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Prices, Profits and Innovation: Examining Criticisms of the Value of New Psychotropic Drugs

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Abstract

High profits and high drug costs have brought increased scrutiny of the pharmaceutical industry over the issue of whether the drugs they produce are worth the costs. I examine several related complaints, including the proliferation of me-too drugs and product reformulations, which some argue have little value relative to their cost; promotion of newer drug classes as more effective than existing, less expensive drugs in the absence of evidence of superior effectiveness; legal strategies to extend market exclusivity that result in high brand drug prices for an extended period of time; and large promotional expenditures that result in higher prices.

Over the past several decades, new drug treatments have been developed for many conditions, including hypertension, cholesterolemia, HIV/AIDS, and depression. Some of these medications were breakthrough drugs that dramatically changed the way certain illnesses are treated and improved morbidity and quality of life for many patients. Others may have added less value from a societal point of view because the level of innovation they represented over existing drugs in the market was smaller.

The industry has been rewarded for its overall efforts at drug development with high accounting profits. For every year from 1995 through 2002, the pharmaceutical industry was the most profitable in the country, and drug manufacturers were more than three times as profitable as the median for all Fortune 500 firms in 2003.[1] Over the same period, there have been rapid rises in drug prices and expenditures, with double-digit annual increases in spending throughout most of the past decade. [2]

Manufacturers have been criticized recently for a variety of inappropriate business practices, including withholding data on patient safety from the Food and Drug Administration (FDA) or peer-reviewed journals (including data on deaths among Vioxx patients and deaths among children taking antidepressants), giving lucrative consulting contracts to physician opinion leaders to speak about the firm's medications, hiring professional writers to write journal articles about the drugs for academic researchers, and promoting drugs for off-label uses.[3]

The combination of high profits and rapidly-rising costs has also brought increased scrutiny to the industry over whether the drugs they produce are worth the high costs.[4] Complaints related to this issue include: proliferation of me-too drugs and reformulations of existing products, which some argue add little value from a societal viewpoint; promotion of newer, more expensive classes of medications as being more effective than existing, less-expensive drugs in the absence of sufficient evidence of superiority; manufacturer-initiated legal strategies to extend market exclusivity that result in consumers and payers paying high brand drug prices for an extended period of time; and excessive promotional expenditures, which drive up drug prices and may add little value for patients.

Psychotropics provide an interesting focus for examining arguments about the value of drug expenditures because of their particularly rapid cost increases. From 1996 to 2001, psychotropic drug spending increased almost 20% a year, relative to 13.1% for drug spending overall.[5] The U.S. spent over $14 billion on psychotropics in 2001.[6] Psychotropics are also interesting because of the high number of brand and generic entrants in recent years, and the unique role of government as a primary payer since many users are Medicaid and/or Medicare enrollees.

Although allegations of withholding safety data and inappropriate marketing practices are important issues that should be investigated further, economics has little to contribute to these investigations. I focus below on an important topic for which economic theory can illuminate the debate: the value of psychotropic innovation. I first discuss whether me-too products and reformulations indeed add little value. I next consider evidence on whether newer, more expensive classes of psychotropic drugs are worth the higher costs using atypical and conventional antipsychotics as an example. Finally, I examine two controversial business practices intended to boost pharmaceutical company profits: legal strategies to extend market exclusivity and direct-to-consumer advertising (DTCA). I explore whether consumers derive any benefits from these practices or whether the practices primarily serve manufacturers.

Me-Too Drugs and Product Reformulations

Industry critics assert that, rather than developing breakthrough drugs, manufacturers focus too much effort on developing drugs that are only marginally different from medications already on the market, including “me-too drugs” and reformulations of existing products.

Me-Too Drugs. The first brand drug using a particular therapeutic mechanism of action is called a “breakthrough drug,” while brand drugs that use the same mechanism of action but enter after the breakthrough drug are called “me-too drugs.” There are three potential benefits of having multiple drugs in the same therapeutic class: 1) new treatments could provide marginal clinical improvements for some or all patients; 2) competition could result in lower prices; and 3) competition to be the breakthrough drug could speed drug development and result in higher quality drugs.

