

What I Learned About Drug Safety Issues From My Experience With Fluoroquinolone Antibiotics

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Objectives:

1. The participant will be able to implement actions and recognize the importance of public comment of FDA policy boards and draft recommendations to help identify and avoid inappropriate pharmaceutical treatment recommendations.
2. The participant will be able to identify unique factors that contributed to safety lapses in the drug approval process and how to use this knowledge to bolster their advocacy.
3. The participant will be able to recognize and discuss what a series of undisclosed permanent side effects, misdiagnoses, and inappropriate denials looks and feels like from a patient perspective.
4. As an example, the participant will be able to discuss the seriousness and potential permanency of quinolone side effects.

Background info

- Quinolones or fluoroquinolones (terms will be used interchangeably) are synthetic antibiotics derived from quinine. They usually contain a fluorine atom.
- “floxed” is a term that came about to refer to the persistent debilitating symptoms that can appear after taking these drugs.

Common Quinolones

- Cipro (Ciprofloxacin)
- Levaquin (Levofloxacin)
- Avelox (Moxifloxacin)
- Floxin (Ofloxacin)
- Others..

Notice the word “flox” in all of them.

Also Lariam (mefloquine) is used as an antimalarial but unfortunately has devastatingly similar neuropsychiatric side effects.

15 Years Of Mystery Illness

- Panic attacks that last hours sometimes days
- Constant state of Anxiety/Terror
- Derealization/Depersonalization
- Numbness/Loss of Sensation
- Insomnia
- Heart Rhythm Abnormalities
- Loss of Language Ability
- Burning Pain & Soreness in Muscles & Joints
- Sharp Stabbing Pains in Chest
- Impairment in Thinking
- Popping & Clicking Sounds from Joints
- Extremely Stiff & Painful Joints
- Vertigo
- Suicidal Thoughts
- Constant Ringing in the Ears
- Auditory & Visual Distortions
- Depression
- Sensation Like Skin was on Fire
- Impaired Memory
- Tremors
- Muscle Twitching & Jerking
- Declining Vision: Inability to Focus Eyes, Floaters, After Images
- Altered Mental States
- Extreme Long Lasting Fatigue
- Sense of Impending Doom
- Tingling Sensations
- Sensation Like Bugs are Crawling on Me
- Slow Wound Healing
- Couldn't Recognize Own Face in Mirror
- Extreme Restlessness & Nervous Energy
- Problems Breathing
- Pallor
- Unusual Sensitivity to Light & Sound
- Akathisia
- Extreme Weight Loss
- Chemical Sensitivity, Especially to Caffeine
- More....

What was Physician Response?

- “There’s no way these antibiotics could cause the symptoms you’re describing.” ~*PCP 2000*
- “Your spine’s not broken, I can’t help you. You have a psychiatric issue with severe somatization, try Paxil.” ~*Leading Area Neurologist 2002*
- “These drugs don’t do what you’re saying has happened, and if they did occasionally, we wouldn’t know anything about it. The best we can do is schedule you for an outpatient psychiatric evaluation in 6 months.” ~*Local Tertiary Research Hospital 2012*
- “We can only see you on an emergency basis, but in order to do that you will need to threaten harm to yourself or others.” ~*Local Private Tertiary Hospital*
- It’s now 2016 and I still can’t get a medical diagnosis that makes any sense or treatment for my issues.

Why does this matter to everyone?

From FDA Pharmacovigilance Review 4/17/2013:

3.3.2 Possible Mechanism of Action: Mitochondrial Toxicity

Fluoroquinolones act by inhibiting DNA gyrase and bacterial topoisomerase IV, both of which belong to the topoisomerase type IIA subfamily. Fluoroquinolones have been found to affect mammalian topoisomerase II, especially in mitochondria (4). In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin caused a loss of mitochondrial DNA (mtDNA), resulting in a decrease of mitochondrial respiration and an arrest in cell growth (5).

Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis (6). Neurodegenerative diseases, like Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress (4,7).

On December 10, 2001, Veterans' Affairs Secretary, Anthony Principi, announced that a VA study revealed that Persian Gulf War Veterans are more than twice as likely as other Veterans to develop ALS.

It is well known that Cipro was widely distributed to soldiers as a prophylactic to counteract the possibility of Anthrax exposure in the Gulf War.

Cipro(Ciprofloxacin) Label History

- First approved by FDA In 1987
- 2008 - First black box warning for tendinopathy

WARNING:

Fluoroquinolones, including CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

- This is 20 years after original approval date

Cipro(Ciprofloxacin) Label History

- 2011 - Label change -Black Box Warning (Myesthenia Gravis)

WARNING:

Fluoroquinolones, including CIPRO[®], are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see WARNINGS).

Fluoroquinolones, including CIPRO, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid CIPRO in patients with known history of myasthenia gravis (see WARNINGS).

