

THE NEW YORKER

THE CRITICS

A CRITIC AT LARGE

HIGH PRICES

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How to think about prescription drugs.

Issue of 2004-10-25

Posted 2004-10-18

Ten years ago, the multinational pharmaceutical company AstraZeneca launched what was known inside the company as the Shark Fin Project. The team for the project was composed of lawyers, marketers, and scientists, and its focus was a prescription drug known as Prilosec, a heartburn medication that, in one five-year stretch of its extraordinary history, earned AstraZeneca twenty-six billion dollars. The patent on the drug was due to expire in April of 2001. The name Shark Fin was a reference to what Prilosec sales—and AstraZeneca's profits—would look like if nothing was done to fend off the ensuing low-priced generic competition.

The Shark Fin team drew up a list of fifty options. One idea was to devise a Prilosec 2.0—a version that worked faster or longer, or was more effective. Another idea was to combine it with a different heartburn remedy, or to change the formulation, so that it came in a liquid gel or in an extended-release form. In the end, AstraZeneca decided on a subtle piece of chemical reengineering. Prilosec, like many drugs, is composed of two “isomers”—a left-hand and a right-hand version of the molecule. In some cases, removing one of the isomers can reduce side effects or make a drug work a little bit better, and in all cases the Patent Office recognizes something with one isomer as a separate invention from something with two. So AstraZeneca cut Prilosec in half.

AstraZeneca then had to prove that the single-isomer version of the drug was better than regular Prilosec. It chose as its target something called erosive esophagitis, a condition in which stomach acid begins to bubble up and harm the lining of the esophagus. In one study, half the patients took Prilosec, and half took Son of Prilosec. After one month, the two drugs were dead even. But after two months, to the delight of the Shark Fin team, the single-isomer version edged ahead—with a ninety-per-cent healing rate versus Prilosec's eighty-seven per cent. The new drug was called Nexium. A patent was filed, the F.D.A. gave its blessing, and, in March of 2001, Nexium hit the pharmacy shelves priced at a hundred and twenty dollars for a month's worth of pills. To keep cheaper generics at bay, and persuade patients and doctors to think of Nexium as state of the art, AstraZeneca spent half a billion dollars in marketing and advertising in the year following the launch. It is now one of the half-dozen top-selling drugs in America.

In the political uproar over prescription-drug costs, Nexium has become a symbol of everything that is wrong with the pharmaceutical industry. The big drug companies justify the high prices they charge—and the extraordinary profits they enjoy—by arguing that the search for innovative, life-saving medicines is risky and expensive. But Nexium is little more than a repackaged version of an old medicine. And the hundred and twenty dollars a month that AstraZeneca charges isn't to recoup the costs of risky research and development; the costs were for a series of clinical trials that told us nothing we needed to know, and a half-billion-dollar marketing campaign selling the solution to a problem we'd already solved. “The Prilosec pattern, repeated across the pharmaceutical industry, goes a long way to explain why the nation's prescription drug bill is rising an estimated 17 % a year even as general inflation is quiescent,” the *Wall Street Journal* concluded, in a front-page article that first revealed the Shark Fin Project.

In “The Truth About the Drug Companies: How They Deceive Us and What to Do About It” (Random House; \$24.95), Marcia Angell offers an even harsher assessment. Angell used to be the editor-in-chief of *The New England Journal of Medicine*, which is among the most powerful positions in American medicine, and in her view drug companies are troubled and corrupt. She thinks that they charge too much, engage in deceptive research, produce inferior products, borrow their best ideas from government-funded scientists, and buy the affections of physicians with trips and gifts. To her, the story of Nexium and drugs like it is proof that the pharmaceutical industry is “now primarily a marketing machine to sell drugs of dubious benefit.”

Of course, it is also the case that Nexium is a prescription drug: every person who takes Nexium was given the drug with the approval of a doctor—and doctors are professionals who ought to know that there are many cheaper ways to treat heartburn. If the patient was coming in for the first time, the doctor could have prescribed what’s known as an H2 antagonist, such as a generic version of Tagamet (cimetidine), which works perfectly well for many people and costs only about twenty-eight dollars a month. If the patient wasn’t responding to Tagamet, the doctor could have put him on the cheaper, generic form of Prilosec, omeprazole.

