

# The Effect of Direct to Consumer Television Advertising on the Timing of Treatment <sup>1</sup>

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We examine how direct to consumer advertising (DTCA) affects the delay between diagnosis and pharmacological treatment for patients suffering from a common chronic disease. The primary data for this study consist of patients diagnosed with osteoarthritis (N=18,235) taken from a geographically diverse national research network of 72 primary care practices with 348 physicians in 27 states over the 1999 to 2002 time period. Brand specific advertising data was collected for local and network television at the monthly-level for the nearest media markets to the practices. Results of duration models of delay to treatment suggest advertising does affect the length of time that patients and physicians wait to initiate therapy. This evidence suggests these effects may be welfare enhancing, in that advertising tends to encourage more rapid adoption among patients who are good clinical candidates for the therapy, and leads to less rapid adoption among some patients who are poor clinical candidates.

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## 1. INTRODUCTION

In August of 1997 the Food and Drug Administration (FDA) relaxed the rules governing television advertising of prescription pharmaceutical products. Before that time, broadcast ads were permitted only to mention either the name of a drug, or a disease against which a drug was effective, but not both. After August of 1997, pharmaceuticals were allowed to mention both the disease and drug brand name (as long as a brief list of side effects was mentioned and a 1-800 number or World Wide Web site was provided with more detailed information). Spending for DTCA for prescription drugs went from \$985 million in 1996 to approximately \$4.2 billion for 2005.(Donohue, Cevalco, & Rosenthal, 2007) This has led to a great deal of debate in the medical profession and among health care insurers and managed care organizations, and an ongoing review of advertising rules by the FDA. However, very little is actually known about the effects of DTCA for the efficient allocation of prescription drugs.

We will examine how DTCA affects physician prescribing patterns and courses of care for patients suffering from a representative chronic condition, osteoarthritis (OA). This condition is of special significance, as one of the major products in this area, Merck's "Vioxx" Cyclooxygenase-2 (COX-2) inhibitor, was forced to withdraw from the market in October of 2004 due to side effects on patients with heart conditions. The side effects of Vioxx have caused considerable criticism of Merck's advertising strategy for Vioxx. (See, for example, editorials from New England Journal of Medicine (Mukherjee, Nissen, & Topol, 2001; Topol, 2004).)

The primary goal of this paper is to determine what effect local and national television advertising on behalf of the two main COX-2 inhibitors had on the treatment decisions that patients made in collaboration with their physicians. In particular, we will examine the impact of DTCA on the time patients wait after diagnosis with osteoarthritis and before initiating treatment with a COX-2 inhibitor. The paper will proceed by first reviewing the literature

on DTCA in Section 2. Section 3 will present a theoretical model of optimal delay to treatment. Section 4 will present details of the data and empirical model we implement. Empirical results are presented in Section 5, and Section 6 concludes with a discussion about future research.

## 2. BACKGROUND AND LITERATURE

### 2.1. Advertising for Cox-2 Inhibitors

Historically, pharmaceutical advertising was done largely through "detailing" - promotion directly from the manufacturer to the physician, either through visits by representatives, contacts by pharmacists, or through advertisements in professional journals. Since the mid-1980s, however, drug companies in the U.S. have increasingly turned their marketing strategies directly towards the consumer. This advertising largely takes place through television media and in newspapers. This change in advertising approach has its share of both critics and advocates.

The pharmaceutical industry in the U.S. is large - accounting for over \$132 billion in retail sales in 2000 alone (NIFHC, 2001). In 2000, Celebrex (celecoxib), the leading COX-2 inhibitor, had sales of approximately \$2.6 billion ("Pharmacia has setback for parecoxib," 2001) - while Vioxx (rofecoxib) sold over \$1.2 billion in the first half of 2000 (News, 2001). In support of Vioxx, Merck spent almost \$161 million in direct to consumer advertising in 2000 (Schumann, 2001) - which was the most spent on DTCA for any prescription pharmaceutical, making it the 39th most advertised brand of any kind in 2000 ("Top brands in network primetime - 2000," 2001). Over the same time periods, Pharmacia and Pfizer jointly spent \$78 million in DTCA supporting Celebrex.

We have chosen to examine the role of DTCA in the context of the market for COX-2 inhibitors. During the period spanned by our data (1999-2002), the two available COX-2 inhibitors were Vioxx and Celebrex. These drugs are appropriate subjects of study for a number of reasons. First, they have been heavily advertised. Second, they are significantly more expensive than alternative pharmacologic treatments for chronic pain. Third, data published

approximately half-way through our sample period indicated that these products may carry a significant risk of adverse cardiac side effects. Consequently, from mid-2001 many physicians began to question the wisdom in their use (Topol, 2004). Additionally, given the widespread suspicion of advertising for prescription drugs, clinicians and policy makers have questioned whether DTCA for Cox-2's might be causing fatalities. Our results will speak directly to this issue, in that if DTCA had a deleterious effect (in terms of matching high risk patients to COX-2 use) then we will get one sign pattern on interaction terms between advertising and patient comorbidities. If, however, DTCA is having a positive effect (by matching patients most suited for COX-2 inhibitors with that therapy) then we will get the opposite sign pattern on the advertising /comorbidity interaction terms.

For this study we have acquired data on television advertising for both Celebrex and Vioxx at the national (network) level, and for the top 75 local media markets in the U.S. This data is aggregated to the monthly level. Celebrex was approved by the FDA in December of 1998 and Vioxx was approved in May of 1999. Thus at least one of the products was available for use over the entire 1999-2002 time period of our analysis. Figure 1 presents the 2000 - 2002 trend for the spending on national television advertising for Vioxx and Celebrex taken from our advertising data base (described below in Section 3).

## 2.2 Literature on the Impact of DTCA

In economic terms, we would expect advertising for prescription drugs to have three possible effects. First, advertisement for a particular prescription product will provide information regarding the symptoms and regarding the fact that effective treatments are available about the medical condition that the drug treats. This may be labeled a "public good" effect, as the information conveyed by advertisements for one brand may aid sales of all brands selling competing products. Second, advertisement may provide important information regarding side effects, contra-indications and the like, that may prompt patients to consult

with their physician regarding a treatment modality. This component of the advertising may be labeled as a “matching” effect, since it would assist patients and physicians in matching treatment regimes. Third, advertising may simply lead patients to demand a product because of the aesthetic or persuasive characteristics of the ad, or the reputational impact of the ad, rather than the efficacy of the drug. This effect may be labeled as a “brand” effect. Since health care markets, including pharmaceuticals, are often characterized by moral hazard (as patients do not generally pay the full cost of the medications they consume), the welfare implications of this third effect are uncertain.

The studies on the impact of advertising in the prescription pharmaceutical market that have been published to date have yielded conflicting results. There is an arm of this literature that is generally supportive of advertising in this market, such as work by Telser and Leffler (Leffler, 1981; Telser, 1975). Keith finds that patient suggestions regarding pharmaceuticals (aspirin for cardiovascular disease) are important determinants in prescription decisions, and that advertising tends to lead to more appropriate care as a consequence (Keith, 1995). In this, Keith is advancing an argument made earlier by Masson and Rubin which posits several mechanisms that could lead to positive impacts from advertising on the efficiency of the pharmaceutical market (including that it might encourage people to associate symptoms with a disease and seek care, or that it might alert people to treatments they were previously unaware of, which would encourage them to seek care) (Masson & Rubin, 1985). For a survey of the more optimistic literature in this area, see Rubin and Kleit (Kleit, 1998; Rubin, 1991).

