STATEMENT

In the medical world, the FDA and drug companies define a side effect as *rare* if it occurs less often than in one in a hundred patients. But I have always believed that some side effects are so terrible that even if they occur in only one in a thousand, or ten thousand, or even as little as one in one-hundred thousand people, it cannot be dismissed and ignored as rare.

The drug companies would have you believe that side effects with the antibiotics Cipro, Levaquin, and their four fluoroquinolone cousins are rare. They are not, and sometimes they are severe and long lasting, or as the FDA finally admits, "permanent." This book contains many such cases, many described by the patients themselves that prove the FDA's point about the severity of many of the reactions to this group of drugs.

The FDA itself has received nearly 50,000 unique case reports in which the only likely culprit is one of these drugs. Yet 50,000 case reports received over fifteen years time (1998-2013) are not many in comparison to the 30,000,000,000 of these antibiotics prescribed each year to patients in America. So the FDA's numbers are only the tip of a mammoth iceberg. The FDA's own studies have proven it identifies only 5 percent or fewer of actual reactions that occur with prescription drugs. Thus, once again the FDA has underestimated the likely actual count of perhaps as many as 500,000 severe reactions to fluoroquinolones, or perhaps far more.

And because most doctors don't read the FDA's dire warnings about the risks, most doctors have little knowledge about these fluoroquinolone toxicity syndrome cases and provide no support to patients who come to them desperately seeking assistance.

That is why I have written this book, and why I have labored since 2001 to offer legitimate, evidence-based ideas for the prevention (highly possible) and treatment (sometimes possible perhaps) of this horrible catastrophe that has persistent in the U.S. for twenty-eight years and even longer in other countries.

Jay S. Cohen M.D.

DEDICATION

This book is dedicated to the hundreds of thousands of people seriously injured, sometimes for years, by Cipro, Levaquin, and four other fluoroquinolone antibiotics. By the FDA's count, the proven number of serious reactions is now around 50,000. According to Rxisk.com, the number is 79,000, but the more likely toll of fluoroquinolone toxicity syndrome cases (FTS) may be 500,000 to 1 million. I wrote this book to alert America and the world about this catastrophe, explain how we can prevent it, and assist others who suffer from the unnecessary ravages of FTS.

Jay S. Cohen M.D.

Foreword

Open Letter to the Senate Committee on Health, Education & Labor Regarding Fluoroquinolone Toxicity Syndrome

May 9, 2014

Dear Senators:

Serious adverse reactions to fluoroquinolone antibiotics (FQs) have been reported in medical journals and to the FDA since the 1980s. Although the FDA has increased the warnings on these drugs (Levaquin, Cipro, Avelox, Floxin, Norflox, Factive), my analysis of FDA data shows that reports continue to climb in number. As of February 2014, approximately 45,000 individual cases of fluoroquinolone toxicity have been reported to the FDA. And, as studies have proven, the FDA receives reports of only 1–5 percent of the actual numbers of adverse reactions that occur.

I have been following these medications for sixteen years and have evaluated in person or by telephone consultation more than 500 people injured by FQs. In 2001, I published an article, "Peripheral Neuropathy with Fluoroquinolone Antibiotics," in the peer-reviewed journal *Annals of Pharmacotherapy*. This article described forty-five cases of severe neurological symptoms such as tingling, numbness, burning pain, twitching, and/or weakness. Moreover, 93 percent of the subjects manifested symptoms in injuries to other vital systems: agitation, impaired cognitive function, intractable insomnia, hallucinations, psychosis, acute manic episodes, joint or muscle pain, or tendon rupture. In many cases, toxicities also involved the cardiovascular and gastrointestinal systems, skin, and sight or hearing. Overall, 90 percent of my subjects experienced toxicity to multiple body systems, hence I have coined the term fluoroquinolone toxicity syndrome.

Of greatest concern, the majority of my cases had lasted more than one to two years and were ongoing. These severe, long-term reactions occurred in a generally young and healthy population. The average patient age was forty-two, many of them athletes. In fact, top athletic organizations now warn athletes to avoid treatment with FQs.

