HACKING FLUOROQUINOLONES

DECIPHERING ADVERSE REACTIONS TO CIPRO, LEVAQUIN AND AVELOX

LISA BLOOMQUIST

About the Author

In 2011, at the age of 32, Lisa Bloomquist was "floxed" by ciprofloxacin, a fluoroquinolone antibiotic. She experienced many symptoms of fluoroquinolone toxicity including peripheral neuropathy, urticaria, loss of energy/stamina, loss of memory and reading comprehension, autonomic nervous system dysfunction, painful and inflamed tendons, muscle weakness, and more. Through a multi-pronged approach to healing, as well as significant trial and error, Lisa recovered from fluoroquinolone toxicity and gained back most of her physical and mental abilities after 18 months of illness. In 2013, Lisa launched www.floxiehope.com, a site to give hope for healing for those adversely affected by fluoroquinolone antibiotics (Cipro/ciprofloxacin, Levaquin/levofloxacin, Avelox/moxifloxacin, Floxin/ofloxacin, and a few others), where she told her story of healing and also published other people's stories of recovery from fluoroquinolone toxicity.

Lisa's mission is to assist people as they go through fluoroquinolone toxicity; to help them find healing and to give them the support they need in order to recover. She does this through publishing stories and blog posts on www.floxiehope.com, as well as hosting The Floxie Hope Podcast, publishing ebooks and courses, writing and researching services,

and through one-on-one coaching. All of Lisa's services are available through www.floxiehope.com.

Lisa is an advocate for fluoroquinolone toxicity awareness, as well as change in how fluoroquinolones are prescribed. She has testified before the U.S. Food and Drug Administration (FDA) twice; first to encourage them to change a ruling that is keeping victims of generic fluoroquinolones from gaining justice, and second to testify about the damage done by fluoroquinolones. She has spoken about fluoroquinolone toxicity on multiple podcasts, including Fearless Parent Radio and Bulletproof Radio with Dave Asprey. She was featured in the CBS 4 Denver news story, "Patients Reporting Serious Adverse Reactions to Popular Antibiotics."

Lisa is a guest-writer on www.collective-evolution.com and www.hormonesmatter.com and is a guest-host on Fearless Parent Radio.

Prior to getting floxed, Lisa was an avid hiker, yogi, cross-fit enthusiast, reader and world-traveler. Getting sick threw a wrench in all of those activities, but she has been adding them back into her life as she has recovered.

Lisa is a Colorado native. She has a Masters in Public Administration from the University of Colorado, Denver. She lives with her boyfriend, Mark, and their cat-child Rickie in Aurora, Colorado. She strives to make the world a better, safer, place.

Disclaimer

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Dedication

This ebook is dedicated to Chandler Marrs, Ph.D. Chandler has been an amazing friend and like-minded associate in my journey through fluoroquinolone toxicity and my mission to "hack" fluoroquinolones. Many of the concepts, and much of the content of this book, were originally published on Chandler's site, www.hormonesmatter.com. There is a wealth of information on www.hormonesmatter.com about adverse drug reactions, adverse vaccine reactions, under-recognized diseases like endometriosis, women's health issues, and, of course, hormones. Chandler is wise and thoughtful, and her ability to connect the dots between complex health issues is greatly appreciated! I encourage you all to check out www.hormonesmatter.com--it is a wonderful site! Thank you, Chandler, for all that you do!

Introduction to Fluoroquinolone Toxicity

What, exactly, *IS* fluoroquinolone toxicity? What happened in my body that made it difficult for me to walk or think? Why did I feel as if I had aged about 20 years in the 2 months after I took ciprofloxacin? Why did it feel as if a bomb had gone off in my body? Where did my endurance go? Why wasn't I able to sweat any more? Where did my reading comprehension go? What kind of drug side-effect is that--losing one's reading comprehension? That can't be a drug side-effect, can it? How can a drug, an antibiotic no less, cause a multi-symptom, chronic illness that involves every bodily system falling apart?

The things that happen to people when they go through fluoroquinolone toxicity are too bizarre to comprehend. How could a formerly active and athletic person suddenly be unable to get out of bed? How could a formerly brilliant person be unable to remember how to do basic tasks that she used to do with ease? How could an antibiotic cause all of the tendons in a person's body to weaken? How could a drug cause crippling, permanent peripheral neuropathy?

It's incomprehensible to most people.

It's incomprehensible until it happens to you, or to a loved one.

When it happens to you, or to a loved one, it becomes devastatingly real. People who have been hurt by a fluoroquinolone antibiotic (Cipro, Levaquin, Floxin, Avelox and their generic equivalents) know that a startling array of symptoms can occur when a person is hurt by a fluoroquinolone. They know that fluoroquinolone toxicity is not *just* tendon damage, or *just* peripheral neuropathy, or *just* liver damage, or *just* nerve damage. Fluoroquinolone toxicity is a multi-symptom, chronic disease that more closely resembles autoimmune diseases, neurodegenerative diseases, and mysterious diseases like fibromyalgia and ME/CFS.

The FDA acknowledged that fluoroquinolone toxicity is not a transient adverse effect in the document entitled, "The Benefits and Risks of Systemic Fluoroquinolone Antibacterial Drugs for the Treatment of Acute Bacterial Sinusitis (ABS), Acute Bacterial Exacerbation of Chronic Bronchitis in Patients Who Have Chronic Obstructive Pulmonary Disease (ABECB-COPD) , and Uncomplicated Urinary Tract Infections (uUTI)"--a 617 page report prepared in preparation for a November 5, 2015 FDA meeting to go over the benefits and risks of systemic fluoroquinolones for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients with COPD, and uncomplicated urinary tract infections. In that report, the FDA stated that:

> *"A review of the FDA Adverse Event Reporting System (FAERS) was performed to characterize a constellation of symptoms leading to disability that had been observed during FDA monitoring of fluoroquinolone safety reports. This constellation of symptoms will be referred to in this review as 'fluoroquinolone-associated disability' (FQAD). While most of the individual AEs that exist*

within FQAD are currently described in fluoroquinolone labeling, the particular constellation of symptoms across organ systems is not. Individuals with FQAD were defined as U.S. patients who were reported to be previously healthy and prescribed an oral fluoroquinolone antibacterial drug for the treatment of uncomplicated sinusitis, bronchitis, or urinary tract infection (UTI). To qualify, individuals had to have AEs reported in two or more of the following body systems: peripheral nervous system, neuropsychiatric, musculoskeletal, senses, cardiovascular and skin. These body systems were chosen as they had been observed to be frequently involved with the fluoroquinolone reports describing disability. In addition, the AEs had to have been reported to last 30 days or longer after stopping the fluoroquinolone, and had to have a reported outcome of disability."

Fluoroquinolone toxicity is a "constellation of symptoms across organ systems." It is a disease that affects every part of a person.

Fluoroquinolone toxicity, like all multi-symptom illnesses, is mind-bogglingly complex. It involves multiple biological systems, and all the systems work together in complex feedback and feedforward loops. Answering the question, *What IS fluoroquinolone toxicity?* is difficult, if not impossible, with our current state of knowledge of the workings of the human body.

