PRESCRIPTION DRUG ADVERTISING AND PATIENT COMPLIANCE: A PHYSICIAN AGENCY APPROACH.

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Abstract

This paper proposes an analysis of both doctors and patients' behavior in an agency model that accounts for the interplay between two highly debated health issues: drug advertising toward doctors and/or patients, and the serious problem of patients' noncompliance with their doctors' prescriptions. Due to the lack of individual data, we adopt a structural approach inspired from the industrial organization literature. The model is estimated semiparametrically with product level data on the U.S. market for anti-glaucoma drugs. The results show that doctors' prescriptions are directly influenced by the probability of noncompliance, as well as advertising aimed at both doctors and patients. Advertisement toward patients (respectively, doctors) contributed to (respectively, slowed down) the reduction of the estimated average noncompliance rate.

Keywords: Direct-to-consumer advertising, prescription noncompliance, physician agency model, structural econometrics, semiparametric estimation.

JEL Classification: I10, L10, 14.

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1. INTRODUCTION

In 1997, the Food and Drug Administration (FDA) simplified the information requirements for direct-to-consumer advertising (DTCA) of prescription drugs. The FDA's decision contributed to a sharp increase in the spending on DTCA (from $624 million in 1996 to $1.3 billion in 1998).[1] This sudden intensification of DTCA fueled the controversy pertaining to the effects of advertisement on the doctor-patient relationship. At the same time, concerns have grown in the medical profession about high rates of patient noncompliance with prescriptions drug regimens.[2] As further explained, noncompliance is clearly a serious problem: a recent study indicates that 70% of patients do not comply with drug prescriptions, resulting in annual losses of $170 billions in the U.S. (Dezii 2000).[3] As we shall see, although it has been recognized by health professionals, and in particular the FDA, the connection between advertising and prescription noncompliance has been ignored in the economics literature.

The aim of this paper is to analyze the prescription and compliance behaviors of respectively doctors and patients, in an agency model that accounts for the interplay between patient noncompliance, direct-to-consumer advertising, and drug promotion toward doctors.[4] More specifically, our goal is to address the following two questions:

(i) How does advertisement and the probability of noncompliance affect the doctor's pre-

[1] These figures are for the entire pharmaceutical industry. See Holmer (1999) and *The National Institute for Health Care Management* (2000).

[2] Compliance is defined in the medical literature as "the extent to which a person's behavior coincides with medical or health advice" (Bentley 1999). In this paper, we adopt the definition used in Ellikson, Stern and Trajtenberg (2000): a patient is said to be noncompliant with his doctor's prescription if either he does not buy the drug ("purchase noncompliance"), or he does not consume the drug in accordance to the doctor's prescription ("use noncompliance"). Noncompliance is, therefore, assumed to be a binary variable.

[3] These losses are generated for instance by unnecessary medical expenses (e.g. additional hospitalizations, admissions in nursing home) and lost productivity.

[4] An agency problem arises when a principal (the patient) hires an agent (the doctor) to perform a task on his behalf, but the goals of the two parties differ.

scription behavior?

(ii) How does drug promotion to doctors and/or patients influence the rate of noncompliance with medication prescription in a given therapeutic class?

The relevance and actuality of these questions may be demonstrated by the public inquiry recently launched by the FDA to determine the benefits and drawbacks of prescription advertisement.[5] Indeed, the FDA, which is contemplating whether or not to regulate further DTCA, specifically asked about the empirical effect of DTCA on prescription habits, and patient noncompliance. In other words, the answers to the questions raised in the present paper may have important consequences, both from an economic and health perspective.

To address these issues however, one cannot estimate a reduced form econometric model due to the current lack of accessible individual data, both at the drug and patient levels, and to the lack of reliable noncompliance data by drug for a specific therapeutic class. Instead, we adopt a structural approach, inspired from the industrial organization literature (Berry 1994, Berry, Levinsohn and Pakes 1995), to estimate the model from market level data. It has to be noted, however, that, drawing extensively from the medical literature on the determinants on noncompliance, we strived to impose just enough structure to enable the estimation of the model from the available data. In particular, the probability of noncompliance with a drug will be estimated semiparametrically.

To explain the doctor-patient relationship, we therefore develop a two-period agency model in the setting of discrete choice theory. In period 1, the doctor prescribes a drug to treat the patient from a finite set of alternative drugs. In period 2, the patient decides whether to comply

[5]Docket 02N-0209 submitted in may 2002. Details and replies to this public inquiry are available on the FDA website at http://www.fda.gov/ohrms/dockets/dockets/dockets.htm.

with this prescription. The patient's choice is assumed to be a rational trade-off between health benefits, and monetary as well as non-monetary costs associated with drug consumption (e.g. side effects, complexity of dosage schedule). The doctor's decision to prescribe a given drug is influenced, in particular, by his expectations of patient noncompliance. Finally, targeted advertisements toward doctors and/or patients influence the decisions of both agents.

This theoretical model is then structurally estimated using a combination of IMS and CMR product-level data on the U.S. market for anti-glaucoma drugs.[6] The data set spans the period 1995 to 1999 and, therefore, it covers the 1997 FDA decision on DTCA. The empirical analysis combines the techniques from semiparametric index models (Ichimura and Lee 1991, Ichimura 1993) and nonparametric models with endogenous variables (Newey, Powell and Vella 1999, Blundell and Powell 2000).

We find that advertisement for a given drug both toward doctors and patients increases the probability that it will be prescribed. Doctors are also sensitive to prices and anticipated noncompliance when they prescribe a drug. The results also suggest that the average non-compliance rate with anti-glaucoma drugs has been considerably reduced between 1995 and 1999. We show that this reduction may well be the net effect of two opposite forces: DTCA appears to have decreased noncompliance, whereas promotion to doctors may have contributed to increase the average noncompliance rate.

In the next section, we provide a review of the related literature, along with a brief background on the relationship between advertisement and noncompliance. In Section 3, we present the model and its theoretical implications. Section 4, describes the estimation strategy and the empirical results.

[6] IMS Health an CMR are two private market research companies, and major sources of information on the health care and advertising industries.

2. Background and Related literature

2.1. Agency Problems in Health Care

The agency literature in health care focuses on the conflicts of interest that may arise between doctors and patients under diverse institutional constraints.[7] Several models of information asymmetry between doctors and patients have been developed. For instance, Ellis and McGuire (1990) model the interaction between doctors and patients as a non-cooperative game in which the conflict is resolved using bargaining theory.

The models developed by Rochaix (1988), and Ellickson, Stern and Trajtenberg (2000) (hereafter EST) are the closest to the one that we develop here. In Rochaix's model, doctors and patients agree on the diagnostic of illness, but hold different views of its severity. EST (2000) consider a similar approach but concentrate specifically on the noncompliance with doctor's drug prescription. The methodology in these papers is similar to the one we are adopting: agents play a sequential game in which the doctor chooses first the treatment and its intensity, but she is uncertain about whether the patient will adhere to the treatment recommendation.[8] Neither Rochaix (1988), nor EST (2000) consider the interplay between advertisement and noncompliance. In addition, these earlier models are purely theoretical and, as we shall see below, EST's model cannot be estimated with currently available data.

Finally, note that the agency approach to modeling drug selection, adopted in this paper, finds additional support from the empirical analysis conducted by Hellerstein (1998) and Stern and Trajtenberg (1998).

[7] For a general overview of this literature, see McGuire (2000). For an overview of agency problems related specifically to drug selection, see Mott et al. (1998).

[8] In this paper, we shall refer to the doctor as "she" and to the patient as "he."

2.2. Compliance Behavior

Although the precise measurement of noncompliance is a controversial topic, noncompliance is widely recognized to be a serious public health problem. EST (2000) report an average rate of noncompliance with drug prescription of 70% (20% purchase noncompliance and 50% use non compliance). Dezii (2000) reports the rate of use noncompliance for the following classes of medication: medications for diabetes (31%), tuberculosis medications (45%), antihypertensives (47%), antipsychotics and schizophrenics (58%), and penicillin for rheumatic fever (67%). As mentioned in the introduction, the annual cost of noncompliance is believed to reach up to $170 billions in the U.S., which would exceed the expenses in prescription medications. Noncompliance also have serious health implications: it has been estimated that up to 11.4% of admissions to hospital resulted from failure to comply with drug regimen (Col, Fanale and Kronholm 1990). A Study by Sullivan, Krelig and Hazlet (1990) also suggests that 125,000 cardiovascular deaths should be blamed annually in the U.S. on noncompliance. In fact, the American Hearth Association has recently stated that "the cost of noncompliance in terms of human life and money is shocking", and has made prescription drug compliance one of the association key issue.[9]

The problem of noncompliance has been primarily addressed in the medical literature. The main questions of interest for the medical profession are: what are the determinants of noncompliance? How is noncompliance influenced by the doctor-patient relationship? How can compliance be improved?[10] Note that in the medical literature, noncompliance was originally seen as the result of the patient's irrational behavior. This view has considerably evolved in

[9] American Heart Association statement, "American Hidden Health Threat ", July 19 1999, available at http://www.americanheart.org/presenter.jhtml?identifier=9206.

[10] See for instance the extensive study of patient noncompliance conducted by Marinker et al. (1997) for the Royal Pharmaceutical Society of Great Britain.

recent years toward a more rational approach (Dezii 2000).

To the best of our knowledge, EST (2000) are the first economists to explicitly analyze noncompliance with drug prescriptions. Their model, however, ignores advertisement and it could be estimated only with detailed data on noncompliance. As noted by the authors, these data do not exist so far. In contrast, we develop a model that may be estimated with available product level data, and without requiring the observation of noncompliance rates.

2.3. Prescription Drug Promotion

Prescription drug promotion by pharmaceutical firms takes two forms: the promotion aimed at doctors, and advertisements directed to consumers. Advertisements toward doctors include visits by pharmaceutical representatives, free samples, advertisements in medical journals, displays and presentations at professional meetings. Such promotions were the only form of advertisement for prescription drugs until 1981, when drug companies expanded their marketing strategies to include direct advertising to patients. Although the most familiar form of promotion toward consumers is targeted to the general population via popular media, such as television or magazines, DTCA is also commonly conveyed directly to patients through web sites, help-lines, personalized mailings, targeted web-advertisement, and in-doctor-office or in-pharmacy information pamphlets. After a brief moratorium in 1983, the FDA permitted DTCA to resume in 1985 under stringent requirements on the informational content of advertisements. DTCA has grown significantly, especially since 1997 when the FDA simplified considerably the information requirements.[11] The recent increase in advertisement spending,

[11] The information constraints related to drug advertising require the advertiser to provide a brief summary relating to the side effects, contraindications and effectiveness of the advertised drug. In the late 1997, the FDA issued a document, the *Draft Guidance for Industry: Consumer-Directed Broadcast Advertisements* , which makes it much easier for the drug advertisers to meet these requirements (Reeves 1998).

combined with the relative shift in the structure of advertising (from promotion to doctors, to DTCA) has intensified the controversy pertaining to the effects of advertising on both doctors and consumers.

