incremental innovations.

One point we should make it clear is that in this study we have no attempt to evaluate the responsiveness of incremental innovation to market exclusivity policies, which is left for future research. For this moment, we assume that if no additional market exclusivity is provided by regulators, no incremental innovation would take place. However, it should be acknowledged that the assumption might not hold as long as the expected gain of demand increases due to incremental innovation is greater than the investment cost, which might happen as improved quality can distinguish products from other competitors and therefore increase the demands. These issues are important and relevant to our study but we can't provide the answer to them with the current dataset. It involves requires additional study which might be the direction of our future research. But we are sure that incremental innovation would be reduced with the removal of market exclusivity provisions. By assuming the extent of withdrawal of incremental innovation, we could provide the lower bound and upper bound of the estimates to our question.

Social welfare, as defined, includes consumer surplus and firm profits. The easier part, firms' profits, can be calculated by demands multiplying the di□erence between price and marginal cost. Our data don't allow us to measure the investment cost of incremental innovation, which requires the R&D input in incremental innovations for each firms. We will put this issue tentatively aside and discuss it after we get the

final results.

On the consumer side, we measure changes in consumer welfare by the compensating variation (CV), defined as the additional expenditure that consumers need in order to achieve the same utility level as before the product quality and price change. By denoting $u_{ij}^t = V_{ij}^t + \epsilon_{ij}^t$, the compensating variation for individual i from period t 1 to period t is:

$$CV_{it} = \frac{u_i^t \quad u_i^{t\ 1}}{\beta_{ip}} = \Delta CS_{it}, \text{ where } u_i^t = \max_j V_{ij}^t,$$

where period t 1 and t are the different product characteristics corresponding to different scenarios (before and after the incremental innovation happens or before and after the market exclusivity expires). The total change of consumer surplus is:

$$\Delta CS = \sum_I \int CV_{it} dP(v, \epsilon) = \sum_I \int CV_{it} dP_v(v) dP_\epsilon(\epsilon)$$
$$= \sum_I \int \frac{\ln[\sum_{j=0}^{J_t} exp(V_{ij}^t)] \quad \ln[\sum_{j=0}^{J_t\ 1} exp(V_{ij}^{t\ 1})]}{\beta_{ip}} dP_v(v).$$

Note that the CV as computed above can be decomposed into two effects. To illustrate it, let's first clarify the notations: incremental innovation is denoted as II and additional market exclusivity as ME. The welfare change from the counter-factual scenario to the real situation can be written as:

$$\Delta = W(II, ME) \quad W(no\ II, no\ ME), \tag{10}$$

where $W(II, ME)$ implies the consumer welfare where there is incremental innovation and additional market exclusivity, similarly, $no\ II$, $no\ ME$ denotes the scenario where there is no incremental innovation and additional market exclusivity.

By manipulating equation 10, we have

$$\Delta = \{W(II, no\ ME) \quad W(no\ II, no\ ME)\} + \{W(II, ME) \quad W(II, no\ ME)\} \tag{11}$$

From equation 11, the consumer surplus can be interpreted as the sum of welfare loss resulting from withdrawal of incremental innovation and the gains from removal of additional market exclusivity, which is exactly the two blocks of values we are interested in.

If Δ is positive, then it implies that granting additional market exclusivity to incremental innovation is valuable since their loss is offset by their benefits. Therefore, we could separately measure the two terms in braces to get the estimate of Δ. For the first term, we will measure the welfare effect from product quality improvements without providing market exclusivity; Secondly, we will consider the price effects of extending market exclusivity while keeping the product quality unchanged with improved level.

Considering the four cases we discussed above, Δ will be calculated separately corresponding to each case. For example, for case 3, Δ is the sum of consumer gains from pediatric usage of the SSRIs without the market exclusivity extension plus the loss of providing the market exclusivity to all the pediatric studies.

5 Data

5.1 Data Sources

Three data sources are employed for this study: the consolidated individual data, medical condition data, and prescribed medicine event data from the Medical Expenditure Panel Survey (MEPS) from 1996 to 2009, the information about new drug application and patent/data exclusivity for drugs from the U.S. Food and Drug Administration (FDA), and self-collecting data about the drug characteristics from package insert labels.

MEPS provides nationally representative estimates of health care uses, expenditures, sources of payment, and health insurance coverage for the U.S. civilian noninstitutionalized population. It follows all the individuals in randomly selected US families for 2 years with 5 rounds of questions, information recorded includes respondents' health status, demographic and socio-economic characteristics, health insurance, medical expenditure, etc.. More importantly, it supplements the survey data by contacting medical providers and pharmacies to acquire detailed and accurate consumption and billing information. For example, if the patient reports purchasing Norvir from a pharmacy, the pharmacy is contacted and required to provide the purchasing history of Norvir for the patient. The survey began 1996 and the most recent wave from 2010 is available. Overall, there are 239,720 individuals including in the survey from 1996 to 2009.[24]

Two datasets from the FDA (Drug@FDA and Orange Book) provide exhaustive information on the drug approvals, supplemental approvals, patent, and data exclusivity. For each approval, whether it is a radical innovation (new molecule entity) or incremental innovation (new formulation, new indication, and new combination) is documented. The subsequent supplemental approvals (including the safety, e□cacy, new indication, new strength, new formulation, label change, patient population change) following each approved drug could be tracked in the FDA database. The information is critically indispensable for our study to identify incremental innovation from radical innovation.

Moreover, the drug characteristics (the strength, dosage form, active ingredient, producer, approval date, patent expiration date, data exclusivity expiration date, type of data exclusivity, etc.) are all available from the FDA. Based on this information, we could generate several important drug characteristics such as dummy of generics and age of molecule for each drug. The only flaws is that it only provides the unexpired data exclusivity information, i.e., once the data exclusivity expires, the information about expiration date, exclusivity type becomes absent from the available dataset. Fortunately, we could uncover the expiration date of the expired drugs from the entry of other competitors (ANDAs approval or marketing date). As a complementary source, USPTO provides more detailed information on the patent and their expiration. To link the MEPS consumption data with FDA drug data, NDC data file in FDA plays an important role in making the match.

A unique self-collecting data is utilized in our study. By reviewing the package insert label for each drug, we construct several variables of drug attributes. These variables mainly lie in two aspects: the indications and side e□ects[25]. Indications

[24] When we started the data cleaning, the data from 2010 wasn't yet available.

[25] There is also information about FDA safety alarms to health professionals and patients about drugs.

are noted in each label and remain the same until the supplement approval has been granted for new indication. We generate several dummies of indications for each drug. We also collect the side effects information for each drug from the clinical trial data. Due to the heterogeneity of the clinical trial across drugs in the sense of the composition of the patients, the drug strength, the length of the clinical studies, etc., the original statistics is not comparable across drugs. To make the statistics meaningful across drugs, we generate variables for each symptom: the ratio of the occurrence rate of the symptom for the patients taking drugs over the occurrence rate for the patients taking placebo[26].

5.2 Products and Incremental Innovations

Our focus is on four active ingredients in selective serotonin reuptake inhibitor (SSRI) anti-depressant drugs, denoted in ATC code as N06AB-. [27] It involves four new molecule entities following with 12 incremental innovations and subsequent generics. [28] Prozac Weekly, Sarafem, as incremental innovations of Prozac are not included in this study due to their limited number of observations.

As shown in Table 1, following the marketing of four new molecule entities: Celexa (1998), Paxil (1992), Prozac (1987), Zoloft (1991) [29], subsequent updated generations are innovated. In our paper, to consider the incremental innovation, we mainly focus on the pediatric use of SSRIs and newly formulated drugs with new drug application to the FDA, such as Lexapro and Paxil CR. New indication uses will not be considered in this paper because the data exclusivity granted to the new indications in our study doesn't extend the market exclusivity due to a longer patent period. Our results, as demonstrated below, illustrate that the utility from new indications is not significant and also ignorable. [30]

If we define products as the drug with constant characteristics, then an updated version implies a new product; therefore, overall there are 12 products plus an out-

The alarms usually happen several years later after the approvals, when the patients utilization of the drug reveals more safety problems. For this category (SSRI), all the drugs have been received the same FDA alarm and therefore, we cannot identify this variable without variation and therefore we didn't include it into our study.

[26] The details to construct side effect variables are illustrated in Appendix A.2.

[27] According to the WHO ATC index, there are nine substances which have ever been approved as medicines. (See http://www.whocc.no/atc_ddd_index/ and search N06AB.) However, three of them have been withdrawn due to safety problem, leaving only 6 molecules in the US market: Citalopram Hydrobromide, Escitalopram Oxalate, Fluvoxamine Maleate, Fluoxetine Hydrochloride, Paroxetine Hydrochloride, and Sertraline Hydrochloride. Among them, Fluvoxamine Maleate is omitted in our analysis because of ignorable market share. Finally we only focus on the remaining five active ingredients.

[28] Escitalopram Oxalate is basically a new formulation of Citalopram Hydrobromide, and therefore, we will treat it as an incremental innovation instead of a new molecule entity.

[29] Enclosed in the parenthesis are the year of first approval.

[30] The market exclusivity granted to new indication or new formulation only protects the updated drug from generic competition, however, the exclusivity for original new molecule entities will expire as usual. We can see from Table 1 that, while the marketing of new version of branded drugs, the generics entered as well. Nevertheless, even with market exclusivity extension on the new indication, the drug producer would generally need a new dosing strength or formulation to make this commercially reasonable since doctors could, and would, write prescriptions for the old version for the new indication. In this sense, it can be expected that the generics could obtain the new indication characteristics as the branded one as long as the drug strength or formulation are the same.

side option in our analysis. The indications for each drug are listed in Table 7 and the side effects for each molecule are also shown in Table 7. [31] Unlike most of the literature which treat drugs in different formulation and different strength as different products, in my study, I treat them as one product, since most depression drugs are administered once daily, I use weighted price across strength and formulation as the product price without further adjustment. Treating these simialar drugs as different products will make the estimation computationally burdensome without gaining benefits.

Products from branded firms and generic producers are distinguished. But we find it from the Table 7 and 7 that the characteristics of the branded drug and the generic one are similar in terms of indications and side effects because of the current legislation (Hatch-Waxman Act: Generic drugs can provide only the proof of bio-equivalence to branded drugs to get abbreviated new drug approval from FDA without carrying on clinical trials but building their safety and efficacy on the clinical data of the branded counterpart). As shown in Table 7, side effects data remain the same for all drugs with the same molecule across years. Finally, the summary statistics of the attributes for these drugs are listed in Table **??**.

The additional market exclusivities granted to the incremental innovations in SSRIs include:

- Prozac was approved for additional six month pediatric exclusivity for its pediatric usage which extend their market exclusivity from Feb. 2001 to Aug 2001;
- Paxil obtained 6-month exclusivity for its pediatric studies extend its market exclusivity from Sep. 2015 to Mar. 2016;
- Zoloft obtained 6-month exclusivity for its pediatric studies extend its market exclusivity from Dec. 2005 to June 2006;
- Lexapro obtained 6-month exclusivity for its pediatric studies extend its market exclusivity from Sep. 2011 to Mar. 2012.[32]

5.3 Sample Selection

As shown in Table 3, among the 239,720 respondents in MEPS, only those with depression (25,001, 92.9 %) [33] [34] and those who has no depression but purchased SSRI anti-depressants (1,914, 7.1%) are included in our analysis. 12,815 (47.6%) of the whole sample have ever purchased SSRI drugs. The rest of the patients: 7,298 (27.1%)

[31] Side effects data keep the same for all drugs with the same molecule which is obtained from the clinical data of branded drug. After Hatch-Waxman Act in 1984, generics could enter into the market based on the clinical data of branded counter-parts with only providing the bio-equivalence to the branded one. Therefore, we could expect that the side-effects of the generics remain the same as the branded one.

[32] We will not investigate the withdrawal of this exclusivity since the time span is out of our data scope.

[33] According to the ICD-9-CM diagnosis codes, if the respondent has condition with code 296 (Episodic mood disorders), 300 (Anxiety, dissociative and somatoform disorders) or 311 (Depressive disorder not elsewhere classified), then we regarded them as having depression.

[34] The condition can be recorded in MEPS for the following reasons: 1. reported by the household respondent for a particular medical event (hospital stay, outpatient visit, emergency room visit, home health episode, prescribed medication purchase, or medical provider visit); 2. reported as the reason for one or more episodes of disability days. 3. Reported by the household level respondent as a condition "bothering" the person during the reference period.

had never purchased the drugs, 6,802 (25.3%) purchased other anti-depressants. The individuals who purchased drugs construct the demand of these products, and the patients who had condition but didn't purchased SSRI drugs make up of the potential market size, we regard them as choosing the outside option.

There is another potential group of patients unobserved in our sample due to their mild condition for which they never sought treatment, and are not reported in the survey. Therefore, we cannot include them. We believe this approach is reasonable as depression is the type of condition that only becomes a disease when it disturbs the mood of the patients and severely a□ects thier daily life.