Commentators like Marcia Angell refute these potential benefits.[7] Dr. Angell argues that me-too drugs add minimal value from a societal viewpoint because there is little evidence that drugs in the same therapeutic class affect patients differently. She also asserts that there is little, if any, price competition in the pharmaceutical market, so additional competitors do not result in lower prices.

If, in fact, patients had the same therapeutic response to all drugs in a class, a new entrant would indeed provide little clinical benefit. For some therapeutic classes, the differences in patient response across drugs are typically small. For example, the clinical literature suggests that patients with acid reflux respond similarly to the various proton pump inhibitors (PPIs), so any marginal clinical improvement associated with a me-too PPI should be small for most patients.[8] However, for drugs that treat more biologically heterogeneous illnesses like many mental illnesses and essential hypertension, there is evidence that patients respond differently to different drugs.[9] For example, the clinical literature suggests that efficacy of the various selective serotonin reuptake inhibitors (SSRIs) may be similar overall but vary for particular patients.[10] Also, the experience of side effects may vary or have different clinical relevance (for example, weight gain for a diabetic patient). As a result, many new psychotropic entrants have typically offered clinical improvements for at least some patients.

Of course, not all entrants represent the same level of innovation. Consider the case of Lexapro, the active isomer of the Celexa molecule. There are no statistically significant differences in

the rates of side effects or discontinuation for Lexapro versus Celexa, although there is some evidence that Lexapro may work slightly faster than Celexa.[11] It is hard to argue that Lexapro represents the same level of innovation for the SSRI class as other SSRIs that were distinct molecules from existing drugs.

Price competition among therapeutically-similar medications has been limited, as Dr. Angell suggests, due in part to manufacturer efforts to differentiate their products through DTCA and other promotion. Also, insurance coverage blunts manufacturer incentives to compete on price since patients with coverage may pay only a small proportion of a drug's cost. Nevertheless, there is evidence of price competition. Although breakthrough drug prices do not always decrease after entry of me-too drugs, the rate of increase over time is slower for breakthrough drugs with more brand competitors.[12] Lu and Comanor also found that launch prices of me-too drugs approved between 1978 and 1987 were lower when there were more brand substitutes available. Increasing the number of brand substitutes from one to two led to a 38% decrease in the ratio of a drug's launch price to the average price of the existing drugs in the class, on average.

Today's widespread use of pharmacy management tools like three-tier formularies, which were not used during the time period studied above, has likely further stimulated price competition for many classes. When there are multiple medications in a class, payers can often negotiate rebates from manufacturers in exchange for preferred formulary status. Because the magnitude of rebates offered to private payers is considered proprietary information, there is little documentation of these rebates in the literature. However, evidence from the Medicaid rebate program, which requires manufacturers to pay rebates of 15.1% of the average manufacturer price or offer Medicaid the best price available in the market (whichever results in the lowest price), shows that the best-price discount on a brand drug is 10−14% higher on average when there are three or more therapeutically similar brand drugs available.[13]

Although the literature suggests there is price competition in the pharmaceutical market, the level of price competition for psychotropics and other drugs that treat relatively heterogeneous conditions is likely to be lower than that for drugs that treat more homogeneous illnesses.[14] For example, because of the difficulty of finding a good treatment match, patients with depression may be less likely to switch antidepressants in response to financial incentives than patients taking PPIs. As a result, three-tier formularies are likely to be less effective at stimulating price competition for drugs like antidepressants than they are for many other types of drugs.[15]

Finally, some me-too manufacturers were competing to be the breakthrough drug and lost the “race,” while others applied for a patent after the breakthrough drug was on the market, hoping to take some of its market share. Intense competition to be the breakthrough drug may result in faster development and perhaps better drugs, so there may be some societal value of the competition itself, although there is no empirical evidence to support this.