Not all economists, however, are so sanguine about the prospects of positive welfare effects from prescription pharmaceutical advertising. Hurwitz and Caves find that - on net - promotional activities by pharmaceutical firms tend to have the effect of preserving market share for existing products and slowing the penetration of new compounds in the market. (Hurwitz & Caves, 1988) King uses monthly sales data in the ulcer drug market to test the effect that

marketing efforts have on the industry (King, 1996). He finds that marketing by a firm causes the demand for the firm's own products to become more inelastic. Similarly, Rizzo, finds that direct to consumer advertising significantly reduced price elasticity in the market (Rizzo, 1999). A reduction in price elasticity would increase opportunities for supra-competitive pricing.

The post-1997 era has presented an opportunity for examination of the new policy regime for DTCA, and much of the literature has been focused on the FDA policy shift. As Zachry and Ginsburg, point out, however, there is a paucity of studies that examine the actual impacts of DTCA (Ginsburg, 2001).

In one of the few such studies, DuBois examines the impact of DTCA through the lens of variation in procedure and drug use (Dubois, 2003). He notes previous evidence that there is a wide geographic variety in the use of various medications, and suggests such variations imply underserved population. DuBois cited several sources that indicate that geographic variations in prescriptions have declined since the relaxation of DTCA regulations, perhaps implying that DTCA is conveying important medication information to previously underserved populations. Calfee, Winston, and Stempinski study whether the August 1997 policy changes at FDA increased the demand for the statin class of drugs, using monthly data from IMSHealth and Scott-Levin for a 58 month period. (Calfee, Winston, & Stempinski, 2002). The authors, however, found that advertising did not have a statistically significant impact on aggregate prescriptions filled. According to the authors, "it may only be possible to detect the effect of DTCA advertising on consumer demand with disaggregated data that link's a patient's cholesterol treatment history with the timing of DTCA expenditures."

## 2. THEORETICAL MODEL

Consider a patient who has been diagnosed with some chronic disease. Upon diagnosis, the patient faces a choice - either initiate or delay treatment. The benefits of treatment are potential improvements in symptoms of the underlying disease. The costs are monetary (the treatment generally must be purchased at some positive market price) and potentially psychic (people often resist taking medication), as well as the cost of any potential side effects. In order to decide whether to initiate treatment, the patient will evaluate her utility with treatment and her utility without treatment, and pick whichever path yields the highest expected value. If the instantaneous utility associated with therapy is not higher than the utility associated with no therapy, then the patient will choose to delay. Each period thereafter, the patient will undertake the same utility calculus, to determine whether to begin therapy or continue to wait.

This model is similar in form to real option theories that have been applied to financial instruments (see for example, Merton (Merton, 1973), and McDonald and Siegel (McDonald & Siegel, 1986)), to the timing of land development (see for example, Arnott and Lewis (Arnott & Lewis, 1979), Titman (Titman, 1985), Capozza and Li (Capozza & Li, 2002), and Capozza and Li (Capozza & Li, 1994)), and even to the timing of initial public offerings (see for example, Benninga, Hemantel, and Sarig (Benninga, Helmantel, & Sarig, 2005)). An interior optimum for the delay to an action can exist when there is a cost to undertaking some action and when the benefits from the action increase over time.

We will motivate our empirical research by exploring a simple model of the timing of treatment for a stylized chronic disease. Consider a patient who has been diagnosed with a condition which reduces her health. Further, assume that the impact on health is cumulative - delaying treatment implies that the health state continues to decay. The progression of the disease can be countered by pharmacological therapy. (Assume for the sake of simplicity that there is only one viable therapeutic option.) The value of that therapy is unknown, but the

patient has expectations about the treatment effect – expectations which can be affected by information, such as physician advice, testimonials from friends, or direct to consumer advertising. Thus, the patient's instantaneous health is:

$$h_t = \begin{cases} H - \delta t, & \text{if no treatment} \\ H - \delta t + \theta(a), & \text{with treatment} \end{cases}$$

where,  $H$  is the base level of health at disease onset,  $\delta$  is the impact of the disease on health during each time period,  $t$  represents time, and  $\theta(\cdot)$  is the expectations around the pharmacologic treatment effect, which can be affected by advertising,  $a$ . Further,  $\theta_a > 0$ , and  $\theta_{aa} < 0$ .

Utility is defined across consumption of some numeraire good,  $x_t$ , and health,  $h_t$ . Consumers may consume one unit of pharmaceutical treatment per period, at price  $P$ , or may continue to delay therapy. Once a person chooses to initiate therapy, she will continue to receive treatment until their death at time  $T$ . (Given the degenerative nature of the disease assumed in this model, once it becomes optimal to purchase treatment, it will necessarily be optimal in every time period after that.)

Consequently, each patient will maximize the present value of lifetime utility by selecting the optimal delay for treatment onset according to:

$$(1) \quad \max_d V = \int_0^d U(I, H - \delta t) e^{-rt} dt + \int_d^T U(I, H - \delta t + \theta(a)) e^{-rt} dt$$

where  $U(\cdot)$  is patient utility defined across income ( $I$ ) and health. The optimal delay to onset,  $d^*$  is defined by taking the first partial of (1) with respect to  $d$ , and setting it equal to zero:

$$(2) \quad \frac{\partial V}{\partial d} \equiv V_d = U(I, H - \delta d) - U(I - P, H - \delta d + \theta(a)) = 0$$

The usual convexity assumptions require that the second partial of (1) with respect to  $d$  be negative, or:

$$(3) \quad \frac{\partial^2 V}{\partial d^2} \equiv V_{dd} = -\delta U_h(I, H - \delta d) + \delta U_h(I - P, H - \delta d + \theta(a)) < 0$$

Given these assumptions, the optimal time to treatment exists,  $d^* = d^*(I, H, \delta, r, a)$ . Note, of course, that one condition for an interior solution is that at time=0 the value of utility without therapy must be greater than the value of utility with therapy. That is, if  $U(I-P, H-\delta t+\theta(a)) > U(I, H-\delta t) \forall t$ , then the patient will choose to initiate therapy immediately, and  $d^* = 0$ . Similarly, if  $U(I-P, H-\delta t+\theta(a)) < U(I, H-\delta t) \forall t$  then the patient will never initiate therapy.

To illustrate the solution, note that:

$$(4) \quad \frac{\partial U(I, H - \delta d)}{\partial d} = -\delta U_h|_{no Tx} > -\delta U_h|_{with Tx} = \frac{\partial U(I - P, H - \delta d + \theta(a))}{\partial d}$$

Since diminishing returns in health imply that the higher levels of health resulting from treatment reduces the marginal utility of health, and the complementarity between income and health will imply further reductions in  $U_h$  with the lower net income resulting from the requirement that some portion of any consumed therapy is paid out of pocket.