As we know, depression is a chronic disease which requires long-term medication treatments. Therefore, refills and repeated purchasing are very common in the survey. Implementing a maximum likelihood estimation based on the full sample is computationally burdensome. Therefore, we will drop them accordingly. In our data, 104,143 purchasing events for the 12, 815 individuals are documented. 70,937 observations are refills and 18,186 are repeated purchasing, which are dropped from our sample and left with 15,020 observations. Among them, 2, 205 observations are switching drugs. For the records with switching, we keep the later drug as their choice and drop the earlier ones. We believe that patients are switching to find a better fit for their condition. Therefore, we have 12,815 purchase records for 12,815 individuals plus 14, 100 patients who chose outside option kept in our study.[35] As evidenced in Table 5, the deletion of refills and repeated purchasing has little e□ect on our demand estimation since the market share remains more or less the same between the MEPS survey sample and our analytic data.

5.4 Variables

The dependant variable used in this paper is the treatment choice dummy of each patient in a period. The treatment choices include the drugs products we illustrate above in section 4.2 and an outside option. Here, we assume if an individual purchase the drugs, he is considered to be taking the medicine, i.e., $choice_{it} = 1$. Patients' compliance to the medication isn't considered in our context.

The details of data construction for the individual characteristics and drug attributes are described in Appendix A. The individual demographics that we use include Age_{it}, $Adult_{it}$ [36], $Male_{it}$. The socio-economic variables include $Years\ of\ education_{it}$ and $Family\ income\ per\ capita_{it}$. Family income per capita is generated by average the total family income across individuals. Income is deflated and measured in 1996 dollars. For children and adolescents, I use their parents' education as the education level since we want to see whether education helps people obtain better health service.

The health-related variables we employed in the study includes health insurance variables (i.e., $Having\ medical\ insurance_{it}$, $Having\ Medicare_{it}$, $Having\ Medicaid_{it}$,

[35] Alternative sample selection method is to keep the observations in individual-year level rather than in individual level since in our analysis, years implies di□erent market with di□erent choice sets and prices. The di□culty in this lies in that the observations will be almost doubled (44,332 vs. 26,915): Estimating a maximum likelihood model with 22 products in 26,915 observations is already computationally burdensome, requiring around 100GB of memory and more than 3 days to process. Doubling the observations makes the current computation resources unsustainable.

[36] We define $Adult_{it} = 1$ if Age_{it} 18

$Drug\ Insurance_{it}$ and subjective perceived status $Perceived\ health_{it}$). As we all know, besides drug price, the insurance coverage plays an important role in the patients choice making as well, especially the drug insurance. Therefore, we include dummies for whether having medical insurance, having Medicare, having Medicaid to control the insurance status for each individual. Unfortunately, the drug insurance coverage is not observable in the survey. To proxy the drug insurance, we construct $out\ of\ pocket\ ratio_{it}$ for each individuals based on their purchasing history.[37]

The drug attribute variables mainly include $Price_{it}$, $Age\ of\ Molecule_{it}$, $Generic_{it}$, indication dummies and side effect variables[38]. $Price_{it}$ is deflated to 1996 price level using CPI in Managed Care Commodities category[39]. $Age\ of\ Molecule_{it}$ is the same for the branded and generics in the same year. It is the period length from the birth of new molecule till the year when purchasing happens. A dummy variable $outside$ is generated to denote whether the individual chooses SSRIs ($outside$ = 0) or outside option ($outside$ = 1). The variable is introduced to facilitate the estimation for outside option.

SSRIs are primarily used to treat major depressive disorder (MDD), besides that, they can also be used to treat obsessive compulsive disorder (OCD), panic disorder (PD), post-traumatic stress disorder (PSD), premenstrual dysphoric disorder (PDD), social anxiety disorder (SAD), bulimia nervosa (BN). As we can see in Table 7, when a drug is initially developed, its clinical trial data only supports the safety and efficacy of one or two indications. As time goes by, the manufacturers carried on subsequent investigation and then more and more indications is supported after the supplemental approval by FDA. This process is one type of incremental innovation that we want to investigate in this paper. Therefore, the same drugs across year may have different indications and therefore bring to the patients different utility, in the following studies, we will control the year and the indication.

6 Results

6.1 Descriptive Statistics

Figure 1 shows the market share of SSRIs (branded and generics) and an outside option. Just as we mentioned above, the market share of outside option is around 50 % in our data, including those who have been diagnosed as depressive but didn't purchased SSRIs. The overall diagnosed depressive patients are increasing from less than 500 MEPS respondents in 1996 to more than 3500 individuals in 2009. The demand for SSRI antidepressants shifted gradually from the branded to the generic starting from 2001, the first year when generic Prozac was available. The market share of generics surpassed that of the branded in 2009. With the expansion of the generics, the patients who prescribed SSRIs reach the highest level in 2009. However, the total

[37] In Prescribed Medicines Files of MEPS, the listed price as well as the price paid by patients are all provided.

[38] Indication dummies and side effect variables have been introduced in the above data subsection and they are listed in Table 12 and Table 13.

[39] CPI source: US Bureau of Labor Statistics.

sale of SSRIs changes in another direction (see Figure 2)[40]. Although the total demand of SSRIs remains high as shown in Figure 1, the sales revenue of SSRIs dropped dramatically in 2007, driven by the sharp decreasing of drug price (See Figure 5). This pattern illustrates that the tough generic competition in this market make Bertrand-Nash model no longer applicable in the last three or four years.

By separating the market share and sales by brands, it's clear to see the strategic behavior of producers (See Figure 3 and 4). For the first five years, the market is mainly divided by three branded products: Paxil, Prozac and Zoloft. With the entry of Celexa and its new formulation Lexapro (produced by Forest Labs), the share of Paxil and Prozac begun to shrink in 2003-2005. The new formulation of Paxil, Paxil CR is not as successful as Lexapro in the market. Lexapro successfully grabbed market share from its ancestor and other brand competitors, achieving the highest sales among SSRIs in 2006, while the sales of Paxil CR become negligible until the end. Another interesting phenomenon about the Celexa and Lexapro is that two or three years before the patent expiration of Celexa (2004), Lexapro is marketed in 2002. Over that time, the demand for Celexa gradually shifted to Lexapro. When the generic Celexa entered into market in 2004, the overall use of Celexa had already gone down significantly, leaving only little market share for the generic counterparts. This observation is consistent with the evidence of Huckfeldt and Knittel (2011) [18], who find large decreases in overall use after patent expiration that begin in the two years before generic entry and continue in the years following. Furthermore, they suggest that it might be due to advertising which shifts demand from the now cheaper original molecule to another patented molecule.

The price trend of SSRI antidepressants across the years are provided in Figure 5. The bar graph indicates the number of generic firms producing the molecule in each year. With the number of generic entries increasing, both prices for the branded and generics go down, although the price reduction doesn't happen immediately after the first generic entry.[41] The turning point is in 2007, when most of the SSRIs prices dropped dramatically. It can be imagined that the pricing strategies should change afterwards from oligopolistic pricing to perfect competition.

The individual demographic statistics of the sample are provided in Table 3 comparing to the national representative sample. Column 1 and 2 shows the mean and the standard deviation for the whole sample in MEPS and the analytic sample in our study; column 3-5 separately show the statistics of the subjects in the sample by three groups: for those who reported that he/she has depression but he/she didn't purchase SSRI drugs; for those who have depression and ever purchased SSRIs; and for those who have no depression condition but purchased SSRIs.

Table 3 reveals that those in the sample are quite distinct from the national population. Compared to the national representative sample, our study sample consists of individuals who are older (45.72 vs. 33.62), more likely to be female, have a lower perceived health status (2.93 vs. 2.21), have a higher prevalence of respiratory diseases (0.09 vs. 0.04), asthma (0.09 vs. 0.05), hypertension (0.28 vs. 0.13), cardiovascular heart disease (0.19 vs. 0.08), diabetes (0.12 vs. 0.05) and are, of course, more

[40] The sales is simulated by assuming each individual has a compliance rate of 0.75 over 365 days in a year when taking the once daily treatment. The price we used is the weighted price over different strengths and dosage forms.

[41] The Hatch-Waxman Act grants 180-days of market exclusivity to the first generic entry which exclude the generic competitors in the short run.

depressive (0.93 vs. 0.03). Our sample has higher insurance coverage (0.88 vs. 0.83), lower out of pocket rate (0.48 vs. 0.54), it might be due to the selection e□ects: individuals in our analytic sample tend to buy more insurance because of their worse health status. Our sample have lower household income (39, 610$ vs. 44, 600$) but higher household income per capita (16, 610$ vs. 15, 330$) which implies that they have fewer dependants in the family. Overall, it shows considerable variation in most of the demographic variables.

Within our sample, there are also significant di□erences across the three groups. For those who reported of having depression, those who chose SSRIs are significantly di□erent from those who chose an outside option for most of the demographic variables, except for the dummies of having HIV, having depression (this doesnt make sense to me). For those who purchased SSRIs, those who are depressive are also distinguished by the all of these variables from sample who are not depressive except for age, household income per capita, having Medicare, having HIV and having cardiovascular heart diseases. (I think this paragraph needs some work, but Im not familiar enough with data to re-write it myself)

Table 5 shows the summary statistics of the drugs. All of the drugs can be used to treat Major Depressive Disorder.[42] A large proportion of the products can be used to treat obsessive compulsive disorder (0.68); around half of these products can be used to treat panic disorder (0.55), and premenstrual dysphoric disorder (0.45). Around one third of the products can be used to treat social anxiety disorder (0.32) and bulimia nervosa (0.32). Over one-fifth of the products can be used to treat posttraumatic stress disorder (0.23). The variation of side e□ects ratios across products seems not large except abnormal ejaculation and anorexia.

6.2 Demand Side

We estimate the model by simulated maximum likelihood estimation.[43] The model contains 109 branded-year fixed e□ects and 115 explanatory variables (including two random coe□cients for price and generic dummy and 113 individual-drug characteristics interaction terms). The full set of parameter estimates is shown -240(e)-sti.wmssime-24051

positive and significant effect on the probability of taking medications (see from the coefficient of the interaction of *Out of Pocket Ratio* and *Outside Option*). Patients with drug insurance tend to purchase the younger medications and generics. The potential explanation for this phenomenon is that the reimbursement conditions and regulations provided by drug insurers encourage insurees to purchase generic drugs. As shown in Table 6, patients with medical insurance tend to purchase drugs with pediatric usage; individuals with higher incomes tend to choose the generics and the drug with pediatric use.

Using estimates of mean utility derived from the first stage MLE estimation, the second-stage demand estimation regresses mean utility on price and other product characteristics. The exogenous variables in the second stage are the indication dummies and brand dummy variables with branded Celexa as the excluded alternative. As shown in Table 12, the dummies of OCD and BN coincide with brand fixed effects, which generates collinearity problem, and therefore they are excluded in the second stage estimation. Even if we couldn't estimate the parameters for these two indications, it doesn't affect our future counter-factual calculation. Our focus is the welfare effect on the discovery of new indications for existing drugs while there is no incremental innovation related to these two indications. Table 7 reports the second-stage results. The first column shows the results from OLS estimation without consideration of price endogeneity. Column 2-4 shows the IV estimation with different IV combinations. The results show that the coefficient on $Price$ is negative and highly significant with a coefficient, -1.443. Note that the price coefficient is much larger than the coefficient on the interaction of $Price$ and $Drug\ Insurance$ of 0.61 (reported in Table 6), which implies that those with drug insurance are actually still responsive to market price. The IVs we used in our main model (column 2) is *Markup*Generic* and *Number of Dosage the Product Has*.

The relevance and validity of the IV have been checked in our study. Corresponding to the model specification in Table 7, Table 8 shows the first stage results of regressing price on IVs and other included exogenous explanatory variables. The results show that the instruments *Markup*Generic* and *Number of Dosage the Product Has* are significantly correlated with prices. The weak instruments tests have been rejected and the over-identification restriction test shows that the null hypothesis of the IVs is independent of the error terms are accepted. For the constructed IV:*years after the first generic entry*; and *number of firms (branded and generics) selling the same molecule in the market*, they didn't pass the overidentification test, therefore, we don't include them in the table. These two variables are all related to the life cycle of the products, therefore, they might be correlated with unobserved error term.

6.3 Supply Side

Based on the assumption of firms' pricing behavior, marginal costs of products in the market are backed up. For the Bertrand-Nash equilibrium, the recovered marginal costs satisfy equation 9: the estimates of marginal costs are built upon the knowledge of observable prices and estimates of demands and their derivatives. The estimated marginal costs and margins ($Margin = (Price \quad MC)/Price$.) are shown in Figure 6.

As we expect, based on the Bertrand-Nash model, the estimated firm margins are much higher for the years after 2006. Considering that the market structure after 2006 tends to be more competitive, as evidenced by numerous generic entries shown

in Figure 5, the margins are overestimated. It highlights that our data limitations pose a severe problem in supply side modeling. Instead of using the estimated cost to recover the counterfactual prices for the years after 2006, we directly infer the counterfactual prices from the prices in market. This inference might not be accurate, but it will provide more reasonable estimates of price than those obtained from the Bertrand-Nash model.

