*Research used to criticize drug marketing also supports the claim that marketing benefits patients.*

# An Uncertain Diagnosis

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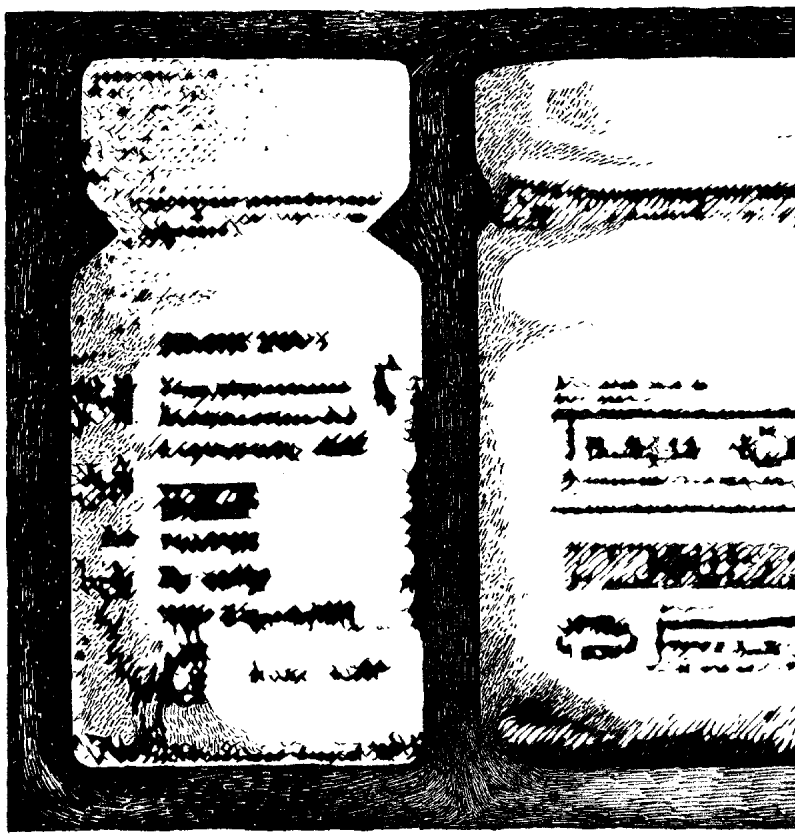
PHARMACEUTICAL SALES REPRESENTATIVES have incentives to "oversell" their products. But they also benefit by providing truthful information about their drugs' benefits. In analyzing the effects of sales and promotion efforts, it is important to consider both the positive and negative aspects of drug marketing.

There is a substantial literature in medical journals examining the marketing and promotional efforts of pharmaceutical firms. This literature is generally critical of those efforts, focusing on the negative aspects of promotion. Although the literature is expressed in empirical and scientific terms and makes use of data, it suffers from some weaknesses. If the same methods and level of rigor were used in analyzing another problem in medicine—say, the effectiveness of a particular remedy—scientific journals would reject the research and the Food and Drug Administration would not approve the remedy.

All studies of the effects of pharmaceutical marketing have essentially the same format: Some group of physicians is the population under study. The physicians interact in some way with pharmaceutical salespeople. Some physician behavior with respect to pharmaceuticals is examined, and it is found to change following the interaction. The researchers then allege that the change demonstrates harmful behavior by the pharmaceutical company and the researchers call for some sort of reform, such as a strengthened code of ethics.

There are three difficulties with this mode of analysis. First, the physician population subject to study is not randomly selected—it seems at least plausible that physicians who attend pharmaceutical sales pitches may want to change their current prescribing behavior, so research indicating a change is not all that surprising and should not be considered worrisome. Second, the literature has examined the effects of promotion mostly in circumstances in which promotion can lead only to harmful outcomes, but it is at least plausible that promotion could have beneficial outcomes by making physicians aware of new treatments. The third problem is more fundamental: The sur-



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rogate endpoint chosen in the analyses—some measure of behavior—is not the true endpoint of interest. The true endpoint of interest should be the health of patients or a clinical surrogate such as lower blood pressure or cholesterol. It is quite possible that the assumed relationship between the surrogate endpoints and the true endpoint—that more medications prescribed is a worse outcome—is sometimes incorrect, and that increased prescribing is often beneficial.

