The Inverse Benefit Law: How Drug Marketing Undermines Patient Safety and Public Health

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Recent highly publicized withdrawals of drugs from the market because of safety concerns raise the question of whether these events are random failures or part of a recurring pattern.

The inverse benefit law, inspired by Hart’s inverse care law, states that the ratio of benefits to harms among patients taking new drugs tends to vary inversely with how extensively the drugs are marketed. The law is manifested through 6 basic marketing strategies: reducing thresholds for diagnosing disease, relying on surrogate endpoints, exaggerating safety claims, exaggerating efficacy claims, creating new diseases, and encouraging unapproved uses.


In 1971, Julian Tudor Hart proposed his inverse care law: “The availability of good medical care tends to vary inversely with the need for it in the population served.” Hart added that the law “operates more completely where medical care is most exposed to market forces.” A takeoff on the inverse square law of physics, the inverse care law attracted attention because it articulated “something everyone knew but nobody said,” which many have subsequently found useful as a heuristic for guiding research and interpreting data.

In a similar vein, we offer the pharmaceutical inverse benefit law: the benefit-to-harm ratio of drugs tends to vary inversely with how aggressively the drugs are marketed. Like Hart, we offer our law as a heuristic device and not as a precise mathematical model.

Like Hart’s law, the inverse benefit law runs counter to commonly held beliefs. First, one might think that the characteristics of the drug itself, not marketing, would determine the benefit-to-harm ratio. Second, the industry prides itself on discovering improved pharmaceuticals, so we have been conditioned to believe that heavily marketed new drugs are both more efficacious and safer than older drugs. Finally, many assume that the US Food and Drug Administration approval process precludes marketing of unsafe or ineffective drugs.

In the past decade, however, many new drugs were found to be less effective or less safe than originally thought. According to the pharmaceutical industry’s self-image, these events represent unavoidable risks and bad luck. But the inverse benefit law holds that they form a pattern that reflects the current realities of the industry’s attempts to maximize sale through aggressive marketing.

We focused on marketing drugs to physicians and not directly to consumers. The industry, however, generally coordinates its marketing activities closely, so that marketing of drugs to consumers and prescribers is often interrelated.

Inverse Benefit Law

The inverse benefit law assumes that low- and high-risk populations receive different degrees of benefit and harm from administration of a drug. The greater chance of benefit, statistically represented by a low number needed to treat (NNT), is concentrated among those patients with the most severe symptoms or the highest level of risk, depicted in Figure 1 as the area under the curve to the right of X. By contrast, the chance of an adverse drug reaction is spread among all members of the population (the entire area under the bell-shaped curve).

Vertical line X in Figure 1 represents an evidence-based threshold, at or above which drug therapy is recommended for the disease or risk state. A common example is a blood pressure or blood glucose measurement—a certain number of standard deviations above the population mean. The drug is properly indicated for the portion of the population represented by the area to the right of X. Used in this subpopulation, the drug is quite effective (low NNT). Because relatively few are exposed to the drug, the number of adverse reactions is low.

If drug companies were content to market their products in an evidence-based fashion—targeting those to the right of the X threshold line—no deleterious effects on public health would result. Unfortunately, with such a small percentage of the population eligible to receive the drug, an evidence-based strategy yields low sales, much to the chagrin of shareholders. The typical marketing
strategy therefore attempts to shift the drug-recommendation threshold from X to Y in Figure 1. The shape of the bell curve dictates that a relatively small left shift in the threshold will demarcate a disproportionately larger area under the curve to the right of Y). Thus, a small change in the cutoff point for drug prescribing can lead to major increases in company revenues.

The population, however, pays a price for aggressive marketing. First, when less severely afflicted or lower-risk patients are given the drug, many more must be treated for 1 patient to benefit (high NNT). A high NNT has important public health implications if the drug is expensive and competes for scarce resources. Second, because more are now exposed to the drug, the number of adverse reactions increases and the benefit-to-harm ratio worsens.

Our claim, therefore, is not that the pharmaceutical industry sets out to market bad drugs. Rather, the scientific arm of the industry works hard to discover new drugs that are both effective and safe. The marketing arm then turns those good drugs into bad drugs, in effect, by extending their use beyond the proper evidence base.

What marketing measures accomplish the left shift? Six mechanisms are described in Table 1 and the following subsections.

