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"Should We Prevent Off-Label Drug Prescriptions? Empirical Evidence from France"

Tuba Tunçel

Toulouse School of Economics

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Abstract

After a drug obtains marketing authorization, the usage depends on the regulation of off-label prescriptions for unapproved indications. We investigate the impact of off-label prescription regulation on physicians' behavior, patients' health, treatment costs, and pharmaceutical firms' pricing with a structural demand and supply model. Exploiting rich panel data on physicians' activities and office visits in France over nine years, we use a model of prescription choice and health outcomes with unobserved patient-level heterogeneity. We identify the demand for on-label and off-label drugs and the effect of prescription choice on health outcomes. On the supply side, we use a Nash-in-Nash bargaining model between the government and the pharmaceutical companies that allows the partial identification of the marginal costs of drugs. Counterfactual simulations show that when we remove off-label drugs from the choice set of physicians, substitution to on-label drugs at constant prices would lead to an increase of 15% in the expenditure on prescription drugs. If we allow bargaining adjustment on drug prices under a ban on off-label prescriptions, the ban would further increase the treatment cost, by 26%, without improving health outcomes.

Keywords: Physician Behavior, Prescription Drugs, Off-Label Drugs, Regulation, Bargaining.
JEL Codes: I18, D12, C51, L65

*Florida State University, United States of America. email: ttuncel[at]fsu.edu

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1 Introduction

While marketing authorizations are given based on evidence of safety and efficacy for the specifically requested indications, off-label drug prescriptions are prevalent (Radley et al. (2006), Berger et al. (2021)). The use of prescription drugs for an indication (e.g., a disease or a symptom) other than the approved indications is called off-label use[1]. The famous example of Avastin, a drug approved for cancer treatment but used widely for the treatment of age-related macular degeneration (AMD), shows the importance of off-label use and its regulation. Even though Avastin is not officially approved in Europe for AMD, there is scientific evidence that it is effective for treating AMD. As the average price of Avastin in Europe is 40 euros per injection, whereas the approved drug for AMD treatment (Lucentis) is approximately 900 euros per injection, there are significant incentives for off-label use of Avastin.

Another example is the off-label use of acetylsalicylic acid, famously known as aspirin, to prevent secondary myocardial infarctions (heart attacks). Preliminary evidence that aspirin could lower the risk of a second heart attack began to emerge in the 1960s and 1970s. However, aspirin was already a cheap generic drug back then, as its patent had expired in 1917, and no company had an incentive to conduct clinical trials to prove that aspirin prevents heart attacks. Thanks to government financing of such studies, aspirin was approved for secondary myocardial infarction only in 1985 (Weisman and Healy (1987)). Until approval, aspirin was used off-label as a heart attack preventive for decades[2].

In the pharmaceutical market, which accounts for 12% of total health spending in the US (roughly 2.1% of US GDP) and 14% of total health spending in France (1.6% of French GDP) (OECD (2017)), off-label use is widespread. Using nationally representative data, Radley et al. (2006) find that, among the 160 most prescribed drugs in the US, off-label prescriptions account for approximately 21% of overall use. Papers on off-label use in Europe typically study this practice within narrowly defined clinical populations such as pediatric patients (Chalumeau et al. (2000), Bücheler et al. (2002)) or inpatients in a single hospital on a single day (Martin-Latry et al. (2007)). Our paper is the first study that identifies the monetary costs and treatment outcomes of off-label prescriptions relative to on-label alternatives and answers the policy-relevant question of whether we should prevent off-label drug prescriptions.

Regulating off-label use is a difficult task mainly because of the unknown costs and benefits involved. Off-label use may provide significant benefits for some patients if their individual needs require using an off-label drug, as in cases where approved treatments have failed (Stafford (2008)). In addition, off-label use may provide financial benefits, as in the use of Avastin to treat AMD. However, if off-label use is ineffective in treatment, it would lead to wasteful spending. Additionally, even if off-label drugs are as effective as approved alternatives for treating a disease, allowing a wider choice of treatments can affect expenses because prices may differ.

We construct and estimate a structural model of demand and supply to derive welfare measures and address policy questions regarding optimal regulation of off-label prescriptions. On the demand side, we model physicians' prescription decisions across on-label and off-label alternatives and study the impact of prescription choice on health outcomes. A critical feature of the demand model is that we jointly estimate the prescription choice and health outcome controlling for selection into treatment based on unobserved patient health state, which can bias the estimates for treatment impact of drugs if not considered.

[1]The term "off-label use" can also apply to the use of a drug in a patient population (e.g., pediatric) or in a dosage form that has not been approved. In this study, off-label use refers to the use of a drug to treat an indication for which the drug has not received approval. To avoid conflicts with patient population-based off-label use, we focus on the sample of adult patients.

[2]Source of this example: Article titled "Drug safety: Off-label drug use" on http://consumerhealthchoices.org/report/off-label-drug-use/.

On the supply side, we use a Nash-in-Nash bargaining model between the pharmaceutical companies and the government in which they negotiate to determine drug prices. We allow the government to care for both the consumer surplus and the cost of treatment. Demand may be price insensitive in health care systems with generous coverage like the one in France. However, the objective to contain the total cost of treatment implies that the government still wishes to lower prices in negotiation with pharmaceutical companies, even if the consumer surplus is price insensitive. Using the estimates of the structural model, we then conduct counterfactual analyses to investigate how banning off-label prescriptions would impact the equilibrium of drug prices, the monetary cost of treatment, and the health outcomes.

We use data from France from 2000 to 2008, a period during which there was no restriction on off-label prescriptions. Physicians were free to choose among drugs, regardless of their label status, and they do not have monetary incentives to prescribe one drug vs. another. The data period and the institutional setting are ideal for studying physician behavior in terms of off-label use. We analyze the share of off-label prescriptions conditional on the diagnosis, that is, the propensity of the physician to prescribe an off-label drug conditional on the diagnosed disease, namely, depression. The existing medical literature on off-label use provides information on which drugs have the highest number of off-label prescriptions. Our analysis is based on depression treatment, for which off-label use is prevalent among French general practitioners. We find that 21% of the drugs prescribed for depression treatment are off-label.

This unique French dataset provides longitudinal information on a representative sample of physicians and all their patients for nine years. The longitudinal dimension of the data on office visits allows us to follow patients' visits to their physicians and thus observe their treatment outcomes. Hence, we can investigate whether treatment outcomes are different for patients treated with approved drugs than those treated with off-label drugs.

We uniquely contribute to identifying the treatment costs and benefits of off-label use relative to on-label alternatives and shed light on how off-label prescriptions versus approved alternatives affect patients' health. Using a model of prescription behavior in which patient-level unobserved heterogeneity is allowed to be correlated with treatment outcomes, we identify the demand for on-label and off-label drugs in depression treatment. We separately identify the impact of treatment choice and the impact of patients' unobserved health state on treatment outcomes using detailing (advertising) expenditures that affect physicians' prescription decisions and that can credibly be excluded from the health outcome equation, conditional on the treatment chosen.

The results show that patients' unobserved health state impacts both the treatment choice and the treatment outcome and that off-label drugs are not worse than the on-label alternatives in terms of the probability of recovery. Consistent with the medical literature, our results show that the treatment impact of drugs is heterogeneous across patients after controlling for both observables and unobserved health state.

Current regulations question policies that would restrict or entirely prevent off-label prescriptions. For example, in France, the current system in effect since 2011 aims at strictly regulating off-label prescriptions with "Temporary Recommendations for Use (TRU)", while in the US, the formulary drug lists of health insurance companies contribute to limiting off-label prescriptions. To shed light on the optimal regulations of off-label use, we evaluate the counterfactual effects of restrictions on off-label prescriptions.

Using the structural model parameter estimates, we first investigate how restrictions on off-label prescriptions would impact choice probabilities, treatment outcomes, and the costs of prescription drugs, keeping the prices of drugs fixed. The counterfactual simulations show that banning off-label prescriptions would lead to an increase in the cost of treatment because of the substitution of off-label drugs with more expensive products, whereas it would not lead to an improvement in terms of health outcomes.

We then explore how the ban on off-label prescriptions would impact the price negotiations between the pharmaceutical companies and the government. Using a Nash-in-Nash bargaining model (as in Crawford and Yurukoglu (2012), Grennan (2013), Gowrisankaran et al. (2015), Ho and Lee (2017)) between the government and pharmaceutical companies allows the partial identification of marginal costs and bargaining parameters thanks to the observed price equilibrium. In this bargaining model, we assume that firms' objective functions are their profits, while the government cares about a weighted sum of consumer surplus and the cost of treatment. Prices are assumed to be determined by a Nash equilibrium of bilateral Nash bargaining problems (Horn and Wolinsky (1988)) between each pair of firm and the government. In this Nash-in-Nash bargaining model, instead of using standard moment conditions coming from the first order conditions, we allow a flexible objective function for one side of the bargaining players and use moment inequalities to set-identify the model parameters.

We set identify the bargaining parameters and the weights the government puts on consumer surplus versus the cost of treatment using marginal cost inequality restrictions. We impose an upper bound on the marginal cost of drugs using the minimum of observed prices (including today's prices which are smaller than drug prices during the sample period) and a zero lower bound. This identification strategy narrows the interval set of the bargaining parameters, which are between 0.76 and 0.93 for the firms. The weight the government puts on consumer surplus is between 0.65 and 1. Using the parameter estimates, we simulate the new equilibrium outcome that would prevail if bargaining on the prices of drugs were to take place under a strict ban on off-label prescriptions.

The Nash bargaining equilibrium implies that the price cost margin of a drug is a function of the drug's value added in consumer surplus, its additional impact on the total cost of treatment, and the price elasticity of demand. The ban can impact drug prices through all these channels, through its effect on total cost, demand, and consumer surplus elasticities.

A drug approved for depression is used not only in its on-label market (depression) but also for indications for which it is not approved: off-label markets. Similarly, a drug approved for depression faces competition from drugs approved for other indications but used off-label in depression treatment. With the ban on off-label use, the drug's market power in the on-label market will increase because the drug will stop facing competition from off-label drugs in this market. However, the drug will lose all the sales in the off-label markets in which it is used when there is no ban. Therefore, whether the aggregate demand for the drug will increase or decrease with the ban relative to without the ban is ambiguous. Hence, the impact of the ban on the negotiated price of a drug can go in any direction depending on the demand for the drug for different indications, the price elasticity of demand for the drug on the on-label indication market when off-label drugs are present, and when they are absent. The ban's impact also depends on the price elasticity of demand for the drug in the off-label indication markets. We thus also estimate the market shares and price elasticity of on-label depression drugs in the off-label markets of these drugs[3].

Similarly, the ban can impact drug prices through the channel of the price elasticity of total spending and consumer surplus of drugs. The value added of a drug in consumer surplus is the marginal surplus provided by the drug relative to the other drugs in the physicians' choice set. As physicians' choice set shrinks with the ban, the marginal surplus of a drug increases and becomes less elastic. Therefore, the ban will increase the price through the channel of consumer surplus elasticity. Overall, the ban's impact on the price of a drug will depend on whether its effects through all these channels go in the same direction or which one dominates if they vary in opposite directions.

[3]The list of the off-label markets for approved drugs for depression treatment is provided later in the text.

When off-label prescriptions are banned, physicians substitute off-label drugs with approved alternatives. Because on-label drugs are more expensive on average, this substitution effect leads to a 15% increase in prescription expenses under the assumption that drug prices are identical to those under the no-ban benchmark.

We estimate the impact of the ban on prices given the values of the bargaining parameters and weights in the identified set. When prices are negotiated under the ban, prices of approved drugs for depression treatment increase in equilibrium. The price increase depends on the combination of the bargaining parameters and weights and ranges from 1% to 23% across drugs. Therefore, the ban on off-label drug prescriptions would increase treatment expenditures even more under the counterfactual bargaining equilibrium prices. The prescription expenses increase by 26% due to both the price and substitution effects. As a result, banning off-label prescriptions would increase the cost of treatment, not only if drug prices are assumed to be the same as those under the no-ban benchmark but also if prices are negotiated under the ban. The counterfactual results also show that the ban does not improve patients' health outcomes.

While there is extensive literature on the determinants of physicians' treatment decisions, studies of physicians' choices between approved and off-label alternatives are sparse. Bradford et al. (2018) provide an important first step in documenting off-label prescription rates and identifying some determinants of such decisions. Shapiro (2018) investigates the impact of detailing on physicians' prescriptions of on-label versus off-label use. Berger et al. (2021) examine whether FDA approval of a supplemental indication (approval of an existing drug for a new indication) increases the use of a drug for that indication.

Our paper is related to some recent literature in the pharmaceutical industry that studies the impact of different counterfactual policies on drug prices using a Nash-in-Nash bargaining supply-side model. For example, Dafny et al. (2022) study how banning drug coupons affects drug prices. In their setting, the impact of a coupon ban on prices is theoretically ambiguous, hence is an empirical question. Grennan et al. (2022) investigate how a ban on meals physicians receive from pharmaceutical firms would impact the drug prices and demand in the statin market. Dubois et al. (2022) investigate the potential role of international reference pricing on the price equilibrium in the US and reference countries that negotiate prices with firms.

Our work, which studies the use of pharmaceuticals given label status and evidence for efficacy, also relates to the literature on the economics of information and regulation in the healthcare industry. Studies in this literature investigate the role of information about efficacy in drug adoption (Ching et al. (2016)), market expansion (Berger et al. (2021)), and market outcomes for medical devices (Grennan and Town (2020)).

The rest of this paper is organized as follows: Section 2 summarizes the relevant information on the institutions and regulations in the French health care system, and Section 3 describes the data and provides descriptive statistics. Section 4 presents the structural models of demand and supply. Section 5 describes the econometric identification and empirical estimates. Finally, section 6 presents the counterfactual analysis, and section 7 concludes.

2 Institutional Background

2.1 Drug Approval Process and Regulations in France

Both the French drug-regulatory agency and the European Medicines Agency (EMA) can issue marketing authorization for drugs in France. For authorization, they require substantial evidence of efficacy and safety determined by clinical trials for a given indication.

The reimbursement of drugs depends on the evaluation of the transparency commission, which assesses each approved drug's safety, efficacy, and ease of use. The commission also takes into consideration the severity of the disease targeted by each specific drug and the availability of alternative therapies. The commission does not evaluate a drug's cost-effectiveness. Instead, it ranks each drug according to a measure of actual medical benefit. The commission also compares the new drugs with the existing ones and assigns a score for improving medical benefits.

Each drug has a reimbursement level according to its rate: 100% reimbursement for irreplaceable drugs, 35% reimbursement for drugs treating disorders that are not considered serious, and 65% for all other drugs (Cohen et al. (2007)). It is worth emphasizing that once the reimbursement level is determined and the drug is on the market, the determined reimbursement level then applies to all prescriptions of the drug regardless of the indication drug is prescribed for, i.e., irrespective of whether the drug is prescribed for an approved or off-label indication. Patients are reimbursed through the national healthcare system according to the determined reimbursement rate. Almost all drugs used in depression treatment have a reimbursement rate of 65%.

After the commission determines the reimbursement level of a new drug, the economic committee on health products negotiates the drug's price with manufacturers. Pricing decisions depend on the medical benefit improvement rating, prices of therapeutic alternatives, the size of the target patient population, expected sales volume, and associated budget impact (Cohen et al. (2007)). It is important to note that a drug's medical benefit improvement score is based on its main indication(s). Potential off-label uses of a drug do not play a role in determining this score.

Unlike in the US, drug samples and direct-to-consumer promotion of prescription drugs are tightly restricted in France (Gallini et al. (2013)).

Figure 2.1 shows an example of three drugs approved for different indications but can be used off-label for unapproved indications. In this example, only drug A is approved for depression, but drugs B and C are also used (off-label) to treat depression, while drug B is approved for alcoholism and drug C for epilepsy. Finally, drug A is also used off-label to treat alcoholism. As we will see later, banning off-label prescriptions would mean that off-label prescriptions displayed with dashed arrows in this example would not be allowed (see figure A.1 in appendix A.3).

2.2 Health Care System

Health insurance is mandatory in France, and all residents are automatically enrolled in the national insurance system with different categories depending on their occupational status. The public national health insurance reimbursement rate is almost always 65% for the drugs prescribed for depression treatment. Even though national health insurance includes different health insurance plans for various occupational groups, they are all regulated under the same statutory framework (Rodwin (2003)).

It is important to note that a specific diagnosis is not required to ensure the patient can fill a prescription.

Doctors in France face a uniform incentive scheme. As in the case of the Italian market discussed by Crawford and Shum (2005), this feature of the French market attenuates the agency problem, which may come into play in the case of a market with heterogeneous third-party payers. For instance, the heterogeneous constraints on doctors' choices induced by drug formularies in the US do not come into play in the French market. Physicians do not have monetary incentives to prescribe one drug vs. another; however, detailing to doctors by pharmaceutical companies may play a role in their prescription choices which we control for in our analysis.

