Patent Monopolies and the Costs of Mismarketing Drugs

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Acknowledgements

Executive Summary

Patent monopolies have long been used as a mechanism for financing innovation and research. The logic is that the government awards a monopoly on a product or process for a limited period of time in order to reward innovation. However, in addition to providing incentives for innovation and research, patent monopolies also provide incentives for a wide-range of rent-seeking behaviors, many of which can have major social costs.

This paper attempts to calculate one category of these costs for prescription drugs. It produces estimates of the costs associated with mismarketing drugs. The estimates are based on assessments of the costs in the form of increased morbidity and mortality associated with five prominent cases of mismarketing over the last two decades.

The five drugs examined are Vioxx, Avandia, Bextra, OxyContin, and Zyprexa. In each case, there was legal action claiming that the manufacturer had deliberately concealed or misrepresented evidence on the safety of the drug. In all five cases, there was either a court ruling against the company or a large settlement paid by the company. This is taken as evidence that the company did, in fact, deliberately misrepresent research that was available to it.

The cumulative costs associated with the increased morbidity and mortality associated with these drugs was $382.4 billion over the 14-year period from 1994–2008. This comes to just over $27 billion a year, an amount that is comparable to what the pharmaceutical industry claims to have been spending on research at the time.

The costs associated with the mismarketing of these five drugs are undoubtedly a small fraction of the total costs to society from mismarketing drugs. These drugs were selected because they were prominent cases where there was sufficient evidence either to win a legal case or force the payment of a substantial settlement. There must be many more cases where companies engaged in similar misrepresentations, but where the harm was not as severe and/or it was not possible to gather sufficient evidence to support a legal case.

However, the evidence from these five drugs alone suggests that the damage done from marketing abuses that result from the perverse incentives created by patent monopolies is quite large relative to the amount of research induced by patents. As a result, it is likely that there are more efficient alternatives to patent supported drug research, such as publicly financed research.

Introduction

The United States spent $373.6 billion on prescription drugs in 2014[1] which represents approximately 12 percent of national health expenditures for that year. Spending on prescription drugs has consistently been the fastest growing component of health care spending. The major reason for the high cost of drugs is patent protection. By giving pharmaceutical companies a legally enforceable monopoly on products that can be essential to life or health, patent protection allows them to charge far more than free market price.

It is difficult to assess how much drug costs are inflated due to patent protection. A simple method would be to assume that prescriptions filled with brand drugs would instead cost the same on average as generic prescriptions. This is plausible since brand drugs as a group are not more expensive to manufacture and distribute than generic drugs. According to data from the National Association of Chain Drug Stores, in 2010 (the most recent year for which data are available), 71.2 percent of the prescriptions they filled were for generic drugs with 28.8 percent were for brand drugs.[2] The average price of a prescription for a brand drug was $166.61 compared with $44.14 for a generic prescription. If all drugs were available at the generic price, and assuming the cost and share ratios from 2010, it would imply a saving of more than 44 percent or more than $160 billion a year based on 2014 drug sales.

However, this figure is likely to hugely understate the potential savings from the elimination of patent protection for prescription drugs. Many generic drugs enjoy protected status indirectly because of patent protection. The first generic drug in a market gets a period of six months as the exclusive generic in order to provide an incentive for generics to enter a market. In addition, brand manufacturers now market their own generics during this period. In these cases, the generic would still sell for well above the free market price due to limited competition. The threat of patent suits may also deter generic manufacturers from entering a market, leaving it less competitive than would otherwise be the case. Some of the chemicals used to produce a drug may still be subject to patent protection even after the main patents have expired as well. This could also lead to higher prices than if all the research associated with developing the drug were in the public domain.

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1   Bureau of Economic Analysis (2015).
2   United States Census Bureau (2012).

Chain drug stores sell hundreds of generic drugs for less than $10 per prescription.[3] As a lower bound, we can assume that all brand drugs would sell for $10, somewhat above the price for the vast majority of generics at the major chain stores. This would imply savings of over $326 billion annually if all drugs were sold without protection in a free market (**Table 1**).