**Reducing Thresholds for Diagnosing Disease**

Consider the example of type 2 diabetes and the glitazone drugs. Management of type 2 diabetes is paradoxical. The largest long-term study revealed that tight control of blood glucose levels did not reduce major macrovascular complications of the disease. Despite strong evidence that maintaining blood glucose at lower levels does not benefit most patients, expert guidelines have steadily lowered the blood glucose level at which diabetes should be diagnosed. When the threshold was lowered from 140 to 126 milligrams per deciliter, 60% of newly diagnosed diabetic patients already would have normal glycohemoglobin levels (the generally agreed-on therapeutic goal) even before initiation of therapy. After lowering the diagnostic threshold even farther leftward to 110 milligrams per deciliter, the NNT rises exponentially, and millions of patients at low risk for any diabetic complications are instead exposed to the risks of medication without offsetting benefits. For example, lower guideline thresholds and aggressive marketing meant that more were exposed to the risks of cardiovascular deaths from rosiglitazone. Had evidence of effect on patient-oriented outcomes been demanded from the start, rosiglitazone would have remained a second-line drug indicated for only a small subset of patients with diabetes.

What accounts for the promulgation of diagnostic guidelines for diabetes that are so poorly grounded in evidence but that serve so well the marketing aims of industry? In one study of financial conflicts of interest among authors of clinical practice guidelines, some authors of all diabetes guidelines had conflicts, and each author with conflicts had a relationship with a mean of 8 different drug firms.

Similar developments have characterized the use of drugs for hypercholesterolemia and hypertension, although fortunately those drugs generally have proved less toxic than rosiglitazone. Cholesterol guidelines recommend drug therapy for groups with progressively lower low-density lipoprotein levels, despite very high NNTs and lack of evidence of benefit of drug therapy as primary prevention. Again, the writers of the guidelines had substantial conflicts of interest.

**Relying on Surrogate Endpoints**

We have become so used to treating hyperglycemia, hypercholesterolemia, and hypertension as diseases that we have forgotten that they are actually surrogate endpoints, in contrast with patient-oriented outcomes such as myocardial infarction, stroke, and death. As a rule, when an at-risk population is identified by a surrogate endpoint, the NNT for
Established, physicians often hesitate to take the risks of those drugs were well recognized. Psychotics in the past. Because dementia-related symptoms occasionally received older antipsychotics, the third generation or atypical antipsychotics illustrates the third mechanism. Elderly patients were heavily marketed as safer than their older counterparts—a claim eventually exposed as erroneous. The result was that primary care physicians prescribed the newer drugs much more liberally in patients with relatively mild symptoms that previously had never been seen as candidates for drug treatment—a substantially left shift in the prescribing threshold.

In similar fashion, promotion of selective serotonin reuptake inhibitor antidepressants has changed the epidemiology of depression. As the presumed safety of the newer drugs prompted physicians to redefine as candidates for pharmacotherapy patients whose depression had previously seemed far too mild to justify taking medication, many more patients became labeled as severely depressed than could be accounted for by any known facts about the incidence of depression. Overall, prescription drugs annually appear to cause about 6 million adverse reactions, 2.2 million hospitalizations, and 111,000 deaths in the United States alone—an inverse benefit epidemic.

Exaggerating Safety Claims

The experience with second-generation or atypical antipsychotics illustrates the third mechanism. Elderly patients with dementia-related symptoms occasionally received older antipsychotics in the past. Because the risks of those drugs were well established, physicians often hesitated to use them or used them in lower doses. The newer antipsychotics are heavily marketed as being much safer than their older counterparts—a claim eventually exposed as erroneous. The result was that primary care physicians prescribed the newer drugs much more liberally in patients with relatively mild symptoms that previously had never been seen as candidates for drug treatment—a substantially left shift in the prescribing threshold.

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Exaggerating Efficacy Claims

One would expect drug marketing routinely to exaggerate efficacy, but this bias would not necessarily lead to a left shift in the prescribing threshold unless another mechanism also was at work.

The rofecoxib scandal illustrates how exaggerated efficacy claims work synergistically with safety-oriented marketing to maximize exposure to unsafe drugs. The selective COX-2 inhibitor group of nonsteroidal anti-inflammatory drugs (NSAIDs) was introduced in the late 1990s. These drugs performed no better than did older NSAIDs as anti-inflammatories or analgesics. Their only advantage was in protecting against gastrointestinal (GI) bleeding, although postmarketing studies showed that the GI risk reduction was modest.

Moreover, both theoretical and empirical considerations suggested the risk of prothrombotic effects. Combining all these facts with the high costs of the new agents yielded an evidence-based recommendation. The X threshold should be based on the combined severity of 2 variables: inflammatory symptoms and relative GI bleeding risk. No more than 3% to 5% of patients would fall into the population who were at high risk for GI bleed and also required an anti-inflammatory drug.