Most of the controversy concerning promotion toward doctors is related to the informative or the persuasive nature of advertising. A sampling of the arguments in this debate may be found in Hurwitz and Caves (1988), and Berndt et al. (1997). Drug makers insist that promotions are informative, but others (including some health practitioners and public health policy makers) are concerned that advertising may inappropriately influence doctors' prescription behavior. The flavor of the debate may be appreciated in the contrast between a manufacturer's view (Holmer 1999), and views expressed by physicians (Rose 1997, Hollon 1999). Note that in this debate, physicians also disagree among themselves (compare Backer et al. 2000 with Westfall and Colorado 2000).

DTCA is currently by far the most controversial issue related to drug promotion. Reeves (1998) provides a comprehensive review of the major steps in the evolution of DTCA regulation. DTCA is still a relatively poorly understood phenomenon despite the prevalence of this topic in the health care literature. This may be explained by the fact that detailed data on DTCA are only starting to be available. The prescription drug advertising regulations in the U.S. allow three types of DTCA: "health seeking advertisement," "reminder advertisement," and "product-specific (or product claim) advertisement." A health seeking advertisement informs the consumers about the existence of a treatment for some particular condition, while encouraging them to consult their doctors for more information. This type of advertisement does not refer to a specific product to be used in the treatment of the condition. In contrast, a reminder advertisement mentions the name of a drug and the drug company, but omits the

drug indication. These were the two prevailing forms of DTCA prior to the 1997 FDA decision. Product-specific advertisement reveals both the drug's name and the indication. Since 1997, it has become the fastest growing form of DTCA.

Opponents of DTCA argue that advertising intrudes upon the doctor-patient relationship. For instance, patients may request from their doctor drugs that have been advertised, even when these drugs are more expensive or not the most appropriate for their condition (see e.g. Peters 2001). Supporters of DTCA, on the other hand, suggest that the information provided through DTCA may educate the public to make more informed medical choices. For instance, it has been recently shown that DTCA encourages untreated patients to consult their doctor (see Wosinska 2002 and Izuka and Jin 2002).[12] An additional potentially important social benefit, mentioned in Wosinska (2002) and explicitly studied here, is the influence of DTCA on compliance. Responses to the FDA public inquiry mentioned in the introduction, indicate that a wide majority of health professionals (including the National Health Council, the National Institutes for Health Care Management, and representants of the FDA) believe that DTCA may help curb down prescription noncompliance. The arguments most frequently advanced are that DTCA acts as a reminder to take the drug, it comforts the patient, and makes him feel better about the drug. These factors have been known for years to influence positively compliance (Marinker 1997). Other respondents to the FDA inquiry, however, expressed skepticism, some even suggesting that the long recitation of side effects imposed by the FDA on DTCA, may in fact reduce the likelihood that a patient complies to his doctor's prescription. In other words, although the effect of DTCA on compliance is a important issue in the medical literature with

[12] Due to the lack of specific information on doctor's visits, we cannot address this issue in the subsequent application. However, as further explained below, DTCA for glaucoma drugs are essentially targeted toward already diagnosed patients, rather than the general population. In other words, DTCA for glaucoma drugs does not directly influence an individual's decision to consult.

serious health and policy implications, it still remains an open question, mostly ignored by economists.

Moreover, promotion to doctors of expensive or poorly-performing drugs may also increase the prescriptions of these drugs, and therefore, may have a negative impact on patients' compliance. Berger et al. (2001) and Wilkes et al. (2000) describe some empirical studies in which the attitudes of different groups of agents (patients, doctors, pharmacists) toward (in particular) DTCA have been analyzed. These analyses, however, do not evaluate the impact of DTCA on prescription and/or noncompliance behavior. More recently, an often-cited study has been conducted by Scott-Levin, a market research company.[13] The study shows a strong positive relation between promotion efforts toward patients, on one hand, and both prescription and sales, on the other hand. However, the link between noncompliance, and both DTCA and promotion to doctors is not addressed in this analysis.

3. A Model of Drug Product Selection

3.1. Preliminaries

It is assumed that an initial examination of the patient by the doctor has led to the diagnosis of a disease, which is common knowledge. The disease may be treated either by one of J alternative drugs in a given therapeutic class, or by an "outside" $J+1$-th method (e.g. surgery). The patient, however, need not blindly follow the doctor's choice regarding the treatment of the disease. It is assumed that the doctor may not know precisely some of the patient's characteristics such as aspects of health history, anti-drug attitude, exposure to DTCA. In addition, the doctor may not know how much the patient trusts her competence.

[13] "Direct-to-Consumer" Advertising Audit (August 2000), www.scottlevin.com.

The doctor's aim is to provide the best care to the patient by prescribing the drug that best matches the patient's observable characteristics (by the doctor). In doing so, the doctor accounts for the expected compliance of the patient with the prescribed drug. An additional factor that may influence the doctor's preference for a specific drug is her exposure to advertisement for that drug. Once the doctor has selected a given drug, the patient then chooses to comply or not with the prescription. This choice is assumed to be a rational trade-off between anticipated health benefits, and both monetary and non-monetary costs associated with compliance with the prescribed drug regimen. The non-monetary costs incurred during the treatment may be more or less subjective, and include side effects, dosage schedules, and uneasiness stemming from anti-drug attitudes. In addition, the patient's decision is assumed to be influenced by DTCA.[14]

To summarize, the doctor-patient relationship is modeled as a sequential game in which the doctor first proposes, and the patient then disposes. The assumption that the doctor makes the first decision is dictated by the real-life fact that the prescription decision power is vested in the physician, even though the patient is free to comply with the prescribed medication. The assumption does not rule out a possible bargaining process that may precede the prescription decision, nor does it necessarily imply a conflict between the doctor and the patient about which drug to choose.

[14]Note that it is implicitly assumed that patients do not observe advertisement toward doctors.

3.2. The model

We consider a two-period game between the doctor and the patient.[15] In period one, the doctor chooses the drug to prescribe; in period 2, the patient reacts to this choice by complying or not with the prescription.[16] The doctor does not observe some characteristics $p \in \mathbb{R}^q$ of the patient. The doctor knows, however, the probability distribution of this vector of characteristics.[17]

The patient's preference is represented by a utility function which depends on the prescribed alternative j ($j = 0, \ldots, J$), the patient's privately known idiosyncratic characteristics p, and the decision variable nc, which can take two possible values 1 (do not comply) and 0 (comply). More precisely, when drug j is prescribed, patient p's utility function over the alternatives (nc) "do not comply" and "comply," is specified as follows:

$$U^P(nc; j, p) = \begin{cases} u_p + \omega_1 & \text{if } nc = 1 \text{ (do not comply)} \\ \theta_{jp} - \overline{y}_{jp} + \omega_2 & \text{if } nc = 0 \text{ (comply)} \end{cases},$$

where $u_p \leq 0$, $\theta_{jp} \geq 0$, $\overline{y}_{jp} \geq 0$ and ω_i ($i = 1, 2$) is a random shock satisfying $E[\omega_i | p, j] = 0$. u_p and θ_{jp} represents the health outcome associated to noncompliance and compliance with the prescription of drug j. The term $\overline{y}_{jp}$ may be interpreted as the inconvenience (or cost) associated with compliance. As mentioned above, this cost may be due to the (high) price of drug j and/or the side effects associated with the consumption of this drug.

The patient's decision will be based upon the expected utility $E_{\omega_1,\omega_2}[U^P(nc; j, p)|p, j, nc]$,

[15] Any dynamic consideration, such as learning or reputation building, is beyond the scope of the present paper.

[16] It is important to note that the game starts when a patient consults his doctor. As previously mentioned, however, DTCA may affect the patient decision to visit his doctor. This factor may be ignored for the purpose of our study since i) DTCA for glaucoma drugs is not targeted toward the general population, and ii) the motivations behind a consultation do not impact the compliance and prescription behaviors in our model.

[17] For the purposes of the paper, we do not need to specify the distributions of patients characteristics.

where $E_{\omega_1,\omega_2}[\,.\mid .\,]$ is the conditional expectation operator taken with respect to ω_i $(i=1,2)$. Patient p's expected utility is then given by

$$\overline{U^P}(nc;j,p)=E_{\omega_1,\omega_2}[U^P(nc;j,p)|p,j,nc]=\begin{cases} u_p & \text{if } nc=1 \text{ (do not comply)} \\ \theta_{jp}-\overline{y}_{jp} & \text{if } nc=0 \text{ (comply)} \end{cases} .$$

We shall assume that $\overline{y}_{jp}$ can be written as $\overline{y}_{jp}=y_j+\eta_{jp}$, where $y_j\geq 0$ may be interpreted as the average costs (over the set of patients) associated with compliance. The average costs y_j is assumed to be common knowledge.[18] The deviation from this average, η_{jp}, still accounts for the interaction patient-drug.

Patient p's optimal decision when prescribed drug j is the indicator function

$$nc^*(j,p)=1_{\{w_{jp}\leq y_j\}}(p) \quad ,$$

where $w_{jp}=\theta_{jp}-u_p-\eta_{jp}$. In other words, patient p chooses not to comply with the prescription if the net expected costs incurred by complying is higher than the average costs associated with noncompliance. The probability of noncompliance, $Pr(nc^*(j,p)=1)=Pr(w_{jp}\leq y_j)=F_j(y_j)$, is the rate of noncompliance with the prescription of drug j, relatively to the probability distribution of the vector p.

We now turn to the doctor's decision. We assume, as it is done in the discrete-choice literature, that drugs are ranked according to an indirect and random utility function

$$U^D(j;nc,d,p)=X_j'\beta_d-nc+\xi_j+\epsilon_{jd} \quad ,$$

[18] Doctors are assumed to know the average costs associated with compliance through the channel of scientific meetings, publications, and various medical communications.

where nc is the patient's decision and ξ_j represents the characteristics of drug j that are observed by the doctor, but unobservable to the econometrician. The components of the vector X_j are the observable characteristics (known to the econometrician) of drug j, and ϵ_{jd} is a random shock. The negative sign in front of the patient's decision (nc) indicates that the doctor gets disutility from noncompliance.

The equilibrium for this game will be found by backward induction. Therefore, anticipating the patient's decision, the physician will substitute $nc^*(j,p)$ for nc in her utility function. However, since the doctor still has incomplete information about the patient's characteristics, she will average out her utility over the set of patients' types (or characteristics), obtaining

$$\overline{U}^D(j;d) = E_p[U^D(j;nc^*(j,p),d,p)|j,d] = X_j\beta_d - F_j(y_j) + \xi_j + \epsilon_{jd} \quad ,$$

where, as explained earlier, $F_j(.)$ represents the rate of patient noncompliance with the prescription of drug j. The doctor then chooses the alternative j^* that yields the highest expected utility, given the anticipated choice of the patient and the doctor's beliefs.

3.3. Theoretical Predictions

We now derive some theoretical predictions. As we shall see, however, to answer the questions raised in the introduction, the model will need to be estimated. Let us start by making a number of simplifying assumptions. Note that these assumptions are also introduced to facilitate the estimation of the model with product-level data.