Because of the impaired healing seen in severe FTS patients, we have long suspected genetic injury from FQs. These drugs were designed to injure the genetic structure of bacteria and thereby kill them, and they are very efficient in doing so. However, testing was never performed to ensure that FQs did not also injure human DNA. A recent study using high performance liquid chromatography with mass spectrometrography has demonstrated that FQs do indeed injure human DNA. Further study on this must now be undertaken.

There is no doubt that fluoroquinolones are important medications that help many thousands of people each year, but the indiscriminate prescribing of these highly potent "big gun" antibiotics for everyday minor infections such as sinusitis, sore throats, or bladder infections is unnecessary and medically unsafe. Medical authorities have repeatedly denounced the overuse of FQs. In my forty-plus years in pharmacovigilance, FQs surpass Vioxx and thalidomide, the greatest culprits of medication injuries in U.S. history, in their degree of permanent harm done.

FDA warnings currently describe many of the adverse effects of FQs. Recently the FDA has finally acknowledged that FQs can cause permanent injury. However, FDA warnings do not adequately describe FTS syndrome, so doctors do not consider FTS as a possible cause for patients' symptoms and instead waste valuable time and expense testing for rare neurologic or rheumatologic disorders, meanwhile discounting or dismissing patients who are suffering severely from FTS. The warnings must be improved and the word about FTS must be spread nationally and worldwide. It can start with you. If you still doubt what I have written here, please examine the extensive literature on FQs' toxicity, beginning with the articles cited below.

Jay S. Cohen, M.D. was an adjunct associate faculty professor at the University of California, San Diego, for three decades and has published more than twenty articles on drug safety in leading medical journals. Based on his articles and books, the FDA invited Dr. Cohen as keynote speaker at an FDA conference on medical safety in 2004. He has also debated FDA officials on drug safety strategies at conferences for the American Society for Clinical Pharmacology and Therapeutics and at the Drug Industry Association. His work has been highlighted in major newspapers and magazines including the New York Times, Newsweek*, and others. During the anthrax scare of 2001, after publication of Dr. Cohen's article on fluoroquinolone risks and his appearance on National Public Radio, within days CDC withdrew its recommendation of Cipro for treating anthrax exposure in favor of other safer and less expensive antibiotics such as doxycycline.*

—Jay S. Cohen, M.D.
MedicationSense.com

Preface: What This Book Is About

Letter sent to Dr. Cohen in January 2015

Subject: My Personal Experience Using Levaquin Antibiotic

Dear Dr Cohen:

I write to you today to say how much I appreciate your research and your articles published on the adverse effects associated with fluoroquinolones. I will attempt to keep my message concise. In January of 2014 I was prescribed Levaquin 500 mg. (once daily for 10 days) for a sinus infection (which did not respond to the Augmentin antibiotic that was prescribed in December, 2013). In mid-January, I took 8 out of the 10 Levaquin tablets that were prescribed. I was feeling that the muscle and joint pains in and around my knees and legs might probably be due to the Levaquin. While taking Levaquin, I continued to exercise regularly using equipment like my treadmill, elliptical and gentle yoga classes 2–3 times per week.

After the discontinuation of Levaquin, my health continued to progressively decline. My muscle and joint pains increased in severity and I noticed a host of other symptoms. My extremities seemed to be cold much of the time and I became overly sensitive to wearing socks or having anything touch my feet including a blanket. My fatigue was so prominent I spent days in bed or on the sofa. I went as long as 6 days without showering because my hands and elbows hurt so much, even with minor tasks. For several months my heart would race on and off, feeling as though I just ran 5k at full speed. It was scary. I had numerous other side effects too numerous to mention.

I saw my physician of 20 years at the University Medical Center. I continued to report my symptoms to my doctor, who initially did not believe I was suffering from a reaction to Levaquin, as she told me it was "very rare." I continued to be in pain daily, at times being almost unbearable to live with. I contemplated "throwing in the towel" more than once. Were it not for having three children who still needed their mother and a husband who did not deserve to be abandoned, I tolerated what seemed to be a "terrible nightmare of pain and body dysfunction." Day in and day out, I just existed and used Advil or aspirin combined with ice packs to numb my pain. I noticed that the NSAIDs may have caused my heart rate to rise. I tried to shower every 2 days, which was hard because of my wrists and elbows being so affected.
I tried to contribute by loading the dishwasher and sometimes do a load of laundry. Often times, I didn't make meals or do much of anything around our home, including driving, grocery shopping, not attending school functions, and going to my son and daughter's games, etc.