The actual use of these agents was driven instead by massive marketing to physicians and the public that these drugs were safer to all patients and even more effective than standard NSAIDs, so that they should be used as first-line drugs in common conditions such as osteoarthritis. At the height of this marketing boom, fully 61% of all NSAID prescriptions were being written for COX-2 drugs.

In 2004, as firms tried to shift even farther to the left by recommending cyclooxygenase-2 drugs for prevention of colon polyps and other conditions, the inverse benefit (cardiovascular risks) finally became so obvious that rofecoxib was removed from the market. By that time, so many patients had been exposed to those drugs that as many as 140,000 excess cases of serious coronary disease might have been caused in the United States by rofecoxib alone.
Creating New Diseases

Creating new diseases has been described as disease mongering.\textsuperscript{29,29} One example is the invention of social phobia with recommendations for selective serotonin reuptake inhibitor antidepressants as therapy.\textsuperscript{30,31}

The recent invention of the disease categories prediabetes and prehypertension suggests that this mechanism works especially well in synergy with surrogate endpoints and the tendency to reduce thresholds for diagnosis. For hypertension, the number of patients who might be subjected to drug therapy and thus inverse benefits has been increased by the concept of a prehypertensive state.\textsuperscript{32}

In synergy with surrogate endpoints, for prehypertension suggests that this disease might be used to drug therapy and thus inverse benefits.\textsuperscript{33}

Rosiglitazone marketing especially benefited from the invention of prediabetes. Experts first justified the creation of this disease by insisting that the recommended treatment was lifestyle intervention only.\textsuperscript{33} Soon, however, the manufacturer of rosiglitazone conducted a trial confirming the drug’s usefulness in preventing the progression from prediabetes to diabetes.\textsuperscript{34} These study results were then used to urge physicians to prescribe rosiglitazone for patients who did not meet the criteria for the diagnosis of diabetes solely on the basis of surrogate endpoints and without data showing reductions in diabetic complications or other patient-oriented benefits.

Through a similar mechanism, osteopenia has become preosteopenia. The shape of the bell curve determines that many more women will be shown to have osteopenia than osteoporosis if testing bone mineral density comes into widespread use. Optimal sales of bisphosphonates require that these women and their physicians be convinced that they have a disease that requires drug treatment.\textsuperscript{35} As with the cyclooxygenase-2 drugs, the optimal marketing campaign to achieve this goal is often a combination of prescriber-oriented and direct-to-consumer advertising.

Encouraging Unapproved Uses

Because deliberately marketing drugs for unapproved uses is illegal, this activity often comes to light only when companies are fined. Recent examples include gabapentin and olanzapine.\textsuperscript{18,36} For example, federal allegations of off-label marketing of quetiapine include influencing the content of continuing medical education programs, hiring leading physicians to give presentations recommending off-label use, and sponsoring ghost-written articles on off-label indications.\textsuperscript{37} Three of 5 prescriptions for antipsychotics are for off-label use, amounting to a significant left shift in the prescribing threshold, despite the fact that 3 of 4 off-label prescriptions generally lack evidence of benefits but expose patients to harm.\textsuperscript{38}

COUNTERING INVERSE BENEFIT

These marketing strategies enhance company sales but expose more patients to the risk of adverse effects, and high NNTs indicate that fewer and fewer receive benefit. Total harms probably outweigh the benefits. To better protect the public health, awareness of the specific marketing strategies helps to focus attention on likely reforms.

Beware of Misleading Guidelines

Reduction of thresholds for high risk and reliance on surrogate endpoints often operate via clinical practice guidelines that either were written by panels with serious conflicts of interest, fail to take into account the community practice setting in which they will be applied, or both.\textsuperscript{39} Although some propose that better disclosure of conflicts of interest among guideline panels would resolve this problem, we argue instead that the important and sensitive task of writing guidelines should be restricted to groups demonstrably free of commercial conflicts of interest.