Before computing welfare changes, the simulated equilibrium prices are estimated based on the estimated consumer preferences and recovered marginal costs. Products characteristics are altered in counterfactual scenarios when we withdrawal incremental innovations. Corresponding to each scenario, there is no pediatric use, new prices, or the newly formulated drugs are removed from the choice set. Based on the simulated demands and recovered marginal costs from the status quo case, we estimate the equilibrium prices. The correspondence of di□erent cases to di□erent scenarios and the assumptions of prices and costs for each scenario are illustrated in Table 9 and 10.

The model used to simulate the prices is for Bertrand Nash Oligopolistic market structure. As we explained before, the Bertrand Nash model tends to overestimate the firm margin when we could identify the generic competitors. Therefore, to get a tentative estimation of welfare change for the years after 2006, we simply assume the price equal to the price we observed in the market, with setting the counterfactual prices without pediatric exclusivity with the price observed one year later. Because we didn't have the status quo of price for generic Paxil CR and generic Lexapro, we have adopted the prices of their ancestors, generic Paxil and generic Celexa.

Figures 7 to 14 show the estimated price changes across scenarios. For example, Figure 13 shows the prices changes from the scenario without pediatric use and pediatric exclusivity to the scenario with pediatric and without pediatric exclusivity. The pink points denote the prices in Scenario 7, while the blue points denote the prices in Scenario 8. The prices of Celexa, Lexapro and Paxil and Paxil CR are slightly lower than the case without pediatric use. Figure 14 shows the prices changes from the scenario with pediatric use and no exclusivity to the scenario with pediatric use and exclusivity. We find that the exclusivity results in overall price increases (from blue points to pink points). Not only have the branded firms charged a higher prices to the patients but so have the generics. Almost all of prices changed from the scenario without market exclusivity to the scenario with market exclusivity, involve price increases (as shown in Figure 8,10, 12, 14). In all these figures, we only considered the years before 2006. As we explained before, the standard Bertrand Nash model couldn't provide reasonable estimates for the case when Medicare Part D introduced and there are numerous generic entries. Therefore, the counterfactual estimates doesnt make much sense.

6.4 Welfare Analysis

As shown in Section 4.4, we measure four counter-factual cases by excluding all the incremental innovations and accompanied market exclusivities and then excluding three di□erent types of incremental innovations separately to consider their di□erent e□ects. To illustrate the magnitude of the benefits and costs side, we need to separate the welfare e□ect by two parts (see Equation (11)), which implies we have to investigate 8 di□erent scenarios. For example, for case 4, we construct a counter-

factual market withdrawing pediatric use from all drugs, and enabling the generics enter one year earlier (for Paxil, Prozac, Zoloft[44][45]) (i.e., $W(noII, noME)$), together with a counterfactual including the pediatric use but still making the generics enter earlier (i.e., $W(II, noME)$). Therefore, we are able to calculate the two effects: $W(II, ME) - W(II, noME)$, $W(II, noME) - W(noII, noME)$, noting that the purchasing records observed in data represent the case $W(II, ME)$.

As shown in Section 4.5, by dividing individual's utility change from an event with the price coefficient, and summing them up, we can obtain the measure of welfare change. The utility change compares the individual utility from status quo with the utility in counter-factual scenarios. Hence, Table 11 and 12 provide the estimates of welfare changes for the years before 2006 and all the years respectively. The profit changes of the firm are for the branded firms. The profit changes of the generic firms are not listed here for several reasons: first, for the years prior to 2006, the generic market share are very small and the magnitude of welfare effects are ignorable; second, for the year after 2006 we couldn't accurately estimate the margin of the generics or their profits.

Overall, the social benefits from incremental innovation outweigh the loss from market exclusivity by a small margin: 1.2 billion dollars for the years before 2006, and 0.5 billion dollars for 1996-2009 (considering the net value of case 1). Considering the incremental innovation separately, the introduction of Lexapro brought large profits to the branded firms, as do the provision for pediatric use. However, the marketing of Paxil CR with exclusivity brings about net negative social welfare. For the consumer surplus from each incremental innovation, patients suffer from "granting exclusivity to incremental innovation;" the net consumer surplus loss from Lexapro is 9.22 billion dollars, from Paxil CR is around 6.29 billion dollars, and from pediatric use is around 6.64 billion dollars for 1996-2005. Due to the overall decrease in drug prices in 2007, the consumer loss for 1996-2009 are reduced for each type of incremental innovation. You might wonder why putting all the incremental innovation together increase the consumer surplus. As shown in the column 3 of Table 11 and 12, the consumer surplus of introducing all the incremental innovations is much higher than the sum of benefits from simply introducing one of the incremental innovations. The reason is that competition effect of multiple incremental innovations drags down the prices in the market. Compared with Figure 10, 12, 14, the counterfactual prices in Figure 8 is lower than their counterparts in other three figures. The competition effect also explains why the loss of branded firm profits is so high in the case of introducing all incremental innovation (20.6 billion dollars in Table 11.)

7 Conclusion

In this paper, I address the following research question: Should additional market exclusivity be granted to incremental innovations to allow innovators to recoup R&D investment cost from monopoly pricing, despite the fact that excluding competition could harm the consumer surplus?

[44] Celexa didn't obtain 6-month pediatric exclusivity.

[45] In our data, we could only identify individual who purchased drugs by years, not months. Therefore, here we can only measure the effect of generic entry one year earlier if we remove the 6-month market exclusivity.

By comparing scenarios of either withdrawing or allowing market exclusivity for incremental innovations with scenarios of withdrawing or retaining incremental innovations, I found that the consumer benefits from incremental innovation are overwhelmed by the consumer surplus loss due to market exclusivity when considering a single incremental innovation, whereas the consumer benefits from innovation outweigh the consumer losses from exclusivity when considering the counterfactual of withdrawal of all incremental innovations and market exclusivities. This result suggests that innovation benefits are primarily driven not by the quality improvements of products but by the competition effect of the introduction of several incremental innovation products in the market.

My research is novel to the literature in the following ways. First, to my knowledge, this is the first paper to combine a measurement of the value of innovated products with a quantification of loss from market exclusivity, which offers a number of interesting and critical policy implications. Second, unlike existing studies, which either adopt aggregate level data with random coefficient models or use individual-level data with conditional logit models to measure the value of pharmaceutical innovation, my paper applies a random coefficient model with patient-level data. I estimate the model with simulated maximum likelihood estimation, taking price endogeneity into account. Although this method brings about difficulties in estimation and is computationally burdensome, it takes advantage of detailed demographic information in micro-level data and also enables individual heterogeneity, resulting in a better fit between model and data. Third, our results suggest that "granting market exclusivity" not only provides incentives to innovate but also fosters a market with improved high-quality products, which hasn't been emphasized in previous studies. Although it excludes generic competition, it justifies branded drug competition. Therefore, taking all these effects into account, "granting the market exclusivity" is favorable because it improves social welfare.

However, our results should be interpreted with caution. For starters, our results are drawn from the incremental innovations of SSRIs antidepressants. For other therapeutic classes of drugs, the conclusion may not hold. Development of innovative medicines is full of uncertainty, as is its value to the patients, which varies across diseases and treatments. Additionally, we haven't been able to consider the substitution effect of market exclusivity—motivating firms to invest their resources in incremental innovation results in decreased investment resources in radical innovation. "Granting additional market exclusivity to incremental innovations" might alter the relative marginal revenue of incremental innovation to radical innovation and therefore distort investment allocation between these two types of innovations. Furthermore, the responsiveness of incremental innovation to market exclusivity hasn't been investigated in this paper. We assume that without market exclusivity, no incremental innovation would be innovated. However, this is still an open question and it will be explored in our future research.

Several questions worthy of future investigation have arisen. First, how large is the role that advertising plays in promoting newly formulated drugs, and could we identify the advertising effects from the improved quality effects in expanding demands for newly formulated drugs? Second, what are the learning behaviors of patients using pharmaceuticals for chronic diseases, and how do patterns of switching from one drug to another differ based on different individual characteristics? Third, will pricing control on the insurer side discourage innovation activities of the branded firms?

As we know, creating drug reference catalogues, legalizing generic substitutions, and setting price caps for brands all tend to encourage consumption of generics instead of their branded counterparts. These questions are potential directions for future research.

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Figure 1: Market Share of SSRIs across year