In analyzing these issues, I will refer to a recent survey article that has received much attention: Ashley Wazana's 2000 *Journal of the American Medical Association* paper "Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?" Because this article is a survey, the discussion will deal with a large portion of the literature.

## SELECTION BIAS I: PHYSICIAN-PHARMACEUTICAL FIRM INTERACTION

The studies surveyed in Wazana's article purport to measure the effect of some type of contact with a pharmaceutical company or representative on some aspect of physician behavior. But the studies may suffer from what is called "selection bias." That is, the physicians who had contact with pharmaceutical representatives may have been self-selected to accept or seek out this contact. For example, a physician may have heard of a new drug through advertising, reading of a medical journal, or discussion with a colleague. If the physician believes the drug may be useful for his practice, he can then seek out a pharmaceutical representative to learn more about the drug or, if approached by a representative, spend time learning about the drug.

In such circumstances, the observed increase in prescribing behavior is at most only partly the result of the contact with the representative. The causality may actually go the other way—the physician may accept the contact because he wants to prescribe the medication. If the representative were not available, the physician might have pursued other avenues to obtain additional information, but it may be that the easiest method is through contact with a salesperson. Thus, any estimate of the effect of the contact that does not take into account the selection issue is biased upward. Wazana does mention self selection, but dismisses the possibility with no analysis, merely calling it "unlikely."

There is evidence that such a bias exists. Wazana cites a 1996 study by Shawn Caudill, Mitzi Johnson, Eugene Rich, and Paul McKinney indicating that physicians who rely more heavily on pharmaceutical representatives for information are more concerned about side effects than about cost to the patient. The study also associates reliance on pharmaceutical representatives with higher cost of prescribing. This information is perfectly consistent with a world in which some physicians are more concerned than others with side effects, perhaps because of personal preferences or perhaps because of the nature of the physician's practice. Such physicians then rely on pharmaceutical sales representatives to provide them information about the side effects. Other physicians who are more concerned about cost to the patient can obtain the cost figures independently of the salesperson. While information on side effects is available, it is more complex and difficult to absorb than information about prices, and so physicians may rely more heavily on sales representatives for information about side effects than for price information.

If this is the explanation of the observed behavior, then the interaction with sales representatives has nothing to do with costs of prescribing, and the concerns expressed in the article