Comparative static analysis of the impact of advertising on the optimally selected delay of treatment is straightforward. Inserting the optimal delay time functional,  $d^*(\cdot)$  into (2), and differentiating with respect to the advertising parameter,  $a$ , and rearranging yields

$$\begin{aligned}
 & \frac{\partial V^2}{\partial d \partial a} \equiv \frac{\partial V^2}{\partial d^2} \cdot \frac{\partial d^*(.)}{\partial a} - U_h \theta_a \frac{\partial a}{\partial a} = 0 \\
 (5) \quad & \Rightarrow \frac{\partial d^*(.)}{\partial a} = \frac{U_h \theta_a}{\frac{\partial^2 V}{\partial d^2}} < 0.
 \end{aligned}$$

The sign of this effect depends upon the sign of  $\theta_a$ . If a patient believes himself to be a good candidate for the treatment, then greater exposure to advertising, or other positive information about the efficacy of the treatment, will reduce the optimally chosen delay to therapy initiation. However, if the advertising conveys information that leads the patient to believe that he is a poor candidate for the treatment – by emphasizing adverse event or highlighting a contraindication from which the patient suffers – then the expected treatment effect will be reduced which will lengthen the optimal delay. Thus, whether the information contained in the ad is “positive” or “negative” will depend upon patient expectations, other diagnoses, and preferences across the characteristics space of the therapy.

There are several implications from the theoretical model for the empirical estimation. First, patients select the optimal delay from diagnosis to therapy. Thus, we will calculate below this delay for each person in the data by estimating a parametric duration model. Second, since pharmacological treatments are better suited to some patients than others, the optimal delay will be a function of the patient’s other clinical diagnoses. Finally, the model implies that this optimal delay will be a function of income, health state, opportunity cost of treatment, and advertising exposure – measured at the point of therapy initiation. We will employ either direct measures or proxy measures for each of these factors.

### 3. EMPIRICAL MODEL

#### 3.1. Empirical Specification

Before specifying an empirical implementation, we note that the decision we will model is one which is joint between the patient and physician. Thus, our question will be “what impact does DTCA have on the likelihood that the physician/patient interaction will result in a prescription?” We will model the length of the spell between diagnosis and initiation of COX-2 inhibitor therapy. There is a long econometric literature on duration modeling, which presents us with various modeling options. Options range from non-parametric methods which impose few distributional restrictions to parametric methods where the distribution of the “time to failure” (to use the language of much of the literature) must be explicitly specified. All versions of the model are based upon estimating the hazard function, or the likelihood that a transition (in our case, between non-use of COX-2 inhibitors and use of COX-2 inhibitors) between states at time  $\Delta t$ , conditional on the spell (of non-use) having persisted to time  $t$ . One common specification for this hazard rate is to assume it is the product of some baseline population average hazard and an individual specific term (which may, or may not, depend upon covariates).

The problem with this proportional hazard model is that it requires the population average effect to be constant over time. A more flexible approach for duration models is presented in Kalbfleisch and Prentis (Kalbfleisch & Prentice, 1981) and by Ridder (Ridder, 1990), and known as Accelerated Failure Time (AFT) models. These models permit the baseline hazard to increase, decrease, or remain constant over time. Figure 2 below presents the empirical hazards for the delay to treatment data we explore. The instantaneous failure rates are not constant for our data, as the proportional hazard assumption is strongly rejected for nearly all covariates in our models. Consequently, we will estimate an AFT version of a duration model. In addition, the decreasing hazard we observe is consistent with a Weibull distribution – which is the distribution we will assume.

In addition to non-constancy in the baseline hazard, we have one other characteristic of the data to accommodate in our model choice. Patients may exit their delay spell in one of two ways: by choosing Vioxx as the treatment to initiate, or by choosing Celebrex. These exit strategies are not likely to be random, and may consequently affect the length of time that the delay spell itself lasts. Thus, we are faced with the possibility of underlying heterogeneity in the duration data, which arises due to unobservable characteristics of the patient. Competing risk versions of the AFT model can account for this data generating process. For applications of the competing risk models in health care, see: (Hamilton, 1997) (Cutler, 1995) and (Picone, Wilson, & Chou, 2003). These models are based on the generalized method of Heckman and Singer (Heckman & Singer, 1984), which model heterogeneous transition frailty as a multiplicative term with a gamma distribution.

Thus, we will model the delay to COX-2 initiation as an AFT hazard function with heterogeneous failures in a competing risk model where the instantaneous hazard follows a Weibull distribution, and the unobservable heterogeneity is modeled as a gamma distribution. The hazard rate is, then:

$$(6) \quad \lambda_i(t, x_i, \beta, \sigma_i, \alpha_j) = \frac{e^{x_i \beta} \alpha_j t^{\alpha_j - 1}}{1 + \sigma_i^2 e^{x_i \beta t^{\alpha_j}}}$$

where  $x_i$  are individual patient and practice characteristics,  $t$  is the duration of the individual delay spell, and  $\alpha_j$  capture the group-level heterogeneity in exit (to Vioxx or Celebrex). For some patients it will be optimal to delay longer than we observe them, and for some it will be optimal to delay indefinitely. Given that we only have data spanning the 1999 to 2002 time period, these two populations will be observationally equivalent - requiring that we take right-hand censoring into account. The model is estimated by maximum likelihood.

Finally, one remaining issue to be addressed is whether any selection effects are at work in the models. It seems plausible that advertising could bring more people to the physician office - which is what we find in prior research

(Bradford, Kleit, Neitert, Mcilwain, & Ornstein, 2006). While this may lead to more diagnoses of osteoarthritis, it is not immediately clear that this would bias our estimates on how long individuals wait before adopting therapy. (Even if the shift in patient population did lead to a change in delay, our estimates are reduced form in nature and thus agnostic with regard to what the actual mechanism of a DTCA effect might be.) However, to assess whether such selection issues are driving the results, we re-estimated, ex post, both versions of the model presented below and included proxy variables for the probability that the patient seeks a visit and the probability that receives a prescription during the month when therapy is initiated. These proxy variables are the percent of all of the physician's monthly office visits that are to osteoarthritis patients and the percent of all the physician's monthly visits to osteoarthritis patients that are associated with a Cox-2 inhibitor prescription, respectively. These variables represent naïve estimates of the probability of a visit and prescription for each patient during the month in which the patient actually began therapy. Since these are practice average measures, they will be exogenous to the individual patient's characteristics, but capture general influences at the practice level on the likelihood that the patient progresses to treatment. The estimated DTCA parameters and the parameters on the DTCA interaction effects were highly robust to inclusion or exclusion of these variables - thus suggesting that selection effects are not playing a large role in generating the results we present below. For the sake of simplicity, therefore, we do not include these models in Table 3 below; however, they are available upon request from the authors.

### 3.2. Data

For this study we have acquired data on television advertising for both Celebrex and Vioxx at the national (network) level, and for the top 75 local media markets in the U.S. This data is aggregated to the monthly level. Figure 1 presents the 2000 - 2002 trend for the dollars spent on national television advertising for Vioxx and Celebrex taken from our advertising data base.