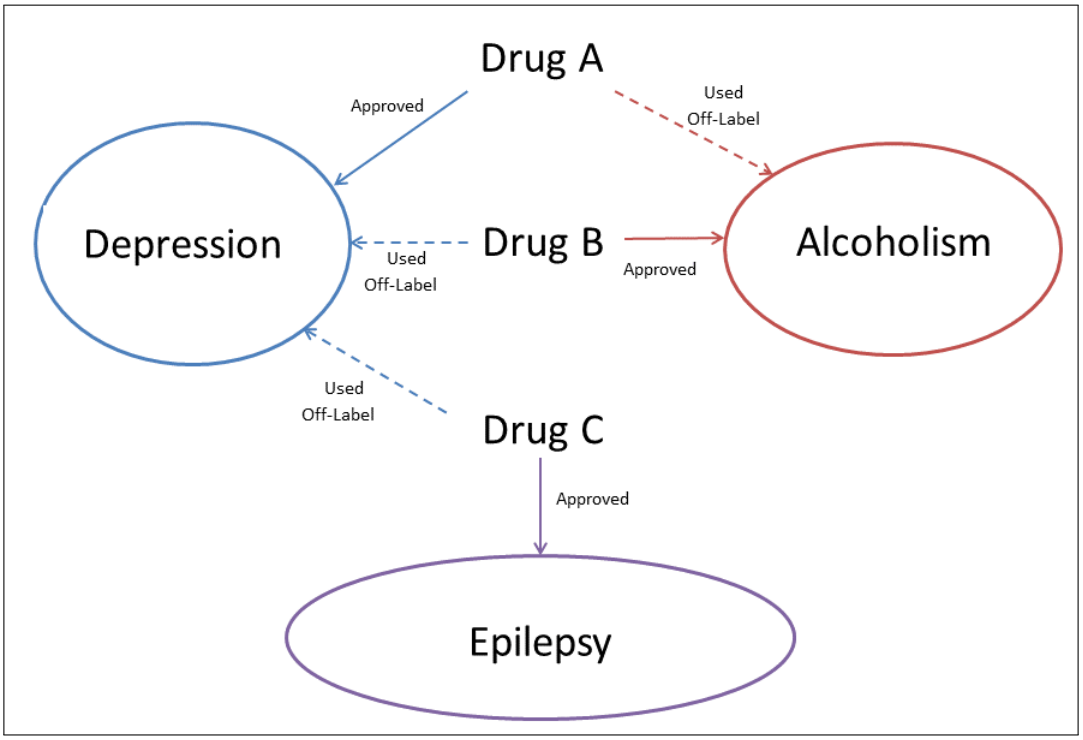


Figure 2.1: *Example of On- and Off-Label Use of Drugs*

3 Data and Descriptive Statistics

3.1 Data

The primary data are proprietary to CEGEDIM, a global technology and services company specializing in health care. They contain all prescriptions written by 386 general practitioners to all their patients in France between 2000 and 2008. The sample of physicians is a representative sample of general practitioners in France. The patient-level anonymous IDs allow us to follow individual patients over time and observe some health outcomes. At the physician level, the dataset includes the physicians' age, gender, and region of operation. At the patient level, it provides socio-demographic information (age, gender, and employment status) and information on health (i.e., chronic disease conditions, body mass index).

For each patient visit, physicians record all diagnoses and indicate the drug therapy used to treat each specific diagnosis, and register the exam results transmitted to them. Thus, we observe all diagnosis-drug prescription pairs for each visit, including details such as dosage and renewal of treatments. Observing the diagnosis and the drug prescribed for each diagnosis is essential for studying off-label prescriptions. The drug-level information is the Anatomical Therapeutic Chemical (ATC) code at the finest level, the reimbursement level, and whether the drug is generic or branded. In addition, for each visit, the patient and physician identification numbers allow us to identify unique physician-patient pairs.

Data about on-label indications of drugs were self-collected from the websites of the ministry of health and the French regulatory agency[4]. Diagnoses are considered as on-label for a drug if they can be matched to the therapeutic indications the drug is approved for by the French drug regulatory agency or the European

[4]http://base-donnees-publique.medicaments.gouv.fr (official website of Ministry of Health) and http://www.theriaque.org (approved by French regulatory agency, HAS)

Medicines Agency. Any diagnosis that cannot be matched to a labeled indication is considered off-label for that drug.

We also use the DRUGDEX System (Thomson Micromedex, Greenwood Village, Colorado), a nationally recognized pharmaceutical compendium in the US that describes efficacy and scientific documentation for prescription drugs. It contains readily available summaries of evidence-based information on drugs' indications (both on-label and off-label). As in Radley et al. (2006), each drug indication is considered to have scientific support if, according to DRUGDEX, its effectiveness has been shown in controlled trials or observed in clinical settings[5]. Combining these data allows us to identify whether a drug is on-label or off-label for a particular indication in France and if an off-label drug has been shown to have efficacy for a specific indication in the medical literature.

Drug prices and drug formats (number of pills and mg per pill in a drug package) are obtained from the drug database of the French Social Security Health Care System ("Base de Médicaments et Informations Tarifaires" on http://www.codage.ext.cnamts.fr). The website reports package formats, reimbursement levels, and drug prices from the 1990s to today at the CIP level (code that identifies the presentation of a drug format, i.e., package). "Defined Daily Dose (DDD)", which is the assumed average maintenance dose per day for a drug used for its main indication in adults, is obtained from the ATC/DDD Index of the World Health Organization (https://www.whocc.no/atc_ddd_index/).

Finally, we also use drug detailing data from the IMS Health Global Promotional Track for France (IMS Health - Base Global Promo Track - [2001 - 2008]), which reports monthly detailing expenditures for each drug to general practitioners in France for the period from May 2001 to December 2008.

3.2 Descriptive Statistics

Table 3.1 provides the shares and the average prices of off-label and approved drugs used in depression treatment. Statistics are based on prescriptions at the visit the patient is diagnosed with depression for the first time. In total, 21% of the drugs prescribed for depression are off-label[6]; for only 14% of them, the medical literature provides evidence that they have efficacy in depression treatment. For the remaining 86% of off-label drugs, there is no (not enough) published research in the medical literature investigating their efficacy in depression treatment, and hence, they are neither shown to be effective nor ineffective in depression treatment. It is important to note that these are not off-label drugs "without efficacy"; these are off-label drugs without any published research on their efficacy in depression treatment. They are called as "Other Off-Label Drugs" throughout the paper.

The average price of on-label drugs, 0.83€, is more than four times as large as the average price of "Other Off-Label Drugs", 0.17€. Table 3.1 also reports the total number of depressed patients over the sample period.

The treatment outcome considered in the analysis is whether the patient recovers from the disease after a specific treatment period. First, we allow for a treatment period; then, we check whether the patient is diagnosed with depression again during an observation period after the treatment period. The recovery is defined by the patient not being diagnosed with depression during this observation period after the treatment period, conditional on still being in the sample.

[5]The information on indications comes from sources in different languages. For the correspondence of diseases in French and English, we use the International Classification of Diseases (ICD) published by the World Health Organization in both languages.

[6]All physicians prescribe off-label drugs and a substantial share of them prescribe an off-label drug around 20% of the time they prescribe a drug for depression. Therefore, the average number of off-label prescriptions across all prescriptions, 21%, is not caused by some physicians aggressively prescribing off-label drugs and others prescribing very little. They all prescribe off-label drugs and a very large share of them prescribe an off-label drug between 15-25% of the time they prescribe a drug for depression treatment (for distribution of the percentage of off-label prescriptions across physicians, see the online appendix).

Table 3.1: *On-Label versus Off-label Prescriptions in Depression Treatment*

	Share	Average Price
On-Label Drugs	79%	0.83€
Off-Label Drugs with Efficacy	3%	0.49€
Other Off-Label Drugs	18%	0.17€
Number of Patients	37,510	

Notes: This table provides the shares and the average prices of off-label and approved drugs used in depression treatment. Price is the price for a one-day treatment calculated using the "Defined Daily Dose (DDD)" assigned by the World Health Organization. For each active ingredient, it is the price per mg times mg per day according to the DDD. The third column shows the average price for a one-day treatment for the drug group in the first column of the corresponding row.

Tables 3.2 and 3.3 show the percentage of patients recovering from the disease for combinations of two treatment periods, six-month and one-year, and two observation periods, six-month and one-year. Note that recovery from the disease is one of the primary health outcomes the medical literature considers in depression treatment (see Kilbourne et al. (2018), Licht-Strunk et al. (2009)). Table 3.2 shows what percentage of the patients recover from the disease six months after the first time they are diagnosed with depression. The table reports treatment outcomes across patients depending on their prescriptions: approved drugs, off-label drugs, off-label drugs with efficacy, and other off-label drugs. Three columns show three different periods. "One-year Period" represents the one-year observation period starting six months after the first diagnosis. "Six-month Period" represents the six-month observation period starting six months after the first diagnosis. "Anytime" represents the entire period starting six months after the first diagnosis until the end of the sample period.

The share of patients who recover from the disease is higher among those prescribed off-label drugs: patients who are prescribed off-label drugs are approximately 11 percentage points more likely to recover than those prescribed approved drugs. The recovery rate is slightly higher among patients prescribed "Off-Label Drugs with Efficacy" than among patients prescribed "Other Off-Label Drugs".

Table 3.2: *Recovery Rates - Six Months after the First Diagnosis*

	No Depression Diagnosis in Six-month Period	No Depression Diagnosis in One-year Period	No Depression Diagnosis Anytime
All Patients	65%	59%	45%
Among Patients who are Prescribed:			
On-Label Drugs	63%	56%	43%
Off-Label Drugs	74%	68%	54%
Off-Label Drugs with Efficacy	75%	69%	55%
Other Off-Label Drugs	74%	68%	54%

Notes: For the "one-year" and "anytime" observation periods, second and third columns, the recovery rates are lower because in these cases, some of the patients have another cycle of depression (relapse cases).

Table 3.3 reports statistics on recovery after a one-year treatment period after the first diagnosis. Recovery rates after one year are approximately five percentage points higher than recovery rates after six months, whereas the recovery patterns among patients prescribed off-label drugs and patients prescribed on-label drugs are the same as in Table 3.2.

These descriptive statistics show clear correlations between prescriptions and health status, which could be a combination of the treatment effects of drugs and selection into treatments by physicians. We will now develop a model which will allow us to disentangle causality effects from correlated effects due to heterogeneity.

Table 3.3: *Recovery Rates - One Year after the First Diagnosis*

	No Depression Diagnosis in Six-month Period	No Depression Diagnosis in One-year Period	No Depression Diagnosis Anytime
All Patients	71%	64%	50%
Among Patients who are Prescribed:			
On-Label Drugs	69%	62%	48%
Off-Label Drugs	78%	71%	58%
Off-Label Drugs with Efficacy	78%	72%	59%
Other Off-Label Drugs	77%	71%	57%

Notes: See the notes in Table 3.2.

We will then identify the counterfactual impact of choices on treatment costs and health outcomes when off-label alternatives become unavailable to the prescriber.

4 Structural Model of Demand and Supply Including the Off-Label Use of Drugs

4.1 A Joint Model of Prescription Choice and Health Outcome

We assume that the drug prescription choice is based on a random utility model in which physician i prescribes drug d to patient j at time t to maximize some payoff function U_{ijdt} specified as follows:

$$U_{ijdt} = \alpha_d(z_i, z_j) - \beta p_{dt} + \gamma_{l(d)} x_{dt} + \lambda_d I_j + \varepsilon_{ijdt}$$

where $\alpha_d(z_i, z_j)$ is a drug-specific effect depending on z_i, and z_j, some observed characteristics of physicians and patients such as age and gender, p_{dt} is the price, x_{dt} is the drug-specific detailing expenditures stock, I_j is an unobserved patient state affecting the propensity to recover (health outcome), which can affect drug preferences differently with coefficient λ_d. ε_{ijdt} is a deviation from the mean utility of d at t assumed to be independent of all other variables. $l(d)$ is a dummy variable indicating whether drug d is on-label or off-label so that $\gamma_{l(d)}$ allows detailing to impact the on-label and off-label use of drugs differently.

To take into account the long-lasting effects of advertising, we build an advertising stock for each month t using all past detailing expenditures for each drug d such that

$$x_{dt} = \sum_{\tau=-\infty}^{t} (0.75)^{t-\tau} (\textit{detailing expenditures})_{d\tau}$$

As health insurance coverage is quite extensive, it is possible that the coefficient β is small or zero, but we allow the out-of-pocket payment of patients to possibly affect drug choices. Moreover, it could be that physicians are not entirely indifferent to price because of the warnings they receive from the government to keep the cost of treatment low. Therefore, with this utility specification, we consider the physician-patient pair as the decision maker, which is reasonable given the features of the French healthcare market (for more information on the French healthcare market, see section 2.2). For details on how our utility specification corresponds to a weighted sum of the physician's and the patient's utilities, see section B.1 in the online appendix.

The unobserved state I_j is assumed to be discrete with two types of patients: high- and low-types. A patient is of high-type such that $I_j = \overline{I}$ with probability q and of low-type such that $I_j = \underline{I}$ with probability $(1-q)$. The drug choice is denoted by $y_{ijt} \in \{1, .., D\}$ and the alternative 0, corresponding to the group of "Other Off-Label Drugs", has a normalized utility $U_{ij0t} = \gamma x_{0t} + \varepsilon_{ij0t}$ (details on choice alternatives are provided in Section 5.1).

Note that the utility specification includes time-invariant drug-specific effects interacting with patient-level observables. Hence, if, for instance, one of the drugs leads to a higher level of efficacy for female patients, or if a drug has more severe side effects for male patients, and if it plays a role in the prescription choice, the utility specification will account for it.

Under the assumption that ε_{ijdt} is independently and identically distributed according to a Gumbel (type I extreme value) distribution, the choice probability of drug d by physician i for patient j, conditional on the unobserved patient state, is

$$P\left(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}, I_j\right) = \frac{\exp\left(\alpha_d\left(z_i, z_j\right) - \beta p_{dt} + \gamma_{l(d)} x_{dt} + \lambda_d I_j\right)}{\sum_{d'=0}^{D} \exp\left(\alpha_{d'}(z_i, z_j) - \beta p_{d't} + \gamma_{l(d')} x_{d't} + \lambda_{d'} I_j\right)} \tag{4.1}$$

The choice probability of drug d by physician i for patient j unconditional on the unobserved patient state is then

$$\begin{aligned} P\left(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}\right) \quad = \quad & q \, \frac{\exp\left(\alpha_d\left(z_i, z_j\right) - \beta p_{dt} + \gamma_{l(d)} x_{dt} + \lambda_d \overline{I}\right)}{\sum_{d'=0}^{D} \exp\left(\alpha_{d'}(z_i, z_j) - \beta p_{d't} + \gamma_{l(d')} x_{d't} + \lambda_{d'} \overline{I}\right)} \\ & + (1-q) \, \frac{\exp\left(\alpha_d\left(z_i, z_j\right) - \beta p_{dt} + \gamma_{l(d)} x_{dt} + \lambda_d \underline{I}\right)}{\sum_{d'=0}^{D} \exp\left(\alpha_{d'}(z_i, z_j) - \beta p_{d't} + \gamma_{l(d')} x_{d't} + \lambda_{d'} \underline{I}\right)} \end{aligned}$$

The recovery status of patient j diagnosed with depression at time t is denoted r_{jt} and equal to one or zero depending on whether the patient has recovered. We assume that it depends on an unobserved propensity to recover from the disease, r^*_{jt}, such that $r_{jt} = 1_{\{r^*_{jt} \geq 0\}}$ where

$$r^*_{jt} = z_j' \theta + \sum_{d=1}^{D} \delta_{jd} 1_{\{y_{ijt} = d\}} + I_j + \eta_{jt}$$

z_j is the patient covariates and δ_{jd} is the treatment effect of drug d, relative to the reference drug, for patient j. This specification allows the unobserved patient state I_j to be correlated with each patient's propensity to recover: *High(low)-type* patients are more (less) likely to recover from the disease. For example, we can consider the *high-type* patients as the mild cases and *low-type* patients as the more severe cases of depression. λ_d allows the unobserved patient state to affect drug preferences differently across drugs. Therefore, the patient state, observed by the physician but unobserved by the econometrician, is allowed to impact both prescription probability and recovery probability.

Assuming that η_{jt} is independent of other variables and standard normal, the probability of recovering conditional on prescription choice y_{ijt} and the unobserved patient-state I_j is

$$P(r_{jt} = 1 | z_j, I_j, y_{ijt} = d, \delta_{jd}) = \varphi\left(z_j' \theta + \sum_{d'=1}^{D} \delta_{jd'} \mathbf{1}_{\{y_{ijt} = d\}} + I_j\right)$$

where $\varphi(.)$ is the normal cumulative distribution function.

