Chapter 4

Fluoroquinolone Toxicity to the Central
and Peripheral Nervous Systems

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FQs can injure the nervous system. The most common injuries involve the peripheral nervous system, the aspect of the nervous system that comprises sensory and motor nerves to the body from the neck down.

The initial reports of neurological side effects from FQs came from France in 1982, then Sweden in 1988, and Britain in 1992.1-3 The wakeup call about the seriousness of peripheral nerve damage from FQs came from the Swedish Adverse Drug Reactions Advisory Committee in 1996.4 The report described thirty-seven cases of peripheral nerve injuries (neuropathies) occurring between 1987 and 1993. Symptoms included abnormal sensations such as tingling or burning (paresthesias), numbness, weakness, loss of sensation, or pain affecting localized or broad areas of the body. These injuries occurred as early as one hour after taking an FQ to as long as four months later. Most patients recovered after two weeks, but symptoms persisted much longer in others.

In 2001, I reported forty-five cases of serious peripheral neuropathies with FQs.5 In my survey, 80 percent of the people defined their reactions as severe, with 71 percent lasting more than three months and 58 percent more than a year. The majority of people were young with an average age of forty-two. Prior to FQ treatment, the majority had no previous medical problems.

These are startling numbers in a generally healthy and young population, and the severity and duration of the injuries confirmed that these were not typical side effects. They were toxic
reactions, direct injuries to human tissue caused by FQs. In many of these cases, the injuries went beyond the person’s nervous system. Here are some examples.

Female age thirty-nine, given Cipro 500 mg twice daily for ten days. Peripheral neuropathies began after four days but was not recognized by her doctors, so the treatment continued, then was changed to Levaquin for another fourteen days. Symptoms: numbness, increased skin sensitivity, pain on touch, electrical sensations, acute burning sensation all over body, tremors, twitching, disorientation, agitation, racing heart, stomach pain, rashes, visual impairment, temperature intolerance. Duration: several years. Severity: severe and disabling. Nerve conduction studies abnormal. No prior medical problems. Subsequent treatment: steroids worsened symptoms, other medications unhelpful.

Male age thirty-four, 190 lbs., received Levaquin 500 mg/day for three weeks for possible prostatitis. Symptoms: mild joint pain and visual problems, resolved quickly. Later Levaquin treatment for sinusitis with other symptoms: twitching; numbness; muscle weakness; reduced coordination; shaking; extreme sensitivity to heat and cold; pain in joints of hands, feet, neck, and jaw; heart palpitations; severe insomnia and fatigue; extreme nervousness; paranoia; occasional suicidal thoughts; blurred vision in right eye. After four months, some side effects improved but some persisted including palpitations, nervousness, joint pain, neck and jaw pain, visual problems. Treatment: Valium reduced twitching and partially reduced nervousness and palpitations.

Female age thirty-one, 150 lbs., treated with Levaquin 500 mg/day for seven days for sinusitis. Symptoms: tingling in both arms initially, then in cheek, then left side of body, which then disappeared. Soon began having burning, numbness, pins/needles, twitching, hypersensitivity, cold intolerance, tendon problems in elbows and wrists with constant pain. Degree: severe: “The pain was unbelievable at times.” Onset: two–three days but “the doctors did not believe I was having an adverse reaction.” Ability to work “markedly reduced, had to give up exercise.” Minimal improvement over six months, then slight improvement. No previous medical problems.

Fortunately, symptoms of FQ-induced neuropathies are often mild and disappear within weeks or months. On the other hand, severe reactions are not rare. From the third quarter of 1997 through the third quarter of 2012, a span of fifteen years, the FDA received 12,053 reported
cases of neurological adverse effects linked to FQs. Our search included only cases in which FQs were the probable cause. Of these cases, 1,585 were defined as disabling. Remember, only 1–5 percent of adverse reactions get reported to the FDA, so the actual numbers may possibly be hundreds of thousands of cases of peripheral neuropathies from FQs.

A Toxic Combination

There are many drugs that can cause peripheral neuropathies. One of them is Flagyl (metronidazole), which is often prescribed for internal infections of the stomach or intestines. Flagyl is often combined with a FQ for treating diverticulitis, a dangerous and potentially lethal infection of the lower bowel. This combination sometimes works well. However, both drugs are well known to cause peripheral neuropathies, and their combined use may significantly heighten this risk. I have received three reports of serious neuropathies from people prescribed Flagyl and a FQ at the same time. Sometimes, combination therapy like this is necessary, but the risk should be acknowledged and the combination of Flagyl and a FQ should be absolutely avoided when possible.

