

Prices, Profits, And Innovation: Examining Criticisms Of New Psychotropic Drugs' Value

Are industry critics justified in arguing that new psychotropic drugs are not worth the high costs?

by **Haiden A. Huskamp**

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; the baseless promotion of newer drug classes as more effective than existing, less expensive drugs; legal strategies to extend market exclusivity that result in high brand-name drug prices for an extended period of time; and large promotional expenditures that result in higher prices. [*Health Affairs* 25, no. 3 (2006): 635–646; 10.1377/hlthaff.25.3.635]

DURING THE PAST SEVERAL DECADES new drug treatments have been developed for many conditions, including hypertension, high cholesterol, HIV/AIDS, and depression. Some of these medications have been breakthrough drugs that dramatically changed the way certain illnesses are treated and that improved morbidity and quality of life for many patients. Others might have resulted in only incremental treatment changes because they were similar to drugs already on the market.

The pharmaceutical industry has been rewarded for its overall efforts at drug development with high accounting profits. For every year from 1995 through 2002, that industry was the most profitable industry in the country, and drug manufacturers were three times more profitable than the median for all Fortune 500 firms in 2004.¹ Over the same period, drug prices and spending have risen rapidly, with double-digit annual spending increases 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 U.S. Food and Drug Administration (FDA) or peer-reviewed journals (including data on deaths among Vioxx patients); giving lucrative consulting contracts to physician

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opinion leaders to speak about a firm's drugs; hiring professional writers to write journal articles for academic researchers about a manufacturer's drugs; and promoting drugs for off-label uses.³

The combination of high profits and rapidly rising costs has also brought increased scrutiny of the industry over whether the drugs it produces are worth the high costs.⁴ Complaints related to this issue include the proliferation of me-too drugs and reformulations of existing products, which, some argue, add little value from a societal viewpoint; the promotion of newer, more costly classes of medications as being more effective than existing, less costly drugs, without sufficient evidence of superiority as to efficacy or side-effect profiles; manufacturer-initiated legal strategies to extend market exclusivity that cause consumers and payers to pay high brand-name drug prices for an extended period of time; and excessive promotional spending, which drives up drug prices and might add little value for patients.

Because of their particularly rapid cost increases, psychotropics provide an interesting focus for examining arguments about the value of drug spending. From 1996 to 2001, spending for psychotropics increased almost 20 percent a year, relative to 13.1 percent for drug spending overall, and the United States spent more than \$14 billion on psychotropics in 2001.⁵ Psychotropics are also interesting because of the high number of brand-name and generic entrants in recent years and the unique role of the government as a primary payer, since many users are Medicaid enrollees or Medicare beneficiaries, or both.

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 here on an important topic for which economics can illuminate the debate: the value of psychotropic innovation. I first discuss the value added by me-too products and reformulations. I next consider the example of atypical and conventional antipsychotics to see whether newer, more expensive classes of psychotropic drugs might be worth the higher costs. Last, I examine two controversial business practices intended to boost drug company profits and explore whether consumers derive any benefits from the practices.

Me-Too Drugs And Product Reformulations

Industry critics assert that instead of developing breakthrough drugs, manufacturers focus too much effort on developing drugs that are only marginally different from medications already on the market.

■ **Me-too drugs.** The first brand-name drug using a particular therapeutic mechanism of action is called a "breakthrough drug"; brand-name 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

at least some patients; (2) competition could lower prices; and (3) competition to be the breakthrough could speed drug development and result in higher-quality drugs.

Marcia Angell, among others, has refuted these potential benefits.⁶ 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 patients' responses 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 there is little to no marginal clinical improvement associated with a me-too PPI for most patients.⁷ However, for drugs that treat more biologically heterogeneous illnesses, such as many mental illnesses and essential hypertension, there is evidence that patients respond differently to different drugs.⁸ For example, the clinical literature suggests that efficacy of the various selective serotonin reuptake inhibitors (SSRIs) might be similar overall but might vary for particular patients.⁹ Also, the experience of side effects might vary or have different clinical relevance (for example, weight gain for a diabetic patient). As a result, many new psychotropic entrants have offered major 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 might work slightly faster than Celexa.¹⁰ It is hard to argue that Lexapro represents the same level of innovation as other SSRIs that are distinct molecules from existing drugs.