Savings from Ending Patent Monopolies			
(dollars)			
	Brand Name Drugs 28.8 percent of market	Generic Drugs 71.2 percent of market	Total Spending (billions)	Total Savings (billions)
Prices, 2010	166.61	44.16	373.6	n.a.
High patent-free price	44.16	44.16	207.7	165.9
Low patent-free price	10.00	10.00	47.0	326.6
Source: United States Census Bureau (2012)			

The rationale for patent rents is that they provide incentive for innovation. The argument is that firms would not undertake large investments in research and development if their innovations could be immediately copied by competitors who did not bear this expense. Most immediately, patents present a tradeoff between the static inefficiency associated with prices that are above marginal cost, compared with the dynamic gains that result from the investment induced by the quest for patent rents.[4] Furthermore, patents raise issues of dynamic efficiency as well. Patents encourage companies to seek out patent rents, often in ways that provide little or no social value. For example, the vast majority of drugs approved by the Food and Drug Administration (FDA) are rated as meriting standard reviews, meaning that they do not involve qualitative breakthroughs over existing drugs. Patent rents encourage drug companies to devote resources to developing drugs that duplicate the function of highly-profitable existing drugs.[5] It will often be useful to have alternative drugs to treat the same condition since not all patients respond the same way. Also, in the context of a system of patent monopolies, multiple drugs are likely to lead to somewhat lower prices. Nevertheless, from a social standpoint, it is likely that researching conditions for which no effective treatment exists would provide a better payoff than finding a new drug to treat a condition for which many options are already available.

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3   For a list of drugs available at Walmart, see http://www.walmart.com/cp/PI-4-Prescriptions/1078664. For a comparable list at Costco, see http://www.costco.com/Pharmacy/drug-directory-main?storeId=10301&catalogId=10701&langId=-1.
4   Boldrin M and Levine DK (2013).
5   Morgan SG et al. (2005).

The resources utilized in maximizing patent rents, such as the sales networks set up by drug companies, the lawyers employed to enforce patents and intimidate potential entrants, and the lobbyists hired to extend and strengthen patents are all sources of waste associated with the system.[6] However, in the case of prescription drugs, there are also major costs associated with the enormous asymmetry between the knowledge available to drug companies and the knowledge available to patients and their doctors. As a result of this asymmetry of knowledge, drug companies will often be in a situation to earn large patent rents by concealing information that show their drugs are less effective than they claimed or possibly even harmful.

One way in which drug companies take advantage of this asymmetry is with "off-label" promotion of their drugs. An off-label use of a drug is one which has not been approved by the FDA. While doctors are free to prescribe drugs for off-label uses, drug companies are prohibited from promoting their drugs for off-label uses. If they want to get a drug approved for additional uses then they have to clear a path by seeking FDA approval. However, they routinely avoid this independent assessment by finding ways to promote their drugs for unapproved uses.[7] Promotion of drugs for off-label uses is harmful to the public because it diminishes drug safety regulation, discourages companies from conducting or revealing internal safety studies, and incentivizes them to seek FDA approval for narrow "label use" that is easier to push through the approval process.

An analysis by Public Citizen found that between 1991 and 2012, there were 239 major (greater than $1 million) criminal and civil settlements reached between state and federal governments and pharmaceutical companies with penalties totaling $30 billion dollars for off-label marketing and other improper practices.[8] Of this amount, 83 percent is due to settlements from 2006 to 2012. Even with increasing lawsuits and penalties, it has become evident that drug companies are not deterred from engaging in these practices. The profit margins from off-label marketing are apparently large enough that fines of this size are inadequate to put an end to the practice.[9]

Off-label marketing is a subset of practices associated with promoting drugs in contexts where drug companies have information that would call in question the safety and/or effectiveness of their drugs. In most cases, the harms that are suffered are not due to unavoidable mistakes but rather are a direct result of the pursuit of patent rents. The drug Avandia (rosiglitazone), manufactured by GlaxoSmithKline provides a clear example of this phenomenon. The drug was approved for treating type II diabetes by the FDA in 1999. In 2007, researchers discovered that the multi-billion dollar drug was associated with a significant increase in the risk for myocardial infarction and other

