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An Analysis of the Diffusion of New Antidepressants: Variety, Quality, and Marketing Efforts

Ernst R. Berndt,[1]* Ashoke Bhattacharjya,[2] David N. Mishol,[3] Almudena Arcelus[3] and Thomas Lasky[2]

[1]*Massachusetts Institute of Technology, Cambridge, MA, USA*
[2]*Janssen Pharmaceutica, Titusville, NJ, USA*
[3]*Analysis Group/Economics, Boston, MA, USA*

Abstract

Background: We are not aware of any published research that quantifies and compares the importance of effectiveness and side effects for pharmaceutical sales, and that simultaneously incorporates the impacts of marketing efforts on the diffusion of new pharmaceutical agents in the U.S. The overall level and market share success of the various selective serotonin reuptake inhibitors ("SSRIs") relative to a representative older generation tricyclic (such as Amitriptyline) provides a useful focus for studying such issues.
Aims of Study: To model jointly the marketing and sales relationships of the SSRIs in the U.S., to quantify the extent to which marketing efforts are responsive to the availability of new scientific information accompanying changes in quality and increases in product variety, and in turn to assess how the new FDA indication approvals and the enhanced marketing initiatives involving product quality and variety affect sales of the SSRI and other novel antidepressants.
Methods: Quarterly US sales, price, quantity and marketing data 1988Q1-1997Q4 are taken from IMS Health for the eight new antidepressants introduced into the US during this time period. Measures of physician-perceived quality attributes of the antidepressants are drawn from Market Measures, Inc., a medical survey research firm. These data are used to construct measures of product quality (effectiveness and side effect profile), and attribute variety across all antidepressants. Multivariate regression methods are used in estimating parameters of a marketing efforts model, a sales demand model encompassing the aggregate of the newer antidepressants, and a product share model. Simulation methods are employed to quantify elasticities.
Results: Since 1988, and relative to amitriptyline, there has been only a rather modest increase in the perceived average effectiveness of the SSRIs and related products, but the side effect profiles have improved substantially. Variety measures for effectiveness show greater increases over time than do those for side effects. Marketing efforts respond to science-based events, such as new FDA indication approvals, and to effectiveness and side-effect quality improvements. Total antidepressant sales are positively and significantly related to price reductions, increased marketing efforts, and the level and variety of side effect profiles involving antidepressants. The level and variety of effectiveness does not significantly affect total antidepressant sales. Order of entry effects are important in affecting product market shares, while marketing efforts and relative quality attributes (particularly a more favorable side effect profile) have positive and significant impacts on relative market shares.
Implications for Health Care Provision and Use: Since patient response to SSRIs and related products is idiosyncratic, greater product variety facilitates better matching of antidepressant with patient. Much of the growth of the SSRIs and related antidepressants since 1988 can be attributed to increased product attribute variety, to improved changes in side effect quality relative to that of the tricyclics, and to the marketing of those improvements.
Implications for Health Policies: Marketing efforts play an important role in diffusing product information. Marketing efforts increase considerably following FDA approval for indications other than depression, and also increase with the average effectiveness and the average side effect rating of the products.
Implications for Further Research: Whether the relatively minor role that perceived effectiveness has in affecting sales relative to perceived side effect profile is unique to antidepressants, or generalizes to other therapeutic classes, merits further examination.

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*__Correspondence to:__ Ernst R. Berndt, Alfred P. Sloan School of Management, Massachusetts Institute of Technology, 50 Memorial Drive, Cambridge, MA 02142, USA.
Tel.: + 1-617-253 2665
Fax: + 1-617-258 6855
E-mail: eberndt@mit.edu
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Background

Economic theory suggests that, *ceteris paribus*, consumers benefit from increased product variety.[1,2] In the context of monopolistic competition, there exists a theoretical literature on factors affecting the optimal amount of variety.[3] Empirical assessments of the effects of variety on overall sales of related products are relatively rare, although the empirical literature on modeling sales of differentiated products is growing.[4-8]

One set of products for which variety could be particularly important involves medications to treat illnesses and disorders. On *a priori* grounds, one would expect that since patient response to many medications is idiosyncratic and uncertain, increases in the variety of medications for treating a particular disorder are likely to be valued by society, for as variety increases more patients are more likely to be matched with

effective medicines.[9] Medications are one example of what Philip Nelson has christened "experience" goods - goods whose quality and effectiveness cannot be assessed definitively prior to consumption, but can only be determined from consumers' own experiences.[10,11] By contrast, for "search" goods, quality and effectiveness can be largely determined by inspection prior to consumption.

There are at least two important implications that follow from the fact that medications are experience goods. First, as has been argued by Nelson, in general one should expect marketing/sales intensity ratios to be higher for experience than search goods (particularly for non-durable experience goods). This follows in large part since advertising and marketing are envisaged as conveying information about the existence and/or quality of the good.[12] Thus one should not be surprised that marketing/sales ratios are relatively high for medications, both prescription and over-the-counter. Moreover, since advertising provides greater benefits for higher quality experience products in establishing reputation and stimulating repeat purchasing, advertising/sales ratios should be greater for higher quality experience goods.[13-17] An implication of this is that once new qualities of an experience good are discovered or established (e.g., the Food and Drug Administration grants approval to a manufacturer to market an existing medication for a new illness or condition), one should expect an increase in marketing efforts, *ceteris paribus*.[18]

Second, as emphasized by Schmalensee,[7] for experience goods, order of entry effects are important, and while these effects inherently have nothing to do with marketing, in practice they may interact. In Schmalensee's framework, when initially skeptical consumers become convinced that the first brand in any product class performs satisfactorily, that brand becomes the standard against which subsequent entrants are rationally judged, and it therefore becomes more difficult for later entrants to persuade consumers to invest in learning about their qualities than it was for the first brand. To induce consumers to make a trial with their brand product, later entrants may therefore need to advertise more intensively and/or lower the price of their products.[19-26]

Aims of the Study

In this paper we examine empirically the impacts of product attributes, variety in these attributes, marketing efforts, order of entry and pricing on the diffusion of a new class of pharmaceuticals. The therapeutic class we examine is that for the treatment of major depressive disorder. The time frame we assess is 1989-97, the decade following introduction of Fluoxetine*****, the first of a new generation of selective serotonin reuptake inhibitors. As measures of quality attributes, we utilize data from a medical survey research firm on physicians' changing perceptions of the effectiveness, side effects and other quality attributes of antidepressants. Our goal is to quantify the impacts of these various factors on the overall market for antidepressants, as well as on sales of individual molecules.

This research focus is important for a number of reasons. First, although effectiveness and side effect profiles of pharmaceuticals are known to affect product success in the marketplace, we are aware of no published research that quantifies and ranks the importance of such attributes in affecting sales, or provides estimates of the extent to which there are trade-offs among them. Here we provide preliminary empirical evidence on the relative importance of these various attributes in affecting sales. Second, controversy exists concerning the role of marketing efforts, and the extent to which marketing provides information and/or seeks to influence physician prescribing behavior.[17, 18, 27, 28] Here we jointly model marketing and sales relationships, and quantify the extent to which marketing efforts are responsive to the availability of new scientific information (e.g., FDA approval of new indications) accompanying increases in product variety, and in turn how these new indications and the enhanced marketing initiatives involving product variety affect sales

Depression and its Treatment: an Overview

Acute depression or major depressive disorder (MDD) is a common illness. Estimates indicate that adult lifetime prevalence is somewhere between ten to twenty percent.[29-31] Moreover, MDD is often a chronic illness characterized by high probabilities of relapse and recurrence.[29, 32-37] There is considerable evidence that in spite of the availability of a number of safe and effective treatments, MDD is underdiagnosed and often is inappropriately treated.[38-42]

Most forms of depression are treatable, although response tends to be somewhat idiosyncratic and unpredictable. Results from clinical trials indicate response rates from those completing first-line pharmacotherapy for acute-phase depression in the range of 50-60 percent, but given the increasing variety of antidepressants now available, non-responders to first-line therapy often respond to other antidepressants.[43-45] It is estimated that with the current range of available therapies, treatment success rates following multiple-line therapy are about 65-80 percent, implying that about 20-35 percent of patients may still be resistant to antidepressant pharmacotherapy.[44-46]

Currently the vast majority of antidepressants block reuptake of the neurotransmitters norepinephrine and/or serotonin, and fall into four principal classes. The first generations of antidepressants were the monoamine oxidase inhibitors (MAOIs), which were followed in the 1950s and 1960s by tricyclics and tetracyclics (TCAs). The selective serotonin reuptake inhibitors (SSRIs) were introduced into the US in 1988, and in recent years they have become by far the most widely prescribed class of antidepressants.[47, 48] Recently a number of other novel antidepressants have been introduced, including serotonin and norepinephrine reuptake inhibitors (SNRIs) and other agents.