Clearly, price competition among therapeutically similar medications has been limited, as Angell suggests, partly because of manufacturers' efforts to differentiate their products through direct-to-consumer (DTC) advertising and other promotion. Also, insurance coverage blunts manufacturers' incentives to compete on price since insured patients might pay only a small proportion of a drug's cost.

However, there is evidence of price competition in the pharmaceutical industry. 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-name competitors.¹¹ John Lu and William Comanor also found that launch prices of me-too drugs approved between 1978 and 1987 were lower when more brand-name substitutes were available.¹² Increasing the number of brand-name substitutes from one to two led, on average, to a 38 percent decrease in the ratio of a drug's launch price to the average price of the existing drugs in the same class.

It is also likely that today's widespread use of pharmacy management tools such as three-tier formularies, which were not used during the time period studied

above, has 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 brand-name drug manufacturers to pay rebates of 15.1 percent 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-name drug is 10–14 percent higher, on average, when there are three or more therapeutically similar brand-name drugs available.¹³

So far, no studies have focused on price competition and entry of brand-name drugs in the area of psychotropic classes. I hypothesize that 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. For example, because of the difficulty of finding a good treatment match, patients with depression might 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 such as antidepressants than they are for certain other types of drugs.¹⁴

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 can result in faster development and perhaps better drugs, so there could be some societal value to 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, such as Remeron Soltab and Paxil Controlled Release (CR), have been introduced. The reformulations often involve less frequent or easier-to-administer dosing. From 1999 through 2004, the FDA approved 510 new drug applications (NDAs), including both new molecular entities (NMEs) and reformulations.¹⁵ Of the 510 NDAs, 29 (5.7 percent) were for drugs with psychotropic indications.¹⁶ However, of the 154 NMEs, only 4 (2.6 percent) were for drugs with psychotropic indications. Thus, NDAs for psychotropics were disproportionately more likely to be reformulations than to be NMEs that might have brought clinical improvement for patients who do not respond well to existing treatments. CMR International estimated that approximately 30 percent of research and development (R&D) spending in 2001 was devoted to reformulations.¹⁷

Development of reformulations can expand a firm’s market share by creating an improved version of an existing drug or effectively extending patent exclusivity beyond the initial patent period. 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 indi-

cation for premenstrual dysphoric disorder. The market shares of Prozac Weekly and Sarafem are each less than 1 percent of antidepressant retail sales in June 2003, so this strategy has not allowed Lilly to maintain a large market share for Prozac.¹⁸ Reformulations of other psychotropics, such as Effexor XR (14 percent of antidepressant retail sales in June 2003) and Wellbutrin SR (13 percent) have better protected market share for the original brand.

Special formulations intended to improve patient compliance could be useful for any class for which compliance is an issue, including drugs used to treat hypertension, diabetes, and HIV. These formulations could be particularly useful for some psychotropic patients, for whom the illness itself might affect the patient's ability to comply with a medication regimen. Whether or not 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 could be extremely high. By contrast, a compliant patient who takes fluoxetine (the generic form of Prozac) might not find the marginal benefit of Prozac Weekly to be worth the marginal cost, particularly if Prozac Weekly is on the third tier of his or her plan's formulary.

New Classes Of Medications

Consumer advocates and others have argued that manufacturers, in the quest for greater profits but without sufficient evidence, have promoted newer, more expensive classes of drugs as being more effective than older, less expensive treatments.¹⁹ Consider the case of antipsychotics, the first of which, introduced in the 1950s and 1960s, represented a tremendous breakthrough in the treatment of schizophrenia. They were effective in reducing the intensity of patients' delusions and hallucinations.²⁰ They 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, were introduced.²¹ These medications have fewer instances of acute EPS as well as little or no evidence of tardive dyskinesia at typical dosages; however, 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 nine to ten times higher than prices for conventional antipsychotics that have lost patent protection.²² 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 and 1.6 million, respectively.²³

■ **Atypical versus conventional antipsychotics.** There is much disagreement in the clinical literature about the relative effectiveness of atypical versus conven-

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tional antipsychotics.²⁴ Until recently, most studies compare 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), which compared several atypical antipsychotics (Zyprexa, Seroquel, Risperdal, and Geodon) and one conventional antipsychotic (perphenazine).²⁵

CATIE, reportedly 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 eighteen months were completed. Zyprexa had the lowest rate of discontinuation overall (64 percent versus 74–84 percent 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, no single drug or class of antipsychotic drugs is clearly superior for all patients. Patients and clinicians must consider real trade-offs in selecting a drug.