- 23 Years After Original Approval Date

Cipro(Ciprofloxacin) Label History

- 2016 Label change looks like this

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning.

- **Fluoroquinolones, including CIPRO[®], have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:**
 - Tendinitis and tendon rupture (5.2)
 - Peripheral neuropathy (5.3)
 - Central nervous system effects (5.4)
- **Discontinue CIPRO immediately and avoid the use of fluoroquinolones, including CIPRO, in patients who experience any of these serious adverse reactions (5.1)**
- **Fluoroquinolones, including CIPRO, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid CIPRO in patients with known history of myasthenia gravis. (5.5)**
- **Because fluoroquinolones, including CIPRO, have been associated with serious adverse reactions (5.1-5.15), reserve CIPRO for use in patients who have no alternative treatment options for the following indications:**
 - Acute exacerbation of chronic bronchitis (1.10)
 - Acute uncomplicated cystitis (1.11)
 - Acute sinusitis (1.12)

- We're now 28 years out from original approval date!

Postmarket Surveillance (Pharmacovigilance)

- These efforts seemed to have dramatically failed in the case of fluoroquinolones.
- Close to 30 years after original approval we're still "discovering" serious previously unrecognized side effects and have no tools available for quantifying the prevalence of them.

MILES' CIPRO (CIPROFLOXACIN HCl) IS FIRST QUINOLONE WITH BROAD SPECTRUM TO CLEAR FDA; FIRM BEGINNING LAUNCH WEEK OF NOV. 2 FOLLOWING OCT. 22 APPROVAL

02 Nov 1987

By The Pink Sheet

Executive Summary

Miles' Cipro (ciprofloxacin HCl) is the first member of the new quinolone class of antibacterial agents to be approved by FDA with a broad spectrum of indications. The drug was approved Oct. 22; the NDA was submitted in February 1986. Approved labeling states that Cipro is indicated for **lower respiratory, skin and skin structure, bone and joint, and urinary tract infections** caused by susceptible gram positive and gram negative organisms. Cipro is also indicated for infectious diarrhea. The only other marketed quinolone in the U.S., Merck's Noroxin (norfloxacin), has one approved indication for urinary tract infections.....

<https://pink.pharmamedtechbi.com/PS012705/MILES-CIPRO-CIPROFLOXACIN-HCl-IS-FIRST-QUINOLONE-WITH-BROAD-SPECTRUM-TO-CLEAR-FDA-FIRM-BEGINNING-LAUNCH-WEEK-OF-NOV-2-FOLLOWING-OCT-22-APPROVAL>

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

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This information is an update to the FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together issued on **May 12, 2016**

Safety Announcement ▼

[7-26-2016] The U.S. Food and Drug Administration (FDA) approved changes to the labels of fluoroquinolone antibacterial drugs for systemic use (i.e., taken by mouth or by injection). These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, we revised the *Boxed Warning*, FDA's strongest warning, to address these serious safety issues. We also added a new warning and updated other parts of the drug label, including the patient Medication Guide.

We have determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.

Patients must contact your health care professional immediately if you experience any serious side

<http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm>

“Approved labeling states that Cipro is indicated for lower respiratory, skin and skin structure, bone and joint, and urinary tract infections caused by susceptible gram positive and gram negative organisms.” 1986

Vs

“We have determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients.” 2016

What's happening now

- European Medicines Agency held an hearing this summer on quinolones. We are waiting to hear what comes out of that. The entire hearing can be viewed here:
(<https://www.youtube.com/watch?v=1vao8o5NGUc&t=174s>)
- The FDA mandated more label updates on all quinolones warning of mental health adverse events and hypoglycemia earlier this summer.
(<https://www.wric.com/news/8-investigates/fda-warns-of-mental-health-risks-linked-to-commonly-prescribed-antibiotics/1294365172>)

Toxicity isn't the only problem....

- Quinolone overuse is contributing to rising rates of antibiotic resistance including the emergence of untreatable “superbugs”
- Quinolone overuse appears to be a driver of potentially deadly *Clostridium Difficile* infections in the hospital setting.
- Agricultural use is exacerbating everything.

C. Diff.

Consumer Reports:

Surprising Remedy for Deadly Hospital Infections

(<https://www.consumerreports.org/hospitals/surprising-remedy-deadly-hospital-infections/>)

“Research published in The Lancet, a British medical journal, shows that when doctors in U.K. hospitals cut back on prescribing Cipro, Levaquin, and other so-called fluoroquinolone antibiotics, the rate of deadly infections from the bacteria known as C. diff dropped a whopping 80 percent.”

Also see:

Antibiotics, not dirty hospitals, the main cause of C. difficile epidemic

(<https://medicalxpress.com/news/2017-01-antibiotics-dirty-hospitals-main-difficile.html>)

“The study concluded that overuse of antibiotics like ciprofloxacin led to the outbreak of severe diarrhoea caused by C. difficile that hit headlines from 2006 onwards. The outbreak was stopped by substantially reducing use of ciprofloxacin and related antibiotics.”