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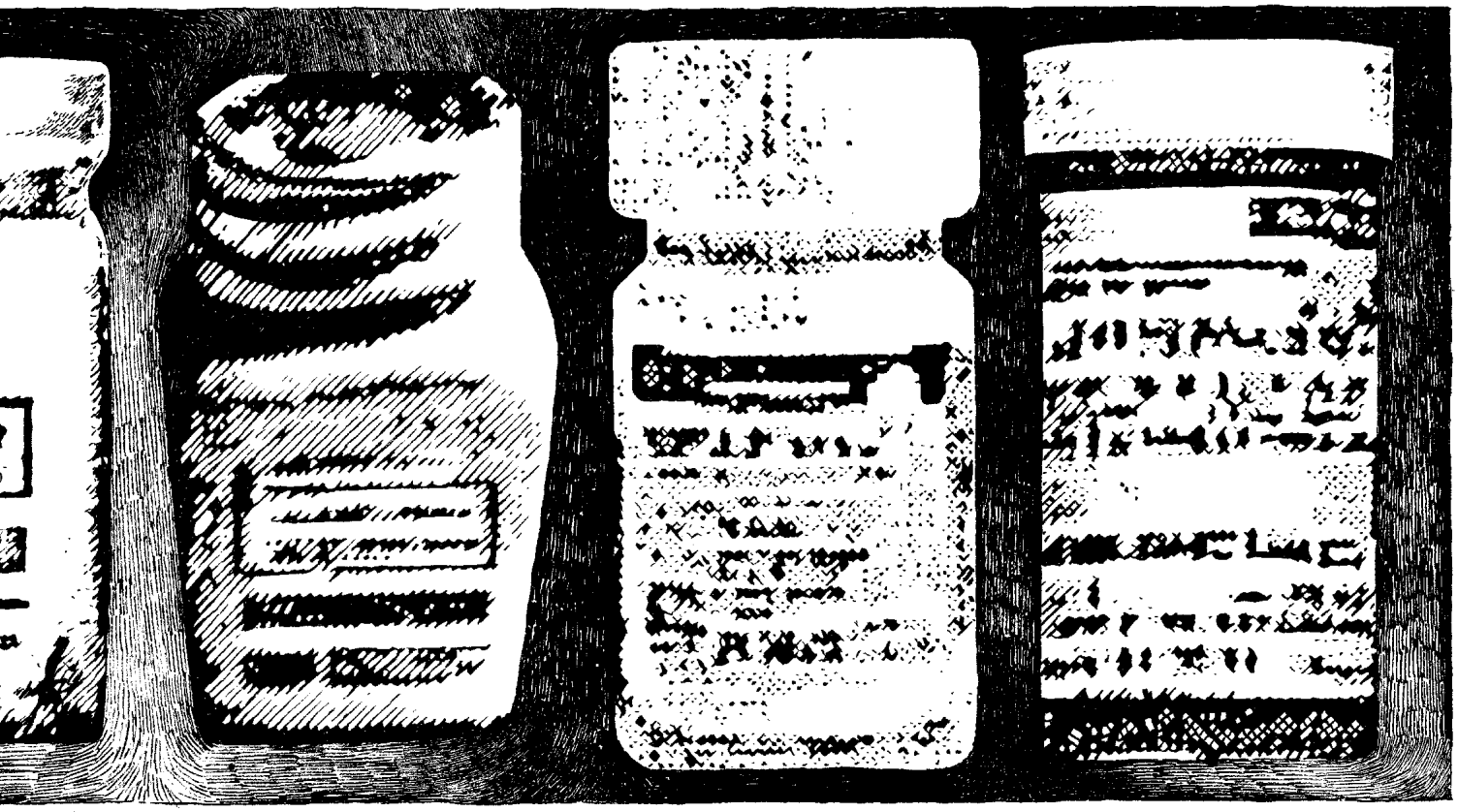

regarding the influence of pharmaceutical sales representatives on cost are misplaced. While there is little direct evidence for this hypothesis, nonetheless, it would be worth considering in addition to the argument that the increase in cost of prescribing is a result of contact with pharmaceutical representatives.

Another possibility is that some physicians read the scientific literature for information while others do not. Anthony Bower and Gary Burkett, in a 1987 study, found that physicians who read certain medical journals are less likely to rely on pharmaceutical representatives. Those who read many journals may always have more knowledge than those who do not. Those who do not read journals may obtain information from pharmaceutical representatives. Thus, any comparison between those who rely on pharmaceutical representatives and those who do not would be flawed. The relevant comparison would be between those who rely on such representatives in situations in which they do and do not have access to medical journals. It is quite possible that the effect of denying them access to salespeople would be reduced knowledge and would lead to worse outcomes.

The best way to avoid selection bias is through random assignment. Some physicians could be chosen to rely on pharmaceutical representatives, and others not. Then behavior of the two sets of physicians could be compared. No study has done that.

## SELECTION BIAS II: INEFFECTIVE DRUGS OVERSTUDIED

In examining the effects of promotion, it is important to understand the theoretical relationship between use of the drug and health outcomes. In some circumstances, any promotion will be harmful because a drug is ineffective. In other circumstances, the opposite is true because a drug is unambiguously effective and thus promotion is helpful. In many cases, the result is theoretically indeterminate and evidence must be examined.