Although the clinical and primary care trial evidence to date suggests that generally there is no statistically significant difference in average treatment response rates among the TCAs,

***** The brand name of Fluoxetine is Prozac.

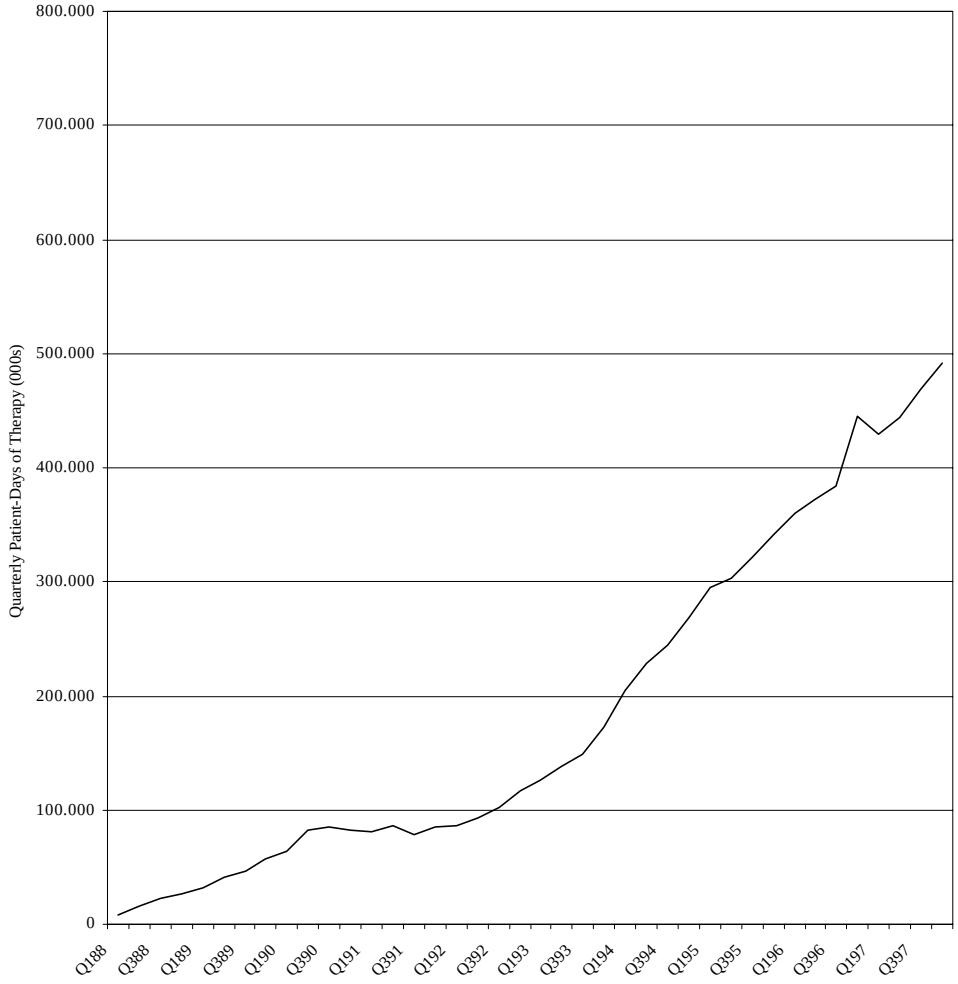


Figure 1. Industry Patients-Days of Therapy for SSRIs and Relative Products Q1 1988 - Q4 1997

SSRIs and SNRIs, there is considerable diversity among them in terms of side effect profiles and adverse interactions with other drugs.[47, 49-51] The SSRIs typically require less titration than the TCAs and SNRIs, and thus offer simplicity in dosing, a feature that is particularly important to non-psychiatrist physicians.[50] Since patient tolerability and compliance impact medical outcomes, the variability in side effect and adverse interaction profiles among the antidepressants has considerable clinical significance.

In particular, because no antidepressant is treatment effective in all patients, and because side effects and adverse interactions are diverse and to some extent unpredictable, there are significant societal benefits to innovations that increase the variety of antidepressant treatments available in the marketplace. As variety increases, more patients are likely to be matched with effective antidepressant pharmacotherapy.

Within the last decade, growth in sales of the SSRI and related antidepressants in the US has been dramatic and remarkable. This growth trend is displayed in **Figure 1**. From 1988Q1 through 1997Q4, quarterly SSRI and related antidepressant sales (measured in patient days of therapy) grew from about 5 million in 1988Q1 to 460 million in 1997Q4, with particularly high growth since 1993Q3.

Methods

Theoretical Considerations and Proposed Hypotheses

We hypothesize that increases in product variety can facilitate the match between a particular patient and a specific antidepressant medication, and thus are likely to increase the size of the overall antidepressant market.[1, 2] *

Consider the depressed patient searching for appropriate antidepressant therapy, aided by a physician. After considering the medical history of the patient and his/her family as well as the constellation of conditions currently being experienced by the patient, and perhaps several other factors (e.g., price, the physician's experiences), the physician suggests a particular antidepressant, and informs the patient of possible side effects. Perhaps the patient indicates that

* Nonetheless, very little empirical literature is currently available regarding optimal treatment choices following failure on an initial antidepressant. Further, a related literature dealing with the positive - contagion-mitigating - and negative - increased resistance - externalities associated with antibiotic prescriptions ascribes a different beneficial role to product variety.[52, 53]

certain side effects are not acceptable, and so the physician suggests an alternative medication. The office visit ends with the patient and physician agreeing on a trial treatment.

The information about the effects of this antidepressant treatment trial on a particular patient is costly to acquire. For example, it may take six or more weeks for the patient and physician to determine whether the patient is responsive to this antidepressant treatment. While side effects may manifest themselves more quickly, it could still take time to determine whether they would subside on their own, or be less intense with a lower dosage.

If the antidepressant is effective without major side effects, the patient is likely to remain on treatment. If the antidepressant is not effective or if important side effects persist, then the physician may prescribe a different antidepressant, often called a "second-line" therapy. Some patients may have to cycle through a number of different antidepressant treatments, taking as long as several years, before a suitable match is found between the drug and the patient. The available data suggest that for about 20-35 percent of depressed patients, currently no antidepressant offers effective relief of symptoms.

There are at least two important implications of this costly information and search framework. First, the matching model helps explain why patient/physician demands for antidepressants are likely to be rather price inelastic. A patient who has finally found an antidepressant that works is likely to develop considerable allegiance to it, and if at all risk averse, is likely to resist changing to a different antidepressant that has just come on to the market, or because of a reduction in the price of another antidepressant. Moreover, physicians who find that their patients are responding quite well to a particular antidepressant are also likely to continue prescribing that drug, at least as a first-line treatment for similar patients. Hence antidepressant medications are a good example of the order-of-entry phenomena for experience goods discussed by Schmalensee.[54] That brand loyalty continues even after the originator drug loses patent expiration and generic drugs enter is well documented in the literature.[22, 47]

Second, as new drugs come onto the market embodying differing side effect and effectiveness profiles, and as information concerning these attributes diffuses, patient/physician search costs can be reduced, and the number of patients receiving effective antidepressant therapy could increase. Product variety, and information concerning that variety, can improve the search and matching process.

Another aspect of variety and experience-based information gathering may facilitate evaluation of alternatives. Since product quality is revealed to the patient once a treatment or a product is tried, the cost of re-switching to a certain product after experimenting with alternative treatments that prove to be less satisfactory compared to the original product in question is negligible, or relatively low. * This reswitching option could significantly lower inertia associated with early entrants, and is formalized in a model of experience goods studied by Bhattacharjya.[55]

Furthermore, even if the new products have the same average efficacy in clinical and primary care trials as do existing antidepressants, it could be the case that the drug works particularly well on one subset of patients (e.g., women), but is not as effective in another subset (e.g., men). In such a case, while average effectiveness of a new drug may be no better, the match between patient and medication may be facilitated by the availability of the new variety, for search costs are reduced. To the extent marketing efforts reliably communicate side effect and effectiveness attributes of new products to physicians and patients, both physicians and patients will value the information from such marketing efforts highly, reducing their search costs.

The economic reasoning underlying the above arguments is drawn in large part from the search literature in labor economics.[56-60] Suppose an individual with a particular set of attributes is looking for employment, and that simultaneously there are many employers searching to find employees embodying certain characteristics. Both workers and employers are heterogeneous. Information about specific wage offers is acquired only by search, as is information about potential employees, and search takes time and money. Employers make offers to selected individuals, and individuals then decide whether to accept the offer. Since obtaining information on employers is a costly process for job searching individuals, and since reliable information on potential employee attributes is also costly to obtain for the employer, the labor market is one in which there is considerable ongoing search behavior. Moreover, information can become stale, as conditions change over time. As a result, at any point in time, both unemployment and help-wanted ads coexist, and wages do not equilibrate supply and demand. The resulting unemployment is often called "frictional."

