Effects of Direct-to-Consumer Advertising on Medication Choice: The Case of Antidepressants

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Although direct-to-consumer advertising (DTCA) has generated substantial controversy, little is known about its effects on consumer and physician behavior. In this article, the authors examine the impact of DTCA and physician detailing on the choice of antidepressant medication. The authors find that detailing has a much greater effect on medication choice in the antidepressant market than does DTCA.

Pharmaceutical promotion has traditionally been aimed at physicians, the "learned intermediaries" who are responsible for prescribing medications. From the mid-twentieth century, when federal regulations began requiring a doctor's prescription for many pharmaceuticals, to the 1990s, pharmaceutical firms relied primarily on "detailing" by pharmaceutical sales representatives and advertising in medical journals to promote prescription drugs. Pharmaceutical marketing strategies have become more diversified in recent years. In addition to detailing and medical journal advertising, firms now promote their products to medical professionals through educational events and directly to the public through mass media advertising. Spending on direct-to-consumer advertising (DTCA) increased from $266 million in 1994 to $2.6 billion in 2002, making this form of pharmaceutical marketing the object of substantial controversy (IMS Health 2003a). In 1997, a Food and Drug Administration (FDA) policy change made broadcast advertising of prescription drugs more feasible and may have contributed to the increase in the use of consumer-directed advertising by the pharmaceutical industry. One study of DTCA suggests that it increases demand for prescription drugs, accounting for roughly 12% of the increase in prescription drug sales between 1999 and 2000 (Rosenthal et al. 2003).

That DTCA increases prescription drug sales indicates little about the effect of advertising on consumer welfare or on competition in pharmaceutical markets. An important question is whether DTCA increases individual product market share, expands total class sales, or both. The weight of evidence to date suggests that DTCA has a significant impact on total class sales but little influence on individual product market share (Ling, Berndt, and Kyle 2003; Narayanan, Desiraju, and Chintagunta 2003; Rosenthal et al. 2003; Wosinska 2002). This result is not surprising, given the agency relationship between physicians and patients. Whereas consumer surveys show that DTCA motivates people to talk to their physicians about prescription drugs, the choice of whether and what to prescribe is ultimately up to the treating physician. Thus, the effect of DTCA is likely mediated by physician preferences, which may in turn be influenced by physician detailing or other forms of pharmaceutical promotion. However, much of the pharmaceutical advertising to consumers is brand specific, and consumer requests for specific drug brands may influence physicians' prescribing decisions. Studies suggest that patient requests have a substantial impact on physician behavior (Soumerai, McLaughlin, and Avorn 1989).

We add to the literature on the demand effects of DTCA by focusing on the antidepressant class. Prior research on antidepressants suggests that DTCA increases the number of people receiving drug treatment for depression, lending further support to the notion that DTCA increases class sales (Donohue et al. 2004). We examine the effect of DTCA on the choice of antidepressant observed at the individual patient level. There are three advantages to using individual-level data. First, we can account for differences in diagnosis that affect the choice of medication, which is important for antidepressant medications because they are used to treat a variety of conditions. Second, individual-level claims data contain more precise information on the out-of-pocket price paid by the consumer for prescription drugs. Third, the use of individual-level data enables us to treat aggregate advertising expenditures as exogenous to individual drug choice, a more tenuous assumption in studies that use aggregate-level data on prescription drug sales and marketing.

We organize this article as follows: In the next section, we review the empirical work on the effects of pharmaceutical promotion. We then provide background on the antidepressant class and depression. Subsequently, we lay out the conceptual framework for drug choice, explain the

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econometric methods used in the analyses, and describe the data sources for this study. Finally, we provide the results and discuss their implications.