I am now almost at the 12 month mark since taking Levaquin. Although my symptoms have improved some, I continue to battle with pain and body dysfunction and have spent numerous appointments at different doctors and specialists (rheumatologist, orthopedics, gastroenterologist, naturopath, and physical therapist) ruling out other causes such as arthritis and autoimmune diseases. Some days are reminiscent of the worst pain I felt between February through May, 2014. Since July 2014, I began having some nausea and pains in my right side and back that progressed to stomach discomfort, reflux, bloating, and continuous belching. After seeing a GI specialist and having numerous tests (upper GI, endoscopy, ultrasound, colonoscopy, CT scan) nothing has surfaced to explain this sudden problem I never had before. Keep in mind, that I eat very healthy, eating salads and fruits and vegetables daily, do veggie juicing, and do not drink soda and rarely drink alcohol. I now plan to follow up with a neurologist who may better be able to help me explain my strange pain in my ankles, tops of my feet, and wrists, knees, elbows, and perhaps why I am experiencing sudden and acute GI problems with no known cause. I continue to have problems doing everyday things like washing my hair.

Dr. Cohen, I just thought I would let you know about my experience. If I can ever be of use in any future or current research on the effect of Levaquin and other fluoroquinolones, I would be happy to submit my records, experience, and information regarding my adverse reaction to the antibiotic Levaquin. Thank you for your time and attention to my letter.

NOTE: The writer of this letter and I never made contact. I do not know about the further course with her terrible toxic reaction to Levaquin. I have now received more than 500 letters or telephone consultations since 1999 from people who’ve suffered side effects of fluoroquinolones.

When you pause to consider that at least 50,00 people, or perhaps ten times more, have or continue to experience symptoms like these, it truly represents a medical catastrophe. Jay S. Cohen M.D.

CHAPTER ONE

EARLY WARNINGS OF SEVERE TOXICITY

Medical toxin: "Medicinal substance that causes tissue injury, debilitation, or death."

First came 9/11, then in October 2001 the anthrax scare, and with it came the first public awareness of the antibiotic Cipro. When the U.S. Centers for Disease Control recommended Cipro for anthrax exposure, I was concerned.

I had spent two years collecting data, writing and rewriting, and then shepherding my article, "Peripheral Neuropathy Associated with Fluoroquinolone Antibiotics," toward publication.[1] It wasn't easy. Several of the peer reviewers didn't like what I was saying in the article and tried to block its approval. Fortunately, the publisher stood firm and set the date for publication for December 2001. With the anthrax scare in October, the publisher and I felt the information was urgently needed when Cipro (ciprofloxacin) became a household name and people began taking or hoarding it without medical basis. Cipro's downsides weren't widely known then, even among doctors. Yet, many of the forty-five subjects of my survey were injured or disabled years after taking the drug, suffering from the neurological, musculoskeletal, psychiatric, and cardiac reactions Cipro could cause.

Injury from a fluoroquinolone (FQ) antibiotic was first reported in 1972. It involved the original, first-generation FQ, nalidixic acid. The report by Bailey, Natale, and Linton read,

> A 22 year old woman with a series of multiple bladder infections and a kidney infection experienced visual distortions, intense brightness from lights, visual hallucinations and became delirious soon after being placed on nalidixic acid. The symptoms disappeared quickly after the medication was stopped. Later that year, the kidney infection returned and one day after again receiving nalidixic acid, the woman developed severe joint pain, swelling, redness and substantial pain. These symptoms began in the feet and ankles, then spread to her knees, hands, wrists, elbows and right shoulder. Soon after, her prior visual disturbances returned. Other symptoms included nightmares, weakness, sudden crying and loss of appetite. Pain limited her ability to move, and many joints were swollen and hot. Finally, the nalidixic acid was discontinued, and over the next 17 days she recovered.[2]

Note that this person's adverse reaction was not limited to one area or system of her body. It wasn't a typical adverse reaction like nausea, dizziness, headache, or constipation. This reaction exhibited neurological, musculoskeletal, psychiatric, and visual aspects. Is was severe, painful, long lasting, and temporarily disabling.

