From Cocaine to Viagra:
An Economic and Social Analysis of the Pharmaceutical Industry

by

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To Mom and Dad, for their unwavering love and support, inspiring characters, superb guidance on my thesis, but most of all, their genes.

An especially heartfelt thank you to my mentor and advisor, Damien Sheehan-Connor, for guiding me through the darkest of tunnels, praising me when I found light, and helping me to refine my ideas both on and off paper. All this he graciously did for me during the year of his sabbatical.
I am forever indebted to Wesleyan for granting me the freedom to pursue an academic schedule that reflects my interests more closely than any pre-constructed major could. What distinguishes liberal arts schools from professional universities, and I think Wesleyan from many of the other liberal arts colleges and universities, is the focus on empowering the student. Whether his, her, or hir extra-curricular interests lie in athletics, drama, student government, activism, or any other activity, Wesleyan offers unparalleled freedom and support to pursue those interests. However, with knowledge and learning the focus of this institution, I believe that the academic individuality embodied by the University Major is prominent at the core of the Wesleyan experience.

I have written my Senior Thesis to be evidence of this liberal academic agenda. Had I the desire to write an economics thesis, I would have majored in
Economics. Similarly, if I had wanted to write a sociology thesis about healthcare, I would have chosen a Sociology or Science in Society Program concentration. If my intention were to put my readers to sleep, I would have worked in a lab and majored in one of the hard sciences. Instead, I chose the path of the University Major, combining my favorite aspects from all of the aforementioned fields. The interdisciplinary nature of this endeavor is highlighted through my pursuit of honors in General Scholarship rather than in any one department of the University. The term “scholarship” is relative; is it not intuitive that General Scholarship should mean something different at Wesleyan than it does at Williams, and still something different at Princeton? The idea of General Scholarship can therefore be expanded to read: General Wesleyan Scholarship. Well, what makes General Wesleyan Scholarship different from General Williams Scholarship and General Princeton Scholarship? The answer lies in what is at the heart of the university experience, for that is what sustains campus life, keeps students excited to learn, and feeds their hunger for knowledge. I have already established that I believe academic individualism is key, but a heart cannot beat without a left and right side, unless of course, you are a reptile. Right next to academic freedom at the core of the Wesleyan experience is the environment that fosters every student’s passion. It is the way that these two sides coexist, and in the case of Wesleyan, meld together, that determines what it means to be a General Scholar. The liberal heart of Wesleyan has earned us the wonderful reputation of being “edgy,” and I have constructed my thesis in line with what I interpret this to mean, whether or not it conforms
to conventions. Above all, I intend the content to be provocative, eye opening, and innovative—drawing from the fields of economics, sociology, and even biochemistry. In line with this, I have written in such a way that is not necessarily formal for a thesis but certainly proper, and as clever as my wit allowed and discretion thought appropriate. In all ways I could think of, I have designed this thesis to be the culminating project of a General Wesleyan Scholar. What follows, therefore, is my attempt at writing what I believe to be a true “Wesleyan” thesis.
Legal and Illegal Drugs: An Overview

Drugs. The word conjures up two meanings: those that are used therapeutically as prescribed by doctors, and those that are illegal and used recreationally. Although legislation and social perceptions have drawn a curtain between the two definitions, parting it can provide insight into many aspects of the modern day pharmaceutical industry. The dichotomy between prescription and illicit drugs overstates their differences, as many of today’s pharmaceuticals are closely related derivatives of some of the most stigmatized recreational drugs. Many would be surprised to find out that cocaine (benzoylmethylecgonine), Ritalin (methylphenidate), crystal meth (methamphetamine), one of the components of Adderall (dextroamphetamine), and MDMA, or ecstasy, (3,4-methylenedioxy-N-methylamphetamine) all share the same active portion of their molecular structures. Termed the pharmacophore, it is contrasted with the auxophore, which is the remaining
portion of the molecule not directly responsible for producing the intended
effects. More often than not, pharmaceutical drugs within the same class (e.g.
SSRIs and statins) will share a pharmacophore. The auxophore is commonly the
target of pharmacological research, as scientists modify it to alter flexibility,
hydrophobicity, or other binding-determining factors. Because all of the drugs I
mentioned have the same pharmacophore, crushing up and snorting Ritalin or
Adderal will produce nearly indistinguishable effects from coke, and analogous
ones to meth and ecstasy. There are many other examples of this in the
pharmaceutical industry. Pain relievers such as Oxycontin (generic- oxycodone),
Percocet (generic- oxycodone and acetaminophen), Vicodin (generic-
hydrocodone and acetaminophen), or any drug with codeine, are all extremely
similar to Heroin, as all are metabolized into some form of morphine in the body.
An anesthetic such as Ketalar (generic- ketamine) is structurally very similar to
phencyclidine (street name- PCP or angel dust), and produces comparable
effects.

Not surprisingly, the prices and consumer price expectations of legal and
illicit drugs differ substantially. On the street, drug users will rarely think twice
about paying $60 for a gram of cocaine or 3.5 grams of marijuana. Yet, many of
these same people are shocked by a $50 or $100 copayment on a one-month
supply of medication that offers tremendous therapeutic value. The
determinants of these differences in prices and price expectations provide a
useful window into the inner workings of the modern prescription drug market.
The best way to look through this window is with your own eyes: imagine that
while working out one day, you start feeling tightness and pain in your chest, but it subsides as soon as you stop exercise. This persists for several weeks, and you decide to see your doctor. After an examination, he informs you that you have elevated blood pressure, and gives you a prescription for the calcium channel blocker Norvasc (amlodipine). Hypertension is not considered an acutely dangerous condition; the main problem is that it puts you at greater long-term risk for heart disease and stroke. You take the prescription to the pharmacy, expecting the medication to cost you around $20- a reasonable price. As you check out, however, the pharmacist tells you that the cost for the one-month supply is $60. Shocked, what are the first questions that you ask? “Even with insurance?”, or maybe, “Is there a generic?” This thought experiment reveals two of the major reasons that patients expect prescription drug prices to be low. Moreover, it is no coincidence that neither insurance nor generic competition are intrinsic in the market for illicit drugs, for which users in turn expect and are more willing to pay higher prices. It is worth noting that generic competition is not the only type of drug-drug competition in the pharmaceutical industry.\footnote{Lichtenberg and Philipson (2002) refer to generic competition as “within-patent” competition because it occurs between firms marketing the same molecule, which was originally protected by one patent. By the same logic, they refer to competition between follow-on drugs as “between-patent” competition because firms are competing with different molecules protected by distinct patents. I will use these terms throughout this thesis.}

While it may more readily come to patients’ minds, follow-on drug competition is also virtually non-existent in the market for underground drugs, and is at least
as important in the scheme of the entire market for prescription drugs. In order to make this analysis more insightful, I therefore expand the scope of competition to include all drug-drug competition, and use it as a lens to explore the relationship between the markets for prescription and illegal drugs.

Similarities between the pharmaceutical and illicit drug industries are seldom, if ever, considered, and I believe that they have been underappreciated. Policy makers, economists, and the public continually battle with ways to regulate drugs of abuse and drugs of medicine. On the surface, these two issues seem to have little in common, but both boil down to concerns over social welfare. The connection to the underground drug industry is easy to see because illicit drugs only cause societal harm. Pharmaceuticals, on the other hand, extend and enhance human life, but many critics point to grossly overestimated research and development (R&D) expenditures, excessive advertising costs, unjustifiably high prices, a lack of innovation, class fractionalization, and the unacceptable risks of some drug introductions as ways in which drug companies are inefficient, immoral, and in desperate need of reform. In this thesis, I use a comparison to the illegal drug industry, and then three carefully selected case studies, to explore the extent to which these allegations are true. As I have mentioned and will later expound upon, drug-

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2 In this thesis, I define a “follow-on drug” as any drug carrying a distinct brand name that is introduced to a given class after the breakthrough drug. This includes reformulations and derivatives of existing drugs only if they are not grouped into the family of their parent molecule. For example, I do not consider Paxil CR a follow-on drug because its sales are included in the Paxil family. I do, however consider Lexapro a follow-on drug even though it is a derivative of Celexa. Further examples and explanation will be offered throughout this thesis.
drug competition proves to be the basis on which the modern-day pharmaceutical industry is built. I pay particular attention to between-patent competition, and find examples of innovation and therapeutic advancement, but also many of resource waste and misleading marketing practices. Interestingly, the troubles I identify within the pharmaceutical industry appear to stem from the same force that fuels the illegal drug industry: irrational demand. Different from the market for illicit drugs, I find that drug companies induce irrational demand primarily through superfluous promotional expenditures, and I ultimately set forth a novel policy that would largely resolve the issue.

The way in which I define "irrational demand" is crucial in understanding my argument as to how it is induced. Broadly, I take it to mean demand for a drug that cannot be explained by the quantifiable clinical benefits that would flow from use of the drug, namely its clinical profile. The clinical profile of a drug is composed of two factors: therapeutic efficacy and adverse side effects. Where the general consensus over illicit drug use is that it confers only negative effects, arguably all demand for underground drugs is irrational. Of course, demand for products never is entirely based upon measurable rational consideration, and I recognize that consumer preferences and biases inevitably creep into the market and contribute to the utilization of any product. When I write below about irrational demand, what I mean is that the primary force that is driving utilization is something other than measurable data regarding demonstrable clinical benefit from the choice that is made. It is therefore important to take as objective an approach as possible when determining the clinical profiles of
drugs. I use the results of published clinical trials to determine how the relative therapeutic and adverse effect profiles of drugs within a class match up, but also note that the source of funding frequently causes bias that heavily skews the findings of studies. I develop the concept of a publication environment in part to detect such biases and determine the real relative therapeutic profiles of competing drugs.3 If follow-on drugs of similar therapeutic profiles perform as well or better than the drugs they are comparable to, I infer that irrational demand is present.

**Health Insurance and Competition**

Calling back to health insurance and drug competition, a closer inspection reveals that they contribute to many of the current differences between the markets for legal and illegal drugs. To take a somewhat economically oriented approach, we can break down each into their supply and demand side components. Health insurance, while a topic of heated and thoughtful debate, has a much more straightforward effect on the pharmaceutical industry than competition does. I plan on addressing the significance of drug competition in great detail, as it is, in fact, the basis for my thesis, so I will briefly tackle the issue of health insurance first.

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3 The publication environment is discussed in greater detail immediately after this introduction.
Health Insurance: Demand Side

It is no secret that health insurance increases prescription drug utilization by reducing the prices that patients must pay for drugs. This effect was documented by the RAND Health Insurance Experiment, a multi-million dollar undertaking conducted from 1974 to 1982. The investigators randomly assigned health insurance plans with different coinsurance rates to nearly 6,000 subjects. Among other findings, they concluded that the copayment a patient faces is inversely proportional to pharmaceutical utilization (Lohr et al., 1986). This effect has persisted in recent years, with copayments continuing to decrease and drug utilization remaining on the rise (Berndt, 2002; IMS, 2011). The connection between insurance and utilization is apparent, but the extent to which low copayments cause overutilization is anything but straightforward. Studies attempting to quantify overutilization generally rely on some combination of average drug prices and estimates of quality adjusted life years (QALYs), and each seems to produce a different result. To do this topic justice is beyond the scope of this thesis, but as I only consider it as a driving force of demand, I will not discuss the effects it has on drug supply.

To put this effect in the context of the previous example, $60 a month, or $2.00 a day, is a small price to pay for a medication that significantly reduces your risk of heart failure and stroke. Without insurance, the Middletown Rite Aid on Main Street charges $104.99 for a month supply of generic amlodipine, and $271.99 for the same supply of Norvasc (Rite Aid, 2012). If you were going
to the pharmacy before 2007 when generic amlodipine was not available, paying $60 for Norvasc would have been 80 percent off! Even with the option of generic amlodipine, I would argue that getting 40 percent off of a potentially life saving medication is a bargain. However, the current structure of copayments means that a month supply of amlodipine can cost as little as $10 per month with good insurance coverage (Rite Aid, 2012). While a 90 percent discount may be towards the upper limit of third party coverage, patients have come to expect to pay very little for their medications, a mindset that fosters high prescription utilization.

**Competition: Supply Side**

As I mentioned, drug competition is prevalent in two forms in any given therapeutic class of drugs. Between-patent competition occurs as soon as the first follow-on drug enters a class, which can be anywhere from months to years after the introduction of the breakthrough drug. Each successive follow-on drug intensifies the competition, and it is a combination of these factors that makes between-patent competition arguably more significant than within-patent competition.\(^4\) One of the most important, if not the primary aspect to pay

\(^4\) A breakthrough drug, sometimes referred to as a pioneer or innovator drug, is the first drug in a given therapeutic class. Examples include Prozac for the SSRIs, or Mevacor for the statins.

\(^5\) Lichtenberg and Philipson (2002) found that between-patent competition impacted the innovator firm’s profits more than within-patent competition. I will discuss this point in further detail in the literature review.
attention to on the supply side is the cost of production. For any breakthrough or follow-on pharmaceutical, the two largest are R&D and marketing. I will get into the details of R&D estimates in the literature review, but for now it suffices to know that they are highly contested. They have been estimated to be as low as $100-$200 million per drug (Relman & Angell, 2002; Light & Warburton, 2011), and as high as $1.32 billion per drug (PhRMA, 2009). The money large pharmas spend to promote their products is also no small bill, exceeding $10 billion in the U.S. in 2010. Advertising can be targeted at healthcare professionals through physician detailing or, to a lesser extent, medical journal advertising, or geared towards patients through what is called direct to consumer advertising (DTCA). Once a drug company has perfected the formula for and synthesis technique of a drug, the marginal cost of production is close to or equal to zero, often described as “pennies per pill” (Frank, 2004). The costs associated with illegal drugs take a very different structure, though are similarly quite large. Rather than R&D and advertising, the costs of illicit drugs are sunk in the risks associated with their production, trafficking, and possession. This type of cost is difficult to quantify because risk is subjective to the person who burdens it. The more senior members of a drug train are likely to be of a higher socioeconomic status, better educated, and have much more to lose than the

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6 Detailing is the practice of sending sales representatives to physicians’ offices to promote a company’s drugs. It includes giving doctors free samples of the company’s newest medication in the hopes that they will give it to their patients to try, and then will continue to prescribe it after the sample runs out.

6 DTCA primarily occurs in the form of television commercials and other ads.

7 The marginal cost of production is the cost of producing one more unit of that good. Today’s mass production techniques frequently result in decreasing marginal costs of production due to economies of scale.
average street-level drug dealer. Marginal costs are low, but must be higher than they are for pharmaceuticals because of the risks of producing them. While the pre- and post- production costs associated with legal and illegal drugs manifest themselves quite differently, they are enormous for both industries and must be recouped through sales revenues.

High costs of production are not a problem in the pharmaceutical industry so long as they translate into drugs that help patients. As critics of follow-on drugs point out, however, a majority of drugs that enter after the breakthrough product do not confer clear clinical advantages over pre-existing treatments in their class (Hollis, 2009). As more of these highly similar follow-on drugs enter a class, the nature of competition begins to resemble that which occurs in the markets for illicit drugs. We will see an example of this in Chapter 3 with the antidepressants. The subsets I focus on, SSRIs and SNRIs, consisted of six branded drugs at the peak of the class, none of which offered any concrete clinical advantages over the others for treating depression or anxiety.\(^8\) To the contrary, there were two that were actually associated with more serious adverse effects, yet their sales performed quite well. Picking one of these antidepressants was often just a matter of physician preference, just as it would be for someone faced with the choice of buying coke from one of six dealers. Some of the dealers might offer products of slightly higher or lower purity, the drug user might perceive differences among product quality that may or may not

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\(^8\) SSRI- selective serotonin reuptake inhibitor. SNRI- serotonin-norepinephrine reuptake inhibitor
be real, or they may simply like one of the dealers more, but it probably does not matter whom her or she buys from. It is in classes like these, critics of follow-ons argue, that prescription drugs do not help patients because they do not add incremental benefits to treatment. Therefore, the expenses to bring them to market and promote them are a waste and should be spent on more innovative R&D.

That which I have just lain out is one of the stronger cases against follow-on drugs. In a similar fashion, most of the best points made by both sides use costs or expenses to support their argument or discredit their opponent’s. Pharmas justify the high prices of drugs by citing high R&D costs, but the opposition contends that R&D estimates are purposefully exaggerated. Supporters of large pharma also defend some of the more similar follow-on drugs on the basis of needing to recoup R&D expenditures. On the other side of the argument, similar follow-on entry fractionalizes the market and reduces the profits of the innovator firm, a problem made worse by high spending on advertising. That both sides rely heavily on cost-based arguments reveals the emphasis they place on the side of supply. For the most part, the study of demand side competition has been limited to the ways in which marketing affects the market share of drugs.\(^9\) Such studies generally find a positive relationship between advertising efforts and individual market share, but they do not discuss how the clinical profiles of the drugs match up. One reason may

\(^9\) This is discussed in some detail in the literature review.
be that there is no clear way to quantify a clinical profile, so the strictly economic nature of these studies prevents the authors from delving into medical journals for the results of clinical trials. Marcia Angell, one of the most prominent critics of follow-on drugs, acknowledges the ability that physician detailing has to distort doctors’ perceptions, but does not see it as the biggest problem in the pharmaceutical industry (Angell, 2004). She believes that excessive follow-on entry is the most troubling, and puts forth a policy requiring all potential follow-on drugs to demonstrate superiority over approved medications through head-to-head trials. I contend that such a policy would be detrimental to the innovation of the pharmaceutical industry.

One of the bases on which I chose the classes for the case studies was the significant social impact each has had on the world. Three of the four were the best selling classes in the U.S. during their peak years, and two of them the best selling in the world.\textsuperscript{10} Even in such significant classes, there is ample evidence of follow-on drugs that offer no clear therapeutic advantages turning huge profits. This is not the case for all drugs introduced into these classes, but we will see that it is true for many. The more similar follow-ons that enter a class, the more the choice facing a doctor becomes analogous to a drug user choosing between drug dealers offering more or less the same product. The costs of producing both types of drugs are high, and the prices paid for them far exceed their

\textsuperscript{10} H2 blockers, proton pump inhibitors (PPIs), antidepressants, and PDE-5 inhibitors for erectile dysfunction. The first two were each the best selling class in the world at their peak, and the third the best selling in the U.S. at its peak.
marginal cost of production. Furthermore, the substantial similarities between the products of each market leads to intense inter-class competition. We might expect the drug-drug rivalry to compete away most of the profits, but instead we see huge profit margins in both cases. We know that sales, and in turn profits, of illegal drugs are fueled almost entirely by irrational demand, for that is the nature of substance abuse. This comparison suggests that we depart from looking at costs to explain the problems in large pharma, and instead pay more attention to the idea of irrational demand.

**Competition: Demand Side**

In the debate over follow-on drugs, irrational demand is present as the driving force for why clinically similar or equivalent follow-on drugs can be so successful, and in some cases even outperform the breakthrough drug of the class. In the market for illegal drugs, arguably all demand is irrational, because drug abuse contributes nothing to society. Even though it may induce euphoria in moderation, it is still detrimental to productivity and health. This type of use is self-reinforcing, and is contrasted with addiction. Abuse among addicts is not driven by the desire to feel good so much as it is to avoid the misery of discontinuation. When used properly, prescription drugs are neither self-reinforcing nor addictive, meaning irrational demand is not inherent in the same way it is in the market for illegal drugs. Yet, we see evidence of it when clinically similar follow-on drugs perform as well or better than the drugs they are
comparable to. Such demand is artificially created in the pharmaceutical industry, and I identify five categories that I believe can explain most irrational demand.