The patient’s insurance company could easily have stepped in as well. It could have picked up the tab for Nexium only if the patient had first tried generic Tagamet. Or it could have discouraged Nexium use, by requiring anyone who wanted the drug to pay the difference between it and generic omeprazole. Both the physician and the insurance company, meanwhile, could have sent the patient to any drugstore in America, where he or she would have found, next to the Maalox and the Pepcid, a package of over-the-counter Prilosec. O.T.C. Prilosec is identical to prescription Prilosec and effectively equivalent to prescription Nexium, and it costs only twenty dollars a month.

Throughout the current debate over prescription-drug costs—as seniors have gone on drug-buying bus trips to Canada, as state Medicaid programs and employers have become increasingly angry over rising health-care costs, and as John Kerry has made reining in the pharmaceutical industry a central theme of his Presidential campaign—the common assumption has been that the rise of drugs like Nexium is entirely the fault of the pharmaceutical industry. Is it? If doctors routinely prescribe drugs like Nexium and insurers routinely pay for them, after all, there is surely more than one culprit in the prescription-drug mess.

The problem with the way we think about prescription drugs begins with a basic misunderstanding about drug prices. The editorial board of the *Times* has pronounced them much too high; Marcia Angell calls them “intolerable.” The perception that the drug industry is profiteering at the expense of the American consumer has given pharmaceutical firms a reputation on a par with that of cigarette manufacturers.

In fact, the complaint is only half true. The “intolerable” prices that Angell writes about are confined to the brand-name sector of the American drug marketplace. As the economists Patricia Danzon and Michael Furukawa recently pointed out in the journal *Health Affairs*, drugs still under patent protection are anywhere from twenty-five to forty per cent more expensive in the United States than in places like England, France, and Canada. Generic drugs are another story. Because there are so many companies in the United States that step in to make drugs once their patents expire, and because the price competition among those firms is so fierce, generic drugs here are among the cheapest in the world. And, according to Danzon and Furukawa’s analysis, when prescription drugs are converted to over-the-counter status no other country even comes close to having prices as low as the United States.

It is not accurate to say, then, that the United States has higher prescription-drug prices than other countries. It is accurate to say only that the United States has a different pricing system from that of other countries. Americans pay more for drugs when they first come out and less as the drugs get older, while the rest of the world pays less in the beginning and more later. Whose pricing system is cheaper? It depends. If you are taking Mevacor for your cholesterol, the 20-mg. pill is two-twenty-five in America and less than two

dollars if you buy it in Canada. But generic Mevacor (lovastatin) is about a dollar a pill in Canada and as low as sixty-five cents a pill in the United States. Of course, not every drug comes in a generic version. But so many important drugs have gone off-patent recently that the rate of increase in drug spending in the United States has fallen sharply for the past four years. And so many other drugs are going to go off-patent in the next few years—including the top-selling drug in this country, the anti-cholesterol medication Lipitor—that many Americans who now pay more for their drugs than their counterparts in other Western countries could soon be paying less.

The second misconception about prices has to do with their importance in driving up over-all drug costs. In one three-year period in the mid-nineteen-nineties, for example, the amount of money spent in the United States on asthma medication increased by almost a hundred per cent. But none of that was due to an increase in the price of asthma drugs. It was largely the result of an increase in the *prevalence* of usage—that is, in the number of people who were given a diagnosis of the disease and who then bought drugs to treat it. Part of that hundred-per-cent increase was also the result of a change in what's known as the *intensity* of drug use: in the mid-nineties, doctors were becoming far more aggressive in their attempts to prevent asthma attacks, and in those three years people with asthma went from filling about nine prescriptions a year to filling fourteen prescriptions a year. Last year, asthma costs jumped again, by twenty-six per cent, and price inflation played a role. But, once again, the big factor was prevalence. And this time around there was also a change in what's called the therapeutic mix; in an attempt to fight the disease more effectively, physicians are switching many of their patients to newer, better, and more expensive drugs, like Merck's Singulair.

