

The Ignored Risks of Fluoroquinolones

by STAN COX

The case studies are scattered around in 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 man, 75, struck with repeated seizures; a 64-year-old diabetic woman with life-threatening hypoglycemia.

All of those people had suffered the side effects of a specific class of antibiotics known as fluoroquinolones. Because they target bacteria and not our own tissues, antibiotics are often not scrutinized for side effects by the Federal Drug Administration (FDA) 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 many drugs, among the most familiar of which are ciprofloxacin (Cipro) and levofloxacin (Levaquin) [1] — showed that psychiatric and central-nervous-system problems occurred in more than 10 percent of patients.[2] Such trials, as well as "adverse drug reaction" (ADR) reports that began to be filed by US doctors and patients once the drugs were being marketed, indicated 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.[3]

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 in reading and writing about the pharmaceutical industry for 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 assaulted with terrible symptoms apparently caused by a widely prescribed fluoroquinolone, I didn't have to wonder any longer.

"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" as they call it (because the generic names of many such drugs contain the letters "flox") 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. Award-winning journalist Stephen Fried was moved to write a book, *Bitter Pills: Inside the Hazardous World of Legal Drugs* (1999) after his wife Diane suffered long-term damage after taking a single pill of a fluoroquinolone called Floxin.

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 on 2001. Since then, he says, "I have

received several hundred emails, 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 [Levaquin] has been used in more than 200 million prescriptions, with a remarkable safety record." [4]

In their practices, doctors often appear to be attributing fluoroquinolone damage to other causes. 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."

The spoils of war

People who find themselves under assault by bacteria (including the 2 million 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 Operation Desert Shield, when the US 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. [5]

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.

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." [6] Of more than 3000 postal employees who took Cipro following the anthrax attacks, 26 percent had problems with their digestive system, and 14 percent reported neurological problems. [7]

Cipro and its newer fluoroquinolone cousins have since become the most frequently prescribed class of antibiotics in the US, accounting for one prescription out of four. By 2003, more than a half-billion prescriptions had been written for Cipro and Levaquin alone. [8] Under contracts then in effect, the Defense Department and Veterans Administration together were dispensing about 9 million doses of fluoroquinolones per year. [9]

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 (Lariam), 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 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.[10] 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 — weak, 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 once again into a terribly weakened state, sleeping little or not at all, his arms and legs almost constantly in 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.

When he had been out of the hospital for five days, feeling wiped out but not ill in any way, 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 remains very weak six weeks later. His doctor has since concluded that he never had pneumonia.

When I went back and looked at my father's 33-page hospital file of doctors' notes, along with the 146-page (!) daily file of medications he'd been given, I saw that his earlier abrupt deterioration, a month into the hospital stay, had coincided with the start of a course of a fluoroquinolone called moxifloxacin (Avelox), also given for suspected (but nonexistent) pneumonia. The just-as-abrupt improvement that led to his discharge occurred a day and a half after his last dose of moxifloxacin.

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." [11]

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.

One of the nurses told us that the cardiac-surgery patients she sees are "generally sent home with about 20 prescriptions." Without some of the drugs he received during surgery and his six-week hospital stay, my father would not have survived. But 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 unnecessary. By one estimate, 20 million unnecessary antibiotic prescriptions are written in the US every year and as many as 100,000 Americans die annually from reactions to prescription drugs of all kinds. [12] 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. [13]

The risks of drugs in general are known to be much higher in elderly patients. As what one letter to the *Journal of Clinical Oncology* called "the 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. [14]

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." [15] 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, healthcare systems, and patient demands and expectations." [16]

Hazardous interactions among medications continue to be a big issue in medicine. Through hard experience, medical administrators have come up with a list of the ten 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.

That won't happen. 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.[17]

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 www.medicationsense.com or the most comprehensive fluoroquinolones victims' site, www.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."

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NOTES

1. See the long list of fluoroquinolones at http://www.fqresearch.org/alphabetical_listings.htm
2. For example, see www.fda.gov/cder/foi/nda/96/020634-1.pdf
3. Galatti et al., Neuropsychiatric reactions to drugs: an analysis of spontaneous reports from general practitioners in Italy. *Pharmacological Research* 3: 211 (2005)
4. Rubinstein and Camm, Carditoxicity of fluoroquinolones. *Journal of Antimicrobial Chemotherapy* 49: 593 (2002)
5. Enserink, Researchers question obsession with Cipro. *Science* 294: 759 (2001)
6. Krucoff, Drug of choice has a downside. *Los Angeles Times*, 29 Oct. 2001
7. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5047a2.htm>
8. Rubinstein and Camm (2002) and *Houston Chronicle*, 1 Nov. 2001
9. <http://www.fbodaily.com/>
10. Mandell and Tillotson, Safety of fluoroquinolones: An update. *Canadian Journal of Infectious Diseases* 13: 54 (2002)
11. <http://www.medicationsense.com/>
12. See references in <http://www.lef.org/magazine/>

13. Both studies referenced by Delafuente, Understanding and preventing drug interactions in elderly patients. *Clinical Reviews in Oncology/Hematology* 48: 133 (2003)

14. Jörgensen et al, Prescription drug use, diagnoses, and healthcare utilization among the elderly. *Annals of Pharmacotherapy* 35: 1004 (2001)

15. Deafuente (2003)

16. Hanlon et al., Suboptimal prescribing in older inpatients and outpatients. *Journal of the American Geriatrics Society* 49: 200209 (2001)

17. Projan, Why is big Pharma getting out of antibacterial drug discovery? *Current Opinion in Microbiology* 6: 427 (2003)