As Figure 1 indicates, at the national level, monthly advertising exposure for the two brands is roughly comparable over the entire 2000-2002 time period. Interestingly, a very different picture emerges at the local level where television advertising spots for Celebrex are always greater than that of Vioxx for the entire period. The value of ads purchased at the local level is much lower in dollar terms than at the national level. Since patients do not generally distinguish between the payment source of a television ad (whether the local station or national network receives the revenue), we will include measures of the total spending on television advertising our in our empirical models. Consequently, we will have both cross-sectional and across time variation in DTCA exposure.

### 3.3. Clinical Data:

Practice Partner, Inc. (Seattle, WA) has marketed a commercial electronic medical record (i.e. Practice Partner) to physician practices for more than a decade. This product is intended to replace paper charts, and has been widely adopted - largely by practices that are community based - for clinical reasons and not for research purposes (nor because the practice has any affiliation with a research group or institution). The Medical University of South Carolina (MUSC) collaborates with the vendor to gain access to the record extracts of practices that were willing to have their data used for research purposes. This led to the development of a geographically diverse national research network of ambulatory, mostly primary care practices that use this single electronic medical record system (known as PPRNet). We will examine data on practices from 1999 through 2002. As of 2002 (the end of the study period), 72 practices in 25 states, with 348 physicians, were network members (see map below).

Each quarter, participating practices run a computer program, developed and maintained by the electronic medical record vendor, to extract patient activity of the previous quarter from the electronic medical record system. This data is taken from the patient's medical record - and so is similar to chart abstraction. The data capture all diagnoses, medications, patient characteristics

(weight, blood pressure, etc), lab tests ordered, and lab results. Currently, the entire research network database has information on 604,111 patients, including 3.6 million patient contacts, 3.8 million prescription records, 10.1 million vital signs, 12 million laboratory records, and 1.3 million preventive services records. We extract a sub-set of this data on 22,011 patients who had ever been diagnosed with osteoarthritis, and who physician had visits in the years 1999-2002. (The time period of analysis is dictated by the availability of advertising data, and not the availability of clinical data.)

A recent assessment of a sub-sample of about 500,000 patients from PPRNet practices indicates that the patient population is approximately 57% female, with a mean age (+/- std. dev.) of 43.1 +/- 21.1 years and has a racial breakdown of approximately 85% Caucasian, 8% African-American, and 4.3% Hispanic. PPRNet practices are located in urban, suburban, and rural areas. Based on a 4-tiered classification scheme for the Rural-Urban Commuting Area codes (Morrill, Cromartie, & Hart, 1999), PPRNet practices are highly representative of the distribution of the U.S. Population as shown in Table 5. Among the 114 practices active as of December 2005, there are 462 physicians, 51 physician assistants (PA), and 63 nurse practitioners (NP). Eighty-nine (78%) are family medicine practices; four of these are family medicine residency programs. Twenty (18%) are internal medicine practices and five (4%) are combined practices of primary care physicians. Thus, the PPRNet practices appear reasonably representative of other primary care practices in the U.S.

### 3.4. Variables

The dependant variables for the models are the length of time each patient waits before initiating therapy with one of the two COX-2 inhibitors after being diagnosed with osteoarthritis. This is calculated as the difference (in days) between the diagnosis date for osteoarthritis (recorded in the clinical data) and the prescribing date for the first instance of a Vioxx or Celebrex prescription.

However, COX-2 inhibitors are used for many complaints in addition to osteoarthritis; additionally, patients may use a COX-2 for occasional arthritis pain, even before a formal diagnosis is made. In these cases, the “delay” would be negative. For such negative delays, the duration between diagnosis and the prescription is set to one day. In addition, most of the patients with a diagnosis of osteoarthritis do not receive a prescription for Vioxx or Celebrex as long as they are observed in the data. Thus, the duration models we estimate will control for this right censoring.

The independent variables fall into several categories, such advertising information, patient individual clinical information, and market/practice characteristics.

We obtained national and local advertising information from Competitive Media Reporting, Inc. (CMR), which collects data on media advertising for all products, including pharmaceuticals, at the market (e.g., city) level. The data is specific to the brand name of the product. Consequently, it is possible to determine which products were advertised, which month they were advertised, how many times they were advertised, and how many dollars were spent on the ads. Patients and physician practices were assigned to the nearest media markets separately by two of the authors. When a practice was close to multiple media markets, they were assigned to the one which was nearest (by driving miles). In addition, we excluded all practices which are unusually far from the nearest media market (more than 100 straight-line miles), in order to avoid any bias from mis-matching of practice and local media market data.

We measure advertising exposure as the total (national and local) dollars spent on ads broadcast for each brand advertised. We add the separate measures for national advertising and local advertising into a single total monthly spending variable. While it is the case that local ads tend to be shown during different times of the day and during different programming, it is unclear that this difference matters empirically. We have estimated versions of our models with the national and local ad spending included separately, and the net results

are not meaningfully different. Additionally, the parameters on national advertising are essentially unchanged in magnitude and significance if we exclude local advertising; so, while there may be some concern that local advertising could be endogenous (a concern that is ameliorated by the use of individual data, typically from only one practice in each media market), the practical biases appear negligible.

Additionally, since the theoretical model suggests that patient characteristics at the time of the switch are the important factors in initiating therapy, and since we have not captured precisely when in the month therapy begins, we will measure potential advertising exposure as the dollars spent in the month preceding the initiation of therapy.

The patient data contains limited demographic and detailed clinical information. For patient demographic information, we include patient age and an indicator variable for whether the patient is female. We also include variables that capture whether the patient has ever been diagnosed with (or treated for) other relevant comorbidities. These include indicator variables for if the patient has ever been diagnosed with heart disease (coronary disease or hypertension), depression, diabetes, hyperlipidemia, or ever treated for gastrointestinal difficulties with proton-pump inhibitors, H2 blockers, or related products.

Imputations of additional descriptive variables can be made from secondary sources. We imputed the price of an intermediate length physician's office visit with an established patient from the American Chamber of Commerce Research Association's (ACCRA) Quarterly Price Reports (<http://www.coli.org/>). These quarterly reports contain average prices for 50 commodities (including physician office visits) for around 300 metropolitan areas. The linking between average physician visit price and the patient was accomplished by using the average price in the metropolitan area nearest the primary care practice site. Average county per capita income, the percent of the county population covered by Medicare, the percent of the county employed in the labor force, the percent of the county population that is Caucasian and African-American, the county

population, and the number of physicians per 10,000 population were also merged onto the data from the Area Resource File. Counties were identified as the county in which the practice is located. This information is available on an annual basis.

In addition to the impact of advertising, another source of information which may affect physician prescribing is medical journals. The late 1990s and early 2000s was a period when a significant amount of research was being conducted on the efficacy and side effects of COX-2 inhibitors. We will control for clinical knowledge in two ways. First, over the period of our study (1999 – 2002) there were over 900 publications in English-language medical journals about COX-2 inhibitors. Of those, 132 were specifically in the area of osteoarthritis. In order to control for the effect of this research on clinical providers, we created a data series which measures the number of publications in each month that had the keywords: rofecoxib, celecoxib, Vioxx, Celebrex, and osteoarthritis. We further refined the measure by dividing it into three series: the number of publications each month that focused on Celebrex, the number of publications each month that focused on Vioxx, and the number of publications each month that focused on both.