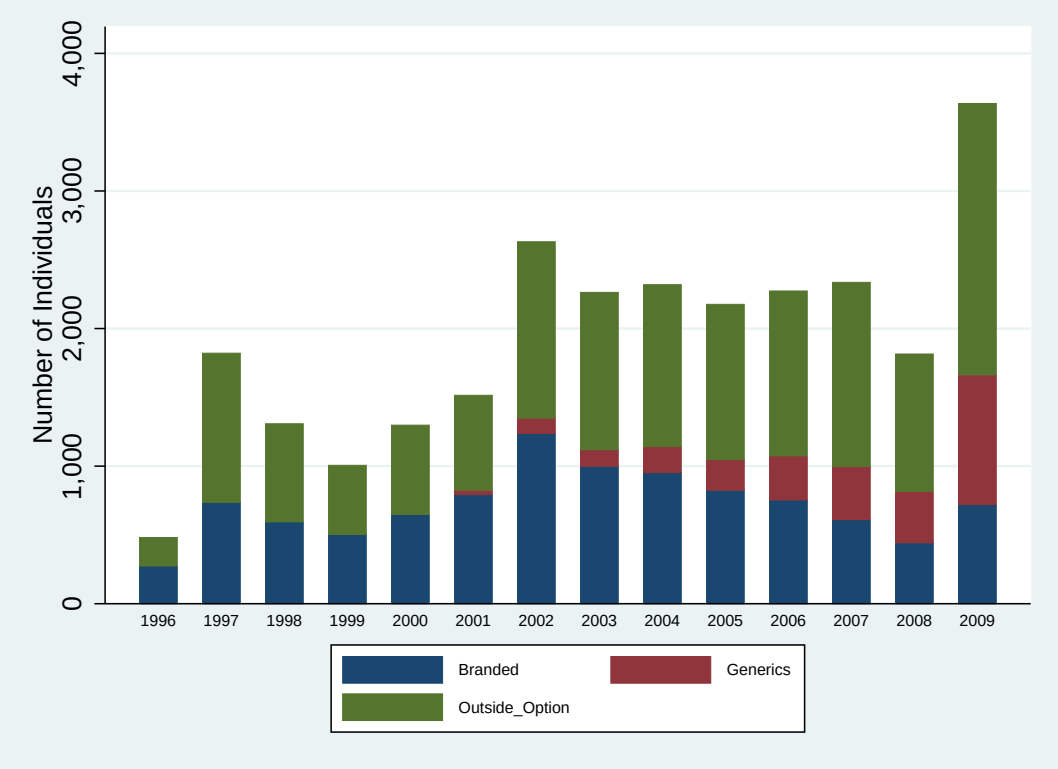

Figure 2: Annual Sales of SSRIs across year

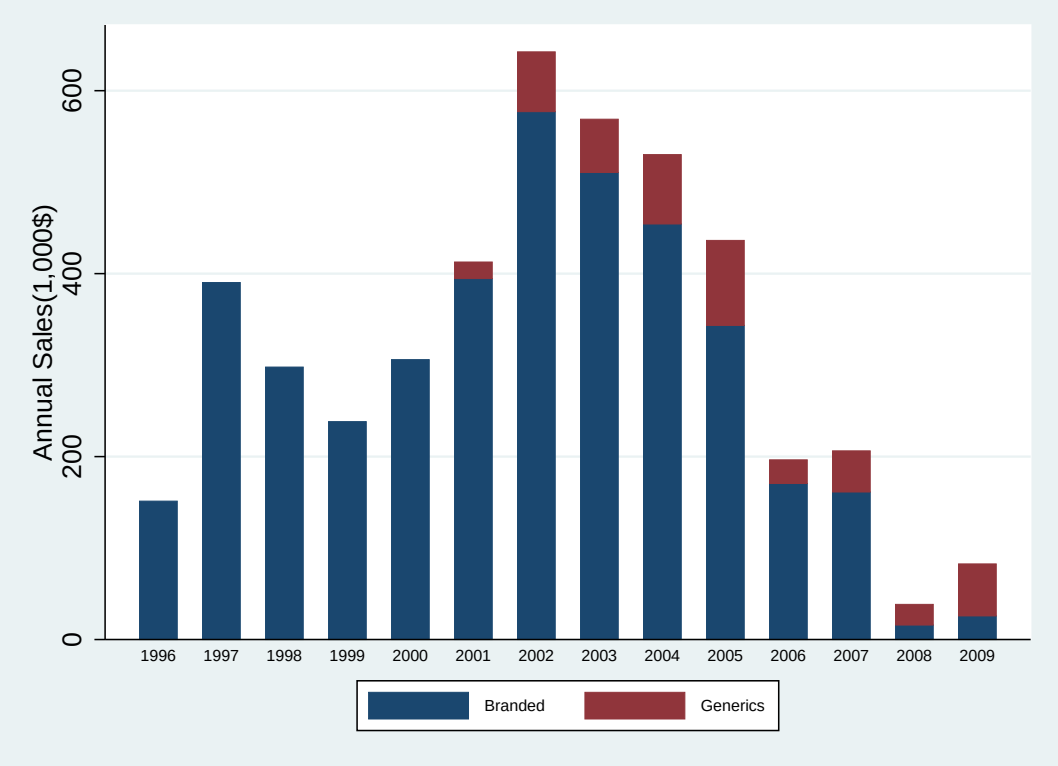

Figure 3: Market Share of SSRIs over Brands across Year

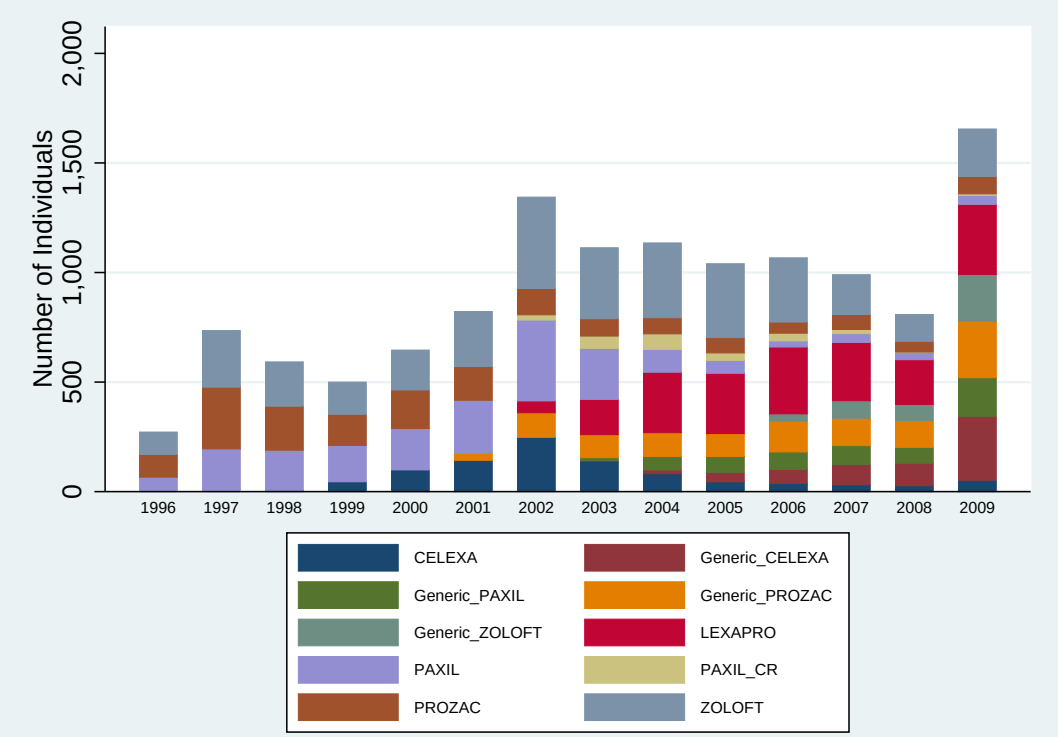

Figure 4: Annual Sales of SSRIs over Brands across Year

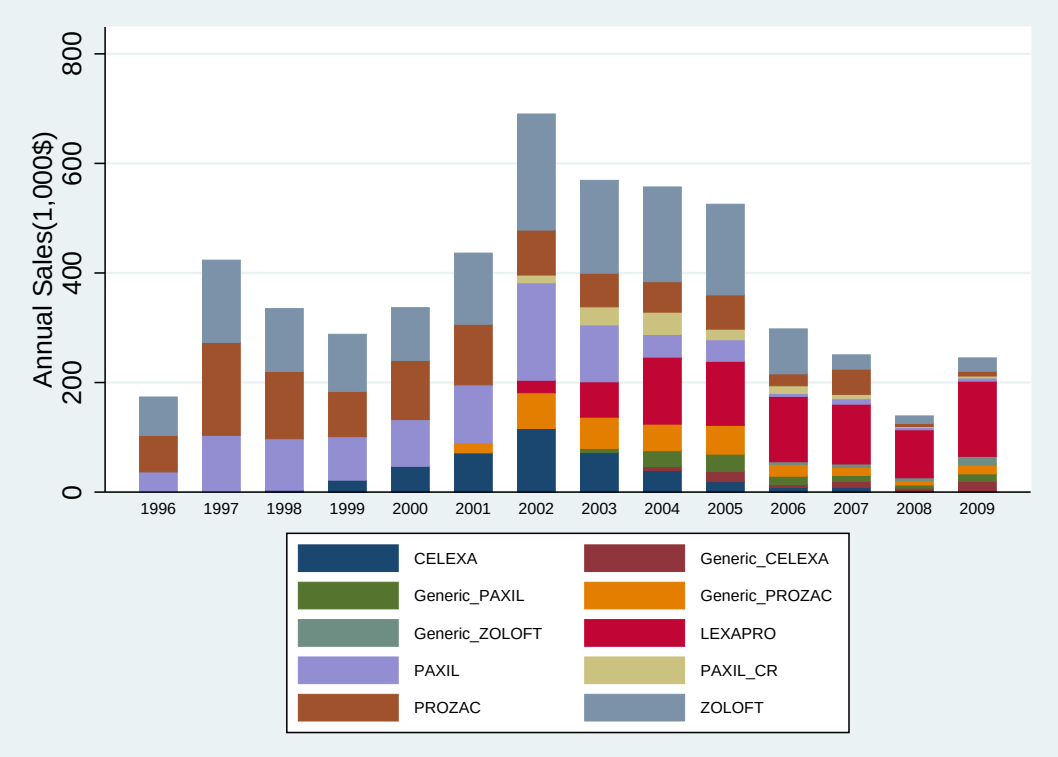

Figure 5: Price Trend with Generic Entry

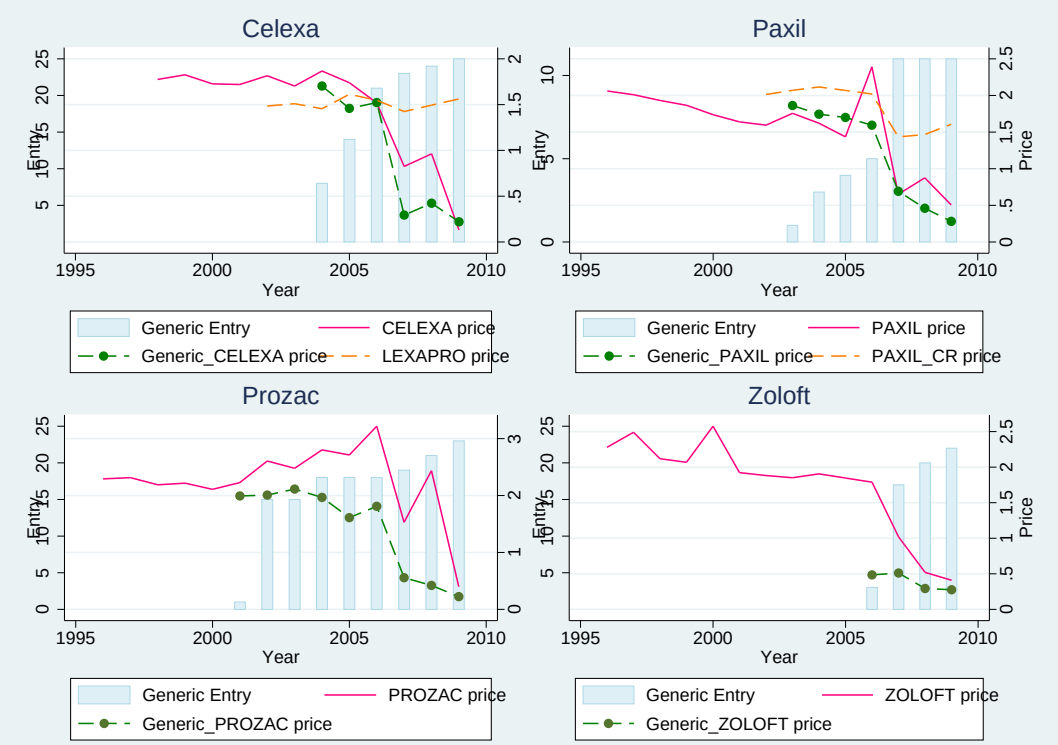

Figure 6: Estimated MC and Margin

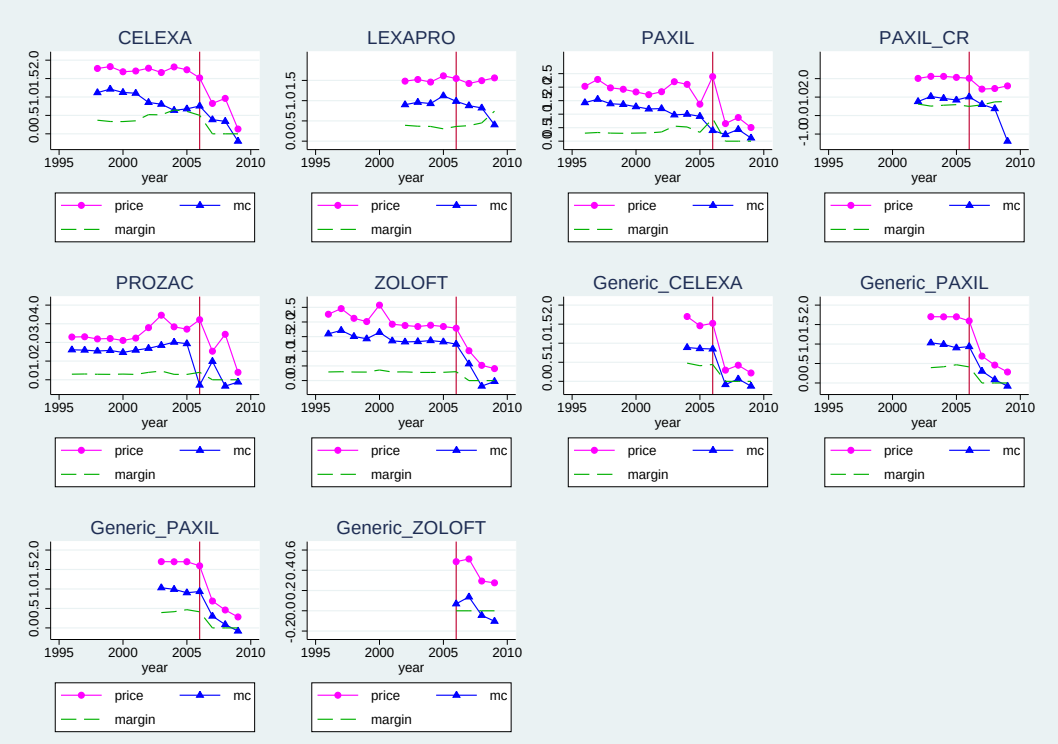

Figure 7: Price Changes from Scenario 1 to Scenario 2

Figure 8: Price Changes from Status Quo to Scenario 2

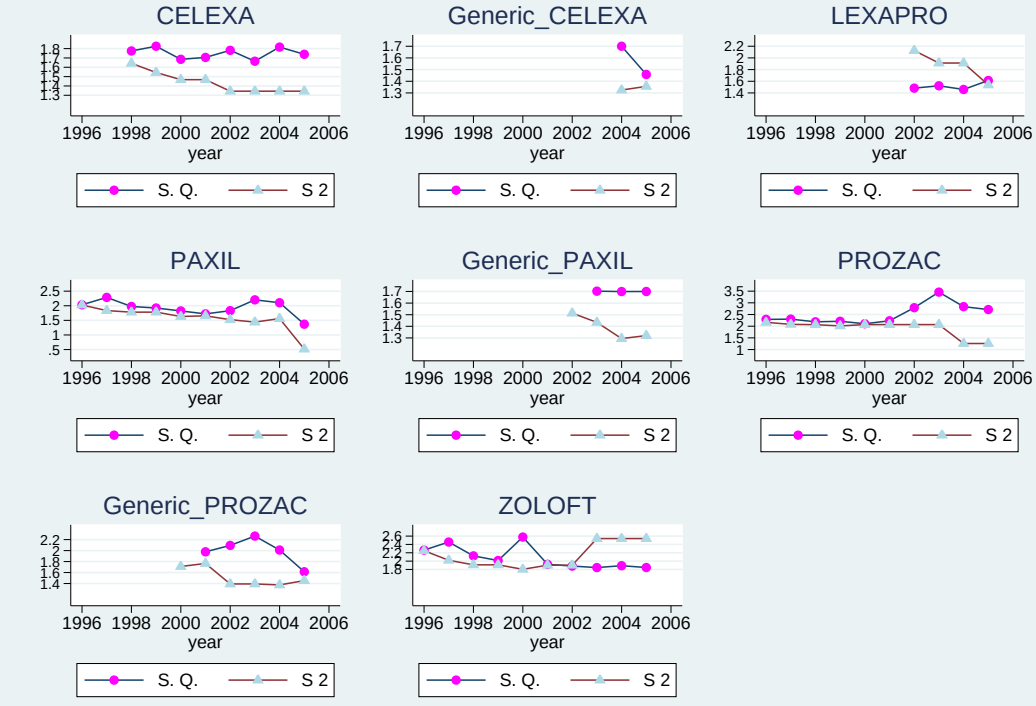

Figure 9: Price Changes from Scenario 3 to Scenario 4

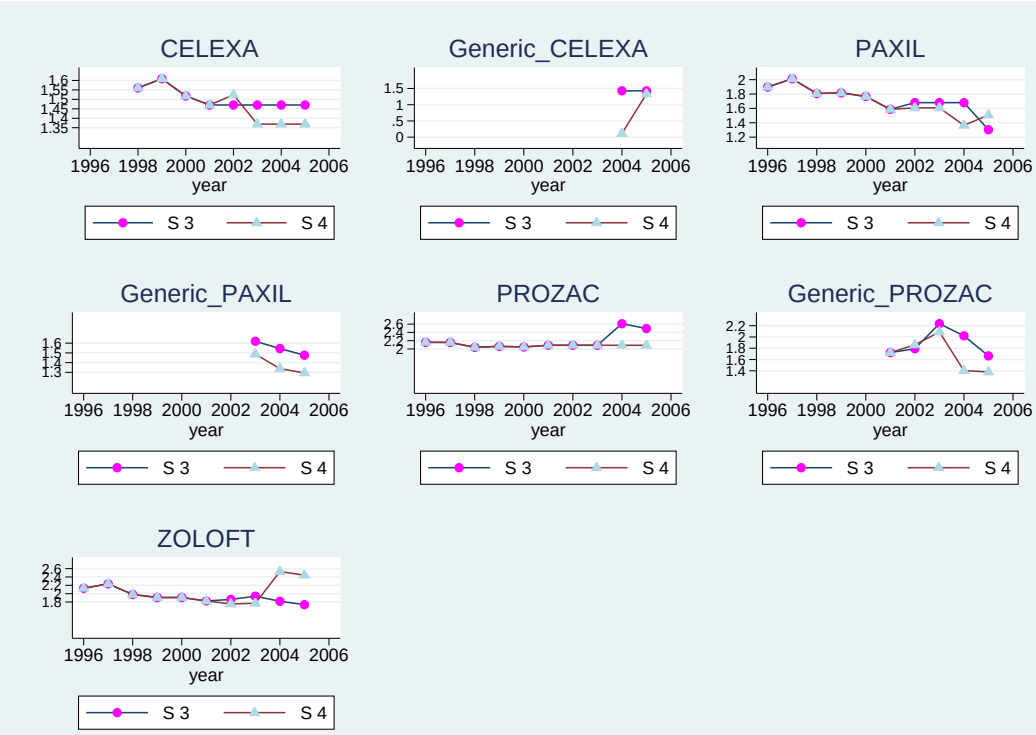

Figure 10: Price Changes from Status Quo to Scenario 4

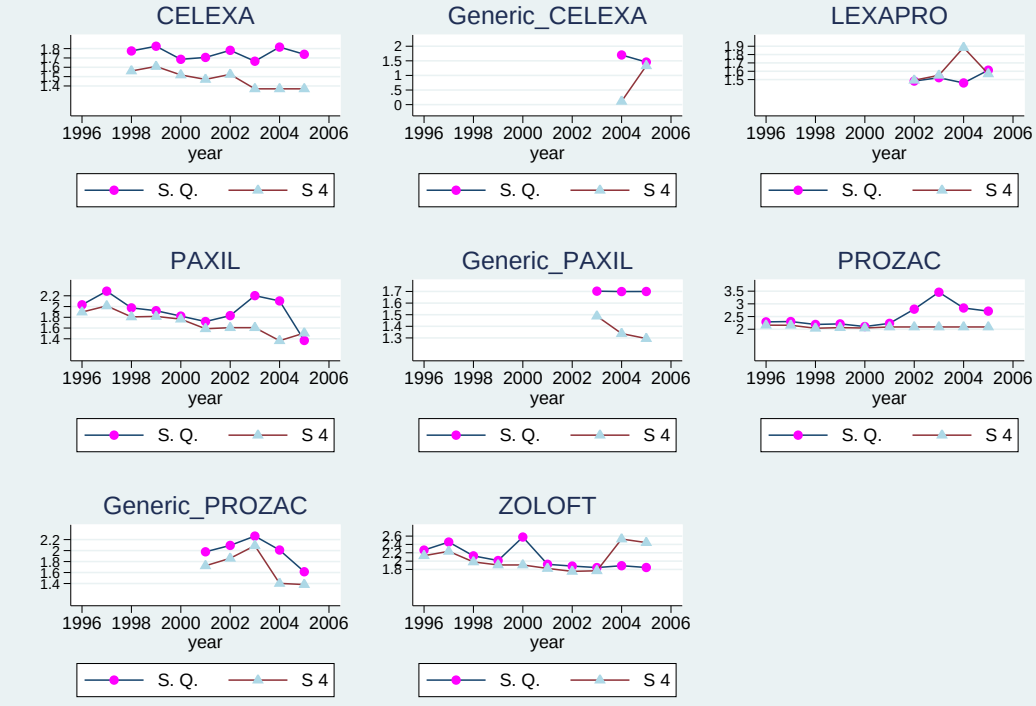

Figure 11: Price Changes from Scenario 5 to Scenario 6

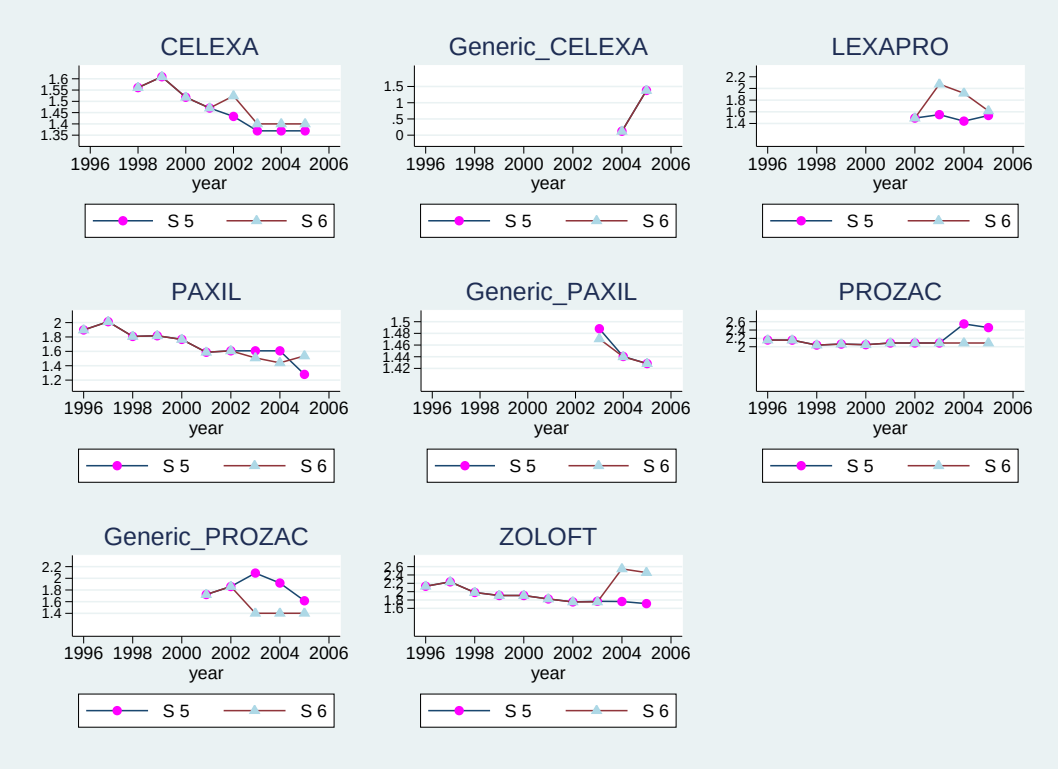

Figure 12: Price Changes from Status Quo to Scenario 6

Figure 13: Price Changes from Scenario 7 to Scenario 8

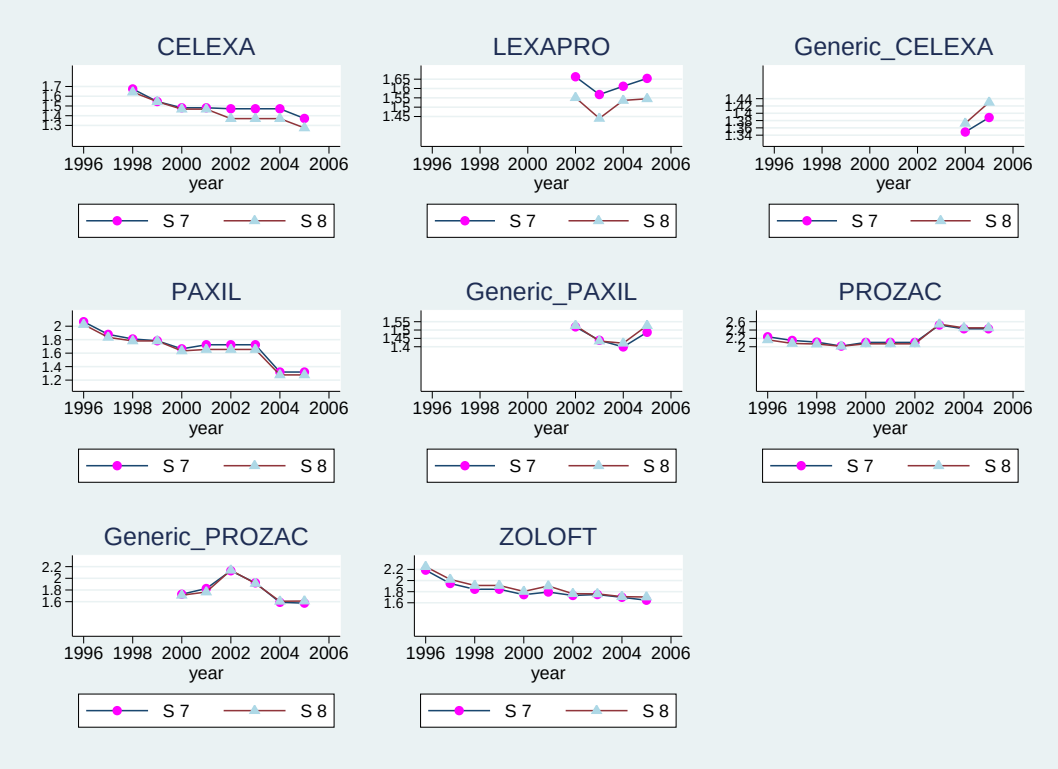

Figure 14: Price Changes from Status Quo to Scenario 8

Table 1: Products and Incremental Innovations in SSRI Anti-depressant Drugs

New Molecule	New Formulation	New Indication	Pediatric Usage	Safety	Generics