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6   Federal Trade Commission (2012).
7   Public Citizen (2010).
8   *Ibid.*, Public Citizen (2012).
9   Matthews S (2013).

cardiovascular incidents.[10] This information was withheld by the company. This misconduct ultimately contributed to a $3 billion settlement with the Department of Justice (DOJ) in 2012.[11]

This is exactly the sort of misbehavior that would be predicted to result from the incentives created by the patent system in pharmaceuticals. GlaxoSmithKline stood to make enormous profits from concealing the risks of Avandia, and due to the proprietary nature of their research, they were in a position to do so. By contrast, if research funding mechanisms had open access requirements, it would be far more difficult to conceal evidence that a drug is ineffective or harmful. Data exclusivity offers a parallel protectionism that is distinct from patent grants: regulatory bodies are prohibited from examining the preclinical and clinical trial safety data of protected drugs when evaluating bioequivalent generics.[12] The rationale given is that the sponsoring company paid for the trials and therefore owns the data. This approach obscures and disregards the public health considerations which are supposed to legitimate the enormous benefits and subsidies provided to the industry. Indeed, this sort of protectionism has contributed to what Donald Light has termed a "risk-proliferation syndrome" that has raised prescription drugs to the fourth-leading cause of death in the United States.[13]

Given the frequency of this sort of misconduct by the pharmaceutical industry, it would be useful to have some measure of the resulting costs in the form of negative health outcomes such as increased morbidity and mortality. The purpose of this paper is to outline a methodology for investigating this question and to provide some preliminary calculations of the costs associated with drug companies' misrepresenting or concealing evidence.

Methods

Our investigation began by studying Department of Justice press releases, reports from the popular media, and the academic literature[14] to generate a working list of the major pharmaceutical settlements of the last 10 years. From this pool, we then identified those that involved drugs which were unlawfully promoted. We further narrowed down this list to identify the drugs with significant

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10   Nissen SE and Wolski K (2007).
11   Wilson (2011).
12   Adamini S et al. (2009).
13   Light DW et al (2011).
14   For example, ProPublica recently published a summary of the largest pharmaceutical settlements of the last few years using DOJ data, see http://projects.propublica.org/graphics/bigpharma and ProPublica (2014).

risk profiles that were downplayed or disregarded during the marketing process. Once these drugs were identified, we performed literature searches using PubMed, Google Scholar, and the New York Times website to acquire clinical trial data and mortality/morbidity tallies. Figures and estimates expressed by expert clinicians were used when they were reported in the press. In some cases, usage and adverse outcome data were not readily available; in these cases, we performed rudimentary calculations to generate a ballpark estimate which will be made explicit in the results section.

Cost analysis was performed using monetary estimates discovered in the literature. The Taylor et al. group reported a mean lifetime cost of stroke per person in the United States of approximately $103,576[15] which corresponds to $156,279 in 2014 dollars. We used this figure to estimate the costs associated with living with drug-induced heart disease. A landmark study published by Zhuo et al. revealed a lifetime diabetes cost of $85,200[16] ($86,582 in 2014 dollars); we used this figure to estimate the cost of excess cases of drug-induced diabetes. In order to calculate the costs associated with premature death, we used an up-to-date "value of life" figure reported by Zenios et al. of $129,090 per quality-adjusted year of life[17] ($142,447 in 2014 dollars). We used mean treatment ages found in the literature and subtracted them from the average lifespan in the U.S. (approximately 79 years) in order to generate years-of-life-remaining estimates (**Table 2**). For excess cardiovascular events, a case fatality (sudden cardiac death) rate of 44 percent was used to determine the proportion resulting in death as described in the results section.

TABLE 2

Years of Life Lost Due to Mismarketing of Drugs			
(years)			
Drug	Mean Age at Event	Life-Years Lost	Source
Vioxx	67	12	Graham DJ et al. (2005)
Avandia	56	23	Nissen SE and Wolski K. (2007)
Bextra	62	17	Nussmeier NA et al. (2005)
OxyContin	50	29	CDC (2010)
Zyprexa	n.a	n.a	n.a.

Notes: Ages used to calculate life-years lost in the event of premature death. These values were multiplied by the value of quality-adjusted life year, $129,090, to generate costs of premature death. Zyprexa is not represented because no premature deaths were computed in this study.