Despite the complexity of the problem, people suffering from fluoroquinolone toxicity still want to know what happened in their bodies. They want to know what went wrong--both out of curiosity, and out of a desire to overcome the damage done. If the mechanisms for the problem are known, perhaps the solution can be found. That is certainly the hope of many.

Unfortunately, the exact mechanism for fluoroquinolone toxicity is not yet known. There are many ways in which fluoroquinolones damage multiple bodily systems. I will be reviewing the many ways that fluoroquinolones have been shown to damage human (and animal) bodies in this e-book, with the hope that with knowledge of the damage that fluoroquinolones do, they can be better understood, and maybe even answers as to how to fix fluoroquinolone toxicity can stem from identification of the problem.

The fluoroquinolone damage mechanisms that I will go over in this ebook are:

1. Mitochondrial toxicity
2. Downgrading of GABA neurotransmitters
3. Mineral depletion
4. Microbiome destruction
5. Thyroid malfunction
6. Fluoride poisoning
7. Mast cell activation
8. Vagus nerve damage

And I will also review how fluoroquinolones are chemotherapeutic drugs.

There are hundreds of journal articles documenting all of these damage mechanisms for fluoroquinolones. They are dangerous drugs—to say the least.

None of the damage mechanisms mentioned are mutually exclusive. They all work synergistically, and are each part of the puzzle of fluoroquinolone toxicity.

This ebook focuses on the damage that fluoroquinolones do—the problem. It does not focus on the solution. For information about how to recover from fluoroquinolone toxicity, please visit www.floxiehope.com. The post, I'm Floxed. Now What? Is an excellent place to start when trying to figure out how to overcome fluoroquinolone toxicity.

Mitochondrial Toxicity

Most people assume that antibiotics kill bacteria, but leave human (and other eukaryotic) cells unscathed. Unfortunately, this assumption isn't correct. Bactericidal antibiotics have been found to damage the mitochondria of human cells.

Mitochondria are present in almost every cell in the body (except for red blood cells and sperm). They are responsible for cellular energy production, cell signaling, apoptosis (the process through which the body kills unhealthy cells), and aging. Mitochondria are vitally important organelles and malfunctioning mitochondria have been linked to many diseases including fibromyalgia, chronic fatigue syndrome / M.E., autism, Gulf War Syndrome, Alzheimer's Disease, Parkinson's, diabetes, cancer, and others.

It is noted by Doctors Bruce H. Cohen, MD and Deborah R. Gold, MD, in Mitochondrial Cytopathy in Adults: What we Know So Far, that:

> *"symptoms (of mitochondrial damage) such as fatigue, muscle pain, shortness of breath, and abdominal pain can easily be mistaken for collagen vascular disease, chronic fatigue syndrome, fibromyalgia, or psychosomatic illness."*

In their April 27, 2013 Pharmacovigilance Review, "Disabling Peripheral Neuropathy Associated with Systemic Fluoroquinolone Exposure," the FDA notes that the mechanism for action through which fluoroquinolones induce peripheral neuropathy is mitochondrial toxicity. The report says:

> *"Ciprofloxacin has been found to affect mammalian topoisomerase II, especially in mitochondria. In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin cause a loss of motichondrial DNA (mtDNA) , resulting in a decrease of mitochondrial respiration and an arrest in cell growth. Further analysis found protein-linked double-stranded DNA breaks in the mtDNA from ciprofloxacin-treated cells, suggesting that ciprofloxacin was targeting topoisomerase II activity in the mitochondria."*

The FDA Pharmacovigilance Report also notes that mitochondrial damage is related to multi-symptom, chronic diseases like optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, lactic acidosis, Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS).

Additionally, a study entitled "Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells" that was published in Science Translational Medicine in 2013 noted that:

> *"Clinically relevant doses of bactericidal antibiotics – quinolones (fluoroquinolones), aminoglycosides, and Beta-lactams – cause mitochondrial dysfunction and ROS overproduction in mammalian cells. We demonstrated that these bactericidal antibiotic-induced effects lead to oxidative damage to DNA, proteins and membrane lipids. Mice treated with bactericidal*

antibiotics exhibited elevated oxidative stress markers in the blood, oxidative tissue damage, and up-regulated expression of key genes involved in antioxidant defense mechanisms, which points to the potential physiological relevance of these antibiotic effects."

Fluoroquinolone antibiotics damage the cellular mechanisms that are needed to repair mitochondrial damage—namely intracellular antioxidant production. The 2013 FDA report notes that, "Under normal circumstances, there is a mechanism to remove or prevent the generation of ROS to avoid cellular damage such as lipid peroxidation, mtDNA mutations, and DNA strand breaks; if this does not happen, it can then lead to even more oxidative damage."

A 2011 study of Indian patients who took various fluoroquinolones to treat urinary tract infections found that, "There was substantial depletion in both SOD and glutathione levels particularly with ciprofloxacin." SODs are superoxide dismutases—enzymes that are necessary for converting superoxide—a powerful oxidant—into oxygen and hydrogen peroxide. Without adequate SOD, superoxide wreaks havoc on every cell in the body. Glutathione is often called the "master antioxidant" and without proper levels of it, oxidants damage cells.

As the FDA noted, when damaged mitochondria produce too much ROS, and the mechanisms to limit the damage (cellular production of antioxidants) aren't working properly, an increasing amount of oxidative damage is done. This is often referred to as the "vicious cycle" of mitochondrial damage—damaged mitochondria produce excess ROS (reactive oxygen species also called oxidative stress or free radicals), those ROS further damage the mitochondria, the further damaged mitochondria produce more ROS, and so on, and so on.

Fluoroquinolone antibiotics damage mitochondria and cause an increase in ROS/oxidative stress. They also deplete cells of antioxidants such as SOD and glutathione, leaving the cells unable to neutralize ROS/oxidative stress. Excess cellular ROS/oxidative stress is related to many chronic, multi-symptom diseases.

How do fluoroquinolones damage mitochondria?

The mechanism of action for Cipro/ciprofloxacin, and all other fluoroquinolones, is:

"The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination."

Mitochondria are ancient bacteria with their own DNA that is separate from nuclear DNA. Fluoroquinolones have been shown to deplete mitochondrial DNA (see the article, "Delayed cytotoxicity and cleavage of mitochondrial DNA in ciprofloxacin-treated mammalian cells" for more information) and it is hypothesized that they inhibit the topoisomerase enzymes that are necessary for mitochondrial DNA replication as well.