FDA Actions

Because of the increasing number of reports of neurological injuries with FQs, the FDA contacted experts, including me, in 2004. The FDA officer asked me, “Do you think the cases in your study and other reports are credible?”

“Yes,” I replied, “I think the problem is real and serious.”

I assume the FDA official was told the same thing by other doctors, because soon thereafter the FDA released an enhanced warning. Nevertheless, the number of reports continued to accelerate. Finally in 2013, after nine more years, the FDA released a new warning about peripheral neuropathies caused by FQs.6,7
If a patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped, and the patient should be switched to another, non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk. Peripheral neuropathy is a nerve disorder occurring in the arms or legs. Symptoms include pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature, or the sense of body position. It can occur at any time during treatment with fluoroquinolones and can last for months to years after the drug is stopped or may be permanent. Patients using fluoroquinolones who develop any symptoms of peripheral neuropathy should tell their health care professionals right away.

And then the FDA finally admitted:

If you are taking a fluoroquinolone drug, know that it may cause symptoms in the arms or legs such as pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature. These symptoms can occur early in treatment and may be permanent.

I can imagine the heated debate at the FDA meeting with medical experts and drug company representatives about whether to include the word permanent in this FDA warning for FQs. A word like this can have powerful consequences in legal proceedings about responsibility for FTS events. This one word might empower tens of thousands of people severely injured by FQs to finally earn recognition and, hopefully, fair compensation.

Central Nervous System Toxicities from Fluoroquinolones

Current FDA warnings of central nervous system reactions to FQs include the following:

Convulsions, toxic psychoses, increased intracranial pressure, CNS stimulation that may lead to tremors, restlessness, dizziness, lightheadedness, anxiety, phobia, depersonalization, drowsiness, weakness, unsteady walking, confusion, malaise, anorexia, increased intracranial pressure, seizures, hallucinations, irritability, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. 8
HOW WE CAN HALT THE CIPRO AND LEVAQUIN CATASTROPHE: THE GREATEST MEDICATION DISASTER IN U.S. HISTORY

These reactions may occur as early as the first dose. Think of that! The first dose!

Seizures are a particular concern. Seizures have been linked with Cipro, Levaquin, and other FQs as far back as the 1980s.\textsuperscript{9–11} Authorities continue to deny risks with FQ eye drops or ear drops, but two people have told me of their serious reactions with these preparations. Seems to me, if one dose of FQ can cause major, long-lasting harm, why not an eye drop? Yes, the dose is lower than with pills, but in 2003 a medical journal from Australia reported a case of seizures triggered by Cipro ear drops.\textsuperscript{12}

The FDA cautions doctors about using FQs in people with a history of seizures or who are taking medications that may predispose them to seizures. FQs lower the seizure threshold in the brain, thereby increasing the risk of seizures. If taken with other drugs that also can lower the seizure threshold, the risk of a seizure with FQs doubles. Anti-inflammatory medications (NSAIDs) such as ibuprofen or naproxen can increase the seizure risk. Thus the use of FQs at the same time as NSAIDs is contraindicated.

To be clear, seizures with FQs can occur in people who do not have these other risk factors, but it is rare. If FQs were needed for a dangerous, life-threatening infection, and there was no alternative antibiotic, the doctor might consider putting the patient on an anti-seizure medication.

A “Mild” Case of Peripheral Neuropathy from Cipro

I spoke to Linda in mid-March 2014, and she consented to my using her abridged story. My comments are enclosed in the brackets.