Empirical Literature on Pharmaceutical Promotion

Physician Promotion

The bulk of pharmaceutical promotion has been aimed at physicians, and thus much of the empirical work on prescription drug promotion has focused on physician-directed marketing efforts, such as detailing. Many previous studies have found that promotion to physicians raised entry costs into a particular therapeutic class and decreased price competition by increasing perceived product differentiation (Bond and Lean 1997; Hurwitz and Caves 1988; Leffler 1981; Vernon 1981). Two studies of antihypertensive and antiulcer medications find that physician promotion reduces the absolute values of price elasticities of demand (King 2000; Rizzo 1999). Another study of antiulcer medications finds that product marketing to physicians increases sales for the advertised product (Berndt et al. 1997). Total therapeutic class marketing to physicians also has been found to increases class sales, though this effect generally declines with the number of products introduced.

Effects of DTCA

Consumer surveys suggest that prescription drug advertising motivates people to visit their physicians for a range of chronic conditions, some of which are newly diagnosed (FDA 1999a; Jim Lehrer 2000; Slaughter and Schumacher 2001; Weissman et al. 2003). A recent study of the impact of DTCA on aggregate sales of prescription drugs in five therapeutic classes with high DTCA expenditures finds that though DTCA is effective in generating increased sales of the therapeutic class as a whole, it has no impact on market share (Rosenthal et al. 2003). Own DTCA for H2-antagonist drugs (before their switch to over-the-counter status) has been found to have a smaller impact on market share than do physician-directed marketing efforts (Ling, Berndt, and Kyle 2003). Similarly, in a study of nonsedating antihistamines, Narayanan, Desiraju, and Chintagunta (2003) find a smaller positive effect of DTCA on market share in that therapeutic class than that of detailing. Most studies on detailing and DTCA use aggregate data on sales and marketing and thus do not take into account the effects of individual characteristics on the demand for prescription drugs. These studies also rely on aggregate measures of price and therefore do not account for the enormous variation in prices of prescription drugs across different types of consumers or for the presence of insurance (Frank 2001).

Using data from the National Ambulatory Medical Care Survey and Competitive Media Reporting data on DTCA spending, Iizuka and Jin (2004) find that DTCA has no effect on physicians' choice of medication. Similarly, using individual-level data on medication choice, Wosinska (2002) finds that advertising for cholesterol-lowering drugs has a small positive impact on drug choice but only for drugs with a preferred status on the health plan's formulary. In addition, Wosinka finds that detailing has a much more significant effect on drug choice than does DTCA. That study does not evaluate whether the effects of DTCA on drug choice are mediated by individual-level factors such as diagnosis, age, or gender. The effects of DTCA are likely to vary across therapeutic classes because of the differences in the diagnosis and treatment of the condition, the level of disability associated with the condition, and the differences in the features of the medications in that class. We examine the effects of pharmaceutical promotion in the antidepressant class.

Background on Depression and Antidepressant Treatment

The antidepressant class has been characterized by a high level of innovation and rivalry in recent years. Technological innovation and increased product variety, along with increased marketing expenditures for these medications, have resulted in dramatic growth in the sales of antidepressants (Berndt et al. 2002). Antidepressant medications ranked third in total sales and second in total number of prescriptions in the United States in 2002 (IMS Health 2003b).

Several features of depression and antidepressant medications make these agents good candidates for DTCA from the pharmaceutical firm's perspective. First, depression is a highly prevalent condition that results in substantial functional impairment (Ormel et al. 1994; Spitzer et al. 1995). Despite the availability of a wide range of effective pharmacological and psychosocial treatments, roughly half of the people with depression receive no treatment (Kessler et al. 2003). Thus, a large potential market exists for antidepressant medications. For various reasons, including greater awareness and acceptance of drug treatment, the proportion of people treated for depression who received medication increased from 37.3% to 74.5% between 1987 and 1998 (Olfson et al. 2002).

Second, newer antidepressants are good candidates for DTCA because they are relatively safe. Newer medications have been found to be as effective as older antidepressants, such as tricyclic antidepressants, and are considered more "user friendly" because they have milder side effect profiles and require less titration by clinicians (Anderson and Tomenson 1994, 1995). As a result of FDA regulations regarding risk disclosure in advertising, drugs with fewer or less serious side effects and contraindications may be more likely to be advertised.[1] Moreover, because there is substantial variety within the antidepressant class with respect to side effects, contraindications, and approved indications, pharmaceutical firms have an incentive to promote these newer products heavily (Berndt et al. 2002).