Product Reformulations. Over the past fifteen years, a number of reformulations of psychotropic medications have been introduced. The reformulations often involve less frequent (e.g., once versus three times daily) or easier-to-administer dosing (e.g., injectibles, fast-dissolving pills). From 1999 through 2004, the FDA approved 510 New Drug Applications (NDAs), including both NMEs and new formulations.[16] Of the 510 NDAs, 29 (5.7%) were for drugs with psychotropic indications.[17] However, of the 154 NMEs, only 4 (2.6%) were for drugs with psychotropic indications. Thus, NDAs for psychotropics were disproportionately more likely to be reformulations than NMEs, and many of the newer psychotropics were reformulations rather than breakthrough or me-too drugs that may have brought clinical improvement for patients who do not respond well to existing treatments. CMR

International estimates that approximately 30% of R&D expenditures was devoted to reformulations.[18]

Development of reformulations can expand a firm's market share by creating an improved version of an existing drug or extend patent exclusivity beyond the initial patent period to some extent for a brand manufacturer. For example, within a year of patent expiration for Eli Lilly's blockbuster antidepressant Prozac the firm released Prozac Weekly, a once-weekly formulation of Prozac, and Sarafem, a form of Prozac with an indication for premenstrual dysphoric disorder. The market shares of Prozac Weekly and Sarafem are fairly small (each less than 1% of antidepressant retail sales in June 2003), so this strategy has not allowed Lilly to maintain a large market share for Prozac.[19] Reformulations of other psychotropics, such as Effexor XR (14% of antidepressant retail sales in June 2003) and Wellbutrin SR (13%), have been more successful in protecting market share for the original brand, however.

Special formulations intended to improve patient compliance may be useful for any class for which compliance is an issue, including drugs used to treat hypertension, diabetes, and HIV. These formulations may be particularly useful for some psychotropic patients, for whom the illness itself may affect the patient's ability to comply with a medication regimen. Whether the benefits exceed the costs depends on how patients value the differences relative to existing drugs. For a patient with severe schizophrenia and a history of poor compliance with oral antipsychotics, the marginal benefit of an injectible over an oral formulation may be extremely high. By contrast, a compliant patient who takes fluoxetine (generic form of Prozac) may not find the marginal benefit of Prozac Weekly to be worth the marginal cost, particularly if Prozac Weekly is on the third tier of their plan's formulary.

New Classes of Medications

Consumer advocates and others have argued that manufacturers, in the quest for greater profits, have promoted newer, more expensive classes of drugs as being more effective than older, less expensive treatments without evidence of superior effectiveness.[20] Consider the case of antipsychotic medications. The first antipsychotics, introduced in the 1950s and 1960s, represented a tremendous breakthrough in the treatment of schizophrenia. These medications were effective at reducing the intensity of patients' delusions and hallucinations.[21] The drugs had troublesome side effects for many patients, however, including a range of movement disorders such as acute extrapyramidal symptoms (EPS) and tardive dyskinesia, which involves involuntary movements of the tongue, lips, face, trunk, and extremities and is often irreversible.

Beginning in the 1990s, a number of "atypical" antipsychotic drugs, including Risperdal, Zyprexa, Seroquel, Geodon, and Abilify have been introduced.[22] While these medications have fewer instances of acute EPS as well as little or no evidence of tardive dyskinesia at typical dosages, they can have other problematic side effects, such as severe weight gain and increases in glucose and lipid metabolism. Furthermore, retail prices of atypicals are as much as 9 to 10 times higher than prices for conventionals that have lost patent protection.[23] Nevertheless, there has been explosive growth in the use of atypicals. As recently as 1996, there were 1.1 million conventional users and just 300,000 atypical users; five years later there were 500,000 conventional users and 1.6 million atypical users.[24]

There is much disagreement in the clinical literature about the relative effectiveness of atypical versus conventional antipsychotics.[25] Most studies compared one or sometimes multiple atypicals with placebo only rather than with conventionals, so there was no evidence directly comparing the two classes. The National Institute of Mental Health (NIMH) recently sponsored a randomized controlled trial called the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) that compared several atypicals (Zyprexa, Seroquel, Risperdal, and Geodon) and one conventional (perphenazine).[26]