Fluoroquinolones have also been shown to damage mitochondrial membranes. The article "Comparison of the effects of subinhibitory concentrations of ciprofloxacin and colistin on the morphology of cardiolipin domains in Escherichia coli membranes" as well as the post, "Fluoroquinolones Damage Mitochondrial Lipids" further explain how fluoroquinolones affect mitochondrial membranes. It is noted in "Comparison of the effects of subinhibitory concentrations of ciprofloxacin and colistin on the morphology of cardiolipin domains in Escherichia coli membranes" that:

> *"We are not the first to report that DNA topoisomerase inhibition can be followed by the alterations at the level of the bacterial membrane. Dougherty & Saukkonen (1985) showed that inhibition of DNA synthesis by nalidixic acid, a DNA gyrase inhibitor, results in morphological changes consistent with a loss of membrane integrity and leakage of intracellular components. Similar results were presented by Wickens et al. (2000), who noticed a decrease of both membrane integrity and membrane potential after exposure of E. coli to CIP. One of the proposed explanations of this finding is that, as a result of processes induced by inhibition of DNA replication, cells lose their capacity to synthesize necessary components and to maintain the proper membrane structure (Dougherty & Saukkonen, 1985)."*

Naladixic acid is the backbone of all fluoroquinolones, and CIP stands for ciprofloxacin. Fluoroquinolones cause a loss of mitochondrial membrane integrity and leakage of intracellular components. That's not good. We need our intracellular components to stay where they should be.

Is Mitochondrial Toxicity the Cause of Fluoroquinolone Toxicity?

The vicious cycle of mitochondrial damage and ROS/oxidative stress is hypothesized to be the cause of fluoroquinolone toxicity. Both mitochondrial damage and ROS/oxidative stress are related to all of the diseases that fluoroquinolone toxicity resembles, and many of the symptoms of fluoroquinolone toxicity.

It is likely that mitochondrial toxicity and resulting ROS are related to other cellular and bodily malfunctions, as there are many feedback and feed-forward loops between bodily systems. I suspect that it is not the only part of the fluoroquinolone toxicity puzzle, but it is a big piece.

Articles about Fluoroquinolone-Induced Mitochondrial Damage

- Science Translational Medicine, "Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells"
- Journal of Young Pharmacists, "Oxidative Stress Induced by Fluoroquinolones on Treatment for Complicated Urinary Tract Infections in Indian Patients"

- Molecular Pharmacology, "Delayed Cytotocicity and Cleavage of Mitochondrial DNA in Ciprofloxacin Treated Mammalian Cells"

Fluoroquinolones Inhibit the Binding of GABA

GABA is the chief inhibitory neurotransmitter in the mammalian central nervous system. It plays the principal role in reducing neuronal excitability throughout the nervous system. GABA is also directly responsible for the regulation of muscle tone. Fluoroquinolones have been shown to downgrade GABA-A receptors.

Many of the CNS symptoms of fluoroquinolone toxicity, including depression, anxiety, psychosis, paranoia, severe insomnia, paraesthesia, tinnitus, hypersensitivity to light and sound, tremors, and suicidal ideation and tendencies, can be attributed to the effects of fluoroquinolones on GABA receptors. Fluoroquinolones "are known to non-competitively inhibit the activity of the neurotransmitter, GABA, thus decreasing the activation threshold needed for that neuron to generate an impulse." Inhibition of GABA-A receptors, as well as activation of NMDA receptors, can lead to the many severe adverse effects of fluoroquinolones on the central nervous system.

To put it into simple, understandable terms—fluoroquinolones do the same thing to GABA neurotransmitters as a protracted benzodiazepine withdrawal. It is noted in "Benzodiazepine tolerance, dependency, and withdrawal syndromes and interactions with fluoroquinolone antimicrobials" that:

> *"Chronic use of benzodiazepines causes compensatory adaptations which cause GABA receptors to become less sensitive to GABA. On discontinuation of benzodiazepines, withdrawal symptoms typically develop which may persist for weeks or months. Antagonism of the GABA-A receptor is believed to be responsible for the CNS toxicity of fluoroquinolones affecting 1–4% of patients treated. Fluoroquinolones have also been found to inhibit benzodiazepine receptor binding. The results of this small study seem to confirm that adverse reactions to fluoroquinolones occur more frequently in the benzodiazepine-dependent population than the 1–4% seen in the general public and may be severe."*

The GABA receptor inhibition effects of fluoroquinolones are potentiated and exacerbated by NSAIDs, including ibuprofen.

It was concluded in an article in The Journal of Neurophysiology in 1991 that, "in the presence of an anti-inflammatory agent, the quinolone antibiotics decrease the affinity of GABAA receptors, the result being induction of epileptogenic neurotoxicities."

Additionally, The article Selective antagonism of the GABAA receptor by ciprofloxacin and biphenylacetic acid published in the British Journal of Pharmacology noted that, "Ciprofloxacin (10–3000 μm) inhibited GABAA-mediated responses in the vagus nerve with an IC50 (and 95% CI) of 202 μm (148–275). BPAA (1–1000 μm) had little or no effect on the GABAA-mediated response but concentration-

dependently potentiated the effects of ciprofloxacin by up to 33,000 times." Let me highlight and reiterate: BPAA, which is a derivative or an NSAID, potentiated the harmful effects of ciprofloxacin on GABA receptors by up to 33,000 times. (WHOA!).

An article in Pharmacology Weekly also noted the effects of fluoroquinolones and NSAIDs on GABA:

> *"Interestingly, the presence of an NSAID or NSAID metabolite can significantly augment this effect and result in an even greater inhibition of GABA-A receptor activity. It is, however, important to note that majority of this effect is related to an NSAID that is only available outside of the United States called fenbufen (Afiancen®, Bifene®, Cincopal®, Cinopal®, Lederfen®, Reugast®).9-11,14 It appears that the metabolite of fenbufen, 4-biphenylacetic acid (BPAA), augments the ability of the fluoroquinolone to inhibit GABA binding to the GABA-A receptor.9-11,14 It is important to note that BPPA itself does not inhibit GABA binding to the GABA-A receptor, but rather when BPAA and the fluoroquinolone come in close proximity they interact in such a way that it results in the ability of the fluoroquinolone antibiotic to inhibit GABA binding to a greater degree than by itself. It is possible that the interaction between a fluoroquinolone antibiotic and BPAA causes some other biologic effect that influences the activity of the GABA-A receptor. In fact, there is some evidence that some fluoroquinolones (mainly enoxacin and norfloxacin) can increase the activity of nuclear activator protein 1 (AP-1) DNA- and cyclic AMP responsive elements (CRE)-binding activities in both the hippocampus and cerebral cortex.14 It has been suggested that increased activity of AP-1 mediated gene expression is important for activity-dependent plasticity in these regions of the brain and thus contribute to the increased risk for seizures.14 Even though fenbufen has been the main NSAID implicated in this adverse drug reaction, other NSAIDs such as indomethacin, ketoprofen, naproxen, ibuprofen have also been shown to augment fluoroquinolone induced GABA-A receptor inhibition in animal studies.9*
>
> *While the data most strongly implicate certain fluoroquinolone antibiotics and NSAIDs, CNS side effects and seizures have been reported with many of the fluoroquinolones, including the ones currently on the market.1-5 This is the reason that the product package inserts for the fluoroquinolone antibiotics not only list the above as potential side effects, but also describe the drug interaction with NSAIDs.1-5 As such, until further evidence suggests otherwise, it would be prudent, especially from a medical legal perspective, for healthcare providers to avoid the use of fluoroquinolones with or without NSAIDs in patients who are at greater risk for seizures (e.g., history of epilepsy, severe cerebral arteriosclerosis) or those with a lower seizure threshold (e.g., patients on medications known to do this, renal dysfunction)."*

NSAIDs increase the neurotoxicity of fluoroquinolones substantially. Another way to look at it, is that NSAIDs are not neurotoxic until they are combined with fluoroquinolones, at which point, they become incredibly neurotoxic.

