The Cure That Kills

When the side effects of medications are worse than the ailments they're prescribed for

The case studies are scattered through the medical journals: a 62-year-old woman with acute psychosis; a 73-year-old man with "severe delirious psychotic features"; a woman of 47 suffering from insomnia and barely able to stand or walk; a 62-year-old woman who ruptures her Achilles tendon; a 64-year-old diabetic woman with life-threatening hypoglycemia.

When, near the end of one of those ask-your-doctor commercials, a fast-talking disembodied voice reads off a drug's side effects, usually over a scene involving fields of waving grass and a puppy dog, it tends to sound like a lot of nasty stuff that's going to happen to someone else.

But while reading and writing about the pharmaceutical industry over the past couple of years, I started wondering about what life is like for the real people who do experience those side effects. Then last fall, when my own father was prescribed two popular antimicrobial drugs, I didn't have to wonder any longer.

He, like the people in those published case studies, was a victim of a specific class of antibiotics known as fluoroquinolones. Clinical trails typically find that about 10 percent of people taking these drugs—among the most familiar of which are ciprofloxacin (Cipro) and levofloxacin (Levaquin)—experience psychiatric and central-nervous-system problems.

Because they target bacteria and not our own tissues, antibiotics are often not scrutinized for side effects by the Federal Drug Administration or manufacturers as carefully as are, say, psychiatric drugs. But in the bodies of people, cats, rats and mice, fluoroquinolones not only kill bacteria but also appear to attach to certain brain and nerve receptors, kill tendon cells, and cause other kinds of havoc.

Clinical trials conducted over three decades in the process of gaining FDA approval for fluoroquinolones—which encompass dozens of antibiotics with "flox" or "ox" in the generic name—showed that psychiatric and central-nervous-system problems occurred in more than 10 percent of patients. Such trials, as well as "adverse drug reaction" (ADR) reports that began to be filed by U.S. doctors and patients once the drugs were being marketed, indicate serious reactions in about 1 to 2 percent of cases in which the drugs are administered.

A study of ADRs in Italy, published in 2005, found that among more than 50 types of drugs, fluoroquinolones accounted for 11 percent of all adverse events and were involved in the largest number of serious problems, edging out antidepressants.

"A Remarkable Safety Record"

If even only one person in 100 suffers a grave side effect of such a popular class of drug, that can mean millions of people affected. At their worst, fluoroquinolones can ruin or, potentially, end lives. On the Internet, people who have been "floxed" come together in forums and discussion groups to swap graphic accounts of searing pain, psychosis, blistering skin, kidney and liver damage, muscle-wasting, tendon rupture, hallucinations, insomnia, suicidal thoughts and panic attacks.

Dr. Jay Cohen, a medical researcher and associate professor at the University of California San Diego, published a paper on peripheral neuropathy caused by fluoroquinolones in 2001. Since then, he says, "I have received several hundred e-mails, most of which relate terrible, often catastrophic reactions to Levaquin, and some to Cipro. These reactions are slow to pass, leaving some people disabled for months or years. It is an awful problem."

Clinical trials and case studies published by doctors in leading medical journals also make it clear that such problems exist, but in the journals, it's common to see conclusions like this, from a 2002 paper: "Levofloxacin has been used in more than 200 million prescriptions, with a remarkable safety record."

In their practices, doctors often appear to blame other factors for damage done by the drugs. Says Cohen, "Unfortunately, many doctors do not know that fluoroquinolones can cause such severe, long-lasting reactions. When a reaction occurs, some doctors deny that it could have been caused by the drug. Doctors order a battery of tests to seek other causes, but the tests usually show nothing." In the early 1990s, award-winning journalist Stephen Fried launched his own dogged investigation of fluoroquinolones after his wife Diane suffered long-term damage from a single pill of a variant called ofloxacin (Floxin) that was popular at the time. In his book, *Bitter Pills: Inside the Hazardous World of Legal Drugs* (Bantam Books, 1999), Fried describes a 1993 FDA advisory committee meeting he attended, in which government and drug-company officials haggled over possible new warnings to be put on fluoroquinolone labels and inserts. Fried helped FDA researchers make their case, but, he wrote in the book, "The doctors leading the [G.D.] Searle [and Company] delegation said something that almost caused me to have a seizure."

"As you know," that doctor told the group, "physicians will not even look at the package insert. If they do, it's for seconds."

The Spoils of War

People who find themselves under assault by bacteria (including the 2 million Americans who get infected each year in hospitals) desperately need antibiotics. And, better late than never, there is a growing awareness that the use of antibiotics must be planned much more rigorously, to curtail the development of resistant bacteria. But the popularity of some of the drugs has as much to do with historical accident as with safety and efficacy.