Second, in August of 2001, Mukherjee, Nissen, and Topol published an influential article in a major medical journal, where they reviewed data available from a major clinical trial which indicated serious statistically significant concerns about the cardiovascular risk associated with Vioxx (rofecoxib). To a lesser, and not statistically significant, extent the paper raised concerns about Celebrex (celecoxib) (Mukherjee et al., 2001). This was the first publication in a major outlet to raise issues about increased risk of myocardial infarction associated with COX-2 inhibitors in general, and Vioxx in particular. These concerns were later to be validated when Merck withdrew Vioxx from the market in October of 2004. We will include an indicator variable which equals 1 after August 2001, and 0 otherwise, to test whether the practicing clinical

community responded to this new information, even in the face of significant DTCA in favor of Vioxx and Celebrex.

### 3.5. Possible Impacts of Advertising

There are several variables which are central to understanding the impact of advertising on patient treatment delay decisions. The first set, obviously, are the measures of advertising spending on behalf of Vioxx and Celebrex. In general, one would expect the impact of Vioxx or Celebrex brand television DTCA to shorten the time that patients wait before initiating any COX-2 inhibitor treatment – in which case the parameter on the advertising measures will be negative and significant. It is possible that the only effect of advertising is class-level. That is, it may not matter which drug is advertised – any advertising for a COX-2 inhibitor may affect the demand for both approximately equally. To evaluate this, we will estimate two versions of the model. The first will include total dollars spent (as both a linear and squared term) in the previous month on both Celebrex and Vioxx as one variable. The second will include separate measures (again, both linear and squared terms) for Celebrex and Vioxx advertising. If television advertising has a pure class effect, then advertisement for Vioxx and Celebrex would have roughly equal effects when entered individually on the delay to therapy for Celebrex (Vioxx) in the separate models we run for delay to initiation for each brand individually.

That advertising has an effect, however, says little about the social welfare impact of DTCA. We can, however, learn something about the welfare effects of advertising by examining its effect on delay to treatment for patients that are likely to benefit from, or be poor candidates for, COX-2 inhibitor use. In particular, patients who have required treatment for gastrointestinal problems using proton-pump inhibitors, H2-blockers, or other similar treatments, are more likely to suffer gastric irritation from NSAIDs, and so are the good candidates for COX-2 inhibitors. In this case, we identified patients with gastrointestinal comorbidities as those who have ever had a prescription for ranitidine (e.g.,

Zantac), famotidine (e.g., Pepcid), cimetidine (e.g., Tagamet), omeprazole (e.g., Prilosec), esomeprazole (e.g., Nexium), lansoprazole (e.g., Previcid), rabeprazole (e.g., Aciphex), pantoprazole (e.g., Protonix), sulcralfate (e.g., Carafate), misoprostol (e.g., Cytotec), Helidac, Prevpac, or metoclopramide (e.g., Reglan). We interacted the advertising measures with the indicator variable for gastrointestinal problems. If advertising improves patient matching, then the parameters on those interactions will be negative and significant - indicating shorter delays to initiation.

In contrast, there are a number of conditions which make a person a poor candidate for use of a COX-2 inhibitor. These include a diagnosis of heart disease (hypertension and other coronary diseases). Individuals with these conditions should initiate therapy with a COX-2 inhibitor less frequently, which translates into longer delay times. However, this set of contraindications was not widely discussed in the clinical community until the publication of the MNT article in August of 2001. Consequently, we will test for the informational components of the DTCA for heart disease by including a three-way interaction term between the advertising measures, the heart disease indicator variable, and the indicator variable for whether the treatment began after August 2001. If the advertising is conveying clinically useful information, then the parameter on this interaction will be positive and significant (indicating that advertisement induces individuals with those comorbidities to wait longer to begin treatment after the contraindication for heart disease was published in the clinical literature).

#### 4.0 RESULTS

Table 1 presents the means and standard deviations of the variables used in our model, including the average delay to treatment (conditional on initiating therapy). More information on the raw delay measures is presented in Table 2, which shows the average delay time between diagnosis and the first long-term use of each COX-2 inhibitor, as well as the number of people who ultimately

adopt each. We find that patients who first adopt Celebrex tend to adopt more rapidly than those who first adopt Vioxx, with a delay of 163 days for the Celebrex users, compared to a delay of 199 days for the Vioxx users. Interestingly, for all of the attention paid to the introduction of COX-2 inhibitors, and the large expenditures on promotion on their behalf, 64% of the sample (11,741 patients) did not adopt one of the COX-2 inhibitors.

We estimate two versions of the hazard function presented in Equation (6). Model 1 contains the advertising measures (as combined national and local dollars spent) for Vioxx and Celebrex together, along with the set of independent variables listed above. Model 2 includes separate measures for total Vioxx and Celebrex monthly advertising, along with the other independent variables. Thus we will estimate the hazard rate in (6) above, where:

$$\underline{x}_i \underline{\beta} \equiv \beta_1 \cdot TV_i + \beta_2 \cdot TV_i^2 + \beta_3 \cdot GI_i \cdot TV_i + \beta_4 \cdot CVD_i \cdot TV_i \cdot TNM_i + \beta_5 \cdot CVD_i \cdot TV_i \cdot (1 - TNM_i) + \beta_6 \cdot GI_i + \beta_7 \cdot CVD_i + \underline{\beta} \cdot \underline{Z}_i + \varepsilon_i$$

and where  $TV$  is either the combined Vioxx and Celebrex national and local advertising dollars, or brand-specific national and local advertising dollars,  $GI$  is the indicator for a gastrointestinal comorbidity,  $CVD$  is the indicator for heart disease comorbidities (cardiovascular disease and hypertension),  $TMN$  is the indicator variable for the post-August 2001 period (which corresponds to the publication of the Topol, Nissan and Mukerjee article which first alerted the medical profession to the increased risk for heart attack associated with the use of some COX-2 inhibitors), and  $\underline{Z}$  represents the remainder of the explanatory variables discussed above. The vector  $\underline{Z}$  also includes individual practice fixed effects. Since in nearly all cases there is only one practice per media market, our practice level fixed effects correspond largely to media market fixed effects. Finally, we rely upon the fixed effects to correcting for clustering (repeated observations) at the physician practice level. The coefficient estimates are presented in Table 3.

In the first model, where the COX-2 television advertising dollars for both brands are summed together, we find that television advertising does have a

significant effect on the delay in treatment. Total television spending has a positive first derivative and negative second derivative – both significant at better than the 1% level. The parameter estimates in Table 3 are not direct measures of the net effect in terms of days of delay. Table 4 presents these net effects for the variables of primary interest, and converts the raw effects to days of delay induced by a one unit increase in the variable of interest. When calculated at the mean of the data, a \$100,000 increase in all COX-2 advertising during the month of diagnosis has the effect of lengthening the time patients wait to begin COX-2 therapy after being diagnosed with osteoarthritis by about 30 days (evaluated at the mean of the data). Note that this in addition to average delay periods of between 160 and 200 days delay (Table 2).