At the time his letter was published, Dr. Bailey contacted the manufacturer and learned it had received "about a dozen reports of side effects relevant to the joints." Thus, as far back as 1972, serious adverse effects were seen and reported.

Eleven years later, in 1983, Bailey published another incident of joint pain from an FQ.[3] Then, in 1988, McEwan and Davey published a case report of bilateral Achilles tendinitis and also noted that by late 1987, fourteen other cases of Cipro-related musculoskeletal adverse events had been reported to U.K. officials including one tendon rupture. They also noted that in France, sixty-three incidents of joint, muscle, and/or tendon pain had been reported.[4] Also in 1987, Cipro, the first modern FQ, was approved in the United States with no major warnings of its potential dangers.

The Fluoroquinolones

FQs are popular antibiotics because they can be used for many types of infections involving the lungs, brain, bone, joints, gastrointestinal tract, bladder, or prostate. The FQ group gains its name from the fluorine atom in its chemical structure. Antibiotics such as penicillin, erythromycin, and tetracycline are called bacteriostatic because they prevent bacteria from multiplying until they die. In contrast FQs are bactericidal, meaning they kill bacteria outright. They accomplish this by attaching to bacterial DNA and preventing its duplication, killing bacteria more quickly than the bacteriostatic antibiotics. Because they are so powerful, FQs are considered "big guns" among antibiotics available today.

Initially introduced in the 1980s, FQs are broad spectrum, meaning they are effective against a wide range of bacteria. They became very popular very quickly, tripling in prescriptions filled between 1995 and 2002 and further increasing in popularity since then. In recent years, FQs have been the most prescribed group of antibiotics in America.

Currently Available Fluoroquinolones

Avelox (moxifloxacin) approved 1999
Cipro (ciprofloxacin) 1987
Factive (gemifloxacin) 2003
Floxin (ofloxacin) 1990
Levaquin (levofloxacin) 1996
Norflox (norfloxacin) 1986

According to the FDA, approximately 23 million office patients received prescriptions for FQs in 2011. Additional millions received FQs in hospitals. Nearly 70 percent of FQ prescriptions are for ciprofloxacin, the generic form of Cipro. Levaquin and its generic, levofloxacin, accounted for about 22 percent, and moxifloxacin (Avelox) for 7 percent of FQ

sales. Norfloxacin, ofloxacin, and gemifloxacin account for less than 1 percent of FQ prescriptions.

The Press Release

This book is not about bad drugs that must be banned. It is about good drugs that have saved hundreds of thousands of people but also have severely injured tens of thousands of others, sometimes permanently. Doctors remain poorly informed, dismissing people with legitimate injuries from FQs. Doctors also continue to prescribe contraindicated drugs such as prednisone that worsen the toll. Currently there are no scientifically proven treatments for what I call fluoroquinolone toxicity syndrome (FTS). My goal in writing *How We Can Halt The Cipro and Levaquin Catastrophe* is to shed much-needed light on a terrible medical problem that persists today and continues to worsen, and to encourage efforts toward finding effective solutions.

Although I had been working quietly on my own for decades trying to reduce the epidemic of side effects with medications (more than 100,000 deaths and 2,000,000 hospitalizations from medication side effects annually in the U.S.), I only heard about the FQ tragedy when contacted by Beth W., an FQ casualty, in 1999 (and she remains a FQ casualty in 2015). She learned about me from the articles I'd published in medical journals on how to prevent medication side effects.[5–22] I had also just finished the highly praised but ill-fated *Over Dose: The Case Against the Drug Companies* (Putnam/Tarcher, 2001), which arrived at bookstores days after September 11, 2001. With the nation traumatized by the 9/11 attack, there was little interest in a book about reforming the U.S. Food and Drug Administration and drug industry.[23]