Asthma is not an isolated case. In 2003, the amount that Americans spent on cholesterol-lowering drugs rose 23.8 per cent, and similar increases are forecast for the next few years. Why the increase? Well, the baby boomers are aging, and so are at greater risk for heart attacks. The incidence of obesity is increasing. In 2002, the National Institutes of Health lowered the thresholds for when people with high cholesterol ought to start taking drugs like Lipitor and Mevacor. In combination, those factors are having an enormous impact on both the prevalence and the intensity of cholesterol treatment. All told, prescription-drug spending in the United States rose 9.1 per cent last year. Only three of those percentage points were due to price increases, however, which means that inflation was about the same in the drug sector as it was in the over-all economy. Angell's book and almost every other account of the prescription-drug crisis take it for granted that cost increases are evidence of how we've been cheated by the industry. In fact, drug expenditures are rising rapidly in the United States not so much because we're being charged more for prescription drugs but because more people are taking more medications in more expensive combinations. It's not price that matters; it's volume.

This is a critical fact, and it ought to fundamentally change the way we think about the problem of drug costs. Last year, hospital expenditures rose by the same amount as drug expenditures—nine per cent. Yet almost all of that (eight percentage points) was due to inflation. That's something to be upset about: when it comes to hospital services, we're spending more and getting less. When it comes to drugs, though, we're spending more and we're getting more, and that makes the question of how we ought to respond to rising drug costs a little more ambiguous.

Take CareSource, a nonprofit group that administers Medicaid for close to four hundred thousand patients in Ohio and Michigan. CareSource runs a tightly managed pharmacy program and substitutes generics for brand-name drugs whenever possible. Nonetheless, the group's pharmacy managers are forecasting at least ten-per-cent increases in their prescription-drug spending in the upcoming year. The voters of Ohio and Michigan can hardly be happy with that news. Then again, it's not as if that money were being wasted.

The drug that CareSource spends more money on than any other is Singulair, Merck's new asthma pill. That's because Medicaid covers a lot of young, lower-income families, where asthma is epidemic and

Singulair is a highly effective drug. Isn't the point of having a Medicaid program to give the poor and the ailing a chance to live a healthy life? This year, too, the number of patients covered by CareSource who are either blind or disabled or have received a diagnosis of AIDS grew from fifteen to eighteen per cent. The treatment of AIDS is one of the pharmaceutical industry's great success stories: drugs are now available that can turn what was once a death sentence into a manageable chronic disease. The evidence suggests, furthermore, that aggressively treating diseases like AIDS and asthma saves money in the long term by preventing far more expensive hospital visits. But there is no way to treat these diseases in the short term—and make sick people healthy—without spending more on drugs.

The economist J. D. Klienke points out that if all physicians followed the treatment guidelines laid down by the National Institutes of Health the number of Americans being treated for hypertension would rise from twenty million to forty-three million, the use of asthma medication would increase somewhere between twofold and tenfold, and the number of Americans on one of the so-called "statin" class of cholesterol-lowering medications would increase by at least a factor of ten. By these measures, it doesn't seem that we are spending too much on prescription drugs. If the federal government's own medical researchers are to be believed, we're spending too little.

The fact that volume matters more than price also means that the emphasis of the prescription-drug debate is all wrong. We've been focussed on the drug manufacturers. But decisions about prevalence, therapeutic mix, and intensity aren't made by the producers of drugs. They're made by the consumers of drugs.

This is why increasing numbers of employers have in recent years made use of what are known as Pharmacy Benefit Managers, or P.B.M.s. The P.B.M.s draw up drug formularies—lists of preferred medications. They analyze clinical-trials data to find out which drugs are the most cost-effective. In a category in which there are many equivalent options, they bargain with drug firms, offering to deliver all their business to one company in exchange for a discount. They build incentives into prescription-drug plans to encourage intelligent patient behavior. If someone wants to take a brand-name oral contraceptive and there is a generic equivalent available, for example, a P.B.M. might require her to pay the price difference. In the case of something like heartburn, the P.B.M. might require patients to follow what's called step therapy—to try the cheaper H2 antagonists first, and only if that fails to move to a proton-pump inhibitor like omeprazole. Employers who used two or more of these strategies last year saw a decrease of almost five per cent in their pharmacy spending.