In the labor market framework, the cost of obtaining information by search is a primary determinant of the extent of unemployment, for as search costs go to zero, other things equal, so too does the number of unemployed at any given point in time. Technological and institutional developments that reduce search costs by making the acquisition of information less costly (e.g., employment services that collect information on both workers and employers, low-cost internet postings of job offers and job searchers) therefore reduce the number of unemployed and increase the number employed, other things equal.

While insights from the matching analogy in labor markets are useful, the construction of a formal model of a matching process for physicians/patients and antidepressant medications is far beyond the scope of this paper. Numerous complexities such as the length of search process, formulary restrictions, patient compliance and tolerability, step protocols, and placebo response are important but difficult to incorporate in a formal and rigorous manner. Nonetheless, this framework is suggestive of a number of hypotheses that might be assessed empirically.

* However, there could be a danger that patients who, for whatever reason, discontinued an effective antidepressant may not receive the same benefit upon resuming use of it.

We hypothesize that marketing efforts will respond positively over time to improvements in the side effect and effectiveness profiles offered in the antidepressant marketplace, both within a product's life cycle and across products. Moreover, we hypothesize that, *ceteris paribus*, increases in product variety and overall product quality will have a positive direct impact on total antidepressant sales, in addition to the indirect positive impact induced by increased marketing efforts. We also hypothesize that order of entry effects will be significant factors affecting both marketing efforts and sales.

Measurement Issues and Definitions

A very large number of possible attributes are associated with a particular antidepressant medication. Side effects could be manifested in many different bodily systems and functions - agitation, sleep disturbances, gastrointestinal discomfort, diarrhea, dryness of mouth, interactions with other drugs, for example. Rather than dealing with many distinct product attributes (which in some cases are very highly intercorrelated, e.g., "incidence of daytime sedation" vs. "effect on quality of sleep"), here we develop composite quality measures in two dimensions - effectiveness and side effects. Within each composite measure, we select several individual attributes for inclusion. Each of the attribute measures is based on survey research from a physician panel undertaken annually by Market Measures, Inc., a New Jersey-based medical marketing information firm that collects a variety of survey data across a wide range of therapeutic classes and disease states (www.mmi-research.com). The physician survey panel is recruited in an ongoing basis from a random sample of each medical professional universe. For the class of antidepressant drugs, and as only one portion of their annual study, MMI received completed self-administered questionnaires from a panel of approximately 300 physicians (about 100 each of psychiatrists, internists and general/family practitioners), in which physicians provided rating scores of 1 to 5 to the various attributes of a particular drug, with higher scores representing better quality. The measures of product quality attributes are based on physicians' changing perceptions of how antidepressants perform in actual clinical practice, rather than how the manufacturers report them based on information from randomized clinical trials. Physicians are surveyed not only in terms of their perceptions of various product attributes, but also in terms of how important the particular attribute is to them. Specifically, physicians are asked to rate each attribute on a 1.0 (least important) to 5.0 (most important) scale. Physicians' scores are weighted by their relative antidepressant prescribing volume, measured by physicians' average number of patients prescribed an antidepressant per specialty, as reported by physicians to MMI. The MMI quality measures are annual; in the quarterly regressions reported below, quantity measures are set to their annual level in all four quarters.

As discussed in further detail below, to construct an aggregate measure of effectiveness for each medication, we compute a weighted average of physicians' mean evaluations on the effectiveness of a particular medication in treating (i) mild to moderate depression, and (ii) moderate to severe depression, where the weights are based on physicians' 1996 responses to questions asking the relative importance of each attribute in prescribing drug therapy to treat depression. For side effects, we construct for each product a weighted average of responses to six specific side effects queries: daytime sedation, anticholinergic side effects, toxicity from overdose, incidence of sexual dysfunction, agitation, and suitability for long-term therapy.

We now outline construction of quality measures, for the "industry" (the SSRI and related products therapeutic class) as a whole, and for individual antidepressant medications.

Product-Specific and "Industry" Measures of Quality

Let a_{jit} represent the rating for attribute j of product i at time t, and let w_{jt} be the attribute-specific "importance weight" taken from physician survey data. Since these specific weights were only explicitly provided for one year (1996) in our 1988-97 MMI sample time frame, we remove the t subscript on w_{jt} and only employ w_j as the j^{th} attribute weight. For product i, the average quality is constructed as

$$\bar{a}_{it} = \sum_{j=1}^{J} a_{jit} \cdot w_j \qquad (1)$$

These product-specific quality measures are computed for both effectiveness and side effects.

At the "industry" or therapeutic class level of aggregation, average quality measures are constructed as

$$\bar{A}_t = \sum_{j=1}^{J} m_{jt} \cdot w_j \qquad (2)$$

where m_{jt} is the arithmetic mean of attribute j over all SSRIs and related products at time t, and w_j is the attribute importance weight defined above. Note that $\bar{A}_t$, the average industry quality index, can vary as new products enter the market, and as physicians' perceptions change.

It will be useful to develop a relative notion of average industry quality, since one research objective is to assess the impact of changing average industry quality on the demand for the aggregate therapeutic class of SSRIs and related products.

The SSRIs and related products have frequently been compared to an earlier generation of antidepressants known as tricylics or tetracyclics (TCAs). Perhaps the best known of the TCAs is Amitriptyline. We choose Amitriptyline to represent the quality of all antidepressants prior to the market entry of Fluoxetine, the first SSRI, because aspects of the side effect and effectiveness profiles of Amitriptyline are similar to those of other TCAs.[47] With Amitriptyline representing pre-SSRI and related product quality attributes, we then construct the industry or therapeutic class average quality "frontier" measure F_t as the proportional difference between the average quality of the SSRIs and related products, $\bar{A}_{1t}$,

and that of the traditional TCA pharmacotherapies, $\bar{A}_{0t}$. Specifically, the SSRI and related products average frontier at time t, F_t, is computed as

$$F_t = \frac{\left(\sum_{j=1}^{J} m_{jt,1} \cdot w_j\right)}{\left(\sum_{j=1}^{J} m_{jt,0} \cdot w_j\right)} = \frac{\bar{A}_{1,t}}{\bar{A}_{0,t}} \qquad (3)$$

where $m_{jt,1}$ is the mean for attribute j over all SSRIs and related products on the market at time t, $m_{jt,0}$ is the value of attribute j for Amitriptyline (a weighted average over the number of physicians in the panel), and w_j is the perceived "importance" weight assigned to attribute j by the physician panel.

Finally, it will also be useful to have product-specific relative measures of quality. We focus on quality competition within the new class of antidepressant medications by calculating the relative distance in product space between product-specific measures of average quality and the industry average. Specifically, the normalized quality distance for product i relative to the industry average is computed as

$$r_{it} = \frac{\bar{a}_{it} - \bar{A}_{t,-i}}{a_{\max} - a_{\min}} \qquad (4)$$

where $\bar{A}_{t,-i}$ is defined as the industry average quality excluding product i and a_{max} and a_{min} are the largest and smallest possible quality ratings, respectively. The value r_{it} is therefore bounded between –1 (poorest quality) and 1 (highest quality). During the time period when Fluoxetine was the only SSRI competitor in the market, the value of r_{it} is defined to equal zero. For each of these industry and product-specific relative quality variables, separate measures are computed for effectiveness and side effects.

Therapeutic Class Measures of Variety

The notion of variety presents measurement challenges, for variety can be measured in a number of ways. We define variety at time t as the total dispersion among the new therapeutic class of antidepressant products on the market at that time. The contribution of product i to total variety in the new therapeutic class is the absolute difference between average quality of product i and the average quality of the products that entered the market prior to product i. Therefore, at any time total variety is simply the sum of the product-specific differences. For example, when there is only one product on the market and a second enters, total variety is computed as the absolute difference between the new entrant's average quality and that of the incumbent. When a third entrant reaches the market, total variety is the sum of the difference between the newcomer's average quality and the average quality of the two incumbents, plus the difference in average quality between the second entrant and the pioneer.

More generally, we compute variety V_t as

$$V_t = \sum_{i=2}^{N} \left| \bar{a}_{it} - \left(\frac{\sum_{j=1}^{i-1} \bar{a}_{jt}}{i-1} \right) \right| \qquad (5)$$

where N is the number of new antidepressant products on the market at time t. This measure of product variety is mathematically equivalent to the measure of product distance in the differentiated product space model implemented by Stavins.[8] It should be pointed out, however, that this measure is invariant to changes in the composition of "variety," insofar as it does not allow one to capture the potentially idiosyncratic responses of patients to products that may be equally 'varied' on average, but whose constituent attributes may differ in opposite directions. This is a constraint imposed on the analysis for reasons of simplification and tractability.