The recovery probability unconditional on the unobserved patient-state is then

$$P(r_{jt}=1|z_j,y_{ijt}=d,\delta_{jd})=q\ \varphi\left(z_j'\theta+\sum_{d'=1}^{D}\delta_{jd'}1_{\{y_{ijt}=d\}}+\overline{I}\right)+(1-q)\ \varphi\left(z_j'\theta+\sum_{d'=1}^{D}\delta_{jd'}\mathbf{1}_{\{y_{ijt}=d\}}+\underline{I}\right)$$

The joint probability of drug choice and treatment outcome can then be written as

$$P(y_{ijt}=d,r_{jt}=1|z_i,z_j,p_{dt},x_{dt},I_j,\delta_{jd})=P\left(y_{ijt}=d|z_i,z_j,p_{dt},x_{dt},I_j\right)\ P(r_{jt}=1|z_j,I_j,y_{ijt}=d,\delta_{jd})$$

The treatment impact of drugs, δ_{jd}, is allowed to be heterogeneous across patients such that

$$\delta_{jd}=\delta_d+\sigma_d\delta_j^d$$

This means that a drug is allowed to have a different treatment impact on two patients with the same observable characteristics and the same unobservable patient state. Assuming that $\delta_j^d\sim N(0,1)$ for all d, we have

$$P(y_{ijt}=d,r_{jt}=1|z_i,z_j,p_{dt},x_{dt},I_j)=\int P\left(y_{ijt}=d|z_i,z_j,p_{dt},x_{dt},I_j\right)\ P(r_{jt}=1|z_j,I_j,y_{ijt}=d,\delta_{jd})\ d\varphi\left(\delta_j^d\right)$$

$$=\int\frac{\exp\left(\alpha_d\left(z_i,z_j\right)-\beta p_{dt}+\gamma_{l(d)}x_{dt}+\lambda_d I_j\right)}{\sum_{d'=0}^{D}\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}+\gamma_{l(d')}x_{d't}+\lambda_{d'}I_j\right)}\varphi\left(z_j'\theta+\sum_{d=1}^{D}\left(\delta_d+\sigma_d\delta_j^d\right)\mathbf{1}_{\{y_{ijt}=d\}}+I_j\right)d\varphi\left(\delta_j^d\right)$$

We can then use simulated maximum likelihood to estimate the model parameters.

The log-likelihood of the sample of physician choices and patient recovery status for all physician-patient pairs will then be $\sum_{(i,j,t)}\ln L(y_{ijt}=d,r_{jt}=1)$ where

$$L(y_{ijt}=d,r_{jt}=1)=\frac{1}{S}\sum_{s=1}^{S}\left\{qF\left(\delta_j^{ds},\overline{I}\right)+(1-q)F\left(\delta_j^{ds},\underline{I}\right)\right\}$$

and

$$F\left(\delta_j^{ds},I_j\right)=\frac{\exp\left(\alpha_d\left(z_i,z_j\right)-\beta p_{dt}+\gamma_{l(d)}x_{dt}+\lambda_d I_j\right)}{\sum_{d'=0}^{D}\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}+\gamma_{l(d')}x_{d't}+\lambda_{d'}I_j\right)}\varphi\left(z_j'\theta+\sum_{d=1}^{D}\left(\delta_d+\sigma_d\delta_j^{ds}\right)\mathbf{1}_{\{y_{ijt}=d\}}+I_j\right)$$

where S is the total number of simulation draws of the random variable δ_j^d.

This model of prescription choice leads to an aggregate demand for drug d that can be written as

$$q_{dt}=\sum_{j\in J}\left\{\frac{q\exp\left(\alpha_d\left(z_i,z_j\right)-\beta p_{dt}+\gamma_{l(d)}x_{dt}+\lambda_d\overline{I}\right)}{\sum_{d'=0}^{D}\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}+\gamma_{l(d')}x_{d't}+\lambda_{d'}\overline{I}\right)}+\frac{(1-q)\exp\left(\alpha_d\left(z_i,z_j\right)-\beta p_{dt}+\gamma_{l(d)}x_{dt}+\lambda_d\underline{I}\right)}{\sum_{d'=0}^{D}\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}+\gamma_{l(d')}x_{d't}+\lambda_{d'}\underline{I}\right)}\right\}$$

where the set J denotes the set of all patients diagnosed with depression.

Once the model is estimated, we can obtain the unconditional recovery probability for each patient as the sum, over all the alternatives, of the conditional recovery probability with each alternative times the

prescription probability of that alternative as

$$\begin{aligned} E\left[r_{jt}\right] &= P\left(r_{jt}=1\right)=\sum_{d=0}^{D} P(r_{jt}=1|y_{ijt}=d)\ P(y_{ijt}=d) \\ &= \sum_{d=0}^{D}\int P\left(r_{jt}=1|z_i,I_j,y_{ijt}=d,\delta_{jd}\right)\ P\left(y_{ijt}=d|z_i,z_j,p_{dt},x_{dt},I_j\right)\ d\varphi\left(\delta_j^d\right) \end{aligned}$$

4.1.1 Exclusion Restriction and Its Validity

For identification of the treatment impact of prescription choice on health outcome, we use an exclusion restriction on detailing expenditures to physicians at the drug-month level. This excluded variable is allowed to affect treatment choice but not treatment outcome conditional on the treatment choice. The model would be identified even if the exogenous covariates in the drug choice equation are the same as the exogenous covariates in the treatment outcome equation. However, it is preferable that some variables in the drug choice equation are excluded from the treatment outcome equation so that our identification is not only driven by parametric assumptions but also comes from exclusion restrictions. If patients treated with more advertised drugs obtain better health outcomes, the model attributes this effect to the drug choice.

Our instrument is valid if the advertisement is correlated with the health outcome only through the prescription choice and is neither directly correlated with the health outcome nor with unobservables that impact the health outcome. Unlike in the US, the direct-to-consumer promotion of prescription drugs is forbidden in France (Gallini et al. (2013)), and patients are not exposed to drug advertisements. Hence, drug advertisement cannot be directly correlated with the health outcome through what patients observe, but only through what physicians receive as detailing. The argument that "seeing drug advertisement can create some sort of a psychological placebo effect on patient's health outcome" would not be valid in our institutional setting.

Our instrument would fail if there were a correlation between detailing expenditures and patients' unobserved health state impacting the health outcome. For instance, if there is time variation in patients' health state within a year (i.e., if they are more severely depressed in the winter) and if there is variation in drug advertisement which is correlated with seasonal variation in patients' health state, then our instrument would not be valid. For this reason, we do a seasonality test of drug advertisement and reject seasonality (for details on the seasonality test in drug advertisement, see the online appendix B.5.1).

Our exclusion restriction would not be valid if there is endogeneity in drug advertisement such that if unobserved variables (unobserved by the econometrician) affecting patients' health outcomes are observed by the detailers and if they target physicians according to their patients' unobservables. There is no direct way to test this. We conduct an indirect test to support our instrument's validity. We estimate our demand model separately for each physician and obtain physician-specific advertisement coefficients, allowing different coefficients for on-label and off-label use of drugs. Then, we check the correlation of these physician-specific advertisement coefficients with the patient characteristics of these physicians, such as the total number of patients and depressed patients the physician has, the share of depressed patients among all patients of the physician, the average age of patients and depressed patients of the physician, the share of females (both among depressed people and among all patients), the average recovery rates at the physician level (the recovery rates after controlling for treatment choice and patient observables). We do not find any significant correlation between physician-specific advertisement coefficients and patient characteristics of the physicians (for details on this correlation test, see the online appendix B.5.2).

The idea of this test is that if, for example, detailing were targeted at physicians with different types of patients, we would likely observe a correlation between physician-specific advertisement coefficients and observable characteristics of their patients. As noted above, we find no evidence of such correlation, which supports the hypothesis of instrument exogeneity. With that said, we, of course, cannot rule out the possibility that there may still be unobserved heterogeneity in patients across physicians, which is known to advertisers. In this case, however, the unobserved characteristics would also need to be uncorrelated with any of the characteristics observed in the data, which we believe to be unlikely.

Our instrument would fail if detailing expenditures affected the health outcome even when we control for the prescription choice. An example of this would be if drug advertisement makes physicians learn how to administer the drug better and affects the health outcome through this mechanism in addition to the pharmacological mechanism of the drug treatment. It would mean that a given antidepressant affects patients differently depending on the physician's actions other than the prescription. We do not observe the content of advertisements physicians receive. Hence, we cannot investigate the informative impact of advertisement and whether the physician's additional action, along with the drug treatment, may matter. Instead, we conduct an indirect test to provide evidence against the possibility of an informative/behavioral effect that impacts the health outcome. For our test, we use the entry of the drug Escitalopram during our sample period. Under the assumption that the informative/behavioral impact of advertisement would occur within the first few years a drug enters the market, we test whether this informative effect is correlated with the patient characteristics of physicians. First, we estimate our demand model separately for each physician and obtain physician-specific advertisement coefficients, allowing a different coefficient for Escitalopram than other on-label drugs and a different coefficient for off-label drugs. Then, we test whether there is a correlation between the physician-specific advertisement coefficients for Escitalopram and the patient characteristics of physicians. The idea of this test is that if firms expect informative advertisements to be more useful for physicians with specific patient characteristics and target physicians accordingly, we would observe a correlation between drug-physician-specific advertisement coefficients and patient characteristics. We do not find any significant correlation between the two (details on the test result are reported in the online appendix B.5.2).

4.2 A Supply-Side Model of Price Setting with Off-Label Drugs

We now show how we can use a price negotiation model *à la* Crawford and Yurukoglu (2012) between the pharmaceutical companies and the regulator to infer the possible changes in the outcomes of these price negotiations if off-label prescriptions are banned.

Let us assume that the price negotiations between the French regulator and pharmaceutical companies can be represented by a bargaining process for the pricing of each drug in which the firm cares about its profit and the government cares about a weighted average of the consumer surplus and the cost of treatment. The fact that the government does not simply account for consumer surplus obtained by the demand shape can be justified by the fact that public health insurance coverage is large, and thus the price elasticity of demand (which may even be zero) may not represent the health insurance budget opportunity cost.

Bargaining models have been used to represent negotiations between insurers and hospitals in the US (Gowrisankaran et al. (2015)) and between hospitals and medical device providers (Grennan (2013)). Dubois and Lasio (2018) show how to identify price cost margins in the French regulatory environment and present conditions under which a model with price caps set by the regulators can be strategically equivalent to a Nash bargaining model. We choose to model the effects of price regulation using bargaining because, in the

counterfactual analysis, we do not intend to change the regulator's price-setting behavior but only physicians' ability in off-label prescriptions.

The profit of the firm for drug d at period t is

$$\Pi_{dt}(\mathbf{p}_t) = [p_{dt} - c_{dt}]\, q_{dt}^{tot}\left(\mathbf{p}_t^{on}, \mathbf{p}_t^{off}\right)$$

where $q_{dt}^{tot}\left(\mathbf{p}_t^{on}, \mathbf{p}_t^{off}\right)$ is the total sales of drug d in markets for both on-label and off-label indications, at the vector of prices $\mathbf{p}_t = \left(\mathbf{p}_t^{on}, \mathbf{p}_t^{off}\right)$ where $\mathbf{p}_t^{on}$ is the vector of prices of all drugs in the relevant on-label market and $\mathbf{p}_t^{off}$ is the vector of prices of all drugs in the relevant off-label market. A drug's price and reimbursement level do not change depending on the indication for which it is prescribed. Hence, the price of a drug is the same whether it is prescribed for an on- or off-label indication. Consequently, the drug's price is the same in vectors $\mathbf{p}_t^{on}$ and $\mathbf{p}_t^{off}$. However, since the set of drugs used for an on-label indication of drug d is different from those used for an off-label indication of drug d, the vectors of prices $\mathbf{p}_t^{on}$ and $\mathbf{p}_t^{off}$ are different.

We assume that ε_{ijdt} is i.i.d. with type I extreme value, and hence, the consumer surplus on the on-label market of drug d has the standard closed form (Small and Rosen (1981)):

$$CS_t(\mathbf{p}_t^{on}) = \frac{1}{\beta}\sum_{j\in J_{on}} \ln\left(\sum_{d'\in D^{on}} q\exp\left(\alpha_{d'}(z_i,z_j) - \beta p_{d't} + \lambda_{d'}\overline{I}\right) + (1-q)\exp\left(\alpha_{d'}(z_i,z_j) - \beta p_{d't} + \lambda_{d'}\underline{I}\right)\right)$$

where D^{on} is the set of drugs prescribed for the on-label indication of drug d, which contains both on-label drugs and off-label drugs, and the set J_{on} denotes the set of all patients diagnosed with the on-label indication of drug d, namely depression[7].

Let us now assume that the price negotiation can be represented by Nash bargaining with a bargaining parameter of μ for the firm. The Nash-in-Nash equilibrium concepts involve that all contracts remain the same if another negotiation fails (see, e.g., Crawford and Yurukoglu (2012), Gowrisankaran et al. (2015), Dubois and Sæthre (2020)). Assuming a Nash-in-Nash equilibrium (Horn and Wolinsky (1988)), whose microfoundation has been recently clarified (Collard-Wexler et al. (2019)), drug by drug amounts to maximizing the Nash product given the other prices:

$$\max_{p_{dt}} \left[\Pi_{dt}\left(\mathbf{p}_t^{on}, \mathbf{p}_t^{off}\right)\right]^{\mu} \left[w\Delta_d CS_t\left(\mathbf{p}_t^{on}\right) - (1-w)\Delta_d TC_t\left(\mathbf{p}_t^{on}\right)\right]^{1-\mu}$$

where Π_{dt} is the firm's profit from sales of drug d. Note that the difference in firm profits with or without drug d is equal to the profit from drug d because we assume firms maximize profits drug by drug. $\Delta_d CS_t(\mathbf{p}_t^{on}) \equiv CS_t(\mathbf{p}_t^{on}) - CS_{t,-d}(\mathbf{p}_t^{on})$ is drug d's value added in consumer surplus for the on-label indication where $CS_{t,-d}(\mathbf{p}_t^{on})$ is the consumer surplus when drug d is not in the physicians' choice set. $\Delta_d TC_t(\mathbf{p}_t^{on})$ is the difference between the total cost of treatment of the on-label indication of drug d when drug d is on the market and when it is not, such that

$$\Delta_d TC_t(\mathbf{p}_t^{on}) = \sum_{\tilde{d}\in D^{on}} p_{\tilde{d}t} q_{\tilde{d}t}(\mathbf{p}_t^{on}) \quad - \quad \sum_{\tilde{d}\in D^{on}\setminus\{d\}} p_{\tilde{d}t} q_{\tilde{d}t}^{-d}(\mathbf{p}_t^{on})$$

[7]Drug advertisement is not included in consumer surplus.

where $q_{\tilde{d}t}(\mathbf{p}_t^{on})$ is the demand for drug $\tilde{d}$ in the on-label market, and $q_{\tilde{d}t}^{-d}(\mathbf{p}_t^{on})$ is the demand for drug $\tilde{d}$ when drug d is absent. w is the weight the government puts on consumer surplus, and hence, $(1-w)$ is the weight the government puts on the cost of treatment.

Note that the consumer surplus absent drug d is

$$CS_{t,-d}(\mathbf{p}_t^{on}) = \frac{1}{\beta}\sum_{j\in J_{on}} \ln\left(\sum_{d'\in D^{on}\setminus\{d\}} q\exp\left(\alpha_{d'}(z_i,z_j) - \beta p_{d't} + \lambda_{d'}\overline{I}\right) + (1-q)\exp\left(\alpha_{d'}(z_i,z_j) - \beta p_{d't} + \lambda_{d'}\underline{I}\right)\right)$$

Since we have a drug-specific time-invariant component in the demand specification, when the government considers consumer surplus in the negotiations, it automatically accounts for drug-specific factors, i.e., average efficacy and side effect profile of drugs.

The first-order conditions of this Nash equilibrium are

$$\frac{\mu}{1-\mu}\frac{\partial \ln \Pi_{dt}\left(\mathbf{p}_t^{on},\mathbf{p}_t^{off}\right)}{\partial p_{dt}} + \frac{\partial \ln\left[w\Delta_d CS_t\left(\mathbf{p}_t^{on}\right) - (1-w)\Delta_d TC_t\left(\mathbf{p}_t^{on}\right)\right]}{\partial p_{dt}} = \mathbf{0} \tag{4.2}$$

Thus, the firm's marginal cost is

$$c_{dt} = p_{dt} + \frac{1}{\left(\frac{\partial \ln q_{dt}^{tot}\left(\mathbf{p}_t^{on},\mathbf{p}_t^{off}\right)}{\partial p_{dt}}\right) + \frac{1-\mu}{\mu}\left(\frac{\partial \ln[w\Delta_d CS_t(\mathbf{p}_t^{on}) - (1-w)\Delta_d TC_t(\mathbf{p}_t^{on})]}{\partial p_{dt}}\right)} \tag{4.3}$$

where $\frac{\partial \ln q_{dt}^{tot}\left(\mathbf{p}_t^{on},\mathbf{p}_t^{off}\right)}{\partial p_{dt}}$ is the price semi-elasticity of aggregate demand in both the on-label and off-label markets.