Those five non-therapeutic determinants can contribute to success in follow-on drugs that offer little to no clinical advantage include: 1) Absolute advertising expenditures. There is a direct and statistically significant correlation between the money drug companies spend on promotion and the success of the drugs they promote. 2) FDA-approved indications. The examples I look at demonstrate that being the only drug in a class with a given FDA-approved indication bolsters sales, even though off-label use of competing drugs proves just as effective. 3) Length of time on the market. A drug accumulates more reported adverse events the longer it is on the market, which can make newer drugs appear to have better side effect profiles. 4) Publication environment. In short, the publication environment relates the results of clinical trials to the events occurring within a market at the time of their publication. A more detailed description follows this introduction. 5) Pricing strategies. Price is frequently a legitimate determinant of demand, as there is a clear inverse relationship between the price of a good and the quantity of it purchased. I present empirical evidence, however, of several strategies drug companies employ to bolster their drugs’ market shares or sales revenues. Points two, three, and four are highly dependent upon the first, because their recognition among physicians is directly related to how much/well they are communicated through detailing. A common practice that will become apparent is of drug
companies coordinating bursts of intense detailing with significant FDA approvals or competing patent expirations.

I conduct each case study in light of these five non-therapeutic determinants and provide greater detail into each. To generalize my findings, strategic and aggressive marketing tactics by pharmaceutical companies are frequently the underlying cause of irrational demand. We see this first in the market for H2 blockers, a class that revolutionized the treatment of ulcers and acid reflux. The innovator drug, Tagamet, was overtaken by the first follow-on drug, Zantac, mainly through marketing efforts emphasizing transient differences in FDA approvals and adverse effects. Introduced over a decade later, the proton pump inhibitors (PPIs) in turn offered greater efficacy over H2 blockers, but irrational demand prevented their immediate replacement of the older class. Within the PPIs, Nexium serves as a model for how the promotion of biased clinical trials, in addition to differences in FDA approvals, can skew how the drug is perceived and lead to success in the face of similar branded drugs and an effectively identical generic alternative. The marketing for Nexium was and continues to be so successful that many people still believe it to be superior to other PPIs, despite the lack of concrete evidence supporting this. I then move on to SSRIs, which offered a new treatment for depression with fewer side effects than the medications that came before them. The results of clinical trials suggest that the SSRIs and SNRIs are the most therapeutically similar drugs of any of the three case studies. The nature of mental illness, however, creates a race to fill niches for specific disorders (e.g., OCD, panic disorder, anxiety
disorders, etc.) that promotes the perceptions of certain drugs as better for certain conditions. The persistent, and often times greater profits of each successive follow-on, makes the antidepressants the archetypal example of the irrational demand that marketing can induce.

The last class of drugs I identify is the phosphodiesterase-5 (PDE-5) inhibitors used to treat erectile dysfunction (ED). They serve as an example for how follow-on drugs can provide clear advantages over pre-existing therapies. The long half-life of Cialis relative to Viagra made its effects last many times longer than Viagra’s, and therefore a more effective treatment for ED. The market responded appropriately to the innovation of Cialis; the market share and sales of Viagra rapidly fell and Cialis’ concomitantly increased. This is not to say that the market was perfectly efficient, however, as Lilly (the manufacturer of Cialis) still had to spend large amounts of resources to promote Cialis. What this points out is that even when a drug is objectively better, it cannot rely on its clinical merits alone to sell itself. The pharmaceutical giants have set a precedent of exorbitant advertising expenditures, and if any drug is to be successful in its class, it at least has to keep up with the promotion of other drugs. Another problem caused by the practice of excessive advertising is that it arguably causes generic underutilization. The very purpose of generic drugs is that they are not associated with any single manufacturer, and therefore subvert the incentives of advertising. That incumbent drugs are heavily backed by advertising, but especially that it can create perceived differences from generic
molecules, makes patients less willing to switch drugs, even though it would cut health care expenditures.

The structure of the thesis from this point is as follows. In chapter 1, I present a review of the literature as it relates to the debate over drug competition. This naturally encompasses part of the heated dispute over the costs of drug production, though the majority of papers focus on follow-on drugs. In chapters 2, 3, and 4, I analyze the markets for GI drugs, antidepressants, and ED drugs, the findings from which I have just summarized. I utilize data I have collected myself from FDA databases and drug companies’ SEC filings, as well as a compilation of data and conclusions from some important publications pertaining to these classes and issues. The wide range of data and analyses on which I draw allows for a particularly insightful look into the pharmaceutical industry, well beyond the scope attainable by a strictly economical meta-analysis. As I discuss in the literature review, to the best of my knowledge, no other study has conducted an analysis of so many classes over such an extensive period of time. In each chapter, I relate my findings to the current debate over follow-on drugs, and in the conclusion, provide a fresh perspective and policy suggestion.
A Note on the Data and Methods

An Explanation of the Publication Environment

I developed the idea of a publication environment as a way to relate the clinical findings of drugs to the state of the market at the time the results were published. It is not empirical by nature, and I admit that it has several limitations, but it also offers some key insights into the classes to which I apply it. In order to identify the results of clinical trials, I conducted searches within PubMed and the Cochrane Library that conformed to a formula I developed and found to yield reasonable results. In searching for literature comparing drugs ‘x’ and ‘y’ (‘x’ and ‘y’ representing the generic molecule names), I would enter “(x AND y) AND (clinical OR compar* OR meta)” into the search builder with no restrictions on the field. Sorting by year, I started at the earliest date and worked forward, taking note of article titles that indicated the paper published the findings of a clinical study or meta-analysis, and contained the name of at least one of the drugs. I restricted my time frame to 5 years pre- and post-introduction of that drug. I downloaded and read any papers whose abstracts mentioned a comparison of the drugs I searched for, or any other drugs in their class. I would note the findings and sources of funding/conflicts of interest if they were reported. Granted, this method is by no means comprehensive, but I believe it to give an accurate overview of the literature surrounding the introductions of drugs.
I then looked for consistency (or lack thereof) among studies comparing drugs of the same class or competing classes. Overwhelmingly, studies funded by a drug firm found their own drug to be superior to those it matched up against, which is consistent with the findings of other authors (Gartlehner et al., 2011, Als-Nielsen et al., 2003). Funding bias is a serious issue, and was prevalent in inter-class comparisons of PPIs and antidepressants. To overcome this, I focused on studies funded by non-industry sources, and these usually found the drugs of contention to be equivalent in most regards. I also looked at meta-analyses, which took into account funding biases, and almost always found that all PPIs and antidepressants were equivalent. Unfortunately, reporting sources of funding and conflicts of interest only became common in the mid 1990s, so it is difficult to draw conclusions about the biases of most articles before then. It was quite apparent when drugs offered objective benefits over their predecessors. Examples relevant to this thesis include PPIs over H2 blockers, SSRIs and SNRIs over tricylcic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), and Cialis over Viagra. I found no articles that disputed any of these claims.

Sources of Data

Data on all drug approval dates, indications, and priority ratings were taken directly from the “FDA Orange Book” and “Drugs@FDA” drug databases. Data regarding adverse drug effects, half-lives, and other drug specific chemistry were taken from the individual drug labels, which I obtained from the
“Drugs@FDA” database. All company financial information was obtained directly from the SEC filings of each company, available through the government-sponsored database “EDGAR.”
CHAPTER 1

Literature Review

Pharmaceuticals in Context

National healthcare expenditures (NHE) amounted to nearly $2.6 trillion dollars in 2010, and accounted for 17.9 percent of our GDP (NHE tables, 2010). The huge amount of money that Americans spend on healthcare, more than any other country, has drawn many scrutinizing eyes searching for ways to cutback on superfluous spending. It may come as a surprise to many, however, that there are much more efficient ways to curb America’s spending on healthcare, as expenditures on prescription drugs only accounted for $260 billion, or 10 percent, of total NHE in 2010 (NHE tables, 2010). The comparatively small amount that we spend on drugs actually explains why the pharmaceutical industry has only attracted attention within the last ten to twenty years. A prominent nineteenth-century economist, Alfred Marshall, described this phenomenon as “the importance of being unimportant.” If expenditures on a good are perceived to be relatively small, then that good generally remains off
the agenda for ways to cut costs (Berndt, 2001). The data support this hypothesis, as the spending on prescription drugs per capita has increased from $159 in 1990 to $839 in 2010. That is not to say this progression has been completely rational, as the traceable and quantifiable nature of drugs makes them an easy topic for economists and policy makers to focus on. Contributing to this is the unrivalled profitability of the pharmaceutical industry, which CNN Money consistently rates as one of the top ten most profitable industries. The top three most profitable pharmaceutical companies in 2010, Merck & Co., Johnson & Johnson, and Bristol-Myers Squibb, reported profits for that year of $12.9, $12.2, and $10.6 billion, respectively (CNN Money, 2010). The latter of these corresponds with a 102 percent increase in profits from 2008.

Interestingly, and I think highly significantly, the two prominent issues that address the debate over wasteful spending are exactly those which differentiate the pharmaceutical industry from the illicit drug industry: health insurance and drug-drug competition. Critics argue that health insurance, particularly increasing third party coverage of prescription drugs, encourages patients to utilize pharmaceuticals when they are not necessary. The argument concerning drug-drug competition is two-tiered. On one level, many argue that spending on the development of follow-on drugs, often referred to as “me-too” drugs, is wasteful because they usually offer little to no therapeutic advantage
over pre-existing drugs.\textsuperscript{1} The other aspect is that patients as a whole do not utilize generic drugs as much as they should, thereby circumventing an effective cost-saving measure. As will become apparent by the conclusion of this thesis, the two are interrelated and should not be considered in isolation.

\textit{Pharmaceuticals in Competition}

Most scholars who are involved in the debate over follow-on drugs stand sharply divided between the two sides of the issue. During my research, I have come across handfuls of economists who hold that the benefits of follow-on drugs far exceed their drawbacks, but I have also found an equal number who will disagree with them to the bitter end. That I can count on one hand the number who walk the dangerous middle ground I think says something about the nature of the argument but, more significantly, the nature of the economic analyses. Econometric analyses of the pharmaceutical industry fall into the field of pharmacoeconomics, which focuses on studying the impacts specific events or trends such as policy changes, drug introductions, or changes in expenditures have on the market and patients. The ability to draw statistically significant generalizations is one of the greatest strengths of pharmacoeconomics, but also its greatest weakness. Properly analyzed data can be useful in helping to shape policies and decisions, but the wide array of data required to draw statistically

\textsuperscript{1} DiMasi and Paquette (2002) point out that the term “me-too” drug attaches a stigma to them by suggesting they copy the breakthrough drug. As we will see, this is usually not the case.
significant conclusions encourages economists to over-generalize. For example, a finding that increased drug entry leads to price competition may be statistically significant, but entirely ignores class distinctions where this finding may not be true. As we will see throughout this thesis, economists on both sides tend to use broad data, which is the primary reason why most support exclusively one side of the argument. Data showing that increased drug entry sometimes lead to price competition but sometimes does not would by definition not be statistically significant; there is generally very little room for middle ground conclusions. To address this problem, many economists restrict their analyses to single classes during a set time period, but this in turn limits their ability to draw conclusions about follow-on drugs as a whole. The best of these I have found either focus on one class for a long period of time, or many classes for a very short period of time. To the best of my knowledge, there have been no attempts to look at multiple classes over a long period of time. One of the strong points of this thesis, therefore, is that it looks at some of the best selling classes of drugs in the world through 2010, and relates the findings of these to the debate over the utility of follow-on drugs.

The Arguments Against Follow-on Drugs

Those who oppose the development of follow-on drugs lay out three main arguments against them: 1) they require large amounts of resources in the form of R&D and advertising, but offer little to no added therapeutic value; 2) they
harm incentives for innovative R&D; and 3) they carry an unacceptable benefit-risk ratio. To some extent, these arguments assume that pharmaceutical companies attempt to imitate the success of breakthrough drugs by simply modifying their chemical structures and marketing the resulting molecules as their own. These arguments also depend on the degree to which follow-on drugs copy breakthrough drugs versus add some clinical value. The first assumption is problematic because most follow-on drugs are a result of parallel development rather than *post hoc* imitation. Between 1990 and 1998, approximately 56 percent of follow-on drugs were already in phase III clinical trials by the time the breakthrough drug for their class was approved, and about 72 percent of them were preparing to enter phase II clinical trials (DiMasi & Paquette, 2004). These data portray a majority of drug development as a race for first in class approval, with one company just happening to win.

The idea that there are varying degrees of follow-on drugs is an important concept that Aidan Hollis addresses. In some cases, follow-on drugs offer advantages in terms of therapeutic efficacy, side effect profiles, and dosing regimens. On the other hand, and what seems to be the case in the majority of follow-on drug introductions encompassed by the three case studies, follow-on drugs diverge very little from the breakthrough drug of their class. One approach to quantify the benefits of follow-on drugs seeking FDA approval is to look at the review rating assigned to them by the FDA. In order to make the drug approval process more efficient, the FDA prioritizes the approval tracks of drugs supported by early evidence suggesting they may bring clinical advantages to
the market. Between 1975 and 1992, drugs were given ratings of A (important therapeutic gain), B (modest therapeutic gain), or C (little to no therapeutic gain). This system was replaced by a two-tier one of P (priority) or S (standard) in 1992. Of 235 follow-on drugs spanning 72 classes approved between 1960 and 1998, 33 percent received an FDA priority rating (DiMasi & Paquette, 2004). One problem with this finding is that the authors funneled all A and B rated drugs into the P classification with the policy change enacted in 1992. Of the 125 drugs from 13 classes approved after 1981 that I identified during the research for this project, only 2 follow-on drugs were given priority ratings, while every breakthrough drug was given a priority rating. In my experience, it seems that P ratings are reserved for breakthrough drugs or exceptionally special follow-ons, so assuming drugs that received a B rating prior to 1992 would be granted a P rating today is presumptuous at best, and a source of overestimation. Other problems with using FDA review classifications to assess the relative qualities of drugs are that the rankings are not always internally consistent, and they are made purely based on preliminary evidence (Grabowski et al., 1976; Wardell et al., 1980). As we consider both sides of the argument over follow-on drugs, it is important to remember that they are not always simple copy-cats of breakthrough drugs as the term “me-too” suggests, and that they sometimes offer clinical advantages, though probably less than a third of the time.
The High Costs of Follow-on Drugs

Critics of follow-on drugs cite high R&D and advertising costs as a largely wasteful allocation of resources. The strongest component of this argument is that it is independent of concerns about parallel development and post hoc imitation. Follow-on drugs resulting from parallel development require just as much pre-clinical research and testing as breakthrough drugs, while designing an imitator drug presumably takes many fewer resources on the pre-clinical end. Both types of drugs, however, have to undergo phase I-III clinical trials, and these have been shown to account for about 70 percent of out-of-pocket R&D spending (Berndt, 2002). Furthermore, the average amount of time drugs spend in clinical testing has increased recently, as have the number of patients involved, making these trials continually more expensive (Berndt, 2001). This means that the most expensive part of R&D is also the part that all drugs have to engage in, regardless of their novelty. Even the differences among the efforts required on the pre-clinical end of testing barely affect a firm’s development expense. A study conducted by the NIH in 2000 found that a majority of the pre-clinical research leading towards drug discovery is done outside of the industry, usually in academia or at the NIH (Relman & Angell, 2002).

The other major expense of pharmaceuticals can be attributed to advertising. While this may not be directly associated with their drug development, it is entrenched in the market for pharmaceuticals and must be accepted as an intrinsic cost. Advertising expenditures are so high that it is
common for them to exceed a drug’s revenue in the first two years on the market (Grabowski, Vernon, & DiMasi, 2002). Looking at the U.S. market as a whole, pharmaceutical companies spent more than $10 billion in DTCA and detailing combined in 2010 (IMS Integrated Promotional Services, 2010). This statistic does not even account for the cost of free samples given to physicians, but the IMS estimation is difficult to find. In 2004, IMS estimated the cost of free samples dispensed to physicians to be nearly $16 billion dollars, so it is likely that $10 billion in marketing is underestimated (Gagnon & Lexchin, 2008). This is another cost that is similarly high among breakthrough and follow-on drugs of all degrees of novelty. We will have a chance to look at this closer in each of the case studies, but generally speaking, drug companies need to remain competitive with their promotional spending if their drug is to be successful. On top of this, drugs in less differentiated markets utilize prodigious advertising to increase their demand and decrease their price elasticity (Rizzo et al., 1999; Windmeijer et al, 2005). A common practice we will see involves companies funding large increases in physician detailing or DTCA when their drug is approved for an indication that no other drug in its class has, even though off-label use of competitor drugs proves just as effective (Azoulay, 2002; Berndt et al., 1996). By doing this they emphasize superficial differences between drugs, and often

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2 Price elasticity (of demand) is an economic measure reflecting how demand for a given product responds to changes in its price. If the sales of a product decrease sharply when its price is increased, it is said to have a high price elasticity. Conversely, if the sales of a product change very little after the same price increase, it is not very price elastic. Huge markets consisting of firms selling identical products (e.g. agriculture) are often considered perfectly elastic, meaning any competition through price will result in zero sales for that firm, and goods that are considered necessities (e.g. insulin shots) are perfectly inelastic because their demand responds very little to price fluctuations.
create false perceptions of superiority. Such practices have constructed a system in which follow-ons that do offer some sort of clinical advantage are not clearly differentiated on the basis of their merits and still require huge amounts of promotion, while drugs that offer no clinical advantages can successfully obscure that fact with millions of dollars in promotion. The presence of excessive follow-on drugs has set a precedent for lofty and wasteful advertising expenditures, and even objectively better drugs must follow suit.

Follow-on Drugs Diminish Innovation

The argument that follow-on drugs diminish innovation to produce new therapies in undertreated conditions stems from the idea that their presence in a market decreases the profits earned from breakthrough drugs (Hollis, 2005). It is true that a pure monopoly confers the greatest financial gains on the producer, but it also is associated with the greatest amount of deadweight loss to society. This highlights the ambiguity of the argument, because critics of me-too drugs presumably mean to find some balanced market size where the profits of the most innovative firms are acceptable and the benefits to society are reasonable. Assuming that this argument opposes excessive follow-on introductions (whatever that may mean), it conceptually makes sense. Between-patent competition (competition between branded drugs), somewhat counter intuitively, is more detrimental to the profits of the innovator firm than within-patent competition (generic competition) (Lichtenberg & Philipson, 2002). The
authors explain this finding with differences between the timing at which each occurs: between-patent competition occurs anywhere from months to years after the first-in-class introduction, whereas within-patent competition generally occurs after the breakthrough drug has been on the market for at least ten years. A similar story exists between generic breakthrough molecules and incumbent follow-on drugs, at least in the markets for H2 blockers, PPIs, ACE inhibitors, SSRIs, and statins. The sales of branded drugs in these classes were not significantly affected by the entrance of a generic breakthrough molecule, and in fact continued to increase in most cases (Jena et al., 2009).