We assume that the coefficient vector β_d does not depend on the doctor's characteristics, and that the noncompliance rate function, $F_j(\,.\,)$, is independent of j. In other words, the noncompliance rate function is assumed to depend on the drug characteristics (j) only through

its arguments (y_j). The average costs y_j associated with compliance is assumed to linearly depend on a vector Z_j of observable characteristics of product j ($y_j = Z_j'\gamma$). These assumptions rule out heterogeneity among doctors and among patients. Note that the most likely source of heterogeneity among patients is related to drug coverage by third parties (e.g. HMO, private insurance, Medicare, Medicaid). To account for this possible heterogeneity, one would need individual-level data describing for every patient, and every drug the precise type of coverage. Such detailed data were not available to us. However, available data on glaucoma patients indicate that the vast majority of patients have some form of coverage.[19] In addition, inspection of several health plans indicates that drugs prescribed for glaucoma, which is a common but potentially debilitating disease, are roughly equally covered by third party payers. Therefore, the potential heterogeneity among glaucoma patients is likely to have a limited effect on the subsequent estimation.

Finally, to obtain closed form solutions, we assume that the random shocks ϵ_{jd} are i.i.d. extreme value distributed, as it is usually done in the discrete choice literature. The probability P_j that drug j is prescribed (the choice probability for drug j) is then of the logistic form, where $j = 0$ refers to the outside alternative. When the outside alternative is assumed to yield zero utility to the doctor (for the purpose of econometric identification of the coefficients, see for instance Ederm and Winer 1999), the choice probability for drug j takes the form

$$P_j = \frac{e^{X_j'\beta - F(Z_j'\gamma) + \xi_j}}{1 + \sum_{r=1}^{J} e^{X_r\beta - F(Z_r'\gamma) + \xi_r}} \quad .$$

[19] Schappert (1995) reports that 61.9% of patients with glaucoma were covered by Medicare, while 36.6% had a private or commercial insurance.

From the above equality, we obtain the following relation:

$$\ln(P_j) - \ln(P_0) = X_j'\beta - F(Z_j'\gamma) + \xi_j \quad , \tag{3.1}$$

where P_0 is the choice probability of the outside alternative.

One can immediately notice that if $F(.)$, the noncompliance distribution, shifts down, then the probability of prescription for any drug will increase relatively to the outside good. In other words, a public policy that succeed in curbing noncompliance will affect the structure of the market by reducing the market share of the outside good.

Three variables will now be considered for the sensitivity analysis of the choice probabilities and the rate of noncompliance. These are the drug price and the advertisement intensities toward doctors and patients. We assume that the price and DTCA enter the utility of a patient through the average cost of compliance, rather than the health outcomes associated to compliance and noncompliance.[20] These two variables are therefore component of the vector Z_j. Let Z_{j1} and Z_{j2} represent the price and the advertisement toward consumers (DTCA). It is implicitly assumed that doctors care about drug prices only to the extent that they may affect their patients' probability of compliance. Advertisement toward doctors influence the doctor's prescription but not the patient's compliance, since we have assumed that advertisement toward doctors are not observed by patients. Therefore, it will be a component of the vector X_j only (say X_{j1}). A last assumption is that the cumulative distribution function $F(.)$ (hereafter cdf) is differentiable and its derivative is denoted by $f(.)$.

Under these assumptions, the derivatives of the probability P_j with respect to the prices

[20] As noted earlier, most glaucoma patients have some form of (partial) coverage. It is widely recognized, however, that the price is still one of the major factor of noncompliance with prescription of anti-glaucoma drugs.

of drug j and drug $k \neq j$ are:[21]

$$\frac{\partial P_j}{\partial Z_{j1}} = -f(Z_j\gamma)\gamma_1 P_j(1-P_j) \text{ and } \frac{\partial P_j}{\partial Z_{k1}} = f(Z_k\gamma)\gamma_1 P_j P_k \quad . \tag{3.2}$$

The equalities in (3.2) show that prescription probabilities are sufficient statistics for their own sensitivity to price. This property is often criticized because the implied elasticity of demand exhibits unrealistic substitution patterns between products. Note, however, that this criticism does not directly apply here since these substitution patterns concern prescription and not purchase probabilities, which should not be considered equivalent due to the presence of purchase noncompliance.

Prediction 1 *: If γ_1 is positive, then an increase in the price of a drug will induce doctors to prescribe that drug less often. A relative increase in the price of another drug k will induce more frequent prescriptions for drug j.*

Note that doctors may not necessarily take into account prices when prescribing a drug. Indeed, the decision of the doctor is comparable to that of a university professor choosing a book for her class. Her objective is to select the best book with the well-being of students in mind.[22] However, few faculty take into consideration prices when selecting a textbook.

We now analyze the effects of DTCA on prescription. The derivatives of P_j with respect to DTCA are as follows:

$$\frac{\partial P_j}{\partial Z_{j2}} = -f(Z_j\gamma)\gamma_2 P_j(1-P_j) \text{ and } \frac{\partial P_j}{\partial Z_{k2}} = f(Z_k\gamma)\gamma_2 P_j P_k \quad . \tag{3.3}$$

[21] Unlike Rizzo (1999) we do not explicitly consider the interaction between price and advertisement.

[22] Note that the professor may be influenced by advertisement and free samples sent by editors, who often (strategically?) "omit" to mention prices.

Prediction 2*: If γ_2 is negative, then an increase in DTCA intensity of a drug increases the likelihood that the drug will be prescribed by doctors and decreases the chances that competing drugs are prescribed.*

This is a realistic feature of the model because advertisement of a drug toward patients is likely to induce them to show interest for that drug when they meet their doctors. This in turn may be perceived by doctors as a signal that the patients will be more likely to comply, should that drug be prescribed. As a consequence, the doctors may be more inclined, caeteris paribus, to prescribe the drug over a less advertised drug. However, γ_2 may be statistically insignificant in our sample if doctors perceive that DTCA does not affect patients' compliance behavior. This hypothesis is reasonable, since it is typically recognized that doctors overwhelmingly underestimate the prevalence of noncompliance (Marinker 1997).

Let us now analyze the influence of advertisement toward doctors on their prescription behavior. This may be seen by computing the following derivatives:

$$\frac{\partial P_j}{\partial X_{j1}} = \beta_1 P_j(1 - P_j) \text{ and } \frac{\partial P_j}{\partial X_{k1}} = \beta_1 P_j P_k \quad . \tag{3.4}$$

Prediction 3*: If β_1 is positive, advertisement toward doctors for a drug has a positive (negative) effect on the prescription probability for that (another) drug.*

The determination of the statistical significance of β_1 will contribute to the debate pertaining to whether or not doctors are actually influenced by promotional efforts of drug companies.

The individual rates of noncompliance $F(Z_j'\gamma) = F_j$ may be aggregated over the alternative drugs into an average rate of noncompliance $\overline{F}$, using the choice probabilities. This rate is given

by the equality

$$\overline{F} = \sum_{j=0}^{J} F_j P_j = \sum_{j=0}^{J} F(Z_j'\gamma) P_j = \sum_{j=0}^{J} F(Z_j'\gamma) \frac{e^{X_j'\beta - F(Z_j'\gamma) + \xi_j}}{1 + \sum_{r=1}^{J} e^{X_r'\beta - F(Z_r'\gamma) + \xi_r}}. \tag{3.5}$$

From relation (3.5), we can assess the influence of both forms of advertisement on the average rate of noncompliance:

$$\frac{\partial \overline{F}}{\partial X_{j1}} = \beta_1 P_j (F_j - \overline{F}) \text{ and } \frac{\partial \overline{F}}{\partial Z_{j2}} = P_j f(Z_j'\gamma)\gamma_2 [1 - (F_j - \overline{F})] \quad , \tag{3.6}$$

where X_{j1} and Z_{j2} stand respectively for the variables representing promotion toward doctors and patients.

Prediction 4*: If γ_2 is negative, then so is the right-hand side of the second equality in (3.6), and an increase in DTCA for any drug will unambiguously lower the average noncompliance rate.*

Prediction 5*: If β_1 is positive and $F_j > \overline{F}$ ($F_j < \overline{F}$) then an increase in the promotion of drug j toward doctors will increase (reduce) the average noncompliance rate.*

Predictions 4 and 5 suggest that, unlike DTCA, the effect of promotion to doctors on the average noncompliance rate is ambiguous. Indeed, advertising for drug j toward doctors will reduce the average noncompliance rate only when drug j has an initially lower than average noncompliance rate. In other words, if drugs with poor compliance rates are advertised to doctors, then they may be induced to prescribe these drugs more often, thus contributing, caeteris paribus, to an increase in the average noncompliance rate.

In summary, we have seen that to fully answer the questions raised in the introduction, we need to estimate the model in order to determine the signs of the structural parameters.

4. Data and Estimation

4.1. Description of the Data

We use a data set, mainly provided by IMS America and CMR, on the U.S. market for anti-glaucoma drugs. The remaining part of the sample was collected from different sources to be mentioned along with the description of the variables that enter in the structural econometric model.

Glaucoma is an eye disease characterized by a high intra-ocular pressure (IOP). It is a common disease affecting some 2.25 million people in the United States. Health practitioners are well aware of the significant noncompliance problem with anti-glaucoma drugs. Indeed, these drugs have several side effects (e.g. decreased vision, eye discoloration, redness), their usage is often inconvenient, and there is no immediate relationship between the use of the drug, and the prevention of the most important consequence of the disease (blindness).

The data set has a panel structure, each 48 observed drugs defining a time series for the years 1995-1999. In other words, there is one observation for each drug and each year. Note that the sample includes seven drugs that were introduced between 1995-1999. Although a drug company may market several anti-glaucoma drugs, we assume that the set of characteristics are independent across products. Every variable is listed below with the corresponding label in parenthesis. To be consistent with the theoretical model, we differentiate three sets of variables X, Z, and Y.

The components of the vector X are the variables influencing directly (i.e. not through the rate of noncompliance) the doctor's preference. These are

- Type of chemical structure (*Class*).

Glaucoma drugs are usually classified according to their type of chemical structure. we consider, the following seven classes.[23]

Class 0 : Beta-adrenergic blocking agents (or beta blockers).

Class 1 : Carbonic anhydrase inhibitors.

Class 2 : Parasympathomimetic agents (or miotics).

Class 3 : Sympathomimetic agents.

Class 4 : Alpha 2-adrenergic agonists.

Class 5 : Prostaglandins analogs.

Class 6 : Multiple ingredients drugs.

This classification is motivated by the medical literature in which side effects profiles and the relative effectiveness of glaucoma drugs are usually presented using a similar classification. *Class* is represented by six dummy variables, with "Class 0" as the reference class.

- Mode of action (*Action*). Anti-glaucoma drugs fall in two broad categories: some lower the intra-ocular pressure by increasing the outflow of the aqueous humor; others lower the IOP by reducing the formation of the aqueous humor. These two categories of drugs also differ by their side effects. Hence, *action* is a binary variable.