■ **Benefits and costs.** In deriving estimates of patient care quality, economists focus on how patients value the trade-offs involved in the use of different antipsychotics. For example, what is the marginal benefit of an atypical antipsychotic relative to a conventional antipsychotic from the patient’s perspective, and how does the marginal benefit compare with the marginal cost?

How a patient weighs the marginal benefits of a particular drug will depend on the patient’s 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 might 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 Philip 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.²⁶

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 conven-

tionals, and the weighing of those costs and benefits will vary with patients' clinical characteristics and values and how the drugs are paid for.

Strategies To Boost Profits

Manufacturers have been criticized for their strategies to boost profits, including legal strategies to extend market exclusivity and use of DTC advertising.

■ **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, payers and consumers must pay high brand-name prices for a longer period of time, which can result in substantial additional expenses.

Manufacturers have used 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, to extend exclusivity. The law allowed a thirty-month stay of FDA approval for abbreviated new drug applications (ANDAs) to market generic drugs when the brand-name manufacturer files suit for patent infringement, and multiple thirty-month stays could be granted if the brand-name 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.²⁷ Although the FTC determined that brand patents were found to be invalid or not infringed on in the patent challenges brought to court by brand-name firms, manufacturers were able to extend market exclusivity during the period that the lawsuits were being resolved, earning millions of dollars in additional revenue in several cases. For example, the FTC reported that Paxil received an additional sixty-five months of exclusivity because of such stays. According to the FTC, net sales of Paxil in the year in which the second thirty-month stay was issued were more than \$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 agreements had been reached between a brand-name manufacturer and the first generic manufacturer that had the potential to “park” the 180-day exclusivity (that is, 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 law and resulted in decreased consumer welfare.

The Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 amended these provisions to address the potential for abuse by allowing only a single thirty-month stay for patents filed before the ANDA was submitted, and 180-day exclusivity to multiple generic firms if several ANDAs are

filed on the same day, although exclusivity can be withdrawn if a firm fails to market under specific time constraints or it is determined that an agreement between brand-name and generic firms violates antitrust laws.²⁸ The changes will not, however, address the potential for a brand-name manufacturer to license a generic manufacturer to produce a generic version, as SmithKline Beecham did to prevent Apotex (the generic firm that filed the first ANDA for Paxil) from having 180 days of exclusivity for the generic form of Paxil.

■ **DTC advertising.** Manufacturers have been criticized for high promotional spending, which is passed on to consumers and payers as higher prices.²⁹ Although manufacturers spend more on R&D than on promotion (\$30.3 billion versus \$19.1 billion in 2001), promotional spending is increasing faster than R&D spending.³⁰

DTC advertising has been particularly controversial, with critics arguing that it results in unnecessary medication use and overuse of costly brand-name drugs. Manufacturers and others argue that such advertising serves an important educational role, making patients better able to serve as partners in their own care and encouraging them to discuss health problems with their physicians.³¹ DTC advertising might also help decrease stigma associated with conditions that are rarely discussed openly and, in some cases, lead to first-time diagnosis and treatment.³²

Consumer surveys have documented that DTC advertising stimulates consumers to request prescriptions for particular brand-name drugs from their physicians.³³ Joel Weissman and colleagues found that about one-third of people surveyed were influenced by a DTC ad to talk with their physician about an advertised drug or health concern.³⁴ Nearly one-quarter of these respondents were given new diagnoses, and 43 percent were prescribed the advertised drug.

Physicians' views of DTC advertising are mixed. Most feel that it helps educate patients about available treatments and results in better discussions with them about their care.³⁵ However, most also believe that DTC advertising does not provide balanced information and that it encourages patients to seek unnecessary treatments.