The press release accompanying my article, "Peripheral Neuropathy Associated with Fluoroquinolone Antibiotics," appeared on October 22, 2001:

> Adverse effects associated with the use of ciprofloxacin (Cipro) and other fluoroquinolone antibiotics are not always benign. Not infrequently, they can be severe and permanently disabling, and they may occur following just one or a few doses, according to a study posted on The Annals of Pharmacotherapy Web site today.[24]

The article described forty-five cases of FQ toxicity involving the peripheral nervous system such as tingling, numbness, weakness, burning pain, twitching, or spasms. In addition, 93 percent of the subjects sustained adverse effects involving other systems: 78 percent experienced central nervous system (CNS) symptoms such as dizziness, agitation, impaired cognitive function, intractable insomnia, or hallucinations; and 73 percent reported musculoskeletal symptoms such as joint or muscle pain or tendon rupture. In many cases, toxicities also involved the cardiovascular and gastrointestinal systems, skin, and sight or hearing. The great majority of the cases were severe, lasting three months in 71 percent and exceeding one year in 58 percent of cases. The average subject age in my survey was forty-two (ages ranged from eleven to sixty-

eight). In 62 percent of the cases, subjects had no other medical disorder except an infection (sinusitis, prostatitis, or urinary infection) that led to FQ treatment. In other words, these people were mostly young, healthy individuals—until FQ therapy.

The media jumped on my article and wrote about it in newspapers and magazines. My telephone rang a lot. I spent a few minutes on NPR's Morning Edition with Bob Edwards. Within days, the CDC announced it was dropping Cipro as the favored antibiotic for anthrax exposure and now recommended much safer antibiotics such as doxycycline.

Anthrax or Cipro?

I wish I could say that was the end of it, but it was just the beginning. Six months later the *Washington Post* carried a story, "Anthrax Patients' Ailments Linger."[25] The story described symptoms such as fatigue, exhaustion, joint pain, and memory problems lingering in some postal workers. The article pointed its finger at anthrax exposure, but I suspected many of the cases were from Cipro toxicity.

Five days later, United Press International posted "Anthrax Ills Mirror Cipro Side Effects" at its website:[26]

> Doctors treating several survivors of last year's anthrax attacks describe a continuing set of symptoms that are similar to reported side effects of the main drug used to treat them. Side effects include joint pain, fatigue, confusion, difficulty concentrating, and memory loss. "They all fit, right down the line," said Dr. Jay S. Cohen. He said Cipro and other fluoroquinolone antibiotics are well documented as sometimes causing psychiatric and neurological side effects, as well as musculoskeletal problems. Doctors following these cases do not know whether the problems suffered by the handful of anthrax survivors are related to Cipro or from anthrax. "It is an interesting possibility," said Dr. Mark Galbraith, an infectious disease specialist in Virginia who is treating one survivor. He discontinued Cipro for his 59 year old patient after two weeks because of a rash and painful joints. Months later, joint pain and difficulty persist. The CDC acknowledged that a percentage of patients did not continue their Cipro because of side effects including joint pain, dizziness, nausea, fatigue, or diarrhea. "A lot of people did stop taking it," said American Postal Workers Union spokeswoman Sally Daridow. The organization has asked Congress to investigate how Cipro and other antibiotics might affect workers long-term.

Congress never did, so in 2004 I sent a letter to Congressman Rush Holt of New Jersey, asking for an investigation.[27] Nothing materialized.

Back to late 2001. In December, the *American Spectator* published the following in *Ben Stein's Diary*:

> We [Stein and another person] talked for a long time about the anthrax threat in D.C. and then about the medicine of choice, Cipro, that's being prescribed for it. Just by fate, I had been given Cipro a few weeks before and had suffered simply horrible, dreadful, unbelievably bad psychological side effects; dread, suicidal thinking, panic. In fact, I had the first real panic attacks I had endured since I stopped taking benzodiazepines about twelve years before. I had been mystified about what was causing them until I looked up Cipro in the paperback edition of the *Physicians' Desk Reference*, only to find that high among the list of side effects are "abnormal fear" and "dread." My doctor pooh-poohed these effects, but when I stopped taking the Cipro, the effects disappeared pronto.[28]