The second model in Table 3 breaks television advertising spending into separate measures for total monthly spending on behalf of Vioxx and total monthly spending on behalf of Celebrex. We find that the results are similar – in that spending on behalf of both brands tends to increase the delay initially, and then lead to a decrease – again, with statistical significance in excess of the 1% level. There is, however, a significant difference in terms of where on this quadratic function the two brands are placed.

In the case of Vioxx, the relationship between total spending and delay of therapy becomes negative at \$2.4 million per month. During the time period of our data, Merck spent approximately \$3.5 million per month on behalf of Vioxx; thus, the marginal dollar spent for Vioxx advertising lead to a reduction in the average delay before initiating any COX-2 therapy of approximately 14 days (Table 4)). In contrast, the relationship between spending for Celebrex and the delay to therapy adoption does not become negative until Pfizer would spend more than \$34.5 million per month. During 1999-2002, Pfizer spent \$6.5 million per month on average – and never more than \$13.8 million per month. This implies that the marginal dollar spent for Celebrex by Pfizer actually lengthens the delay in initiating any COX-2 treatment by approximately 41 days (Table 4). Thus, the positive effect of joint advertising spending on delay to adoption in the

first model is driven completely by Celebrex ads. This curious reverse association between Celebrex television advertising and the use of Celebrex is consistent with other recent research we have conducted which examined the association between television advertising and the rate of prescribing for Vioxx and Celebrex at the physician practice level (Bradford et al., 2006).<sup>2</sup>

Given that we find that television advertising on behalf of the COX-2 inhibitors has some effect on the delay to use, the next question to address is whether this effect is welfare enhancing or not. As discussed above, some patients are better candidates for COX-2 use, in that they have exhibited the sorts of gastrointestinal sensitivities for which Vioxx and Celebrex were designed. Other patients have hypertension and coronary disease comorbidities which make them poor candidates for using COX-2 inhibitors, since these conditions have been recognized as contraindications for COX-2 use since the publication of the TNM article. As discussed above, we estimate models with interactions between total television advertising (local and national) and the GI indicator variable, the heart disease and pre-TNM indicators, and the heart disease and post-TNM indicators.

Table 3 presents the relevant parameters. We find strong evidence for welfare-enhancing informational effects. The interaction between total COX-2 inhibitor advertising and the indicator variable for gastrointestinal sensitivity is negative and highly significant in both models. In terms of the magnitude of the effect, patients with GI comorbidities reduce their wait time to adopt COX-2 inhibitor treatment by between 2 and 2.4 days for every additional \$100,000 in monthly COX-2 inhibitor advertising (Table 4).

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<sup>2</sup> We also estimated versions of the duration of delay for Vioxx and Celebrex separately, including spending on both brands in each equation. In those models we found that the general effects demonstrated in the second column of Table 3 hold: Vioxx spending generally has a net effect of reducing the delay to therapy adoption for both Vioxx and Celebrex, while Celebrex has a net effect of lengthening the delay for both brands. Those results are available upon request.

The effect of advertising on patients with heart disease comorbidities (cardiovascular disease and hypertension) depends upon whether we observe the therapy being initiated prior to the publication of TNM or after. Prior to TNM, patients with cardiovascular comorbidities actually adopted COX-2 inhibitor therapy more rapidly when exposed to increased advertising. Given the information about the potential cardiac dangers associated with COX-2 inhibitor use (especially Vioxx), this is contrary to what would improve social welfare. However, prior to the publication of the TNM paper, this risk was poorly appreciated in the clinical community. However, once the TNM paper was published, we find a strong positive impact on delay to therapy initiation for patients with diagnosed heart disease when exposed to greater levels of COX-2 inhibitor advertising. This is the direction one would expect if the ads provide real information that assists patients and physicians to more optimally match therapies. In fact, the post-TNM interaction effect is larger than the pre-TNM interaction effect by approximately 6 – 8 days.<sup>3</sup>

Recall that we proposed relatively strong tests of whether DTCA for COX-2 inhibitors lead to welfare enhancing or reducing effects. If increasing DTCA is associated with reductions in the time patients who are good candidates for the therapy wait before initiating treatment *and* is associated with increases in the time patients who are poor candidates wait before initiating treatment, then the advertising must be providing useful information to the clinical matching process. In this case, DTCA has at least some welfare enhancing characteristics. We find exactly this pattern in our interactions between patients with previously treated GI difficulties (good candidates) and with previously diagnosed heart disease (poor candidates). In addition, the expected positive effect from the heart disease only shows up after the first important clinical publication to demonstrate that patients with heart disease are, in fact, at increased risk from

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<sup>3</sup> Note that while the absolute magnitudes of the pre- and post-TNM interaction effects are quite different between the two models, the net effects are quite similar.

COX-2 inhibitor use. Taken together, this evidence strongly supports the neoclassical view of advertising as information – and throws the strong criticism that pharmaceutical DTCA has recently received into question.

Finally, Table 3 presents parameters which test whether patients and clinicians respond to information from the clinical literature. As discussed above, we included measures of gross publication rates in the month preceding initiation of COX-2 use for papers which discuss COX-2 inhibitors (either generically, or focusing on a specific brand) in the context of care for patients with osteoarthritis. While the measures of clinical publication rates are uniformly statistically significant, there is little consistency in the parameter values (except for publications involving only Celebrex – which tended to always increase delay times). We take this as evidence that clinical publications are measurably important for the prescribing patterns of primary care clinician in community practice, we cannot characterize how the effect is felt. This is likely because some publications are favorable toward the effectiveness (and cost-effectiveness) of COX-2 inhibitors and some are pessimistic. However, our data do not currently characterize the tenor of the publication. More research on how clinical information and DTCA information interact appears warranted.

## 5. CONCLUSIONS

The increased use of television advertising by manufacturers of prescription pharmaceutical has been a controversial development over the last five to ten years in the United States. While the use of such advertisement has grown dramatically since the early 1990s, to date there have been few studies which have empirically examined the effect of these ads on patient care. The primary goal of this paper is to determine what effect local and national television advertising on behalf of the two main COX-2 inhibitors had on the treatment decisions that patients made in collaboration with their physicians. In particular, the treatment decision we studied is the time patients choose to wait before initiating treatment with either Vioxx or Celebrex. Using data on 18,235