CATIE, the most expensive study ever funded by the NIMH, provides important information on the relative effectiveness of the medications studied. Almost three-quarters of patients discontinued the study medication before 18 months were completed, suggesting limited effectiveness of antipsychotics based on this outcome measure. Zyprexa had the lowest rate of discontinuation overall (64% versus 74% to 84% for the other drugs), the longest duration of successful treatment, and the lowest rate of hospitalizations for an exacerbation of schizophrenia symptoms. However, Zyprexa patients gained more weight (two pounds per month on average) and experienced greater increases in glucose and lipid metabolism than patients taking the other drugs. Thus, although Zyprexa performed better on several outcomes, there is no single drug or class of antipsychotic drugs that is clearly superior for all patients, and there are real tradeoffs to be considered by a patient and her clinician in selecting a drug.

The Institute of Medicine has identified six characteristics of high quality health care: safe, effective, patient-centered, timely, efficient, and equitable.[27] Economists also focus on "patient-centered" care, asking how patients value the tradeoffs involved in use of the different antipsychotics. What is the marginal benefit of an atypical relative to a conventional from the patient's perspective, and how does the marginal benefit compare to the marginal cost?

How a patient weighs the marginal benefits of a particular drug will depend on her clinical characteristics and values. For example, a patient with a family history of diabetes might be willing to accept the higher EPS risk that comes with conventionals to avoid the weight gain and metabolic effects associated with Zyprexa use. A different patient, who wishes to avoid the discomfort as well as the stigma associated with tardive dyskinesia, might place greater value on a lower EPS risk. Assessing marginal benefit may be more difficult in cases where efficacy and safety are less certain, such as off-label prescribing. For example, concerns have been raised by the FDA and Wang and colleagues about increased risk of death associated with antipsychotic use among elderly patients with dementia-related psychosis, which is an off-label use for these medications.[28]

The case of atypical antipsychotics shows just how difficult it is to generalize about the relative effectiveness of newer drug classes and whether they are worth the costs. Atypicals offer both marginal benefits and marginal costs over conventionals, and the weighing of those costs and benefits will vary with patients' clinical characteristics and values and how drugs are paid for.

Strategies to Boost Profits

Manufacturers have been criticized for a number of strategies they have adopted to boost profits, including legal strategies to extend market exclusivity and use of DTCA.

Legal Strategies

Legal strategies to extend market exclusivity have angered industry critics, who argue that manufacturers have exploited loopholes in the patent system to earn higher profits. As a consequence of these actions, payers and consumers must pay high brand prices for a longer period of time, which can result in substantial additional expenditures.

Two provisions of the Hatch-Waxman Act of 1984, legislation intended to speed generic entry and extend patent terms to reflect regulatory delays during the FDA approval process, were common targets. The law allowed a 30-month stay of FDA approval for abbreviated new drug applications (ANDAs) to market generic drugs when the brand manufacturer files suit for patent infringement, and multiple 30-month stays could be granted if the brand manufacturer filed additional patents after the ANDA was submitted. The law also granted the firm submitting the first ANDA a 180-day period of marketing exclusivity.

In 2002, the Federal Trade Commission (FTC) studied ANDAs filed between 1992 and 2000 to assess whether abuses of these provisions had occurred.[29] Although the FTC determined that brand patents were found to be invalid or not infringed in the patent challenges brought to court by brand firms, manufacturers were able to extend market exclusivity during the period that the lawsuits were being resolved, earning manufacturers millions of dollars in additional revenue in several cases. For example, the FTC reported that Paxil received an additional 65 months of exclusivity because of stays granted in response to lawsuits for infringement of patents filed after ANDA application. According to the FTC, net sales of Paxil in the year that the second 30-month stay was issued were over $1 billion, which suggests that this legal strategy may have resulted in additional net sales for SmithKline Beecham of more than $2 billion and much higher costs for patients and third-party payers. The FTC also concluded that there had been agreements reached between a brand manufacturer and the first generic manufacturer that had the potential to "park" the 180-day exclusivity (i.e., the firms agreed that the generic firm would not market the generic). Although these strategies were legal under the Hatch-Waxman Act, they had consequences unintended by some of the architects of the legislation and resulted in decreased consumer welfare.

