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

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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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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.

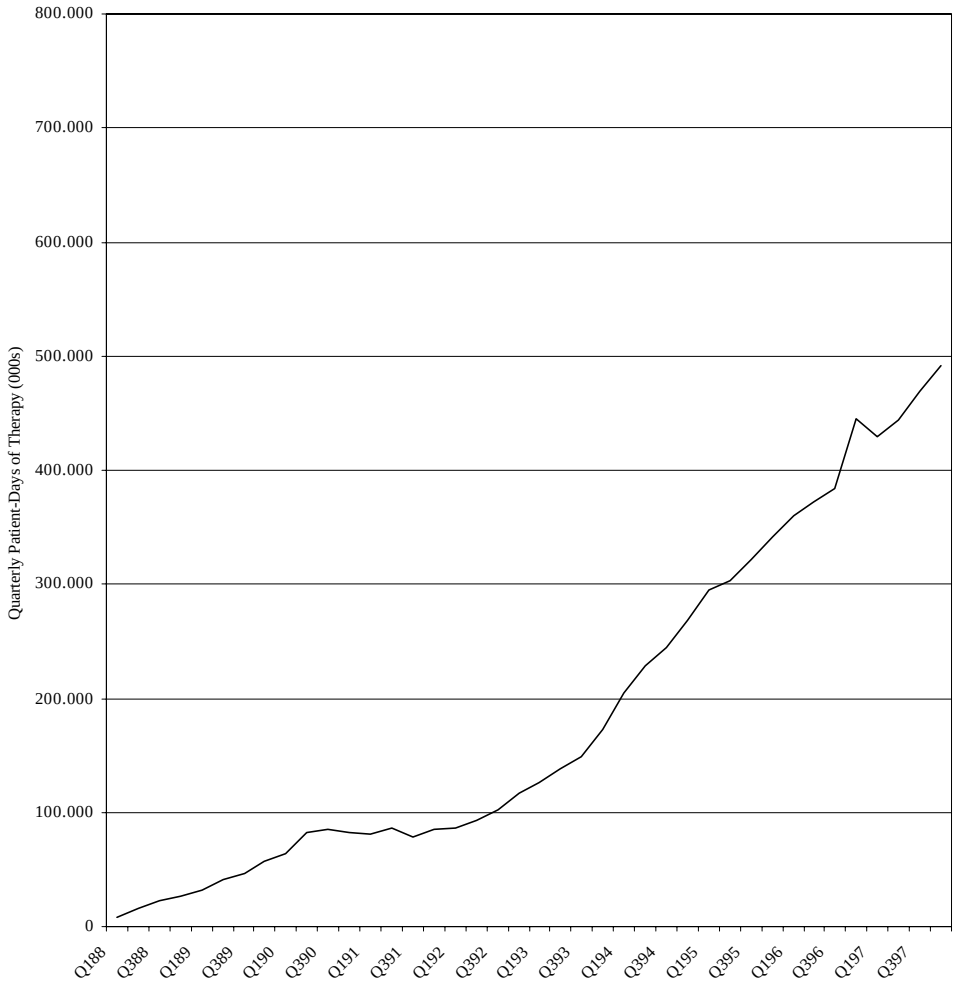

Figure 1. Industry Patients-Days of Therapy for SSRIs and Relative Products Q1 1988 - Q4 1997

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, $\bar{A}_{1t}$,

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