There is no mention of these successes in "The Truth About the Drug Companies." Though much of the book is concerned with the problem of such costs, P.B.M.s, the principal tool that private health-care plans use to control rising drug costs, are dismissed in a few paragraphs. Angell's focus, instead, is on the behavior of the pharmaceutical industry. An entire chapter, for instance, centers on the fact that the majority of drugs produced by the pharmaceutical industry are either minor variations or duplicates of drugs already on the market. Merck pioneered the statin category with Mevacor. Now we have Pfizer's Lipitor, Bristol-Myers Squibb's Pravachol, Novartis's Lescol, AstraZeneca's Crestor, and Merck's second entrant, Zocor—all of which do pretty much the same thing. Angell thinks that these "me-too" drugs are a waste of time and money, and that the industry should devote its resources to the development of truly innovative drugs instead. In one sense, she's right: we need a cure for Alzheimer's much more than we need a fourth or fifth statin. Yet me-too drugs are what drive prices down. The presence of more than one drug in a given category gives P.B.M.s their leverage when it comes time to bargain with pharmaceutical companies.

With the passage of the Medicare prescription-drug-insurance legislation, late last year, the competition created by me-toos has become even more important. The bill gives responsibility for managing the drug benefit to P.B.M.s. In each therapeutic category, Medicare will set guidelines for how many and what kinds of drugs the P.B.M.s will have to include, and then the P.B.M.s will negotiate directly with drug companies for lower prices. Some analysts predict that, as long as Medicare is smart about how it defines

the terms of the benefit, the discounts—particularly in crowded therapeutic categories like the statins—could be considerable. Angell appears to understand none of this. “Medicare will have to pay whatever drug companies charge,” she writes, bafflingly, “and it will have to cover expensive me-too drugs as well as more cost-effective ones.”

The core problem in bringing drug spending under control, in other words, is persuading the users and buyers and prescribers of drugs to behave rationally, and the reason we’re in the mess we’re in is that, so far, we simply haven’t done a very good job of that. “The sensitivity on the part of employers is turned up pretty high on this,” Robert Nease, who heads applied decision analysis for one of the nation’s largest P.B.M.s, the St. Louis-based Express Scripts, says. “This is not an issue about how to cut costs without affecting quality. We know how to do that. We know that generics work as well as brands. We know that there are proven step therapies. The problem is that we haven’t communicated to members that we aren’t cheating them.”

Among the costliest drug categories, for instance, is the new class of antiinflammatory drugs known as COX-2 inhibitors. The leading brand, Celebrex, has been heavily advertised, and many patients suffering from arthritis or similar conditions ask for Celebrex when they see their physician, believing that a COX-2 inhibitor is a superior alternative to the previous generation of nonsteroidal anti-inflammatories (known as NSAIDs), such as ibuprofen. (The second leading COX-2 inhibitor, Merck’s Vioxx, has just been taken off the market because of links to an elevated risk of heart attacks and strokes.) The clinical evidence, however, suggests that the COX-2s aren’t any better at relieving pain than the NSAIDs. It’s just that in a very select group of patients they have a lower risk of side effects like ulcers or bleeding.

“There are patients at high risk—people who have or have had an ulcer in the past, who are on blood-thinning medication, or who are of an advanced age,” Nease says. “That specific group you would likely start immediately on a COX-2.” Anyone else, he says, should really be started on a generic NSAID first. “The savings here are enormous,” he went on. “The COX-2s are between a hundred and two hundred dollars a month, and the generic NSAIDs are pennies a day—and these are drugs that people take day in, day out, for years and years.” But that kind of change can’t be implemented unilaterally: the health plan and the employer have to explain to employees that in their case a brand-new, hundreddollar drug may not be any better than an old, one-dollar drug.