The suddenness of Stein's reaction and its severity are typical of many accounts of FQ toxicity. In my study, 58 percent of patients developed reactions within three days of starting an FQ. Also, 70 percent had symptoms like Stein's involving the central nervous system such as severe agitation, panic, impaired thinking, hallucinations, suicidal ideation, insomnia, "brain fog." Typically, Stein's doctor dismissed the reaction, although there were no other credible explanations for his symptoms. Stein's toxic reaction cleared quickly. He was one of the lucky ones.

Stein's doctor's ignorance wasn't anything unusual either. At the same time, the health editor of a national magazine wrote that a thirty-day course of ciprofloxacin "wouldn't cause a healthy adult much harm."[29]

Thousands Seeking Help

After publishing "Peripheral Neuropathy Associated with Fluoroquinolone Antibiotics," I began to receive letters and emails. This one arrived a few months later in early 2002.

> Dear Dr. Cohen,
> I am a 30 year old female with no medical problem before. I was given Cipro for three days for a suspected urinary tract infection in March 2002, though my culture came back clean later. I have been having muscle/tendon/joint pain since. I was so devastated last week while reading e-mails from an adverse drug reactions forum, since most of them are saying that the symptoms would go on and on for years. I almost cried on the way home from work last week as I was driving by the beach and worrying I might never be able to run on the beach again. What's troublesome about this whole situation is the lack of awareness of the doctor about this problem. Like some cases in your paper, my doctor too dismissed the idea that my symptoms have anything to do with Cipro and no one warned me of anything before I took it. I do wish one day down the road, people could at least get a warning from their doctors before they took the medicine. Sincerely, L.H.

She was a bioengineer at a local biotech company. I felt badly because I had little help to offer her. Today I could offer many suggestions (see Chapters 8-15) but still there is no well proven remedy. “At least you listen,” she said to me. “At least you believe me. You understand the harm these drugs can do.”

From 2001 up to the present, I have continued to consult with people from the U.S. and Canada who’ve been “floxed,” the term used by people badly injured by FQs, although we rightly could use the word poisoned. Over the last fifteen years, I have spoken with approximately 500 such people who’ve been floxed.

“Only 400 cases—what’s the big fuss, Cohen?” you might ask. The number today is about 50,000 cases reported to the FDA, and the number is likely ten or twenty times higher. Rxisk.org has recorded a count of 79,000, although I believe the true count is much higher. This is the definition of an epidemic, and it is wholly man-made.

In the beginning of 2014, I spoke with Chris. When his sinus headache did not improve with the Z-Pack (azithromycin), the doctor prescribed the FQ Avelox and also prednisone, a steroid. Prednisone is commonly prescribed with an antibiotic for sinus infections because it can shrink swollen sinus membranes. However, steroids are absolutely contraindicated for use with an FQ. Chris did not take the prednisone because within three hours of his first Avelox pill, he experienced intense tingling in his arms and legs, pain in his back and sternum, muscle weakness, and trouble walking. He went to urgent care and was inaccurately diagnosed with an allergic reaction and given prednisone again, which he then took. His symptoms intensified: “I felt I was going to die. I had trouble breathing. My heart was pounding. I could barely walk, off balance, severe pain. Everything felt like it was going crazy in my body.”

Chris’s primary care doctor recognized it was a reaction to Avelox and referred him to a neurologist and rheumatologist. He had scores of blood tests, an MRI, and a CAT scan. All were normal, but clearly he wasn’t. None of the doctors had any suggestions for treatment.

From his reaction in September 2013 to our conversation five months later, some of Chris’s symptoms had abated, but he continued to have others. Chris explained, “I still have joint pain, leg swelling, popping sensations in my joints, and tingling and electrical pain in my arms and legs. I cannot exercise and continue to have trouble sleeping.”

This time around I was able to offer several suggestions, and at that moment I decided it was time for me to write this book. I hope you find it useful.

Next Week: CHAPTER TWO: 45,000 CRIES FOR HELP