- Age (*Drug_ Age*). This variable represents the number of months separating the current date from the date the drug was launched on the market. Following Rizzo (1999), this

[23] The classification is based on Munger (2001), *World of Drug Information* (2000), Lewis et al. (1999) and *CBS Health Watch* (1999). In addition, we have separated single from multiple ingredients drugs. The latter are put in a separated class (class 6).

variable is assumed to capture life cycle patterns typically observed for pharmaceutical products.

- Detailing costs (*Dcosts*). This variable represents the largest part (roughly 75%) of advertising toward doctors. It includes the annual expenses for keeping representatives in the field. However, it does not contain the other expenses involved in support of the detailing effort, such as free samples. The variable is a deflated version of the corresponding IMS variable. The deflator used is the producer price index for pharmaceutical preparations. Advertising will be considered here as a flow. This assumption finds support in Rizzo (1999) who found that current detailing flows have stronger effects than detailing stocks on the elasticity of demand.

The components of the vector Z are the variables that influence the patient's total costs (i.e. monetary and non-monetary) of compliance. These are

- Price (*Dayprice*) is the wholesale price deflated by the consumer price index for pharmaceutical preparations.[24] Each price is computed by dividing the wholesale price of a drug by the number of days of treatment. The latter is estimated from the recommended dosage found in the *Physician's Desk Reference*.

- Direct-to-consumer advertising (Dtca). This variable represents the deflated annual amount of DTCA spent by the pharmaceutical companies on each drug in our sample. Although some drug companies advertise in popular media, most of the DTCA for glaucoma drugs is targeted toward patients through (e.g.) specialized magazines, medical websites, direct-mailing, or informative pamphlets.

[24] This price data are collected from the *Red Book, Drug Topics,* Montvale, NJ.

- Dosage schedule (*Howfreq*). This variable shows the frequency of use of the drug as recommended in the Physician's Desk Reference. When the frequency is a range, we choose the upper bound of the range.

- Form of presentation (*Form*). This is a dummy variable that indicates whether the drug has other forms of presentation than drops.

Finally, the dependent variable Y is based on the annual market share for each drug. To construct these shares, the quantities are computed as the ratio between sales and the price of a day of treatment. The quantities are thus in days of treatment. Following the extensive analysis by Hattenhauer et al. (1999), we set the annual share of the outside treatment (surgery) to 23%.

Table 1 summarizes the sales, prices, the spending on each type of advertisement, the total advertisement (promotions to doctors and patients) to sales ratio, and the number of months since the drug was launched over the entire period 1995-1999. Notice that drug promotion to doctors is more than six time larger than DTCA. This ratio is slightly above the pharmaceutical industry average, since glaucoma drugs do not belong to the small class of highly advertised drugs. Note also that the standard deviations of the sales and advertisements variables are large. This may be explained by the fact that the market for anti-glaucoma drugs is dominated by few products, which account for most sales and advertisement (in 1999, 8 out of 46 products accounted for roughly 83% of the sales). The high correlation between advertisement and sales is illustrated in Graphs 1 and 2. Anti-glaucoma drugs may be broadly divided in two groups: the first includes highly advertised products with increasing sales (see Graph 1); the second includes less advertised drugs with decreasing sales (see Graph 2). Note also that although *Xalatan* and *Alphagan* are equally advertised, and their price ratio remains constant over

time, the sales of *Xalatan* have increased considerably compared to *Alphagan*. As we shall see later on, this empirical observation may be explained by the difference in noncompliance rate between the two products. Finally, Graph 3 indicates a clear increase in price over time, but the advertisement to sales ratio does not exhibit any obvious trend.

4.2. Estimation Strategy

Equation (3.1) is the basic equation to be estimated. More precisely, we wish to estimate the parameters vectors β, γ, and the unknown cdf $F(.)$. Since $F(.)$ does not have a known analytical form, and that we want to impose the least structure possible, we are led to perform a semiparametric estimation of the unknowns in our model. To do this, however, we first need to address the following two problems.

4.2.1. Sample Selection

The prescription probabilities, in the left-hand-side of equation (3.1) are not observed in our sample. The only information available to us is the sales in dollars for each drug. The sales and prescriptions, however, are not equivalent since many prescriptions are not turned into sales due to purchase noncompliance, which is believed to affect around 20% of all prescriptions. Failure to distinguish between prescriptions and sales (as in Wosinska 2002), would lead to severely biased estimates in the present study. Indeed, the unobserved purchase noncompliance is generally believed to be influenced by variables entering the right-hand-side of equation (3.1), such as the price, or the drug reputation generated in part by DTCA.

The drug sales, however, are sufficient to estimate the model. Indeed, from such data we can compute $P(j|B)$ the share (in quantity) of drug j in the population of filled prescriptions,

where B stands for "A Prescribed Drug is Bought." So, $P(j|B)$ is the probability that drug j is prescribed, conditional on a drug being bought. Recall that we denoted by P_j the corresponding unconditional probability. By Bayes rule, we have

$$P(j|B) = \frac{P_j P(B|j)}{P(B)} \quad ,$$

where $P(B|j)$ is the probability of purchase if drug j is prescribed and $P(B)$ is the unconditional probability of purchase (the proportion of purchased drugs among prescribed drugs). Dividing both sides of the preceding equality by the analogous expressions for the outside alternative and taking logarithms, we obtain,

$$\begin{aligned} \ln \frac{P(j|B)}{P(0|B)} &= \ln \frac{P_j}{P_0} + \ln \frac{P(B|j)}{P(B|0)} \\ &= X_j'\beta - F(Z_j'\gamma) + \xi_j + \ln \frac{P(B|j)}{P(B|0)}, \end{aligned}$$

where the last equation is obtained from (3.1).

As noted above, we observe only the probability $P(j|B)$. Therefore, if we define a new unobservable variable $\tilde{\xi}_j$ as

$$\tilde{\xi}_j = \xi_j + \ln \frac{P(B|j)}{P(B|0)},$$

we can rewrite the original model as

$$Y_j = \ln \frac{P(j|B)}{P(0|B)} = X_j'\beta - F(Z_j'\gamma) + \tilde{\xi}_j. \tag{4.1}$$

Equation (4.1) may then be estimated from the available data, provided that the purchase

probability of a drug is driven by its price and the reputation generated by its level of DTCA.[25]

It has to be noted that this approach will not allow us to estimate the magnitude of the parameters, but only their signs. This, however, is sufficient to determine the signs of the derivatives (3.2) to (3.6), and, therefore, we will be able to answer the questions raised in the introduction.

4.2.2. Endogeneity

As it is traditionally the case with discrete choice models, the unobserved characteristics (to the econometrician) are likely to be correlated with the prices and advertisement variables. Therefore, the estimation method must account for this endogeneity problem. We handle this problem by applying the "control function method" (see e.g., Newey, Powell and Vella 1999, or Blundell and Powell 2000).

The method consists of including as additional regressors to equation (4.1) the residuals of the nonparametric regressions of the endogenous variables on the instruments. Endogeneity is therefore treated in that approach as an omitted variable problem. In the present context, the endogenous variables are the detailing costs (*Dcosts*), the prices (*Dayprice*) and DTCA (*Dtca*). Let us denote the vector of endogenous variables by N and the remaining exogenous variables as e. Equation (4.1) may then be written as $Y_j = \phi(N_j, e_j) + \tilde{\xi}_j$, in which $E(Y|N_j, e_j) \neq \phi(N_j, e_j)$ because of the endogeneity problem.

Consider now the nonparametric regression equations $N_{i,j} = m_i(e_j) + u_{i,j}$ $(i = 1, 2, 3)$, where $u_{i,j}$ are uncorrelated error terms and $m_i(.)$ are unknown functions. Our application of the method relies on the assumption that in the presence of both u and e, the variable ξ is

[25] This assumption appears reasonable since prices and reputation are the principal information available to patients at the time of purchase.

correlated only with $u = (u_1, u_2, u_3)'$:

$$E(\xi|u, e) = E(\xi|u), \text{ and } E(u|e) = 0 \quad . \tag{4.2}$$

These assumptions imply

$$E(Y|N, e) = \phi(N, e) + E(\xi|N, e) = \phi(N, e) + E(\xi|u) = \phi(N, e) + \varphi(u) \quad ,$$

where $\varphi(u) = E(\xi|u)$. The method therefore consists in two steps: in step 1, we perform a nonparametric regression of each of the endogenous on the exogenous variables. In other words, we sequentially estimate the equations

$$N_{i,j} = m_i(e_j) + u_{i,j} \ \ (i = 1, \ldots, 3). \tag{4.3}$$

we obtain the residuals $\hat{u_i}$ from these regressions. In step 2, we estimate a modified version of equation (4.1):

$$\begin{aligned} Y_j = \ln P(j|B) - \ln P(0|B) &= E[\ln P(j|B) - \ln P(0|B)|X, Z, \hat{u}] \\ &= X_j'\beta - F(Z_j'\gamma) + \varphi(\hat{u_j}'\delta) + \overline{\xi}_j \quad , \end{aligned} \tag{4.4}$$

where $\hat{u} = (\hat{u_1}, \hat{u_2}, \hat{u_3})'$ is the vector of residuals obtained in step 1.

To verify whether our model's hypotheses, and in particular the hypothesis in equation (4.2), may be considered reasonable, we also estimate nonparametrically the more general

model

$$Y_j = \Phi(N_j, e_j) + v_j \quad , \tag{4.5}$$

in which $E(Y|N_j, e_j) = \Phi(N_j, e_j)$. If our model is correctly specified, then $\Phi(N_j, e_j) = \phi(N_j, e_j) + \varphi(u_j)$, or equivalently $\overline{\xi}_j = v_j$. The informal verification technique, will therefore consist in comparing the estimated residuals of the two econometric models in equations (4.4) and (4.5).[26]

4.2.3. Practical Considerations

To avoid the curse of dimensionality, we have assumed that the nonparametric multiple regressions in steps 1 and 2 are index models (Ichimura and Lee 1991, Ichimura 1993). To ensure the identification of the parameter γ, we further assume that $\|\gamma\| = 1$. Although, the nuisance parameters (δ, λ) are identified only up to a multiplicative factor, the expressions $\varphi(u'\delta)$ and $m(e'\lambda)$, if regarded as parameters, are identified. This identification issue is not a serious problem here, since δ and λ are nuisance parameters, and we are only interested in the signs of β and γ. The cdf $F(.)$ is estimated nonparametrically as follows,

$$\hat{F}(Z_j'\gamma) = \frac{1}{n}\sum_{r\neq j}^{n} K(\frac{Z_j'\gamma - Z_r'\gamma}{h_K}) \quad ,$$

where n is the sample size, γ is a vector of parameters to be estimated, $K(x)$ is a cdf associated with a kernel derivative $k(.)$, and h_K is a bandwidth controlling the smoothness of the kernel estimates. In practice, we select $K(x) = (1 + e^{-x})^{-1}$, the cdf of a logistic distribution.