The Medicare Modernization Act (MMA) of 2003 amended these provisions to address the potential for abuse by allowing: 1) a single 30-month stay only for patents filed before the ANDA was submitted; and 2) multiple generic firms to receive 180-day exclusivity if several ANDAs are filed on the same day, although exclusivity can be withdrawn if the firm fails to market under specific time constraints or it is determined that an agreement between brand and generic firms violates antitrust laws.[30] The changes would not, however, address the potential for a brand manufacturer to license a generic manufacturer to produce a generic version as SmithKline Beecham did to prevent Apotex (the generic firm filing the first ANDA for Paxil) from having 180 days of exclusivity for the generic form of Paxil.

DTCA

Manufacturers have been criticized for high promotional spending, which is passed onto consumers and payers in the form of higher drug prices.[31] Although manufacturers spend more on R&D than on promotion ($30.3 billion vs. $19.1 billion in 2001), promotional spending is increasing faster than R&D expenditures.[32]

DTCA has been a particularly controversial form of drug promotion, with critics arguing that DTCA results in unnecessary medication use and overuse of expensive brand-name drugs. Manufacturers and others argue that DTCA serves an important educational role, making patients better able to serve as partners in their own care and encouraging patients to discuss health problems with their physicians.[33] DTCA may also help decrease stigma associated with conditions that are rarely discussed openly and, in some cases, lead to first-time diagnosis and treatment.[34]

A number of consumer surveys have documented that DTCA stimulates consumers to request prescriptions for particular brand drugs from their physicians.[35] Weissman and colleagues found that approximately one-third of individuals surveyed were influenced by a DTC ad to have a discussion with their physician about an advertised drug or health concern.[36] Nearly one-quarter of these individuals were given new diagnoses, and 43% were prescribed the advertised drug.

Physician views of DTCA are mixed. Most feel that DTCA helps educate patients about available treatments and that DTCA results in better discussions with patients about their care.[37] However, most also believe that DTCA does not provide information in a balanced manner and that DTCA encourages patients to seek unnecessary treatments.

Antidepressants are among the medications with the highest DTCA expenditures.[38] DTCA for antidepressants results in increased antidepressant prescribing, although evidence on the appropriateness of prescribing is mixed. Donohue and colleagues found that DTCA expenditures were associated with a small increase in appropriate duration of antidepressant use among those diagnosed with depression who initiated medication treatment.[39] A recent randomized controlled trial found that standardized patients (actors following strict protocol for presenting their condition) who presented with symptoms of major depression were more likely to receive minimally appropriate initial treatment if they reported seeing a DTC advertisement and requested either a specific drug or any antidepressant than if they made no mention of an advertisement or an antidepressant.[40] This suggests that DTCA may result in more appropriate treatment of major depression for some patients.

However, the results were not all positive for DTCA. The trial also used standardized patients presenting with symptoms of adjustment disorder with depressed mood, a condition for which there is no evidence supporting antidepressant use. Adjustment disorder patients who requested an antidepressant after reporting they saw a DTC ad were more likely to receive an antidepressant prescription than patients who did not mention seeing a DTC ad or request an antidepressant. The study found an even larger prescribing gap for adjustment disorder patients who made a brand-specific request versus those who made no antidepressant request than was found for major depression patients. This suggests that DTCA may differentially stimulate prescribing for conditions for which there is no clear clinical indication.

Thus, evidence on the usefulness of DTCA for psychotropics is mixed at best. DTCA may be responsible for an increased rate of antidepressant use and a slightly higher rate of appropriate treatment, but DTCA also results in overuse and inappropriate use. There is no evidence documenting the extent of overuse or inappropriate use, so it is impossible to weigh this against the increases in appropriate use.