The harm of follow-on introductions is made worse by the fact that the period of exclusivity that breakthrough drugs enjoy before follow-on entry is shortening. Between 1970 and 1998, the average amount of time a breakthrough drug had on the market before second-in-class entrance decreased from 8.2 to 1.8 years (DiMasi & Paquette, 2004). As the authors note, this may not be bad if it is occurring because of increased technological advancement and higher returns per period of time, but scholars such as Hollis interpret it as less time for firms to make money. Profits are also hampered if price competition occurs as a result of increased entry, though lower prices arguably instill greater social welfare. Several analyses have been conducted studying the effects of and extent to which price competition occurs, and the results are by no means congruent. As such, it is more useful to discuss price competition as it applies to each class, though I will make a few general observations here. An older study looking at drug introductions between 1978 and 1987 found that the greater
number of incumbent drugs that were on the market at the time a drug was introduced corresponded to a lower relative launch price to the previous introduction (Lu & Comanor, 1998). Launch prices were still on average higher than the mean price of pre-existing drugs: ‘A’ rated drugs were launched 3.11 times higher, ‘B’ rated drugs 2.21 times higher, and ‘C’ rated drugs 1.15 times higher. Another interesting finding was that the closer the launch price was to the median price of treatment, the more the average real price of treatment rose over the subsequent eight years. For the sake of brevity, it suffices to say that there are further studies in which additional entrants led to no observable price competition, and in some cases, price increases (Hollis, 2005). We actually see an example of this “reverse price competition” first hand in the case of H2 blockers for treating stomach ulcers and acid reflux.

Unlike the first argument laid out against follow-on drugs, the issue of decreasing incentives is highly contingent upon the extent to which the follow-on drug is a “me-too” drug. If drug manufacturers expect the entrance of similar products to enter soon after the introduction of their own product, they have less of an incentive to spend money on pioneering new drugs. On the other hand, if they have reason to believe that they will compete with fewer, more differentiated products, and enjoy a longer period of exclusivity, breakthrough R&D becomes more profitable. In the first scenario, the R&D undertaken to produce the highly similar drugs yields little social benefit, and the high advertising expenditures fragment the market and reduce the innovator firm’s profits. The later case, however, is associated with R&D justified by clinical
benefits, and the advertising costs, though high, will have more of a class-expanding effect. Contrary to the way markets for most goods behave, therapeutically similar pharmaceuticals primarily compete through marketing rather than price, as it is generic drugs that compete through price (Hollis, 2005).

Follow-on Drugs Have a Low Benefit-Risk Ratio

The argument about the risks of follow-on drugs, as put forth by Hollis, is entirely theoretical, though my analysis of the market for antidepressants provides it with some empirical legs on which to stand. It applies strictly to follow-on drugs that are highly similar to their predecessors, but merits discussion, as a majority of them seem to fall into this category. Consider a market consisting of only a few drugs, all of similar clinical profiles. Presuming they have all been on the market for several years, phase IV clinical trials and patient/physician experience have ensured their safety. If an additional drug offering no significant therapeutic advantages is introduced, phase I-III clinical trials have only assessed its efficacy and short-term side effects. Long-term effects are unknown, and therefore the new drug poses a risk with no added benefit (Hollis, 2005). As we will see in more depth, this argument applies to the market for antidepressants. The introductions of Paxil and Effexor added few, if any, therapeutic advantages to treating depression or anxiety. Eight to ten years after their launches, several investigations were undertaken exploring an
increased risk of suicide while taking these drugs, culminating in FDA-mandated black box suicide warnings being added to antidepressant labels in 2004.

This point, as well as the other two to some extent, would be resolved if only those follow-on drugs that offered clear clinical advantages over pre-existing treatments were allowed to enter the market. Whether the advantages are in the form of higher rates of healing, faster response times, or fewer adverse side effects, critics contend that clinical trials should be able to clearly demonstrate these benefits. Some scholars have proposed policies that attempt to limit the harm caused by follow-on drugs, the most notable of which would require drugs seeking FDA approval to demonstrate some form of clinical advantages in direct head to head clinical trials with what is deemed to be the market leader (Angell, 2004). Due to the issue of parallel development that DiMasi and Paquette identified, perhaps a more reasonable policy would allow for an 18 month window after first in class introduction during which subsequent drugs need not demonstrate head to head superiority (Hollis, 2005).

The Other Side: In Support of Follow-on Drugs

The arguments in favor of follow-on drugs can be broken down into two elements: 1) they promote and are necessary for pioneering innovation; and 2) the presence of many drugs benefits patients. The second component helps
consumers specifically through price competition, providing more therapeutic options and addressing under-treatment of some conditions.

Follow-on Drugs and Innovation

The positive correlation between follow-on drugs and innovation is supported by several distinct arguments. The first, simply put, is that follow-on drugs are sometimes quite innovative. We will see an example of this in a case study of erectile dysfunction (ED), which Cialis turns into a condition that can be treated 24/7, something Viagra cannot offer. Even by the most liberal estimates, however, fewer than one-third of follow-ons bring clinical advantages to the table. Thus, a second argument comes into play which applies to drugs that arise from parallel development. Consider five similar molecules being concurrently developed by five different drug companies. All else being equal, each firm has a one in five chance that its product will make it to market first. Hollis argues that it is the prospect of being the first mover that incentivizes innovative R&D, and that the knowledge of four imminent competitors makes it less likely that they will undertake such efforts. He therefore reasons that policies limiting the entrance of follow-on drugs will incentivize innovative R&D. DiMasi opposes this perspective and argues that drug companies are risk averse, so they will be more turned off by the 80 percent chance of failure than they are enticed by the 20 percent chance of success. By this logic, the success of follow-on drugs ensures firms that they will make money even if they do not produce the
breakthrough drug, thereby making them more likely to undertake risky R&D (DiMasi, 2005).

Another way follow-on drugs foster innovation is through technology spillovers. There is little doubt about the importance of incremental improvements of technology. Advancements are generally made in small steps rather than large leaps; think about the development of computers from the 1950s to the present day. Similarly, in order to create better medications tomorrow, it is necessary for pharmaceutical companies to invest in R&D today. In the pharmaceutical industry, the funding for this R&D comes from the sales of the drugs it produces. If one views “me-too” drugs as stepping-stones leading towards truly innovative drugs, then the resources they consume do not seem as wasteful (Cockburn, 2004). This logic applies in a shorter term setting as well. If multiple firms are conducting research on similar molecules, there is the potential that a breakthrough of one group may significantly benefit the research of competing groups (Henderson & Cockburn 1993). Such diffusion of knowledge leads to more rapid technological advancement, and arguably benefits society as a whole.

**Benefits of Competition**

In most markets, the presence of many substitutable products causes price competition that drives down the prices of all goods. Proponents of follow-ons affirm that they produce the same effect and thereby lower health care
expenditures. A study by DiMasi confirms the findings of Lu and Comanor that drugs of greater therapeutic value are launched at higher prices (they argue the premium is justified by clinical merit), but using newer data find that drugs reviewed under standard priority are launched at prices below the mean cost of treatment for that class (DiMasi, 2000). The presence of more drugs in a class also gives third party payers more leverage to bargain for price discounts, and can pass savings along to patients. In contrast to other works, the study also finds that there is little evidence of price increases with follow-on entry beyond that associated with inflation, and that real prices of prescriptions usually stay flat or decline.

Another benefit to having multiple drugs in a class, even similar ones, is that it gives patients choices. It is not uncommon for two seemingly similar drugs to elicit different responses in the same patient. This effect is particularly common, for example, in the market for antidepressants. A primitive trial and error tactic is frequently implemented in order to find the most effective medication for a patient. Very little technology exists today that allows physicians to make medication decisions a priori, so there is some value in having multiple options available (DiMasi & Paquette, 2004). This is a delicate argument, however, because while two or three follow-ons may be useful, four or five may be excessive. Determining the point at which this distinction occurs would seem to be an arbitrary assignment (Relman & Angell, 2002).
One of the stronger points made against follow-on drugs is the excessive promotional spending they both encourage and require, although as many proponents of follow-on drugs point out, increased advertising expenditures are not always entirely wasteful. DTCA has actually been shown to expand the sales of an entire class of drugs rather than affect individual drugs’ market shares (Rosenthal et al., 2003). The rationale behind this is that a commercial for a specific drug, say, an antidepressant, may cause a patient to see his or her doctor about depression, and may even cause the patient to request a specific antidepressant, but it ultimately is up to the physician which drug is prescribed. In many situations, the doctor prescribes whichever medication he or she has had the best experiences with. In this sense, DTCA can increase social welfare by encouraging treatment. In other cases, the physician gives the patient free samples of whichever incumbent drug happens to stock his or her cabinets. It is worth noting, however, that DTCA also has the potential to lead to overtreatment of a disease by causing patients to associate with conditions they see on TV (Horwitz, 2002). We must remember that doctors rely on customer satisfaction to maintain a patient base, so it is in their best interest to oblige patient’s request for a general type of drug, even if it is not clear they require it. This argument is also limited by the fact that DTCA accounts for less than half of total promotional expenditures, and the social benefit it carries with it does not apply to other methods of advertising, namely physician detailing.
A Matchup of Both Sides

If anything is clear at this point, it is that the outcome of the debate over follow-on drugs is anything but clear. The largest issue at hand is the extent to which follow-on drugs differentiate themselves from breakthrough drugs and other pre-existing therapies. Some do so naturally through legitimate clinical merits, but most do so superficially through aggressive marketing strategies. Scholars such as Hollis believe that that these expenditures would be better used towards developing therapies for conditions with fewer treatments. In response to this, DiMasi and his followers first point out that reallocation of R&D expenditures is frequently not plausible because the development of most follow-on drugs overlap. They go on to make two more points about costs: DTCA can address under-treatment in some cases, and the costs drug companies incur are a necessary investment to promote the development of future therapies. Hollis points out the paradoxical nature of the latter consideration: one of the purposes of “me-too” drugs is to produce revenue that will fund the development of more innovative drugs, but the profitability of innovative drugs are directly damaged by “me-too” drugs. Another argument critics of follow-on drugs make is that the prospect of between-patent competition diminishes the rewards of innovation and therefore disincentive risky R&D. The counterargument to this is that the uncertainty of a winner take all scenario may dissuade risk averse firms to an even greater extent from undertaking in innovative R&D. In other words, the likelihood of a successful follow-on drug incentivizes innovative research. The scientific discoveries that result from the
research process also expand our knowledge and benefit society through spillovers. DiMasi and his adherents further add to the debate by claiming that the entrance of follow-ons benefits consumers through price competition and by giving patients more choices. Hollis and others cite studies and examples that question the prevalence of price competition, as well as the point at which the number of follow-ons becomes excessive. They also point out that each new follow-on can have dangerously low benefit-cost ratios, but DiMasi contends that this only applies to follow-ons that are perfect substitutes to pre-existing treatments.

A significant issue that is not necessarily intrinsic to the argument against follow-on drugs, but nevertheless important in the context of the case in their favor, is the true cost of R&D. This is an issue equally as intriguing and contentious as the utility of follow-on drugs, but because it only relates to it tangentially, I will just provide an overview of the debate and emphasize how it relates to drug-drug competition. A landmark study by DiMasi, Hansen, and Grabowski (DHG) calculated the cost of R&D per drug to be around $800 million in 2000 (DiMasi, Hansen and Grabowski 2003). A revision conducted by the Pharmaceutical Research and Manufacturers of America (PhRMA), the trade association for almost all American branded drug manufacturers, adjusted that estimate to $1.32 billion per drug in 2006 (PhRMA, 2009). This statistic has risen even in the last few months, with a Forbes article suggesting the cost for developing a single drug is somewhere in the range of $4-$11 billion (Herper, 2012)! The standard explanation for these staggering figures is that they
account for the cost of all the drugs that failed during the course of producing a single successful one. Only one out of every thousand potential drug leads will make it through pre-clinical screening, and fewer than 15 percent of these will make it through clinical trials and gain FDA approval (Relman & Angell, 2002; CBO, 2006). In other words, the people who make these estimates assume that the chances of a single molecule to actually make it to market are less than one in five thousand.

The argument that follow-on drugs help companies recoup R&D expenditures and provide a financial source for future R&D endeavors relies on the reasoning that the cost of R&D is truly very high. However, the aforementioned estimates are strongly contested with some legitimacy. One of the biggest criticisms of such high estimates is that the financial data and drugs used to make the estimations are not disclosed (Relman & Angell, 2002). Light and Warburton critically analyzed what data are available from the DHG and PhRMA estimations, and found that a more realistic cost of developing a single drug is around $200 million (Light & Warburton, 2011). They bring to light the questionable nature of the accounting methods used to produce these figures, which consider the opportunity cost of developing pharmaceuticals.³ While investors in pharmaceutical companies may have other ventures in which to put their money, drug companies must invest in R&D if they wish to remain in

³ The opportunity cost of an investment refers to revenue that is theoretically lost by not being able to invest the resources in the next best way. For drug companies, the opportunity cost of R&D could be the money that they would have made had they instead invested in the equity market.
business, so their investments really do not carry an opportunity cost in the true sense of the word. They show that simply removing the “opportunity cost” from the calculations halves the final estimate! Another critique of the DHG figure is that it does not account for R&D tax breaks. In calculating income, drug companies subtract the money they spend on R&D, and therefore avoid paying corporate income tax on it. With a current tax rate of about 35 percent, this amounts to a significant amount of money that these firms get back from the government. Drug companies are in essence asserting, “you owe us for all our R&D costs, plus what we would have made had we not undertaken the project in the first place” (Light & Warburton, 2011). The economists responsible for the high estimates maintain that their methods of accounting are both standard and reasonable, and while I am not qualified to provide my own analysis of them, I imagine that Bernie Madoff also assured his investors of the legitimacy of his methods.

The nature of these economic disputes encourages participants to vehemently argue for only one side. Realistically, R&D estimates probably fall somewhere in between these two extremes, but the point is that they are most likely not as high as pharmaceutical companies claim. Another problem with the argument that high R&D expenses require the success of follow-on drugs is that a significant portion of R&D is not funded or conducted by the industry. In 2004, the National Institutes of Health (NIH) contributed $28.5 billion of taxpayer’s money towards R&D (CBO, 2006). While the constituents of PhRMA spend many times more on R&D than the government does, mainly as a result of having to
fund clinical trials, it is important to realize that many drug discoveries occur outside of the pharmaceutical industry and are licensed in to be taken to market. Ultimately, I will relate my findings from the three case studies to the current debate over follow-ons.

Chapter 1 Figures

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Figure 1.1. NHE breakdown by largest healthcare sectors. Source: Abridged from NHE tables, 2010.
CHAPTER 2

Ulcers and Acid Reflux

Treating Gastrointestinal Disorders: A Background

Until 1977, the common treatments for stomach ulcers were limited to antacids and costly elective surgery. Antacids were also used to combat acidic hypersecretory disorders, gastroesophageal reflux disease (GERD), and associated esophagitis and heartburn. They work by neutralizing the acidic environment of the stomach, but do nothing to address the underlying cause of acid secretion. As such, antacids conferred limited symptomatic relief, and ulcers treated with them frequently relapsed. In 1977, Smith, Kline & French (now GlaxoSmithKline) introduced the first H2-receptor antagonist (H2RA), Tagamet (cimetidine). H2 blockers compete with histamine in binding cells that line the stomach wall, a necessary step in inducing acid secretion. By actually suppressing secretion rather than simply raising the pH of the stomach, H2RAs revolutionized the treatment of gastrointestinal disorders. The clinical
importance of this class of drugs is evidenced by its tremendous success; in 1986 Tagamet’s annual revenues exceeded $1 billion and thus became the world’s first blockbuster drug.


Tagamet entered a market consisting of patients who were severely undertreated, creating demand by offering relief for heartburn and acid reflux when previously little was known, in addition to a more efficacious treatment for stomach ulcers. The therapeutic significance of H2RAs was clearly understood, and the FDA accordingly gave Tagamet priority review status during the approval process. Not surprisingly, between 1977 and 1992, the number of patient days of H2RA therapy grew at an impressive rate of about 15 percent in the U.S. [Figure 2.1] (Berndt et al. 1996). After its introduction, Tagamet enjoyed a six-year monopoly of the H2RA market, during which its price fell from about $1.00 per day to $0.80 per day. In 1983, Glaxo\(^1\) launched Zantac (ranitidine) at a price of $1.25 per day of therapy, 56 percent higher than the price for Tagamet. Zantac’s price premium was not merited by therapeutic advantages; several clinical studies conducted around the time of Zantac’s introduction concluded that both drugs were equally effective at healing both gastric and duodenal ulcers, as well as resolving the associated symptoms (Walt RP et al., 1981;  

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\(^1\) Pre-merger with SmithKline Beecham.
Kellow J et al., 1983; Lee FI et al., 1983; Barr GD et al., 1982; Langman MJ S et al., 1980). What Zantac did offer which Tagamet did not was a twice a day formulation (Tagamet was four times a day), which made dosing easier and theoretically increased patient compliance. That the remission rates of the two drugs were the same suggests that compliance was of little importance, but the issue was entirely rendered moot when Tagamet introduced its own twice a day formulation 18 months later. Additionally, Zantac was a more potent molecule, which meant that it required a smaller dose than Tagamet to produce the same effect. In terms of clinical efficacy, however, this did not impart any benefits.

The other two H2RAs that exist today, Pepcid (famotidine) and Axit (nizatidine), were introduced in 1986 and 1988, respectively. Similar to Zantac, both drugs were shown to be no better or worse in treating ulcers than their competing H2RAs (Simon et al., 1985; Naccaratto et al., 1987). Yet, whereas Zantac was extremely successful in capturing market share, commanding 25 percent within one year on the market, the third and fourth follow-ons were not nearly so. Pepcid controlled 8 percent within one year, and Axit only 4 percent [Figure 2.2]. In 1993, before any generic or OTC entry, Zantac controlled 53 percent of the market, Tagamet 21 percent, Pepcid 15 percent, and Axit 9 percent. Zantac was still the price leader at $1.80 per day, Pepcid was the lowest at $1.41, and Tagamet and Axit fell in between these. It should be noted that these prices are adjusted for inflation, which means that counter intuitively, the prices of all drugs rose with time despite the increasingly competitive market [Figure 2.3]. The first ten years of competition highlight how the development of
this class was driven by irrational demand: three follow-on drugs, all therapeutically comparable to each other and the market leader, became available within six years of each other, but one was so tremendously successful that it overtook the long-time market leader despite costing more, while the other two combined did not even control a quarter of the market. The question begging to be asked is: why did Zantac surpass Tagamet in sales within four years, while two other drugs offering similar clinical profiles did not even get close? The answer is present in at least four of the five non-therapeutic determinants: aggressive marketing, differences in FDA-approved indications, different side effect profiles caused by length of time on the market, and pricing strategies. The publication environment may also have had an impact on the sales of Zantac and Tagamet, but reporting sources of funding and conflicts of interest was not common practice in the 1980s and early 1990s, so I must unfortunately omit an analysis of the publication environment from this class.