Quantities of Antidepressant Medications

To quantify the diffusion of antidepressant medications, a measure is needed that is comparable across different products. IMS Health provides data on revenues, units sold by product and what they call extended units (essentially number of tablets or capsules). Quarterly sales data to retail outlets (projected to national levels based on data from 28,000 retail pharmacies) were made available to us covering the 1988Q1 through 1997Q4 time period. The products included in our analysis are Fluoxetine, Buproprion HCL, Sertraline HCL, Paroxetine HCL, Venlafaxine HCL, Nefazodone HCL, Fluvoxamine Maleate and Mirtazapine.* Since typical daily dosing is likely to vary across drugs and perhaps over time, the extended units measure is standardized by dividing extended units by the average number of tablets administered per day, using Retail Provider Perspective data from IMS Health. This provides a quantity measure of total patient-days of antidepressant pharmacotherapy that is consistent across products and over time. Price per day of therapy is then computed as revenue divided by the patient day quantity measure. To adjust for overall inflation, this nominal price measure is divided by the overall US Consumer Price Index (1982-84=1.00).

For each time period beginning 1988Q1, total patient days of therapy is computed for the benchmark TCA, Amitriptyline, and is denoted as Q_{0t}. Quantity measures for each product in the new classes of antidepressant medications are noted as q_{1i}, where the subscript i refers to product i in the new classes of antidepressant medications (defined in turn by subscript 1). Total patient-days of therapy for the class of SSRIs and related products is the sum of the individual

* The brand names of the products included in the analysis are: Fluoxetine (Prozac), Buproprion HCL (Wellbutrin), Sertraline HCL (Zoloft), Paroxetine HCL (Paxil), Venlafaxine HCL (Effexor), Nefazodone HCL (Serzone), Fluvoxamine Maleate (Luvox) and Mirtazapine (Remeron).

quantities over the N products,

$$Q_{1t} = \sum_{i=1}^{N} q_{1it} \qquad (6)$$

The total quantity of antidepressant medications sold at time t is then the sum of Amitriptyline plus the sales of SSRIs and related products, i.e.,

$$Q'_t = Q_{0t} + Q_{1t} \qquad (7)$$

Shares of traditional and total new antidepressant medications in total antidepressant medications are computed as $s_{0t} \equiv Q_{0t} / Q'_t$ and $s_{1t} \equiv Q_{1t} / Q'_t$, respectively.

Marketing Efforts and Information Stocks

New marketing efforts at time t are measured as the sum of quarterly marketing expenditures associated with physician detailing contacts (excluding product samples) plus quarterly expenditures for advertising in medical journals. These quarterly marketing data are taken from the National Journal Audit and Integrated Promotional Services data constructed by IMS Health, and are first separately deflated by the Bureau of Labor Statistics producer price indexes for "Finished Goods" and "Advertising - Professional Periodicals," respectively, each indexed to 1982-84 = 100.[20, 21]

Since marketing efforts provide long-lived information, it is important that cumulative carry-over effects from previous marketing efforts be accommodated and distinguished from the new current-period marketing efforts. Using the perpetual inventory method, M_t, the cumulative marketing information stock at the end of time t, is defined as

$$M_t = (1-\delta) \cdot M_{t-1} + L_t$$

$$= \sum_{\tau=0}^{t} (1-\delta)^{\tau} \cdot L_{t-\tau} \qquad (8)$$

where L_t is the flow of new marketing information efforts during quarter t (real expenditures on physician detailing plus that on medical journal advertising), and δ is the quarterly depreciation rate. Since δ is unknown, it is estimated using econometric methods described below. M_t is constructed separately for each product, and is summed over products at each point in time to obtain an aggregate measure for the SSRIs and related products therapeutic class.

Specification of Estimating Equations

We now specify equations whose parameters we estimate using econometric procedures.

The Marketing Equation

We expect that marketing efforts for product i depend on: the age of the product (AGE); its order of entry (ENTRY); the number of other competing antidepressant products currently on the market (COMP, and its square, COMPSQ); whether the product has received FDA approvals for use in one, or two or more conditions other than major depressive disorder (indicator variables NONDEP1 and NONDEP2); whether the product has a new dosage sustained release formulation (NEWVER); and to allow for ramping up of marketing efforts in the four quarters immediately following product launch, a series of four indicator variables (RU_1 through RU_4).[10, 11, 18, 19, 28, 61, 62] With respect to product quality, we expect marketing efforts to increase with increases in effectiveness (EF) and with the absence of adverse side effects (SE). We implement this with a simple linear equation having L_{it} (real marketing expenditures for product i in quarter t) as the dependent variable, and where the remainder of the equation takes on the form

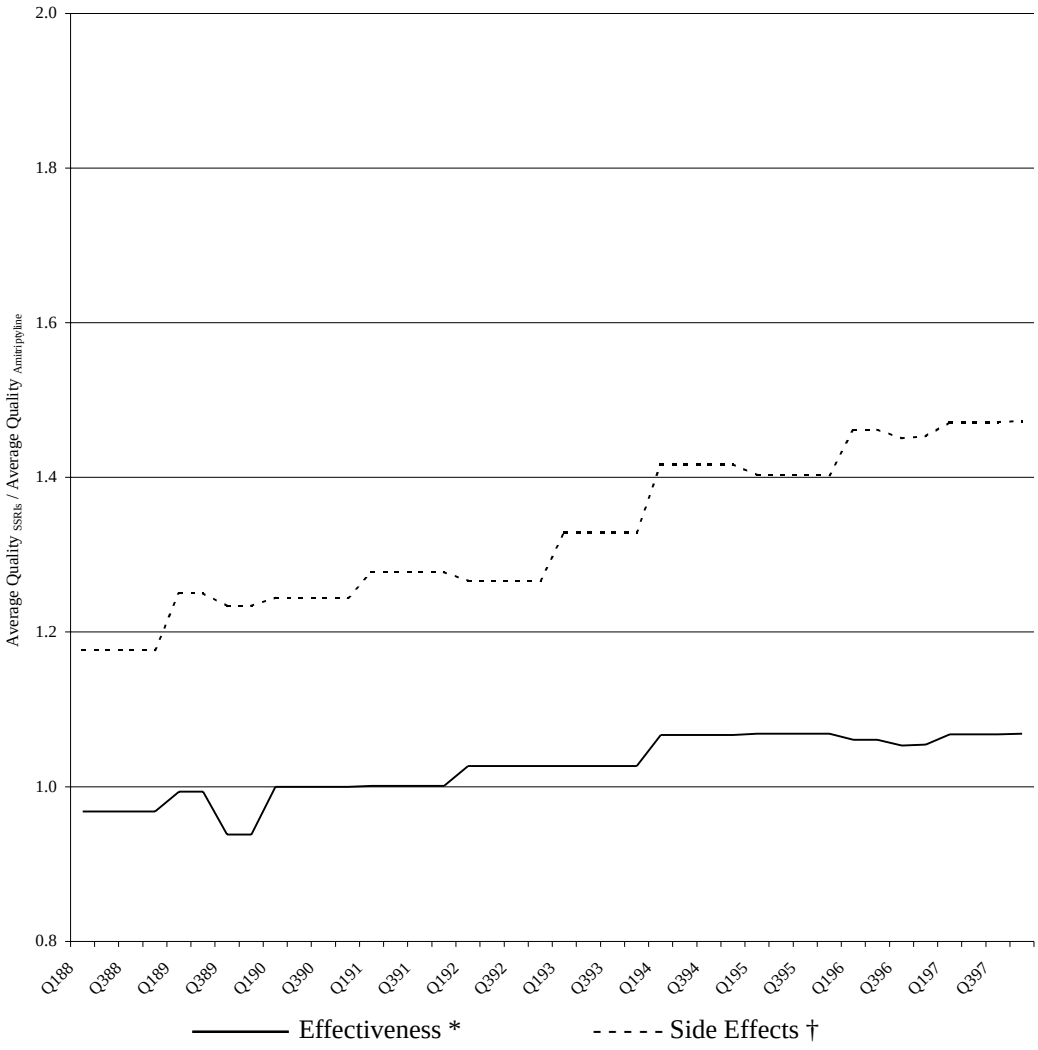
$$\begin{aligned} L_{it} &= \alpha_0 + \alpha_1 AGE_{it} + \alpha_2 ENTRY_i + \alpha_3 COMP_{it} \\ &+ \alpha_4 COMPSQ_{it} + \alpha_5 NONDEP1_{it} + \alpha_6 NONDEP2_{it} \\ &+ \alpha_7 NEWVER_{it} + \sum_{k=8}^{11} \alpha_k RU_{k-7,it} + \alpha_{12} EF_{it} + \alpha_{13} SE_{it} + \varepsilon_{it} \end{aligned} \qquad (9)$$

where ε_{it} is a random disturbance term. Consistent with our discussion concerning experience goods (p. 3-6), we expect the estimate of α_1 will be negative, that estimates of α_1, α_5, α_6, α_7, α_k, α_{12}, and α_{13} will be positive, but we are *a priori* uncertain about the signs of α_5, α_6, and α_4. We treat each of these regressors as predetermined or exogenous, and estimate parameters in Eqn. (9) by ordinary least squares (OLS).