Reduce Exaggerated Safety and Efficacy Claims

Skewed claims often arise from studies that are designed primarily to aid drug marketing, not to expand the scientific base for prescribing. Public health calls for independently funded and designed trials focused on safety and efficacy and for creating a neutral agency such as a branch of the National Institutes of Health or the Agency for Healthcare Research and Quality to conduct drug trials, including comparative effectiveness research.\textsuperscript{40} In this connection, we find it worrisome that the final health reform bill passed by Congress in 2010 calls for creation of an agency for comparative effectiveness research that will be susceptible to influence by commercial interests.\textsuperscript{41}

Minimize Creation of New Diseases

The phenomenon of disease mongering occurs often through commercially sponsored research coupled with commercially based clinical guidelines. Critics of the methods currently being used by the American Psychiatric Association for the preparation of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders charge, for example, that expert panels routinely exaggerate the purported benefits of expanding diagnostic labels but seem blind to the risks of both adverse drug effects and labeling previously healthy individuals as having a mental illness.\textsuperscript{42}

Limit Unapproved Uses

Most off-label prescriptions have no scientific justification. Some off-label uses, however, are quite rational, posing a regulatory challenge. Some authors propose formal informed consent requirements before patients can be administered drugs for unapproved uses.\textsuperscript{43} This area requires further study.

Avoid Commercial Marketing by Prescribers

Although it is difficult today to find refuge from omnipresent commercial marketing of pharmaceuticals, evidence-based prescribing is not helped by the fact that 94% of US physicians in 2003 to 2004 freely engaged with sales representatives or other industry marketing activities.\textsuperscript{44} Efforts such as the National...
Physicians Alliance’s Unbranded Doctor Campaign may begin to move practicing physicians toward more evidence-based practice.45

CONCLUSIONS

Not all marketing of prescription drugs is bad for the public health. A campaign, for example, to increase the use of measles vaccine would not be problematic from the standpoint of the inverse benefit law because it would not lower the threshold of use below baseline. Occasionally, a drug with a highly favorable benefit-to-harm ratio is underused, and an effective marketing campaign could be salutary. Seldom, however, is there much profit to be made from these occasional examples of beneficial pharmaceutical marketing.

By allowing a for-profit industry to exercise so much influence on its practice, education, and research, the medical profession has compromised the integrity of medical science and the patient’s and public’s ability to trust the advice offered by physicians.46 The inverse benefit law both identifies the fundamental dynamics of the problem and points the way to some possible regulatory solutions. Ultimately, however, the problem requires that physicians assert their professional responsibilities and shed their current dependency on the pharmaceutical industry for both gifts and information.47 Academic medical centers and medical professional organizations must take the lead in emphasizing professional values.48,49

Even if physicians resist the implications of the inverse benefit law, key political leaders have caught on. The Physician Payment Sunshine Act, requiring drug and device firms to report payments to physicians, had bipartisan support and was ultimately included in the recent health reform legislation.50

In 1971, Hart suspected that market forces would undermine rather than promote the health of the population. The inverse benefit law suggests that exposing more people to a worsening benefit-to-harm ratio in pharmaceuticals is not merely an incidental side effect of the industry’s business plan. Rather, these risks to public health are inherent in the current drug marketing system. Physicians and their professional organizations must see clearly why and how this is so to make the proper ethical choices about relationships with the pharmaceutical industry. Similarly, regulators and policymakers need to be aware of these dynamics to develop better ways for both physicians and patients to access valuable, effective drugs in a safe marketplace.

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Contributors
H. Brody conceptualized the idea and wrote the first draft. D.W. Light suggested the final title and helped revise the article extensively.

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No protocol approval was needed for this study because no human participants were involved.

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23. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated...
Forcing the Navy to Sell Cigarettes on Ships: How the Tobacco Industry and Politicians Torpedoed Navy Tobacco Control

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In 1986, the US Navy announced the goal of becoming smoke-free by 2000. However, efforts to restrict tobacco sales and use aboard the USS Roosevelt prompted tobacco industry lobbyists to persuade their allies in Congress to legislate that all naval ships must sell tobacco. Congress also removed control of ships’ stores from the Navy. By 1993, the Navy abandoned its smoke-free goal entirely and promised smokers a place to smoke on all ships. Congressional complicity in promoting the agenda of the tobacco industry thwarted the Navy’s efforts to achieve a healthy military workforce. Because of military lobbying constraints, civilian pressure on Congress may be necessary to establish effective tobacco control policies in the armed forces. (Am J Public Health. 2011;101:404–411. doi: 10.2105/AJPH.2010.196329)

AT MORE THAN 30%,^2,^12 THE prevalence of smoking in the military is 50% higher than is the civilian rate, with a 40% prevalence among those aged 18 to 25 years^3 and nearly 50% among those who have been in a war zone.^4 From 1998 to 2005, tobacco use in the military increased 7.7% from 29.9% to 32.2%, reversing the decline of prior decades. A tobacco-friendly military culture persists, including the availability of cheap tobacco products,^5 liberal smoking breaks,^6 and easily accessible smoking areas. Smoking damages health and readiness^6–^11 and increases medical and training costs.^12–^15 In addition to short-term 

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