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15   Taylor TN (1996).
16   Zhuo et al. (2013).
17   Zenios SA et al. (2009).

Results

Drug Mortality and Morbidity

1. **Vioxx (rofecoxib).** In perhaps the most notorious drug withdrawal case, Merck was found to have withheld important information regarding the unique cardiovascular risks of this COX-2 inhibitor. In 2011, Merck agreed to pay $950 million to resolve criminal and civil charges in regards to the improper marketing of Vioxx.[18] Dr. David Graham, associate director of the FDA's Office of Drug Safety, in a landmark paper published in The Lancet estimated that, between 1999 and 2004, Vioxx resulted in 88,000 to 140,000 excess cases of serious heart disease. Furthermore, using case-fatality rate statistics from the American Heart Association, Graham et al. estimated that 44 percent of these cases likely resulted in death[19]: approximately 50,000. (See Appendix for calculations.)

2. **Avandia (rosiglitazone).** Still on the market despite intense controversy, inappropriate marketing of this diabetes drug contributed to GlaxoSmithKline's $3 billion payout to the government to resolve civil and criminal charges. The drug was found to have life-threatening cardiovascular side effects which were intentionally played down by the company in order to protect sales. The FDA itself estimated that the drug was responsible for approximately 83,000 excess heart attacks between 1999 and 2007.[20] Using the case fatality rate of 44 percent, approximately 36,520 of these cases resulted in death.

3. **Bextra (valdecoxib).** This drug contributed to Pfizer's $2.3 billion settlement for off-label promotion in violation of the Food, Drug, and Cosmetic Act.[21] Approved to treat arthritic pain in 2001, a Pfizer subsidiary was found guilty of promoting the drug to treat pain conditions at dosages the FDA declined to approve; it was removed from the market in 2005. Used by 7 million patients worldwide,[22] CNN reported that by April 2005, more than half of Bextra's $1.7 billion in profits were the result of off-label promoting.[23] Using hazard ratios found in the literature, we generated a ballpark figure of 47,440 excess cardiovascular incidents. With a case fatality rate of 44 percent, approximately 20,870 of these cases resulted in death.

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18   Department of Justice (2011).
19   Graham DJ et al. (2005).
20   Senate Finance Committee (2010).
21   DOJ (2009a).
22   Ray WA et al. (2004).
23   Griffin (2010).

4. **OxyContin (oxycodone)/opiate analgesics.** Since 1999, there has been a 300 percent increase in the sale of prescription-strength painkillers (i.e. analgesics) such as OxyContin.[24] In 2008, prescription painkillers were responsible for 14,800 overdose deaths which is more than cocaine and heroin combined.[25] Purdue Pharmaceuticals was intensely pursued by the DOJ and ultimately ordered to pay $600 million in criminal fines for aggressive promotion tactics and misbranding the drug as minimally habit-forming.[26] The company's portfolio includes other pain medicines including hydrocodone, oxycodone, fentanyl, codeine, and hydromorphone. Due to the biomolecular properties of these drugs, dependency on one confers addiction to the rest. Though very successful from a commercial perspective, the extraordinarily addictive OxyContin has been recognized as a public health disaster: it became the leading drug of abuse in the U.S. by 2004.[27] Purdue's aggressive marketing campaign heavily contributed to the marked rise in opiate narcotic prescriptions during the 1990s. Using the market share of OxyContin as a proportion of opioid prescriptions in the U.S. generally, we estimate that since its release in 1996 to the criminal proceedings in 2007, the drug has been responsible for approximately 29,600 overdose-related fatalities. A study published by researchers from the University of Washington and the University of Pennsylvania also investigated the economic costs of nonmedical use of prescription opioids.[28] They found that, in 2006, the costs of OxyContin abuse with regard to abuse treatment, medical complications, productivity loss (minus mortality), and criminal justice proceedings totaled $5.6 billion. We used this figure to estimate an expanded cost of $38.6 billion dollars for the time period analyzed i.e. 1996–2007. We attribute this amount to "abuse-related costs" (**Table 3**).