**H2RAs: Explaining What Happened**

**Aggressive Marketing**

To understand the impact of marketing on physician prescription patterns, researchers have defined two sorts of physician detailing: class-expanding and class-fragmenting. In the case of a monopoly, the two are the same in that all marketing expands the patient base of the class, and feeds
exclusively into the sales of that drug. In a competitive model, firms engage in rivalrous marketing in which they try to promote only their drug and therefore fragment the class. Even as much as firms try to advocate for their own drugs and demote their competitors', any form of advertising inevitably expands awareness of a class and therefore creates spillovers. Empirical evidence shows this to be the case in the market for H2 blockers, though spillovers are considerably less than 100 percent efficient (Berndt et al., 1996). This is exactly the positive spin that scholars like DiMasi attach to advertising, but it should be noted that this diffusion of knowledge decreases with competition (i.e. more follow-on entry). Logically, the total effect that spillovers have on the market is a function of all of the detailing done, so class-expanding advertising is therefore most accurately measured by cumulative detailing stocks [Figure 2.4].2 The nature of this type of advertising means that it depreciates at a rate equal or close to zero; once a physician has knowledge of a class of drugs, it does not go away. Class-fractionalizing advertising is a different story, because its purpose is to persuade physicians to prescribe one drug over others. This means that the goal of a drug rep is to go to a physician and provide him or her with information that subverts the exact same work of another drug rep. For the H2RA class, this rate at which class-fragmenting advertising depreciates is about 40 percent (Berndt et al., 1996). Drastically increased detailing efforts hypothetically should correspond with better short-run performance of that drug, thus making

2 Cumulative detailing stocks are calculated by summing all the minutes of physician detailing that have occurred up to that point.
month-by-month detailing minutes a more useful tool to assess this type of marketing. Particularly insightful conclusions can be drawn when we consider how distinct spikes and troughs in detailing efforts correspond to exclusive FDA approvals, important drug introductions, and patent expirations of competing drugs.

As expected, Tagamet was able to accumulate many thousand more minutes of detailing than any of the other H2RAs due to its longer time on the market [Figure 2.5]. As a class-expanding measure this was highly productive, but that Zantac was detailed with many times the effort of Tagamet immediately upon its introduction points to class fractionalization [Figure 2.4]. It is somewhat difficult to see from the monthly data that detailing efforts for Zantac remained on average greater than those for Tagamet, but the fact that the curves tracking their cumulative stocks converge proves Zantac was detailed more forcibly over the ten years after its introduction. The slopes of Pepcid and Axid’s cumulative detailing curves are not as steep as Zantac’s, which means that they too were not detailed as rigorously. There is a positive and significant relationship between absolute detailing levels and drug sales (Berndt et al., 1996), but this is only a small part of Zantac’s coup. After all, more detailing was done for Axid than Pepcid, but Pepcid was a more successful drug. None of the detailing efforts for these drugs, however, differed so significantly that they could account for the vast disparities between each drugs’ relative success, implying that the relationship between detailing and sales is not linear.

Assuming that every patient wants the best drug possible, it makes sense that
small differences in detailing emphasizing certain clinical factors could have a disproportionately large effect on sales. I therefore propose that the absolute amount of detailing is not as important as the quality of detailing. By quality I do not mean the conviction of the sales representative, though had Billy Mays been a drug rep for Avid it presumably would have fared better, but rather what the detailer can discuss with the physician. By law, sales representatives can only convey information to doctors that is supported by the FDA or published journals, which makes differences in FDA approvals and adverse effect profiles very useful tools when there is no conclusive evidence of clinical superiority.

**FDA Approvals**

This is one instance when FDA-approvals can arguably be associated with therapeutic differences; the initial advantage that Zantac held over Tagamet was the approval of a twice daily dosing versus a four times daily dosing. Anyone who has ever taken prescription drugs can understand how this convenience can easily lead to greater patient compliance rates. However, I maintain that in themselves, FDA-approvals are not inherently therapeutic for two reasons. One is that the purpose of the FDA approval is to determine the safety and efficacy of a drug, indication, or formulation based on the results of lab, but mostly clinical trials. Because the FDA does not conduct any testing themselves, an indication is merely a reflection of exogenous clinical results. Therefore, any advantages that a new drug, indication, or extended release or dosing time formulation bestows
would be clearly demonstrated by the clinical trials and meta-analyses I identify through journal publication databases. We see that this is precisely the case here: the different dosing times did not cause significant differences in ulcer healing rates or resolution of GERD in the studies I previously cited or in those whose purpose was to examine the differences in dosing times, which suggests that patient compliance was a non-issue (Dawson, Jain, & Cockel, 1984; Walt et al., 1981; The Belgian Peptic Ulcer Study Group, 1984). The lack of clinical differences reinforces the idea that FDA approvals mean that what is approved is safe and effective, but do not signify superiority unless backed up by clinical evidence.\(^3\) The second reason is that, at least within the classes I have identified, exclusive FDA approvals are often transient and superficial. Transience comes into play with Zantac’s exclusivity on a twice a day dosing regimen, which only lasted for 18 months.

The superficial nature of many FDA approvals is highlighted through Zantac’s exclusive indication in treating GERD and its symptoms. Both drugs were only indicated in stomach ulcers when they were respectively launched, though clinical trials demonstrated them equally as effective at treating GERD. Glaxo cleverly sought out FDA approval for the indication in GERD, which it gained in 1986, making it the only drug on the market to be officially approved for that use. This gave Zantac a huge leg up because Glaxo sales reps could then

\(^3\) Cialis, as we will see, is a perfect example of this. Clinical trials showed that men preferred it to Viagra because of its once a day formula, and it consequently is the only ED drug to have an FDA approval for this.
boast that Zantac was the only H2 blocker approved by the FDA to treat GERD. Such claims allude to superiority, and unless a doctor took the time to look into the clinical trials, could conceivably make such an assumption. Glaxo took advantage of this exclusive approval as evidenced by the marked spike in detailing efforts in 1986,\textsuperscript{4} which on average remained higher thereafter [Figure 2.4]. The counter-argument to the effect that the GERD indication had is that many doctors do prescribe drugs off-label, so would not have been affected by the indication in GERD. However, a survey of physicians conducted at the end of the 1980s about the quality of GI drugs clearly demonstrated that doctors perceived Zantac as more effective in healing ulcers and damage done by GERD (Scouler, 1993). There is likewise a transient aspect to this FDA approval, as Tagamet gains its own indication in GERD in 1991. An interesting subtlety is that after Tagamet catches up to Zantac in this regard, the number of Tagamet prescriptions stops falling and remains level until generics become available in 1994 [Figures 2.2 and 2.6].

**Length of Time on Market**

After a drug has completed phase III clinical trials, been approved by the FDA, and launched, it starts phase IV trials. These post-approval studies are generally aimed at continual surveillance for adverse events, finding new uses

\textsuperscript{4} Berndt et al. (1996) showed this to be significantly correlated with the approval for indication in GERD.
for the drug, or demonstrating its safety in new populations (e.g. children or pregnant women). Patients and their physicians are asked to report all adverse side effects to the FDA, which in turn requires pharmaceutical companies to update their drugs’ labels with any significant changes. As such, drugs tend to accumulate more reported adverse events the longer they are on the market (Berndt et al., 1996). Tagamet, which had already been on the market for 6 years when Zantac was launched, had accumulated many more adverse reports by the time Zantac, Pepcid, and Axid respectively launched. Such differences are misleading and contradict the double-blinded clinical trials that demonstrated equivalent side effect profiles. While I have no data depicting the progression of annual reports against each of these drugs, I do for the PDE-5 inhibitors. In Chapter 4, we see that the number of annual reports against Cialis and Levitra, both introduced five years after Viagra, converged with the number reported events against Viagra the longer the two newer drugs were on the market. The markets for ED treatment and ulcer treatment certainly have their differences, but it is not inconceivable that a similar pattern may have occurred in the market for H2 blockers. Back in the late 1980s and early 1990s, however, the ability of a detailer to tell a physician that Zantac had fewer side effects than Tagamet was very powerful and perpetuated the perception of superiority. The results of the same physician survey I previously mentioned reveal that doctors perceived Tagamet to have the most drug interactions, followed by Zantac, then Pepcid, and finally Axid- perfectly in line with their order of entry (Scouler,
1993)! As one might expect, the number of adverse effects a drug carried in this market had a negative and significant impact on their sales (Berndt et al., 1996).

Something that is more difficult to quantify economically, but seems important to consider, is the psychology that drives the adoption of newly introduced drugs. I am not qualified to talk in detail about the underlying rationale of consumption behavior, but I think it is reasonable to argue that novel products are inherently appealing. If a drug company were to take a drug they already sold, wrap it in a new capsule, and attach a different name to it, I suspect that it would see some amount of sales purely on the basis that novelty is associated with technological progress and therefore greater efficacy. In fact, we see practices very similar to this in the markets for PPIs (Nexium) and antidepressants (Lexapro), but we will come to these later. This is its own form of irrational demand, and while drug companies may not be directly responsible for it, it naturally works in their favor whenever a follow-on drug is introduced.

**Pricing**

Berndt and co-authors identify a peculiar pricing phenomenon that also contributed to why Zantac overtook Tagamet. Recall that Zantac was introduced at a price 56 percent higher than Tagamet’s, but that by 1993 this premium had fallen to about 25 percent [Figure 2.3]. The prices of both drugs increased, but Tagamet’s did so at a faster pace. The results of their econometric analysis indicate that a decrease in the relative price of one medication to another, even if
that medication is more expensive, significantly negatively affects the sales of the competing medication (Berndt et al., 1996). Based on the data that I have access to, it is impossible to determine if the fall of Zantac’s relative price to Tagamet’s was an explicit price strategy employed by Glaxo. Glaxo did, however, decide to set the price of Zantac above the price of Tagamet. To patients and doctors who saw advantages of Zantac, paying more for it was quite a rational decision. From an objective standpoint, however, paying more for Zantac was irrational given the ample evidence available that showed there was a cheaper and equally effective alternative.

**H2RAs versus PPIs: The Matchup**

Proton pump inhibitors have largely replaced H2 blockers in treating ulcers, GERD, and hypersecretory conditions. They offer objective advantages over their predecessors in terms of the time and rate of disease remission (van Pinxteren, Sigterman, Bonis, Lau, & Numans, 2010). PPIs inhibit the most downstream mechanism in the secretion of stomach acid: the actual release of acidic protons (H+ ions) into the stomach. Consequently, they have an almost immediate effect on acid production, and are dispensed in delayed release capsules that provide for a steadier dose of the drug throughout the day. The first PPI, Prilosec (omeprazole), was launched in the U.S. by Merck & Co. in
1989. The advantages that PPIs brought to the table for the treatment of GI disorders were clearly understood at the time, as evidenced by the FDA priority review classification and many clinical trials that demonstrated the superiority of PPIs (Walt RP et al., 1993; Classen M et al., 1985; Dammann HG et al. 1986). It should also be noted that PPIs offered more convenient doses over H2 blockers. These changed based on the indication so will be discussed in more detail later, but a general rule of thumb is that PPIs required half the number of daily doses that H2RAs did.

**PPIs: The Early Years (1988-1991)**

We left the market for H2RAs in 1993, but let us rewind four years to see the effect that the introduction of Prilosec had. The distinction between the DS (H2 only) and DS (7 drugs) curves now becomes important, as the difference between them is an estimate of the number of Prilosec prescriptions [Figure2.1]. With such strong evidence supporting Prilosec’s therapeutic advantages, one might expect patients and doctors to substitute to it

5 Omeprazole was developed and marketed worldwide by Astra AB (now AstraZeneca) under the name Losec, but U.S. rights were licensed to Merck & Co. on account of their stronger presence there. Astra began buying back the rights from Merck in 1998.

6 Both curves include the prescriptions for the four H2 blocking drugs, but “7 drugs” adds in three more antiulcer medications: Carafate, Cytotec, and Prilosec. Carafate became available in 1981 and had little impact on the market, and Cytotec had limited use in NSAID associated ulcers, but its popularity plummeted in 1991 when it was found to be a potent abortifacient. Prilosec was the most popular of the three, so the gap between the two DS curves is a rough, albeit overestimated, indicator of the use of Prilosec.
immediately. Yet, we clearly see that the number of H2RA prescriptions dispensed vastly exceeds Prilosec prescriptions, and continues to increase until at least 1993 [Figure 2.1]. The explanation for this slow adoption lies in the barriers to entry that the first drug of a class is faced with. Gaining the trust of doctors is arguably the most important and difficult feat for a pioneer. Doctors are much more likely to adopt an innovative drug based on their own experiences or those of their colleagues rather than the words of sales representatives, invariably making it a slow process. (Schum et al., 1998; Coleman, Katz, and Menzel, 1957). It did not help that on top of this, the drugs Prilosec was trying to usurp were the two best selling pharmaceuticals in the world at the time. In the U.S., the lone detailing team of Merck had to go up against the teams promoting Zantac, Tagamet, Pepcid, and Axid. Patients who experienced chronic heartburn were already stable on one of the H2 blockers, so they may have seen little point in “rocking the boat.” Prilosec was also disadvantaged because it did not carry an FDA-approved indication in stomach ulcers (until 1991 it was only indicated in GERD), while the H2RAs did. Given the importance of FDA-approved indications in forming physicians' perceptions, lacking an ulcer indication may have initially limited its adoption as short-term treatment among new patients. Considering these barriers to entry, it is reasonable to expect widespread adoption of Prilosec to take several years.
**H2RAs Slacking, PPIs Picking It Up (1992-1999)**

The H2RA market became subject to increasing competition during this time, both from generic and over the counter (OTC) medications. The first of the large shocks to the market was the introduction of several generic versions of cimetidine (Tagamet) in 1994. The total quantity dispensed of the other three incumbents proceeded to rise [Figure 2.6], which might suggest that patients substituted to them, were it not for the fact that the number of new prescriptions remained steady, and then fell [Figure 2.7]. Instead, the increased use of the remaining incumbent H2RAs in mid- to late 1995 can be explained by the coinciding approval of OTC versions of Pepcid, Tagamet, and Zantac (OTC Axid became available in May of 1996). It seems highly likely, therefore, that H2 blockers were able to compete with PPIs on the grounds that they exclusively offered OTC heartburn relief, but that most new patients were prescribed a PPI.

It makes perfect sense then, that by the time my data picks up in 1994, Prilosec’s annual global revenues exceeded $2 billion [Figure 2.8]. Interestingly, it was able to achieve this success without matching the list of indications that the H2RAs were approved for. A strong yet simple explanation is that drug companies emphasize differences in FDA-approved indications between similar drugs to induce irrational demand for their product, but when a product is objectively better, as was the case with PPIs, demand naturally increases to reflect that. As we will see within the PPI class however, drug companies, namely AstraZeneca, were again guilty of creating false perceptions of
superiority. The main difference is that over a decade had passed since the
Zantac anomaly. We must remember that H2 blockers were the first blockbuster
class, so drug companies were still learning the best ways to market such
popular drugs. The success of Zantac was as much savvy and adaptive decisions
on the part of Glaxo as it was mistakes and missed opportunities by SmithKline
& French. Henry Wendt, the then chief executive of SK&F, admitted that
SmithKline “could have improved many aspects of the marketing programme....
Glaxo won regulatory approval for a twice-daily dose of Zantac, in contrast to
Tagamet's four-times-a-day dose, and at a lower overall total dose in milligrams.
Physicians drew the obvious inference: Zantac appeared to be a more potent and
longer-acting agent.” As he looked back at the defeat his drug suffered, he noted,
just as I do, that “all Zantac's initial comparative advantages [had] largely
disappeared as a result of the continuing clinical development [of Tagamet],” but
by then it was already too late. Looking forward, he identified “competitiveness”
as “essential” in future success as the markets within the pharmaceutical
industry developed.

An increase in competitiveness is exactly what we see as the PPI class
continued to expand through the 1990s, fueled by the approval of Prevacid
(lansoprazole) in 1995, Aciphex (rabeprazole) in 1999,\(^7\) and Protonix
(pantoprazole) in early 2000. Similar to the H2 blockers, a majority of clinical
studies demonstrated no significant advantages of any of the drugs over the

\(^7\) Financial data not available until 2000
others (Kromer et al. 1999). Each company raced to gain indications in all of the GI related disorders as quickly as possible. By 1999, Prilosec and Prevacid had identical lists of indications. The extensive clinical trials of Achipex actually merited its initial FDA approval for indications in four of the five disorders Prilosec and Prevacid were approved for, gaining the fifth within a year, and Protonix had gained all five indications within two years. Unfortunately, I do not have access to promotional expenditures for the PPIs, so cannot speak to how well marketing efforts coordinated with FDA approvals. Up until this point, there were no long periods during which any of the drugs possessed a characteristic that none of the other drugs had. Given how important this was for strategic marketing in the class for H2RAs, it seems less likely that it played as large of a roll in this class. Accordingly, the first four drugs’ revenues align very closely with the model discussed by Berndt (1996) and Robinson, Kalyanaram, & Urban (1994), with each successive drug thus far experiencing proportionately fewer than the previous [Figure 2.8]. Importantly, this is how we would expect the market to look among similar drugs in which the perceived qualities of the drugs closely reflected the real qualities.

8 Duodenal ulcers, gastric ulcers, GERD, erosive esophagitis, and hypersecretory conditions.
Nexium, OTCs, and Generics (2001-2010)

So far, it appears that there has been little evidence of irrational behavior in the market for PPIs. That changed with the introduction of Nexium (esomeprazole) in 2001. The similarity of its chemical name to that of Prilosec’s (omeprazole) is apparent; simply the addition of a two-letter prefix. In fact, Nexium is manufactured by the same company, which by this point had merged to become AstraZeneca. Nexium was not approved by the FDA as a new molecular entity (NME), rather, it was classified as only a new derivative. The rationale behind this is chemical. Prilosec actually contains two molecules that are perfect mirror images of each other, and therefore are not super-imposable. Molecules that fit this description are called enantiomers, and when both are present in equal amounts comprise a racemic mixture, or racemate. It turns out that the S-enantiomer is exclusively responsible for the effects of Prilosec, so AstraZeneca decided to isolate that from the racemate and market it as Nexium. What this means, of course, is that if you have taken Prilosec, you have also effectively taken Nexium.

Many physicians today would tell you that Nexium is superior to other PPIs because it is once a day rather than twice a day, requires smaller doses, and the absence of the inactive enantiomer makes the drug more effective while reducing the adverse effects. They would then be surprised when you informed

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9 Nexium was introduced in Europe in 2000.
10 Exactly half the dose, in fact, because half of a dose of Prilosec is essentially inactive.
them that they were wrong on most accounts. When Nexium was initially approved, it only carried indications for esophagitis and GERD. According to their drug labels, all proton pump inhibitors are recommended for once daily use to treat GERD, gastric ulcers, active duodenal ulcers, and erosive esophagitis.

Many doctors prescribe the earlier PPIs at lower doses twice daily, but clinical trials do not support an added benefit of this practice (Klok et al., 2003). The way the clinical trials were designed, however, was extremely dubious. Klok et al. (2003) looked at 41 clinical studies and found that the only significant evidence of superiority was in head to head trials comparing Nexium 40 mg once daily to Prilosec 20 mg twice daily. I would be concerned about the methodologies of the studies if we did not see such a relationship, however, because 40 mg of Nexium is twice the active ingredient as in 40 mg of Prilosec.

Of course, the authors of AstraZeneca’s trials did not mention this, nor did they ever design a study to compare at 40 mg of Nexium with 80 mg of Prilosec. As we will see through anecdotal evidence at the end of this section, detailers emphasized Nexium’s “superiority” through detailing.

The real difference in dosing is only in the elimination of *H. pylori* to reduce the risk of duodenal ulcer recurrence. In triple therapy with clarithromycin and amoxicillin, Nexium need only be taken once daily, whereas the other PPIs have to be taken twice daily. The rationale is that the fewer times a day a patient has to take a drug, the more likely he or she is to comply. The

11 Independently sponsored by the Cochrane Foundation
Irony is that while Nexium only has to be taken once a day in triple therapy, the two antibiotics have to be taken twice a day no matter with which PPI they are taken! While there are some truths to the perception of dosing frequencies, the advantages are certainly not what the detailers make them out to be.