Quinolones in Media

- **8News Investigates: Could this antibiotic permanently damage your health?** (<https://www.wric.com/news/8news-investigates-could-this-antibiotic-permanently-damage-your-health/1093631173>)
- **8News Investigates: Doctors left in dark about prescription drug dangers** (<https://www.wric.com/news/8news-investigates-doctors-left-in-dark-about-prescription-drug-dangers/1093814095>)
- **FDA, researchers looking into prescription drug after complaints, 8News investigation** (<https://www.wric.com/news/fda-researchers-looking-into-prescription-drug-after-complaints-8news-investigation/1093703956>)
- **FDA to hold hearing on benefits of 3 common antibiotics** (<http://wric.com/2015/10/02/fda-to-hold-hearing-on-benefits-of-3-common-antibiotics/>)
- **Patients share horror stories from commonly used antibiotics** (<http://wric.com/2015/11/05/patients-share-horror-stories-from-commonly-used-antibiotics-with-fda/>)
- **"Cipro had fried her liver": Virginia woman says common antibiotic killed her mother** (<https://www.wric.com/news/8-investigates/cipro-had-fried-her-liver-virginia-woman-says-common-antibiotic-killed-her-mother/1078313658>)
- **Local woman says popular antibiotic killed her husband** (<https://www.wsbtv.com/news/local/local-woman-says-popular-antibiotic-killed-her-hus/54041156>)
- **CALL 6: Mother blames antibiotic for son's death** (<https://www.theindychannel.com/news/call-6-investigators/call-6-mother-blames-antibiotic-for-sons-death>)
- **FDA issues new label changes for common antibiotics** (<https://www.wric.com/health/fda-label-changes-for-fluoroquinolones-to-include-warnings-of-serious-side-effects/1093876544>)
- **FDA Panel Seeks Tougher Antibiotic Labels** (<https://www.wsj.com/articles/fda-panel-seeks-tougher-antibiotic-labels-1446784061>)
- **FDA Panel Says Fluoroquinolones Need Stronger Warnings** (<https://www.medscape.com/viewarticle/854067>)
- **Evidence Lacking for Some Fluoroquinolone Use, FDA panel says risk-benefit data don't support current labeling** (<https://www.medpagetoday.com/InfectiousDisease/GeneralInfectiousDisease/54528>)
- **Could Taking That Antibiotic Have Serious, Long-Term Consequences?** (https://health.usnews.com/health-care/patient-advice/articles/2018-08-30/could-taking-that-antibiotic-have-serious-long-term-consequences?src=usn_fb)
- **When antibiotics turn toxic, Commonly prescribed drugs called fluoroquinolones cause rare, disabling side effects. Researchers are struggling to work out why.** (<https://www.nature.com/articles/d41586-018-03267-5>)

Academic Publications

- An Update on Fluoroquinolones: The Emergence of a Multisystem Toxicity Syndrome ([https://www.urologypracticejournal.com/article/S2352-0779\(16\)30219-9/abstract](https://www.urologypracticejournal.com/article/S2352-0779(16)30219-9/abstract))
- Treatment of the Fluoroquinolone-Associated Disability: The Pathobiochemical Implications (<https://www.hindawi.com/journals/omcl/2017/8023935/>)
- Exploration of the neurotoxicity of ciprofloxacin or gatifloxacin single dose in rat cortex and hippocampus (<https://academicjournals.org/journal/AJPP/article-full-text-pdf/4BCF40A50432>)
- Ciprofloxacin impairs mitochondrial DNA replication initiation through inhibition of Topoisomerase 2 (<https://academic.oup.com/nar/advance-article/doi/10.1093/nar/gky793/5088042>)
- Opportunities to Improve Fluoroquinolone Prescribing in the United States for Adult Ambulatory Care Visits (<https://academic.oup.com/cid/article/67/1/134/4823098?guestAccessKey=04d2ffb7-cb51-42f0-b002-df96d9bddd>)

CDC Related Antibiotic Stewardship Resources

- Thinking of a Fluoroquinolone? Think Again (<https://www.medscape.com/viewarticle/898636>)
- Antibiotic Stewardship: A Panel Discussion for Clinicians (<https://www.facebook.com/medscape/videos/10156221145019189/>)
- Be Antibiotics Aware: Smart Use, Best Care (<https://www.cdc.gov/grand-rounds/pp/2018/20180515-antibiotics-aware.html>)
- Antibiotic Prescribing and Use (<https://www.cdc.gov/antibiotic-use/index.html>)
- Antibiotic / Antimicrobial Resistance (AR / AMR) (<https://www.cdc.gov/drugresistance/intl-activities/amr-challenge.html>)

Thank you!

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