Note that once we know the demand shape, we also have

$$\begin{aligned}
\frac{\partial \Delta_d CS_t\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} &= \frac{\partial CS_t\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} - \frac{\partial CS_{t,-d}\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} \\
&= \frac{1}{\beta}\sum_{j\in J_{on}} -\beta\left\{q\frac{\exp\left(\alpha_d(z_i,z_j) - \beta p_{dt} + \lambda_d\overline{I}\right)}{\sum_{d'\in D^{on}}\exp\left(\alpha_{d'}(z_i,z_j) - \beta p_{d't} + \lambda_{d'}\overline{I}\right)}\right. \\
&\quad \left. +(1-q)\frac{\exp\left(\alpha_d(z_i,z_j) - \beta p_{dt} + \lambda_d\underline{I}\right)}{\sum_{d'\in D^{on}}\exp\left(\alpha_{d'}(z_i,z_j) - \beta p_{d't} + \lambda_{d'}\underline{I}\right)}\right\}
\end{aligned}$$

and

$$\frac{\partial \Delta_d TC_t\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} = \sum_{\tilde{d}\in D^{on}} \frac{\partial p_{\tilde{d}t} q_{\tilde{d}t}\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} - \sum_{\tilde{d}\in D^{on}\setminus\{d\}} \frac{\partial p_{\tilde{d}t} q_{\tilde{d}t}^{-d}\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} = q_{dt}\left(\mathbf{p}_t^{on}\right) + \sum_{\tilde{d}\in D^{on}} p_{\tilde{d}t}\frac{\partial q_{\tilde{d}t}\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}}$$

Moreover, the profit of the firm in both markets is

$$\Pi_{dt}\left(\mathbf{p}_t^{on},\mathbf{p}_t^{off}\right) = \left[p_{dt} - c_{dt}\right] q_{dt}^{tot}\left(\mathbf{p}_t^{on},\mathbf{p}_t^{off}\right) = \left[p_{dt} - c_{dt}\right]\left[q_{dt}^{on}\left(\mathbf{p}_t^{on}\right) + q_{dt}^{off}\left(\mathbf{p}_t^{off}\right)\right]$$

implying that

$$\frac{\partial \Pi_{dt}\left(\mathbf{p}_t^{on}, \mathbf{p}_t^{off}\right)}{\partial p_{dt}} = q_{dt}^{on}\left(\mathbf{p}_t^{on}\right) + q_{dt}^{off}\left(\mathbf{p}_t^{off}\right) + \left[p_{dt} - c_{dt}\right]\left[\frac{\partial q_{dt}^{on}\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} + \frac{\partial q_{dt}^{off}\left(\mathbf{p}_t^{off}\right)}{\partial p_{dt}}\right]$$

where

$$\frac{\partial q_{dt}^{on}\left(\mathbf{p}_t^{on}\right)}{\partial p_{dt}} = -\beta \sum_{j \in J_{on}} \left\{P\left(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}, I_j, on\right)\left(1 - P\left(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}, I_j, on\right)\right)\right\}$$

and

$$\frac{\partial q_{dt}^{off}\left(\mathbf{p}_t^{off}\right)}{\partial p_{dt}} = -\beta \sum_{j \in J_{ojj}} \left\{P\left(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}, I_j, off\right)\left(1 - P\left(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}, I_j, off\right)\right)\right\}$$

which are also known from demand estimates. $q_{dt}^{on}\left(\mathbf{p}_t^{on}\right)$ and $q_{dt}^{off}\left(\mathbf{p}_t^{off}\right)$ are the demand for drug d in the on-label and off-label markets, respectively. The set J_{off} denotes the set of all patients diagnosed with the indications drug d is not approved for but used off-label (off-label indications of drug d). Note that antidepressants are used off-label in the treatment of the following diseases: alcoholism, anguish, anxiety, asthenia, bipolar, dementia, headaches and migraines, high blood pressure, insomnia, other psychotic disorders, pain, smoking, and schizophrenia. In estimating firms' profits, the demand for each drug in each of these markets is taken into account, hence, the profits coming from these markets are included in firms' total profits.

In the case where demand is price insensitive and thus $\beta = 0$, equation (4.3) simplifies to

$$c_{dt} = p_{dt} + \frac{\Delta_d TC_t\left(\mathbf{p}_t^{on}\right) - \frac{w}{1-w}\,\Delta_d CS_t\left(\mathbf{p}_t^{on}\right)}{\frac{1-\mu}{\mu}\,q_{dt}\left(\mathbf{p}_t^{on}\right)}$$

We do not think that the Nash-in-Nash with Threat of Replacement (NNTR) bargaining solution *à la* Ho and Lee (2019) is appropriate in our application, given the institutional setting we are studying. The channel through which exclusion generates bargaining leverage under NNTR does not match the institutional realities of the French market. In France, price negotiations occur after a drug is approved for an(some) indication(s). Hence, the label status and the regulatory policy concerning off-label prescriptions are exogenous to price negotiations. The approval process and price negotiations are conducted by different authorities. These two regulatory bodies are independent, and they act sequentially. Therefore, we do not think it would be realistic to consider that the authority negotiating drug prices can credibly threaten a firm to replace its drug with another drug of a different label status.

5 Econometric Identification and Empirical Estimates

5.1 Demand Model Identification and Estimates

The most commonly used on-label drugs in depression treatment are Selective Serotonin Reuptake Inhibitors (SSRIs), which include the active ingredients Citalopram, Escitalopram, Fluoxetine, Paroxetine, and Sertraline[8].

[8]Escitalopram enters the market during the sample period in 2005. This choice set variation, which is exogenous to consumers, is useful for the identification of the demand model.

In estimating choice probabilities, they are considered distinct alternatives in the physicians' choice set. All the remaining approved active ingredients, each of which has a smaller market share, are classified under the choice called "Other On-Label Drugs ". Off-label drugs are classified under two distinct categories: "Off-Label Drugs with Efficacy", which are the off-label active ingredients for which scientific evidence from the medical literature shows their efficacy in the treatment of depression, and "Other Off-Label Drugs", which include all the other off-label active ingredients and is the reference alternative in the estimation (details on the drugs aggregated under alternatives "Other On-Label Drugs", "Off-Label Drugs with Efficacy" and "Other Off-Label Drugs" can be found in appendix A.1). In total, there are eight exclusive alternatives in the physicians' choice set (because co-prescriptions are less than 3% of the cases, they are excluded from the analysis).

Patients diagnosed with depression but did not receive any drug prescription are excluded from the analysis as their share is only 0.4% of all depression patients. To avoid dealing with the impact of learning about patients' response to prescription choice, as in Crawford and Shum (2005) and Dickstein (2021), we consider the prescription choice on the first visit at which the patient is diagnosed with depression[9].

The treatment outcome considered in the analysis is whether the patient recovers from the disease after six months. First, we allow for a six-month treatment period; then, we check whether the patient was diagnosed with depression again in the one-year period after the six-month treatment period[10]. The recovery is defined by the patient not being diagnosed with depression during this one-year observation period after the six-month treatment period, conditional on still being in the sample. Given that the sample period ends in December 2008, only the patients diagnosed with depression until the end of June 2007 are included in the analysis[11]. The patients who stopped visiting their family physician during or after the six-month treatment period, who are no longer in the sample, are not included in the analysis. The share of patients who stopped visiting their family physician is the same for patients treated with on-label drugs and those treated with off-label drugs (see appendix A.4). Additionally, the share of dropouts among non-depressed patients is the same as the share among depressed patients, which provides evidence that the reason some depressed people stop visiting their family physician is not related to the label status of drugs prescribed for their depression treatment. Instead, these dropouts are likely due to households moving both within and out of the city.

Table 5.1 provides the results of the joint estimation of treatment choice and treatment outcomes, taking into account unobserved patient heterogeneity, which can potentially affect both the treatment choice and the treatment outcome. In the estimation, we normalize the higher value of I_j to 0.5 and the lower value of I_j to -0.5, and we estimate the shares[12] (q). The reference category is "Other Off-Label Drugs"; therefore, coefficients are interpreted relative to "Other Off-Label Drugs". For instance, the positively significant coefficient for patients' age for the on-label drug "Citalopram" means that older patients are more likely to obtain a "Citalopram" prescription relative to an "Other Off-Label Drug". The drug-specific function of physician and patient characteristics (age and gender) control for the time-invariant variation across drugs.

[9]The correlation between prescriptions at the first visit of diagnosis and the prescriptions during the entire treatment period is provided in the online appendix. The online appendix also provides the estimation of the treatment outcome equation conditional on the drug that is prescribed the most often during the treatment period.

[10]For robustness, we allowed for combinations of six-month or one-year treatment periods with six-month or one-year observation periods after the treatment period. The recovery rates are higher after one year of treatment; however, the impacts of counterfactual policies are the same.

[11]To visit a psychiatrist, patients need a referral from their family physician. We can observe whether a patient is referred to a specialist. The patients who are referred to a psychiatrist on the first visit of depression diagnosis or within the six-month treatment period are not included in the analysis. The patients referred to a specialist after the six-month period are considered "still-depressed"; hence, the treatment outcome of recovery is zero for them.

[12]For robustness, we jointly estimate the demand and health outcome equation, normalizing the types' values to different numbers. The estimation and counterfactual results in all the cases are consistent with the current results and are reported in the online appendix.

Detailing expenditures to general practitioners at the drug-month level are excluded from the health outcome equation. Although the model would be identified when the exogenous covariates in the drug choice equation are the same as the exogenous covariates in the treatment outcome equation, it is preferable that some variables in the drug choice equation are excluded from the treatment outcome equation so that our identification is not only driven by parametric assumptions but also comes from exclusion restrictions. We use drug advertising as an excluded variable in the health outcome equation. Advertising affects drug choices but, conditional on the drug choice, it should not impact the health outcomes. The model attributes the change in health outcomes correlated to a different drug choice steered by advertising to the drug choice (for a detailed discussion on the validity of the exclusion restriction, see section 4.1.1).

The first part of Table 5.1 reports the parameters of the estimation of treatment choice, including the impact of unobserved patient-state on the prescription choice of each alternative through λ_d.

To identify price sensitivity, we use the exogenous variation in prices introduced by generic entries after the patent expiration of three molecules (Citalopram, Sertraline, Paroxetine) during our sample period (Grennan et al. (2022) use a similar variation in prices introduced by generic entry). The results show that demand is price sensitive with a significantly negative coefficient for price[13]. Additionally, detailing expenditures positively affect the demand in the on-label market. However, its impact on the demand in the off-label market is limited, similar to the findings in Shapiro (2018). This result is coherent with the fact that pharmaceutical firms can advertise their drugs for on-label use but are not allowed to advertise them for off-label use. Though it is coherent with the regulation, we still cannot identify whether the minimal impact of drug advertisement on off-label use is because firms are not advertising drugs for off-label use or because, even though they do, physicians' response to these advertisements is limited.

The second part of Table 5.1 reports the parameters of the treatment outcome equation. The drug-specific coefficients in part 2 of Table 5.1 are the δ_ds in the model, drug d's treatment effect relative to the control group. The simulated estimation is based on 400 normalized Halton draws for δ_j^d for each patient[14].

A statistically significant parameter of unobserved heterogeneity, λ_d, means that there is unobserved selection into treatment, which impacts both the prescription and recovery probabilities. The δ_ds show the average treatment impact of each drug relative to "Other Off-Label Drugs" after controlling for the unobserved patient-level heterogeneity. The estimate of q shows that 70% of the patients are high types; hence, 30% are low types. The negatively significant estimates of λ_d for the on-label alternatives show that these active ingredients are less (more) likely to be prescribed to high (low) types, which are the patients who are more (less) likely to recover from the disease due to their unobserved state. The severity of the disease can be an example of this type of heterogeneity, i.e., relatively more severe cases (low-types) are more likely to be prescribed the on-label alternatives relative to "Other Off-Label Drugs", and because they are more severe cases, they are less likely to recover from the disease.

For comparison, we estimate the model assuming no correlation between the unobserved patient state affecting prescription choices and treatment outcomes, which means imposing $\lambda_d = 0$ for all d. The treatment choice model is then a logit, and the recovery model is a binary probit model. Table 5.2 provides the parameters of the binary probit estimation of the treatment outcome in this case (Table B.14 in the online appendix

[13]In the case of depression treatment, there is almost no variation in reimbursement rates across drugs, as they are almost all reimbursed at 65%. Therefore, we take into account the price in the estimations, not the reimbursement rate, which would just be scaling down the price of all the drugs by the same constant.

[14]Halton sequences are preferred to pseudo-random draws, thanks to two desirable properties. First, they give more even coverage over the domain of the mixing distribution. Because the draws for each observation are more evenly spread, the simulated probabilities vary less over observations relative to the probabilities calculated by random draws. Second, with Halton draws, the simulated probabilities are negatively correlated over observations, and this negative correlation decreases the variance in the simulated likelihood function (Deb and Trivedi (2006)).

Table 5.1: *Joint Estimation of Treatment Choice and Treatment Outcome*

Part 1: Treatment Choice Equation

	Alternative Specific Parameters				
	Patients'		Physicians'		λ_d
	Age	Sex	Age	Sex	
On-Label Drugs					
Citalopram	.015	-.086	-.016	-.107	-3.513
	(.001)	(.044)	(.003)	(.052)	(.779)
Sertraline	.006	-.243	.004	-.425	-8.549
	(.002)	(.076)	(.005)	(.108)	(1.134)
Paroxetine	.013	-.274	.009	-.453	-9.050
	(.002)	(.075)	(.005)	(.106)	(1.135)
Fluoxetine	.011	.027	-.004	-.196	-4.168
	(.001)	(.042)	(.003)	(.049)	(.906)
Escitalopram	.012	-.164	.009	-.508	-7.175
	(.002)	(.068)	(.004)	(.093)	(.939)
Other	.022	-.207	.004	-.096	-5.417
	(.001)	(.037)	(.002)	(.046)	(.900)
Off-Label Drugs with Efficacy	-.011	-.273	-.002	-.130	.932
	(.002)	(.068)	(.004)	(.084)	(.880)

Parameters Common Across Alternatives

	Advertising		Share of
Price ($-\beta$)	On-Label	Off-Label	*High Types (q)*
-1.526	.225	.020	.691
(.338)	(.013)	(.019)	(.021)

Part 2: Treatment Outcome Equation

	δ_d	Std. Err.	σ_d	Std. Err.
On-Label Drugs				
Citalopram	-.160	(.051)	1.118	(.236)
Sertraline	.615	(.087)	.866	(.262)
Paroxetine	.743	(.067)	1.317	(.217)
Fluoxetine	-.171	(.045)	.807	(.208)
Escitalopram	.343	(.097)	1.434	(.429)
Other	-.102	(.058)	1.115	(.182)
Off-Label Drugs with Efficacy	.120	(.145)	.805	(.405)

	Coef.	Std. Err.
Patients' Age	-.019	(.001)
Patients' Sex	-.093	(.020)
Constant	.918	(.052)
Observations	37,510	

Notes: Standard errors are in parentheses. Advertising is the natural logarithm of the stock of advertising. The "Sex" variable is 1 for females and 0 for males.

reports the parameters of the logit estimation of treatment choice). The control group is "Other Off-Label Drugs", and the drug-specific coefficients are the δ_ds in the model. As a baseline for the analysis, we do not allow for heterogeneity in treatment impact across patients; hence, $\sigma_d = 0$.

δ_ds are significantly negative for all the approved drugs in Table 5.2, which means that, when we ignore the unobserved health state, patients treated with approved drugs have lower recovery rates than patients

Table 5.2: *Binary Probit Estimation of Treatment Outcome*

	Coefficient	Std. Error	Marginal Effect	Std. Error
Patients' Age	-.013	(.000)	-.005	(.000)
Patients' Sex (female=1)	-.080	(.014)	-.030	(.005)
On-Label Drugs				
Citalopram	-.293	(.026)	-.110	(.010)
Sertraline	-.289	(.028)	-.108	(.010)
Paroxetine	-.285	(.022)	-.107	(.008)
Fluoxetine	-.289	(.025)	-.108	(.009)
Escitalopram	-.315	(.033)	-.118	(.012)
Other	-.340	(.021)	-.127	(.008)
Off-Label Drugs				
with Efficacy	-.015	(.043)	-.006	(.016)
Constant	1.163	(.027)		
Number of Observations			37,510	

Notes: Standard errors are in parentheses.

treated with "Other Off-Label Drugs". The average recovery rate with alternative "Off-Label Drugs with Efficacy" is not different from the average recovery rate with "Other Off-Label Drugs".

Once we control for the unobserved heterogeneity, the relative average treatment impact parameter for the on-label alternatives is either positive or slightly negative, according to the results reported in the second part of Table 5.1. The significantly positive estimates for δ_d for the alternatives "Sertraline", "Paroxetine", and "Escitalopram" show that, on average, the treatment impact of these drugs relative to "Other Off-Label Drugs" is positive, in contrast to the results presented in Table 5.2, which does not take into account unobserved heterogeneity. The average relative treatment impact of the alternatives "Citalopram", "Fluoxetine", and "Other On-Label" drugs is negative despite the selection into treatment based on unobservables. Similar to the result in Table 5.2, the estimate for the δ_d parameter is not statistically different from zero for the alternative "Off-Label Drugs with Efficacy". Overall, the results in Table 5.1 show that there is unobserved patient-level heterogeneity that impacts both drug choice and recovery status.