Jerry Avorn, Milton Chen, and Robert Hartley's well-known 1982 paper shows that physicians' beliefs about drugs often match advertising claims—even when those claims conflict with independent data. The article discusses two classes of drugs, cerebral vasodilators as a treatment for senile dementia and propoxyphene for pain. According to Avorn and his co-authors, cerebral vasodilators have been shown to be ineffective and propoxyphene has been shown to be no more effective than aspirin. The authors show that pharmaceutical companies advertise both drugs and physicians respond to the advertising.

This study did identify a flaw in information flows in the health care system. Pharmaceutical representatives have an incentive to promote their products, even if the products have been shown to be ineffective. Sometimes there will be countervailing forces, and other representatives from other companies will counter the incorrect information. However, in the circumstances discussed in the paper, those countervailing forces would be lacking. Although propoxyphene is no more effective than aspirin, there are few incentives for pharmaceutical companies to promote aspirin because it is off-patent and no company promoting it could expect to gain sufficient sales to justify the cost. That is, no firm has exclusive property rights in aspirin, so no firm has an adequate incentive to spend resources on promotion because other firms would be able to "free ride" on the expenditures—although some companies may engage in limited advertising if they have a large-enough market share (e.g., Bayer aspirin). Similarly, although vasodilators are ineffective for senile dementia, there was no more effective remedy available, and so again no countervailing force. Thus, in such circumstances, promotion is socially harmful.

Although the study did identify some harm from promotion, there are some factors mitigating that harm. In the case of cerebral vasodilators, the authors noted that the remedy had at one time been thought to be effective. They also found that older physicians (who were more likely to have learned about the supposed but illusory benefits of cerebral vasodilators in school) were more likely to prescribe the remedy, so this belief may be a residue of training and, at least in part, independent of pharmaceutical promotion (although such promotion could reinforce the incorrect knowledge). For propoxyphene, the authors indicate that many patients want something other than aspirin and physicians might prescribe the drug to satisfy that preference; there is no evidence presented that propoxyphene is worse than aspirin, although it is more expensive. Again, the prescribing may be the result of forces in addition to pharmaceutical promotion and may be in response to patient preferences.

As the FDA approval process requiring proof of efficacy becomes stricter, this class of events should become less common. But a finding of harm from promotion where there is no better alternative provides limited information about the promotion process in general.

**EFFECTIVE MEDICINES** In the opposite case in which an effective patented medicine is actively promoted and no equally effective alternative exists, a study of pharmaceutical promotion would always find a beneficial effect because some physicians will learn of the patented medicine from pharmaceutical representatives. I have not seen such studies in the literature.

> In a case in which an effective, patented medicine is promoted, research would find a beneficial effect from the promotion.

The lack of such studies may be because medical researchers mostly look for harmful effects of promotion.

One interesting source of data would be those diseases for which many effective medicines exist and compete with each other through promotion. Those medicines may have similar therapeutic effects but may differ in other ways such as dosing, side effects, or price. Under such circumstances, advertising and promotion can perform a useful function by allowing the market to sort. Physicians may learn of properties of each medicine from promotional efforts. Some physicians may rely on one medicine that suits the majority of patients in the practice; other physicians may maintain a portfolio and prescribe according to the match between particular patients and each drug.

It is also possible that physicians would respond to promotional effort independently of other characteristics of the medicine or of their patients; the promotion could be mainly self-seeking for pharmaceutical companies. Promotion might be leading to optimal sorting or merely leading to bias. More nuanced studies would be needed to sort out the effects. Moreover, if the medicines are all efficacious, then promotion will be beneficial for patients because physicians will learn about some effective medicine even if the message they receive is biased in favor of one medicine.