Many, but not all, people who have experienced fluoroquinolone toxicity, are not able to tolerate NSAIDs. And many, but not all, people who suffer from a delayed reaction to fluoroquinolones, had that reaction "set off" by an NSAID.

Is the inhibition of GABA the cause of fluoroquinolone toxicity?

Anyone who has been through protracted benzodiazepine withdrawal (which has similar effects on GABA as fluoroquinolones, as mentioned above) can tell you that it affects all aspects of the body and mind, and the effects are a syndrome that can last for years after the drug "should" be completely out of a person's system. It is certainly possible that the effects of fluoroquinolones on GABA is the root cause of fluoroquinolone toxicity.

As I noted above, there are many potential damage mechanisms for fluoroquinolones. They all work together and are likely all part of the fluoroquinolone toxicity puzzle.

Articles about fluoroquinolone-induced GABA damage:

- Toxicology Mechanisms and Methods, "Ciprofloxacin-induced neurotoxicity: evaluation of possible underlying mechanisms."
- British Journal of Clinical Pharmacology, "Neurotoxic effects associated with antibiotic use: management considerations"
- Pharmacology Weekly, "What is the mechanism by which the fluoroquinolone antibiotics (e.g., ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin) can increase a patient's risk for developing a seizure or worsen epilepsy?"

Fluoroquinolones Deplete Magnesium and Iron

Magnesium

Fluoroquinolones have been shown to deplete cells of magnesium. Magnesium is necessary for more than 300 enzymatic reactions and it is a vital mineral—we cannot survive without it.

Sufficient magnesium has been linked to reductions in mitochondrial DNA mutations. Many of the symptoms of fluoroquinolone toxicity are symptoms of magnesium deficiency, and some people have proposed that fluoroquinolone toxicity IS magnesium deficiency. Magnesium depletion certainly has a role in fluoroquinolone toxicity, but whether or not it is the primary factor has not yet been established.

The issue of fluoroquinolone depletion of intracellular magnesium, and one ensuing health complication—diabetes mellitus (type-2 diabetes), is described well in the article, "Fluoroquinolone antibiotics and type 2 diabetes mellitus:"

> *"Fluoroquinolones are broad-spectrum antibiotics derived from nalidixic acid that inhibit bacterial topoisomerases. Although very effective therapeutically, fluoroquinolones have been linked with serious side effects such as tendinopathy, peripheral neuropathy, retinopathy, renal failure, hypertension, and seizures. These effects can be rationalized as resulting from a drug-induced magnesium deficiency, and according to the hypothesis it is not coincidental that they resemble the complications resulting from type 2 and gestational diabetes. There has, moreover, been a history of dysglycemia associated with certain fluoroquinolone antibiotics. Gatifloxacin was withdrawn from clinical use after reports of drug-induced hyperglycemia and other fluoroquinolones have been reported to interfere with glucose homeostasis."*
>
> *"The precise mechanism by which fluoroquinolones might induce intracellular magnesium deficiency is unclear. It may involve the metal-chelating properties of the 3-carboxyquinolone substructure that is common to all fluoroquinolone antibiotics and the fact that the 6-fluoro substituent on the pharmacophore gives rise to sufficient lipophilicity that the drugs can dissolve in and penetrate cell membranes. It has been suggested that intracellular fluoroquinolones may exist almost exclusively as the magnesium complex. Diffusion or active transport of such a complex into the extracellular environment would lead to depletion of intracellular magnesium – a process that may be stoichiometric or catalytic and would be only very slowly reversible, if at all. Thus, the effects of fluoroquinolones on intracellular magnesium levels might be considered to be almost cumulative (and it is noteworthy that the side-effects of fluoroquinolone therapy may manifest or persist many months after treatment). Alternatively, it is perhaps possible that fluoroquinolones could affect magnesium metabolism by disruption of renal reabsorption of this electrolyte."*

Magnesium supplementation has alleviated symptoms of fluoroquinolone toxicity for many "floxies."

Iron

Information about the effects of fluoroquinolones on intracellular iron are found in the article, "Non-antibiotic effects of fluoroquinolones in mammalian cells" which was published in the July, 2015 issue of The Journal of Biological Chemistry. All excerpts from the article are quoted and italicized.

> *"Here we show that the FQ drugs Norfloxacin, Ciprofloxacin, and Enrofloxacin are powerful iron chelators comparable to Deferoxamine, a clinically-useful iron chelating agent."*

Fluoroquinolones suck iron out of (chelate) cells just as well as drugs that are meant to suck the iron out of cells (Deferoxamine). Iron is an essential mineral that is critical for transporting oxygen throughout the body. Chelation of iron from cells can be detrimental to health in multiple ways including, "delayed cognitive function, poor exercise performance and lowered immune function. In children, iron deficiency anemia can cause psychomotor and cognitive abnormalities resulting in future learning difficulties."

> *"We show that iron chelation by FQ leads to epigenetic effects through inhibition of α-ketoglutarate-dependent dioxygenases that require iron as a co-factor."*

Iron depletion leads to adverse epigenetic effects through inhibition of iron-dependent enzymes. This is a very big deal—Fluoroquinolones can change genetic expression (epigenetics) in human cells. Later in the article it is noted that, "This is the first study to show global epigenetic changes induced by FQ antibiotics." It had been previously postulated in "Epigenetic side-effects of common pharmaceuticals: A potential new field in medicine and pharmacology" (2009) that all fluoroquinolone adverse effects were the result of epigenetic changes, but "Non-antibiotic effects of fluoroquinolones in mammalian cells" describes the first study of human cells that shows epigenetic changes caused by fluoroquinolones. Epigenetics wasn't even a notion, much less a field of study, when the FDA approved fluoroquinolones, drugs whose mechanism of action is, "inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination."

Dioxygenases are enzymes that are necessary for aerobic life. Fluoroquinolones inhibit α-ketoglutarate-dependent dioxygenases, which require iron as a co-factor. Depletion of α-ketoglutarate-dependent dioxygenases leads to changes in how genes are expressed.

Fluoroquinolones were also found to inhibit several demethylases, "enzymes that remove methyl (CH3-) groups from nucleic acids, proteins (in particular histones), and other molecules. Demethylase enzymes are important in epigenetic modification mechanisms. The demethylase proteins alter transcriptional regulation of the genome by controlling the methylation levels that occur on DNA and histones and, in turn, regulate the chromatin state at specific gene loci within organisms." FQs were found to inhibit "Jumonji domain histone demethylases, TET DNA demethylases, and collagen prolyl 4-

hydroxylases, leading to accumulation of methylated histones and DNA, and inhibition of proline hydroxylation in collagen, respectively. These effects may explain FQ-induced nephrotoxicity and tendinopathy."