The minimal advantages that Nexium offered over the other drugs in its class do not seem significant enough to explain why it surpassed Prevacid in sales and experienced well more than twice the success of two other drugs that were introduced at around the same time. In fact they are not, and the answer as to how Nexium “Zantaced” the other PPIs is in AstraZeneca’s devious marketing strategies. Astra timed the release of Nexium to precede Prilosec’s patent expiration, which occurred in parts of the world in 2000, and most of the rest in 2001. Where Prilosec held the most market share of any of the PPIs, they presented the drug as a better version of Prilosec, thereby hoping to switch patients from it to Nexium, steal market share from Prevacid, and outperform Aciphex and Protonix. An extremely informative Wall Street Journal article by Gardiner Harris discusses this strategy (Harris, 2002). He identifies the practice of patenting abstract ideas to delay the onset of generic omeprazole, thus giving Astra more time to make money off of Nexium and switch patients to it. Astra patented the idea of using Prilosec in combination with antibiotics, and then argued that generic omeprazole would violate this patent by allowing doctors to do just that. The company also patented a metabolite of Prilosec that only lasts briefly in the body, then claimed that generic omeprazole would naturally
infringe on this. Harris describes some first-hand accounts of the aggressive marketing employed by Astra during this time:

“Dr. Halper asked the salesman why Nexium was better. ‘The proof’s in the healing rates,’ said the live salesman, who cited data comparing 40 mg of Nexium to 20 mg of Prilosec. ‘We’re safer, with no drug-to-drug interactions’” (Harris, 2002).

This report of an actual detailing visit confirms that drug reps emphasized the biased clinical trials and side effect profiles. Harris also describes salesmen stocking the doctor’s cabinets with free samples of Nexium, recognizing that even if doctors saw Prilosec and Nexium as equivalent, they would be more likely to prescribe whatever they had for free in their closet.

AstraZeneca achieved its goals, as the sales of Prevacid begin to flatten when Nexium was introduced, and Aciphex and Protonix sales grew at considerably slower rates [Figure 2.8]. An OTC version of Prilosec became available in 2003, which may account for why the sales curves of the three remaining incumbents all experience notable decreases in slopes between 2003 and 2004. The marked decrease in sales of Prevacid in 2007 is not due to generic entry, but rather to accounting issues. The maker of Prevacid, Takeda Pharmaceuticals, stopped reporting their global net sales in 2006, and only released their consolidated sales that omitted revenue from licensing. Although the patents protecting Protonix were not set to expire until 2011, they were subject to several law suits, and two “at risk” generics entered the market in
2007. Besides these events, the market seems to adjust naturally to increasing competition. A point of future study will be the evolution of Dexilant (dexlansoprazole), which was launched in 2009. It is analogous to Nexium in that it is a single enantiomer of Prevacid (lansoprazole).

Until the introduction of Nexium, the PPIs were an example of how there is little inherently wrong with follow-on drugs. Nexium, however, served as another example illustrating how drug companies can manipulate patient and doctor perceptions in order to induce irrational demand. In both classes, these follow-on drugs seem to do anything but lead to more innovation as DiMasi suggests follow-ons do; these particular drugs harmed the sales of the most innovative drug in their respective classes. Still, the PPIs departed from the H2RAs in one significant way: the powerful effect that the publication environment had on shaping perceptions established it as a prime marketing tool, a theme we will return to. In another sense, PPIs can be viewed as a follow-on class to the H2 blockers, over which they offered therapeutic superiority. One question worth asking is if the clinical advantages that Prilosec offered over the H2 blockers were worth the extra price. This perspective becomes more important when studying SNRIs, which are themselves a follow-on class to the SSRIs, though arguably confer no added benefit.
Chapter 2 Figures

Figure 2.1. Taken from Berndt et al. 1996, Figure 7.1. Number of patient-days of duodenal ulcer therapy by H2RAs (H2 Only) by drugstore and hospital sales.

Figure 2.2. Taken from Berndt et al. 1996, Figure 7.3. Number of patient-days dispensed by drugstores of duodenal ulcer therapy by H2RAs by drug.
Figure 2.3. Taken from Berndt et al. 1996, Figure 7.4. Real drugstore prices of H2RAs.

Figure 2.4. Taken from Berndt et al. 1996, Figure 7.5. Monthly minutes of detailing for Tagamet and Zantac.
Figure 2.5. Taken from Berndt et al. 1996, Figure 7.6. Monthly cumulative minutes of detailing for all four H2RAs.

Figure 2.6. Taken from Jena et al. 2009, Exhibit 2. Monthly quantities of H2RAs grouped by Tagamet and follow-ons, including prescription and over the counter quantities
Figure 2.7. Taken from Jena et al. 2009, Exhibit 8. Number of new prescriptions for all follow-on drugs normalized for first generic entry.

Figure 2.8. Global annual revenues of proton pump inhibitors by drug and as a class.
CHAPTER 3

Depression

_Treating Depression: A Brief Background_

Prior to the advent of selective serotonin reuptake inhibitors (SSRIs), the only FDA-approved drug classes to treat major depressive disorder (MDD), anxiety disorders, and other non-psychotic mental illnesses were the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Both of these other classes of drugs are effective at resolving the symptoms of many mental illnesses, but they are associated with significant adverse side effects and risks. TCAs are toxic to the heart and central nervous system in high doses, and were the leading cause of prescription drug poisoning fatalities in 2003 (Rosenbaum & Kou, 2005). MAOIs are typically reserved for resistant depression, and patients must be highly motivated to get better because they require major lifestyle changes (Clarke & Ramsay, 2011). The most notable is
the highly restrictive MAOI diet, which limits one’s amount of tyramine intake. Excessive tyramine consumption while on MAOIs is fatal. The first SSRI, Prozac (fluoxetine), was introduced by Lilly in January of 1988. Clinical trials demonstrated that SSRIs were at least as effective as TCAs and MAOIs, but only shared the mildest side effects with them (Cole, 1988; Boyer & Feighner, 1989). Accordingly, the FDA awarded Prozac with a priority review classification, the only antidepressant since 1988 to get one. In 1994, Effexor (venlafaxine) became the first serotonin-norepinephrine reuptake inhibitor (SNRI), a similar class as suggested by the name. Also used to treat a wide variety of mental disorders, the last decade has seen SNRIs become a first-line treatment for pain disorders and fibromyalgia (FM). The popularity of antidepressants has grown wildly since the introduction of Prozac in 1988. By the cutoff date for this analysis in 2010, antidepressants were the second most widely prescribed drug in the U.S. (second to lipid regulators), corresponding to $11.6 billion in sales (IMS Health National Prescription Audit PLUS 2010, IMS Health National Sales Perspectives 2010).

1 Tyramine is found in high concentrations in aged meats and dairy products, red wine, and a long list of other foods.
2 Approved in the last few days of 1987, which is often confused with its launch date.
3 These side effects, common to all three classes, include loss of libido, weight gain, nausea, dry mouth, diarrhea, and more.
4 Chronic musculoskeletal pain (CMP) and diabetic peripheral neuropathic pain (DPNP).
Overview of Findings

Like the H2RAs and PPIs for treating GI disorders, there is no strong evidence that any one of the SSRIs or SNRIs is better than another for treating mental illnesses. Unlike PPIs, however, which offered objective clinical benefits over the older H2 blockers, it is currently understood that SNRIs provide minimal, if any, therapeutic advantages over SSRIs. Despite the lack of real clinical differences among antidepressants, a survey of physicians and the success of one follow-on drug after another suggests that antidepressant utilization is extensively driven by irrational demand. All five non-therapeutic determinants of demand play roles in driving utilization. I address the publication environment and differences in FDA approvals first as I suspect they are the most important, though length of time on the market, pricing strategies, and absolute marketing expenditures also prove to be significant. I find that the results of clinical trials are variable and often contradictory, and significant funding biases makes them a prime tool for detailers. The large number of subsets of mental illnesses allows firms to differentiate their products by being the first to obtain indications in a disorder, and they often coordinate marketing efforts with these approvals. The effect that length of time on the market and pricing strategies have on doctors’ perception of the antidepressants is seen through a survey of physicians. Absolute advertising expenditures may be significant at times, but I find that strategic spikes in advertising coinciding with events such as FDA approvals or competing generic entries are more efficient. These factors compound at different times and explain why so many clinically
similar drugs see success, even as more generic alternatives become available. I do my best to address these factors in the order in which I have just presented them, though I sometimes must deviate based on the role that each plays in different time periods. In support of DiMasi’s argument, there is some evidence of price competition and societal benefit in having more drugs. More in line with the Angell-Hollis viewpoint, however, I contend that the price competition does not save consumers as much money as increased generic utilization would, and that the number of follow-ons is excessive and the resources used to bring them to market and promote them would be better allocated elsewhere.

Therapeutic Profiles of Antidepressants: An Introduction to the Publication Environment

The reason that the publication environment is such a driving factor for demand of antidepressants is because many clinical trials comparing drugs produce findings contrary to their real therapeutic profiles. I first explain why I believe that the nature of depression and other mental disorders allows for such skewed clinical results. I then present the most reliable studies to exhibit the comparable levels of efficacy among the antidepressants, also noting differences in side effect profiles. I explain how company-sponsored head-to-head trials divert physicians’ perceptions of relative quality away from how they actually match up, and give examples of such trials. Without the context of the real therapeutic profiles of these drugs and the biases of many of these studies, one
might conclude that one drug actually was superior to another. I argue that this is exactly the conclusion that many physicians draw, a position supported by survey and sales data. This erroneous deduction affects prescribing practices and fuels the irrational demand for clinically similar follow-on drugs.

The Nature of Antidepressants

Even today, the underlying pathologies of the non-psychotic mental disorders remain shrouded in mystery. Similarly, the precise mechanism by which SSRIs and SNRIs treat depression is not fully understood. They are generally implicated in neurosignalling pathways, where they interfere with the reuptake of serotonin from the synaptic cleft. The prolongation of serotonin signaling is believed to elevate mood and treat the psychological basis of depression. In contrast to GI disorders, the presence and symptoms of which can easily be quantified through stomach acidity, esophagoscopy, and the apparent existence of reflux or ulcers, depression is determined in a more subjective way that relies on patient reporting and physician interpretation. Scales such as the Hamilton Depression Rating Scale (HAMD) have been created in an attempt to attach more quantifiable numbers to depression, but even these

5 The junction of two neurons is referred to as the synapse. The presynaptic neuron releases neurotransmitters, such as serotonin, into the space between the neurons, called the synaptic cleft. These neurotransmitters bind to receptors on the postsynaptic neuron, which perpetuates the signal, or action potential, so it can be carried to its final destination. The neurotransmitters are then reabsorbed into the axon of the signaling neuron or broken down.

6 There are multiple versions of the HAMD consisting of slightly different groups of items, but they fulfill very similar roles.
can produce different outcomes from the same patient based on the observer completing the test (Bauer et al., 2004). The subjectivity of depression makes it a difficult disease in which to compare relative levels of treatment efficacy. The results between studies can change based on methodologies alone, and the potential for funding bias is considerable (Als-Nielsen et al., 2003; Gartlehner et al., 2011). In this class and ones of similar subjective natures, it is especially important that there is congruence among findings supporting the superiority of a single method of treatment. A lack of consistency in outcomes suggests, if anything, that there are small or inconsistent differences between drugs. If trials funded by a single company continually contradict other studies, it is prudent to be especially skeptical.

The clinical trials I identify suggest that publication bias is prevalent, which often produces articles that strongly support one course of treatment over others. The outcomes of these clinical trials can be conveyed to physicians through detailing, which can in turn affect their relative perceptions of drugs and prescribing practices. A thorough and independently sponsored meta-analysis actually found that the net effect of the industry-sponsored studies indicated no significant difference between antidepressants for treating MDD or anxiety disorders (Gartlehener et al., 2011). The authors identified 248 studies published between 1980 and 2011, and reported the results of comparisons between various SSRIs and SNRIs in an impressive, and painfully detailed, 954

7 Sponsored by the Agency for Healthcare Research and Quality
Their screening process for selection removed trials of poor quality, but could not control for sponsorship bias because a majority of clinical trials are funded by the manufacturer of the drug being studied. When they compared the extent to which the results of the studies supported the drug of the sponsor, they concluded that sponsorship bias heavily affects the outcomes of studies, a finding that has been supported by other scholars as well (Als-Nielsen et al., 2003).\(^8\) Specific examples will be discussed in more detail later in this section.

The meta-analysis also looked at head-to-head trials as an effective way to directly compare the efficacy of two drugs, but pointed out that they are the most susceptible to sponsorship bias because they only compare two drugs. Imagine ten industry-sponsored trials comparing Prozac to Zoloft. Presumably, only Eli Lilly and Pfizer will sponsor these studies, as this match up would benefit Merck or any other pharma very little. The Lilly studies are more likely to find that Prozac is superior, and Pfizer studies to find that Zoloft is superior. If Lilly sponsors fewer trials than follow-on manufacturers (which actually happens to be the case), then a meta-analysis trying to be as encompassing as possible would find follow-on drugs superior to Prozac based on head-to-head trials alone. On the other hand, ten trials each comparing five drugs, still sponsored by their respective manufacturers, would give a fairer perspective because the results would be more evenly distributed. To briefly demonstrate

\(^8\) Als-Nielsen et al. analyzed 370 trials and found that those funded by for-profit companies were more than 5 times as likely to recommend the experimental drug being tested than those whose money came from nonprofit sources.
this point, the meta-analysis included multiple studies for each of the following
drug comparisons, and made the following conclusions about statistically
significant differences in response rates in MDD: Celexa versus Lexapro-
Lexapro was higher;\(^9\) Prozac versus Paxil- no difference; Prozac versus Zoloft-
Zoloft was higher; Prozac versus Effexor- Effexor was higher; Paxil versus
Cymbalta- no difference; Zoloft versus Effexor- no difference. That so many of
the follow-ons were pitted against Prozac in head-to-head comparisons reveals
the common approach companies took to try to discredit the long time market
leader. It is no coincidence that, with one exception, every study that found a
follow-on superior to Prozac was sponsored by the manufacturer of that follow-
on. The authors noted that differences in response rates here were minimal at
best, and did not hold up when the head-to-head trials were matched up
transitively and broader trials included. As such, they concluded that differences
among the antidepressants are not substantial in treating MDD or anxiety.

For example, just a few of the studies drawn on to conclude that Prozac
and Paxil had similar levels of efficacy were published over a period of almost
ten years (Cassano et al., 2002; Chouinard et al., 1999; Fava et al., 1998; De Wilde
et al., 1993; Schone & Ludwig, 1993). Even though a broad objective analysis of
the SSRIs as a whole revealed no significant differences in effectiveness between
them for treating MDD or anxiety disorders, the results of Gartlehner et al.
suggest that individual industry sponsored head-to-head trials generally

\(^9\) These studies were all sponsored by Forest and did not account for the fact that equal doses of
the two drugs corresponds to half the active ingredient for Celexa.
portrayed follow-on drugs as superior to Prozac and to each other, but the later had a net effect of zero because the findings of each company conflicted with those of its competitors.

The ability of the different antidepressants to maintain a response or remission in MDD is also similar, as is their efficacy in treating anxiety disorders. In terms of side effect profiles, the authors identified trends between antidepressants, though pointed out that the absence of objective scales in many studies was problematic. In general, Paxil is associated with a 52 percent higher incidence of nausea and vomiting, and Zoloft with higher rates of diarrhea, as compared to other SSRIs. The rates of discontinuation because of adverse events are similar among all SSRIs, but are alarmingly higher for the SNRIs as compared to the SSRIs: Cymbalta 67 percent higher and Effexor 40 percent higher, with no trend in the types of adverse events.

An important point that the previous meta-analysis did not delve into was the controversy surrounding some of the more severe adverse events with which antidepressants have been associated. It does point out that SSRIs and SNRIs are both potent inhibitors of liver enzymes, which can cause serious interactions with anything that has a high first-pass metabolism. This is mainly a problem in antidepressants like Prozac that have long half-lives because of the sustained concentration of the drug in the liver. Drugs with shorter half-lives, on the other hand, are associated with more withdrawal-like effects. Drug-drug interactions, which are predictable and largely avoidable if patients are careful,
may be less dangerous than psychological reactions, which can manifest themselves unexpectedly and result in self-destructive behavior. The meta-analysis does not emphasize the severity of these reactions.

Cases of antidepressant related suicides picked up a lot of attention in the early 2000’s, especially in connection with Paxil and Effexor. In 2004, a committee of the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK was charged with responding to these concerns, and conducted a comprehensive review of these incidences. Among their conclusions were that Paxil and Effexor were associated with a greater frequency of discontinuation syndrome than other antidepressants (Committee on Safety of Medicines [CSM], 2004). Still, they reported that there was not enough evidence to suggest that these drugs definitively caused higher rates of suicide. A study sponsored by the BBC investigated the issue further, and factored in patient reporting of adverse reactions. Doing so, they found that the CSM review suffered from significant underestimation of reported adverse events of Paxil and Effexor (Medawar & Herxheimer 2004). Such contentious results are particularly concerning when considering that it is common practice for drug companies to withhold clinical trials from publication finding that their drug is ineffective, causes harm, or both (Whittington et al., 2004). The effects of unpublished trials are difficult to study; Whittington et al. contacted the manufacturers of all antidepressants requesting unpublished data, but none was forthcoming. They were still able to identify fifteen unpublished trials pertaining to Prozac, Paxil, Zoloft, Celexa, and Effexor, and infer that the risk profiles for all but Prozac were underestimated. Two
unpublished studies stood out that reflected especially poorly on Effexor: one which remained unpublished on account of high rates of discontinuation due to adverse events, and the other due to suicide-related events.

By observing the publications produced from all facets of the market over a long period of time, we are able to see that the antidepressants generally offer the same benefits to patients. Company sponsored studies may suggest otherwise on an individual trial basis, and this information can be conveyed to physicians through detailing. In terms of side effects, Prozac has a higher potential than most antidepressants to interact with other drugs that are metabolized by the liver. However, Paxil, Effexor, and later Cymbalta, are associated with the worst symptoms of discontinuation syndrome, an unpredictable, debilitating, and often times dangerous side effect. While these risks may be worth it for those who believe that one of these medications works better for them than the alternatives, these disadvantages were obscured by company-sponsored studies.


Prozac enjoyed a four-year monopoly epoch after its introduction in 1988. At the end of this, Prozac was approaching the status of blockbuster drug as its annual sales neared $1 billion. At the start of 1992, Pfizer launched Zolof
(sertraline), making it the first follow-on drug in the class.\textsuperscript{10} SmithKline Beecham (now GlaxoSmithKline) introduced Paxil (paroxetine) a year later, and Luvox (fluvoxamine) was introduced by the Belgian company Solvay in early 1995.\textsuperscript{11} Celexa was a slightly later entrant, introduced by Forest in 1998. Considering the equivalent therapeutic profiles of these SSRIs, we would expect the (n+1)\textit{th} rule to apply and the sales of each successive drug to be somewhere on the order of 40 percent lower than the previous. The inferior side effect profile of Paxil would actually merit a particularly poor performance from this medication. With the exception of Celexa, however, the market unfolds quite differently [Figure 3.1]. In 2000, the year before generic fluoxetine became available, Prozac’s annual sales amounted to more than $2.5 billion. Somehow, both Paxil and Zoloft had nearly caught up to the market leader with annual sales of $2.3 and $2.1 billion, respectively. Luvox was a far less successful drug and saw its best sales that year with $250 million, remarkably lower than 40 percent of the blockbusters’, which had not yet peaked. Celexa’s yearly revenue was $430 million, but it had only been on the market for two years and ultimately did approach 50 percent of Paxil’s and Zoloft’s sales. The divergence of Zoloft, Paxil, and Luvox from the predicted model makes sense if we look at the market in light of the five non-therapeutic determinants I have identified.