Another interesting source of data would be those diseases for which effective patented and unpatented medicines exist. Of course, only the patented medicine would be promoted. The effect of promotion in this case would likely be an increase in costs because patented medicines are generally more expensive than generics. However, if the medicines are equally effective, there would be no health effects (except that some patients might not take the prescribed medicine who would have taken the less expensive unpatented medicine). If the patented medicine is better in some respects, then promotion would have highly ambiguous effects, depending on whether the patients receiving the patented medicine found the extra benefits worth the extra costs. In addition, because there is little or no promotion of the unpatented medicine, physicians might not learn about this medicine at all. Then the only alternative would be the patented and promoted medicine. In this case, a mechanism for informing physicians about the properties of the unpatented medicine would be valuable, although it is difficult to identify such a mechanism.

## CHOICE OF ENDPOINTS

The goal of medicine is patient welfare. Thus, the best endpoint for examination of the effects of promotion would be a measure of patient health and welfare, perhaps with some attention to cost. Wazana is quite clear, however, that this endpoint was never used, noting, "No study used patient outcome measures." Thus, all studies rely on surrogate endpoints.

A useful surrogate might be prescribing behavior. If it could be shown that contact with pharmaceutical representatives led to incorrect prescribing, then this would be evidence of likely harm. But there is, in fact, little or no such evidence. Of the 29 studies considered by Wazana, only six deal with prescribing, including one that deals with additions to a formulary. The other 23 studies deal with attitudes of physicians toward pharmaceutical representatives or with frequency of contact between physicians and the representatives.

Of the six studies relating to prescribing behavior, only Flora Haayer's 1982 paper is alleged to deal with explicitly harmful prescribing, called "nonrational prescribing." This is a study of physicians in the Netherlands in 1982. The Netherlands in 1982 differs in significant ways from the contemporary United States. For example, methods of compensation and reimbursement are different, and the drug approval process is also different. Also, there have been changes in medical behavior (such as the rise of HMOs, which monitor prescribing behavior) and information sources (for example, the Internet) since 1982. If a 1982 study of U.S. prescribing behavior were used to justify a current policy proposal, there would be some concern over that use; a study from another era and another country must be treated with even greater care when applied to behavior in the contemporary United States.

Because Haayer's is the only study that actually looks at prescribing behavior, it must be given some credence. But before major policies are drafted in response to its findings, some replication in a contemporary setting would be useful. To return to the drug approval analogy, the FDA would not approve a drug based on a 1982 study from the Netherlands.

This is especially true because the Haayer study has some odd results. For example, reading general medical journals is also associated with nonrational prescribing. The main result of the study, however, is that rational prescribing is a function of physician characteristics; in this context the study cannot determine if reliance on information from the pharmaceutical industry leads to nonrational prescribing or if those physicians who prescribe nonrationally for other reasons (perhaps unwillingness to study the appropriate literature) are also more likely to rely on pharmaceutical representatives for information.

A 1996 study by Roger Springarn, Jesse Berlin, and Brian Storm found that when an employee of a drug manufacturer presented grand rounds, residents who attended made some decisions more correctly and others less correctly. This study does discuss selection bias and makes a convincing case that there was no such bias. However, the sample was only 22 residents. And there is no discussion of the net benefits of the correct and incorrect decisions, and so no ability to judge whether the promotional activity was harmful or beneficial.

The other four studies do not demonstrate any harmful prescribing at all. Caudill, Johnson, Rich, and McKinney's 1996 study shows higher cost of prescribing by physicians more concerned with side effects than with cost. James Orlowski and Leon Wateska's 1992 study shows that attendance at symposia in resorts is associated with increased prescribing of the drugs made by the sponsoring companies. But there is no showing that the drugs are inferior or harmful, and the authors note, "It is possible that the changes in prescribing patterns of the two drugs studied were the result of a recognition that the new drugs were safer or more effective than their predecessors or that they filled a unique therapeutic niche."