[26] More traditional tests, such as the Hausman test, cannot be applied in the present context due to the semiparametric structure of the model.

Similarly, the functions $m_i(.)$ $i = (1, 2, 3)$ and $\varphi(.)$ are estimated nonparametrically by

$$\hat{m}_i(e_j'\lambda) = \frac{\sum_{r\neq j}^{n} N_{i,r} g(\frac{e_j'\lambda - e_r'\lambda}{h_{m_i}})}{\sum_{r\neq j}^{n} g(\frac{e_j'\lambda - e_r'\lambda}{h_{m_i}})} \text{ and } \widehat{\varphi}(\hat{u}_j'\delta) = \frac{\sum_{r\neq j}^{n} [Y_r - X_r'\hat{\beta} + \hat{F}(Z_r'\hat{\gamma})] g(\frac{\hat{u}_r'\delta - \hat{u}_j'\delta}{h_\varphi})}{\sum_{r\neq j}^{n} g(\frac{\hat{u}_r'\delta - \hat{u}_j'\delta}{h_\varphi})} \quad , \tag{4.6}$$

where $g(.)$ is a gaussian kernel, h_{m_i} and h_φ are bandwidths, and $\beta, \gamma, \lambda, \delta$ are parameter vectors to be estimated. Following Pagan and Ullah (1999), the optimal bandwidths in all nonparametric estimations are approximated by least squares cross-validation.

To estimate the parameters λ in step 1, we solve the following minimization problems:

$$\min_{\hat{\lambda}} R_n(\hat{\lambda}) = \frac{1}{n}\sum_{k=1}^{n} W(e_k)[N_k - \hat{m}_i(e_k'\hat{\lambda})]^2 \quad i = 1, \ldots, 3 \quad , \tag{4.7}$$

where $W(.)$ is a standard weighting function that may be chosen optimally in order to minimize the variance of the estimator.

In step 2, the parameters (β, γ, δ) are estimated by solving

$$\min_{\hat{\beta},\hat{\gamma},\hat{\delta}} S_n(\hat{\beta}, \hat{\gamma}, \hat{\delta}) = \frac{1}{n}\sum_{i=1}^{n} W(X_i, Z_i)[Y_i - X_i'\hat{\beta} + \hat{F}(Z_i'\hat{\gamma}) - \widehat{\varphi}(\hat{u}'\hat{\delta})]^2 \quad . \tag{4.8}$$

The optimal weight functions $W(.)$ are approximated sequentially by estimating the covariance matrix of the estimates in equations (4.7) and (4.8). Under standard regularity conditions on the kernel functions and the bandwidths, Ichimura (1993) shows that the parameters are consistent and asymptotically gaussian.

4.3. Results

We report in Table 2 the results of the estimations conducted in step 2.[27] Recall that the magnitude of the effects of the explanatory variables on the prescription probabilities and the average noncompliance rate cannot be evaluated from the values of the estimated parameters.[28] Therefore, we will only discuss here the economic interpretation that may be given to the signs of the parameters. Before describing the estimation results, let us point out that Graph 4 indicates that the residual estimated with our model (i.e. equation 4.4), and the residuals estimated with the general model (i.e. equation 4.5), are very similar.[29] This result therefore suggests that the hypotheses imposed to derive our structural model may be considered reasonable.

All the components of the vectors β and γ but two (the parameters associated with the variables *Class 1* and *Form*) are significantly different from zero. Note also that all the statistically significant parameters have the expected signs. In particular, β_3 to β_7 are all negative, which indicates that the drugs in class 1 (the beta blockers) are prescribed more often. This was expected, since beta blockers have remained over time the mainstay therapy for glaucoma. β_9 is positive, which suggests that there is a first mover advantage, in the sense that a drug introduced earlier is more prescribed than a newer drug with similar characteristics. In other words, the sample tends to indicate the presence of learning and/or habit formation on the part of doctors. Finally, γ_1 is significant and positive, which indicates that doctors are sen-

[27] The estimates of the nuisance parameters, δ and λ, are not reported here for the sake of brevity, since they have no economic interpretation.

[28] This also implies that we will not be able to conduct some ex-post simulations to predict how a change in variables may affect doctors and/or patients behavior.

[29] More specifically, the null hypothesis that $\widehat{\widehat{\xi}}$ and $\widehat{v}$ have the same distribution cannot be rejected by a Kolmogorov-Smirnov test (P-value=0.127). In addition, the null hypothesis that the slope parameter is equal to 1 in the regression of $\widehat{v}$ on $\widehat{\widehat{\xi}}$ cannot be rejected (P-value=0.153).

sitive to price changes. This result confirms several empirical studies that demonstrate that when patients pay less for a drug, doctors write more prescriptions for that drug, as a response to increased requests by patients (see Lavizzo-Mourrey and Eisenberg 1990). In our model, these requests influence doctors decisions only through the anticipated reduction in patient noncompliance.

As expected, β_1 and γ_1 are both positive, while γ_2 is negative. Therefore, we are now in position to answer the two questions raised in the introduction. Advertisement for a given anti-glaucoma drug toward doctors and/or patients increases the number of prescriptions for that drug. In other words, contrary to the opinion expressed by many doctors, advertisements toward doctors affect their prescription behavior, independently of the characteristics of the advertised drug. In addition, although not directly exposed to DTCA, doctors are indirectly influenced by DTCA through their patients' expected noncompliance.

DTCA unambiguously lowers the average rate of noncompliance with anti-glaucoma drugs. This result tends to support the opinions of proponents of DTCA recently expressed in front of the FDA. However, we cannot assess from our analysis, whether the reduction in noncompliance is due to the information content of DTCA, or to the fact that doctors tend to prescribe drugs with a high DTCA intensity, which are likely to be preferred by patients. In contrast, promotion to doctors has an ambiguous influence on the average noncompliance rate. Indeed, the average noncompliance rate increases when the advertised drug has initially a higher than average rate of noncompliance. In other words, if the average compliance rate is taken as a component of health care quality, then advertisement toward doctors have a negative impact on patients when the drugs advertised to doctors have a high noncompliance rate. To determine whether this was the case on the market for anti-glaucoma drugs, we now turn to the estimation of the

noncompliance rates.

We report in Table 3 the estimated probability of noncompliance for each product and each year. In addition the annual average noncompliance rates are shown in Table 4. First note that the overall, as well as the individual rates of noncompliance are consistent with the corresponding rates found in the literature for anti-glaucoma drugs (Wick and Zani 2000) and for other therapeutic classes (Dezii 2000). More specifically, Rotchford and Murphy (1998) evaluate the noncompliance rate of the Drug *Timolol* in 1998 at around 51%, while we estimate the corresponding rate at 55%. Simon (1999) also reports an approximate noncompliance rate of 62% for the drug *Diamox*, while our figures range between 66.1% in 1995 to 59.6% in 1999.[30] These results suggest that the model and the estimates are sensible.

Graph 5 indicates that the annual distributions of noncompliance rates across products are rather concentrated around their modes and slightly asymmetric with a predominance of rates above the mean. Table 4 and Graph 5, also clearly show a decline in noncompliance (both at the average and individual level) between 1995 and 1999. In particular, the noncompliance mode in 1995 (slightly above 0.7) has become highly improbable in 1999. Note also that the average noncompliance rate decreases sharply after the 1997 FDA decision on DTCA (see Table 4). This result may be explained by the fact that, as previously noted, DTCA unambiguously reduces the average rate of noncompliance. We should not exclude, however, that the growing concerns among doctors also played a role in the reduction of average noncompliance. However, recall that advertisement toward doctors has an ambiguous effect on the average noncompliance rate. Graph 6, actually shows that the most highly advertised drugs toward doctors have

[30] See the document on compliance by the *Glaucoma Associates of New York* at www.glaucma.net/gany/patser/compliance.html. These are the only two individual noncompliance rates for anti-glaucoma drugs we were able to find in the literature.

a noncompliance rate above average. In other words, advertisement toward doctors had a negative impact on the average noncompliance rate with anti-glaucoma drugs between 1995 and 1999.

Let us now concentrate on two of the most popular products (*Xalatan* and *Alphagan*). First, note that every year between 1996 and 1999, *Xalatan* has the smallest noncompliance rate among all products in our sample. This is a remarkable result for our structural model, since *Xalatan* is known among doctors to be the most convenient drug to use. Indeed, *Xalatan* is a once a day eye drop, while its competitors (except *Cosopt*, a recently introduced multiple-ingredient drugs) require at least 2 applications per day. This result may also partially explain why, although *Alphagan* and *Xalatan* are equally advertised, and their price ratio remained constant over time, the markets share for *Xalatan* grew at a faster rate than that of *Alphagan*. Indeed, we have seen that, caeteris paribus, doctors prefer to prescribe a drug with a higher compliance rate.

5. Conclusion

This paper is the first integrated study of patient noncompliance and drug advertising toward doctors and/or patients in a physician agency model. The object was to determine the influence of noncompliance and advertising on doctors' prescription behavior, and the effect of advertising on patients' noncompliance. To address these questions, we opted, due to data limitations, for a parsimonious discrete choice model with no more structure than was necessary to estimate the parameters with the data currently available. The model describes the prescription behavior of a doctor facing a patient who may fail to comply with the prescription. We apply semiparametric techniques to estimate the structural model using U.S. product level

data on anti-glaucoma drugs. In particular, these econometric techniques allow us to estimate the individual, as well as the aggregated noncompliance rates. The estimation results suggest that (i) doctors are sensitive to drug prices and noncompliance, and their prescription behavior is influenced by both types of advertisement; (ii) the overall noncompliance rate on the market for anti-glaucoma drugs is estimated at around 58%, and it is shown to decrease significantly between 1995 and 1999; (iii) DTCA (respectively, promotion to doctors) contributed to (respectively, slowed down) the reduction of the overall noncompliance rate observed in our sample.

Note, however, that the estimation results generated by structural models may be influenced by the restrictions, and the functional forms imposed. In the present paper, we strived to set the most neutral restrictions possible, and not to impose any functional forms when possible. As an illustration, the probability of noncompliance was estimated semiparametrically. The estimation results, however, appear sensible, and the estimated noncompliance rates are in accordance with the few figures available in the medical literature.

Note also that some aspects of the glaucoma market and the doctor-patient relationship have not been fully taken into consideration in the paper. These include, on the theoretical side, long term care which allow the patient and the doctor to learn about each other as times goes by. On the empirical side, we did not consider heterogeneity among doctors and among patients. Finally, we did not account for other parties entering the agency problem such as, for instance, HMOs or insurance companies. We are currently looking for data to investigate these extensions.