\textsuperscript{10} It was approved in December of 1991, which is often confused with the launch date

\textsuperscript{11} Introduced in 1993 in parts of Europe.
Early FDA Approvals and Initial Marketing

FDA-approved indications play an especially important role in the market for mental illnesses because of the vast numbers of disorders. The three blockbuster drugs were all initially approved exclusively for MDD [Table 3.1]. Luvox, interestingly, was only approved to treat Obsessive-Compulsive Disorder (OCD), perhaps in an attempt to differentiate itself through niche marketing. Its sales speak to the success of this effort, which may have failed in part because Prozac was also approved to treat OCD in 1994. In 1996, Paxil became the only drug approved for Panic Disorder (PD) until Zoloft gained the indication in 1997. The year of exclusivity that Paxil enjoyed is arguably less important than the fact that Prozac was not officially indicated in this until 2002, which may help explain why the two follow-ons were able to gain ground in the following years. What Prozac did get exclusively approved for in 1996 was an indication in bulimia nervosa (BN). It remains the only antidepressant currently approved for BN, but this may reflect the small market and limited profitability of an indication in it. Unfortunately, I do not have access to advertising expenditures as early as any of these indications, so cannot determine if these approvals synergize with detailing efforts.
The year in which my data on advertising expenditures does start, Prozac was detailed significantly more than any other drug I study [Figure 3.3].\textsuperscript{12} Lilly does not maintain this lead, and its monthly expenditures soon joined the other companies’ in the hodgepodge of detailing efforts. The market then experienced a big shock with Forest’s introduction of Celexa in 1998. Launched more than a decade after Prozac, the SSRIs had had plenty of time to accumulate a long list of adverse side effects and reactions (Drug labels as listed on FDA website, 1998). The novelty of Celexa, coupled with monthly detailing expenditures that amounted to nearly $12 million within less than half a year, helps explain why Celexa saw the amount of success it did in the face of already established giants, while a drug like Luvox did not [Figure 3.1]. It is somewhat surprising that Celexa did as well as it did during this time of intense indication competition, being approved only for MDD. The power of the brute marketing tactic that Forest employed to distinguish Celexa then becomes apparent, spending double what most other firms were on their drugs [Figure 3.3]. Forest’s detailing of Celexa dropped significantly in mid-1999, which corresponded to a drastically dampened growth rate for the following fiscal year [Figure 3.1]. Celexa’s sales abruptly picked back up in line with their old growth rate when Forest resumed its aggressive marketing and again started detailing Celexa more than any other antidepressant in mid-2000. The relationship between absolute marketing and growth of sales suggests that marketing is a significant driving force in this class.

\textsuperscript{12} The cluttered graph makes this point difficult to discern, but it spends about $2 million more a month than the next most advertised drug (Paxil).
Other factors, such as novelty or differences in indications can make marketing a more potent tool, which would explain why all firms did not simply double their advertising expenditures.

**Increasing Competition for Indications with Strategic Marketing**

The next important indication that was approved was in May of 1999 for Paxil’s use in Social Anxiety Disorder (SAD). Paxil was the first SSRI to be approved for SAD, and econometric analysis reveals that Glaxo increased its total promotional spending in response to this approval (Huskamp, Donohue, Koss, Berndt, & Frank, 2008). While its monthly detailing costs only increased by a little more than $2 million over the course of 1999, the truly remarkable change occurs within DTCA, which increased from effectively zero to $10 million in only 2 months [Figures 3.3, 3.5]. The effect this had on the perception of Paxil is profound: at that time Paxil was the most widely prescribed antidepressant for anxiety disorders, used in nearly one third of all cases, and the only drug to be prescribed more in cases of anxiety than it was in any other mental illness (Donohue & Berndt, 2004). While DTCA generally just has a class-expanding effect, the authors found that Glaxo used it so effectively for Paxil that anxiety disorders were the only mental illness for which DTCA had an effect on drug choice. Interestingly, 1999 marks the year when Paxil pulled ahead of Zoloft in annual sales [Figure 3.1].

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13 Further discussion of this can be found in the literature review.
In December of 1999, Zoloft became the first drug in its class to be approved for post-traumatic stress disorder (PTSD). This approval coincided with an increase in monthly detailing spending from around $6 million to nearly $10 million, marking the first time in several years that Pfizer had spent significantly more on detailing than any other manufacturer [Figure 3.3]. We see a similar occurrence with Lilly's introduction of Sarafem\textsuperscript{14} for premenstrual dysphoric disorder (PMDD) in late 2000. The spike in advertising is not evident in detailing expenditures, which had started to deteriorate by this time on account of impending generic entry, but rather in monthly DTCA expenditures, which increased from nil to $14 million in a single month (Huskamp et al., 2008) [Figure 3.5]. It seems unlikely that this is a multi-million dollar coincidence, and can actually be explained by Lilly's decision to attach this new indication to Sarafem rather than Prozac. Besides the benefits of an extra three years of patent protection reformulations receive, Lilly cleverly created a sub-market for PMDD. A small portion of women responding to these advertisements would already be on antidepressants and informed that they were currently taking a similar medication. Others might see their doctor and end up being diagnosed with depression, producing a class-expanding effect. The largest group, however, would be seeing the doctor purely for their PMDD symptoms, and thus not want a drug that was associated with any other stigmatized mental illness. Lilly remained the only company to market an antidepressant approved for

\textsuperscript{14} Sarafem is also fluoxetine, and was approved by the FDA as a reformulation of fluoxetine. Its sales are included in the Prozac family.
PMDD until 2002, but the effect this had on Prozac family sales was muffled by the entrance of generic fluoxetine in 2000 and 2001.

Applying the Publication Environment

A milestone in the antidepressant market that I have not mentioned thus far was the introduction of Effexor (venlafaxine) in 1994.\textsuperscript{15} It differed from the other antidepressants at the time because it is SNRI, and the first one at that. The rationale behind its development was that norepinephrine is also thought to be involved in mood regulation, so heightening its signaling effects might add an incremental benefit to antidepressants. As I have already outlined, however, SNRIs were not shown to be more effective at treating mental disorders than any of the SSRIs. Pharmacology provides a partial explanation, as the norepinepherine reuptake inhibition is extremely dose dependent; at low doses Effexor acts almost exclusively as an SSRI (Schweizer & Rickels, 1997). Physicians must therefore implement aggressive dosing regimens to take advantage of the norepinephrine reuptake inhibition, but this in turn accentuates the adverse side effects caused by its short half-life.\textsuperscript{16} While I do not have access to Effexor’s sales prior to 1998, the fact that they were only $545 million after being on the market for five years means that it was very slow to be

\textsuperscript{15} No data available prior to 1998.  
\textsuperscript{16} Effexor’s drug label cites its half-life at eleven hours, the shortest of any antidepressant. Remember that Effexor was one of the antidepressants most associated with withdrawal and suicide.
adopted [Figure 3.2]. Prilosec similarly took quite a while to take off, which I associated with barriers to gaining doctors’ trust and a lack of important indications that the H2RAs carried. The homology of SNRIs to SSRIs presumably lessened the extent to which trust hampered Effexor’s growth, though indications were still a problem.\textsuperscript{17} The main difference between the situations of Prilosec and Effexor was that Prilosec actually offered objective advantages over the H2 blockers. However, we see that Effexor is a prime example of how the publication environment can overcome a lack of clinical superiority through inducing irrational demand.

The first way in which Wyeth differentiated Effexor from the rest of the antidepressants was through an extended release formula, Effexor XR, which was approved in late 1997.\textsuperscript{18} Whether it was understood or not at the time, Effexor carried one of the worst side effect profiles of the class. The XR formulation helped remedy that to a small extent by prolonging the time over which the drug was released by a few hours. As a psychological driving force of demand, however, the extended release formulation was considerably more significant. For a drug intended to treat chronic conditions, longer time of effect is generally associated with being better. Even though Prozac, Zoloft, and Celexa all had longer half-lives than Effexor XR, that was not conveyed through their brand names. Effexor overcame the limitation of lacking important FDA-

\textsuperscript{17} MDD and anxiety disorders were, and continue to be, the two largest markets for antidepressants in terms of sales (Chen & Rizzo, 2010). Effexor was only indicated in MDD until 1999.

\textsuperscript{18} From this point on, I use Effexor to mean sales of the Effexor family, which includes Effexor XR, unless otherwise specified.
approved indications when it was approved for Generalized Anxiety Disorder (GAD) in 1999. It joined Paxil as the only other antidepressant indicated in anxiety, but was able to find its own niche in GAD rather than SAD. Remember though, that clinical trials at the time demonstrated that off-label use of Prozac, Zoloft, or Celexa was equally effective in treating anxiety. Both Effexor approvals corresponded with statistically significant increases in detailing efforts,\(^{19}\) suggesting that Wyeth actively conveyed these distinctions to physicians. It is also worth noting that the absolute expenditures effect could have played a small role, as the spike in detailing brought Effexor up from well below average levels in 1997 [Figure 3.3].

Effexor was still missing one key component that Prilosec relied on for success: demonstrable clinical superiority. Wyeth was able to bypass this by funding several convincing clinical trials that concluded Effexor XR was a superior treatment to other antidepressants. The first head-to-head trial of Effexor was conducted against Prozac and published in 1996 (Dierick et al., 1996). This was followed by two more in 1998 and 1999 that matched up against Prozac, the latter of which specifically studied Effexor XR (Costa e Silva, 1998; Rudolph & Feiger, 1999). All three found that Effexor was as well tolerated as Prozac, but “may have” had advantages over it. A meta-analysis in 2001 concluded that Effexor had higher remission rates as compared to the

\(^{19}\) It is difficult to tell from Figure 3.3, but the XR approval corresponds with an increase in monthly detailing expenditures from about $2.2 to $4.8 million, and the GAD indication from about $4.3 to $8 million in 4 months.
SSRIs as whole (Thase, 2001). It is no surprise that we see Effexor’s annual revenues triple in less time than it had taken it to break half a million. Given the availability of data to me, it is difficult to discern how much of this growth is attributed to the publication environment versus the FDA approvals. I can say, however, that the study suggesting Effexor superior to all SSRIs had a huge effect on the direction of research; a Web of Science search reveals that it has since been cited an impressive 748 times. The importance of this study may have in part contributed to the visible growth in sales rate from 25 to 40 percent in 2001. It is also worth noting that I did not identify any clinical trials prior to 2001 that depicted Effexor as equivalent or inferior to any SSRI. The wave of publications continued throughout the decade, with results being published in 2002, 2004, 2005, 2006, and beyond, though with increasing contention over the findings (Smith et al., 2002; Nemeroff & Owens, 2004; Han & Wang, 2005; Rush et al., 2006; others). To emphasize my point about the biases of these studies, the Conflict of Interest sections of all these cited papers include phrases like, “This study was supported by Wyeth-Ayerst Research,” “Both authors were salaried employees of Wyeth Pharmaceuticals” and “[author’s initials] is a paid consultant to Wyeth-Ayerst Laboratories.”

**Length of Time, Pricing, and Perceived Quality**

So far, we have explained the surprising success of follow-on antidepressants mainly through costly and potentially misleading marketing
efforts by pharmaceutical companies to create perceived differences where previously few existed, as well as to overcome the barriers of some significant adverse side effects. I have talked comparatively little about how drugs’ relative lengths of time on the market affect their perceived quality. If the market for antidepressants were comparable to the one for H2 blockers, we would expect that low numbers of reported adverse events for newer drugs would correspond to both higher perceived quality and sales (Berndt et al., 1996). A survey that polled several hundred physicians between 1999 and 2002 about their relative perceptions of antidepressants confirms that this is the case (Chen & Rizzo, 2010). Doctors were asked to rate the antidepressants based on their experience with them in ten areas relating to efficacy, interactions, and side effects, and the results were pooled to quantify overall perceived efficacy. The results, from best to worst quality were as follows: 1- Celexa, 2- Zoloft, 3- Effexor XR, 4- Prozac, 5- Effexor, 6- Paxil. That Effexor and Paxil occupy the fifth and sixth spots aligns with their true side effect profiles. Prozac, however, had an arguably better side effect profile than Effexor XR, but because of the psychological advantages may not have fared as well. It makes sense that Celexa, being the newest drug, was thought to be the highest quality, and that Zoloft, possessing a half-life of about two days would be somewhere in the middle.

Another interesting point that this study brings up is the pricing scheme that these drugs employed. The authors suggest that drug companies assess the side effect profiles of their products prior to launch, and launch drugs of lower quality at higher price (Chen & Rizzo, 2010). A lower quality drug stands to gain
less in market share by lowering its price than a drug of higher quality, so companies attempt to maximize profits early on. As we saw with the H2 blockers, a significant reduction in relative price of a drug may also lead to increased sales (Berndt et al., 1996). On the reverse side, a drug of comparable or higher quality is more likely to engage in price competition in order to steal market share early on, then either raise or lower its price more slowly (Chen & Rizzo, 2010). In accordance with this model, Paxil and Effexor were introduced at higher prices which fell more quickly than the other antidepressants I focus on, Celexa is introduced at the lowest price, and Prozac and Zoloft fall somewhere in between [Figure 3.4]. The results of this study demonstrate that relative lengths of time on the market can affect perceptions of drugs and in turn sales, as can pricing strategies.

A Brief Summary Thus Far

The first twelve years of the SSRIs were categorized by drug success through irrational demand. Zoloft and Paxil entered the market four and five years after Prozac did, respectively. Being newer treatments, it is likely that the fewer adverse effects reported against them contributed to their relative growth over Prozac. All three blockbusters contended for exclusivity on FDA-approved indications, coordinating approvals with increased marketing efforts. Zoloft and Paxil both fared well in this regard, but Paxil’s indication making it the only SSRI approved to treat SAD was arguably the most important of these approvals.
Effexor and Luvox were introduced six and seven years after Prozac, and were both slow to gain sales because of their relatively low promotional expenditures and lack of ways to differentiate themselves from the other antidepressants. The extended release formulation and indication in GAD accomplished just that, but studies sponsored by Wyeth also promoted the perception that the new SNRI class that Effexor pioneered was superior to the SSRIs. Celexa was the last drug introduced during this time period, and proved that a drug of perceived paramount quality could be successful based almost entirely on colossal advertising expenditures. Firms utilized different pricing strategies to maximize the success of their drug early on if it had more serious side effects, or tried to capture market share by undercutting competitors if their drug was of higher quality. The way in which physicians actually perceived the antidepressants at the end of this time period confirms the ability of the non-therapeutic determinants of success to distort real clinical profiles and in turn drive irrational demand.

While I attribute the actions of drug companies to the growth of these products’ sales, I must also point out that the continuing expansion of the market for antidepressants through the early 2000’s meant that some level of growth was inevitable [Figure 3.9]. Nevertheless, drugs with substantially riskier side effects (i.e., Paxil and Effexor) enjoyed more success than most other antidepressants, yet the therapeutic benefits of all second-generation antidepressants were comparable for treating MDD and anxiety. Non-therapeutic determinants of success, most of which pharmaceutical companies
are directly responsible for and are resource dependant (i.e., marketing expenditures, clinical trials for FDA-approvals, reformulations), perturbed the correctional effects of the market and made some drugs more successful than was merited. I believe that this would not have happened had the promotional costs of some of these large pharmaceutical companies been curbed. Not only would this have allowed more resources to be allocated to serving undertreated diseases, but it would have caused people to switch to therapeutically equivalent generics and reduce healthcare expenditures.

Generic Entry, SNRIs, and Beyond (2001-2010)

False Perceptions Causing Waste

August 3, 2001 was a gloomy day for Eli Lilly. The patent on their first ever blockbuster drug had expired, and generic fluoxetine hit the U.S. market. Prozac started experiencing generic competition in parts of Europe the year before, and their sales had declined accordingly [Figure 3.1]. The U.S. expiration contributed to an even steeper drop, and by 2002 Prozac's annual revenue was only $730 million, down from a peak of nearly $3 billion per year. Lilly took advantage of one of Prozac's greatest historical weaknesses, its long half-life, and Prozac Weekly joined Sarafem as the newest member to the Prozac family in 2001. It is worth noting that Lilly replaced a significant amount of its detailing expenditures on Prozac with detailing for Prozac Weekly, and the company's
overall expenditures increased [Figure 3.7]. The sales of generic fluoxetine quickly replaced those of the incumbent, but because members of the Prozac family kept selling, there was a mild increase in utilization of total fluoxetine associated with Prozac’s patent expiration [Figure 3.6]. Surprisingly, the presence of a less expensive generic alternative did not negatively affect the sales of the branded competitors, which actually continued to rise [Figures 3.1 and 3.6].

This increased utilization of follow-ons cannot be explained by a pricing response strategy because the prices of the follow-on drugs did not decrease to compete with generic fluoxetine (Jena et al., 2009). At this time, somewhere around 80 percent of insured patients had the same copayment for all branded pharmaceuticals, and the differences between copayments for generic and incumbent antidepressants was minimized by third-party benefits (Donohue & Berndt, 2004; Jena et al., 2009). Advertising also fails to explain the lack of response to generic entry, as there is no statistically significant trend among Paxil’s, Celexa’s, or Zoloft’s advertising in response to generic fluoxetine entry (Huskamp et al., 2008). The sudden plummet of advertising for Prozac created a similar void to the one created by Tagamet’s patent expiration. In that case, the clinically superior PPIs, stepped in, but in this case there were only highly similar follow-ons. Another potential explanation is that the switching costs between molecules, namely the hassle and risks of trying a new medication, were high, so patients continued to take the same incumbent. However, the number of new prescriptions for follow-on drugs continued to increase in the
presence of generic fluoxetine, so even new patients who had a choice between branded and generic picked the former [Figure 3.7]. In this confusing situation, it is insightful to apply some of the deductive powers of the great Sherlock Holmes: when you have eliminated all which is impossible, then whatever remains, however improbable, must be the truth. The only remaining explanation for why patients did not substitute to generic fluoxetine is that they and/or their physicians perceived significant differences between fluoxetine and the other drugs. This evidence supports the findings of the previous study on quality perception, and implies that perceived differences created largely by excessive marketing were significant enough to prevent switching to cost-saving alternatives.

**More FDA Approvals and Follow-On Entrants**

2001 was also a big year for Paxil, as GSK released Paxil CR, and received an FDA approval for an indication in GAD. As has been the norm, GSK increased its advertising to correspond with the approval (Huskamp et al., 2008). The detailing done for Paxil CR almost entirely replaced that done for the immediate release version [Figure 3.8]. While generic paroxetine proceeded to enter the market in 2003, Paxil family sales did not drop as low as Prozac’s did in the face of its own generic competition. GSK’s annual report for that year reveal the cause to be persistent sales of Paxil CR, which gained three years of patent
protection with its approval.\textsuperscript{20} The stabilization of Prozac's unfortunate sales curve that we begin to see in 2003 may have been helped, however, by its FDA approval to treat MDD in pediatrics that same year, making it the first antidepressant to be approved in children for any mental illness.