The "Industry" Sales Equation

At the "industry" or SSRI and related products therapeutic class level of aggregation, we expect the quantity demanded (Q_{1t}, number of patient days of antidepressant therapy) to depend on the industry average price per patient day of therapy (P_t), aggregate industry stocks of marketing efforts (M_t), industry frontier measures of effectiveness (EF_t) and side effects (SEF_t), and the variety among antidepressant products in effectiveness (EV_t) and side effects (SEV_t). Since the diffusion of information depends in part on recent experiences with a medication, and since physicians need time to transfer patients from one medication to the next, we model diffusion as following a simple partial adjustment process, which implies adding lagged sales as a regressor and estimating a partial adjustment parameter λ. In the partial adjustment framework, the gap between the long run equilibrium demand and the current demand level is closed by the proportion (1- λ) in each time period. Hence, when adjustment to long-run equilibrium is instantaneous, $\lambda = 0$, and when there is no adjustment $\lambda = 1$.[8, 18, 60]

To measure the aggregate industry stocks of marketing efforts M_t (and to mitigate impacts of simultaneity), we sum up over all products at time t the predicted marketing



* **Effectiveness**: Mean of response rating: Mild to Moderate Depression, Moderate to Severe Depression
† **Side Effects:** Mean of Response Rating: Low Daytime Sedation, Low Anticholinergic, Low Toxicity from Overdose, Low Incidence of Sexual Dysfunction, Minimal Agitation, Suitable for Long-term Therapy

Figure 2. Relative Product Quality Frontiers Measures Between SSRIs and Related Products and Amitriptyline

expenditures based on the OLS parameter estimates of Eqn. (9), and then insert these summed predicted expenditure flow values into the perpetual inventory marketing stock Eqn. (8). Our "industry" sales equation is therefore

$$\begin{aligned}\ln Q_{1t} &= \lambda \ln Q_{1,t-1} + \beta_0(1-\lambda) + \beta_1(1-\lambda)\ln P_t \\ &+ \beta_2(1-\lambda)\ln M_t + \beta_3(1-\lambda)\ln EF_t + \beta_4(1-\lambda)\ln SEF_t \\ &+ \beta_5(1-\lambda)EV_t + \beta_6(1-\lambda)SEV_t + \mu_t\end{aligned} \qquad (10)$$

where μ is a random disturbance term. To estimate the marketing information deterioration rate δ we specify a grid of values for δ, estimate parameters in Eqn. (10) by least squares conditional on alternative grid values for δ, and then choose that combination of δ and the parameter estimates that results in the lowest value of the sum of squared residuals. Based on our earlier discussion, we expect the estimate of β_1 to be negative, those of β_2, β_3, β_4, β_5, and β_6 to be positive, while $0 < \lambda < 1$.

The Product Share Model

The "industry" Eqn. (10) indicates how aggregate sales for SSRIs and related products change given the entry of a new molecule that alters values of the right-hand side variables. We now discuss our modeling of the factors that affect individual market shares earned by each new (and incumbent) entrant to the market. We hypothesize that what the entrant achieves in the marketplace depends on factors such as price, order of entry, product age, marketing efforts, and relative product quality.[20, 21] The general formulation is

$$\frac{q_{it}}{\sum_{j\neq i}^{J} q_{jt}} = f(ENTRY_i, AGE_{it}, P_{it}, M_{it,} REF_{it}, RSE_{it}) \qquad (11)$$

where the dependent variable is the quantity share of entrant i relative to the total quantity of all other products on the market (excluding product i) in quarter t and REF_{it} and RSE_{it},

the measures of normalized product effectiveness and side effects, are as defined in Eqn.(4) above.

While the specification of market share and demand models traditionally draws on the economic theory of consumer behavior, in the prescription drug marketplace principal-agent problems may preclude a direct application of the economic theory framework in which consumers maximize utility given prices and budget constraints. We follow King[62] by employing a modified version of the traditional logit discrete choice model where demand for a new entrant's product, q_{1i}, is measured relative to the demand for all other new entrants currently on the market, Σq_{1j} ($j \neq i$), plus the traditional depression therapy product amitriptyline, Q_0. Define the share of the new entrant s_{1it} as

$$s_{1it} \equiv \frac{q_{1it}}{Q'_t} \quad , \tag{12}$$

where Q'_t is as defined in Eqn. (7) above, and

$$1 - s_{1it} \equiv \frac{(Q'_t - q_{1it})}{Q'_t} \quad . \tag{13}$$

Taking the logarithm of the ratio of Eqns. (12) and (13) gives us the logistic diffusion expression

$$\ln\left[\frac{s_{1it}}{1-s_{1it}}\right] = \ln\left[\frac{q_{1it}}{Q'_t - q_{1it}}\right] \quad , \tag{14}$$

which permits diffusion of the new product initially to be rapid, but then eventually to taper off as saturation is approached.[63]

There are two important facets concerning the specification of the Q'_t measure of quantity in the logistic expression of Eqn. (14). First, since Q'_t includes both the traditional TCA Amitriptyline and the new SSRI and related products medications, Q_{0t} serves the role of an "outside good" in the consumer demand framework, whereby the consumer is confronted with choosing between the representative traditional TCA medication Amitriptyline or newer SSRI and related product medications.[4, 18, 62, 64] Second, on a more practical level, this specification allows us to estimate the model using data from the first six quarters of the study period during which Fluoxetine had a 100 percent market share within the new class of SSRI and related products. Had Q_{0t} been excluded, use of these observations would not be feasible.

For estimation purposes, we specify the share model as a semi-log specification:

$$\ln\left[\frac{s_{1it}}{1-s_{1it}}\right] = \gamma_0 + \gamma_1 ENTRY_i + \gamma_2 AGE_{it} + \gamma_3 P_{it} + \gamma_4 M_{it} + \gamma_5 REF_{it} + \gamma_6 RSE_{it} + \upsilon_{it} \tag{15}$$

where the REF and RSE variables are normalized quality ratings for effectiveness and side effects of product i relative to the industry average at time t (as defined in Eqn. (4)), the other variables are as defined previously, and υ_{it} is a random disturbance term. Note that for M_{it}, the marketing stock of information for product i, we employ OLS estimates of Eqn. (9) to predict product-specific marketing expenditures, along with the perpetual inventory Eqn. (8) to convert predicted expenditures into marketing stocks. Thus estimation of Eqn. (15) involves two-stage least squares. [20,21,62]

The inclusion of normalized quality measures as explanatory variables reflects the fact that the denominator of the dependent variable includes not only the share of traditional drug therapy but also shares of competing new drug therapy products. We hypothesize that what the new entrant achieves in the marketplace of new antidepressant products relative to any competing new products in the market depends on, *inter alia*, relative quality comparisons. Although these normalized quality variables will change along with physicians' perceptions over time, they will also change as new molecules enter the market. Consistent with our discussion of experience goods (p. 3-6), we expect estimates of γ_1 and γ_2 to be negative, and those of γ_3, γ_4, γ_5, and γ_6 to be positive.

With this product share model, we have an unbalanced panel data set, for the eight products entered the market at different times between 1988 and 1997. This results in a total of 164 quarterly observations, with the number of time series observations typically being larger than the number of cross-sectional observations. We stack the data and estimate the model using two-stage least squares, allowing for first-order autoregressive disturbances, and retaining the first observation for each product in the estimation process.