To conclude, it is important to note that the modeling of the interplay between noncompliance and advertising allows us to capture realistically the behaviors of both doctors and

patients and their consequences on the glaucoma market. For instance, the relative performance of *Xalatan* compared to, for instance, *Alphagan* may be partially explained by the significantly lower estimated noncompliance rate of *Xalatan*. Finally, the empirical relevance of the interplay between noncompliance and advertising is demonstrated by the introduction of the two newest drugs since 1999 (*Lumigan* and *Travatan* have been approved by the FDA in 2001). The launch of these two drugs is accompanied by an important advertising campaign (both to doctors and patients) and their ease of use is comparable to *Xalatan*. In particular, just like *Xalatan*, *Lumigan* and *Travatan* are both once-a-day eye drops.[31]

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Table 1 : Descriptive Statistics For Glaucoma Drugs Market (1995-1999)					
	Sales (in $ thousand)	DTCA (in $ thousand)	Promotion to Doctors (in $ thousand)	Number on Months since Drug Launch	Advertisement to Sales Ratio
Mean	15,961.552	36.481	226.914	154.76	0.0184
Standard Deviation	35,280.041	88.567	521.719	112.23	0.071
Max	30,3036.00	704.263	2,803.976	405.00	0.733
Min	3.00	0.00	0.00	3.00	0.00

TABLE 2 : Estimation Results			
β_1 (Dcosts)	0.15778** (0.05830)	γ_1 (Dayprice)	0.90522** (0.31903)
β_2 (Class_1)	0.98207 (0.72300)	γ_2 (Dtca)	-0.11105** (0.02763)
β_3 (Class_2)	-3.99400** (1.42761)	γ_3 (Form)	0.39417 (0.31001)
β_4 (Class_3)	-4.88625** (1.28372)	γ_4 (Howfreq)	0.11347** (0.04721)
β_5 (Class_4)	-0.32154** (0.08625)		
β_6 (Class_5)	-6.38211** (1.50321)		
β_7 (Class_6)	-3.84021** (0.93720)		
β_8 (Action)	2.67688* (1.35288)		
β_9 (Drug_Age)	1.11245** (0.34832)		
Bandwiths step 1 :	$H_{m1} = 0.52737$ $H_{m2} = 0.78003$ $H_{m3} = 0.40327$	Bandwiths step 2 :	$H_K = 0.41499$ $H_k = 0.45885$ $H_\phi = 0.60423$
Objective Function in step 2 : 1.73622E-6			

Numbers in parenthesis refer to standard deviations. Standard deviations have been estimated by a standard Bootstrap technique.
** (*) indicates parameters significantly different from 0 at a 5% (10%) level.
Optimal Windows have been approximated by Least Squares Cross Validations.

TABLE 3 : Estimated Prescription and Noncompliance Rates per Drug and Year

Drug Name	Non-compliance Rate (F_j)	$F_j - \overline{F}_t$	Drug Name	Non-compliance Rate (F_j)	$F_j - \overline{F}_t$
Year 1995					
ACETAZOLAMIDE 0000 USA	0.57257	-0.06202	MIOCHOL 1187 NSV	0.54515	-0.10632
ADSORBOCARPINE 1187 ALC	0.69796	0.10112	MIOCHOL SY/PK PLUS 1288 NSV	0.49770	-0.02099
AKARPINE 0576 AKO	0.65864	-0.01330	MIOCHOL SYSTEM PAK 1188 NSV	0.46299	-0.08850
AKBETA 0894 AKO	0.59697	-0.01074	MIOCHOL-E 0894 NSV	0.58722	-0.06752
BETAGAN 0386 ALL	0.58850	0.03267	MZM 1293 NSV	0.72726	0.08338
BETIMOL 0695 NSV	0.60145	0.00783	NEPTAZANE 1187 SZO	0.56804	0.06319
BETOPTIC 0985 ALC	0.68713	0.01039	OCUPRESS 0492 NSV	0.69925	0.00333
BETOPTIC S 0290 ALC	0.61889	0.01456	OCUSERT PILO-20 1187 ALZ	0.67718	0.08116
DARANIDE 0875 MSD	0.79058	0.04668	OCUSERT PILO-40 1187 ALZ	0.69596	0.08095
DIAMOX 0362 SZO	0.66137	0.03280	OPTIPRANOLOL 0790 BSP	0.58581	-0.02473
EPIFRIN 1269 ALL	0.52246	-0.02474	P1 E1 0466 ALC	0.50131	-0.09639
E-PILO 0566 NSV	0.53396	-0.10650	P2 E1 0466 ALC	0.47645	-0.13007
EPINAL 1187 ALC	0.65713	-0.02939	P4 E1 0466 ALC	0.53782	-0.09785
EPPY/N 1275 B.H	0.51950	-0.05560	P6 E1 1187 ALC	0.56338	-0.07037
GLAUCON 1187 ALC	0.55094	-0.08184	PHOSPHOLINE IODIDE 1187 WYE	0.56342	0.02470
GLAUCTABS 0894 AKO	0.73754	0.11881	PILAGAN 0688 ALL	0.59111	0.01474
HUMORSOL 1187 MSD	0.72026	0.03071	PILOCAR OPHTH 0466 NSV	0.55792	0.00390
IOPIDINE 0588 ALC	0.77915	0.05917	PILOPTIC 1084 OTP	0.56463	-0.01840
ISOPTO CARBACHOL 1187 ALC	0.52889	0.00911	PROPINE 0680 ALL	0.68684	0.08343
ISOPTO CARPINE 0566 ALC	0.65635	0.00491	TIMOPTIC 0978 MSD	0.51767	-0.02273
LEVOBUNOLOL HCL 0000 USA	0.75541	0.02333	TIMOPTIC-XE 0194 MSD	0.70295	0.09072
METHAZOLAMIDE 0000 USA	0.85122	0.12392	TRUSOPT 0595 MSD	0.61150	0.02728
Year 1996					
ACETAZOLAMIDE 0000 USA	0.61712	-0.03943	MIOCHOL SY/PK PLUS 1288 NSV	0.50286	-0.01384
ADSORBOCARPINE 1187 ALC	0.61460	0.01720	MIOCHOL SYSTEM PAK 1188 NSV	0.51694	-0.06658
AKARPINE 0576 AKO	0.54567	-0.00127	MIOCHOL-E 0894 NSV	0.50811	-0.06896
AKBETA 0894 AKO	0.58061	0.01681	MZM 1293 NSV	0.76332	0.08338
AKPRO 0296 AKO	0.70242	0.07226	NEPTAZANE 1187 SZO	0.66214	0.08851
ALPHAGAN 1096 ALL	0.63938	0.03038	OCUPRESS 0492 NSV	0.64231	0.01611
BETAGAN 0386 ALL	0.52078	0.03728	OCUSERT PILO-20 1187 ALZ	0.64167	0.06883
BETIMOL 0695 NSV	0.62154	-0.02296	OCUSERT PILO-40 1187 ALZ	0.78075	0.08362
BETOPTIC 0985 ALC	0.59037	0.04292	OPTIPRANOLOL 0790 BSP	0.60477	-0.03464
BETOPTIC S 0290 ALC	0.66361	0.04265	P1 E1 0466 ALC	0.47888	-0.12868
DARANIDE 0875 MSD	0.67762	0.07241	P2 E1 0466 ALC	0.47836	-0.14431
DIAMOX 0362 SZO	0.63495	0.04263	P4 E1 0466 ALC	0.44124	-0.09275
EPIFRIN 1269 ALL	0.68805	0.00682	P6 E1 1187 ALC	0.53918	-0.09269
E-PILO 0566 NSV	0.43656	-0.15781	PHOSPHOLINE IODIDE 1187 WYE	0.63526	0.04512
EPINAL 1187 ALC	0.57977	-0.05725	PILAGAN 0688 ALL	0.53100	0.02557
GLAUCON 1187 ALC	0.46122	-0.11708	PILOCAR OPHTH 0466 NSV	0.60870	0.02287
GLAUCTABS 0894 AKO	0.69487	0.07429	PILOPTIC 1084 OTP	0.59196	-0.02097
HUMORSOL 1187 MSD	0.71503	0.03577	PROPINE 0680 ALL	0.59134	0.02805
IOPIDINE 0588 ALC	0.59024	0.08977	TIMOLOL MALEATE 0000 USA	0.64645	0.03531
ISOPTO CARBACHOL 1187 ALC	0.55527	-0.01692	TIMOPTIC 0978 MSD	0.62733	0.01204

Drug Name	Non-compliance Rate (F_j)	$F_j - \overline{F}_t$	Drug Name	Non-compliance Rate (F_j)	$F_j - \overline{F}_t$
Year 1996					
ISOPTO CARPINE 0566 ALC	0.58414	-0.02033	TIMOPTIC-XE 0194 MSD	0.60870	0.59622
LEVOBUNOLOL HCL 0000 USA	0.63021	0.02483	TRUSOPT 0595 MSD	0.68490	0.66044
METHAZOLAMIDE 0000 USA	0.74696	0.05760	XALATAN 0896 PHU	0.37780	0.38212
MIOCHOL 1187 NSV	0.54051	-0.08260			
Year 1997					
ACETAZOLAMIDE 0000 USA	0.41103	-0.07556	MIOCHOL 1187 NSV	0.49581	-0.07812
ADSORBOCARPINE 1187 ALC	0.66797	0.02811	MIOCHOL SY/PK PLUS 1288 NSV	0.54438	-0.02315
AKARPINE 0576 AKO	0.65607	0.00451	MIOCHOL-E 0894 NSV	0.50128	-0.03073
AKBETA 0894 AKO	0.56994	0.01209	MZM 1293 NSV	0.73088	0.06862
AKPRO 0296 AKO	0.63469	0.03335	NEPTAZANE 1187 SZO	0.71980	0.07033
ALPHAGAN 1096 ALL	0.67364	0.03716	OCUPRESS 0492 NSV	0.56008	0.03130
BETAGAN 0386 ALL	0.60232	0.05001	OCUSERT PILO-20 1187 ALZ	0.70222	0.08709
BETIMOL 0695 NSV	0.58175	-0.00303	OCUSERT PILO-40 1187 ALZ	0.70273	0.06365
BETOPTIC 0985 ALC	0.70155	0.05789	OPTIPRANOLOL 0790 BSP	0.54969	0.00873
BETOPTIC S 0290 ALC	0.65464	0.04328	P1 E1 0466 ALC	0.39883	-0.10647
CARBACHOL 0000 USA	0.36974	-0.17917	P2 E1 0466 ALC	0.44332	-0.10420
DARANIDE 0875 MSD	0.73049	0.04425	P4 E1 0466 ALC	0.43510	-0.09946
DIAMOX 0362 SZO	0.62206	0.05168	P6 E1 1187 ALC	0.50264	-0.08719
EPIFRIN 1269 ALL	0.53493	-0.00354	PHOSPHOLINE IODIDE 1187	0.60018	0.03452
E-PILO 0566 NSV	0.47857	-0.09341	PILAGAN 0688 ALL	0.62906	0.02567
EPINAL 1187 ALC	0.52033	-0.01966	PILOCAR OPHTH 0466 NSV	0.55703	-0.00276
GLAUCON 1187 ALC	0.51314	-0.08121	PILOPTIC 1084 OTP	0.49130	-0.02144
GLAUCTABS 0894 AKO	0.61961	0.06109	PROPINE 0680 ALL	0.64189	0.08332
HUMORSOL 1187 MSD	0.65424	0.04004	TIMOLOL MALEATE 0000 USA	0.59393	0.01073
IOPIDINE 0588 ALC	0.68971	0.09915	TIMOPTIC 0978 MSD	0.57622	0.04607
ISOPTO CARBACHOL 1187 ALC	0.57482	-0.02103	TIMOPTIC-XE 0194 MSD	0.67590	0.05489
ISOPTO CARPINE 0566 ALC	0.47457	-0.00910	TRUSOPT 0595 MSD	0.65691	0.05582
LEVOBUNOLOL HCL 0000 USA	0.59580	0.00981	XALATAN 0896 PHU	0.38181	-0.21106
METHAZOLAMIDE 0000 USA	0.78250	0.07057			
Year 1998					
ACETAZOLAMIDE 0000 USA	0.45277	-0.05127	METHAZOLAMIDE 0000 USA	0.59508	0.08474
ADSORBOCARPINE 1187 ALC	0.47347	0.01222	MIOCHOL 1187 NSV	0.47584	-0.08364
AKARPINE 0576 AKO	0.51200	0.01975	MIOCHOL SY/PK PLUS 1288 NSV	0.42657	-0.04850
AKBETA 0894 AKO	0.57913	0.03222	MIOCHOL-E 0894 NSV	0.47415	-0.04963
ALPHAGAN 1096 ALL	0.62633	0.05320	MZM 1293 NSV	0.57854	0.10222
AZOPT 0498 ALC	0.65823	0.05864	NEPTAZANE 1187 SZO	0.75373	0.12115
BETAGAN 0386 ALL	0.51768	0.05111	OCUPRESS 0492 NSV	0.56400	0.05602
BETIMOL 0695 NSV	0.48200	-0.00080	OCUSERT PILO-20 1187 ALZ	0.66754	0.04991
BETOPTIC 0985 ALC	0.60478	0.00601	OCUSERT PILO-40 1187 ALZ	0.49532	0.05800
BETOPTIC S 0290 ALC	0.64996	0.04107	OPTIPRANOLOL 0790 BSP	0.45552	0.00798
CARBACHOL 0000 USA	0.32013	-0.16915	P1 E1 0466 ALC	0.48481	-0.08170
COSOPT 0498 MSD	0.37045	-0.09427	P2 E1 0466 ALC	0.43155	-0.09818
DARANIDE 0875 MSD	0.57495	0.04116	P4 E1 0466 ALC	0.42893	-0.07330
DIAMOX 0362 SZO	0.60213	0.02675	P6 E1 1187 ALC	0.53101	-0.05032