Similarly, a P.B.M. might choose to favor one of the six available statins on its formulary—say, AstraZeneca’s Crestor—because AstraZeneca gave it the biggest discount. But that requires, once again, a conversation between the health plan and the employee: the person who has happily been taking Pfizer’s anti-cholesterol drug Lipitor for several years has to be convinced that Crestor is just as good, and the plan has to be very sure that Crestor *is* just as good.

The same debates are going on right now in Washington, as the Medicare program decides how to implement the new drug benefit. In practice, the P.B.M.s will be required to carry a choice of drugs in every therapeutic category. But how do you define a therapeutic category? Are drugs like Nexium and Prilosec and Prevacid—all technically known as proton-pump inhibitors—in one category, and the H2 antagonists in another? Or are they all in one big category? The first approach maximizes the choices available. The second approach maximizes the bargaining power of P.B.M.s. Deciding which option to take will have a big impact on how much we end up paying for prescription drugs—and it’s a decision that has nothing to do with the drug companies. It’s up to us; it requires physicians, insurers, patients, and government officials to reach some kind of consensus about what we want from our medical system, and how much we are willing to pay for it. AstraZeneca was able to do some chemical sleight of hand, spend half a billion on advertising, and get away with the “reinvention” of its heartburn drug only because that consensus hasn’t yet been reached. For sellers to behave responsibly, buyers must first behave intelligently. And if we want to create a system where millions of working and elderly Americans don’t have to struggle

to pay for prescription drugs that's also up to us. We could find it in our hearts to provide all Americans with adequate health insurance. It is only by the most spectacular feat of cynicism that our political system's moral negligence has become the fault of the pharmaceutical industry.

There is a second book out this fall on the prescription-drug crisis, called "Overdosed America" (HarperCollins; \$24.95), by John Abramson, who teaches at Harvard Medical School. At one point, Abramson discusses a study that he found in a medical journal concluding that the statin Pravachol lowered the risk of stroke in patients with coronary heart disease by nineteen per cent. That sounds like a significant finding, but, as Abramson shows, it isn't. In the six years of the study, 4.5 per cent of those taking a placebo had a stroke versus 3.7 per cent of those on Pravachol. In the real world, that means that for every thousand people you put on Pravachol you prevent one stroke—which, given how much the drug costs, comes to at least \$1.2 million per stroke prevented. On top of that, the study's participants had an average age of sixty-two and most of them were men. Stroke victims, however, are more likely to be female, and, on average, much older—and the patients older than seventy in the study who were taking Pravachol had *more* strokes than those who were on a placebo.

Here is a classic case of the kind of thing that bedevils the American health system—dubious findings that, without careful evaluation, have the potential to drive up costs. But whose fault is it? It's hard to blame Pravachol's manufacturer, Bristol-Myers Squibb. The study's principal objective was to look at Pravachol's effectiveness in fighting heart attacks; the company was simply using that patient population to make a secondary observation about strokes. In any case, Bristol-Myers didn't write up the results. A group of cardiologists from New Zealand and Australia did, and they hardly tried to hide Pravachol's shortcomings in women and older people. All those data are presented in a large chart on the study's third page. What's wrong is the context in which the study's findings are presented. The abstract at the beginning ought to have been rewritten. The conclusion needs a much clearer explanation of how the findings add to our understanding of stroke prevention. There is no accompanying commentary that points out the extreme cost-ineffectiveness of Pravachol as a stroke medication—and all those are faults of the medical journal's editorial staff. In the end, the fight to keep drug spending under control is principally a matter of information, of proper communication among everyone who prescribes and pays for and ultimately uses drugs about what works and what doesn't, and what makes economic sense and what doesn't—and medical journals play a critical role in this process. As Abramson writes:

When I finished analyzing the article and understood that the title didn't tell the whole story, that the findings were not statistically significant, and that Pravachol appeared to cause *more* strokes in the population at greater risk, it felt like a violation of the trust that doctors (including me) place in the research published in respected medical journals.

The journal in which the Pravachol article appeared, incidentally, was *The New England Journal of Medicine*. And its editor at the time the paper was accepted for publication? Dr. Marcia Angell. Physician, heal thyself. ✦