Celexa 1998	Lexapro 2002	Lexapro 2003 (Form.)			Generic Celexa 2004
Paxil 1992		Paxil 1999		Paxil CR 1999	Generic Paxil 2003
		Paxil 2001			
		Paxil CR 2002 (Safety)			
		Paxil CR 2003 (Safety)			
Prozac 1987		Prozac 2000	Prozac 2003 (Ind.)		Generic Prozac 2001
		Prozac 2006 (Ped.)			Generic Prozac 2003 (Ped.)
					Generic Prozac 2006 (Ped.&Ind.)
Zoloft 1991 (Ped)		Zoloft 2002 (Ped.)			Generic Zoloft 2006 (Ped.)
		Zoloft 2003 (Ped.)			

Note: 1. 4 new molecule entity followed with 12 incrementally innovated drugs and 6 generics(totally 22 products+ outside option); 2. Safety implies less side effects here; 3. The parenthesis includes the already having incremental innovations; 4. Form.– new formulations; Ind.– new indications; Ped.– pediatric usage.

Table 2: Sample Selection

	Conditions			No Conditions; SSRIs
	Conditions; No SSRIs		Conditions; SSRIs	
	No Drugs	Other drugs		
No. of Obs.	7, 298	6, 802	10, 901	1, 914
Percentage	27.10%	25.30%	40.50%	7.10%
Total	26, 915			

Note: (No)Conditions: The respondents reported that they have (no) depressive condition. (No) SSRIs: The respondents purchase (no) SSRI antidepressants. No Drugs: The respondents didn't purchase any antidepressants. Other Drugs: The respondents purchased other class of antidepressants.