The next big shock to the market was the introduction of Lexapro (escitalopram) by Forest in 2002. Analogous to the case of Nexium and Prilosec, Lexapro is simply one enantiomer from the racemic mixture of Celexa. The similarities continue, as it was introduced a year before the patent expiry of Celexa to give Forest time to switch patients to the new drug. The rapidity with which Forest replaced the marketing of Celexa is truly impressive [Figure 3.8]. The effect of their efforts can be seen by the curve that sums the sales of Celexa and Lexapro, which experiences a mild depression coinciding with the entrance of generic citalopram, but quickly recovers and proceeds to outperform its predecessor [Figure 3.2]. A compounding factor may also have been the novelty of the drug. The physician survey that culminated in 2002 identified Celexa as the antidepressant of highest quality, so it follows that an even newer “improvement” of this medication would be perceived as still higher quality than any antidepressant marketed at that time. Given how similar this reformulation was to the Prilosec-Nexium one, the anecdotal evidence from the PPI class portraying the tactics used by large pharmas reinforces the methods and

\textsuperscript{20} Current patent regulations award drug reformulation approvals an additional three years of exclusivity.
resulting success that drug companies had in creating irrational demand for Lexapro here.

The last antidepressant of importance that I will discuss is the SNRI Cymbalta (duloxetine), which was introduced by Lilly in 2004. This drug proves to be the archetype of utilizing FDA-approved indications. While initially just approved for MDD, Cymbalta became the first of the antidepressants to be approved for diabetic peripheral neuropathic pain (DPNP), fibromyalgia (FM), and chronic musculoskeletal pain (CMP) in 2004, 2008, and 2010, respectively [Table 3.1]. By picking up an indication in GAD in 2007, it also became approved for the two largest non-psychotic mental illnesses. Several studies compared duloxetine with other medications for treating pain conditions, with mixed results. One particularly sound review sponsored by the Oxford Pain Research Trust looked at more than 2,000 patients from six reputable studies and concluded that duloxetine was just as effective at treating pain disorders as other antidepressants (Sultan, Gaskell, Derry, & Moore, 2008). While six may seem like a small number of studies, multiple papers identified the lack of clinical evidence comparing duloxetine to other drugs as a problem, and expressed the need for more comparative trials (Miller & Rabe-Jablonska, 2005; Lunn, Santos, & Craig, 2010). The evidence of Cymbalta’s advantages may be questionable, but its side effect profile is demonstrably worse. It shares a short half-life with Effexor and Paxil, measured at about twelve hours. During clinical trials testing Cymbalta for its use in stress urinary incontinence (SUI), a 19 year old college girl hanged herself from the shower rod in her bathroom, sparking a
debate over the safety of the drug (Lenzer, 2005). In addition to studies of other reported cases of suicides, data came out also linking Cymbalta to fatal liver failure (Salem & Karam, 2008; Hanje, Pell, Votolato, Frankel, & Kirkpatrick, 2006). Studies funded by Lilly found Cymbalta safe and effective in treating SUI, though reported discontinuation rates due to adverse effects were among the highest of any of the antidepressants (Schagen, Lange, Jonasson, Chen, & Viktrup, 2008; Hurley, Turner, Yalcin, Viktrup, & Baygani, 2006). Still no definitive conclusions were drawn as to the drug’s safety, but the FDA did not approve Cymbalta for SUI due to concerns over suicides and liver failure. Additionally, in 2004 the FDA mandated that the antidepressant packaging display a “black box” warning label identifying a possible increased risk of suicidal thinking and behavior.

Data on marketing do not cover the introduction and life of Cymbalta, but anecdotal evidence indicates that its success was rooted in the same factors that contributed to the success of the five follow-on drugs before it. Being the first antidepressant to break into the market for pain disorders, Lilly appears to have utilized the same aggressive marketing tactics that GSK and Wyeth did when Paxil and Effexor broke into the market for anxiety. Lilly's advertising was probably made more effective by the marketing vacuum created by the patent expirations of Paxil in 2003, and Zoloft in 2006. There is also the fact that it was the newest drug, and carried all the advantages of novelty, including limited data on adverse side effects. As marketing has proven to be the primary way to induce demand for drugs of this class, the success of an antidepressant is highly
contingent on the level of marketing and how distinct sales reps can make their drug seem. Cymbalta fared quite well in these regards: Lilly had a lot of money to spend and detailers had a lot to go on without having to worry about intense between-patent competition. Another likely explanation for Cymbalta’s success may have been intense DTCA. Lilly utilized DTCA strategies to promote Sarafem for PMDD. Pain disorders are similar to PMDD in the sense that they do not inherently carry the same social stigmas as mental disorders. Therefore, reaching out to patients directly with a treatment specifically for their disorder has the potential to be effective at leading them to initiate a talk with their doctor.

The discussion of antidepressants ends with the entrance of generic sertraline and venlafaxine in 2006 and 2008, respectively. Annual sales of Zoloft sharply declined with competition, as we would expect [Figure 3.1]. Effexor sales also dropped rapidly, but may have been partially held up by patent exclusivity on Effexor XR that lasted until 2011. It is difficult to tell what effect these events had on the market for SSRIs and SNRIs because generics had since flooded the market, and the increasing prevalence of different types of antidepressants and combination therapies outside the scope of this work added a lot of noise (e.g., Wellbutrin, atypical antipsychotics, etc.). The ultimate decline in sales of the first big four antidepressants (Prozac, Zoloft, Paxil, and Effexor) is

21 Some generic competition had begun in Europe as early as 2005, but most of the world was affected starting in 2006.
22 The first generic venlafaxine was actually produced by Teva starting in 2006, but it had exclusivity on generic manufacturing.
a good sign. It indicates that whatever irrational demand drove the sales of these follow-ons in the first place did not ultimately prevent within-patent competition from taking over.

Conclusion

Taken as a whole, I think that the antidepressants undermine the argument in favor of me-too drugs. There is only one objectively innovative drug, and that is Prozac. We then see seven follow-on drugs enter the market, and six of them perform very well, fueled by irrational demand. The follow-on drugs did not necessarily cause the innovative drug’s sales to fall as Zantac did with Tagamet. Still, their therapeutic profiles did not merit the high level of their success. Because pharma could reliably produce irrational demand through marketing, they were more inclined to produce excessive follow-on drugs. This in turn caused a waste of R&D resources to develop them, advertising expenditures to promote them, and increased healthcare expenditures by dissuading generic utilization.
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Table 3.1 (Above) and Legend (Right). List of all major FDA-approved indications and dates for SSRIs and SNRIs.

**Key:**

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<tr>
<th>Abbreviation</th>
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<tr>
<td>MDD</td>
<td>major depressive disorder</td>
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<td>OCD</td>
<td>obsessive compulsive disorder</td>
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<td>BN</td>
<td>bulimia nervosa</td>
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<td>PMDD</td>
<td>premenstrual dysphoric disorder</td>
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<td>PD</td>
<td>panic disorder</td>
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<td>PTSD</td>
<td>post-traumatic stress disorder</td>
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<td>SAD</td>
<td>social anxiety disorder</td>
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<td>GAD</td>
<td>generalized anxiety disorder</td>
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<td>DPNP</td>
<td>diabetic peripheral neuropathic pain</td>
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<td>FM</td>
<td>fibromyalgia</td>
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<td>CMP</td>
<td>chronic musculoskeletal pain</td>
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<td>Reform.</td>
<td>Reformulation</td>
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Unless otherwise specified, the approval date is for short-term use in adults

- A - For use in adults
- P - For pediatric use
- LT - Long term use
Figure 3.1. SSRI annual global sales by individual drugs.
Figure 3.2. Consolidated SSRI and Selected SNRIs annual global sales by individual drugs.

Figure 3.3. Taken from Donahue and Berndt 2004, Figure 4. Monthly detailing expenditures by antidepressant.
Figure 3.4. Taken from Chen and Rizzo 2010, Figure 1. Trends in pricing of antidepressants years after relative drug introductions.

Figure 3.5. Taken from Donahue and Berndt 2004, Figure 3. Monthly DTCA expenditures by antidepressant.
Figure 3.6. Taken from Jena et al. 2008, Exhibit 4. Number of units of antidepressants sold by fluoxetine and collective follow-ons. Note the error in labelling Prozac’s sales prior to patent expiration as fluoxetine molecule sales.

Figure 3.7. Taken from Jena et al. 2008, Exhibit 8. Number of new prescriptions for follow-ons by therapeutic class. Note SSRI follow-ons.
Figure 3.8. Taken from Huskamp et al. 2008, Figure 1. Monthly detailing expenditures (millions $) for a. Prozac and Prozac Weekly; b. Paxil and Paxil CR; and c. Celexa and Lexapro.
Figure 3.9. Whole class sales of SSRIs and SNRIs. Note that the jump from 1997 to 1998 for SSRIs is a result of the sudden availability of data for Paxil in that year. Had data been accessible since 1994, such a jump would not have occurred.
CHAPTER 4

Erectile Dysfunction

Overview of the Market and Treatments

Erectile dysfunction (ED) affects an estimated 100 million Americans, and about 1 in 2 men at some point during their life (Keith, 2000). These statistics do not even take other parts of the world into account, so it is clear just how beneficial and lucrative treatments for ED can be. The current first-line treatment for ED is any one of the three FDA-approved phosphodiesterase-5 (PDE-5) inhibitors: Viagra (sildenafil), Levitra (vardenafil), or Cialis (tadalafil). Failing these, other options include topical creams in conjunction with injections, prosthetic implants, external devices (e.g. vacuum therapy or neuronal stimulation\(^1\)), or non-FDA-approved alternative therapies (e.g. herbal remedies).

\(^1\) Viberect became the first FDA-approved device to treat ED by using vibratory stimulation in 2011.
In 2010, the global annual revenue for all PDE-5 inhibitors was nearly $4.2 billion and showed no sign of slowing [Figure 4.1].

The similarities between Viagra and Levitra are remarkable: the substitution of a methyl group with an ethyl group, which is to say, the addition of a single carbon. Cialis is a more original structure, which corresponds to more differentiated pharmacodynamic and pharmacokinetic profiles. They all bind and inhibit PDE-5 with comparable efficacy, but Cialis and Levitra are many times more potent than Viagra and therefore require smaller doses (Wright et al., 2006; Mehrotta et al., 2007). Between the two newer drugs, Levitra is actually a more potent inhibitor of PDE-5, but differences in potency among drugs do not translate into significant therapeutic advantages (Pak et al., 2008; Grover et al., 2003; von Keitz et al., 2004; Goldstein et al., 2007; Wright et al., 2006). The prominent chemical differences manifest themselves through the drugs’ half-lives. Concentrations of Viagra and Levitra are reported to half within about 4 hours, whereas Cialis takes 17.5 hours (Mehrotta et al., 2007; Wright et al., 2006). Accordingly, Cialis can be taken anywhere from 0.5 to 36 hours prior to sexual activity, Viagra 0.5 to 4 hours prior, and Levitra 1 to 4 hours prior (FDA drug labels; Mehrotta et al., 2007). This feature of Cialis is what arguably makes it a superior drug. Only one dose of each can be taken daily, but a single dose of Cialis effectively resolves ED until the next dose is due

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2 Levitra and Cialis are available in 5, 10, and 20 mg doses, while Viagra comes in 25, 50, and 100 mg strengths.
24 hours later. Viagra and Levitra only address ED for a short period of time once per day.

Cialis has the potential to induce different adverse events than the other two PDE-5 inhibitors, but all ultimately offer similar side effect profiles. The problem inherent with any of these drugs is their off-target binding of other phosphodiesterases. For example, Viagra and Levitra inhibit PDE-6 to some extent, an enzyme found in the retina whose inhibition causes some patients to see blue or experience other vision problems. Cialis, on the other hand, is a more potent inhibitor of PDE-11, which is found primarily in the liver and can cause back pain or alterations in sperm quality. These side effects are not prevalent, and clinical trials have continually demonstrated equivalent side effect profiles (Pak et al. 2008, Grover et al., 2003; von Keitz et al., 2004, Goldstein et al., 2007; Wright et al., 2006). What this means, of course, is that the PDE-5 inhibitors are an example of a class in which a follow-on drug is superior to the breakthrough as well as other follow-ons. This class makes for an especially insightful case study because Levitra and and Cialis were introduced within months of each other, so differences in lengths of time on the market and environment the drugs were introduced into are non-factors. In the classes we have previously looked at, follow-on drugs offering little to no advantages have been able to experience success in the presence of a market leader and other follow-on competition. Pharmaceutical companies have relied on spending exorbitant amounts of resources to differentiate their products, but the lack of distinct advantages have

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3 This point will be demonstrated empirically.
meant that all drugs in the class continue to grow. In contrast to this model, Cialis brought with it a clear advantage for ED treatment, causing most new patients to adopt it and experienced ones to switch to it from Viagra. Cialis therefore outperformed Levitra while simultaneously biting into the market share of Viagra. Cialis’ annual revenues already exceeded $500 million after one full year on the market, and were just $200 million shy of Viagra’s by 2010 [Figure 4.1]. In the following analysis, I will portray the development of the market for PDE-5 inhibitors and show that the success of Cialis is a result of its superiority to Viagra and Levitra.

_A Truly Revolutionary Drug (1998-2002)_

There is little doubt about the importance of Viagra as a life changing therapy for millions of men, and indirectly women, worldwide. Were I feeling particularly bold, I might argue that its significance ranks among that of many of the life saving drugs developed over last century based purely on the number of relationships it has improved or rescued. Granted, I have not had much experience with marriage since I proposed to my preschool teacher, nor have I much with the drug in question, but I imagine that most people would agree that a close physical relationship is essential for good quality of life. Many men seemed to agree, as more than 3 million prescriptions for Viagra were written worldwide from the time of its introduction in April of 1998 to the end of that fiscal year (Pfizer Annual Report, 1998). Because ED was previously such an undertreated condition, Viagra saw one of the highest launch year revenues of
any drug with $788 million. By 2002, the year before follow-on competition, its annual revenues approach $2 billion [Figure 4.1].

That Viagra became adopted so quickly identifies an interesting characteristic of the market for these drugs. Erectile dysfunction manifests itself in very obvious ways. It is also a disorder that men generally want to address immediately. As such, overwhelming numbers of men who had ED in 1998 would have gone immediately to their doctor when they caught wind of Viagra. No lab tests, no hesitation, no waiting. Just a simple conversation with the doctor and then it was off to the pharmacy, prescription in hand. There were of course some barriers to entry, namely skepticism and pride, but that it gained more than 70 percent of its peak global revenues and U.S. prescriptions in less than two years on the market speaks to how quickly it was adopted [Figures 4.1 and 4.2]. This meant that by the time Levitra and Cialis were introduced five years after Viagra, there could not have been tremendous room for expansion of the market. Pfizer had already been spending hundreds of millions of dollars a year on DTCA and other forms of promotion, so it seems unlikely that large numbers of men remained oblivious to this treatment [Figure 4.3]. Because the use of ED drugs is age dependent, a steady supply of men feed demand for them. For the same reason, however, the market experiences an unusually high dropout rate, as the patients these drugs appeal to are more susceptible to death or discontinuation due to extreme age. From a theoretical standpoint, we would expect the net effect these have on growth to be small because aging is constant and inevitable. Other factors that should be considered to explain an expanding
market include more frequent use by patients (e.g. from several times a month to several times a week), and an expansion of the age range over which these drugs are utilized.

Levitra and Cialis: From Monopoly to Oligopoly (2003-2010)

Bayer introduced Levitra in August of 2003, and Lilly quickly followed with Cialis in November. Levitra got off to a quick start in the U.S. with nearly half a million prescriptions written for it in its first quarter on the market [Figure 4.2]. However, Levitra’s growth nearly stopped altogether as soon as Cialis became available. That Levitra’s global revenues slowly rose means that its price increased, its use in other parts of the world increased, or some combinations of the two occurred. No matter which indicator of growth you look at, Cialis performed significantly better than Levitra. Cialis also proved detrimental to the quantity sales of Viagra in the U.S., which plummeted from about 4 million a quarter to 2.5 million a quarter in the five years following Cialis’ introduction. The factors I previously identified limiting market expansion apply, at least in the U.S., where the number of whole class prescriptions barely increased over that five year period [Figure 4.2]. The data on global revenues tells a similar story; the introduction of Cialis caused a drop in Viagra’s revenues that it took five years to recover from [Figure 4.1]. The cause for the increase in class revenues is again unclear, but it does mean that patients across the world continued to value these drugs more, and bought more, paid more for them, or both.
To confirm that we are not confounding the success of Cialis with the non-therapeutic determinants we have seen, let us first explore advertising expenditures. While Cialis’ introduction did correspond with aggressive DTCA and professional promotion, Pfizer consistently spent more to promote Viagra than either Lilly or Bayer did for their drugs [Figure 4.3]. The difference was most prevalent with regard to professional promotion (i.e. detailing and journal advertising), on which Pfizer spent an average of $11.8 million per month between 2002 and 2008, while Lilly and Bayer only spent $6.7 million and $5.6 million, respectively (David & Markowitz, 2011). DTCA expenditures were more similar among all drugs; Viagra had an average of $4.1 million per month, Cialis $4.7 million, and Levitra $3.1 million. Pfizer promoted Viagra significantly more than Lilly did Cialis, so Cialis’ success cannot be explained by aggressive marketing. If anything, absolute promotional expenditures would suggest that Viagra should have dominated Cialis. As for Cialis and Levitra, the difference in their total promotional spending is nowhere near proportional to the disparities of their success, so is not a strong explanatory factor.

FDA-approved indications also differ very little among drugs. All three were initially approved for a single indication in ED with the same dosing regimen. In 2008, Cialis became the first (and still the only) PDE-5 inhibitor to be approved for once daily use, though this was not as significant as it sounds. The advantage of Cialis over its two competitors was always that it could be taken once a day to treat ED for a full 24 hours. The FDA-approval of this dosing regimen merely reinforced the ways patients were already using Cialis, so did
not have a profound effect on the market. What will likely make more of a splash, though is unfortunately outside the scope of this work, is Cialis’ approval to treat the signs and symptoms of benign prostatic hyperplasia (BPH), aka an enlarged prostate, in October of 2011. Most health insurance plans do not provide much, if any, coverage for voluntary therapies, such as PDE-5 inhibitors for ED. By also gaining an indication in BPH, Lilly may have increased the patient base for Cialis by giving insurers a legitimate reason to extend coverage to it.