Bower and Burkett's 1987 study shows that physicians relying on pharmaceutical representatives are less likely to prescribe generics. But the study also finds that those physicians are less like-

ly to fully trust generics, so it is not surprising that those physicians would favor more-expensive patented medications.

M. Y. Peay and E. R. Peay's 1988 study found that in Australia, physician contact with "detailmen" regarding a drug was the most persistent predictor of a favorable reaction by physicians to the drug. However, the drug in question, temazapam, was apparently a minor advance over competing drugs and, so, the adoption was not obviously harmful or inappropriate. The Peays' study can be interpreted as showing that contact with detailmen was associated with a beneficial outcome.

Marjorie Bowman and David Pearle's 1988 study found that attendance of a "continuing medical education" course was associated with somewhat increased prescribing of the product manufactured by the sponsors of that course, although the increases were marginal. In all cases, there were potentially three or more competing drugs with similar benefits, side effects, and costs. The courses seemed to increase use of all drugs in the class. (Two courses involved calcium channel blockers and one involved beta blockers.) If the drugs are net beneficial, then a strong implication is that the courses improved patient welfare. Oddly, the study does not address that possibility; it does ask, "Are these results bad?" but never provides an answer or even a careful discussion, and never considers patient welfare.

The sixth and final significant study to examine prescribing behavior is Mary-Margaret Chren and Seth Landefeld's 1994 paper, which dealt with another intermediate endpoint: requests by physicians for additions to a formulary. In this study, it was found that physicians are more likely to request that a drug be added to a hospital formulary if the physician had contact with a representative of the company manufacturing the drug and that no physician requested such an addition unless he had such contact. In a 1994 letter to the *Journal of the American Medical Association,* which published the study, I argued that Chren and Landefeld's evidence is perfectly consistent with physicians learning of the benefits of a drug and requesting its addition to the formulary; many of the added drugs represented a "major therapeutic advance" over existing drugs. The paper offered no evidence of harm from the other requested drugs, and the fact that most of them were added to the formulary indicates that they may have had some nontherapeutic benefit such as a lower price, reduced side effects, or more favorable dosing.

The authors subsequently replied to my letter, but their response presented no evidence against my position. Their main argument was, "We believe that physicians should not learn about drugs from those who stand to benefit from their choices." Chren and Landefeld also indicate that the fact that pharmaceutical promotion influenced physicians' drug choices "rather than the possible merits of the choices themselves, should concern us as physicians."

This is an odd argument. Should the method of obtaining information be more important than the interests of patients in receiving appropriate medication? Moreover, it is common in the health arena for information to come from "those who stand to benefit from their choices"—a surgeon may recommend surgery; an internist may recommend a follow-up visit; a dentist may suggest a filling. In all those cases, the provider of the information also benefits from the information.

**OVERVIEW** We thus have the following situation: There is no evidence in the literature of harm to patients from pharmaceutical marketing and promotion. There is weak and ambiguous evidence of improper prescribing based on one uncontrolled study in the Netherlands in 1982, but that study's age and circumstances raise questions about its use in meaningful policy decisions. Indeed, it seems ironic that researchers who are skeptical of information provided by pharmaceutical companies are willing to advocate major policy changes based on much weaker evidence of harm from promotional activities.

None of the other studies discussed by Wazana deal with harm from pharmaceutical marketing. The studies merely show that contact with pharmaceutical marketing representatives leads to favorable impressions of pharmaceuticals, or that gifts from companies lead to more frequent contacts with representatives. Those effects would be harmful if it were known that promotion led to incorrect prescribing or that prescribing led to reduced health. That is, the other 23 studies in Wazana's data set deal with surrogate endpoints that would be harmful only if it were known that the actual endpoint was harmful. Because that is not known, none of those studies demonstrates any harm or any behavior that should be controlled or penalized.

All of the studies do find one similar result: promotion is associated with increased use of the promoted drug. However, the studies then make an invalid leap to concluding that the increase is undesirable. The evidence supporting that leap is ambiguous at best, and most of the studies do not consider alternative explanations.