Third, advertising may have a substantial role in antidepressant use because of the complex nature of the conditions the medications are used to treat. Not only are these medications effective for many different conditions, but each condition also is highly heterogeneous. For example, depression encompasses several *Diagnostic and Statistical Manual IV* diagnoses and subtypes. Studies of major depres-

[1]The FDA (2000) requires advertisements that include both the drug name and the therapeutic indication to disclose all major side effects and contraindications in the advertisement.

sive disorders reveal heterogeneity with respect to biology, family history, pharmacologic response, genetics, and course of illness (Depression Guideline Panel 1993a). Although the effectiveness of antidepressants is similar at the population level, the effects of the medications vary widely at the individual patient level (Huskamp 2003; Kroenke et al. 2001). Because the effectiveness of any given medication for a particular patient is uncertain, advertising has great potential to influence medication choice.

Data and Methods

Conceptual Framework

In analyzing choices of antidepressants, we borrow from traditional models of demand for health care and prescription drugs (Newhouse 1993). We assume that the choice of antidepressant is influenced by three sets of factors: (1) characteristics of the person choosing the medications, (2) features of the medications, and (3) physician preferences.

Individual-Level Factors

We assume that medication choice will vary by demographic characteristics such as age and gender. In general, older age is correlated with greater use of medications and thus a greater risk of drug interactions. There is variation in the antidepressant class with respect to contraindications and the risk of drug interactions. For example, Prozac (fluoxetine) and Paxil (paroxetine) have a higher risk of some drug interactions than does Zoloft (sertraline) (Spina and Scordo 2002). Thus, we expect the probability of choosing Prozac and Paxil to be lower among older people. We also expect antidepressant choice to vary by clinical factors, including mental illness diagnosis. For example, we expect people with anxiety disorders to be more likely to fill prescriptions for Zoloft, Paxil, and Effexor (venlafaxine), because these products have been approved by the FDA for treating anxiety disorders.

Features of the Medications

Surveys show that roughly two-thirds of people who ask their physician for a prescription for a brand they have seen advertised have their request honored (FDA 1999a; Jim Lehrer 2000; Slaughter and Schumacher 2001). Thus, we hypothesize that antidepressants with higher DTCA spending are more likely to be chosen. We assume that various other features of the medications influence drug choice directly and/or through their interaction with marketing or individual-level characteristics, including price, length of time on the market, therapeutic indications, and side effects. Because our study population had insurance coverage, we use prescription drug copayment as the price faced by patients for the antidepressant medications. We expect a drug's choice probability to decrease with the copayment amount, ceteris paribus. In addition, we hypothesize that drugs that have been on the market longer are more likely to be chosen because they are more familiar to consumers and physicians. We assume that drugs with a greater number of FDA-approved therapeutic indications are more likely to be chosen. In addition, we expect drugs with a high incidence of side effects to have a lower probability of being chosen.

Physician Preferences

Because of their agency relationship with patients, physicians exercise a significant amount of influence over demand for medical care (McGuire 2001). We assume that detailing expenditures significantly affect physicians' prescribing behavior and hypothesize that a drug's choice probability will increase with spending on detailing to physicians. Because we had data on product-specific spending on detailing, we include this form of promotion as a characteristic of each drug.

Overview of Analytical Strategy

There has been substantial variation in the marketing strategies for antidepressants with respect to the use of DTCA. Our study attempts to connect the cross-sectional and temporal variation in marketing strategy to medication choice. The time period for this study, January 1997 through December 2000, encompasses the change in FDA policy that made broadcast advertising of prescription drugs more feasible. In August 1997, the FDA (1999b) clarified its policy on broadcast advertising of prescription drugs by issuing a draft guidance to the industry. Before 1997, it was difficult to air product-claim advertisements that mentioned the name of the product and the condition it was meant to treat because of rules on the provision of the approved product labeling information that contained information on risks and benefits. As a result, most television advertisements for prescription drugs were "reminder advertisements," which provided the name of the drug but not the condition it was meant to treat, or "help-seeking advertisements," which discussed a condition but did not mention any specific treatments. The policy change led to a shift in the composition of television advertisements from primarily reminder and help-seeking advertisements to mainly product-claim advertisements.