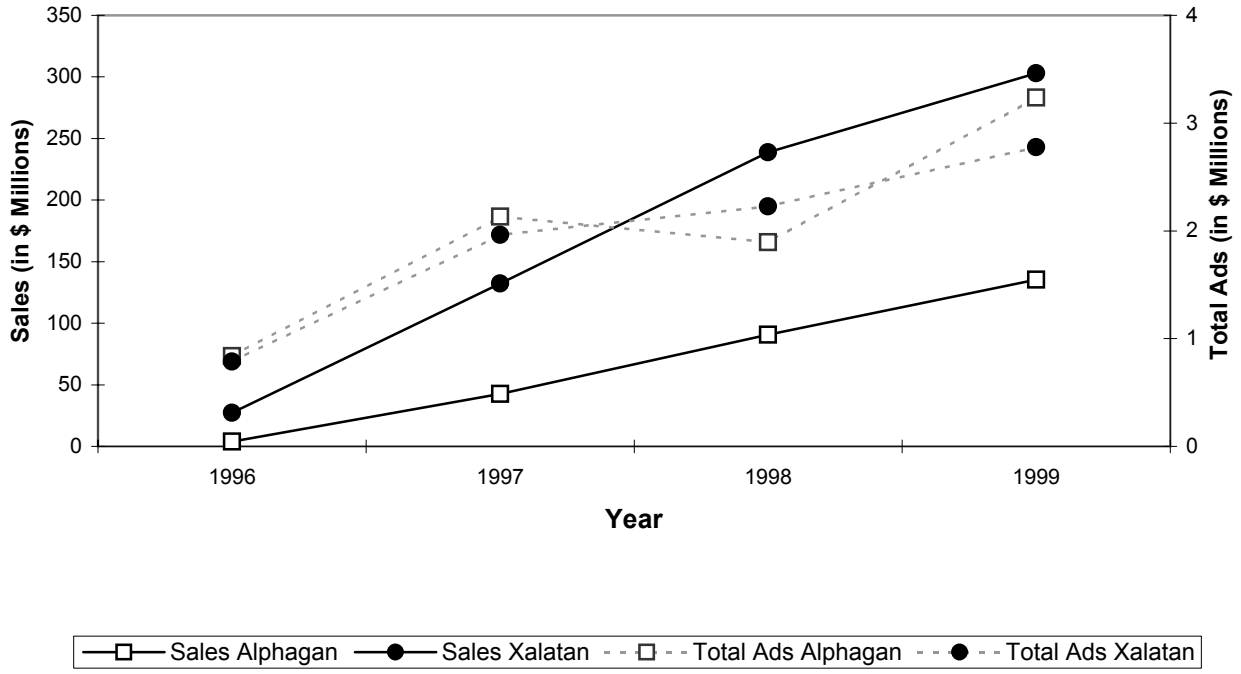
Drug Name	Non-compliance Rate (F_j))	$F_j - \overline{F}_t$	Drug Name	Non-compliance Rate (F_j)	$F_j - \overline{F}_t$
Year 1998					
EPIFRIN 1269 ALL	0.54357	-0.00690	PHOSPHOLINE IODIDE 1187 WYE	0.54975	0.02121
E-PILO 0566 NSV	0.44775	-0.05447	PILAGAN 0688 ALL	0.58706	0.03901
EPINAL 1187 ALC	0.46141	-0.01678	PILOCAR OPHTH 0466 NSV	0.59780	-0.00282
GLAUCON 1187 ALC	0.36642	-0.11026	PILOPTIC 1084 OTP	0.53848	0.03188
GLAUCTABS 0894 AKO	0.49378	0.08103	PROPINE 0680 ALL	0.58245	0.03418
HUMORSOL 1187 MSD	0.43393	-0.00712	TIMOLOL MALEATE 0000 USA	0.55276	0.02686
IOPIDINE 0588 ALC	0.54189	0.08727	TIMOPTIC 0978 MSD	0.61469	0.01322
ISOPTO CARBACHOL 1187 ALC	0.57857	-0.02221	TIMOPTIC-XE 0194 MSD	0.60681	0.06442
ISOPTO CARPINE 0566 ALC	0.46991	-0.00010	TRUSOPT 0595 MSD	0.57521	0.03905
LEVOBUNOLOL HCL 0000 USA	0.53654	-0.00893	XALATAN 0896 PHU	0.30934	-0.18357
Year 1999					
ACETAZOLAMIDE 0000 USA	0.48968	-0.07308	METHAZOLAMIDE 0000 USA	0.54706	0.05197
ADSORBOCARPINE 1187 ALC	0.52214	0.01095	MIOCHOL 1187 NSV	0.41087	-0.10192
AKARPINE 0576 AKO	0.52735	0.03327	MIOCHOL SY/PK PLUS 1288 NSV	0.41705	-0.02320
AKBETA 0894 AKO	0.51062	0.01998	MIOCHOL-E 0894 NSV	0.43054	-0.03195
ALPHAGAN 1096 ALL	0.60492	0.04055	MZM 1293 NSV	0.57306	0.05814
AZOPT 0498 ALC	0.60332	0.07485	NEPTAZANE 1187 SZO	0.55054	0.07674
BETAGAN 0386 ALL	0.53304	0.00998	OCUPRESS 0492 NSV	0.63062	0.05835
BETIMOL 0695 NSV	0.51323	-0.02500	OCUSERT PILO-20 1187 ALZ	0.57981	0.08149
BETOPTIC 0985 ALC	0.52846	0.02611	OCUSERT PILO-40 1187 ALZ	0.48887	0.09507
BETOPTIC S 0290 ALC	0.54402	0.02885	OPTIPRANOLOL 0790 BSP	0.46262	-0.00729
CARBACHOL 0000 USA	0.37303	-0.15294	P1 E1 0466 ALC	0.40836	-0.10381
COSOPT 0498 MSD	0.38690	-0.09909	P2 E1 0466 ALC	0.42706	-0.06775
DARANIDE 0875 MSD	0.61626	0.05175	P4 E1 0466 ALC	0.51588	-0.05754
DIAMOX 0362 SZO	0.59579	0.06588	P6 E1 1187 ALC	0.45817	-0.05949
EPIFRIN 1269 ALL	0.51246	-0.01465	PHOSPHOLINE IODIDE 1187 WYE	0.50265	0.04703
E-PILO 0566 NSV	0.43288	-0.07882	PILOCAR OPHTH 0466 NSV	0.43719	-0.04466
GLAUCON 1187 ALC	0.42522	-0.07068	PILOPTIC 1084 OTP	0.50884	-0.00557
GLAUCTABS 0894 AKO	0.54631	0.07988	PROPINE 0680 ALL	0.50620	0.08396
HUMORSOL 1187 MSD	0.49728	0.03302	TIMOLOL MALEATE 0000 USA	0.35565	-0.09735
IOPIDINE 0588 ALC	0.57951	0.07887	TIMOPTIC 0978 MSD	0.58149	0.04210
ISOPTO CARBACHOL 1187 ALC	0.49711	-0.01527	TIMOPTIC-XE 0194 MSD	0.51521	0.04347
ISOPTO CARPINE 0566 ALC	0.52460	0.04838	TRUSOPT 0595 MSD	0.63449	0.09324
LEVOBUNOLOL HCL 0000 USA	0.48639	-0.03975	XALATAN 0896 PHU	0.23169	-0.24664