Conclusion

Rapidly-rising drug costs and high profits have made pharmaceutical manufacturers a frequent target of criticism. Manufacturers argue that high prices are necessary to allow them to recover R&D costs and to preserve incentives for future R&D investments. Consumer groups and others have called for price or profit controls, arguing that the high profits earned by manufacturers should be balanced with the goals of ensuring access to medications at a reasonable price.

After considering evidence on the value of recent psychotropic innovations, I conclude that most psychotropic entrants in recent years (whether new classes of medications, me-toos or reformulations) have value in terms of marginal improvements in health or functioning for at least some subset of patients. Additional entrants may have resulted in some price competition, although we lack empirical evidence of the effect of psychotropic entry on pricing and competitive behavior in the era of pharmacy management. The marginal benefit of psychotropic entrants and entrants in other classes that treat biologically heterogeneous conditions may be greater than that for entrants in certain other classes like PPIs. Also, special compliance issues for some patients with mental illness may result in higher marginal benefit of reformulations for a subset of patients. However, in spite of the marginal benefits for some patients, the key question is whether the marginal benefits exceed the marginal costs.

The controversy over atypical versus conventional antipsychotics highlights some of the difficulties involved in determining whether newer medications are more cost-effective than existing drugs. CATIE results suggest that there is no antipsychotic that is clearly dominant for all patients with schizophrenia. Given the large and growing expenditures for atypicals,

payers have to consider relative costs of the various antipsychotics. The cost increases for psychotropics have hit Medicaid particularly hard. For example, Medicaid, which was responsible for 80% of atypical prescriptions in 2001, experienced an annualized rate of growth in atypical spending of 92.4% from 1996 to 2001.[41] These increases are unsustainable in a period of state budget crises, and states are desperately trying a variety of approaches to influence drug use and control expenditures.[42] Soon, Part D plans will also have to grapple with controlling the costs of these drugs because a sizeable number of atypical users are Medicare enrollees. While carefully-designed management tools could help control costs without negatively affecting patients, individual patient characteristics and preferences must have a role in prescribing decisions through tools like incentive or stepped formularies, nonformulary exceptions processes or appeals for nonformulary coverage in order for efficient utilization to occur.

While the relative effectiveness of alternative drug therapies is not always clear, the value of certain manufacturer practices that result in higher drug prices and expenditures are more obvious. Legal strategies to extend market exclusivity, resulting in higher profits and higher drug expenditures, are welfare reducing for patients and payers. The net impact of DTCA is unknown because of insufficient documentation of the magnitude of overuse and misuse resulting from DTCA, although it seems clear that DTCA is not completely welfare-enhancing for patients or payers either.

The literature on the value of recent psychotropic innovations and competition within these markets is somewhat limited. Additional research in several areas would help us better understand the value of new psychotropic drugs. These areas include: studies of competition in the era of pharmacy management (i.e., how pharmacy management tools affect pricing and entry behavior of psychotropic manufacturers); studies of how economic profits vary by characteristics of the medications in order to understand whether it might be desirable to grant patent extensions for certain types of drugs; the impact of the MMA changes to the Hatch-Waxman provisions on manufacturer behavior and profits; and quantification of overuse and inappropriate drug use resulting from DTCA, particularly in subpopulations like patients with mental illness and for different types of ads (i.e., help-seeking ads that describe an illness versus reminder ads that name a medication but not the conditions it treats).

Many have argued that we need more objective, head-to-head studies of competing drugs. CATIE provides the best evidence yet on the relative effectiveness of atypical and conventional antipsychotics for treating schizophrenia. Yet even CATIE, the “King Kong” of studies of its kind, is unable to answer all questions on this issue, such as the relative effectiveness of atypicals and the conventionals that were not studied due to resource limitations. At a cost of $42.1 million for CATIE, it is unlikely that the government will continue funding large studies of this kind. The FDA should consider requiring head-to-head comparison studies of all or several representative drugs that treat a particular illness (not just comparisons of a single drug or drugs in the same class to placebo) in order to secure FDA approval. Such studies could provide useful information for clinicians, patients and payers in the absence of federally-funded studies.

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