Estimates of σ_d in Table 5.1 show that the treatment effect of each drug, relative to the reference group, is heterogeneous across patients, even after controlling for observables and patient-level unobserved state. This means, for some patients, treatment with "Citalopram", for instance, leads to lower recovery rates than treatment with "Other Off-Label Drugs". However, for some other group of patients, it leads to higher recovery rates, even though the average relative impact for this alternative, δ_d, is negative. σ_d estimates show the heterogeneity in the relative treatment effect of each drug relative to the reference group.

A statistically significant estimate of σ_d means that for some patients, drug d leads to higher recovery rates than "Other Off-Label Drugs" whereas, for another group of patients, it leads to lower recovery rates than "Other Off-Label Drugs". It does not mean that drug d is detrimental to some share of the population; it just means it is worse than "Other Off-Label Drugs". Heterogeneity in treatment impact of drugs across patients in depression treatment is a well-documented result in the medical literature (see, e.g., Simon and Perlis (2010), Perlis (2014), Uher et al. (2012)). The coefficients of the observed patient characteristics in Table 5.1 show that older patients and female patients are less likely to recover from depression.

Table 5.3 reports the quantiles of the relative treatment effects of the drugs relative to the reference alternative "Other Off-Label Drugs". For every on-label alternative, there is a group of patients for whom the on-label alternative is better than "Other Off-Label Drugs", and another group of patients for whom

"Other Off-Label Drugs" is better than the on-label alternative. Hence, for all the on-label drugs, there are some patients for whom the treatment effect relative to "Other Off-Label Drugs" is positive, with the lowest share of patients being 42% for "Fluoxetine" treatment.

Table 5.3: *Quantiles on the Marginal Effect of Treatment*

	Quantiles					Percentage with Positive Relative Treatment Effect
	25%	50%	75%	95%	Mean	
On-Label						
Citalopram	-24.8	-5.2	17.5	46.2	-3.9	44%
Sertraline	1.0	17.6	31.9	55.7	16.5	76%
Paroxetine	-4.7	19.5	37.5	64.7	16.5	71%
Fluoxetine	-21.0	-5.5	11.9	34.6	-4.7	42%
Escitalopram	-17.7	10.9	30.9	61.5	7.5	59%
Other On-Label	-23.5	-3.3	18.8	47.5	-2.4	46%
Off-Label						
with Efficacy	-13.1	4.0	19.6	42.8	3.4	56%

Notes: The quantiles are in terms of percentage points showing the treatment impact of the drug in the first column relative to the reference alternative "Other Off-Label Drugs". For instance, the first cell shows that for 25% of the patients, recovery rates when treated with "Citalopram" are at least 24.8 percentage points lower than recovery rates when treated with "Other Off-Label Drugs". The last column shows the percentage of patients for whom the drug in the first column leads to a positive treatment impact relative to "Other Off-Label Drugs".

5.2 Supply-Side Identification and Estimates

We now present our identification strategy on parameters of the supply-side model and estimates of these parameters.

The first-order conditions (4.2) depend on demand, parameters μ, w and marginal costs c_{dt}. We can set identify μ and w using some simple and robust cost restrictions imposing that marginal costs of drugs are positive and smaller than the lowest observed prices for these drugs. Using (4.3), the firm's marginal cost depends on the demand parameter vector denoted by $\mathbf{\Lambda}$ and the supply-side parameters μ and w as follows

$$c_{dt}\left(\mathbf{\Lambda},\mu,w,\mathbf{k}_t\right)=p_{dt}+\frac{1}{\left(\frac{\partial \ln q_{dt}^{tot}\left(\mathbf{p}_t^{on},\mathbf{p}_t^{off}\right)}{\partial p_{dt}}\right)+\frac{1-\mu}{\mu}\left(\frac{\partial \ln[w\Delta_d CS_t(\mathbf{p}_t^{on})-(1-w)\Delta_d TC_t(\mathbf{p}_t^{on})]}{\partial p_{dt}}\right)}$$

where $\mathbf{k}_t$ is the vector of observed variables used to obtain marginal costs (prices and characteristics).

We then assume that true marginal costs c_d^0 are time invariant and that ζ_{dt} is mean independent of true cost c_d^0 such that

$$c_{dt}\left(\mathbf{\Lambda},\mu,w,\mathbf{k}_t\right)=c_d^0+\zeta_{dt}$$

These imply the moment condition

$$E\left(c_{dt}\left(\mathbf{\Lambda},\mu,w,\mathbf{k}_t\right)\right)=E\left(c_d^0+\zeta_{dt}\right)=c_d^0$$

Using the set of natural economic inequalities that cost should be positive and lower than price at any time,

$$0\leq c_d^0\leq \underline{p_d}\equiv\min_t p_{dt}\qquad \forall d=1,..,D$$

we obtain the following moment inequalities:

$$0 \leq E\left(c_{dt}\left(\mathbf{\Lambda}, \mu, w, \mathbf{k}_t\right)\right) \leq \underline{p_d} \quad \forall d = 1, .., D$$

Note that we could slightly generalize by allowing marginal costs c_d^0 to vary over time and then use time-specific upper bounds on the cost. In practice, the minimum price $\underline{p_d}$ will be the minimum price of the corresponding drug d over an observation period that goes beyond the period of estimates of costs[15], until 2018.

Then, for a given vector of demand parameters $\mathbf{\Lambda}$, the identified set of supply-side parameters is

$$S_{(\mu,w)}\left(\mathbf{\Lambda}\right) = \left\{(\mu, w)\,|0 \leq E\left(c_{dt}\left(\mathbf{\Lambda}, \mu, w, \mathbf{k}_t\right)\right) \leq \underline{p_d},\, \forall d = 1, .., D\right\}$$

and can be empirically estimated using

$$\hat{S}_{(\mu,w)}\left(\mathbf{\Lambda}\right) = \left\{(\mu, w)|0 \leq \frac{1}{T}\sum\nolimits_{t=1}^{T} c_{dt}\left(\mathbf{\Lambda}, \mu, w, \mathbf{k}_t\right) \leq \underline{p_d},\, \forall d = 1, .., D\right\}$$

where T is the maximum number of years we have in our sample. Remark that demand parameters are unknown and, while they are independently estimated, we should also account for the uncertainty in estimates of $\mathbf{\Lambda}$ and obtain random sets $\hat{S}_{(\mu,w)}\left(\mathbf{\Lambda}\right)$. The asymptotic theory of these identified sets can be studied using methods proposed by Chernozhukov et al. (2007) or Andrews and Barwick (2012) for a fixed $\mathbf{\Lambda}$ but would require some extension when $\mathbf{\Lambda}$ is unknown and estimated from an auxiliary model. For simplicity, we use the estimated parameter $\widehat{\mathbf{\Lambda}}$ to compute the identified set $\hat{S}_{(\mu,w)}(\widehat{\mathbf{\Lambda}})$ and make some robustness checks with respect to $\widehat{\mathbf{\Lambda}}$.

We also impose the restriction that all agreements in a network generate positive gains-from-trade for parties involved. This restriction is not binding for the firms since the disagreement profits are zero. It is also not binding for the government surplus for any value of w in the identified set after imposing the cost restrictions. Note that payor expenditures (TC) are net of patient expenditures. In the identified set[16], the bargaining power of the firm, μ, takes values between 0.76 and 0.93, and the weight the government puts on consumer surplus, w, is between 0.65 and 1. The shaded area in figure 5.1 shows the whole identified set for μ and w. For instance, when $\mu = 0.80$, w takes values between 0.93 and 1, whereas when $\mu = 0.92$, w takes values on a smaller range, between 0.66 and 0.71. Because it would not be feasible to do the counterfactuals for all the combinations of μ and w, we will provide the marginal cost estimates and counterfactual results for some combinations of μ and w in the identified set, which are marked by cross signs in figure 5.1.

Table 5.4 provides the average prices during the sample period, prices in 2018, and the marginal cost estimates of on-label alternatives for these combinations of μ and w.

Note that the bargaining model is scale-invariant. Using drug sales data at the national level would mean scaling up all the components of the bargaining model by the same constant and would lead to the same

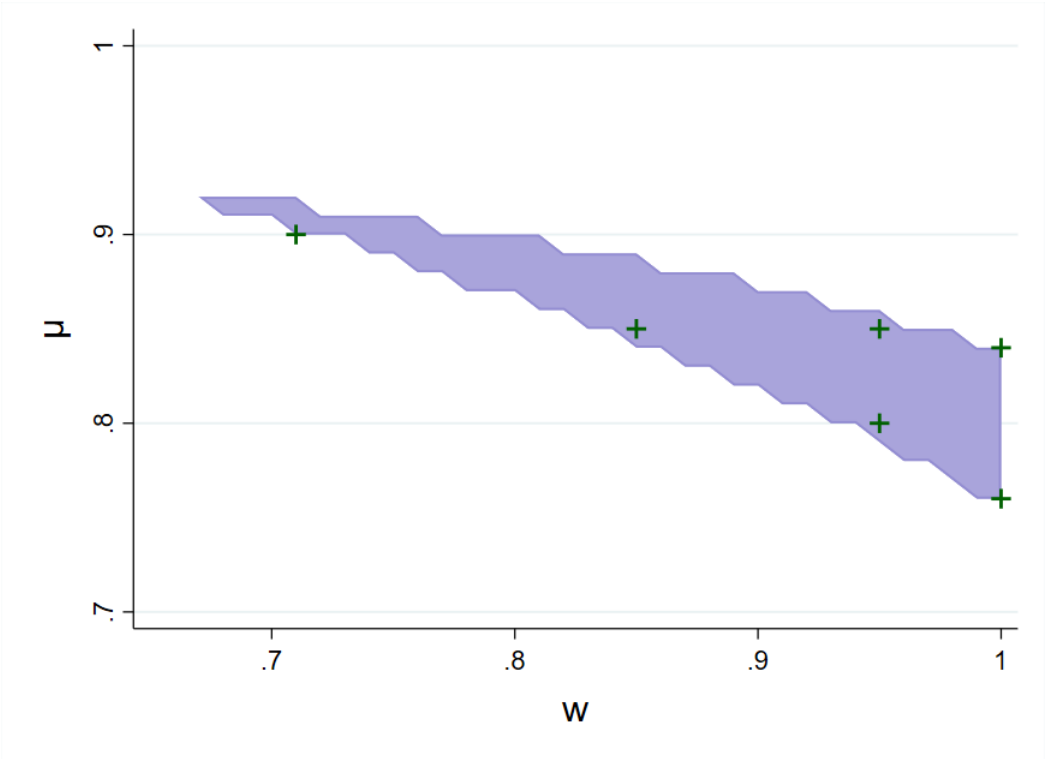
[15] Drug prices decrease over time in France mostly due to generic entry and/or regulatory changes.

[16] In the estimation of the profit function, quantities include all the visits, not only the first visit. Market shares of choice alternatives across the first visit prescriptions and across all visits are very similar. The impacts of advertisement and price on demand across all the visits are also similar to their effects on demand on the first visit prescriptions (for details on market shares and demand estimation including all visits, see the online appendix).

We use product-by-product bargaining as most firms have a single product on this market except one. We assume, for simplicity, that the only firm (Lundbeck) with two products (Citalopram and Escitalopram) on this market is bargaining at the active ingredient level. We also assume, for simplicity, that the aggregate choice alternative "Other On-Label Drugs" behave similarly in price setting as an additional firm. Firms that market the main molecules on this market do not have a considerable share in this aggregate alternative.

equilibrium prices. Thus, parameter estimates would not be affected by rescaling to aggregate drug sales at the national level.

Figure 5.1: *Identified Set for the Bargaining Parameter and the Weight*



Notes: The cross signs represent the combinations of μ and w for which we provide the marginal cost estimates and counterfactual results.

Table 5.4: *Marginal Cost Estimates of On-Label Drugs*

	Average Price During Sample Period (€)	Prices in 2018 (€)	Marginal Cost (€/DDD)					
Bargaining Parameter (μ)			0.76	0.80	0.84	0.85	0.85	0.90
Weight on CS (w)			1	0.95	1	0.85	0.95	0.71
Citalopram	.836	.271	.266	.258	.207	.258	.217	.268
Sertraline	.804	.286	.228	.206	.174	.181	.171	.155
Paroxetine	.776	.204	.151	.129	.098	.104	.096	.080
Fluoxetine	.744	.267	.121	.112	.055	.109	.067	.107
Escitalopram	.685	.209	.074	.059	.006	.046	.012	.031
Other On-Label Drugs	.928	.526	.319	.318	.248	.341	.267	.424

Notes: This table reports the average prices during the sample period, prices in 2018, and the marginal cost estimates of on-label alternatives for some combinations of μ and w. Price is the price for a one-day treatment calculated using the DDD assigned by the World Health Organization. For each active ingredient, it is the price per mg times mg per day according to the DDD.

6 Counterfactual Simulation of a Ban on Off-Label Prescriptions

Using the structural choice model, we perform counterfactual simulations of prescription choices when off-label drugs are not in physicians' choice set. Before 2011 in France, physicians were perfectly free to prescribe off-label drugs if they wanted to. However, the current regulation under "Temporary Recommendations for Use (TRU)" in France aims to strictly regulate off-label prescriptions. In the US, the formulary drug lists of health insurance companies contribute to limiting off-label prescriptions. We thus predict counterfactual prescriptions in the case of an off-label ban by simulating demand if off-label drugs were removed from the physicians' choice set.

After simulating such prescriptions, we simulate the associated expected cost at the observed prices had the prices been identical in the case of an off-label ban. In the second part of the counterfactual analysis, using the supply-side bargaining model, we will investigate how prices would have been different had negotiations taken place under a ban on off-label prescriptions and simulate the associated counterfactual expected demand and treatment cost using the counterfactual prices.

6.1 Theory

6.1.1 Keeping Prices Fixed

Assuming prices would be the same in the case of a ban on off-label use, we can simulate not only the counterfactual prescription choices but also their expected costs and the expected recovery rate of patients simply by removing off-label alternatives from the physicians' choice set.

Removing off-label drugs from the choice set, the counterfactual choice probability that physician i will prescribe an approved drug to patient j is now equal to

$$\begin{aligned} P_c\left(y_{ijt}=d|z_i,z_j,p_{dt},x_{dt},I_j\right) &= q\ \frac{\exp\left(\alpha_d\left(z_i,z_j\right)-\beta p_{dt}+\gamma_{l(d)}x_{dt}+\lambda_d\overline{I}\right)}{\sum\limits_{d'\in D_{on}^{on}}\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}+\gamma_{l(d')}x_{d't}+\lambda_{d'}\overline{I}\right)} \\ &+ (1-q)\ \frac{\exp\left(\alpha_d\left(z_i,z_j\right)-\beta p_{dt}+\gamma_{l(d)}x_{dt}+\lambda_d\underline{I}\right)}{\sum\limits_{d'\in D_{on}^{on}}\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}+\gamma_{l(d')}x_{d't}+\lambda_{d'}\underline{I}\right)} \end{aligned}$$

where $D_{on}^{on}=D^{on}\backslash\{d''\in D^{on}|l(d'')=0\}$ is the set of all on-label drugs for the indication for which d is on-label ($l(d)=1$ if drug d is an approved drug for depression and 0 otherwise). Note that because the reference group is "Other Off-Label Drugs", with a ban on off-label drugs, the choice probability of the reference group is 0.

The ex-ante expected cost of treatment for patients diagnosed with the on-label indication is

$$\sum\nolimits_{j\in J_{on}}\sum\nolimits_{d\in D^{on}}P\left(y_{ijt}=d|z_i,z_j,p_{dt},x_{dt},I_j\right)p_{dt} \tag{6.1}$$

As defined above, D^{on} is the set of drugs prescribed for the on-label indication of drug d, which contains both on-label and off-label drugs. The treatment cost ex-post, after removing off-label drugs from the choice set, in this on-label indication market is

$$\sum\nolimits_{j\in J_{on}}\sum\nolimits_{d\in D_{on}^{on}}P_c\left(y_{ijt}=d|z_i,z_j,p_{dt},x_{dt},I_j\right)p_{dt} \tag{6.2}$$

Therefore, the change in the expected cost is the difference between (6.1) and (6.2). Drugs approved for depression treatment are, on average, more expensive than off-label drugs used in depression treatment. Thus, we would expect the cost of treatment would increase with the ban on off-label prescriptions when we assume on-label drug prices will be the same under the ban. When off-label drugs are no longer in the choice set, physicians will necessarily substitute approved drugs for off-label drugs. Because approved drugs are more expensive alternatives, expected prescription expenses will increase due to this substitution effect.