Many possible mechanisms for the tendinopathy and compromised collagen integrity caused by fluoroquinolones have been proposed. It has been suggested that fluoroquinolone caused destruction of connective tissues are due to metalloprotease (MMP) malfunctions, magnesium depletion, and the NO/ONOO cycle. In "Non-antibiotic effects of fluoroquinolones in mammalian cells" it is asserted that iron chelation, and the inhibition of enzymes that utilize iron, are behind the fluoroquinolone-caused musculoskeletal adverse effects:

> *"These results suggest, for the first time, that FQ treatment can cause unanticipated epigenetic effects. Moreover, we suggest that the well-established linkage between FQ treatment and tendinopathy reflects impairment of collagen maturation by FQ. We suggest that it is the inhibition of collagen 4 prolylhydroxylases by FQ mediated iron chelation, and repression of collagen P4H1 and LH1 transcription that underlies the peculiar tendinopathy side effects of FQ antibiotics."*

And:

> *"FQ are potent iron chelators capable of inhibiting 2-KG dependent dioxygenases because of the crucial role of iron in the active site. We show that FQ treatment inhibits collagen maturation. Prolyl 4- hydroxylase and lysyl hydroxylase are iron dependent enzymes essential for the post-translational modification of collagen. Both play central roles in collagen maturation through hydroxylation of proline and lysine residues to mediate collagen cross-linking. Covalent crosslinks are required for the tensile strength of collagen fibers (64). We suggest that it is iron chelation by FQ that accounts for suppressed collagen hydroxylation, giving rise to tendinopathies."*

And:

> *"Additionally, suppression of HIF-1a can have drastic effects on vascularization and energy metabolism in connective tissues, contributing to decreased blood flow in an already hypoxic and avascular tissue. We suggest that these three insults - inhibition of prolyl and lysyl dioxygenases, reduction of P4HA1 and LH1 mRNA levels, and reduced tendon vascularization upon HIF-1a depletion – together account for FQ induced tendinopathies."*

To sum up the excerpts, fluoroquinolones chelate iron from cells, this leads to inhibition of iron-dependent enzymes, which lead to epigenetic changes that result in collagen malformation and tendinopathies. It should also be noted that fluoroquinolones chelate other minerals, including magnesium, from cells, and magnesium-dependent enzymes are inhibited by fluoroquinolones as well.

All doctors and researchers, and the FDA, should note that in chelating necessary minerals from the body, fluoroquinolones are not only inhibiting necessary enzymatic reactions, they're also changing genetic expression, and that the long list of severe adverse

effects of fluoroquinolones may be due to adverse expression of genes. Neither long-term, nor intergenerational effects of fluoroquinolones, are currently known.

So… what should floxies do with this information? Personally, I supplement iron and I find that it helps me immensely. Not everyone can, or should, supplement iron though. Too little iron is bad, but too much is also harmful. The prudent thing to do is to get your iron levels tested and to supplement if necessary under the care of your doctor.

When I corresponded with Dr. Maher, one of the authors of "Non-antibiotic effects of fluoroquinolones in mammalian cells," he noted that, "I would simply emphasize that what we demonstrate in this work involves human cells grown in culture, and lab conditions, and we want to make it clear that these are findings of potential mechanisms of fluoroquinolone antibiotics that could be relevant for patients, but we provide no direct data related to human patients or treatments. Further studies will be required to understand if these or related effects actually occur in people."

I am thankful to Doctors Badal, Her and Maher for their work on "Non-antibiotic effects of fluoroquinolones in mammalian cells!" Of course, caution should be used when drawing conclusions from their results. Though I shouldn't draw conclusions about how FQs react in a complex human body from how human kidney cells react in a petri dish, I don't think that it's completely out of line to say that the potential implications of this research are huge. The chelation of minerals from cells by fluoroquinolones may be leading to epigenetic changes in the people who take fluoroquinolones. What this means for their health is not currently known.

The epigenetic adverse effects of fluoroquinolones were found to be reversible by exposing the floxed cells to iron, and studies have shown that magnesium, vitamin E, MitoQ and NAC can reverse some of the effects of fluoroquinolones, so please have hope, hang in there, and take your mineral supplements (under the supervision of your doctor, yada, yada).

Articles about Fluoroquinolones Chelating Magnesium and Iron from Cells

- Medical Hypotheses, "Fluoroquinolone antibiotics and type 2 diabetes mellitus"
- The Journal of Biological Chemistry, "Nonantibiotic Effects of Fluoroquinolones in Mammalian Cells."
- Proceedings of the National Academy of Sciences of the United States, Biochemistry, "Quinolone Binding to DNA Mediated by Magnesium Ions"

Fluoroquinolones Damage the Microbiome

As powerful antibiotics, OF COURSE fluoroquinolones damage the microbiome. They are designed to kill bacteria, and they do it effectively. Fluoroquinolones disrupt the DNA and RNA replication process for bacteria. They do so indiscriminately, killing both "good" and "bad" bacteria. Destroying the microbiome with drugs that are like a nuclear bomb to both good and bad bacteria is consequential to all areas of health. Microbiome health is increasingly being connected to all diseases of modernity, including autism, Alzheimer's, Parkinson's, fibromyalgia, Lupus, and more.

The following was originally posted on January 12, 2015 on www.hormonesmatter.com *as "*The Harmful Effects of Antibiotics on the Human Microbiome.*"*

The Harmful Effects of Antibiotics on the Human Microbiome

How many articles about the importance of the microbiome—and the relationship between microbiome health and chronic, devastating diseases—need to come out in order for the cognitive dissonance around antibiotic safety to stop?

People assume that all antibiotics are safe drugs, that they damage bacteria but leave people and animals unharmed. People assume (soap commercials have conditioned us well) that bacteria are bad, that they are harmful and make us sick, and that human life is improved when they are killed. Many also assume that all antibiotics are created equally and that the more powerful an antibiotic, the better. Most people assume that there are no long-term consequences from taking antibiotics.

There is ample evidence that these assumptions are false, and that a microbiome that is disturbed by antibiotics makes people more anxious, intolerant of pain, and sick with a variety of diseases.

A disrupted microbiome has been connected with development of Parkinson's Disease (PD), as shown in "Gut microbiota are related to Parkinson's Disease and clinical phenotype," published in the journal Movement Disorder. It was found that patients with PD had less Prevotellaceae (a type of gut microbe) than those in the control group, and that, "The relative abundance of Enterobacteriaceae was positively associated with the severity of postural instability and gait difficulty." It is also pointed out in the study that the reason for examining the relationship between PD and the gut microbiome is that:

> *"In the course of PD, the enteric nervous system (ENS) and parasympathetic nerves are amongst the structures most frequently and earliest affected by alpha-synuclein pathology. Accordingly, gastrointestinal dysfunction is an important non-motor symptom in PD and often present years before motor symptom onset. Recent research has shown that intestinal microbiota interact with the autonomic and central nervous system via diverse pathways including the ENS and vagal nerve."*

The microbiome profoundly affects neurotransmitters and thus mental health, as is shown in "The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner" published in Molecular Psychiatry, as well as "That Gut Feeling" published in the American Psychological Association magazine, Monitor on Psychology. The article, "Altering your gut bacteria could ease anxiety and depression" on www.sciencealert.com is also interesting and informative. All of the articles point to the finding that, "that tweaking the balance between beneficial and disease-causing bacteria in an animal's gut can alter its brain chemistry and lead it to become either more bold or more anxious" (quote from "That Gut Feeling") and that temperament changes were induced by gut microbiome alterations. If you're feeling anxious or depressed, you may want to look at your past antibiotic use. Our guts and our brains communicate through a variety of signaling mechanisms including "the autonomic nervous system (ANS), the enteric nervous system (ENS), the neuroendocrine system, and the immune system" as well as the vagus nerve.