The huge commercial success of the fluoroquinolones can be traced to 1990 and the first Gulf War, when the U.S. military was concerned that Iraqi forces with whom they were soon to do

battle were planning to use anthrax as a bacterial weapon. The armed forces ordered 30 million doses of the fluoroquinolone ciprofloxacin—Cipro—to be administered to troops as a preventative measure. That drug was chosen mainly because it was new, and the Iraqis would not have been expected to have selected an anthrax strain resistant to it.

Although no anthrax attack is known to have been launched in Kuwait or Iraq (and Desert Storm veterans have blamed the side effects of the antibiotic for some of the symptoms of Gulf War Syndrome), Cipro got the reputation as a kind of superdrug, and sales rose through the 90s. The actual anthrax attacks of October 2001 triggered a wave of panic-buying and pill-swallowing, and Cipro's manufacturer Bayer responded by producing 200 million additional doses within two months.

At the time, a shocked David Flockhart, chief of clinical pharmacology at the Indiana University School of Medicine, told the *Los Angeles Times*, "Cipro is basically a big gun whose benefits outweigh its risks in certain circumstances, but the bigger gun you use, the more damage you can expect as collateral." Of more than 3,000 postal employees who took Cipro following the anthrax attacks, 26 percent had problems with their digestive system, and 14 percent reported neurological problems.

Cipro and its newer fluoroquinolone cousins have since become the most frequently prescribed class of antibiotics in the United States, accounting for one prescriptions out of four. By 2003, more than a half-billion prescriptions had been written for Cipro and Levaquin alone. Under contracts then in effect, the Defense Department and Veterans Administration together were dispensing about 9 million doses of fluoroquinolones per year.

The quinolone family of antibiotics grew out of research on anti-malarial drugs, which also carry a heavy load of side effects. One member of that family, a malaria medication called mefloquine (Larium), has become notorious for causing problems that include, according to FDA, "psychiatric symptoms ranging from anxiety, paranoia and depression to hallucinations and psychotic behavior. On occasions, these symptoms have been reported to continue long after mefloquine has been stopped."

In what passes for innovation in the pharmaceutical industry, companies continue to modify the chemical structure of fluoroquinolones in search of similar, effective antibiotics that can be patented. One recent study warned that members of the newest generation of such drugs, judging from their chemical structures, are even more likely to cause adverse side effects than are now-popular ones like Cipro and Levaquin. Because the truly informative testing of drugs occurs not during the FDA approval process but through their use by millions of patients, a lot of people are certain to experience damage from these drugs first-hand.

One Victim's Story

At 77, my father was a specimen of good health who ate a solid vegetarian diet and would regularly bike 20 or more miles in a day. So it came as a terrible blow when, in October, he had to go in for emergency cardiac artery bypass and valve-replacement surgery. Complications of the surgery kept him hospitalized longer than expected—with two more trips to the operating

room—weakened, exhausted, and down to only 125 pounds from his former 155.

A full month after being admitted, he finally seemed to begin recovering. But at that point, he plunged into a terribly weakened state, sleeping little or not at all, his arms and legs in almost constant, uncoordinated motion, unable to walk without falling backward. That went on for almost two weeks, until he made a quick turnaround, regained his ability to walk, and was discharged.

We were all astonished and grateful, but wondered how he had improved so suddenly. Weeks later, when I went back and looked at his 33-page hospital file of doctors' notes, along with the 146-page daily file of medications he'd been given, I saw that his abrupt deterioration had coincided with the start of a course of a fluoroquinolone called moxifloxacin (Avelox), given for suspected pneumonia. The just-as-abrupt improvement occurred a day and a half after his last dose of moxifloxacin. But at the time of his discharge, we didn't know that; indeed, we'd never heard the term "fluoroquinolone."

When he had been out of the hospital for five days, still fatigued and very shaky but not ill, a physician's assistant decided that he needed an antibiotic prescription in case he might have pneumonia. The drug was Levaquin. He took the first dose that night, and by the following evening, he was going downhill fast. He spent almost all of the next day in bed, too weak to walk or even sit up, spending most of the time with his eyes closed or in a blank stare, making bizarre sounds and gestures.

Unable to get any answers from his doctors, my mother and I, in desperation, stopped giving him the Levaquin. (As a geneticist, I was as aware as anyone of the rule that says never to stop an antibiotic in mid-course, but we were indeed desperate.) Within 36 hours, he had begun improving remarkably but remained very weak for months. His doctor has since concluded that he never had pneumonia.

Who's Minding the (Drug)store?

The label for Levaquin includes information that is typical for fluoroquinolones: "Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause ... tremors, restlessness, anxiety, lightheadedness, dizziness, confusion and hallucinations, paranoia, depression, nightmares, insomnia and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose."