The ex-ante expected recovery rate for patient j using the ex-ante prescription choice probabilities is

$$E\left[r_{jt}\right] = \sum_{d \in D^{on}} P(r_{jt} = 1 | z_j, I_j, y_{ijt} = d) P(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}, I_j) \tag{6.3}$$

while the expected counterfactual recovery rate r_{jt}^c using the new prescription choice probabilities is

$$E\left[r_{jt}^c\right] = \sum_{d \in D_{on}^{on}} P(r_{jt} = 1 | z_j, I_j, y_{ijt} = d) P_c(y_{ijt} = d | z_i, z_j, p_{dt}, x_{dt}, I_j) \tag{6.4}$$

6.1.2 Price Negotiations Under a Ban on Off-Label Use

If the government bans off-label prescriptions, the negotiated drug price equilibrium is likely to be different. With the off-label ban, the choice probability of drug d by physician i for patient j who is diagnosed with an approved indication of drug d is

$$\begin{aligned} P_c\left(y_{ijt} = d | z_i, z_j, p_{dt}^{ban}, x_{dt}, I_j\right) &= q \frac{\exp\left(\alpha_d\left(z_i, z_j\right) - \beta p_{dt}^{ban} + \gamma_{l(d)} x_{dt} + \lambda_d \overline{I}\right)}{\sum_{d' \in D_{on}^{on}} \exp\left(\alpha_{d'}(z_i, z_j) - \beta p_{d't}^{ban} + \gamma_{l(d')} x_{d't} + \lambda_{d'} \overline{I}\right)} \\ &+ (1-q) \frac{\exp\left(\alpha_d\left(z_i, z_j\right) - \beta p_{dt}^{ban} + \gamma_{l(d)} x_{dt} + \lambda_d \underline{I}\right)}{\sum_{d' \in D_{on}^{on}} \exp\left(\alpha_{d'}(z_i, z_j) - \beta p_{d't}^{ban} + \gamma_{l(d')} x_{d't} + \lambda_{d'} \underline{I}\right)} \end{aligned} \tag{6.5}$$

where, as defined above, D_{on}^{on} is the set of all the on-label drugs for the on-label indication considered (depression), and p_{dt}^{ban} is the price of drug d negotiated with the regulator under the ban on off-label use. Note that because the reference group is "Other Off-Label Drugs", with a ban on off-label drugs, the choice probability of the reference group is 0.

We can simulate the new price equilibrium in the case of a ban on off-label prescriptions, assuming that the same bargaining model would apply. For any drug $d \in D_{on}^{on}$, its new price, p_{dt}^{ban}, would be the solution of

$$\max_{p_{dt}^{ban}} \left[\Pi_{dt}^{ban}\left(\mathbf{p}_t^{ban}\right)\right]^{\mu} \left[w \Delta_d CS_t^{ban}\left(\mathbf{p}_t^{ban}\right) - (1-w) \Delta_d TC_t^{ban}\left(\mathbf{p}_t^{ban}\right)\right]^{1-\mu}$$

where $\Pi_{dt}^{ban}\left(\mathbf{p}_t^{ban}\right)$ is the firm's profit for drug d when off-label drugs competing with d are banned, and $\mathbf{p}_t^{ban}$ is the vector of prices of all on-label drugs when off-label drugs are banned. $\Delta_d CS_t^{ban}\left(\mathbf{p}_t^{ban}\right) \equiv CS_t^{ban}\left(\mathbf{p}_t^{ban}\right) - CS_{t,-d}^{ban}\left(\mathbf{p}_t^{ban}\right)$ is the consumer surplus provided by drug d for the on-label indication where

$$CS_t^{ban}\left(\mathbf{p}_t^{ban}\right) = \frac{1}{\beta} \sum_{j \in J_{on}} \ln\left(\sum_{d' \in D_{on}^{on}} q \exp\left(\alpha_{d'}(z_i, z_j) - \beta p_{d't}^{ban} + \lambda_{d'} \overline{I}\right) + (1-q) \exp\left(\alpha_{d'}(z_i, z_j) - \beta p_{d't}^{ban} + \lambda_{d'} \underline{I}\right)\right)$$

and

$$CS_{t,-d}^{ban}\left(\mathbf{p}_t^{ban}\right)=\frac{1}{\beta}\sum_{j\in J_{on}}\ln\left(\sum_{d'\in D_{on}^{on}\setminus\{d\}}q\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}^{ban}+\lambda_{d'}\overline{I}\right)+(1-q)\exp\left(\alpha_{d'}(z_i,z_j)-\beta p_{d't}^{ban}+\lambda_{d'}\underline{I}\right)\right)$$

The firm's profits are now

$$\Pi_{dt}^{ban}\left(\mathbf{p}_t^{ban}\right)=\left[p_{dt}^{ban}-c_{dt}\right]q_{dt}^{ban}\left(\mathbf{p}_t^{ban}\right)$$

where $q_{dt}^{ban}\left(p_t^{ban}\right)$ is the aggregate demand for drug d in the case of an off-label ban. Marginal costs are estimated according to (4.3). Note that in the case of a ban, by definition, drug d's market share in the off-label indication markets is zero. Therefore, with the ban on off-label use, the aggregate demand for drug d can increase or decrease relative to the benchmark case where off-label use is allowed. The market share of drug d in the on-label market increases with the ban as there is no competition from off-label drugs in the on-label market for drug d (in the depression market). However, drug d will lose all sales in the off-label markets. A list of off-label markets for antidepressants is provided in section 4.2.

The marginal impact of drug d on the total cost of treatment is now

$$\Delta_d TC_t^{ban}\left(\mathbf{p}_t^{ban}\right)=\sum_{\tilde{d}\in D_{on}^{on}}p_{\tilde{d}t}^{ban}q_{\tilde{d}t}^{ban}\left(\mathbf{p}_t^{ban}\right)-\sum_{\tilde{d}\in D_{on}^{on}\setminus\{d\}}p_{\tilde{d}t}^{ban}{q_{\tilde{d}t}^{ban}}^{-d}\left(\mathbf{p}_t^{ban}\right)$$

which is the difference between the total cost of treatment when drug d is in the choice set and the total cost when drug d is absent. ${q_{\tilde{d}t}^{ban}}^{-d}\left(\mathbf{p}_t^{ban}\right)$ is the demand for drug $\tilde{d}$ when drug d is absent at equilibrium prices under the ban.

The first-order condition can be written as

$$\frac{\mu}{1-\mu}\frac{\partial\ln\Pi_{dt}^{ban}\left(\mathbf{p}_t^{ban}\right)}{\partial p_{dt}}+\frac{\partial\ln\left[w\Delta_d CS_t^{ban}\left(\mathbf{p}_t^{ban}\right)-(1-w)\Delta_d TC_t^{ban}\left(\mathbf{p}_t^{ban}\right)\right]}{\partial p_{dt}}=\mathbf{0} \tag{6.6}$$

Using this system of first-order conditions, we can find the new prices as solutions of this system given the estimated marginal costs:

$$p_{dt}^{ban}=c_{dt}+\frac{1}{\left(\frac{-\partial\ln q_{dt}^{on}\left(\mathbf{p}_t^{ban}\right)}{\partial p_{dt}}\right)+\frac{1-\mu}{\mu}\left(\frac{-\partial\ln\left[w\Delta_d CS_t^{ban}\left(\mathbf{p}_t^{ban}\right)-(1-w)\Delta_d TC_t^{ban}\left(\mathbf{p}_t^{ban}\right)\right]}{\partial p_{dt}}\right)}$$

where $\frac{\partial\ln q_{dt}^{on}\left(\mathbf{p}_t^{ban}\right)}{\partial p_{dt}}$ is the price semi-elasticity of demand at the new price equilibrium in the on-label market and $\frac{\partial\ln\Delta_d CS_t^{ban}\left(\mathbf{p}_t^{ban}\right)}{\partial p_{dt}}$ is the price semi-elasticity of the additional consumer surplus by drug d under the ban when off-label drugs are not in the choice set.

This estimation allows us to compute the counterfactual prescription probabilities of on-label drugs for each patient and the market shares given the new prices. We can then predict the associated counterfactual treatment expenses and recovery probabilities.

Note that price cost margin is a function of price elasticity of demand and price elasticity of drug d's marginal contribution to the government's surplus at the new price equilibrium. Hence, it is a function of drug d's additional value added to the consumer surplus and additional cost by drug d at the new prices. The ban can impact drug prices through its impact on these elasticities. As mentioned before, whether the aggregate demand for drug d will increase or decrease with the ban vs. without the ban is ambiguous because $q_{dt}^{tot}\left(p_t^{on},p_t^{off}\right)=q_{dt}^{on}\left(p_t^{on}\right)+q_{dt}^{off}\left(p_t^{off}\right)$ is the sum of the sales of drug d on the on-label market and all the

off-label markets for which drug d is used, whereas $q_{dt}^{on}\left(p_t^{ban}\right)$ is the on-label sales of drug d when no competing off-label drug is present to treat the on-label indication of drug d. Therefore, whether $\frac{\partial \ln q_{dt}^{on}\left(\mathbf{p}_t^{ban}\right)}{\partial p_{dt}}$ is larger or smaller than $\frac{\partial \ln q_{dt}^{tot}\left(\mathbf{p}_t^{on},\mathbf{p}_t^{off}\right)}{\partial p_{dt}}$ is ambiguous. Semi-elasticities can be ranked in any direction depending on the price at which they are evaluated and the price elasticity of drug d in the on-label indication market when off-label drugs are present and when they are absent, and its elasticity in the off-label indication markets.

Similarly, the ban can impact drug prices through the channel of the price elasticity of the consumer surplus value added of drugs. The consumer surplus value added of drug d is the additional surplus provided by drug d relative to the other drugs in the physicians' choice set. Physicians' choice set shrinks with the ban; hence, the marginal surplus of drug d relative to the drugs in the new choice set increases, meaning $\Delta_d CS_t^{ban}\left(p_t^{ban}\right) > \Delta_d CS_t\left(p_t^{on}\right) > 0$. The order of derivatives of the consumer surplus value added of drug d with respect to price is such that $\frac{\partial \Delta_d CS_t^{ban}\left(\mathbf{p}_t^{ban}\right)}{\partial p_{dt}} < \frac{\Delta_d CS_t(\mathbf{p}_t^{on})}{\partial p_{dt}} < 0$. Then, in the case of homogeneous preferences, the semi-elasticity of $\Delta_d CS$ is larger with fewer drugs than with more drugs in the choice set, $\frac{\partial \ln \Delta_d CS_t(\mathbf{p}_t^{on})}{\partial p_{dt}} < \frac{\partial \ln \Delta_d CS_t^{ban}\left(\mathbf{p}_t^{ban}\right)}{\partial p_{dt}} < 0$. Therefore, the ban has an increasing impact on the price through the channel of consumer surplus elasticity. With heterogeneous preferences, the ban's effect through the channel of CS semi-elasticity is theoretically ambiguous (for details, see the online appendix B.2.2).

In short, the overall impact of the ban on drug prices through these channels is ambiguous. It can increase drug prices if the effects go in the same direction, but it can also decrease the prices if the effect through demand elasticity is in the opposite direction of and dominates the effect through consumer surplus elasticity (for a detailed investigation of the impact of the ban on prices of on-label drugs, see the online appendix B.2).

6.2 Empirical Results

6.2.1 Banning Off-Label Prescriptions while Keeping the Prices of On-Label Drugs Constant

In this section, we simulate counterfactual prescription probabilities, their expected costs, and the expected recovery of patients under a ban on off-label prescriptions, assuming that prices will be the same as in the benchmark scenario of no ban. Two cases are worth considering in the counterfactual analysis. In one of them, prescriptions of all off-label drugs are banned, and in the other case, prescriptions of "Off-Label Drugs with Efficacy" are allowed, whereas prescriptions of off-label drugs for which there is no information in the medical literature on efficacy in depression treatment, "Other Off-Label Drugs", are banned.

Table 6.2 reports the expected cost of a one-day treatment per patient for the cases when off-label prescriptions are allowed and for the two counterfactual scenarios. In both counterfactual scenarios, the cost increases, and the increase is larger when we ban all off-label drugs. The expected cost increases, from a benchmark of 66 euro cents per day, by 15.2%, when we ban all off-label drugs, and by 11.7% when we ban only "Other Off-Label Drugs" and still allow for prescriptions of "Off-Label Drugs with Efficacy".

Table 6.3 shows the expected recovery rate after a six-month treatment period after the first diagnosis. First, the probability of recovery after six months, conditional on the drug treatment, is calculated using the estimated parameters of the structural model. Then, given the estimated prescription probabilities, the unconditional recovery probability is calculated according to Eqn. 6.3 in the benchmark and Eqn. 6.4 in the counterfactuals. The unconditional recovery probability is the sum over all the alternatives of the recovery probability conditional on treatment with each alternative multiplied by the prescription probability of that alternative. Table 6.3 provides statistics on the unconditional recovery probability. The first column is the case when all drugs are in the physicians' choice set; the second column shows the case when all approved drugs and off-label drugs with efficacy are in the choice set; the third column shows the expected recovery

probability when only approved drugs are in the choice set. The results show that removing the off-label drugs from the choice set does not greatly impact the recovery probability; recovery probability decreases to 0.54, by 1.8%, from a benchmark probability of 0.55.

These results show that while keeping prices identical, banning off-label prescriptions has little impact on recovery rates for depression after a six-month treatment period but raises expenditures on drugs as physicians substitute off-label drugs with more expensive on-label alternatives.

6.2.2 Banning Off-Label Prescriptions and the New Price Equilibrium

Now, we investigate what prices of on-label drugs would be if the negotiations were to take place under a strict ban on off-label prescriptions. Then, we will identify the change in the expected cost of treatment and the change in the expected recovery rate, both of which also depend on new prices through the counterfactual choice probabilities. When off-label drugs are banned, the market share of on-label drugs in the depression market will increase. However, the on-label drugs for depression treatment are used off-label for treating other diseases. Therefore, with an off-label ban, these drugs' market shares in the treatment of other diseases will decrease to zero even though their shares in the depression market will increase. The impact of an off-label ban on the aggregate sales of the drugs approved for depression is thus ambiguous. We, therefore, also estimate the sales of these drugs in the markets for the off-label indications they are used. The list of off-label indications for antidepressants is provided in section 4.2.

After removing off-label drugs from the choice set, the counterfactual choice probability that physician i will prescribe an approved drug for which $l(d) = 1$, to patient j is given by Eqn. 6.5. Then, the expected treatment cost for this on-label indication for patient j is

$$\sum\nolimits_{d \in D_{on}^{on}} P_c\left(y_{ijt} = d | z_i, z_j, p_{dt}^{ban}, x_{dt}, I_j\right) p_{dt}^{ban}$$

We can now identify the change in the expected cost of treatment and, finally, the change in the expected recovery rate that also depends on new prices through the counterfactual choice probabilities of alternatives.

Table 6.1 presents the differences between the prices in the benchmark scenario of no-ban and the prices in the counterfactual case of a ban estimated using the system of first-order conditions in (6.6) for different values of μ and w in the identified set. When off-label drugs are banned, we observe an increase in the prices of on-label alternatives in all six combinations of μ and w. The price increase depends on the drug and the values of μ and w and ranges from 1% to 22.9%.

In the last column of Table 6.2, we provide the expected cost of a one-day treatment per patient when off-label drugs are banned, and drug prices are negotiated under the ban, for given values of $\mu = 0.85$ and $w = 0.85$. The expected prescription expense of drug treatment increases by 26.8% in the counterfactual scenario when drug prices are allowed to be different under the ban, which is higher than the increase when drug prices are kept constant, 15.2%. When off-label drugs are banned, physicians substitute them with on-label drugs. Because, on average, on-label drugs are more expensive, this substitution effect leads to an increase in prescription expenses. When off-label drugs are banned and prices are negotiated under the ban, the prices of on-label drugs are higher than those in the benchmark scenario. Hence, the prescription expenses increase due to both price and substitution effects. Therefore, in the second and third columns of Table 6.2, the increase in prescription expenses is due to the substitution effect, whereas the increase in the last column is due to both substitution and price effects.

Similarly, Table 6.3 compares the probability of recovery six months after the first diagnosis in the same four cases. The decrease in the average recovery rate in the counterfactual scenario when drug prices are

Table 6.1: *Counterfactual Price Changes in the Case of a Ban on Off-Label Prescriptions*

μ	0.76	0.80	0.84	0.85	0.85	0.90
w	1	0.95	1	0.85	0.95	0.71
Drugs						
Citalopram	.043 (5.3%)	.064 (8.0%)	.045 (5.6%)	.103 (13.0%)	.062 (7.7%)	.156 (20.0%)
	[-.111,.363]	[-.096,.398]	[-.126,.401]	[-.065,.453]	[-.109,.420]	[-.020,.522]
Sertraline	.008 (1.0%)	.010 (1.3%)	.011 (1.4%)	.013 (1.7%)	.012 (1.6%)	.017 (2.2%)
	[-.139,.322]	[-.144,.338]	[-.151,.359]	[-.148,.356]	[-.151,.362]	[-.152,.377]
Paroxetine	.020 (2.7%)	.023 (3.1%)	.025 (3.4%)	.028 (3.8%)	.027 (3.6%)	.032 (4.3%)
	[-.139,.362]	[-.143,.380]	[-.151,.404]	[-.146,.401]	[-.150,.406]	[-.150,.422]
Fluoxetine	.064 (9.4%)	.084 (12.3%)	.067 (9.8%)	.118 (17.4%)	.083 (12.2%)	.155 (22.9%)
	[-.101,.405]	[-.087,.441]	[-.115,.448]	[-.062,.492]	[-.101,.465]	[-.033,.546]
Escitalopram	.022 (3.5%)	.028 (4.4%)	.028 (4.5%)	.038 (5.9%)	.032 (5.1%)	.049 (7.5%)
	[-.134,.351]	[-.135,.372]	[-.145,.395]	[-.133,.399]	[-.142,.400]	[-.130,.427]
Other On-Label	.071 (8.2%)	.087 (9.9%)	.080 (9.3%)	.115 (12.7%)	.090 (10.3%)	.162 (17.0%)
	[-.097,.420]	[-.087,.452]	[-.106,.469]	[-.069,.497]	[-.097,.480]	[-.029,.562]

Notes: This table reports the difference between the prices of on-label drugs in the benchmark scenario of no-ban and their prices in the counterfactual case of a ban on off-label prescriptions for different values of the bargaining parameter of the firm, μ, and the weight on CS, w. Confidence intervals at the 90% significance level constructed by 500 bootstrap draws drawn from the estimated distribution of parameters are in square brackets. Percentage change is reported in parentheses.