We focused on six antidepressants in three categories of medications: selective serotonin reuptake inhibitors (SSRIs), which include Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), and Celexa (citalopram); serotonin norepinephrine reuptake inhibitors (SNRIs), which include Effexor (venlafaxine); and serotonin antagonist and reuptake inhibitors (SARIs), which include Serzone (nefazodone). The FDA has approved all of the study drugs for the treatment of depression, and some of the drugs have received FDA approval to treat other mental disorders. None of the drugs' patents had expired before the end of the study period. We did not have access to promotional spending data on (and thus did not include) SSRIs that did not have an indication for depression (i.e., Luvox [fluvoxamine]); antidepressants that had generic equivalents at the time of the study (i.e., Desyrel [trazodone]); older-generation medications, such as tricyclic antidepressants; or products that represented a small share of the antidepressant market or products used primarily to treat conditions other than depression (i.e., Remeron [mirtazapine] and Wellbutrin [buproprion], respectively). None of these medications was advertised to consumers, and thus we do not include them in the study.

Econometric Method

Discrete choice analyses often use a conditional logit model (sometimes called a multinomial logit model). The condi-

tional logit model will yield only correct estimates of the effect of promotion on antidepressant choice if the six medications are viewed as equally substitutable (or not substitutable) for one another. This requirement is related to the independence of irrelevant alternatives (IIA) property of the conditional logit, which assumes that the ratio of probabilities of choosing any two alternatives is independent of the attributes of any other alternatives in the choice set (McFadden 1981). If, however, some of the drugs are viewed as closer substitutes for one another than other drugs in the antidepressant class (e.g., SSRIs), a modeling procedure that relaxes the IIA assumption is more appropriate. To evaluate the extent to which these six antidepressants had similar cross-elasticities of substitution, we modeled antidepressant choice using both a conditional logit analysis and a nested logit model.

For the nested logit analysis, we imposed a hierarchical structure on the drug choice process by grouping the medications (Figure 1). Providers would theoretically choose to prescribe a SSRI, a SNRI, or a SARI and then choose among drugs within each subcategory.[2] The nested logit model allows the variance to differ across groups while the IIA assumption is maintained within the groups. In the nested logit model, the probability that person i chooses drug t is equal to

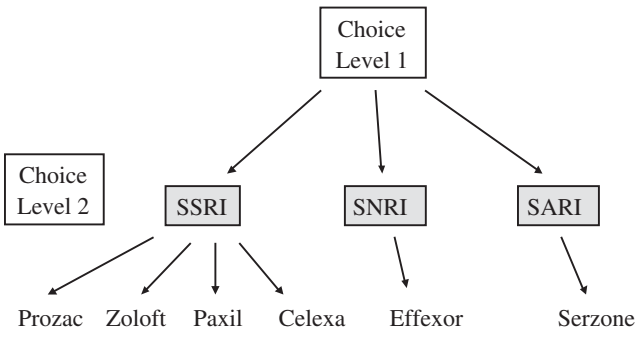
$$(1) \qquad P_{it}^{n} = \Pr(D_{it} = 1|X) = P_{t|c} \times P_c, \text{ and}$$

$$P_{it}^{n} = \frac{e^{X_{it}\alpha}}{\sum_{t=1}^{J_1} e^{X_{it}\alpha}} \times \frac{e^{\rho_c I_c}}{\sum_{c=1}^{C} e^{\rho_c I_c}},$$