Table 4 : Overall Noncompliance Rate with Glaucoma Prescription per Year

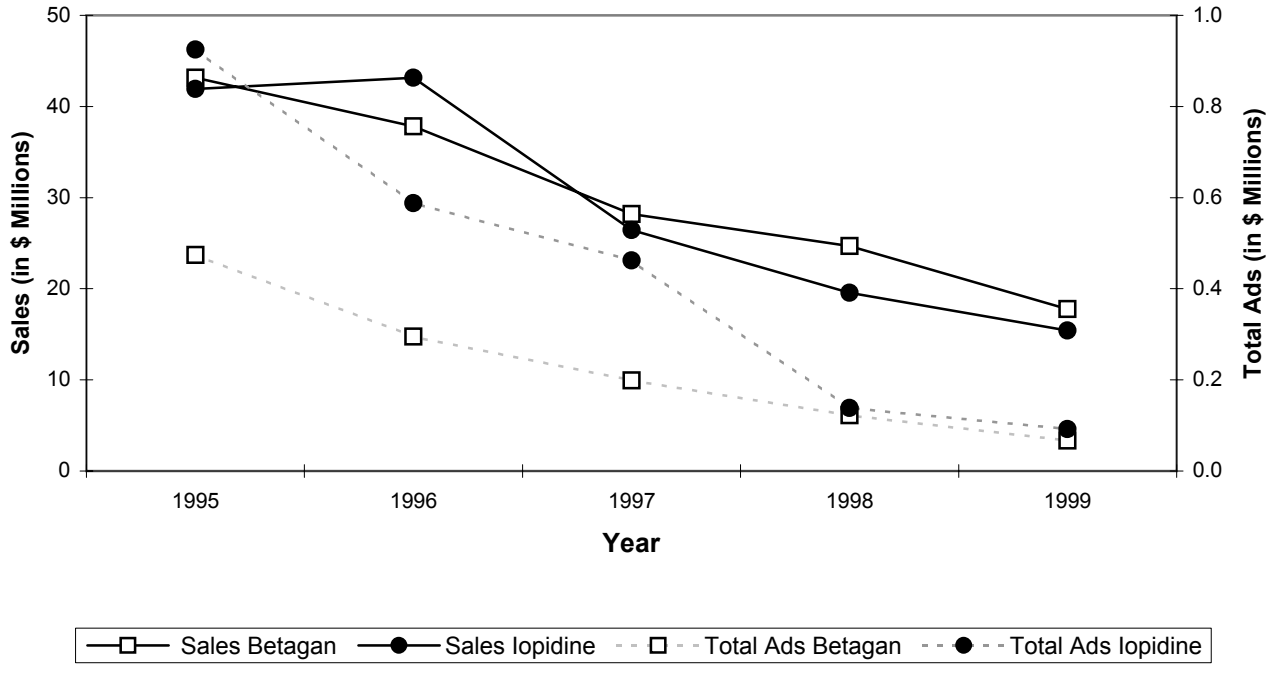
Year	1995	1996	1997	1998	1999
Noncompliance Rate	0.62071 (0.01264)	0.59069 (0.01573)	0.58177 (0.01183)	0.51496 (0.00973)	0.47643 (0.01034)

Numbers in parenthesis refer to standard deviations. Standard deviations have been estimated by a standard Bootstrap technique.

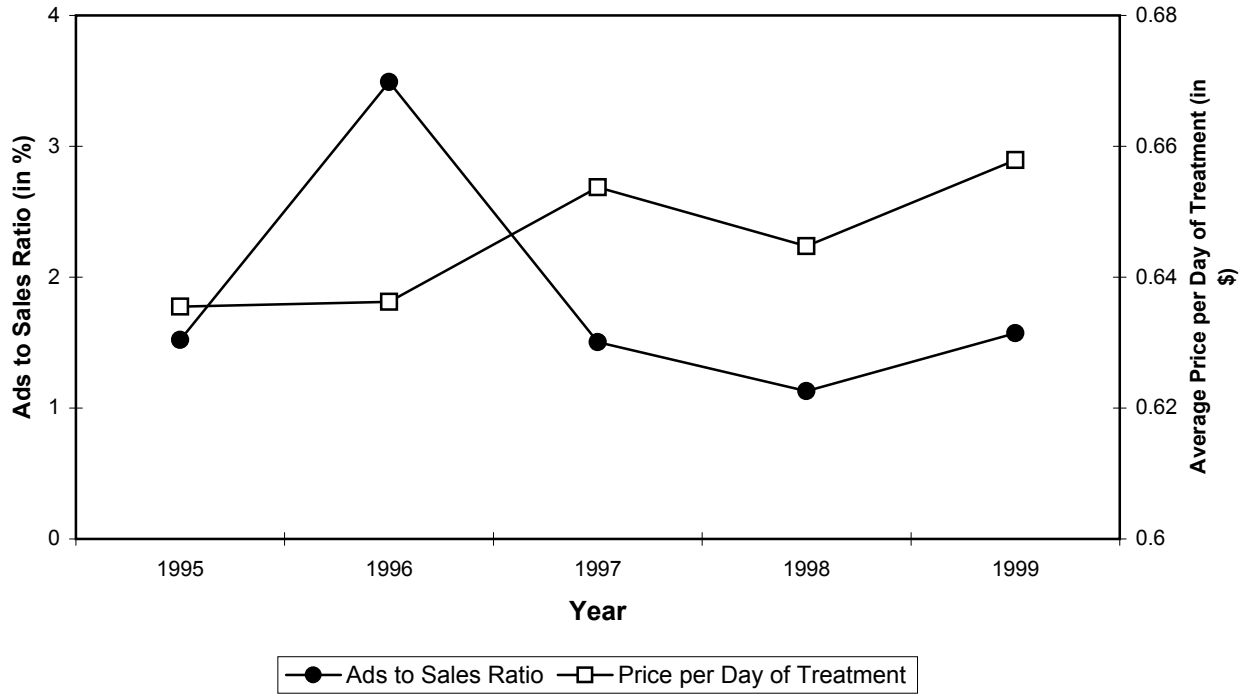
Graph 1 : Evolution of Sales and Advertisement Products with Sustained Promotion Effort



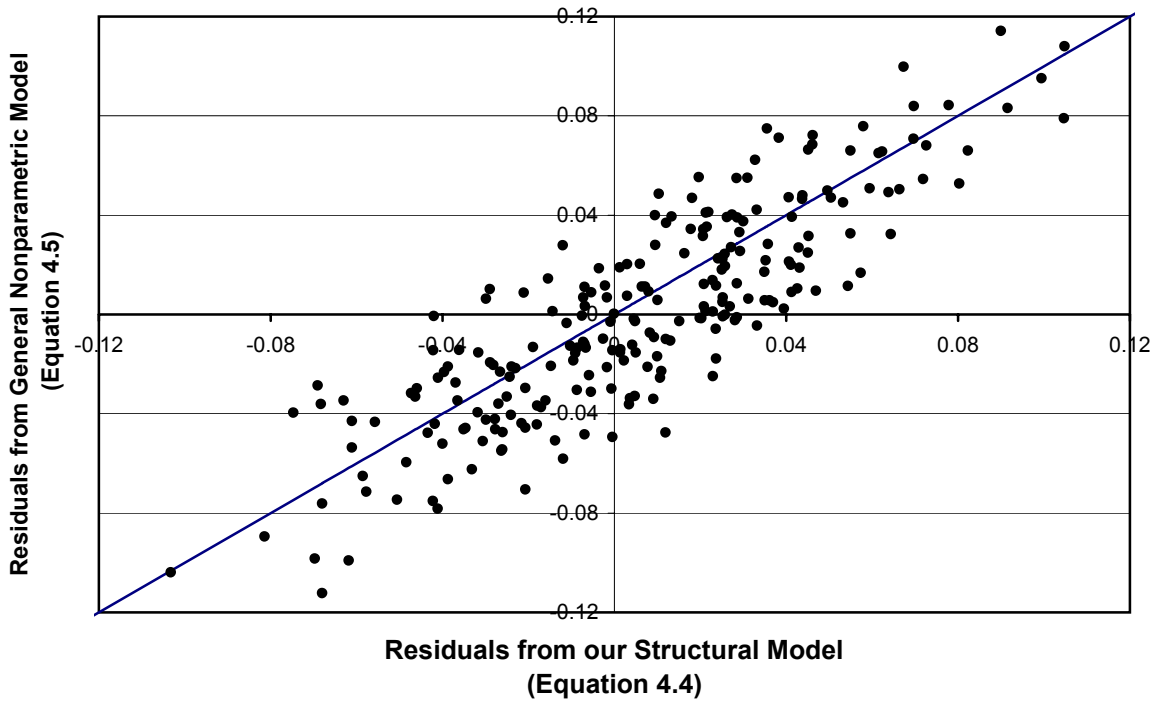
Graph 2 : Evolution of Sales and Advertisement Products with Decreasing Promotion Effort



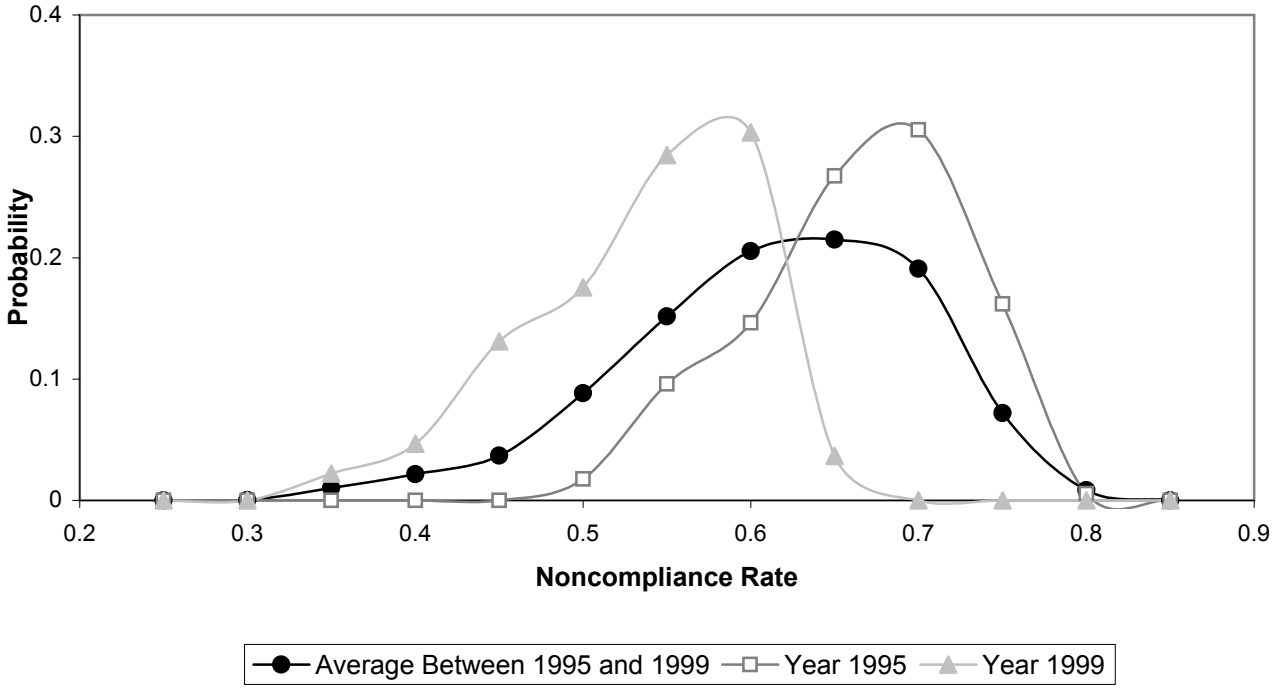
Graph 3 : Evolution of Prices and Ads to Sales Ratio



Graph 4 : Comparison of Estimated Residuals



Graph 5 : Probability Density Function of Noncompliance



Graph 6 : Relative Rate of Noncompliance and Advertisement toward Doctors

(Products with at least 10,000$ of Advertisement toward Doctors)