Data Analytic Procedures

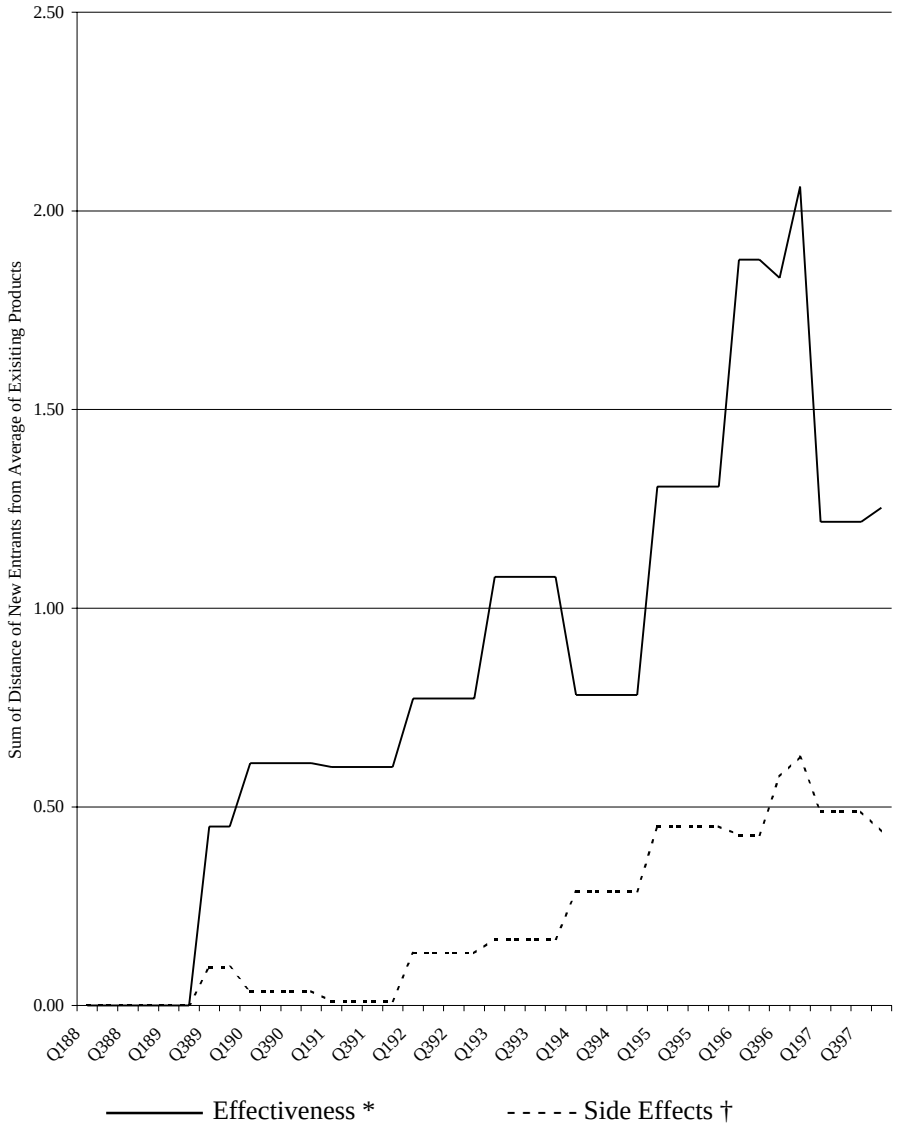
Parameters in the three regression equations were estimated using SAS or the Time Series Processor (TSP) econometric software packages. Ordinary linear least squares (OLS) procedures in SAS were employed in the marketing equation, while TSP's two-stage nonlinear least squares procedures were employed in the "industry" equation, where the marketing stock variable is endogenous. Since this equation includes a lagged dependent variable as a regressor, Durbin's h-test was used to test for first-order autoregressive (AR1) disturbances. In the product share equation, the TSP procedure of generalized two-stage least squares was employed, with the AR1 procedure retaining the first observation for each product. Statistical significance of individual parameter estimates was assessed using finite sample t-tests (marketing equation) or large sample z-scores ("industry" and product share equations), along with 95% critical values.

Results

The data employed here are described in detail in a Data Appendix available from the authors.

Data Trends

As was shown in **Figure 1**, since the introduction of Fluoxetine into the market in 1988, growth in terms of patient days of therapy for the SSRI and related product class of



* **Effectiveness**: Mean of response rating: Mild to Moderate Depression, Moderate to Severe Depression
† **Side Effects:** Mean of Response Rating: Low Daytime Sedation, Low Anticholinergic, Low Toxicity from Overdose, Low Incidence of Sexual Dysfunction, Minimal Agitation, Suitable for Long-term Therapy

Figure 3. Variety of SSRI and Related Products Market As Measured by the Total Dispersion of New Entrants Relative to All Existing Products

antidepressant drug therapy has been substantial, with a marked increase beginning in late 1993 and continuing through 1997. By the end of 1997, quarterly sales approximated 460 million patient days of therapy, which is roughly equivalent to 5.1 million patients. The average real price (in 1982-84 constant dollars) per patient day of therapy at retail stores in 1997 for all SSRIs and related products was approximately $1.40, which in 1997 dollars is about $2.10.

In terms of trends in drug effectiveness and side effect qualities, as seen in **Figure 2**, relative to the effectiveness of a prominent TCA (Amitriptyline) for the treatment of mild to moderate depression, since 1988 as new antidepressants have been launched there has been only a rather modest increase in the perceived average effectiveness of the SSRIs and related products. However, relative to the profile of the same TCA, over the same time period the SSRIs and related products have been perceived to have considerably improved side effect profiles. Hence for SSRIs and related products average side effect profiles appear to have improved more than average effectiveness measures.

Measures of attribute variety display interesting trends as well. As seen in **Figure 3**, when Buproprion HCL entered in 1989Q3, Fluoxetine was the only SSRI on the market, and the differing side effect profiles of these two products resulted in a considerable increase in the amount of treatment variety available in the marketplace. Side effect treatment variety was relatively stable thereafter until Sertraline HCL entered in 1992Q1 and Paroxetine HCL in 1993Q1, and continued to increase as products such as Fluvoxamine Maleate, Nefazodone HCL, and Mirtazapine, having somewhat differing side effect

Table 1. Marketing model (estimated standard error in parentheses)

Variable	I		II	
	Parameter Estimate ($000s)	p-Value	Parameter Estimate ($000s)	p-Value
Intercept	-3992.25 (784.04)	<0.0001	-36586.00 (3995.21)	<0.0001
Age of product	-188.05 (49.22)	0.0002	-126.80 (39.03)	0.0014
Order of entry	-917.37 (251.90)	0.0004	-568.83 (200.03)	0.0051
Number of competing products	2676.88 (379.60)	<0.0001	2064.62 (302.97)	<0.0001
Number of competing products squared	-258.25 (40.40)	<0.0001	-207.72 (31.98)	<0.0001
Non-depressive disorder approval indicator 1	2317.11 (702.14)	0.0012	828.65 (568.78)	0.1472
Non-depressive disorder approval indicator 2	4337.08 (696.14)	<0.0001	2613.79 (571.30)	<0.0001
New dosage sustained release version	825.11 (952.79)	0.3879	847.16 (759.45)	0.2664
Ramp up effect dummy 1 (first quarter=1)	-489.13 (761.92)	0.5219	224.89 (605.31)	0.7108
Ramp up effect dummy 2 (second quarter=1)	2751.49 (750.60)	0.0003	3404.25 (595.57)	<0.0001
Ramp up effect dummy 3 (third quarter=1)	1230.59 (742.38)	0.0995	1693.05 (584.22)	0.0043
Ramp up effect dummy 4 (fourth quarter=1)	430.14 (737.36)	0.5605	831.35 (579.65)	0.1536
Effectiveness	-		4795.11 (635.19)	<0.0001
Side effects	-		5844.92 (2013.03)	0.0042
N	164		164	
Adjusted R-squared	0.39		0.63	

Data Sources: IMS Health (Integrated Promotional Services, National Journal Audit) and Market Measures Inc.

profiles (low incidence of sexual dysfunction, minimal agitation, suitability for long term therapy) entered the market.

While the measure of side effect variety in **Figure 3** generally has a substantially rising trend with time, the measure of effectiveness variety shows even more movement than that for side effects, with effectiveness variety increasing with the launch of Paroxetine HCL in 1993, Nefazodone HCL and Fluvoxamine Maleate in 1995, and Mirtazapine in 1996. Unlike the average quality measures, variety measures for side effects show considerably smaller increases over time than do variety measures for effectiveness. The noticeable decline in effectiveness variety in 1997 is due to a change in physicians' perceptions; a comparison of the MMI ratings between 1996 and 1997 revealed a reduction in the overall dispersion of the attribute ratings.

Econometric Findings

Marketing Model

OLS estimates of the parameters in the product marketing model are presented in **Table 1**. Two sets of results - with and without physicians' perceived quality ratings - are tabled, where in each case the dependent variable represents the product-specific combined real marketing expenditures for detailing

Table 2. "Industry" demand model (estimated asymptotic standard error in parentheses)

	I			II	
Variable	Parameter Estimate	p-Value	Variable	Parameter Estimate	p-Value
Partial adjustment parameter	0.465 (0.066)	<0.001	Partial adjustment parameter	0.465 (0.066)	<0.001
Short -Run Impact			Long- Run Impact		
Intercept	1.125 (0.123)	<0.001	Intercept	2.104 (0.287)	<0.001
ln (Price per therapy day)	-0.419 (0.155)	0.011	ln (Price per therapy day)	-0.783 (0.258)	0.002
ln (Stock of marketing)	0.245 (0.064)	0.001	ln (Stock of marketing)	0.458 (0.078)	<0.001
ln (Effectiveness frontier)	0.451 (0.731)	0.542	ln (Effectiveness frontier)	0.843 (1.389)	0.544
ln (Side effects frontier)	1.312 (0.531)	0.019	ln (Side effects frontier)	2.453 (0.949)	0.010
Effectiveness variety	-0.036 (0.049)	0.463	Effectiveness variety	-0.068 (0.091)	0.454
Side effects variety	0.576 (0.145)	<0.001	Side effects variety	1.078 (0.292)	<0.001
N	39			39	
δ	0.036			0.036	
Durbin's h-test for AR(1) disturbances	-0.426	0.670		-0.426	0.670
Adjusted R-squared	0.996			0.996	

Data Sources: IMS Health (Integrated Promotional Services, National Journal Audit, Retail Provider Prospective) and Market Measures Inc.

and journal advertising (in thousands of 1982-84 dollars).