where P_c is the probability of choosing drug class c, J_c is the number of drugs in class c, and $I_c = 1n\{\Sigma_{t=1}^{J_t} e^{X_{it}\alpha}\}$. The parameter ρ, called the inclusive value, is a measure of the cross-elasticity of substitution within the nests and is estimated in the nested logit model. McFadden (1981) shows that theoretically the value of ρ falls between 0 and 1. If ρ = 1, all six drugs have the same degree of substitutability for one another, and the conditional logit model is the appropriate specification. The conditional logit is a special case of the nested logit, in which ρ is restricted to equal 1. If $0 < \rho < 1$, the nested logit model is the preferred specification. We used a likelihood ratio test to determine the proper model specification (Hausman and McFadden 1984). The likelihood ratio is $-2(L_r - L_u)$, where L_r is the log-likelihood value of the conditional logit model, and L_u is the log-likelihood value of the nested logit.

[2]This grouping is relevant only for the SSRI nest, which has more than one choice.

Figure 1. Antidepressant Choice Decision Tree for Nested Logit Model



Data

The data set we used in the analysis consists of health insurance claims for the use of medical services and prescription drugs, marketing data on pharmaceutical promotion, and information on various characteristics of the study medications. The medical claims data were obtained from The Medstat Group's MarketScan database. MarketScan contains medical and pharmacy claims for beneficiaries of a group of large, self-insured companies. The data set for 1997 to 2000 contains enrollment information and claims records for 5,718,683 people from 30 large employers located throughout the United States. The data set also includes information on the benefit designs of the more than 100 indemnity and managed care plans used by these large employers.

We used product-specific monthly data on DTCA (including print, radio, and television advertising) and detailing to physicians. We obtained monthly data on DTCA spending from Competitive Media Reporting, which tracks local and national advertising campaigns. We obtained information on monthly spending on detailing to physicians from Scott-Levin Inc., an independent medical information company that conducts market research on the pharmaceutical industry. Scott-Levin imputes spending on detailing from a panel of more than 11,000 office and hospital physicians who track their encounters with pharmaceutical representatives. The panel is geographically representative, includes members of 31 clinical specialties, and accounts for approximately 2% of the U.S. physician population.

Study Sample

We identified all claims for the six study drugs from the prescription drug claims data file in the MarketScan database. Because drug choice is likely to be affected by previous experience with a particular medication, we limited the sample to the first prescription for each person observed in our data collection period. To prevent censoring of observations, we required patients to be enrolled in a MarketScan health plan for at least six months before the first prescription drug claim for an antidepressant. To identify new prescriptions, we imposed a six-month pretreatment period, during which there could be no prescriptions for the study drugs. Therefore, all prescription drug claims included in the analysis were filled between July 1, 1997, and December 31, 2000. People for whom health plan information was unavailable or who lacked coverage for prescription drugs were excluded from the analysis.

Explanatory Variables

Our main explanatory variables were monthly spending on DTCA and monthly detailing spending for each of the study medications. Previous studies of drug marketing have found

that though the effects of promotion last beyond the period during which marketing expenditures are incurred, the effects diminish over time (Gonul et al. 2001; Ling, Berndt, and Kyle 2003; Narayanan, Desiraju, and Chintagunta 2003). Therefore, we constructed cumulative measures of spending on advertising to consumers and physician promotion and treated both forms of promotion as depreciating assets. We used promotional spending for the month in which the prescription was filled plus the discounted sum of spending from the previous six months. We applied a monthly depreciation rate of 20% based on estimates from previous analyses of pharmaceutical promotion (Narayanan, Desiraju, and Chintagunta 2003). We used a natural logarithm transformation for the promotional variables to adjust for the skewed distribution of the data. To assess whether the effect of DTCA was moderated or mediated by the level of spending on physician detailing, we included an interaction term in the model: DTCA × detailing.

To examine whether the effect of pharmaceutical promotion on medication choice varied in response to the FDA's policy change regarding broadcast advertising, we created a binary variable coded as 1 if the prescription was filled after December 1997 (several months after the draft guidance was released) and interacted it with DTCA and detailing.