In 2004, the FDA issued a new warning on fluoroquinolones, stating that treatment should be stopped if patients felt strange neurological symptoms like "pain, burning, tingling, numbness, and/or weakness ... in order to prevent the development of an irreversible condition." In 2005-06, the Illinois attorney general and the group Public Citizen petitioned the FDA to add a so-called "black box" warning to packages, this one regarding the danger of tendon rupture, a well-documented effect of the drugs. So far, no action has been taken.

Jay Cohen responded to FDA's addition of the 2004 statement by asking, "The question is, will doctors notice these warnings? Doctors do not reread package inserts or the PDR every time they prescribe the same drug. Moreover, the package inserts of quinolones are very long, and

the information can easily be overlooked. Perhaps the greatest usefulness of the new warnings may be for patients who develop side effects with quinolones and who consult the Physician's Desk Reference [PDR], or for doctors who consult the PDR after patients complain about side effects."

In that sense, the warning does its job, but too late for the patient: Once my father was in big trouble, I indeed looked up the fine-print warnings. Among several of his doctors with whom I discussed his experience with fluoroquinolones afterward, none had known that the drugs can have serious effects on the central nervous system—yet none was surprised that they do.

Without the many other drugs he received during surgery and his six-week hospital stay, my father would not have survived. And in seeming to recover from two "floxings" within only a few weeks, my father was luckier than many other patients. However, as he struggled to regain his health, he twice had his recovery reversed (and, it seems, nearly ended altogether) by the side effects of drugs prescribed for an illness that he never actually had.

Tragically, his overmedication is not unusual. Studies of outpatients have consistently shown that more than half the drugs they were taking were not needed. By one estimate, 20 million unnecessary antibiotic prescriptions are written in the United States every year. As many as 100,000 Americans die annually from reactions to prescription drugs of all kinds. With a toll like that, the costs of overmedication can't fully be measured in dollars. (And one study found that only 6 percent of adverse reactions are accurately reported.)

A survey of patients admitted to two hospitals' emergency departments found that for half of those patients who were taking multiple drugs at the time, it was the pharmaceuticals themselves that had landed them in the emergency room. Another survey of patient charts found that three-fourths of the time, the documents did not accurately list all the drugs being taken.

The risks of drugs in general are known to be much higher in elderly patients. As what one paper called the nation's "leading drug consumers," our older friends and relatives have far too many opportunities for drugs to interact with an existing medical condition or another drug. At any given time, says one study, 78 percent of people over 65 years of age are on medications—and half of that group are regularly taking five or more drugs.

Elderly patients not only take more drugs, they also have more health problems that can magnify the side effects and often mislead patients and doctors about what ails them. In the words of one researcher, "It is easy to ascribe decline in functional status to worsening disease or old age and not thoroughly investigate the contribution of inappropriate drug therapy." That's what happened to my father; until the drug effects became too obvious to ignore, we all assumed he was still suffering aftershocks of surgery.

Another study put its finger on the bigger problem, noting that despite having learned in medical school about systematic approaches to prescribing, "physicians learn how to prescribe in 'real-world' settings ... and they are influenced by their peers, pharmaceutical company marketing, health-care systems, and patient demands and expectations."

Hazardous drug interactions continue to be a big issue in medicine. Through hard experience, medical administrators have come up with a list of the 10 most dangerous drug interactions, and two of those involve fluoroquinolones. But as for actually preventing such problems, there is always more talk than action. Were a proposed drug to be safety-tested not only on its own, but in combinations with other drugs, its sponsoring company would have to shell out many times as much money and spend a lot more development time.

Don't hold your breath for that. Drug executives are already threatening to stop developing antibiotics altogether, because in the companies' eyes, they don't justify the cost of research and testing. That's because they are usually prescribed only for a matter of days at a time, not for many years like the more profitable lifestyle drugs and treatments for chronic diseases.

Having in their inventories a class of antibiotics that's so popular among physicians and on which so many chemical variations-on-a-theme are possible, companies are not acknowledging the toll being taken by fluoroquinolones on vulnerable patients. Jay Cohen says, "As far as I can tell, the manufacturers have not lifted a finger to try to help these people, nor have they undertaken research to try to explain these reactions and to develop measures to help patients avoid them."

He adds that drugs like Levaquin, Cipro, or Avelox "should not be used as first line antibiotics. Other, safer drugs should be tried first. The need for antibiotic therapy with fluoroquinolones should be gauged carefully, and unnecessary use should be avoided."

Unfortunately, most people don't learn about the risks of fluoroquinolones or other drugs until, like me, they encounter them first hand and look around for information. Then they find sites like Cohen's MedicationSense.com or the most comprehensive fluoroquinolones victims' site, FQResearch.org. That site is urging that the drugs never be used "unless there is a direct threat to the patient's life or limb."

This story first appeared in Counterpunch*, Jan. 2008. Stan Cox is a plant breeder and writer in Salina, Kan. His book,* Sick Planet: Corporate Food and Medicine*, will be published by Pluto Press in April 2008.*