Table 3: Individual Demographics

Variables	All MEPS sample (96-09)	Sample Employed in Study	Having Conditions No SSRIs.	Having Cond.; SSRIs	No Cond.; SSRIs
Age	33.62	45.72***	44.03	47.55***	47.78
	[22.55]	[19.04]	[19.58]	[18.04]	[19.47]
Male	0.48	0.32***	0.36	0.28***	0.31***
	[0.50]	[0.47]	[0.48]	[0.45]	[0.46]
Adult (age>18)	0.70	0.92***	0.9	0.95***	0.92***
	[0.46]	[0.27]	[0.30]	[0.22]	[0.27]
Years of Education	9.36	11.75***	11.43	12.15***	11.82***
	[5.60]	[3.64]	[3.89]	[3.26]	[3.62]
Household Income	15.33	16.61***	15.85	17.36***	17.85
Per Capita (1996$)	[15.36]	[16.41]	[16.47]	[16.37]	[15.94]
Household Income	44.6	39.61***	37.77	40.88***	46.00***
(1996$)	[38.40]	[36.61]	[36.17]	[36.52]	[39.26]
Perceived Health	2.21	2.93***	2.86	3.03***	2.85***
Status	[0.95]	[1.04]	[1.04]	[1.04]	[1.05]
Having Medical	0.83	0.88***	0.85	0.92***	0.94***
Insurance	[0.37]	[0.32]	[0.36]	[0.27]	[0.24]
Having Medicare	0.13	0.24***	0.22	0.26***	0.27
	[0.34]	[0.43]	[0.42]	[0.44]	[0.44]
Having Medicaid	0.22	0.25***	0.26	0.24***	0.20***
	[0.42]	[0.43]	[0.44]	[0.42]	[0.40]
Out of Pocket Rate	0.54	0.48***	0.51	0.43***	0.46**
	[0.27]	[0.36]	[0.30]	[0.41]	[0.41]
Having Respiratory	0.04	0.09***	0.08	0.11***	0.08***
Diseases	[0.20]	[0.29]	[0.27]	[0.31]	[0.26]
Having Asthma	0.05	0.09***	0.08	0.10***	0.07***
	[0.22]	[0.29]	[0.28]	[0.31]	[0.26]
Having HIV	0.00	0.00***	0	0	0
	[0.03]	[0.06]	[0.06]	[0.07]	[0.06]
Having Hypertension	0.13	0.28***	0.26	0.31***	0.28***
	[0.34]	[0.45]	[0.44]	[0.46]	[0.45]
Having Cardiovascular	0.08	0.19***	0.17	0.21***	0.2
Heart Diseases	[0.27]	[0.39]	[0.38]	[0.41]	[0.40]
Having Diabetes	0.05	0.12***	0.11	0.14***	0.11***
	[0.23]	[0.33]	[0.31]	[0.35]	[0.32]
Having Depression	0.03	0.93***	1	1	0
	[0.17]	[0.26]	[0.00]	[0.00]	[0.00]
Observations	239720	26915	14100	10901	1914

Note: Standard Deviation is enclosed in the bracket. Income is deflated at 1996 dollar level. The t-test significances are shown by stars: Stars in Column 2 compare Column 1 and 2; Stars in Column 4 compare Column 3 and 4; Stars in Column 5 compare Column 4 and 5. $p < 0.01$.

Table 4: Manufacturers and Market Share

Products	Analytic Sample		Survey Sample	
	Purchasing Obs.	Market Share	Purchasing Obs.	Market Share
CELEXA	966	7.54	7, 588	7.29
LEXAPRO	1, 869	14.58	14, 591	14.01
PAXIL	1, 961	15.3	15, 632	15.01
PAXIL CR	257	2.01	1, 959	1.88
PROZAC	1, 666	13	14, 099	13.54
ZOLOFT	3, 388	26.44	27, 603	26.5
Generic CELEXA	620	4.84	4, 301	4.13
Generic PAXIL	568	4.43	5, 119	4.92
Generic PROZAC	1, 115	8.7	10, 261	9.85
Generic ZOLOFT	405	3.16	2, 990	2.87
Total	12, 815	100	104, 143	100

Table 5: Summary Statistics of Product Attributes

Variable	Mean	Std. Dev.	Min	Max
Indications				
MDD	1	0	1	1
OCD	0.68	0.48	0	1
PD	0.55	0.51	0	1
PSD	0.23	0.43	0	1
PDD	0.45	0.51	0	1
SAD	0.32	0.48	0	1
BN	0.32	0.48	0	1
Side E□ects				
Headache	1.16	0.15	1	1.38
Asthenia	1.80	0.57	1	2.82
Nausea	2.46	0.57	1.5	3.51
Diarrhea	1.85	0.34	1.57	2.57
Anorexia	2.20	1.08	1	3.33
Insomnia	1.94	0.33	1.1	2.33
Anxiety	1.53	0.40	1	2
Somnolence	2.61	0.70	1.8	3.84
Rash	1.49	0.57	1	2.6
Abnormal Ejaculation	13.95	10.48	3.42	29.24
Pediatric	0.36	0.49	0	1
Observation	22			

Note: MDD=Major Depressive Disorder; OCD=Obsessive Compulsive Disorder; PD=Panic Disorder; PSD=Posttraumatic Stress Disorder; PDD=Premenstrual Dysphoric Disorder; SAD=Social Anxiety Disorder; BN=Bulimia Nervosa; Pediatric=The safety and e□cacy of the drug for pediatric usage have been established. The values of the side e□ect variable are calculated as the ratio of hazard rate of the patients who take drugs with respect to the hazard rate of the patients who take placebo.

Table 6: Selected Estimates in SMLE

	Variance	Age	Age2	Medical Insurance	Drug Insurance	Medi-care	Medi-caid	Educ-ation	Log(Inc. Per Cap.)	Perceived Health
Price	0.72***	-7.58***	3.64***	-0.05	0.61***	-0.04	-0.23***	0.16	0.07**	0.04
	(.22)	(2.45)	(1.15)	(.09)	(.1)	(.06)	(.08)	(.14)	(.03)	(.03)
Outside		1.35	-0.23	-0.97***	0.31***	-0.55**	0.13	0.14	-0.12	0.03***
Option		(10.9)	(5.1)	(.31)	(.)	(.23)	(.23)	(70.88)	(.13)	(.)
Agemole		0.93	-0.23	-0.13	-0.67***	-0.23**	-0.02	-0.05	-0.09	-0.18***
		(4.9)	(2.3)	(.12)	(.16)	(.09)	(.09)	(.24)	(.06)	(.05)
Generic	0.29	-4.63	2.41	-0.12	0.73***	0.01	0.03	0.01	0.13***	0
	(.45)	(3.61)	(1.69)	(.12)	(.1)	(.09)	(.09)	(.16)	(.04)	(.03)
Pediatric		-0.2		0.22**	-0.38***	0.19***	0.02	0.05	0.07*	0.05
		(.14)		(.09)	(.13)	(.06)	(.07)	(.32)	(.04)	(.05)

Note: The simulated maximum likelihood estimation includes 109 branded-year fixed e□ects and 115 explanatory variables (including two random coe□cients for price and generic dummy and 113 individual-drug characteristics interaction terms). We listed the parameters we interested here. To see the full picture of the estimation, please check the appendix Table. Standard errors are included in parenthesis. $p < 0.1$; $p < 0.05$; $p < 0.01$.

Table 7: Estimates of Mean Utility on Prices

	OLS	IV: Model I	IV: Model II	IV: Model III
Price	0.388***	-1.443***	-1.680***	-1.304***
	(2.81)	(-2.96)	(-2.94)	(-2.76)
Pediatric	-0.494*	0.166	0.252	0.116
	(-1.87)	(0.46)	(0.65)	(0.33)
Agemole	0.717***	-0.0219	-0.118	0.0341
	(2.78)	(-0.05)	(-0.26)	(0.09)
Constant	-1.125*	2.794**	3.300**	2.497**
	(-1.85)	(2.32)	(2.41)	(2.13)
Brand Dummies	Yes	Yes	Yes	Yes
Indication Dummies	Yes	Yes	Yes	Yes
Observations	96	96	96	96
R-squared	0.67	0.15	0.00	0.23

Note: 1. Dependent variable is the estimated drug-year mean utility; 2. The IVs used in the Column 2 is markup*generic, number of dosage; in column 3 is number of dosage; in column 4 is markup*generic, markup, demand*generic, number of dosage. 5. The Brand Dummies include Generic Celexa, Generic Paxil, Generic Prozac, Generic Zoloft, Lexapro, Paxil, Paxil CR, Prozac, Zoloft and outside option, the excluded one is Celexa. 6. The Indication Dummies include PDD, PSD, SAD, PD. OCD and BN are dropped due to collinearity problem. 7 . t statistics is included in parentheses. 8. $p < 0.1$, $p < 0.05$, $p < 0.01$

Table 8: The Relevance of IV

	Model I	Model II	Model III
Markup			-0.44
			(-0.54)
Markup*Generic	-32.21**		-31.36**
	(-2.1)		(-2.02)
Demand			0
			(-0.04)
No. of Dosage	-0.01**	-0.02**	-0.01**
	(-2.58)	(-2.92)	(-2.55)
Pediatric	0.67***	0.53***	0.66***
	(3.59)	(2.89)	(3.56)
Agemole	-0.35***	-0.35***	-0.37***
	(-2.96)	(-2.97)	(-2.79)
Constant	2.11***	2.12***	2.33***
	12.53	12.64	5.23
Brand Dummies	Yes	Yes	Yes
Indication Dummies	Yes	Yes	Yes
R squared	0.78	0.77	0.78
	96	96	96

Note: 1. Dependent variable is weighted averaged prices at brand-year level. 2. The Brand Dummies include Generic Celexa, Generic Paxil, Generic Prozac, Generic Zoloft, Lexapro, Paxil, Paxil CR, Prozac, Zoloft and outside option, the excluded one is Celexa. 3. The Indication Dummies include PDD, PSD, SAD, PD. OCD and BN are dropped due to collinearity problem.4. t statistics is included in parentheses.5. $p < 0.1$, $p < 0.05$, $p < 0.01$

Table 9: Counterfactual Scenarios

II	W (II, no ME)	W (no II, no ME)
1. All incremental innovations	scenario 2	scenario 1
2. Lexapro as a new formulation of Celexa	scenario 4	scenario 3
3. Paxil CR with improved safety	scenario 6	scenario 5
4. Pediatric use	scenario 8	scenario 7

Table 10: Market Exclusivity Changes across Counterfactuals

II	W (II, no ME)	W (no II, no ME)
	Prices	Prices
1. All incremental innovations	Generic Paxil, Prozac and Zoloft entered one year earlier, Generic Lexapro and Generic Paxil CR entered with Generic Celexa and Generic Paxil	Generic entries for Paxil, Prozac and Zoloft are one year earlier,
2. Lexapro as a new formulation of Celexa	Generic Lexapro entered with Generic Celexa	No Lexapro developed and no generic Lexapro entering
3. Paxil CR with improved safety	Generic Paxil CR entered with Generic Paxil	No Paxil CR developed and no Generic Paxil CR entering
4. Pediatric use	Generic Paxil, Prozac and Zoloft entered one year earlier	Generic Paxil, Prozac and Zoloft entered one year earlier

Note: Prices are calculated in simulation, but are subjected to changes with exclusivity removal. For example, if the exclusivity of Prozac is reduced for one year, competitive market present one year earlier from 2001 to 2000. Then the price curve shift one year earlier.

Table 11: Welfare Changes (Billion Dollars)(for years before 2006)

II	W (II, ME)-W (II, no ME)		W (II, no ME)-W (no II, no ME)	
	Consumer	Branded Firm	Consumer	Branded Firm
1. All incremental innovations	-15.7	18	19.5	-20.6
2. Lexapro as a new formulation of Celexa	-7.95	-0.5	-1.27	12.8
3. Paxil CR with improved safety	-7.87	0.3	1.58	-2.07
4. Pediatric use	-11.1	13.6	4.46	-0.6

Table 12: Welfare Changes (Billion Dollars)

II	W (II, ME)-W (II, no ME)		W (II, no ME)-W (no II, no ME)	
	Consumer	Branded Firm	Consumer	Branded Firm
1. All incremental innovations	-27.4	21	29.4	-22.5
2. Lexapro as a new formulation of Celexa	-15.8	4.31	6.32	11.8
3. Paxil CR with improved safety	-12.9	6.35	8.10	-10.1
4. Pediatric use	-16.5	14.3	12.0	-1.27

Table 13: Drug Indications

Ingredient	Brand Name	Entry	MDD	OCD	PD	PSD	PDD	SAD	BN	Ped.
CITALOPRAM	CELEXA	1998	1	0	0	0	0	0	0	0
HYDROBROMIDE	Generic CELEXA	2004	1	0	0	0	0	0	0	0
ESCITALOPRAM	LEXAPRO	2002	1	0	0	0	0	0	0	0
OXALATE	LEXAPRO	2003	1	0	0	0	0	1	0	0
FLUOXETINE	PROZAC	1987	1	1	0	0	0	0	1	0
HYDROCHLORIDE	PROZAC	2000	1	1	0	0	1	0	1	0
	Generic PROZAC	2001	1	1	0	0	1	0	1	0
	PROZAC	2003	1	1	0	0	1	0	1	1
	Generic PROZAC	2003	1	1	0	0	1	0	1	1
	PROZAC	2006	1	1	1	0	1	0	1	1
	Generic PROZAC	2006	1	1	1	0	1	0	1	1
PAROXETINE	PAXIL	1992	1	1	1	0	0	0	0	0
HYDROCHLORIDE	PAXIL	1999	1	1	1	0	0	1	0	0
	PAXIL	2001	1	1	1	1	0	1	0	0
	PAXIL CR	1999	1	0	0	0	0	0	0	0
	PAXIL CR	2002	1	0	1	0	0	0	0	0
	PAXIL CR	2003	1	0	1	0	1	1	0	0
	Generic PAXIL	2003	1	1	1	1	0	1	0	0
SERTRALINE	ZOLOFT	1991	1	1	1	0	0	0	0	1
HYDROCHLORIDE	ZOLOFT	2002	1	1	1	1	1	0	0	1
	ZOLOFT	2003	1	1	1	1	1	1	0	1
	Generic ZOLOFT	2006	1	1	1	1	1	1	0	1

Note: Entry: Approved or Supplemental approved by FDA; MDD=Major Depressive Disorder; OCD=Obsessive Compulsive Disorder; PD=Panic Disorder; PSD=Posttraumatic Stress Disorder; PDD=Premenstrual Dysphoric Disorder; SAD=Social Anxiety Disorder; BN=Bulimia Nervosa; Ped.=The safety and e□cacy of the drug for pediatric usage have been established.