5. **Zyprexa (olanzapine).** An atypical antipsychotic drug approved for the treatment of schizophrenia and bipolar disorder, Eli Lilly intentionally played down the drug's most notable side effects such as diabetes and obesity.[29] Furthermore, they were aggressive in promoting the drug for patient groups not approved by the FDA including children and the elderly: categories of people at particularly high risk.[30] The New York Times revealed that Eli Lilly urged geriatricians to use Zyprexa to sedate elderly patients in nursing homes even though the drug increases the risk of sudden death, heart failure, and serious infection in

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24   Centers for Disease Control and Prevention (2011a).
25   CDC (2011b).
26   Meier (2007).
27   Van Zee A (2009).
28   Hansen RN et al. (2011).
29   Koro CE et al. (2002).
30   Harris (2009).

elderly patients with dementia.[31] In its January 2009 settlement with the DOJ, the company agreed to pay $1.4 billion for off-label drug marketing.[32] To put this fine in context, it is worth noting that sales from Zyprexa in 2007 alone reached $4.8 billion. In a study published in the American Journal of Psychiatry,[33] researchers at Yale showed that the increased risk of developing diabetes attributable to Zyprexa as opposed to a conventional antipsychotic in schizophrenia patients is 0.6 percentage points. Using figures from this paper, we calculated that Zyprexa caused approximately 42,600 excess cases of diabetes from its approval in 1996 to 2008.

Associated Costs and Value of Life Analysis

For Vioxx, the lifetime costs accrued due to excess cases of cardiovascular (CV) disease totaled $10.0 billion. The costs for premature death totaled $85.5 billion. For Avandia, the lifetime costs accrued due to excess cases of CV disease totaled $7.3 billion. The costs for premature death totaled $119.6 billion. For Bextra, the lifetime costs accrued due to excess cases of CV disease totaled $4.2 billion. The costs for premature death totaled $50.5 billion. For OxyContin, the costs for premature death totaled $63.0 billion and abuse-related costs totaled $38.6 billion.[34] For Zyprexa, the lifetime costs accrued due to excess cases of diabetes totaled $3.7 billion. The sum total costs for all five drugs combined is $382.4 billion (Table 3).

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31   *Ibid.*
32   DOJ (2009b).
33   Leslie DL and Rosenheck RA (2004).
34   For the calculation of abuse-related costs, see Appendix.

TABLE 3

Morbidity/Mortality Statistics Associated with Five Unlawfully Promoted Drugs and their Associated Costs			
Drug	Associated Morbidity/Mortality	Time Period	Calculated Cost (2014 dollars, billions)
Vioxx (Merck)	64,000 excess cardiovascular events, 50,000 deaths	1994–2004	95.5
Avandia (GSK)	46,480 excess cardiovascular events, 36,520 deaths	1994–2007	126.9
Bextra (Pfizer)	26,570 excess cardiovascular events, 20,870 deaths	2001–2005	54.7
OxyContin (Purdue)	15,260 overdose related fatalities, and abuse-related costs	1996–2007	101.6
Zyprexa (Eli Lilly)	42,600 excess cases of diabetes	1996–2008	3.7
		Total Costs	382.4

Notes: The excess CV events represented in this table are cases without sudden cardiac death, i.e. the number of deaths was subtracted out from the total CV events described above. All monetary values are in 2014 dollars.

Discussion

There are clearly serious limitations to this study. In many cases, public information was unavailable; as indicated, we substituted computational assumptions. For example, cohort data pulled from retrospective analyses found in the literature were combined with worldwide drug usage figures found in the popular press. The ratios of domestic to international sales were used to generate estimates for domestic drug usage. Such methods undoubtedly lead to imprecise measurements. However, it is reasonable to conclude that our estimates are at least in the right order of magnitude. The non-overlapping time periods analyzed represent another significant caveat of this study. The start points are drug release dates but the end points were arbitrarily limited by the data that was available to us. Though some end points (e.g. for Vioxx) represent the year of withdrawal for the market, some drugs (e.g. Zyprexa) are still available. As such, this problem would be corrected by improved access to usage information.