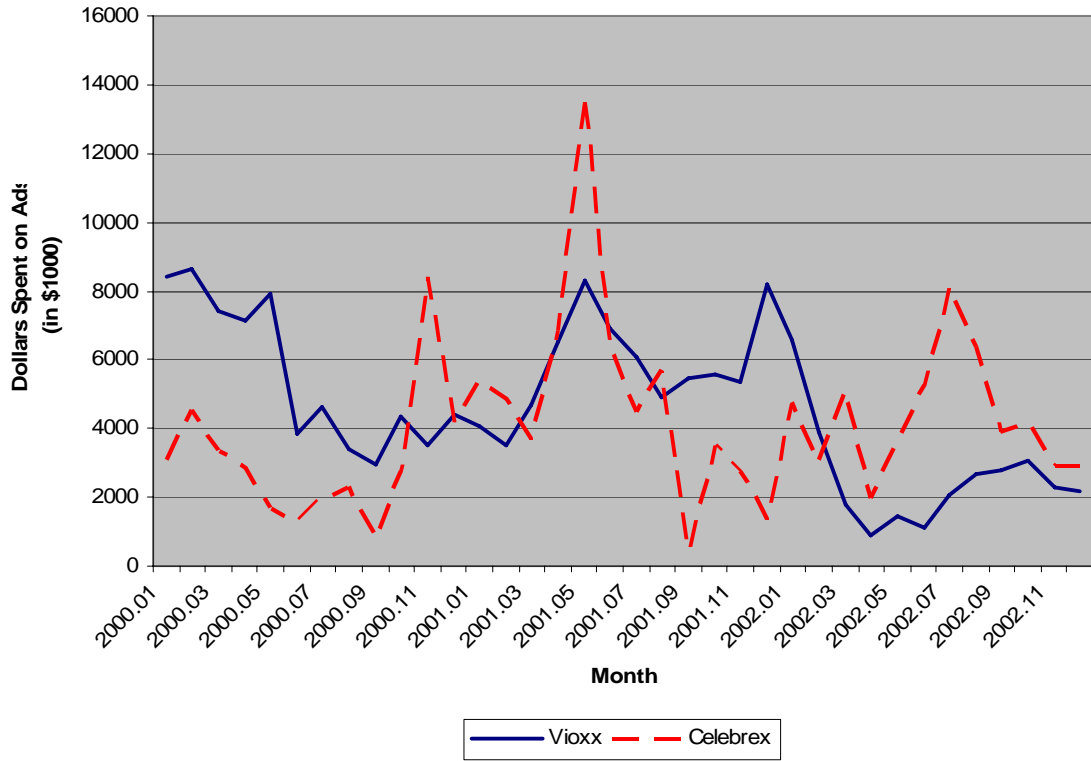
patients from a set of geographically dispersed community-based primary care practices, we have measured the determinants of the delay between diagnosis for osteoarthritis and onset of COX-2 inhibitor therapy. To accomplish these goals, we estimated a series of competing risk duration regressions, using an Accelerated Failure Time model.

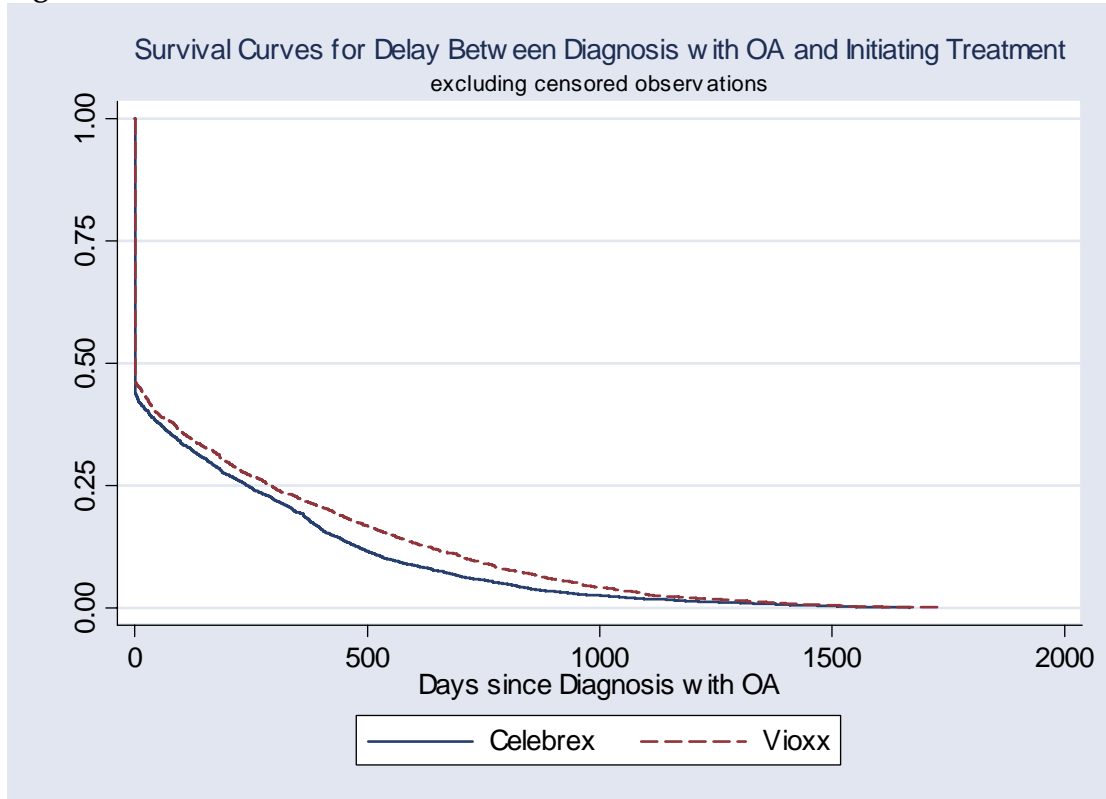
Despite the importance of our study, there are limitations. First, without monthly data for pharmaceutical detailing we were unable to account for the impact and interaction of detailing directly. Such physician-based marketing remains a larger component of pharmaceutical marketing efforts than DTCA advertising. It is possible that DTCA and detailing efforts were coordinated; if so, the DTCA effects measured here might have included some detailing effect. Personal communication with pharmaceutical representatives, however, suggested that since both Vioxx and Celebrex were such important products to the manufacturers the representatives discussed these products at every opportunity. This implies that there would be little correlation between the levels of detailing and local or national variation in advertising, which in turn would minimize the potential for bias in the results. Second, practices also generally have a supply of pharmaceutical samples on hand to give patients when they write a prescription. The availability of samples may influence which product is prescribed. Again, personal communication with physicians and pharmaceutical representatives suggested that most physicians would typically have had a stock of samples of both on hand, implying that the potential for omitted variables bias is limited. Additionally, the practice-level fixed effects included in the models capture any general tendency to favor one drug over another.

In summary, we find that increases in television advertising for Vioxx is associated with shorter wait times between diagnosis and use. On the other hand, Celebrex television advertising is associated with longer delays to COX-2 adoption. Finally, we also present evidence that the effect of DTCA may tend to improve economic efficiency, in that advertising tends to shorten the delays to adoption for patients who are better candidates for COX-2 use, and lengthens the

delay to adoption for patients who are worse candidates for the use of COX-2 inhibitors.