## CONCLUSION

Among those writing about pharmaceutical marketing, the maintained hypothesis seems to be that such marketing is harmful. Numerous policy recommendations are made based on this analysis: regulation of behavior, ethical codes, and other restraints. There is a website, *nofreelunch.org,* that claims, "We are health care providers—physicians, pharmacists, nurses, dentists, among others—who believe that pharmaceutical promotion should not guide clinical practice, and that over-zealous promotional practices can lead to bad patient care. It is our goal to encourage health care practitioners to provide high quality care based on unbiased evidence rather than on biased pharmaceutical promotion."

There currently is no objective basis for any belief that pharmaceutical marketing is always or even mostly harmful. Of course, drug companies undertake such activities for the purpose of selling drugs and making money; they do not provide information to physicians in order to advance the public interest. But one of the major bases for a market economy is the understanding that activities undertaken for private profit often lead to public benefits. There is no evidence that this is not true in the pharmaceutical industry, and no reason to believe that it is not. There are circumstances when we would expect promotion to be unambiguously harmful and circumstances

when it would be unambiguously beneficial. In the majority of cases, there is no theoretical prediction and evidence must be examined. But the literature to date has focused on the first class of situations, when we could predict in advance that promotion would be harmful.

There is evidence that pharmaceutical use in the aggregate is beneficial. Frank Lichtenberg's 2003 paper shows that investment in pharmaceutical research and development has a very high payoff and has led to significant increases in life expectancy and real incomes. In order for drugs to have beneficial effects, physicians must learn about them. Provision of such information to physicians is expensive, on both the demand and the supply side. That is, it is expensive to communicate the information to physicians, and it is expensive (in terms of lost time) for physicians to absorb the information. The pharmaceutical companies are in the best position to bear the costs of information provision. They know the information, and know it sooner than others. Thus, while there are other methods of information dissemination, the pharmaceutical companies are in a position to play a crucial role in the process. What appears to the physician-authors as "bribery" may also be viewed as compensation to the physicians for the opportunity cost of time to learn about drugs. The literature particularly decries "free lunches" paid for by pharmaceutical representatives, but an informal seminar over lunch is an efficient way to communicate with busy people.

A 1983 study by Jerry Avorn and Stephen Soumerai suggests that "academically based 'detailing'" could provide better information to physicians than could pharmaceutical representatives. This study demonstrates that objective detailers could inform physicians that certain therapies are inappropriate. Avorn and Soumerai suggest that Medicaid, HMOs, or the Veteran's Administration might be willing to pay for such programs. But as yet, none of those entities have shown themselves eager to do so. In fact, even though this study was published in a prestigious journal in 1983, no one in the United States has, to any major extent, adopted the approach advocated in the article and paid for the sort of interaction that it describes. That is not surprising because the cost of providing information to physicians regarding drugs is estimated to be about $11 billion per year. The only parties willing to spend the large amount of resources needed to communicate effectively with physicians are the pharmaceutical companies.

Economists sometimes refer to the "Nirvana Fallacy." This is a comparison of an imperfect, actual world with a perfect, ideal world. In such a comparison, the actual world always loses. But we cannot live in an ideal world. We must compare actuals with actuals. Even though the drug promotion process may be flawed, it is difficult to think of a feasible alternative. It might be better if all physicians regularly read medical journals, but they do not.

Of course, the academic physicians who write the critical papers are in a position to spend more time absorbing research from professional journals. But practicing physicians have other demands on their time, and are generally not in a position to spend time in this way. Even if they did, the time away from practice also would be costly.

In the world in which we live, the best source of information about pharmaceuticals for many physicians is often the industry itself. If we limit or restrict the ability of the industry to communicate, the result will be less information. If regulations or codes of ethics make this communication more difficult or more expensive, the cost will not be borne only by the pharmaceutical companies. The major effect will be that many physicians will learn less about drugs, and an endpoint of reduced health of patients. R

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