It is important for our "value-of-life" analysis to be properly understood. The emergence of costly medical technologies has made necessary the calculation of the financial value of one year of life to properly carry out cost-benefit analyses. This question also arises in lawsuits seeking damages. For research and development purposes, the question that needs to be answered in order to determine whether or not expensive medical interventions should be pursued is, "How much are we, as a society, willing to pay to improve health outcomes?"[35] For this study, we used an estimate published

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35   Stanford Graduate School of Business (2008).

recently by researchers at Stanford:[36] $129,000 for one quality-adjusted year of life (QALY) in 2009 dollars translated to $142,447 for one QALY in 2014 dollars. This amount was multiplied by years of life lost (Table 2) to generate the cost associated with premature death due to drug intervention.

Ultimately, our investigations revealed a $382.4 billion toll imposed by the inappropriate marketing of five drugs. We chose five drugs for the sake of simplicity and because the information available to us limited the number of cases that facilitated meaningful calculation. For example, if we were unable to find or generate an estimate for how many patients were prescribed a specific drug in the United States, then we excluded that case from our analysis. Given that there have been many prominent cases of drug mismarketing in recent years, the calculations in this study would be improved with of the inclusion of a larger number of examples of mismarketing. **Table 4** outlines an additional seven prominent examples of pharmaceutical marketing violations which would merit the methodologies described and employed in this study. An expanded study would require the corresponding morbidity and usage statistics that we found for the five drugs we used.

TABLE 4

Potential Off-label Promotion Violators for Future Investigation				
Drug	Settlement amount (millions of dollars)	Year	Company	Source
Risperdal	2200	2013	J&J	DOJ (2013)
Depakote	1500	2012	Abbott Labs	DOJ (2012a)
Aranesp	762	2012	Amgen	DOJ (2012b)
Serostim	704	2005	Serono	DOJ (2005)
Seroquel	520	2010	AstraZeneca	DOJ (2010)
Abilify	515	2007	Bristol-Myers	DOJ (2007)
Neurontin	430	2004	Pfizer	DOJ (2004)

The $382.4 billion figure can probably best be taken as providing an order of magnitude of the costs associated with the concealing and misrepresentation of research findings. Since these costs were calculated over a 14-year period it implies annual costs of about $27 billion a year. While these drugs were selected because they were prominent examples of especially harmful incidents of misrepresentation, the total costs from misrepresentation and concealment would almost certainly be at least two or three times as large as the amount attributable to this small group of drugs.

It is also important to remember that the bulk of these costs are associated with deliberate acts of concealment and misrepresentation, not honest mistakes. Mistakes and oversights will invariably occur in medical research. However, in the cases cited here the companies were charged with

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36   *Ibid.* See also Zenios SA (2009).

deliberately concealing or misrepresenting evidence for the purpose of increasing sales of their drugs. This is behavior that is directly associated with patent rents. If, for example, this research was all in the public domain and carried through by researchers who had no direct financial interest in the sales of a drug, it is unlikely that they would go to elaborate lengths to misrepresent or conceal research findings, or that they would be successful if they tried. In other words, the costs documented here are the result of the incentives provided by patent monopolies in the same way that the research itself is motivated by patent monopolies.

A useful reference point for this calculation of losses is the amount of money that the pharmaceutical industry was spending on research at the time. Over the period from 1994 to 2008, the industry's spending on research averaged less than $25 billion a year.[37] This means that the estimated damages due to inappropriate marketing of just these five drugs are comparable to what the entire industry was spending on research. While there is a large amount of uncertainty around these calculations, it is certainly plausible that a full measure of the costs associated with mismarketed drugs would equal or exceed the patent supported research over this period, and quite possibly by a large amount. This would be a strong argument for seeking more efficient alternatives to patent-supported research.

This is an issue that deserves an important place on the United States and world policy agenda, particularly in the context of the Trans-Pacific Partnership and the Trans-Atlantic Trade and Investment Pact.[38] One of the major goals of the United States in these and other trade pacts currently being negotiated is to strengthen patent and related protections for prescription drugs. The justification is that increased patent rents will provide a greater incentive to the pharmaceutical industry, leading to more innovation. This drive for greater protections is being resisted by many other countries. India, in particular, has been opposed to tightening patent protections, seeking to advance its generic drug industry.