The negative and significant coefficients on entrant and product age (in quarters) indicate that, *ceteris paribus*, later entrants have ever lower marketing efforts (reflecting, perhaps, lower expected sales), and that marketing efforts decline over time as the product ages. The coefficient on number of competitors and its square are positive and negative, respectively, and their magnitudes suggest that when the total number of competitors is small, successive but early entrants have ever larger marketing efforts. However, when there is a very large number of competitors, the successive individual product marketing efforts are reduced. Product marketing efforts are largest when the number of competitors is about five.

The positive coefficient estimates on the first (significant only in the first column) and second non-depression indication variables are consistent with the notion that firms expend considerable additional marketing efforts in informing physicians of these FDA approvals. When evaluated at the sample mean, the results imply that marketing efforts are nearly doubled for a firm with a product approved for two or more indications other than depression therapy. Although the coefficient on release of a line extension (enhanced version) is positive, it is not statistically significant.

As expected, marketing efforts are particularly intense in the quarters immediately following product launch. The small and insignificant estimate on the first quarter launch variable likely reflects variability in the point in time during that quarter when the product was launched (e.g., 1st month, 3rd month). The very substantial positive coefficient on the second quarter variable indicates that firms market information about their new product very aggressively following product launch; the third quarter coefficient is also positive (significant in column II), but is smaller than that for quarter two on the market. Although the fourth quarter

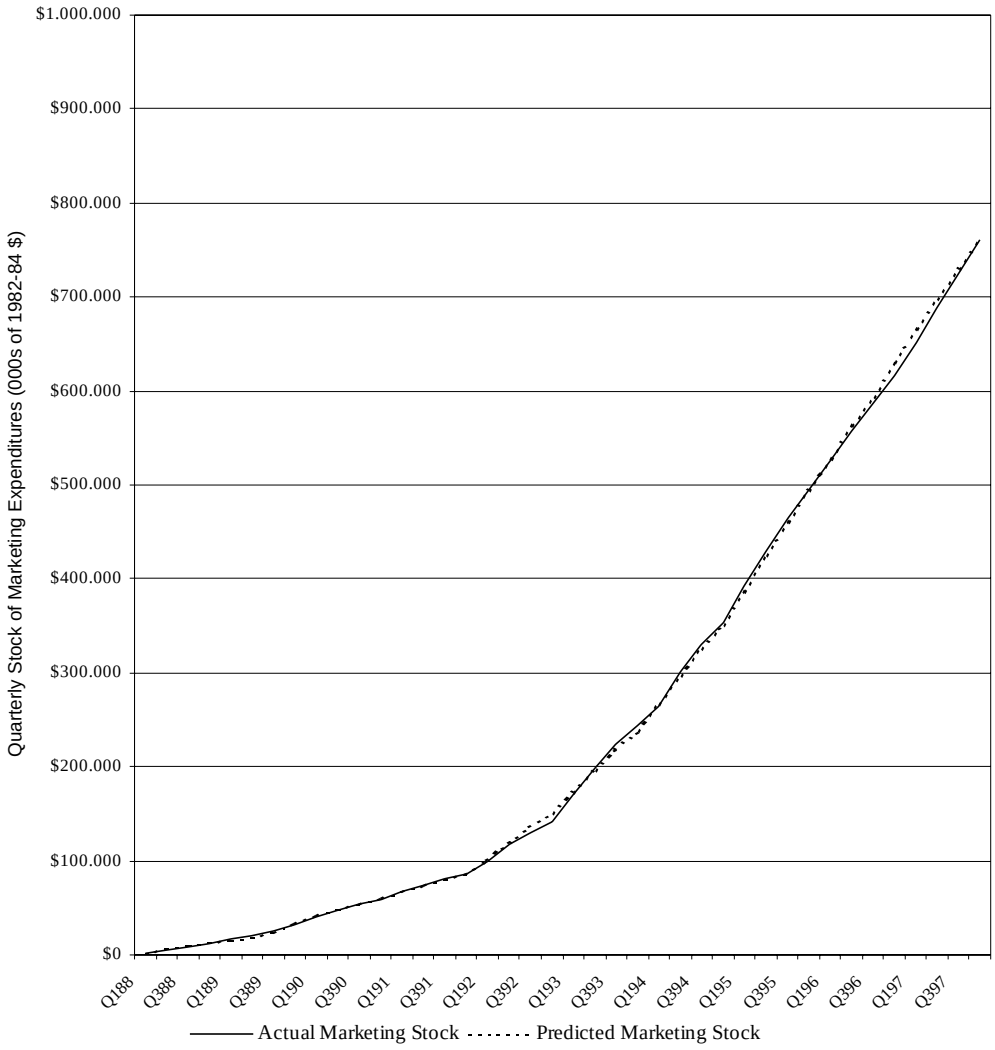


Figure 4. Comparison of Actual and Predicted Stock of Marketing Expenditure for SSRIs and Related Products

coefficient is positive and smaller than that for earlier quarters, it is not significant.

In the second regression that includes product quality variables, average product quality is clearly shown to have a large and statistically significant impact on a firm's marketing efforts. As hypothesized, firms with higher quality products devote more resources marketing information about those products to the physician community, other things equal. The results imply that greater marketing occurs regardless of whether superior quality manifests itself through the product's effectiveness and/or its side effects profile. Moreover, the inclusion of product quality in the model has a substantial effect on several other variables. One finding is that the marketing efforts due to FDA approvals of non-depression indications fall, with enhanced marketing efforts occurring only after a firm receives its second non-depression indication approval. Another is that when the quality measures are included, the order of entry coefficient falls (in absolute value) by about 40%.

In summary, coefficient estimates in the product marketing effort equations are clearly consistent with the notion that marketing responds to science-based events, conveying information to physicians on the existence of a recently launched product, new non-depression indication FDA approvals, and effectiveness and side-effect quality improvements.

A useful check on the reliability of this marketing model can be obtained by summing up the predicted marketing efforts over all products in each quarter, creating an industry marketing stock variable using the perpetual inventory Eqn. (8), and then comparing this to the actual, observed marketing stock. In **Figure 4**, we display the two series (assuming $\delta = 0$, an assumption we relax later when we estimate δ). The predicted and observed industry marketing stocks are very similar, and have a correlation coefficient of 0.99.

"Industry" Demand Model

In **Table 2** we present two-stage least squares estimates of parameters in the market demand model (the marketing stock measure is endogenous), where the dependent variable is the logarithm of "industry" days of therapy. The quarterly data

Table 3. Product share model (estimated asymptotic standard error in parentheses)

Variable	I		II	
	Parameter Estimate	p-Value	Parameter Estimate	p-Value
Intercept	-2.910 (0.248)	<0.001	-2.860 (0.229)	<0.001
Order of entry	-0.262 (0.021)	<0.001	-0.246 (0.020)	<0.001
Age of product	0.009 (0.005)	0.104	0.009 (0.006)	<0.133
Price per patient day of therapy	-0.207 (0.146)	0.157	-0.157 (0.140)	0.261
Stock of marketing	0.065 (0.005)	<0.001	0.048 (0.005)	<0.001
Relative Efficacy	-		1.717 (0.714)	0.016
Relative Side Effects	-		3.981 (1.681)	0.018
N	164		164	
δ	0.181		0.154	
Adjusted R-squared	0.982		0.984	
Estimated AR(1) Coefficient	0.944 (0.178)		0.938 (0.169)	

Data Sources: IMS Health (Integrated Promotional Services, National Journal Audit, Retail Provider Prospective) and Market Measures Inc.

are from 1988Q2 through 1997Q4 (39 observations). For those regressors involving logarithms, the coefficients can be interpreted as elasticities. Since the model formulations can be motivated by a partial adjustment process (as physicians write new prescriptions for new patients and gradually switch others as old prescriptions are scheduled for refills), the product terms, $\beta_j(1-\lambda)$,j=1,...,6 can be interpreted as short-run elasticities, while β_j are long-run elasticities, and λ is the quarterly partial adjustment parameter (zero if adjustment is instantaneous, one if entirely non-responsive). Estimates in Column I of **Table 2** are least squares estimates of the composite product parameters, while the nonlinear least squares estimates in Column II unravel and provide separate estimates of the component parameters (and their asymptotic standard errors).