Table 6.2: *Expected Prescription Expense of Drug Treatment (€)*

Choice Set		When All Drugs are in the Choice Set (Benchmark)	When "Other Off-Label Drugs" are Removed		When All Off-Label Drugs are Removed		When All Off-Label Drugs are Removed (Counterfactual Prices) ($\mu = 0.85, w = 0.85$)	
Patients		Expenses	Expenses	Change	Expenses	Change	Expenses	Change
All	Mean	.657 [.550,.707]	.734 [.730,.738]	.077 (11.7%)	.757 [.756,.757]	.100 (15.2%)	.833 [.658,1.199]	.176 (26.8%)
	Min.	.564 [.463,.631]	.675 [.668,.680]	.111 (19.7%)	.739 [.738,.739]	.175 (31.0%)	.810 [.635,1.174]	.246 (43.6%)
	Max.	.729 [.649,.757]	.771 [.768,.773]	.042 (5.8%)	.781 [.780,.781]	.052 (7.1%)	.862 [.686,1.229]	.133 (18.2%)
Female	Mean	.655 [.545,.707]	.734 [.730,.738]	.079 (12.1%)	.756 [.755,.756]	.101 (15.4%)	.832 [.657,1.198]	.177 (27.0%)
Male	Mean	.662 [.562,.709]	.735 [.731,.737]	.073 (11.0%)	.760 [.759,.761]	.098 (14.8%)	.835 [.659,1.202]	.173 (26.1%)
Old	Mean	.680 [.573,.725]	.747 [.744,.750]	.067 (9.9%)	.762 [.762,.762]	.082 (12.1%)	.839 [.664,1.205]	.159 (23.4%)
Young	Mean	.643 [.536,.697]	.727 [.723,.731]	.084 (13.1%)	.754 [.753,.755]	.111 (17.3%)	.829 [.654,1.196]	.186 (28.9%)

Notes: This table provides a comparison of the mean, min., and max. values of the expected prescription expense per patient in the four cases: when all drugs are in the choice set (first column); and for the three counterfactual scenarios reported in the first row of the last three columns. Expected prescription expense is the cost of a one-day treatment, which is the sum, over all the active ingredients, of price per day times the prescription probability for each active ingredient. The price per day is the price per mg times mg per day according to the DDD for each active ingredient. Old patients are patients older than 60. Confidence intervals at the 90% confidence level constructed by 500 bootstrap draws drawn from the estimated distribution of parameters are in square brackets. Percentage change is reported in parentheses.

allowed to be different is 2.2%, slightly larger than the decrease when drug prices are kept constant. Tables 6.2 and 6.3 report the counterfactual results for given values of $\mu = 0.85$ and $w = 0.85$. The counterfactual results for the other values of μ and w are reported in the online appendix B.4. For all values of μ and w, the expected cost of treatment increases with the ban on off-label drugs, and for none of the values, the ban leads to an improvement in the health outcome.

To emphasize the importance of heterogeneity in our model and to show the heterogeneous impact of the ban across patients, we depict the density distributions of the choice probabilities of the "best alternative" across patients. We define the "best alternative" for each patient as the drug that leads to the highest recovery rate according to our health outcome model, which takes into account the heterogeneous health state of patients and the heterogeneous treatment impact of the drugs across patients. Using our parameter estimates of the health outcome equation, we predict the recovery rate conditional on treatment with each alternative for each patient. We take the alternative that produces the highest recovery rate for each patient,

Table 6.3: *Expected Recovery Rate After Six Months*

Choice Set		When All Drugs are in the Choice Set (Benchmark)	When "Other Off-Label Drugs" are Removed		When All Off-Label Drugs are Removed		When All Off-Label Drugs are Removed (Counterfactual Prices) ($\mu = 0.85, w = 0.85$)	
Patients		Recovery Probability	Recovery Probability	Change	Recovery Probability	Change	Recovery Probability	Change
All	Mean	.548 [.467,.636]	.542 [.448,.635]	-.006 (-1.1%)	.538 [.448,.622]	-.010 (-1.8%)	.536 [.453,.618]	-.012 (-2.2%)
	Min.	.298 [.199,.404]	.302 [.207,.405]	.004 (1.3%)	.301 [.206,.403]	.003 (1.0%)	.311 [.223,.406]	.013 (4.4%)
	Max.	.827 [.807,.861]	.813 [.758,.858]	-.014 (-1.7%)	.801 [.768,.831]	-.026 (-3.1%)	.790 [.754,.822]	-.037 (-4.5%)
Female	Mean	.539 [.454,.629]	.533 [.435,.629]	-.006 (-1.1%)	.529 [.435,.617]	-.010 (-1.9%)	.527 [.441,.612]	-.012 (-2.2%)
Male	Mean	.571 [.499,.651]	.565 [.478,.650]	-.006 (-1.1%)	.560 [.478,.637]	-.011 (-1.9%)	.558 [.482,.631]	-.013 (-2.3%)
Old	Mean	.458 [.360,.559]	.457 [.354,.559]	-.001 (-0.2%)	.454 [.353,.551]	-.004 (-0.9%)	.457 [.364,.549]	-.001 (-0.2%)
Young	Mean	.600 [.529,.680]	.591 [.502,.678]	-.009 (-1.5%)	.586 [.502,.663]	-.014 (-2.3%)	.582 [.504,.657]	-.018 (-3.0%)

Notes: This table compares the mean, min., and max. values of the unconditional recovery probability in the four cases: when all drugs are in the choice set (first column); and for the three counterfactual scenarios reported in the first row of the last three columns. Old patients are patients older than 60. Confidence intervals at the 90% significance level constructed by 500 bootstrap draws drawn from the estimated distribution of parameters are in square brackets. Percentage change is reported in parentheses.

and we name this the "best alternative". Then, for each patient, we predict the prescription probability of this patient-specific "best alternative" and in Figure 6.1, we plot the density distributions of these probabilities.

Figure 6.1 reports the distributions in the benchmark case of no-ban and the counterfactual cases of restrictions on off-label use. The first column of Figure 6.1 depicts the counterfactual distribution of the choice probabilities of the "best alternative" when "Other Off-Label Drugs" are banned whereas "Off-Label Drugs with Efficacy" are allowed. The second column reports the counterfactual distribution when all off-label drugs are banned. The two graphs are similar as the share of "Off-Label Drugs with Efficacy" in depression treatment is relatively small. Note that the "best alternative" is the best one among all alternatives, including both on- and off-label drugs. We do not change the definition of the "best alternative" in the counterfactuals.

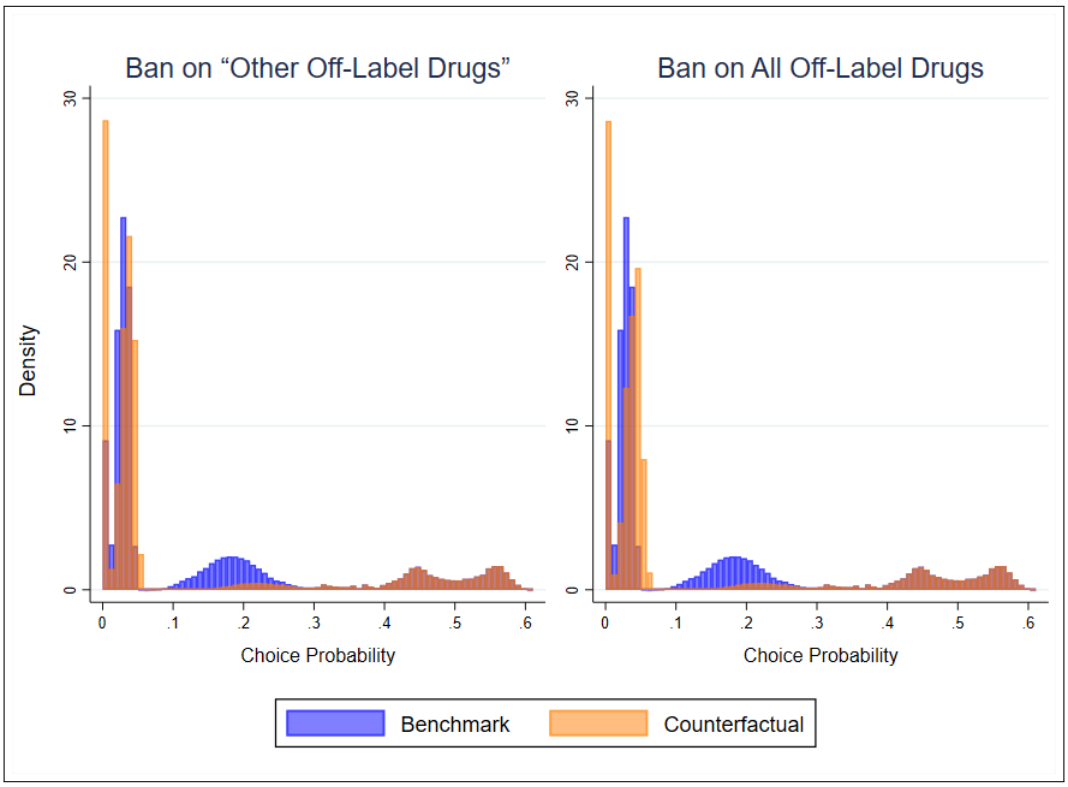
The main takeaway from the figure is that in the counterfactual scenarios of restrictions on off-label use, there is a probability mass at zero. This is because, in the counterfactuals, for all the patients for whom the drug leading to the highest recovery rate is an off-label drug, the choice probability of the "best alternative" is zero since off-label drugs are not in the physicians' choice set. Therefore, banning off-label drugs leaves these patients without their "best alternative" in depression treatment. For the choice probabilities between 0 and 0.06, going from the benchmark to the counterfactual, the distribution slightly shifts towards the right. This shift comes from the patients for whom the "best alternative" is an on-label drug. In the benchmark, these patients have a positive prescription probability of off-label drugs. In the counterfactuals, when off-label drugs are not in the choice set, the prescription probabilities of on-label drugs, including their "best alternative", increase. The distribution's right tail mainly includes the patients for whom the "best alternative" is an on-label drug with a very high prescription probability. Banning off-label prescriptions does not change much for this group of patients.

6.2.3 Another Counterfactual Scenario: Higher Price Sensitivity of the Prescription Choice

In this section, we investigate how the ban would impact the treatment costs and treatment outcomes if the price sensitivity of demand were 20% higher than our estimate. This counterfactual scenario would represent the situation in other institutional settings with less generous insurance and higher price sensitivity of the prescription choice.

Table 6.4 reports the expected cost of a one-day treatment per patient when we consider a 20% higher price sensitivity of demand. It shows the expected cost of treatment for the cases when off-label prescriptions

Figure 6.1: *Distributions of the Choice Probabilities of the "Best Alternative"*



are allowed, the benchmark, and the three counterfactual scenarios as in Table 6.2. For the benchmark case, we simulate what the drug prices would be if the price sensitivity of demand were 20% higher than our estimate, when $w = 0.85$ and $\mu = 0.85$, using the marginal cost estimates at these values of w and μ. We use the same simulated prices in the first two counterfactual scenarios, keeping prices identical to the benchmark case. For the last counterfactual scenario, first, we investigate what prices of on-label drugs would be if the negotiations were to take place under a strict ban on off-label prescriptions and if the price sensitivity of demand was 20% higher. The last column of Table 6.4 shows the expected cost of a one-day treatment with these counterfactual prices.

Similar to the results in Table 6.2, the cost of a one-day treatment increases in all of the counterfactual scenarios where we restrict off-label prescriptions. The increase is the largest in the last column when we ban all off-label drugs and consider that the negotiations take place under a strict ban on off-label prescriptions. However, the increase in the expected cost of treatment under the counterfactual scenarios is smaller when we consider a 20% higher price sensitivity of demand in Table 6.4 than the increase in Table 6.2. In the counterfactual policy with the drug prices identical to the benchmark case, the increase in the expected cost of treatment is smaller than in Table 6.2 because the higher price sensitivity of the prescription choice makes the patient-physician pair substitute off-label drugs with relatively cheaper drugs among the on-label alternatives. Under the ban and with the corresponding counterfactual prices, the increase in the expected cost of treatment in Table 6.4 is smaller than in Table 6.2 not only because the patient-physician pair chooses relatively cheaper drugs but also because the increase in prices of on-label drugs due to the ban is smaller as the demand is more price sensitive.

Table 6.5 shows the expected recovery rate after a six-month treatment period when we consider a 20% higher price sensitivity of the prescription choice. It provides the unconditional recovery probabilities for the cases when off-label prescriptions are allowed and for the three counterfactual scenarios as in Table 6.3. The results are similar to those in Table 6.3. The average recovery rate slightly decreases when off-label prescriptions are restricted.

Table 6.4: *Expected Prescription Expense of Drug Treatment (with 20% Higher Price Sensitivity) (€)*
(when $\mu = 0.85, w = 0.85$)

Choice Set		When All Drugs are in the Choice Set (Benchmark)	When "Other Off-Label Drugs" are Removed		When All Off-Label Drugs are Removed		When All Off-Label Drugs are Removed (Counterfactual Prices)	
Patients		Expenses	Expenses	Change	Expenses	Change	Expenses	Change
All	Mean	.576 [.488,.619]	.644 [.641,.647]	.068 (11.8%)	.659 [.658,.659]	.083 (14.4%)	.721 [.594,.953]	.145 (25.2%)
	Min.	.502 [.415,.563]	.602 [.598,.606]	.100 (19.9%)	.640 [.640,.641]	.138 (27.5%)	.699 [.572,.930]	.197 (39.3%)
	Max.	.638 [.572,.662]	.676 [.673,.677]	.038 (6.0%)	.682 [.682,.682]	.044 (6.9%)	.749 [.621,.980]	.111 (17.4%)
Female	Mean	.574 [.483,.619]	.644 [.640,.646]	.070 (12.2%)	.657 [.657,.657]	.083 (14.5%)	.720 [.593,.951]	.146 (25.4%)
Male	Mean	.581 [.499,.621]	.645 [.642,.647]	.064 (11.0%)	.661 [.660,.662]	.080 (13.8%)	.723 [.595,.955]	.142 (24.4%)
Old	Mean	.595 [.508,.634]	.654 [.651,.656]	.059 (9.9%)	.663 [.663,.663]	.068 (11.4%)	.726 [.599,.958]	.131 (22.0%)
Young	Mean	.566 [.477,.611]	.638 [.635,.641]	.072 (12.7%)	.656 [.655,.656]	.090 (15.9%)	.718 [.590,.949]	.152 (26.9%)

Notes: This table compares the mean, min., and max. values of the expected prescription expense per patient when we consider a 20% higher price elasticity of demand than our estimate. It provides the statistics in the four cases: when all drugs are in the choice set (first column); and the three counterfactuals reported in the first row of the last three columns. For other details, see notes in Table 6.2.

Table 6.5: *Expected Recovery Rate After Six Months (with 20% Higher Price Sensitivity)*
(when $\mu = 0.85, w = 0.85$)

Choice Set		When All Drugs are in the Choice Set (Benchmark)	When "Other Off-Label Drugs" are Removed		When All Off-Label Drugs are Removed		When All Off-Label Drugs are Removed (Counterfactual Prices)	
Patients		Recovery Probability	Recovery Probability	Change	Recovery Probability	Change	Recovery Probability	Change
All	Mean	.549 [.468,.636]	.543 [.449,.635]	-.006 (-1.1%)	.539 [.448,.623]	-.010 (-1.8%)	.537 [.454,.618]	-.012 (-2.2%)
	Min.	.299 [.200,.404]	.303 [.208,.406]	.004 (1.3%)	.302 [.207,.404]	.003 (1.0%)	.312 [.224,.407]	.013 (4.3%)
	Max.	.827 [.807,.861]	.813 [.759,.858]	-.014 (-1.7%)	.802 [.768,.832]	-.025 (-3.0%)	.790 [.754,.823]	-.037 (-4.5%)
Female	Mean	.539 [.455,.630]	.533 [.436,.629]	-.006 (-1.1%)	.530 [.436,.617]	-.009 (-1.7%)	.528 [.442,.613]	-.011 (-2.0%)
Male	Mean	.572 [.499,.652]	.566 [.479,.651]	-.006 (-1.0%)	.561 [.479,.638]	-.011 (-1.9%)	.559 [.483,.632]	-.013 (-2.3%)
Old	Mean	.458 [.361,.560]	.457 [.355,.560]	-.001 (-0.2%)	.455 [.354,.552]	-.003 (-0.7%)	.458 [.365,.550]	.000 (0.0%)
Young	Mean	.601 [.529,.680]	.592 [.502,.679]	-.009 (-1.5%)	.587 [.503,.664]	-.014 (-2.3%)	.583 [.504,.658]	-.018 (-3.0%)

Notes: This table compares the mean, min., and max. values of the unconditional recovery probability given the prescription probabilities when we consider a 20% higher price elasticity of demand than our estimate. It provides the statistics in the four cases: when all drugs are in the choice set (first column); and the three counterfactuals reported in the first row of the last three columns. For other details, see notes in Table 6.3.