The fact that incentives from patent rents lead firms to promote drugs in ways that impose large costs on patients and society should raise additional questions about the desirability of patent protection as a mechanism for financing research. Other mechanisms for financing research have been proposed, such as a prize system or direct public funding.[39] Of course the U.S. government already spends $30.9 billion annually funding biomedical research[40] through grants administered by

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[37]   This figure is taken from Pharmaceutical Research and Manufacturers of America (2014). For the data for years prior to 2004, see Van Oster P. (2011), "Drug Discovery and Human Development: Human Cytome Project," [http://www.vanosta.be/hcpphrm.htm]. These numbers would have to be adjusted upward to be put in 2014 dollars.

[38]   The New York Times Editorial Board (2013).

[39]   See Stiglitz (2006) and Baker (2004).

[40]   National Institutes of Health (2015).

the National Institutes of Health, so direct public funding is already an integral part of the drug development process. The proposal is to expand this funding and have NIH's mission extend to the development and testing of drugs. By having all research in the public domain and taking away the patent rents associated with marketed drugs, direct funding would both remove the incentive and hugely lessen the ability to misrepresent research in order to promote drugs for uses that may not be appropriate.

Conclusion

All drugs carry side effects which inevitably increase morbidity and mortality risks. To minimize these risks drug manufacturers need to provide all available safety data for a given drug and respect the law when marketing drugs. What we find, however, is that patent protectionism enables and encourages manufacturers to conceal adverse safety data that might harm sales and to seek approval for the narrowest indications for use, especially when they can promote the drug for off-label uses post-approval. Research carried out by Kesselheim and Avorn at Harvard shows that routine regulatory oversight as currently practiced fails to fully uncover important hazard statistics associated with widely marketed drug products including Vioxx, Bextra, and Zyprexa.[41] For every drug case they examined, however, they concluded that "the litigation process revealed new data on the incidence of adverse events, enabled reassessments of drug risks through better evaluation of data, and influenced corporate and regulatory behavior…In performing these tasks, lawyers and their clients often find themselves serving as drug safety researchers of last resort." Safety data should not have to come to light *ex post facto*: that is, after the harm to patients has been done. Furthermore, even though litigation has a positive influence on corporate behavior, it is clearly not enough. It is still extremely profitable to illegally market a drug.

Off-label promotion and the concealment of adverse drug safety data are predictable outcomes of government-issued patents to the pharmaceutical industry. In addition to the other inefficiencies associated with patent-driven innovation, they impose a significant burden to sick patients and the economy. In a case examination of five unlawfully promoted drugs, we have shown the financial burden to be approximately $382.4 billion or more than $27 billion a year for the period examined. Given that that there are several more similar cases not studied here, this estimate is just a fraction of the total cost imposed by the perverse incentives of patent protectionism. Furthermore, financial

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41   Kesselheim A.S. and Avorn J. (2007).

characterization understates the human suffering caused by drugs that perhaps should never have been available to the public at all. With health spending skyrocketing in the United States—indeed, across the globe—more efficient alternatives to drug development merit serious consideration.

Appendix

The cost calculations for Vioxx began with the "88,000 to 140,000 excess cases of serious heart disease" figure calculated by Dr. David Graham and using the average of these two extremes: 114,000. The case fatality rate employed by Graham in estimating the number of deaths that likely resulted from these excess cases of heart disease was 44 percent. Hence, approximately 50,000 excess deaths and 64,000 excess cases of heart disease. The former figure was multiplied by the value of life reported by Zenios et al. (2009) and by the calculated life years lost (Table 2) in order to generate the cost associated with premature death. The latter figure was multiplied by the lifetime costs associated with stroke reported by Taylor et al. in order to generate the cost associated with unnecessary disease. Analogous calculations were made for the remaining drugs with appropriate modifications. The case fatality rate of 44 percent was used for Bextra and Avandia due to stroke being included in their list of adverse events, which are already cardiovascular in nature. For example, an important study conducted by Graham et al. in 2010 concluded that prescription of rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality.[42]