As seen in Column II of **Table 2**, the estimate of λ is about one-half, and is highly significant; thus all long-run elasticities are almost twice their short-run values. The long-term price elasticity estimate is about –0.8 and significant, while the long-run marketing stock elasticity is about 0.5, suggesting decreasing returns to marketing. The quarterly depreciation rate δ was estimated at 0.036, implying an annualized depreciation rate for industry marketing efforts of about 15 percent.

Of particular interest here are the industry sales impacts of perceived average levels of effectiveness and side effects, and impacts of the perceived variety of effectiveness and side effect attributes embodied in products available in the marketplace. Regarding average levels, as seen in **Table 2**, while the estimate of β_3 (the sales elasticity with respect to average effectiveness) is positive but insignificant, the estimate of β_4 (sales elasticity with respect to average side effects) is large (2.45) and significant, implying that, *ceteris paribus*, as the perceived average side effect profile of the new group of antidepressant products improves by, say, 5 percent, "industry" sales will increase by around 12 percent.

Finally, with respect to variety, again it is side effects that are more important for sales than is effectiveness. Specifically, while the estimate of β_5, the coefficient on effectiveness variety, is close to zero and insignificant, that of β_6, the coefficient on side effect variety, is about unity and statistically significant. An implication is that increased variety in side effect profiles among alternative antidepressant products has a positive and significant impact on "industry sales", reflecting perhaps a greater number of better matches between idiosyncratic patients and antidepressant medications.

In summary, the estimated "industry" demand model indicates that sales are positively and significantly related to

price reductions, increased marketing efforts, and the level and variety of side effect profiles of antidepressants available in the marketplace.

Product Share Model

Parameter estimates of the logistic product share model are given in **Table 3**. Quarterly data for up to eight products comprise a total of 164 observations in an unbalanced panel. The estimation procedure allows for first-order autocorrelation of residuals within each product, and for endogeneity of the marketing stock variable. Estimates in the first column of **Table 3** exclude normalized relative effectiveness and side effect quality attribute variables, while those in the second column include them. Here we focus on the latter estimates.

Both order-of-entry and product age variables have the expected signs (negative and positive, respectively), but only the former is statistically significant. Although the estimated price coefficient is negative as expected, it is not significant. By contrast, the predicted stock of marketing has a positive and highly significant impact on a product's diffusion process. The quarterly depreciation rate, δ, estimated in a manner similar to that in the market level model, resulted in the sum of generalized squared residuals being minimized when $\delta = 0.154$. This implies an annualized depreciation rate of approximately 49 percent.

The normalized quality attribute variables both have positive and statistically significant coefficient estimates, with that on side effects being twice as large as that on effectiveness. Computed at the sample product share means, the estimated impact of a 0.05 percent increase (approximately one standard deviation) in product quality over the mean for effectiveness and side effects is a 1.0 and 2.2 percentage point increase, respectively, in product share.†

Thus, product quality - but particularly a more favorable side effect profile - has a very substantial impact on product market share.

Finally, it is interesting to note that in comparing parameter estimates in Columns I and II of **Table 3**, one finds that the magnitude of the marketing stock coefficient is about 25 percent smaller when the product attribute variables are included. Hence, because marketing efforts respond to variations in product quality (recall our earlier discussion on findings for the marketing model), the distinct or direct impact of marketing on sales is overstated when product quality characteristics are not properly incorporated into the model. Note also that product quality has both direct (see **Table 3** coefficient estimates) and indirect (**Table 1**) effects on sales, the latter occurring because marketing efforts are responsive to variations in product quality, and in turn marketing efforts have a direct positive impact on sales.

† The estimated impact is calculated as

$$\frac{\partial S_i}{\partial X} = \beta * (1 - \text{SHARE}) * \text{SHARE},$$

where β is the parameter estimate, and SHARE is the sample mean product-level quantity share.

Discussion

Findings and Limitations

Although the theoretical literature on product quality, product variety, marketing efforts and sales outcomes is extensive, to date there is very little published empirical research examining their interrelationships. Focusing on the US market for antidepressant medications in the decade following the launch of Fluoxetine in 1988, we have attempted to quantify and rank the various relationships affecting the diffusion of these new products. While alternative conceptual and empirical measures of product quality and variety are possible, the measures employed in this paper (based on surveys of physician perceptions) are intuitively plausible and possess face validity. The analysis predicated on these measures suggests that both side effect product quality and side effect product variety have a positive direct impact on industry sales. We also find that product quality increases (both in effectiveness and side effects) have an additional indirect effect on industry sales through their enhancement of marketing efforts. While the above results do not preclude the possibility that these increases in product variety may be partly endogenous as a supply-side response to anticipated demand increases, the multi-year length of the drug development process implies that any such supply response would involve a long and uncertain time lag.

With respect to the role of prices, we find that the long-run "industry" demand price elasticity is about –0.8, but that within the SSRI and related product therapeutic class, market shares of individual products are not price sensitive, other things equal. It is worth noting that although contemporaneous prices charged by later entrants were typically lower than that of Fluoxetine, from 1988 through 1997 the average real price per therapy day increased slightly (5 %, not shown). Real prices of all products in this class generally increased over time, even as the number of entrants also increased. Thus, the negative estimated price elasticity does not reflect a simple underlying negative mathematical relationship between average real price and number of entrants, for in these data this relationship is slightly positive, not negative.

Marketing efforts play a very prominent role in our framework, for they convey information on product availability and product quality. We find that marketing efforts increase considerably following FDA approval for indications other than depression, in the four quarters following product launch, and that these marketing efforts increase with the average effectiveness and the average side effects rating of the product. Based on evaluations at sample means (calculations not shown), we find that quarterly marketing elasticities with respect to the last two quality measures are very large, 4.1 and 4.4, respectively.

At the "industry" (SSRI and related product therapeutic class) level, we find that sales are more responsive to physicians' perceptions of the level of side effects quality than to their perceptions of effectiveness, and that while effectiveness variety has no significant impact on sales, side effect variety has a very substantial positive impact. These results suggest

that much of the growth of the SSRIs and related products since 1988 can be attributed to improved changes in their side effect quality relative to that of the prominent previous generation tricyclic antidepressant, amitriptyline, to the increased variety of SSRI side effect profiles, and to the marketing of these attributes.

At the level of individual products, we find that both relative product effectiveness and relative product side effects contribute positively to a product's market share, but that side effects play a much larger role. When evaluated at the sample means, a one standard deviation in normalized product quality improvement for effectiveness and side effects results in a 1.0 and 2.2 percentage point increase, respectively, in market share.

Three limitations of this research should be noted. First, our composite side effect and effectiveness quality measures are averages over several component attributes, whose distinct magnitudes may differ. Also, other quality attributes, such as dosing simplicity, are not incorporated into these measures. * It is possible that by excluding dosing simplicity we have overstated the magnitudes of the side effect and effectiveness quality measures.

Second, physicians' perceptions of the quality attributes of antidepressant medications are based not only on their own experiences with patients, and those of their medical colleagues with whom they interact (and their patients), but it is likely that these physicians' perceptions are also affected by drug manufacturers' marketing efforts. Simultaneity between marketing efforts and physicians' perceptions of product quality would be very challenging to model, given the multitude of factors affecting physicians' perceptions. This is a topic worthy of further analysis. We note here, however, that since the MMI quality measures are annual, they do not vary by quarter within a year. This mitigates (but would not necessarily eliminate) any simultaneity between marketing and perceived quality in the regressions based on quarterly data.

Third, the relative importance weights for the various quality components are only available from MMI for one year, 1996. Physicians' ranking and weighting of the component quality attributes may have changed over time with experience and the availability of new information, but our composite quality measures do not capture any such variability.

Implications for Health Care Provision, Use and Health Policy

Since patient response to SSRIs and related products is idiosyncratic, greater product variety facilitates better matching of antidepressant with patient. Much of the growth of the SSRIs and related antidepressants since 1988 can be attributed to increased product attribute variety, to improved changes in side effect quality relative to that of the tricyclics, and to the marketing of those improvements. Marketing efforts play an important role in diffusing product information.

Implications for Further Research

The relatively minor role that effectiveness plays in affecting sales when compared to that of side effects may be different for therapeutic classes other than antidepressants. While there appears to have been more improvement in side effect attributes than in average effectiveness within the antidepressant class of drugs since 1988, in other therapeutic areas, such as in the treatment of schizophrenia, or in gastroesophogeal reflux disease, this comparison could differ. The analyses of such variations could be the subject of useful future research.

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