Table 14: Side effects of drugs

Ingredient	Brand Name	Headache	Asthenia	Nausea	Diarrhea	Anorexia	Insomnia	Anxiety	Somnolence	Rash	AbnEja
CITALOPRAM HYDROBROMIDE	Celexa	1	1	1.5	1.6	2	1.1	1.33	1.8	1	6
PAROXETINE HYDROCHLORIDE	Paxil	1.38	2.82	3.51	1.89	1	2.33	1.68	3.84	2.6	29.24
FLUOXETINE HYDROCHLORIDE	Prozac	1.1	1.83	2.34	1.57	3.33	1.9	2	2.4	1.33	3.42
SERTRALINE HYDROCHLORIDE	Zoloft	1.08	1.71	2.27	2	3	1.9	1.33	1.86	1.5	14
ESCITALOPRAM OXALATE	Lexapro	1	1	2.14	1.6	1	2.25	1	3	1	10
PAROXETINE HYDROCHLORIDE	Paxil CR	1.35	1.56	2.2	2.57	1	1.89	1	2.75	1	26

Note: The values in this chart are calculated as the ratio of hazard rate of the patients who take drugs with respect to the hazard rate of the patients who take placebo. AbnEja=Abnormal Ejaculation.

Table 15: Estimated Coe□cients by SMLE

	Variance	Age	Age2	Medical Insurance	Drug Insurance	Medicare	Medicaid	Education	Log(Income/Per Capita)	Perceived Health	Male	Adult
Price	0.72	-7.58	3.64	-0.05	0.61	-0.04	-0.23	0.16	0.07	0.04		
	(.22)	(2.45)	(1.15)	(.09)	(.1)	(.06)	(.08)	(.14)	(.03)	(.03)		
Outside Option		1.35	-0.23	-0.97	0.31	-0.55	0.13	0.14	-0.12	0.03		
		(10.9)	(5.1)	(.31)	(.)	(.23)	(.23)	(70.88)	(.13)	(.)		
Agemole		0.93	-0.23	-0.13	-0.67	-0.23	-0.02	-0.05	-0.09	-0.18		
		(4.9)	(2.3)	(.12)	(.16)	(.09)	(.09)	(.24)	(.06)	(.05)		
Generic	0.29	-4.63	2.41	-0.12	0.73	0.01	0.03	0.01	0.13	0		
	(.45)	(3.61)	(1.69)	(.12)	(.1)	(.09)	(.09)	(.16)	(.04)	(.03)		
Pediatric		-0.2		0.22	-0.38	0.19	0.02	0.05	0.07	0.05		
		(.14)		(.09)	(.13)	(.06)	(.07)	(.32)	(.04)	(.05)		
OCD		0.56	-0.2					-0.17	0.07		-0.05	
		(6.28)	(2.95)					(.)	(65.3)		(.06)	
PD		2.97	-1.44					-0.01	-0.05		-0.08	
		(4.32)	(2.03)					(.32)	(.11)		(.04)	
PSD		0.21	-0.12					0.28	0.03		0.06	
		(4.68)	(2.2)					(.21)	(.11)		(.05)	
PDD		2.83	-1.44					-0.08	-0.07		0.01	
		(3.24)	(1.53)					(.19)	(.09)		(.04)	
SAD		-1.72	0.83					-0.08	-0.02		0.05	
		(3.24)	(1.52)					(.2)	(.1)		(.04)	
BN		-1.35	0.43									
		(6.02)	(2.83)									
Headache					-0.03			-0.3		-0.02	-0.06	
					(.)			(55.82)		(52.51)	(78.84)	
Asthenia					0.46			-0.46		-0.07	-0.11	
					(.)			(36.)		(.)	(.)	
Nausea					0.2			0.05		-0.01	0.01	
					(.)			(19.81)		(.)	(.)	
Diarrhea					0.35			-0.48		-0.01	-0.22	
					(48.06)			(.)		(7.54)	(34.63)	
Anorexia					0.25			0.3		0.1	-0.03	
					(11.21)			(.)		(7.98)	(17.25)	
Insomnia					0.37			-0.05		-0.13	0.1	
					(.)			(7.22)		(8.99)	(22.3)	
Anxiety					-0.2			0.28		0.14	-0.15	
					(87.2)			(15.92)		(3.14)	(65.65)	
Somnolence					-0.17			0.65		0.17	-0.19	
					(31.52)			(7.69)		(8.38)	(.)	
Rash					-0.36			-0.2		-0.05	0.34	
					(.)			(.)		(.)	(56.97)	
Abnormal		-0.02			0.03			0.01		0.09	0.13	-0.03
Ejaculation		(.14)			(35.)			(6.21)		(.)	(65.46)	(.04)

Note: Standard errors in parenthesis; The coe□cient in"variance" column report the estimated standard errors for random coe□cients.

Table 16: Estimated Brand-year Fixed E□ects

Brand	Year	Coe□cients	St. Dev.	
CELEXA	1999	0.5944	0	***
CELEXA	2000	0.6875	0	***
CELEXA	2001	1.1787	126.5858	
CELEXA	2002	1.6683	0	***
CELEXA	2003	1.1544	0	***
CELEXA	2004	0.8158	0	***
CELEXA	2005	0.2667	204.5615	
CELEXA	2006	0.2525	0	***
CELEXA	2007	0.0014	39.1229	
CELEXA	2008	0.0033	0	***
CELEXA	2009	-0.5079	46.7675	
Generic CELEXA	2004	-1.4079	0	***
Generic CELEXA	2005	-0.5361	204.5532	
Generic CELEXA	2006	0.2513	0	***
Generic CELEXA	2007	-0.1771	38.9684	
Generic CELEXA	2008	0.6432	0	***
Generic CELEXA	2009	0.8733	46.7913	
Generic PAXIL	2003	-2.3003	0	***
Generic PAXIL	2004	-0.6239	0	***
Generic PAXIL	2005	-0.2568	204.587	
Generic PAXIL	2006	0.1326	0	***
Generic PAXIL	2007	-0.133	38.4602	
Generic PAXIL	2008	-0.2701	0	***
Generic PAXIL	2009	0.081	46.7616	
Generic PROZAC	2001	-0.7943	126.7596	
Generic PROZAC	2002	0.3069	0	***
Generic PROZAC	2003	0.4464	0	***
Generic PROZAC	2004	0.5114	0	***
Generic PROZAC	2005	0.3457	204.5877	
Generic PROZAC	2006	0.9155	0	***
Generic PROZAC	2007	0.2055	38.2897	
Generic PROZAC	2008	0.4778	0	***
Generic PROZAC	2009	0.55	46.8321	

Table 15 (Continued)

Generic ZOLOFT	2006	-1.4861	0	***
Generic ZOLOFT	2007	0.094	38.4213	
Generic ZOLOFT	2008	0.1555	0	***
Generic ZOLOFT	2009	0.9183	46.8527	
LEXAPRO	2002	-0.7663	0	***
LEXAPRO	2003	0.7873	0	***
LEXAPRO	2004	1.4238	0	***
LEXAPRO	2005	1.7422	204.629	
LEXAPRO	2006	1.9867	0	***
LEXAPRO	2007	2.2416	0	***
LEXAPRO	2008	2.3089	0	***
LEXAPRO	2009	2.2379	0	***
PAXIL	1996	1.1513	0	***
PAXIL	1997	0.9485	158.4299	
PAXIL	1998	2.3501	0	***
PAXIL	1999	1.4254	0	***
PAXIL	2000	1.1311	0	***
PAXIL	2001	0.9739	126.6269	
PAXIL	2002	1.3784	0	***
PAXIL	2003	1.4426	0	***
PAXIL	2004	0.7399	0	***
PAXIL	2005	-0.282	204.6364	
PAXIL	2006	0.283	0	***
PAXIL	2007	-0.298	0	***
PAXIL	2008	-0.0249	0	***
PAXIL	2009	-0.5776	0	***
PAXIL CR	2002	0.2468	0	***
PAXIL CR	2003	2.155	0	***
PAXIL CR	2004	2.4827	0	***
PAXIL CR	2005	1.9279	204.4874	
PAXIL CR	2006	2.5338	0	***
PAXIL CR	2007	1.7259	0	***
PAXIL CR	2008	0.0901	0	***
PAXIL CR	2009	0.8844	0	***
PROZAC	1996	0.9969	0	***
PROZAC	1997	0.7645	158.4463	
PROZAC	1998	2.059	0	***
PROZAC	1999	0.7415	0	***
PROZAC	2000	0.7803	0	***

Table 15 (Continued)

PROZAC	2001	1.3177	126.7304	
PROZAC	2002	1.2438	0	***
PROZAC	2003	1.1617	0	***
PROZAC	2004	1.0946	0	***
PROZAC	2005	1.1955	204.5415	
PROZAC	2006	1.0298	0	***
PROZAC	2007	0.7707	0	***
PROZAC	2008	1.4179	0	***
PROZAC	2009	0.1152	0	***
ZOLOFT	1996	1.6903	0	***
ZOLOFT	1997	1.5853	158.4378	
ZOLOFT	1998	2.6623	3.0816	
ZOLOFT	1999	1.163	0	***
ZOLOFT	2000	1.4136	0	***
ZOLOFT	2001	1.7355	126.7906	
ZOLOFT	2002	1.6021	0	***
ZOLOFT	2003	1.8479	0	***
ZOLOFT	2004	2.193	0	***
ZOLOFT	2005	2.4159	0	***
ZOLOFT	2006	2.4739	0	***
ZOLOFT	2007	2.0074	38.575	
ZOLOFT	2008	1.4936	0	***
ZOLOFT	2009	1.3749	46.8219	
NO DRUG	1996	0.1615	0	***
NO DRUG	1997	0.7016	158.468	
NO DRUG	1998	2.2866	3.191	
NO DRUG	1999	1.0758	0	***
NO DRUG	2000	0.9876	0	***
NO DRUG	2001	1.5885	126.723	
NO DRUG	2002	2.3198	0	***
NO DRUG	2003	2.3048	0	***
NO DRUG	2004	2.7708	0	
NO DRUG	2005	3.1811	0	***
NO DRUG	2006	3.6272	0	***
NO DRUG	2007	4.5614	38.3853	
NO DRUG	2008	4.7049	0	***
NO DRUG	2009	5.0505	46.8131	

Table 17: The Entry of Generic Manufacturers by year

Trade name	Manufacturers	Entry Year
CELEXA	FOREST LABS	1998
CITALOPRAM HYDROBROMIDE	AUROBINDO	2004
CITALOPRAM HYDROBROMIDE	DR REDDYS LABS LTD	2004
CITALOPRAM HYDROBROMIDE	ACTAVIS ELIZABETH	2004
CITALOPRAM HYDROBROMIDE	COREPHARMA	2004
CITALOPRAM HYDROBROMIDE	SANDOZ	2004
CITALOPRAM HYDROBROMIDE	MYLAN	2004
CITALOPRAM HYDROBROMIDE	WATSON LABS	2004
CITALOPRAM HYDROBROMIDE	ALPHAPHARM	2004
CITALOPRAM HYDROBROMIDE	CARACO	2004
CITALOPRAM HYDROBROMIDE	IVAX SUB TEVA PHARMS	2004
CITALOPRAM HYDROBROMIDE	ROXANE	2004
CITALOPRAM HYDROBROMIDE	APOTEX INC	2004
CITALOPRAM HYDROBROMIDE	EPIC PHARMA	2005
CITALOPRAM HYDROBROMIDE	PLIVA	2005
CITALOPRAM HYDROBROMIDE	BIOVAIL LABS INTL	2005
CITALOPRAM HYDROBROMIDE	TARO	2006
CITALOPRAM HYDROBROMIDE	TEVA PHARMS	2006
CITALOPRAM HYDROBROMIDE	SILARX	2006
CITALOPRAM HYDROBROMIDE	MUTUAL PHARM	2006
CITALOPRAM HYDROBROMIDE	AUROBINDO PHARMA LTD	2006
CITALOPRAM HYDROBROMIDE	INVAGEN PHARMS	2006
CITALOPRAM HYDROBROMIDE	AMNEAL PHARMS NY	2006
CITALOPRAM HYDROBROMIDE	TORRENT PHARMS	2007
CITALOPRAM HYDROBROMIDE	NATCO PHARMA LTD	2008
CITALOPRAM HYDROBROMIDE	GLENMARK GENERICS	2009