There were no pre-existing morbidity and mortality statistics reported for Bextra; thus, we carried out our own estimations. We started with the usage figure of 7 million patients worldwide reported in Ray WA (2004) and examined Pfizer's 2005 earning statement to ascertain the domestic versus international distribution of sales revenue.[43] We used this ratio as a general indicator of domestic usage as a proportion of worldwide usage, i.e. 7 million patients. In the first nine months of 2005, Bextra posted earnings of $869 million worldwide and $771 million in the U.S. alone (thus, $98 million internationally). Using the assumption that the U.S. spends twice as much per drug on average than the rest of the world[44], we corrected this ratio by dividing the domestic proportion in half:

$$\frac{771}{2} \div \left[\frac{771}{2} + 98\right] = 79.7\%$$

According to CNN, by April 2005, more than half of Bextra's $1.7 billion in profits came from off-label prescriptions.[45] We then assumed that, of the 7 million patients prescribed Bextra worldwide,

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42   Graham DJ et al. (2010).
43   Pfizer Inc. (2005).
44   Lutz (2012).
45   See Griffin (2010).

3.5 billion patients were prescribed for post-operative pain, the main unapproved usage it was promoted for. Several reports have agreed that there is an approximately 3-fold higher risk of cardiovascular events with Bextra over placebo.[46] For our calculations, we used an event rate of 2.6 percent in Bextra patients versus 0.9 percent in placebo patients: figures drawn from the literature.[47]

$$3.5 \ million \ \times \ 0.26 = 91,000$$
$$3.5 \ million \ \times \ .009 = 31,500$$
$$91,000 - 31,500 = 59,500 \ excess \ CV \ events$$

Of 59,500 excess cardiovascular events due to Bextra, 79.7 percent were presumably in the United States: 47,440 events. Using the 44 percent fatality rate, approximately 20,870 died.

For OxyContin, we started with the CDC estimate that opioid pain relievers were responsible for 14,800 deaths out of 20,444 prescription drug overdose deaths in 2008. Furthermore, Oxycodone-derived products accounted for 15 percent of the market.[48] Thus, we calculated roughly 2.220 overdose deaths due to OxyContin in 2008. Given that prescribing of this compound increased 300 percent from 1999, we used a corrected mean figure of 1387.5 per year.[49] Notably, this figure agrees well with other estimates found in the literature.[50] Multiplying by the 11 years from its release in 1996 to the settlement in 2007, we computed a mortality figure of approximately 15,260 deaths from overdose. From the Hansen et al. paper, we found abuse related costs associated with OxyContin (subtracting costs due to mortality) to be $5.6 billion in 2006 alone. This included elements such as treatment for abuse of the drug, medical complications, productivity loss, and criminal justice. Given that prescribing increased 300 percent from 1999, we corrected this figure to a mean of $3.5 billion per year. Multiplying by 11 years (i.e. from 1996–2007), this yields $38.6 billion.

When researching Zyprexa, we discovered in the mainstream press that 23 million people worldwide were taking the drug in 2008.[51] In a release to investors, Eli Lilly reported that, in the first quarter of 2008, Zyprexa sales totaled $1.1 billion: $500 million domestically and $600 million internationally.[52] As in the case of Bextra, we assumed that the U.S. spends twice as much on drugs as the rest of the world. Furthermore, we used the domestic vs. international sales distribution to estimate the number of patients taking Zyprexa in the U.S. We calculated that U.S. prescriptions accounted for 29.4

46   Furberg et al. (2005).
47   Aldington S et al. (2005).
48   Walsh et al. (2008).
49   See CDC (2011a-b).
50   See Hansen RN (2011).
51   Brenson (2008).
52   `Eli Lilly (2008).

percent of the total; 23 million x 0.294 = 6.8 million U.S. patients.[53] The American Journal of Psychiatry paper referenced in the results section stated an attributable diabetes risk of 0.6 percent.[54] Thus, we estimated 42,600 excess cases of diabetes due to Zyprexa.

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53 Notably, our calculation fits the scale of a similar figure reported in the mainstream media, see
    http://www.nytimes.com/2007/10/06/business/06zyprexa.html.
54 See Leslie DL (2004).

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