The connection between microbiome health and Alzheimer's Disease is described in "Alzheimer's disease and the microbiome" published in Frontiers in Cellular Neuroscience (and the referenced articles are interesting too). In it, it is noted that, "GI tract-abundant gram-positive facultative anaerobic or microaerophilic Lactobacillus, and other Bifidobacterium species, are capable of metabolizing glutamate to produce gamma-amino butyric acid (GABA), the major inhibitory neurotransmitter in the CNS; dysfunctions in GABA-signaling are linked to anxiety, depression, defects in synaptogenesis, and cognitive impairment including Alzheimer's Disease."

Rheumatoid Arthritis is connected to microbiome health in the article on the NIH web site, "Gut Microbes Linked to Rheumatoid Arthritis," in which it is noted that, "The immune system is influenced by the microbiome, a network of microorganisms that live in and on the human body. These microbes outnumber the body's cells by 10 to 1. Trillions of microbes—both helpful and harmful—reside in the digestive tract. The gut microbiome has been linked to arthritis in animal studies."

Inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis are connected to microbiome health in "Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment" published in Genome Biology. In the article, it is stated that, "The inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis result from alterations in intestinal microbes and the immune system."

The microbiome has been shown to affect both Type 1 and Type 2 diabetes. In "Intestinal microbiota and type 2 diabetes: From mechanism insights to therapeutic perspective" published in the World Journal of Gastrointerology the relationship to Type 2 diabetes is shown. In "Type 1 diabetes: role of intestinal microbiome in humans and mice" published in the Annals of the New York Academy of Sciences the connection to Type 1 diabetes is shown.

More general information about the relationship between the microbiome and human health can be found on the National Institute of Health's Human Microbiome Project web site.

Thousands of articles about the importance of the microbiome have come out. Millions of dollars have been spent studying the microbiome and its relationship to human health. Antibiotics indiscriminately destroy bacteria in the microbiome, and some even lead to oxidative stress in the microbiome. Yet misconceptions about antibiotic safety persist. Why is that?

Greg Spooner answered that question perfectly. He said:

> *"I think the reason for this is that the early antibiotics (like penicillin) were quite safe and they spared us from very serious infections that often lead to death. Our life expectancy jumped at this point, and they were rightly considered miracle drugs. But this was also their downfall, as they quickly became so overused that they lost their efficacy and killed off many people's helpful biomes. When FQs (fluoroquinolones) came out, most docs probably thought they were just "better" antibiotics that were still effective. 'All progress is precarious, and the solution of one problem brings us face to face with another problem.' - Martin Luther King Jr"*

Indeed.

Antibiotics, as a class of drugs, have saved millions of lives. That is undeniable. But their value in life-threatening situations does not negate their consequences. The increased risk of Parkinson's, Alzheimer's, depression, anxiety, inflammatory bowel diseases, diabetes and other diseases that result from microbiome disruption, should be weighed carefully and conscientiously against the risk of harm from the diseases that are treated with antibiotics. This analysis isn't being done currently. Both patients and physicians will need to shift their thinking about antibiotic safety for a proper safety analysis to be conducted. Unfortunately, the proper safety analysis involves comparing immediate and acute pain to potential future pain, and humans are horrible at doing that kind of analysis.

Also, as Greg pointed out, the value and safety of one antibiotic does not mean that all antibiotics are equally safe and valuable. Though penicillin is not kind to the microbiome, it doesn't cause multi-symptom, chronic illness like fluoroquinolones do. Fluoroquinolones are broad-spectrum antibiotics that not only kill bacteria, they deplete mitochondrial DNA and induce a massive amount of oxidative stress, not only in the microbiome, but in the body generally. Fluoroquinolones are related to the diseases mentioned above not only through the destruction of the microbiome inflicted by them, but also through the destruction of mitochondria and disruption of cellular mineral homeostasis.

It would be a good place to start for the dangers of fluoroquinolones to be considered before they are prescribed. After all, fluoroquinolones have an extensive list of adverse

effects (the Cipro warning label is 43 pages long) that include tendon ruptures and seizures, among hundreds of other adverse effects. There are thousands of patients screaming about how they have been hurt by fluoroquinolones, and demanding that they be used more prudently.

All antibiotics should be used with care and consideration of potential future consequences. Those antibiotics with the most severe adverse effects should be looked at most closely and immediately. Fluoroquinolones are not worth the harm that they cause in most cases. Restriction of the use of fluoroquinolones is a good place to start in thinking about antibiotics as dangerous, consequential drugs. They are, indeed, consequential, dangerous drugs.

The role that antibiotics and the microbiome play in the many chronic diseases of modernity is just starting to be recognized. Though recognition has been slow to come about, there are thousands of articles about the importance of the microbiome. Perhaps it is time for us to consider more prudent use of antibiotics, especially the most potent and destructive ones (like fluoroquinolones).

Fluoroquinolones Cause Thyroid Dysfunction

The following information is written by JMR and was published on www.hormonesmatter.com *as* Fluoroquinolone Antibiotics and Thyroid Problems: Is there a Connection? *on May 7, 2015. It is republished with permission from the author. Additional information about the connection between thyroid problems and fluoroquinolones can be found on JMR's web site,* www.fluoroquinolonethyroid.com

Fluoroquinolone Antibiotics and Thyroid Problems: Is there a Connection?

One Fateful Day – And a Journey into the Enigmatic World of Thyroid Related Problems Begins

I remember the day of March 19, 2010 very well. That was the last day I ever went jogging. That was the last day I could have hopped on my bike and ridden 50 miles if I wanted to. That was the last day I ate my favorite breakfast of a 3-egg omelet topped with cheese and veggies, with 3 pieces of whole wheat toast slathered in butter and jam, 3 pancakes on the side, and at least a quart of milk. That was the last day I worked in my profession, brought home a paycheck, and was self sufficient financially. It was the day before I started taking Ciprofloxacin, a fluoroquinolone (FQ) antibiotic, for a simple UTI. And it was the last day I was a normal person with a normal life.

By March 25, 2010 – six days later — I was completely bedridden with severe pain in what felt like every tendon in my body, along with peripheral and central neurological symptoms and other symptoms from the side effects of that drug. These adverse effects are collectively called "Fluoroquinolone Toxicity Syndrome" (FQT), or "floxed" for short. And although I didn't realize it then, my physical, professional, financial, and personal life as I knew it was over. Within a few days and a few pills, I joined the ranks of the chronically disabled, those with "chronic invisible illnesses", and "Romney's 47%." It's five long years later, and I still struggle with the aftermath of taking those few pills. I regret every single day since then that I ever even considered a fluoroquinolone antibiotic for a simple UTI.