Table 16 (Continued)

Trade name	Manufacturers	Entry Year
PAXIL	GLAXOSMITHKLINE	1998
PAROXETINE HYDROCHLORIDE	APOTEX	2003
PAROXETINE HYDROCHLORIDE	ALPHAPHARM	2004
PAROXETINE HYDROCHLORIDE	SANDOZ	2004
PAROXETINE HYDROCHLORIDE	TEVA	2005
PAROXETINE HYDROCHLORIDE	APOTEX INC	2006
PAROXETINE HYDROCHLORIDE	ZYDUS PHARMS USA	2007
PAROXETINE HYDROCHLORIDE	MYLAN	2007
PAROXETINE HYDROCHLORIDE	ROXANE	2007
PAROXETINE HYDROCHLORIDE	CARACO	2007
PAROXETINE HYDROCHLORIDE	TEVA PHARMS	2007
PAROXETINE HYDROCHLORIDE	AUROBINDO PHARMA	2007
PAROXETINE HYDROCHLORIDE	ACTAVIS ELIZABETH	2010
PROZAC	LILLY	1991
PROZAC WEEKLY	LILLY	2001
FLUOXETINE HYDROCHLORIDE	BARR	2001
FLUOXETINE HYDROCHLORIDE	TEVA	2002
FLUOXETINE HYDROCHLORIDE	SANDOZ	2002
FLUOXETINE	WATSON LABS	2002
FLUOXETINE HYDROCHLORIDE	MALLINCKRODT	2002
FLUOXETINE HYDROCHLORIDE	PLIVA	2002
FLUOXETINE HYDROCHLORIDE	ALPHAPHARM	2002
FLUOXETINE	MUTUAL PHARMA	2002
FLUOXETINE HYDROCHLORIDE	MYLAN	2002
FLUOXETINE HYDROCHLORIDE	CARLSBAD	2002
FLUOXETINE HYDROCHLORIDE	DR REDDYS LABS INC	2002

Table 16 (Continued)

Trade name	Manufacturers	Entry Year
FLUOXETINE HYDROCHLORIDE	PHARM ASSOC	2002
FLUOXETINE HYDROCHLORIDE	LANDELA PHARM	2002
FLUOXETINE HYDROCHLORIDE	ACTAVIS MID ATLANTIC	2002
FLUOXETINE HYDROCHLORIDE	IVAX SUB TEVA PHARMS	2002
FLUOXETINE HYDROCHLORIDE	BEIJING DOUBLE CRANE	2002
FLUOXETINE HYDROCHLORIDE	NOVEX	2002
FLUOXETINE HYDROCHLORIDE	HI TECH PHARMA	2002
FLUOXETINE HYDROCHLORIDE	LANNETT	2004
FLUOXETINE HYDROCHLORIDE	RANBAXY	2004
FLUOXETINE HYDROCHLORIDE	PAR PHARM	2004
FLUOXETINE HYDROCHLORIDE	SILARX	2007
FLUOXETINE HYDROCHLORIDE	WOCKHARDT	2008
FLUOXETINE HYDROCHLORIDE	AUROBINDO PHARMA	2008
FLUOXETINE HYDROCHLORIDE	ALEMBIC PHARMS LTD	2009
FLUOXETINE HYDROCHLORIDE	AUROBINDO PHARM	2009
FLUOXETINE HYDROCHLORIDE	DR REDDYS LABS LTD	2010
FLUOXETINE HYDROCHLORIDE	EDGEMONT PHARMS LLC	2011
ZOLOFT	PFIZER	1991
SERTRALINE HYDROCHLORIDE	IVAX SUB TEVA PHARMS	2006
SERTRALINE HYDROCHLORIDE	TEVA	2006
SERTRALINE HYDROCHLORIDE	RANBAXY	2007
SERTRALINE HYDROCHLORIDE	WATSON LABS	2007
SERTRALINE HYDROCHLORIDE	APOTEX INC	2007
SERTRALINE HYDROCHLORIDE	MYLAN	2007
SERTRALINE HYDROCHLORIDE	ACTAVIS ELIZABETH	2007
SERTRALINE HYDROCHLORIDE	SUN PHARM INDS (IN)	2007
SERTRALINE HYDROCHLORIDE	ZYDUS PHARMS USA	2007

Table 16 (Continued)

Trade name	Manufacturers	Entry Year
SERTRALINE HYDROCHLORIDE	MUTUAL PHARM	2007
SERTRALINE HYDROCHLORIDE	SANDOZ	2007
SERTRALINE HYDROCHLORIDE	TORRENT PHARMS	2007
SERTRALINE HYDROCHLORIDE	PLIVA HRVATSKA DOO	2007
SERTRALINE HYDROCHLORIDE	ROXANE	2007
SERTRALINE HYDROCHLORIDE	AUROBINDO PHARMA	2007
SERTRALINE HYDROCHLORIDE	INVAGEN PHARMS	2007
SERTRALINE HYDROCHLORIDE	LUPIN	2007
SERTRALINE HYDROCHLORIDE	DR REDDYS LABS LTD	2007
SERTRALINE HYDROCHLORIDE	WOCKHARDT	2008
SERTRALINE HYDROCHLORIDE	MATRIX LABS LTD	2008
SERTRALINE HYDROCHLORIDE	AUSTARPHARMA LLC	2009
SERTRALINE HYDROCHLORIDE	HIKMA PHARMS	2009
SERTRALINE HYDROCHLORIDE	ACTAVIS TOTOWA	2010
LEXAPRO	FOREST LABS	2002
ESCITALOPRAM OXALATE	ALPHAPHARM	2007

8 Appendix

8.1 Data Construction

8.1.1 Individual-level Data

The individual characteristics are constructed from MEPS Full Year Consolidated files. The Full Year Consolidated file includes demographic and labor market information, sample weights, health status and a rich set of health insurance coverage information. MEPS provides the date of birth for each respondents which can be used to calculate the Age. $Years\ of\ Education$ is collected for each respondents at the first round of interviews. We generate a $Adult$ dummy for each individual, $Adult$ = 1 if his/her age is greater than or equal to 18 years old. Family Yearly Income is summarized over all household members from three components: person's total income; person's refund income; person's sale income. In MEPS, total person-level income is the sum of all income components with the exception of person's refund income and person's sale income to match as closely as possible the CPS definition of income; For our purpose, we will sum them up to obtain the measure of total individual income. By averaging family income within household members, we obtain Family Income Per Capita. After deflated to 1996 dollars level, we define the income variable as $Log(Family\ Income\ Per\ Capita/1000 + 1)$ to avoid the scale problem in MLE. In the survey, respondents are asked the following question during each round: "*In general, compared to other people of the same age, would you say that your health is excellent, very good, good, fair, or poor?*" Based on this question, the perceived health status of each respondent are evaluated from 1 (excellent) to 5 (poor). The variable $Perceived\ Health\ Status$ in our study is the mean over rounds. MEPS constructs a medical insurance variable which summarizes health insurance coverage for the person in each year. Our medical insurance variable $Having\ Medical\ Insurance$ equals to one if the summarized insurance variable indicates the person has either public or private health insurance. Whether the individual participates in $Medicare$ or $Medicaid$ or not is provided by MEPS. All the purchasing observations for SSRI drugs are precisely recorded in MEPS Prescribed Medicines Component Files. The Prescribed Medicines Component collects information from the actual pharmacies where survey participants obtain their prescriptions. The information obtained from pharmacies includes the national drug code and name of the drug, the strength and quantity obtained, for what condition the drug is prescribed, the total price, as well as the amounts paid by di□erent insurance sources and the patient. Based on the price information provided by MEPS Prescribed Medicines Component Files, we can easily construct $Out\ of\ Pocket\ Rate$ by dividing the price paid by patients with the total price. Most of the individuals have purchasing records (not restricted to SSRI drugs) in the data which can be used to generate this variable. Less than 10 % of the individuals have no information of $Out\ of\ Pocket\ Rate$. The mean of $Out\ of\ Pocket\ Rate$ in that year is utilized for these observations. A large part of the observations in our study are those who have depression condition. Before we describe the sample construction, the first thing to know is the depression condition dummy. Condition information is provided in Medical Condition Files. The condition can be included in MEPS condition roster only for the following reasons: reported by the household respondent for a particular medical event (hospital stay, outpatient visit, emergency room visit, home health

episode, prescribed medication purchase, or medical provider visit); reported as the reason for one or more episodes of disability days; or reported by the household level respondent as a condition "bothering" the person during the reference period. We define a respondent as having depression if the ICD-9-CM code equal to one of the following: 296 for episodic mood disorders, 300 for anxiety, dissociative and somatoform disorders, code 311 for depressive disorder not elsewhere classified. By merging the Medical Condition File with Full Year Consolidated File, we could obtain the sample that has depression. Combining all those who purchased SSRI anti-depressants with those who have depression conditions gives us the analytic sample.

8.1.2 Drug-level Data

One of the key drug characteristics is price, which we constructed by averaging prices across strengths and dosage forms by sales weight. All prices have been adjusted to unit level, i.e., price per pill; and are deflated to 1996 dollar level by CPI for Managed Care Commodities category (Source: US Bureau of Labor Statistics). The information about drug characteristics is obtained from package insert labels. At the section of Indications and Usage in labels, indications of drugs are enumerated. We generate seven indication dummies for each product, including Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), Panic Disorder (PD), Post-traumatic Stress Disorder (PSD), Premenstrual Dysphoric Disorder (PDD), Social Anxiety Disorder (SAD), and Bulimia Nervosa (BN). Indications of each product are listed in Table 13. As we see from the table, when a generic drug enters into market, it automatically obtains the new indication of the branded as long as they are therapeutically equivalent, for example Generic Prozac 2001 and Prozac 2000. The reason lies in that the branded firm cannot forbid it without providing new indications within a new strength or a new formulation since physicians could and would prescribe generics for the new indication of the branded one (as long as they are the same). If the safety and e□cacy of a drug for pediatric use are provided, then we can regard the drug as having pediatric use. However, the di□culty is that in the label, the safety and e□cacy data for pediatric usage are specific to each indication, for example, the e□cacy of ZOLOFT for the treatment of OCD was demonstrated in clinical trials. However, safety and e□cacy in the pediatric population other than pediatric patients with OCD have not been established. If we consider the pediatric usage for each specific indication will increase the number of dummies several times which brings about an estimation problem, therefore, here as long as the safety and e□cacy data for one indication have been established, we will regard this drug with $Pediatric\ Use = 1$. The side e□ects information is obtained from the Adverse Reactions Section in the labels. We choose the 10 most common symptoms which bother patients most into our data: Headache, Asthenia, Nausea, Diarrhea, Anorexia, Insomnia, Anxiety, Somnolence, Rash, and Abnormal Ejaculation (these do not need to be capitalized). For each symptom, the side e□ect ratio is defined as the occurrence rate of the patients taking medicine with respect to the occurrence rate of the patients taking placebo. To illuminating the generating process, the example of Prozac's label is illustrated below: As shown in Figure 15, for symptom nausea, the incidence of nausea is: 21 % of 1728 Major Depressive Disorder patients taking Prozac vs. 9% of 975 subjects feeling nausea who have taken placebo; 26 % of 266 patients taking Prozac to treat OCD felt nausea, while 13 % of 89 OCD patients taking placebo felt nausea; 29% of 450

Figure 15: Part of the Table in Section Adverse Reactions in the label of Prozac

Bulimia Nervosa patients taking Prozac vs. 11% of 267 BN patients taking placebo; 12 % of 425 Panic Disorder patients taking Prozac vs. 7 % of 342 PD patients taking placebo. Then the hazard rate ratio variable for nausea can be computed as:

$$\frac{\frac{1728\ .21+266\ .26+450\ .29+425\ .12}{1728+266+450+425}}{\frac{975\ .09+89\ .13+267\ .11+342\ .07}{975+89+267+342}} = 2.34$$

Alternative IVs are constructed in the following way: the number of dosages is the count of strengths and formulations for a molecule produced by one firm is available; years after generic entry is the period length from the generic entry year till the year when purchasing happened; the number of firms (branded and generics) selling the same molecule in the market is specific in each year.