7 Discussion and Conclusion

We develop a structural model of the demand and supply of off-label drug prescriptions using a unique dataset that provides longitudinal information over nine years on a sample of physicians, their office visits, and all their patients. On the demand side, we build a model of prescription behavior with potential unobserved patient-level heterogeneity, which is allowed to be correlated with treatment choices and treatment outcomes. We, then, estimate the demand for on-label and off-label drugs for depression treatment. The results show

that there is significant patient-level heterogeneity impacting both the treatment choice and the treatment outcome. We find that, on average, treatment outcomes with off-label drugs are not worse than those with on-label alternatives. On the supply side, we develop a Nash-in-Nash bargaining model between the government and pharmaceutical firms in which prices are determined by the Nash equilibrium of bilateral Nash bargaining problems.

We perform counterfactual analysis by simulating the demand, supply, and associated treatment outcomes in the case of a ban on off-label use. We consider two cases of counterfactual scenarios. In the first one, we assume that drug prices are the same in the case of a ban on off-label drug prescriptions. In the second counterfactual scenario, we allow drug prices to be different under a ban by allowing the ban to impact the bargaining outcome. We then simulate the associated counterfactual expected demand, treatment cost, and treatment outcome using the counterfactual equilibrium prices. The results suggest that banning off-label prescriptions would increase the cost of prescription drugs due to a substitution effect in the first counterfactual scenario and a substitution effect and higher prices in equilibrium in the second counterfactual scenario. In both cases, banning off-label prescriptions does not lead to significant changes in average health outcomes.

This analysis shows that regulatory decisions concerning physicians' ability to be flexible in their prescription behavior regarding the label status of drugs may be an important factor in determining welfare and health expenditures. We have shown that banning off-label prescriptions would not positively affect health outcomes, on average, but would significantly increase drug expenditures. The argument that strict enforcement of label-status-based prescriptions can improve health outcomes and decrease expenses by strictly controlling physicians' behavior does not seem to be valid in this context.

In our setting, in the case of depression treatment, off-label drugs are, on average, cheaper because they are mostly older drugs. How restrictions on off-label use impact health costs depends on whether off-label drugs are off-patent and, thus whether they are cheaper. We would expect off-label uses of drugs to usually increase over time as we learn about the efficacy of drugs for unapproved indications (see McKibbin (2023) for the case of oncology drugs). Therefore, we think it is also likely to be the case in the treatment of other diseases that off-label drugs are mostly off-patent and hence cheaper than on-label drugs. Therefore, we expect that when we ban off-label prescriptions, the increase in treatment costs due to the substitution effect will prevail for other diseases.

Even though our application is based on French data, we would expect our results to apply to other countries with similar institutional settings, like other west European countries with generous health coverage for prescription drugs and where drug prices are determined through negotiations between the government and pharmaceutical firms. We think, also in these settings, the restrictions on off-label prescriptions would increase treatment costs not only due to the substitution effect but also the price effect.

It is worth emphasizing that we do not analyze the behavior of pharmaceutical companies in terms of demands for the approval of different indications. Their behavior would possibly be different in the counterfactual environment where they would anticipate physicians' inability to use off-label prescriptions. Analyzing this in the counterfactual environment would require modeling the investment decisions in clinical trials and regulatory applications for approval as a determinant of profit maximization. We leave this interesting question for future research.

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A Appendix

A.1 Details on Aggregated Choice Alternatives and Off-Label Drugs

Table A.1 provides details on the share of drugs aggregated under the choice alternatives "Other Off-Label Drugs", "Off-Label Drugs with Efficacy", and "Other On-Label Drugs". For instance, among "Other Off-Label Drugs", 81% are nervous system drugs. Among them, psycholeptics have the highest share, 91%, and among psycholeptics, anxiolytics have the highest percentage, 56%. Among all the off-label drugs, considering both "Other Off-Label Drugs" and "Off-Label Drugs with Efficacy", 84% are nervous system drugs.

Table A.1: *Drug Classification of Off-Label and "Other On-Label" Drugs*

	Percentage		
Drugs in Alternative "Other Off-Label Drugs"			
Nervous System (N)	81%		
Psycholeptics (N05)		91%	
Antipsychotics (N05A)			6%
Anxiolytics (N05B)			56%
Hypnotics and Sedatives (N05C)			38%
Antiepileptics (N03)		2%	
Other Nervous System		7%	
Alimentary Tract and Metabolism (A)	8%		
Other	11%		
Drugs in Alternative "Off-Label Drugs with Efficacy"			
Alprazolam (N05BA12)	87%		
Buspirone (N05BE01)	7%		
Olanzapine (N05AH03)	5%		
Other	1%		
Drugs in Alternative "Other On-Label Drugs"			
Other Antidepressants (N06AX)	82%		
Non-Selective Monoamine Reuptake Inhibitors (N06AA)	12%		
Other	6%		

Notes: This table gives information on the share of drugs aggregated under the choice alternatives "Other Off-Label Drugs", "Off-Label Drugs with Efficacy", and "Other On-Label Drugs". ATC codes are in parentheses.

Table A.2 reports the active ingredients, ATC codes, and drug classifications of off-label drugs, separately for the drugs in the choice alternative "Off-Label Drugs with Efficacy" and the major drugs in the alternative "Other Off-Label Drugs". Note that the table reports information about the drugs in the French market during our sample period, which means that the same drug may have a different label status in another country or during another period. For instance, "Bupropion", an antidepressant, has efficacy and is approved for depression treatment in the US. However, it is not approved for depression in France. It is approved only as a smoking cessation aid. Hence, it is included in the choice alternative "Off-Label Drugs with Efficacy" for depression treatment in the French market during our sample period.

A.2 Clarification on the Definition of Off-Label Prescriptions

As mentioned before, in this study, off-label use refers to the use of a drug for an indication for which the drug has not received approval. In the data, we observe which diagnoses are made at each office visit for a given patient. We also observe which drug is prescribed for each diagnosis. Using the three cases below as

Table A.2: *Active Ingredient, ATC Code and Drug Classification of Off-Label Drugs*

Drugs among "Off-Label Drugs with Efficacy"			Drugs among "Other Off-Label Drugs"		
Active Ingredient	*ATC 5th Level Code*	*ATC 3rd Level Name*	*Active Ingredient*	*ATC 5th Level Code*	*ATC 3rd Level Name*
Flupentixol	N05AF01	Antipsychotics	Sulpiride	N05AL01	Antipsychotics
Olanzapine	N05AH03	Antipsychotics	Risperidone	N05AX08	Antipsychotics
Aripiprazole	N05AX12	Antipsychotics	Oxazepam	N05BA04	Anxiolytics
Alprazolam	N05BA12	Anxiolytics	Potassium clorazepate	N05BA05	Anxiolytics
Buspirone	N05BE01	Anxiolytics	Lorazepam	N05BA06	Anxiolytics
Lamotrigine	N03AX09	Antiepileptics	Bromazepam	N05BA08	Anxiolytics
Bupropion	N06AX12	Antidepressants	Clobazam	N05BA09	Anxiolytics
Modafinil	N06BA07	Psychostimulants	Prazepam	N05BA11	Anxiolytics
Pramipexole	N04BC05	Dopaminergic Agents	Nordazepam	N05BA16	Anxiolytics
Selegiline	N04BD01	Dopaminergic Agents	Ethyl loflazepate	N05BA18	Anxiolytics
Buprenorphine	N07BC01	Drugs Used in Addictive Disorders	Hydroxyzine	N05BB01	Anxiolytics
			Meprobamate	N05BC01	Anxiolytics
			Etifoxine	N05BX03	Anxiolytics
			Zopiclone	N05CF01	Hypnotics and Sedatives
			Zolpidem	N05CF02	Hypnotics and Sedatives
			Valerianae radix	N05CM09	Hypnotics and Sedatives
			Valpromide	N03AG02	Antiepileptics
			Magnesium	A12CC30	Other Mineral Supplements

Note: This table reports the active ingredients, ATC codes, and drug classifications of off-label drugs, separately for the drugs in the choice alternative "Off-Label Drugs with Efficacy", and the major drugs in the alternative "Other Off-Label Drugs".

examples of possible diagnosis-prescription pairs at a given office visit, we explain how off-label prescriptions are determined in this study and how we were conservative in determining them.

In case 1, the patient is diagnosed with depression and alcoholism. A drug approved for depression is prescribed for the depression diagnosis (an on-label drug for depression), and another drug is prescribed for the alcoholism diagnosis. In the analysis, the patient in case 1 is considered a depression patient who is being treated with an on-label drug. In case 2, the patient is diagnosed only with depression (the patient does not have an alcoholism diagnosis). A drug that is not approved for depression but is approved for alcoholism is prescribed for the depression diagnosis (an off-label drug for depression). In the analysis, the patient in case 2 is considered a depression patient who is being treated with an off-label drug. In case 3, the patient is diagnosed with depression and alcoholism. A drug that is not approved for depression but approved for alcoholism is prescribed for the depression diagnosis, and another drug is prescribed for the alcoholism diagnosis. In this case, there are two possibilities: it could be that the physician prescribes an off-label drug to treat depression. The second possibility is that the physician believes that depression is a secondary condition to alcoholism. Therefore, he prescribes two drugs to treat alcoholism, does not prescribe any drug for depression, and considers that depression will go away once alcoholism is treated. To be conservative in determining off-label prescriptions, we exclude cases such as case three in the analysis. These cases correspond to only 0.98% of off-label prescriptions and 0.21% of all prescriptions. To determine these cases, for every drug not approved but prescribed for depression, we check for which indications the drug is approved and whether the patient is diagnosed with any of these indications.

- Case 1:

  - Diagnosis: Depression → Prescription: A drug approved for depression (an on-label drug for depression)

  - Diagnosis: Alcoholism → Prescription: A drug for alcoholism

- Case 2:

  - Diagnosis: Depression → Prescription: A drug not approved for depression (an off-label drug for depression), which is approved for alcoholism (an on-label alcoholism drug)

  - No Alcoholism Diagnosis

- Case 3:

  - Diagnosis: Depression → Prescription: A drug not approved for depression (an off-label drug for depression), which is approved for alcoholism (an on-label alcoholism drug)

  - Diagnosis: Alcoholism → Prescription: A drug for alcoholism

A.3 Graphical Example of Banning Off-Label Drug Prescriptions

Figure A.1 shows an example of three drugs approved for different indications but can be used off-label for non-approved indications and what happens when off-label prescriptions are banned. In this example, only drug A is approved for depression, B is approved for alcoholism, and C is for epilepsy. Drugs B and C are used off-label in the treatment of depression. Drug A is also used off-label to treat alcoholism. When off-label prescriptions are banned, drugs B and C can no longer be used in depression treatment; hence, the market share of drug A in the depression market will increase with the ban. However, drug A can no longer be used in alcoholism treatment; hence, all the sales of drug A in the alcoholism market will disappear with the ban. How the aggregate demand for drug A changes with the ban depends on how much its demand will increase in the depression market and how much it loses in the off-label markets, i.e., the alcoholism market in Figure A.1.

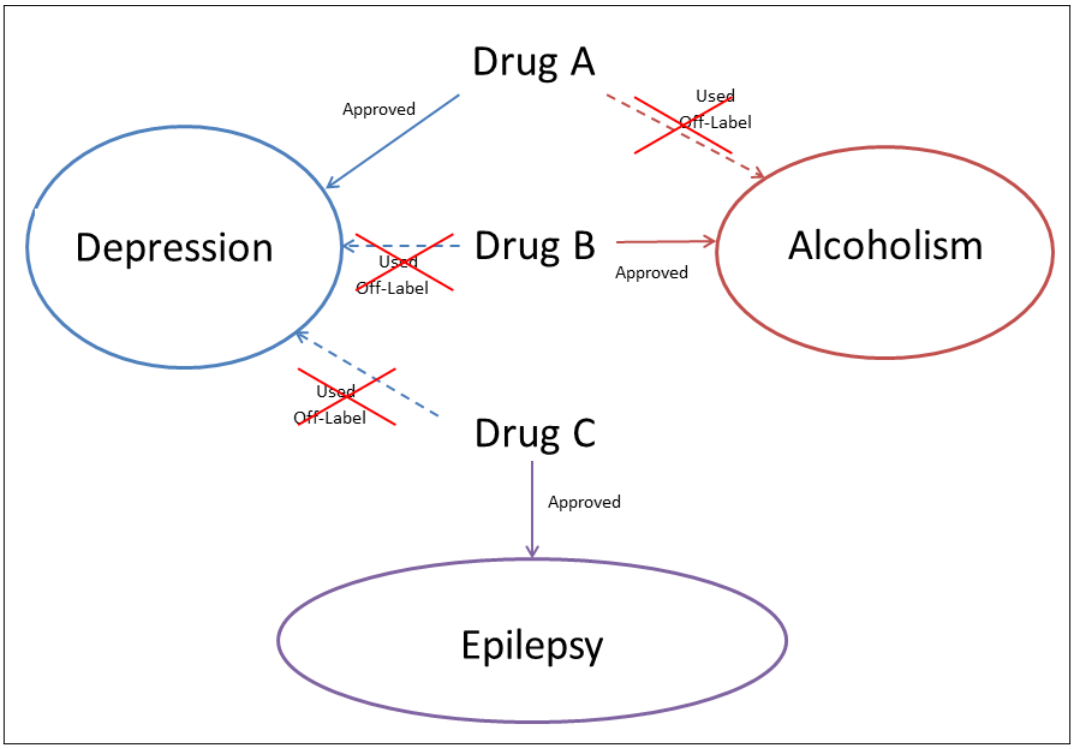

Figure A.1: *An Example of Banning Off-Label Drug Prescriptions*

A.4 Dropouts

Table A.3 shows the percentage of patients who stopped visiting their physicians among the non-depressed and depressed patients and patients prescribed approved vs. off-label drugs. We call these patients "dropouts"; however, it is worth emphasizing that the objective of the data is to follow physicians, not patients, over time. Therefore, when a patient changes her generalist (for instance, when moving to another place), she is no longer in the dataset. It would be worrying if dropout rates were different among patients receiving approved drugs than those receiving off-label drugs. The share of patients who stopped visiting their physician among patients who were prescribed approved drugs is not much different from that among patients who were prescribed off-label drugs. Additionally, the share of dropouts among non-depressed patients is the same as that among depressed patients, which provides evidence for the argument that dropouts among depressed people are not caused by the label status of drugs prescribed for depression treatment. Instead, these dropouts are likely due to households moving both within and out of the city.

As a thought experiment, we investigate how the results would be different if we included the dropouts and re-estimate the health outcome model. We explore how much the share of recovered patients among dropouts must differ from the share in our main sample to overturn the results reported in Table 5.2. First, we assume that the percentage of recovered people among the patients treated with on-label drugs is the same in the dropout sample as in our primary sample reported in Table 3.2. Given that, we evaluate how much the share of still-depressed patients among the dropouts treated with off-label drugs must be higher than the share among patients of our main sample. Even if we consider that all dropouts treated with off-label drugs are still depressed, it is not enough to overturn the results with our main sample reported in Table 5.2. On average, on-label drugs still do not lead to higher recovery rates than off-label drugs. Then, we investigate how much the share of recovered patients among the dropouts treated with approved drugs must be higher than the share among the same group of patients in our main sample when we assume all the dropouts treated with off-label drugs are still depressed after the treatment period. We find that, to overturn the results obtained with our main sample, the share of recovered patients among dropouts treated with on-label drugs must be at least as high as 79%, which is 24 percentage points (44%) higher than the recovery rate among the remainers treated with on-label drugs.

To summarize, on-label drugs lead to statistically higher recovery rates than "Other Off-Label Drugs", contrary to the results reported in Table 5.2, only when we assume that the recovery rate among dropouts treated with off-label drugs is zero and the recovery rate among dropouts treated with on-label drugs is at least 79%. We believe this is highly unlikely to be the case.

Table A.3: *Dropout Rates among Patients*

	Percentage		Percentage
Among Nondepressed Patients	15.74	*Among Depressed Patients that are Prescribed:*	
Among Depressed Patients	14.95	On-Label Drugs	14.49
		Off-Label Drugs	15.68
		Off-Label Drugs with Efficacy	16.36
		Other Off-Label Drugs	15.57

Notes: This table shows the percentage of patients who stopped visiting their physicians among the nondepressed and depressed patients and patients prescribed approved vs. off-label drugs. The statistics in this table exclude the patients who appear only once in the data over the nine-year sample period.