So what does all this have to do with the thyroid gland? Well, like most victims of this toxicity, all my extensive traditional medical testing during the acute phase of the reaction, as well as for the first year and a half after, gave normal or negative results. Astoundingly enough, despite being severely disabled and feeling essentially non-functional, according to the medical profession, I was the picture of health on paper. Until I finally decided to do more than a TSH test to check my thyroid status. That's when I discovered I had all the anti-thyroid antibodies. And that's really when my journey into the enigmatic world of "thyroid problems" began in earnest.

Having the antibodies for both Hashimoto's Thyroid Disease and Grave's Thyroid Disease makes for an astounding array of symptoms. Many of them appeared to mimic or overlap my symptoms of Fluoroquinolone Toxicity. Naturally, as a result of these

observations, and my experiences with these conditions, I started questioning as to how much fluoroquinolone antibiotics caused severe endocrine disruptions, in particular of the thyroid axis.

The Thyroid Fluoroquinolone Epidemic: Where is the Research?

There is a lot of published research available showing how damaging the FQ's are too many different body systems and cellular processes, but almost none of it includes the thyroid system or the endocrine system in general. I suspect that someday, studies will be published showing the association between fluoroquinolones and thyroid abnormalities. Until then, it will be up to patients themselves to try and figure out if this association exists for themselves. In my case, my suspicions were further strengthened when I found that thyroid hormone medications, both T4 and T3, dramatically and profoundly affected all my floxing symptoms. Even more interesting to me, iodine alone did the same. I also found it interesting that a significant number of flox victims reported hormonal disruptions of all types post flox, such as with sex hormones, adrenal hormones, thyroid hormones, dysglycemias presumably in association with insulin hormone, and Vitamin D, which is also considered a hormone. This was also true of me after I was floxed. Eventually, I created a website summarizing my observations, experiences, interpretations, and hypotheses on these possible correlations.

I had several intentions in creating the website, and one of them is to start the conversation about this potential link between fluoroquinolones and thyroid related problems, hopefully leading to unbiased studies and research in this area. I believe it is sorely needed. According to the U.S. Preventive Services Task Force Clinical Guidelines:

> *"The annual number of dispensed prescriptions of levothyroxine sodium in the United States increased by 42% over a 5-year period, from 50 million in 2006 to 71 million in 2010. In 2013, there were more than 23 million new prescriptions and refills for a single name brand of thyroid hormone in the United States, making it the most commonly prescribed drug in the country."*

This implies there are a lot of "thyroid problems" out there. According to several recent News investigations airing across the country, the FQ antibiotics are one of the top five drugs prescribed in the US each year. In our current day and age, we are bombarded by many substances which are known or suspected endocrine disrupters, including affecting the thyroid system. Could the epidemic of FQ usage be contributing to the epidemic of thyroid-related problems resulting in patients receiving thyroid medication for life? It would not surprise me if this were the case. I hope association studies, along with causation studies, will be done someday. Until then, those of us with thyroid disorders are on our own in looking at FQ antibiotic usage history and questioning this association for ourselves.

In my case, it was pretty clear cut that the acute symptoms I experienced right after starting the antibiotic were actually caused, or at a minimum, triggered by the antibiotic. My flox symptoms were pretty classic for these reactions all around, and there is plenty of research, as well as anecdotal stories, to substantiate this. But were my symptoms also "thyroid related"? In other words, did the antibiotic affect my thyroid system, either primarily and directly, or secondarily through a "cascade effect", and at least some of these floxing symptoms I experienced were actually "thyrotoxic" symptoms as well? I think the answer is yes. These are the issues that I explore in my website, and I will briefly present here.

Tendon Pain and Ruptures: A Link between FQ Antibiotics and Endocrine Disorders?

One of the most well known adverse effects of FQ antibiotics are tendon problems. Most flox victims will experience some level of tendon pain at some point in time during their flox reaction. Regardless of what other symptoms occur with FQT, the severe tendon pain that can occur, sometimes with resultant ruptures, is distinctive, idiosyncratic, and unique to FQ antibiotic use alone. It is a hallmark of FQT. So much so, that an FDA "Black Box Warning" about it exists for all fluoroquinolone antibiotics.

It turns out there just aren't a whole lot of things in life, either natural or synthetic, that can cause sudden spontaneous tendon ruptures or severe tendon pain and tendinopathies –but all of the endocrine disorders can. This includes: hyperadrenocorticism (cortisol), diabetes (insulin), parathyroid disorders (calcium/PTH/Vitamin D), hyper and hypothyroidism (tyrosine/iodine/thyroid hormone), hyper/hypo sex hormones (estrogens/testosterone), and probably other steroid and sex hormones and their metabolites as well (see references). A specific genetic metabolism disorder of tyrosine, which is a major component of thyroid hormones, can also cause spontaneous tendon rupture later in life as a first manifestation of this disorder. Many rheumatic diseases also often have an associated, if not underlying, endocrine component (especially thyroid related). Additionally, conditions that at first glance appear to be unrelated, such as chronic renal failure, often have a high association with endocrinopathies, in particular, parathyroid hormone abnormalities. The parathyroid glands are intimately associated with the thyroid gland via proximity alone; if thyroid gland architecture is destroyed, presumably these glands could be affected too.

I took a fluoroquinolone antibiotic and developed severe, systemic tendon pain, Type 2 Diabetes, and two Autoimmune Thyroid Disorders. A legitimate question could be: Are fluoroquinolone antibiotics severe endocrine disrupters, which, among other symptoms, can result in tendon pain, tendinopathies, and tendon rupture?

I then found that the thyroid hormone medications T4 and T3, as well as iodine alone, profoundly affected my tendon pain and other symptoms, capable of making these symptoms dramatically better — or much worse. This, too, seemed to support the

argument that the fluoroquinolones had somehow damaged my thyroid system, as supplying exogenous hormone in the form of medication now could make such dramatic differences in my symptoms.

One of my hypotheses is that people with healthy and normally functioning thyroid glands or other endocrine systems can probably withstand these dramatic changes in the hormonal axes that may be occurring while on the FQ – at least, up to a point. For people who don't react at all to these drugs, they probably never even feel the fluctuations, as their hormonal axes can automatically adjust rapidly. But I would suspect that anyone with any underlying genetic predisposition, or possibly harboring a subclinical, latent, or silent endocrinopathy might be "pushed over the edge" into full blown clinical pathology. This is actually what I think may have happened with me, even though I had no overt indications of any kind of thyroid or endocrine disorder prior to taking the Cipro.