I am a thirty-seven-year-old professional woman with two small children who was very healthy until January 2014. I previously did cardio five times a week, weight training three times a week, and ate a healthy diet. On December 27, 2013, I went to Urgent Care for a possible urinary infection and was prescribed Cipro 500 mg twice daily for six days [recommended dosage by the manufacturer is 250 mg twice daily—Linda’s dosage was double]. Below is a timeline of my symptoms and doctor visits:
12/31/2013 Began Cipro prescription for six days, no side effects.
1/5/14 Finished Cipro prescription, still no side effects.
1/17/14 First onset: tingling and numbness in both feet.
1/20 Tingling and numbness now in hands and feet.
1/23 Tingling and numbness spread up my calves and elbows.
1/24 Electrical shocks throughout my body. Vertical shocks down my arm or leg. My primary doctor was on vacation so I met with another physician who diagnosed me with hyperventilation and offered a prescription for Xanax. I declined.
1/27 Tingling and numbness everywhere; deep muscle pain in right arm. Blood tests taken at ER were normal. Referred to neurologist who checked my reflexes and stated that I didn’t have MS. He ordered an MRI of my spine and put me on magnesium oxide and methocarbamol [a muscle relaxant].
1/28–2/11 Continued muscle pains throughout body. One day it would be in my right arm intensely for three hours and disappear, then in left calf, then lower back. Each day it was in a different area and would come and go for a few hours, then a few days with no symptoms.
2/1 Electrical shocks became electrical bursts, feeling like being pinched or stung. Experiencing these thirty to fifty times a day.
2/3 Severe lower back pain.
2/11 Intense pain in right leg, extending from foot to hip and buttocks. While driving, my foot was too weak to hold the brake pedal down, so I had to use both feet to brake [motor nerve neuropathy causing weakness].
2/12 Muscle pain continuing in right leg from knee to my hip and buttocks. Increased right knee and hip pain with walking. Lower back pain intermittently. Muscle pain has settled in my right leg. Electrical bursts, tingling, and numbness about 80 percent of each day.
2/13 I stopped the muscle relaxers and magnesium oxide because of no benefit [JSC: magnesium was a good idea, but magnesium oxide is poorly absorbed].
2/17 Blood tests for autoimmune disorders normal.
2/20 Saw neurologist: MRIs normal. Neurologist gave me a diagnosis of paresthesia [abnormal nerve symptoms] from no known cause. I didn’t understand why I had paresthesias when I was completely healthy before this. I started doing my own research. It was then that I learned about Cipro and realized that my symptoms were similar to the FDA warnings. Note, I told all of my doctors that I’d had a possible urinary infection and received Cipro at Urgent Care.
3/6 I asked my primary doctor about Cipro. Seemed like she didn’t want to talk about it, so she referred me to these doctors: orthopedist for my hip, rheumatology, endocrinology, another neurologist, cardiology, urologist, and allergist!

3/10 I met with a second neurologist. He basically told me to get on with my life. When I mentioned Cipro to him, his words were that I needed to stop reading. He ordered an EMG that I will have next week. He indicated that if the EMG came back normal and showed that I didn’t have a peripheral neuropathy, then I had to drop the idea of Cipro. I felt very frustrated and angry. [JSC: An EMG is a nerve test that measures major nerve trunks but often not the small nerves of the skin involved in an FQ-caused neuropathy. Either the neurologist was uninformed or ordered the test to shut Linda up.]

3/11 I met with a naturopathic doctor. I told her about my symptoms and then mentioned I had taken Cipro. She was the first doctor who, when I said “Cipro,” said there is a connection with Cipro and nerve problems. [JSC: Any doctor can easily see the connection in any official FDA information about FQs, where the warnings are apparent and often in black-box warnings.]

Linda began treatment with the naturopath, receiving intravenous glutathione, which helps some people but not others injured by FQs [JSC: Newer ideas in Chapter 11]. Linda’s story is typical of the neurological reactions people can encounter with FQs. The failure of Linda’s own doctors to identify her reaction and their absurd refusal to consider the possibility of FTS is commonplace. Is it ignorance, fear of lawsuits, or distrust of their own patients’ intelligence? Whatever it is, it can be pernicious.

Linda asked me, “Is Cipro a possibility for the symptoms I am experiencing?”

I answered, “Almost certainly.”

She asked, “Is there a test that can be done to confirm that?”

“Unfortunately not.”

She asked, “What are the chances of recovering from this? Are there any treatments that might help me?”

I answer questions like these much better than I used to. Because of my experience and increased knowledge, I can comfortably say to people like Linda, “Based on the details of your case, I think your chances are fairly good even though after three and a half months you still have considerable discomfort, substantial neurological sensory symptoms, and some muscle
weakness. On the good side, your symptoms have settled into specific areas, involving no new areas recently. Thus, the toxic reaction seems to have plateaued.” I added, “Those are good signs.” I told her about both natural and medicinal therapies that might help reduce her symptoms and expedite healing. “We even have a few studies that have shown improvement, not in people but in animals, but it is a start.”

Also of note, the doctor had prescribed for Linda 500 mg to be taken twice daily, double the dosage recommended by the manufacturer of Cipro and the FDA for mild urinary tract infections. By doubling Linda’s dose of Cipro, the doctor likely increased Linda’s risk of adverse effects. The amounts, 250 versus 500 mg, may sound tiny, but medications are some of the most powerful substances in the world. Just look at what one pill can do to some people’s systems. Slight increases in dosage may have profound effects. At the proper dose, Linda may not have experienced any side effects or at least her reaction might have been milder. The overmedication of FQs happens frequently, sometimes with dire consequences.