Antidepressants are among the medications with the highest DTC advertising expenditures.³⁶ DTC advertising for antidepressants results in increased antidepressant prescribing, although evidence on the appropriateness of prescribing is mixed. Julie Donohue and colleagues found that these advertising expenditures were associated with a small increase in appropriate duration of antidepressant use among those diagnosed with depression who initiated medication treatment.³⁷ 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 antidepressant.³⁸ This suggests that DTC advertising might result in more appropriate treatment of major depression for some patients.

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However, the results were not all positive for DTC advertising. 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 that they saw a DTC ad were more likely to receive an antidepressant prescription than those who did not mention seeing an ad or request an antidepressant. The study found an even larger prescribing gap for patients with adjustment disorder who made a brand-specific request versus those who made no antidepressant request than was found for major depression patients. This suggests that DTC advertising might differentially stimulate prescribing for conditions for which there is no clear clinical indication.

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

Conclusions

Rapidly rising drug costs and high profits have made drug manufacturers a frequent target of criticism over whether the drugs they produce are worth the costs. But are the criticisms justified?

■ **Market exclusivity extensions and advertising.** Critics are on solid ground in challenging the various legal strategies used by the industry to extend market exclusivity. These strategies result in higher profits and higher drug spending while reducing welfare for patients and payers. Congress has recently acted to curb these abusive tactics, and further reforms might be warranted.

The critics are also right to question the drug industry’s DTC advertising practices. Although we do not yet know all the effects of DTC advertising of psychotropic medications, current studies indicate that the usefulness of DTC advertising is mixed at best and probably insufficient to justify the enormous promotional costs that are passed on to patients and payers as higher prices.

■ **Relative-value question.** On the broader question of the relative value of newly developed drugs, virtually all psychotropic entrants in recent years (whether new classes of medications, me-too drugs, or reformulations) have positive marginal benefits for at least some patients. While the value to consumers and payers clearly varies across drugs and patients, on average, the marginal benefit in terms of clinical improvements attributable to psychotropic entrants and entrants in other classes

that treat biologically heterogeneous conditions might be greater than that for entrants in classes such as PPIs.

The controversy over atypical versus conventional antipsychotics highlights some of the difficulties involved in determining whether newer medications are more cost-effective than existing ones. CATIE results suggest that no antipsychotic is clearly dominant for all patients with schizophrenia. Given the large and growing spending for atypicals, payers have to consider their relative costs. The cost increases for psychotropics have hit Medicaid particularly hard. Medicaid paid for 75 percent of atypical prescriptions in 2002, and its spending on atypicals experienced an annualized rate of growth of 92.4 percent from 1996 to 2001.³⁹ These increases are difficult to sustain in a period of state and federal budget crises, and states are desperately trying a variety of approaches to influence drug use and control spending.⁴⁰ Medicare 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. Unfortunately, pharmacy management tools are likely to result in weaker price competition for psychotropics and other drugs that treat biologically heterogeneous conditions than for drugs that treat more homogeneous illnesses, so controlling the costs of psychotropic drugs might be particularly difficult.

Although payers such as Medicaid must make decisions about drug coverage and management by weighing marginal costs and benefits for their population as a whole, individual patients' characteristics and preferences must have a role in prescribing decisions for efficient use to occur. This could be achieved through the use of carefully designed tools such as incentive or stepped formularies and flexible prior authorization, nonformulary exceptions, and appeals processes that allow patients with a high marginal benefit for a nonpreferred or noncovered drug to obtain some coverage for it.

■ **Kinds of research needed.** The complexity of the issues discussed in this paper underscores the need for additional research, so that we can better assess the value and cost-effectiveness of new psychotropic drugs. Additional research is warranted, including studies of competition in the era of pharmacy management (how pharmacy management tools affect the pricing and entry behavior of psychotropic manufacturers); studies of how economic profits vary by characteristics of the medications, which could help us understand whether it might be desirable to grant patent extensions for certain types of drugs; the impact of MMA changes to the Hatch-Waxman provisions on manufacturers' behavior and profits; and quantification of overuse and inappropriate drug use resulting from DTC advertising, particularly among patients with mental illnesses and for different types of ads (such as 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, could not answer all questions on this issue, such as the relative effectiveness of atypicals and the conventionals that were not studied because of resource limitations. It is unlikely that the federal government will continue funding large studies of this kind, given CATIE’s more than \$40 million price tag. 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) 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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NOTES

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