We took two alternative approaches to modeling the effects of drug characteristics on antidepressant choice. In the first approach, we explicitly analyzed the effects of drug characteristics such as the amount of time on the market and number of indications. This approach assumes that all of the variation in a drug's choice probability is attributable to the characteristics we identified in the analysis. As an indicator of the time a drug had been on the market, we used the number of months between the FDA approval date and the month in which the antidepressant prescription was filled. We obtained data on initial FDA approval dates from the FDA's (2003b) *Orange Book*. We obtained data on the number of indications from the *Physicians' Desk Reference* (Medical Economics Co. 2002) and the FDA's (2003a) Web site, which posts product labeling changes. No previous study has compared the incidence of side effects across all six of the study medications. Instead, we obtained information on the side effect profiles of the study drugs from the Depression in Primary Care Guidelines developed by the Agency for Health Care Policy and Research, the *Physicians' Desk Reference*, and other sources (Delgado and Gelenberg 2001; Depression Guideline Panel 1993b). Although newer antidepressants have similar incidences of many side effects, they appear to differ with respect to the risk of sedation or activation side effects and sexual dysfunction. The side effects variable was coded as 1 for drugs with a higher incidence of these side effects.

We constructed a measure of relative price for antidepressants based on the claims data by estimating out-of-pocket prices for the medications not chosen. We used the median copayment for each antidepressant for patients in the same health plan during the year in which the prescription was filled to approximate the price the patient would have paid for the medications not chosen.

Our second approach to modeling the effects of drug characteristics on drug choice uses fixed effects for the drugs. We included DTCA, detailing, and out-of-pocket price in the analysis, along with indicator variables for each drug except Prozac (fluoxetine), which we used as the reference drug. This approach requires fewer assumptions about the key attributes of the medications in the choice set and the relationship between the main explanatory variables and drug choice.

We also included individual-level variables such as age and gender in the analysis. We included age as a binary variable (less than or equal to 44 years [the mean age] or more than 44 years). We identified whether people had been diagnosed with major depression within six months (before or after) of the index prescription (based on the presence of an outpatient claim with a diagnosis of major depression current episode [International Classification of Diseases (ICD)-9 code 296.2] or major depression recurrent episode [ICD-9 code 296.3]). We also identified people who had been diagnosed with an anxiety disorder within six months (before or after) of the antidepressant prescription (based on the presence of an outpatient claim with a diagnosis of anxiety [ICD-9 code 300.0], phobic disorders [ICD-9 code 300.2], obsessive-compulsive disorder [ICD-9 code 300.3], or prolonged post-traumatic stress disorder [ICD-9 code 309.81]).

The effects of these two variable types (attributes of the medications and attributes of the people in the sample) were specified differently in both the conditional logit and the nested logit model. We included the individual-specific variables (e.g., gender), which did not vary across the medication choices, as interaction terms. Prozac × (individual-level parameter) served as the reference category for each individual-level characteristic. Therefore, the parameter estimates for the individual-specific variables correspond to the probabilities of a person choosing each medication relative to the probability of choosing Prozac. In contrast, the parameter estimates for the medication-specific variables (e.g., DTCA, detailing) reflect how these characteristics affect the overall choice probabilities.

We examined whether the effects of DTCA and detailing on medication choice varied across patients and products. Because of the heterogeneity among consumers who fill prescriptions for antidepressants and the differences in the marketing strategies of the drugs in our study, we tested whether the effects of DTCA varied across mental illness diagnoses. We interacted DTCA spending with the major depression and anxiety disorder indicator variables and added these parameters to the nested logit model. We also interacted the promotional spending variables with months after the approval date to assess whether the effects of DTCA and detailing varied on the basis of how long a particular drug had been on the market.

Results

Descriptive Results

We identified 25,716 subjects who filled at least one prescription for one of the six study medications between July 1997 and December 2000. Of those, 27.3% filled prescriptions for Zoloft (sertraline), 25.9% for Prozac (fluoxetine), 25.0% for Paxil (paroxetine), 10.2% for Celexa (citalopram), 7.1% for Effexor (venlafaxine), and 4.5% for Serzone (nefazodone). The newer antidepressants gained market share over the time period (Figure 2).

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