The reason that relative lengths of time on the market are important to take into consideration is because drugs accumulate more reported adverse events over time (Berndt et al., 1996). The market for ED drugs confirms this effect, as Viagra had many times the number of yearly and cumulative events reported against it than either Cialis or Levitra did in 2003 [Figure 4.4]. Over the next five years, Viagra received about 50 percent of all reported adverse side effects, and Cialis and Levitra split the remaining 50 percent about equally (David & Markowitz, 2011). Taken at face value, these numbers erroneously suggest that the two newer drugs had superior side effect profiles, and we cannot discount this as a reason for why Viagra’s market share was hurt by them. A closer look at the graph in the context of the development of the market reveals that there is more going on though besides just the order of entry. Imagine the first several years that Viagra was on the market, during which time millions of men worldwide jumped on this treatment. All of these men experienced the same common side effects and proceeded to report them all at
once. The number of annual reports leveled off around 600 in 2001, which suggests that most men who were untreated before 1998 had since started Viagra, and that the market had reached a natural equilibrium. There are two points worth noting about the shock that occurred in 2003. One is that the number of reports against Viagra rose slightly. One of many explanations for this is that DTCA for Cialis and Levitra caused some spillover and expanded the entire market. The other point is that there were more than twice as many annual reports against Viagra than against the newer drugs. This might be a concern if there were not more than three times as many people taking Viagra than either of the other drugs [Figure 4.2]. What this really reveals is that the patient base for Cialis and Levitra was fed by three types of people: patients new to the market for ED drugs, patients who switched from Viagra and reported the adverse effects of the new drugs, and patients who switched from Viagra but experienced the same side effects so did not feel the need to report them. As the dust settled along with patients’ prescriptions, the number of reported adverse effects for all drugs began to converge, a trend that presumably continued through 2008 [Figure 4.4]. This supports the findings of handfuls of clinical trials that have not detected significant differences in side effects among the drugs, and also suggests that the length of time on the market and widespread use of these drugs has caused patients to come to expect certain side effects, realize they are normal, and consequently not report them.

The fourth of the non-therapeutic determinants, price competition, is more difficult to study in this market due to a lack of data. For this study, we are
limited to using global revenues and quantities of U.S. prescriptions. We can draw some conclusions about prices on the basis that price is the quotient of revenue and quantity, but these can only be very general. In the U.S., we know that the market for ED drugs topped out between 4.5 and 5 million prescriptions per quarter [Figure 4.2]. The slow rate of class expansion thereafter was largely a result of a widening of both ends of the age range over which the use of these drugs was acceptable. We also know that in the U.S., the sales of Viagra fell, those of Cialis increased steadily, and those of Levitra increased with the speed of a turtle. The data on international revenues tells a slightly different story, diverging in a few key ways. The sales of Viagra fell much more slowly and then recovered, and the sales of Cialis and Levitra increased more rapidly, both of which contributed to a profound growth of class revenues. Because decreases in revenues were less harsh than decreases in quantities, and that increases in revenues were more accelerated than increases in quantities, we know that the prices of these drugs increased with time, their international utilization increased with time, or some combination of the two. The important point to note is that it is highly unlikely that the price of any of these drugs decreased, so a model of price competition is not relevant.

Drugs for erectile dysfunction are different from most other pharmaceuticals because they are lifestyle drugs. Viagra, Levitra, and Cialis are all meant to make men feel the way they want to feel, not to modify the activity of some enzyme buried in smooth muscle, or even to simply address a physical symptom. Comparing side effect or clinical profiles of these drugs is simply not
adequate. For a group of lifestyle drugs, the best one is that which provides the most positive experience in all aspects of life to the greatest number of patients. Ranking these drugs is therefore a subjective measure, but if enough patients agree then it becomes objective. Clinical trials determining the relative quality of ED drugs rely on patients to report the efficacy of the drugs, because it is their perception of how well they work that truly matters. Double-blinded studies have been conducted in which men are given either Cialis or Viagra with dosing instructions that may or may not match up to the drugs they are given. After several weeks, the drugs and/or instructions are switched, allowing for comparisons between groups of all different combinations. Men overwhelmingly prefer Cialis to Viagra; two studies found the ratios to be 66 percent to 33 percent, and 73 percent to 27 percent (Grover et al., 2003; von Keitz et al., 2004). Interestingly, the name attached to a drug does not affect perceptions, as an open-label study found that 71 percent of men preferred Cialis to Viagra (Goldstein et al., 2007). A more recent study quantified the perceived efficacies of Cialis and Viagra by surveying men on the frequency, length, desire, and satisfaction of intercourse, as well as on overall satisfaction with the drug they took (Pak et al., 2008). Men who took Cialis reported higher levels of all of these measures than those who took Viagra, though only the increase in sexual desire was statistically significant. Also, the increased level of satisfaction compared to no treatment was more statistically significant among men taking Cialis than among those taking Viagra. To some extent, these clinical trials could be considered the publication environment. Unlike the markets for
proton pump inhibitors or antidepressants, there is very little controversy about which drug men prefer. The publication environment, therefore, is an accurate reflection of the relative qualities of the drugs.

Conclusion

The five non-therapeutic determinants that have so effectively been able to explain previous markets we looked at turn out to be much more flaccid explanations in rationalizing the success of Cialis. Cialis and Levitra were promoted far less than Viagra was, and the slightly higher advertising of Cialis cannot account for its disproportionate success over Levitra. For the majority of their lives, all drugs were indicated solely in erectile dysfunction, and Cialis’ approval for once daily use in 2008 was like giving an artist green paint when he already had blue and yellow. The novelty of Cialis and Levitra could have contributed to their growth on Viagra to some extent, but does not address why Cialis was more successful than Levitra. Pricing was a more difficult issue to address for this market, but it seems unlikely that aggressive pricing strategies by any of the incumbents could have determined the direction of the market. The success of Cialis is rooted in men’s overwhelming preference for it, which is a reflection of its superiority. The market naturally rewarded Cialis for its innovation, and reallocated much of the market share to it. Despite the advantages it offered, Lilly still had to spend millions of dollars a month to promote Cialis, highlighting the fact that being a better drug is not enough in the face of a clear market leader. Though Lilly did not spend quite as much as Pfizer,
it is still necessary for a new entrant to a class to keep up with the amount of advertising its competitors are doing. It does not matter if you sell the greatest product in the world if you do not reach your customers, or competitors can sway them easily. A policy that limited the amount of promotional expenditures would address this issue by keeping advertising costs low and consistent across all products, therefore making a truly innovative one standout.
Chapter 4 Figures

Figure 4.1. Viagra, Cialis, and Levitra revenues and PDE-5 whole class revenues.

Figure 4.2. Taken from David G and Markowitz S 2011, Figure 1. Number of Viagra, Cialis, Levitra and whole class prescriptions dispensed in thousands.
Figure 4.3. Taken from David G and Markowitz S 2011, Figure 2. Total DTCA and professional promotion monthly expenditures by drug in

Figure 4.4. Taken from David G and Markowitz S 2011, Figure 4. Number of reported adverse events by drug and year.
CONCLUSION

Think back now to the pharmacy in which this thesis began. When you discovered that your medication was going to cost you several times more than expected, you may have inquired into possible generic alternatives. Do you think that you would have the same thought process now? Might you walk into the pharmacy with different price expectations after reading this work? Researching for and writing this thesis certainly opened my eyes to the ways in which behind the scenes competition affects the drugs I take every day. For starters, it has made every trip down to Rite Aid a bit more exciting, as my mind becomes flooded with thoughts about how signs posted in the windows advertising “Rite Aid now carries generic Lipitor equivalents” haunt the dreams of every Pfizer executive. I speculate about the tactics AstraZeneca and Novartis are implementing to promote Crestor and Lescol in the wake of the huge vacuum that Lipitor left behind with its patent in December 2011.
Crestor, Lescol, and even Lipitor belong to a group of hundreds of follow-on drugs that offer very few, if any, benefits over other medications in their classes. In this thesis, we have seen a majority of the H2 blockers, PPIs, SSRIs, and SNRIs fall into the same category. Economists and patients alike get up in arms about the ability of drug companies to bring these types of follow-on drugs to market. They use words like “wasteful” and “uncreative” to describe them, and question the direction in which the market is heading. Is there any innovation left in the pharmaceutical industry? This was a serious concern for many people at the end of the 1990’s and into the new century, as the number of new molecular entities (NMEs) approved per year fell from more than fifty in 1996, to seventeen in 2002 (CBO, 2006). A 2004 New York Times article identified the increasingly prevalent practice of drug companies licensing previously abandoned or repurposed molecules from small biotech startups to develop, rather than researching potential drug leads in-house (Pollack, 2004). There is little doubt that the structure of R&D has changed dramatically over the last decades, and will continue to do so well into the future (Cockburn, 2004). Maybe the development of high throughput screening methods that allow drug companies to effortlessly test hundreds of thousands of molecules per day take the rational design process out of developing drugs. Maybe all the low hanging fruit has already been picked, and it takes more time and effort to find suitable drug targets. The New York Times article also presented the other side of the argument, however, which is that licensing drugs and discovering new uses for them is a different type of innovation. Evidence points to a recent upturn in the
number of NMEs approved annually: 2011 saw the second highest number of approvals since 2000 with 30 NMEs, half of which were given a priority rating by the FDA (Center for Drug Evaluation and Research [CDER], 2011).

These are all provocative issues, and opponents of follow-on drugs cite them as further evidence of waste and lack of innovation in R&D expenditures, but the fact of the matter is that these arguments do not address some key issues. Follow-on drugs, me-too drugs, second-, third-, fourth-in-class drugs—whatever you want to call them—they are not inherently bad. On the contrary, I am inclined to agree with DiMasi in that they are necessary for the existence of the pharmaceutical industry. The most obvious reason is because they have the potential to bring therapeutic advantages to their class; Cialis is just one example of several. Even to the extent that most are not this beneficial, we must consider that the majority of early-entrance follow-ons are developed concurrently. Policies such as those put forth by Hollis and Angell would add uncertainty to the costs and success of the development process, and therefore disincentivize firms to undertake risky R&D in the first place. Given the high rates of failure, even once a drug has made it to clinical trials, it is necessary to have multiple drugs in development; otherwise, you may end up with none at all. It is also difficult to tell which drugs will offer clear advantages until they make it to phase II or III clinical trials. Plus, as history has shown, there is always the small chance of discovering an important drug serendipitously! The modern pharmaceutical

4 Dramamine is one such example, as is penicillin.
drug is one of the most important developments of the last century, and we do not want to do anything to directly impair firms’ incentive or ability to further develop it. This, however, is where I depart from DiMasi’s camp.

I find his and subsequent estimations of R&D expenditures to be fictitious at best, created with the interest of pharmaceutical companies in mind. Follow-on drugs are not needed to recoup the costs of drug development; blockbusters that produce tens of billions of dollars in revenue over their lives do that and then some. We are not paying for high R&D costs when we buy a prescription, so much as we are paying for the advertising that has influenced our (and our physicians’) decision to buy it. The real problem, which is what my research has revealed to me, is not directly with follow-on drugs, but rather with their post-production marketing. We saw clear examples of it with Zantac, Nexium, Paxil, Effexor, Cela, Lexapro, and several more. It is too easy for pharmaceutical companies to use exorbitant and/or coordinated marketing expenditures to distort physicians’ and patients’ perceptions of drugs and induce irrational demand. Of the many problems associated with this practice, both moral and economical, I will focus on the three economic ones I find the most harmful: 1) marketing expenditures are excessive and the resources would be better spent on productive R&D; 2) the false perceptions of superiority can prevent switching to cheaper generic substitutes; and 3) excessive marketing can actually lead to the adoption of riskier drugs that have the potential to harm patients. We already have seen each of these in action, but I will provide a brief description of each for the sake of clarity.
Marketing Expenditures are Excessive

From the examples I have provided, it appears that a fair amount of marketing is directed at emphasizing superficial differences between drugs. This practice causes competition through marketing, part of which requires firms to expend more resources to remain competitive. Reigning in these expenses would promote competition through real therapeutic differences. One limitation is that I cannot quantify how much social welfare is created through DTCA-induced class expansion. Berndt and coworkers (1996) did show, however, that these spillovers are considerably less than 100 percent efficient, and I think it is reasonable to assume that a portion of the expansion is attributable to overtreatment. Money saved by reducing pre- and post-production costs could be reinvested back into more productive R&D, rather than research for late-entrance follow-ons. If pharmas knew that they could not spend as much on promotion, this would further incentivize firms to explore potential drugs that might better sell themselves by offering therapeutic advantages.

False Perceptions of Brand Superiority Prevents Switch to Generics

I have presented evidence in line with other studies demonstrating that the entrance of the generic breakthrough molecule does not decrease the sales of the incumbent follow-ons of that class, which actually increase in many cases. Differences are perceived between drugs of the same class even if they are not merited, and my analysis of the antidepressants (and GI drugs to some extent)
finds that strategic and aggressive advertising efforts are largely responsible. The perceived differences make switching between drugs, even to a cheaper one, unacceptable for most patients. I suspect that if patients and doctors fully understood how the majority of pharmaceuticals truly matched up, it would be more common for patients to switch from an incumbent molecule to a generic one.

**Excessive Marketing Can Lead to Adoption of Riskier Drugs**

The impression of superiority that marketing can create is dangerous if it promotes the adoption of riskier drugs. The textbook example of this is Paxil. Despite being associated with more withdrawal symptoms and suicidal tendencies than any of the other SSRIs, GlaxoSmithKline took advantage of its exclusive approval for social anxiety disorder to induce demand for it. While this is an isolated example, even a single case of a drug company knowingly putting patients at risk is unacceptable. In the literature, I discuss Hollis’ theoretical evaluation of this issue.

**My Policy Proposal**

The most effective policy to remedy the situation is one that minimizes advertising expenditures as well as the harm done to innovation. When constructing such a policy, it is helpful to understand what truly incentivizes pharmaceutical companies. On a basic level, each drug a company invests in is a lottery, or better yet, a gamble. For simplicity, let us narrow the scope of the
analogy only to physician detailing of drugs that gain FDA-approval, as this is the
most prevalent form of promotion. In a market free from all forms of
advertising, only innovative drugs, whether they arise from parallel or post hoc
development, will be a winning bet. The payout comes from the patients, who
effectively act as the casino. The dealers represent doctors, who serve as an
intermediary between pharmaceutical companies and patients. Portrayed
kindly, detailing is frequently a matter of distracting the dealer so that the
gambler can change his or her bet to a winning one nearly every time. At its
worst, it could be viewed as bribing the dealer. Every once in a while, the
gamble will legitimately pay off, and an innovative drug will result. But if the
gambler knows that most dealers can be fooled so money can be made off of
most bets, he or she will gamble excessively. The key, therefore, is to ensure the
dealer does not get distracted.

DiMasi suggests that we alert the dealer to these tricks by supporting
impartial and comprehensive studies comparing all aspects of comparable drugs.
This is an excellent idea, but the results of these studies may not reach all
doctors, and have little effect on those who receive benefits directly from
pharmaceutical companies. Additionally, it does not address the practice of
dispensing free samples, which also distorts the market for a given class by
perpetuating prescriptions for whichever incumbents stock the closet at the
doctor’s office. To better remedy this situation, we need to actively reduce the
acts of deception. I suggest that in addition to DiMasi’s proposal, the FDA put
caps on the amount which pharmas can spend on certain types of marketing.
Expenditures in excess of this would be subject to escalating tax rates, approaching something in the ballpark of 60 to 75 percent. Alternatively, some form of a progressive promotional tax would accomplish a similar effect. The truth is that right now the gamblers have the odds by a long shot. Hypothetically, reducing the odds so that they were only slightly in favor of the gambler (i.e., still allowing some advertising) would create more social welfare and still result in life-saving drugs. In fact, it has the potential to produce more innovative drugs: if pharmaceutical companies knew that patients and doctors were more informed about real differences (or lack thereof) between medications, and that they only had a limited amount resources to promote them, they would gamble in a more rational way based on whether they stood a decent chance to win. The policy put forward by Angell\(^5\) is akin to lowering the odds once the bet has already been placed, which would drastically reduce the chance that any company would gamble at all. Hollis attempts to remedy this problem by allowing for an 18 month window after first-in-class approval, during which new drugs would not need to demonstrate clinical superiority. DiMasi contends that this is arbitrary and fixes very little because phase III clinical trials last an average of three years.

I would like to end this thesis by coming full circle and tying it back into our initial discussion of illegal drugs. We have seen both the structural and

\(^5\) Angell’s policy would require potential drugs to demonstrate superiority to the first line treatment in the class in order to gain FDA approval. This adds to the already high costs of clinical trials, and further decreases the chance of success. Additionally, if new drugs are approved during head to head trials, the drug seeking approval may be forced to match up against these drugs too, thereby having to hit a moving target.
effectual similarities between some of today's most stigmatized illicit drugs and widely used prescription drugs. One of the most prevalent differences that exists today between the two industries is government regulation. Interestingly, this has not always been the case. In his essay about the development of the branded pharmaceutical, Harvard Professor Jeremy Greene comments on the lack of regulation and branding within the pharmaceutical industry throughout the early twentieth century (Greene, 2010). Doctors would formulate their own slightly tweaked recipes for a given drug, which would be on file at the local pharmacy. Pharmacists would then make that drug themselves, a process strikingly similar to how underground drug producers today can turn out the same products but with slight differences in quality based on their methods. Both the legal and illicit drug industries have been shaped extensively over the past 70 years by government regulations. The U.S. government determined that there was no significant social benefit to illicit drug production or use, so government intervention has been aimed at criminalization of production and use, as well as eradication of supply. Conversely, government intervention in pharmaceutical drug industry has been aimed at better quality control and increasing government regulation. This led to the adoption of branding of drugs throughout the 1940s and 50s, and generic drugs naturally accompanied branded ones as capitalists saw an easy opportunity to make money. According to Greene, the development from an unregulated industry to the one we are familiar with today is primarily a result of government regulation and the ensuing generic and brand name pharmaceuticals it produced. Greene's theory
corroborates the findings of our thought experiment from the pharmacy, and confirms the importance of between- and within-patent competition as major factors in shaping pharmaceutical markets.

Greene’s analysis is correct as far as it goes. In this thesis, one of the things I have done is further tracked the development and significance of between-patent competition. The effect of competition on drug prices, market size, and market share appears to defy conventional understanding of how market forces work. Markets appear to perform illogically, in that follow-on drugs frequently perform much better than their therapeutic profiles would predict. In this sense, the demand for pharmaceutical drugs frequently takes on many of the characteristics of the illegal drug industry, in which irrational demand drives purchasing decisions regarding highly similar compounds. Of course, this analogy only goes so far: the destructive nature of drug abuse is driven by addictive compounds whose use is self-reinforcing. The illegal drug industry is naturally fueled almost entirely by irrational demand. While some have questioned the ethical standards of the pharmaceutical industry, they produce products intended to help patients. Some of their practices may be scientifically misleading, but they are generally legal.

I believe that the analysis in this thesis does establish, however, that despite the good that the pharmaceutical industry has accomplished, the current emphasis on marketing of very similar pharmaceuticals has had a corrosive effect on social benefit over the past thirty years. There is progressively less
innovation at times of record profits, with correspondingly diminishing returns in public welfare. Put in perspective with the development of the pharmaceutical industry as a whole, it seems that one of the driving causes for the diversion of the two industries, competition between patented molecules, has recently served an opposite role, which is to say that it is frequently a cause for irrational demand. Arguably, the time has come not to criminalize the behavior of pharmaceutical companies, but to mitigate the damage caused by profligate spending on advertising to drive incessant demand. This will not be an easy challenge to address. Advertising frequently is considered free speech that is difficult to regulate, despite possible social benefits. A discussion of this complex topic is beyond the scope of my thesis. However, if we allow this behavior to continue unabated, what will happen to the pharmaceutical industry in 50, 100, or 200 years? At what point do we as patients turn around and refuse to indulge the superfluous advertising of pharmaceuticals? It stands to reason that conveying the real clinical profiles of prescription drugs to patients and doctors, as well as reducing drug companies’ ability to distort these, will pave the way to a more innovative pharmaceutical industry.
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