Figure 1: National Celebrex and Vioxx Advertising Dollars



**Figure 2:**

<b>Table 1: Data Description</b>		
<b>N = 18,235</b>		
<b>Variable</b>	<b>Mean</b>	<b>Standard Deviation</b>
Average delay between diagnosis with OA and first use of COX-2 inhibitor (for 6494 uncensored observations)	178.422	304.496
Total dollars in COX-2 advertising, month preceeding therapy (in \$100,000s)	99.767	40.053
Total dollars in COX-2 advertising squared, month preceeding therapy (in \$100,000s)	11557.730	6317.694
Total dollars in Vioxx advertising, month preceeding therapy (in \$100,000s)	35.009	17.176
Total dollars in Vioxx advertising squared, month preceeding therapy (in \$100,000s)	1520.648	1413.734
Total dollars in Celebrex advertising, month preceeding therapy (in \$100,000s)	64.758	31.272
Total dollars in Celebrex advertising squared, month preceeding therapy (in \$100,000s)	5171.554	3203.501
Patient has received gastrointestinal treatment	0.381	0.486
Patient has been diagnosed with heart disease	0.696	0.460
Interaction between gastrointestinal treatment and total COX-2 inhibitor advertising dollars	35.715	53.269
Interaction between heart disease and total COX-2 inhibitor advertising dollars during pre-TNMperiod	56.575	57.886
Interaction between heart disease and total COX-2 inhibitor advertising dollars during post-TNMperiod	53.578	58.177
Number of journal publications discussing COX-2 inhibitors in month preceeding therapy	0.344	0.996
Number of journal publications discussing Vioxx in month preceeding therapy	0.977	0.760
Number of journal publications discussing Celebrex in month preceeding therapy	2.223	1.175
Therapy initiated in 1999	0.071	0.257
Therapy initiated in 2000	0.512	0.500
Therapy initiated in 2001	0.061	0.240
Patient age at therpay initiation	65.531	13.864
Patient is female	0.678	0.467
Patient has been diagnosed with depression	0.181	0.385
Patient has been diagnosed with diabetes	0.179	0.383
Patient has been diagnosed with hyperlipidemia	0.354	0.478
County population	523489	1358298
Number of physicians per 1000 population in county	147.098	52.533
County per capita income	25845.46	5223.66
Number of Medicare enrollees in county	2.277	2.279
Percent of county residents who are employed	47.738	6.685
Percent of county population that is Caucasian	80.914	8.026
Percent of county population that is African-American	11.896	7.963
Average price for intermediate length physician visit	56.574	7.255

<b>Table 2: Delay Between OA Diagnosis and First COX-2 Use (Number of Patients)</b>		
	<i>Average delay for Patients who do not adopt Vioxx</i>	<i>Average delay for patients who adopt Vioxx</i>
<i>Average delay for Patients who do not adopt Celebrex</i>	776.9 (11741)	199.1 (2760)
<i>Average delay for patients who adopt Celebrex</i>	162.7 (3734)	-
(Total Patients)		(18,235)

<b>Table 3: Accelerated Failure Time Duration Models of Time Between Diagnosis and Treatment for OA Patients</b> <i>Coefficients of Model</i> <i>(T-Statistics in Parentheses)</i>		
Variable	Model 1 Combined Vioxx and Celebrex Total Advertising	Model 2 Separated Vioxx and Celebrex Total Advertising
Total dollars in COX-2 advertising, month preceeding therapy (in \$100,000s)	0.070 17.300	
Total dollars in COX-2 advertising squared, month preceeding therapy (in \$100,000s)	-0.0002 -11.91	
Total dollars in Vioxx advertising, month preceeding therapy (in \$100,000s)		0.0482 4.17
Total dollars in Vioxx advertising squared, month preceeding therapy (in \$100,000s)		-0.0010 -9.12
Total dollars in Celebrex advertising, month preceeding therapy (in \$100,000s)		0.0687 14.79
Total dollars in Celebrex advertising squared, month preceeding therapy (in \$100,000s)		-0.0001 -2.39
Patient has received gastrointestinal treatment	-0.0182 -0.16	0.0970 0.87
Patient has been diagnosed with heart disease	-0.3110 -2.51	-0.3271 -2.63
Interaction between gastrointestinal treatment and total COX-2 inhibitor advertising dollars	-0.0029 -2.17	-0.0037 -2.69
Interaction between heart disease and total COX-2 inhibitor advertising dollars during pre-TNMperiod	-0.0451 -22.87	-0.0044 -2.16
Interaction between heart disease and total COX-2 inhibitor advertising dollars during post-TNMeriod	0.0554 32.82	0.0132 7.03
Number of journal publications discussing COX-2 inhibitors in month preceeding therapy	0.1709 5.39	-0.1664 -4.79
Number of journal publications discussing Vioxx in month preceeding therapy	-0.0542 -1.77	0.1468 4.31
Number of journal publications discussing Celebrex in month preceeding therapy	1.2403 26.41	0.9796 22.66
Therapy initiated in 1999	1.9057 5.42	-0.3832 -1.03
Therapy initiated in 2000	2.5651 8.18	1.6536 5.44
Therapy initiated in 2001	-2.9144 -9.41	-2.4908 -8.10
Patient age at therpay initiation	0.0157 5.87	0.0163 6.23
Patient is female	-0.0118 -0.16	-0.0283 -0.39
Patient has been diagnosed with depression	-0.0762 -0.90	-0.0919 -1.11
Patient has been diagnosed with diabetes	0.1694 1.85	0.1244 1.38
Patient has been diagnosed with hyperlipidemia	0.1950 2.51	0.2036 2.66
County population (in 1000s)	-0.00003 -5.99	-0.00003 -6.15
Number of physicians per 1000 population in county	0.0021 1.18	0.0034 1.95
County per capita income	0.00003 1.52	0.00001 0.48
Number of Medicare enrollees in county	-0.1345 -1.39	-0.3372 -3.47
Percent of county residents who are employed	-0.0871 -5.30	-0.0838 -5.30
Percent of county population that is Caucasian	-0.0159 -1.30	-0.0108 -0.93
Percent of county population that is African-American	-0.2625 -4.44	-0.2604 -4.53
Average price for intermediate length physician visit	0.0686 6.35	0.0517 4.85
Constant	9.8063 4.40	12.7530 5.89
LR Test of Overall Significance	11957.97	13164.55
p-value	<0.0001	<0.0001

<b>Table 4: Accelerated Failure Time Duration Models of Time Between Diagnosis and Treatment for OA Patients</b>		
<i>Net Marginal Effects: Change in Days of Delay to Treatment for a One Unit Change in the Explanatory Variable</i>		
<b>Variable</b>	<b>Model 1 Combined Vioxx and Celebrex Total Advertising</b>	<b>Model 2 Separated Vioxx and Celebrex Total Advertising</b>
Total dollars in COX-2 advertising, month preceding therapy (in \$100,000s)	30.7	-
Total dollars in Vioxx advertising, month preceding therapy (in \$100,000s)	-	-13.7
Total dollars in Celebrex advertising, month preceding therapy (in \$100,000s)	-	40.8
Interaction between gastrointestinal treatment and total COX-2 inhibitor advertising dollars	-2.0	-2.4
Interaction between heart disease and total COX-2 inhibitor advertising dollars during pre-TNM period	-31.0	-2.8
Interaction between heart disease and total COX-2 inhibitor advertising dollars during post-TNM period	38.1	8.6

<b>Table 5: Rural/urban distribution of PPRNet practices and patients</b>			
	<b>PPRNet Practices</b>	<b>PPRNet Patients</b>	<b>U.S. Population</b>
Urban core areas	64%	66%	71%
Small town/rural area	17%	15%	10%
Suburban area	10%	12%	9%
Large Town area	9%	7%	10%



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