Additional Links to Consider Relating Fluoroquinolones to Thyroid System Damage

I don't profess to even begin to know the millions of ways fluoroquinolones could possibly exert their damaging effects on the thyroid or endocrine system in general. However, that didn't stop me from thinking about this problem. As I said, I hope research studies will be initiated in this area sooner than later. In the meantime, I came up with several mechanisms of FQ-Induced Thyroid Pathology to consider as possibilities, to narrow down the search. Additional unintentional targets of fluoroquinolones that I considered could have thyroid-related repercussions included targets such as Mitochondria, Acetylcholine, Steroid Receptors and Hormone Response Elements and their common pathways, Selenium dependent enzymes and proteins, halogenated peroxidase enzymes, iodine receptors located on most or all cells as well as on the thyroid gland, and more, as I briefly describe here. I think one of the more interesting observations is the fact that new fluoroquinolone derivatives are now being considered for use as "tyrosine kinase inhibitors" (TKI's). TKI's are relatively recent chemotherapy drugs developed to fight cancer – and one of their adverse effects appears to affect the thyroid system with some rather alarmingly high statistics. From my perspective, there appeared to be striking similarities between thyroid abnormalities occurring with TKI's and the thyroid abnormalities I suspect may occur with the FQ's, which I describe here.

Fluoroquinolone Antibiotics: Consider the Risks

Thyroid disorders, especially autoimmune based ones, are no joke. Autoimmune Thyroid Disorders are not simply disorders of the thyroid gland; in my opinion, they are systemic disorders, affecting many or all of the cells and tissues in the body, which is why there can be such widespread and potentially devastating symptoms. There are numerous environmental stressors that contribute to thyroid disease and endocrine disease, and the fluoroquinolone antibiotics may be one of them. Fluoroquinolones exert many damaging effects, and if they are damaging the thyroid axis directly or indirectly via a cascade effect,

actually causing anti-thyroid antibody production, or even if they are triggering or unmasking a subclinical or silent condition in susceptible patients to an active pathological condition, this is of serious concern – or it should be. A "silent" condition means just that – you don't know you have that predisposition. I can say from my own experience that taking a fluoroquinolone antibiotic is a hell of a way to find out. It is Pharma's responsibility to provide adequate warnings and risks of this possibility, and the medical profession's responsibility to make sure adequate testing rules out these antibodies along with other potential risk factors, before prescribing a fluoroquinolone antibiotic. Sadly, neither of these things is happening right now. Until it does, I think anyone considering taking a fluoroquinolone antibiotic for a simple infection, such as uncomplicated UTI or sinusitis, should be aware of the risk factors and possible alternatives.

Based on what I've learned in the past several years, I believe anyone with pre-existing endocrinopathies of any type (whether they're known or not), to be at increased risk for these adverse reactions. I also believe that anyone who has experienced any kind of flox reaction has now gotten a warning sign, and is at increased risk of developing an overt or clinical endocrinopathy as a result of being floxed at any time after. One of the few supportive pieces of evidence for this hypothesis is buried in Table 3, Page 136 of a Mayo clinic paper here. Note the at risk population includes people with autoimmune or endocrine disorders (diabetes, thyroid, parathyroid) and steroid usage (ie, Prednisone, inhalers, anabolic steroids, etc).

The best approach, of course, is to stay away from these drugs altogether if at all possible. In my opinion based on my own experience, developing a lifelong severe thyroid disorder – or any other disorder — to solve a short term problem such as an uncomplicated infection with a fluoroquinolone antibiotic, isn't worth the risk.

References and Resources:

1. Musculoskeletal Complications of Fluoroquinolones: Guidelines and Precautions for Usage in the Athletic Population
2. The Risk of Fluoroquinolone-Induced Tendinopathy and Tendon Rupture: What Does The Clinician Need to Know?
3. Spontaneous rupture of Achilles tendon: missed presentation of Cushing's syndrome.
4. Spontaneous rupture of Achilles tendon and Cushing's disease. Case report.
5. Incidence and predictors of hospitalization for tendon rupture in type 2 diabetes: the Fremantle diabetes study.
6. Musculoskeletal Complications of Diabetes
7. Biomechanical Properties of Achilles Tendon in Diabetic vs. Non-diabetic Patients.

8. Spontaneous and serial rupture of both Achilles tendons associated with secondary hyperparathyroidism in a patient receiving long-term hemodialysis.
9. Simultaneous chronic rupture of quadriceps tendon and contra-lateral patellar tendon in a patient affected by tertiary hyperparatiroidism.
10. The level of vitamin D in the serum correlates with fatty degeneration of the muscles of the rotator cuff.
11. Parathyroid disease.
12. Primary hyperparathyroidism due to atypical parathyroid adenoma presenting with peroneus brevis tendon rupture.
13. Thyroid hormones and tendon: current views and future perspectives. Concise review.
14. Thyroid hormones increase collagen I and cartilage oligomeric matrix protein (COMP) expression in vitro human tenocytes.
15. Suspected role of ofloxacin in a case of arthalgia, myalgia, and multiple tendinopathy. (Inhaled steroids and moderate hypothyroidism precipitating factors).
16. Could Low Total and Free Testosterone Levels be risk factor for Achilles Tendon Ruptures in Males.
17. Pathological rupture of the distal biceps tendon after long-term androgen substitution.
18. Effect of estrogen on tendon collagen synthesis, tendon structural characteristics, and biomechanical properties in postmenopausal women.
19. Female Athletes with Higher Estrogen Levels May Have Higher Injury Risk.
20. Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women.
21. Successive ruptures of patellar and Achilles tendons. Anabolic steroids in competitive sports.
22. Spontaneous rupture of the anterior cruciate ligament after anabolic steroids.
23. Spontaneous rupture of the extensor pollicis longus tendon after anabolic steroids.
24. Spontaneous tendon ruptures in alkaptonuria.
25. Rheumatic manifestations of endocrine disease.
26. The endocrine system and connective tissue disorders.

27. Same Disease, Different Symptoms: It's all in the Mitochondria.
28. Your Mighty Mitochondria.
29. Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology Pharmacovigilance Review. (References provided for mitochondrial toxicity within the document).

Fluoroquinolones and Fluoride Poisoning

In the 4+ years that I've been studying fluoroquinolones, I've thought that the quinolone core was the most damaging part of fluoroquinolones, and that the fluoride added to it just made it more potent. I thought that the fluorination of the quinolone helped it to penetrate cells so that the quinolone core could do damage, but that the fluorine itself wasn't the damage mechanism. After all, nalidixic acid, the precursor of fluoroquinolones that is not fluoridated, is a dangerous drug with multiple adverse effects.

A couple of things have been making me re-think my notion that fluoride is not as damaging as the quinolone core. First, fluoride is an endocrine disruptor that interferes with iodine absorption and thyroid functioning. Second, acute fluoride poisoning can cause multi-symptom, chronic illness and many of the symptoms of fluoroquinolone toxicity.

As noted in the "Fluoroquinolones Cause Thyroid Dysfunction" section, fluoroquinolones are endocrine disruptors that can lead to a variety of thyroid illnesses.

It is noted in the book, Fluoride in Drinking Water: A Scientific Review of EPAs Standards (2006) that:

> *"In summary, evidence of several types indicates that fluoride affects normal endocrine function or response; the effects of the fluoride-induced changes vary in degree and kind in different individuals. Fluoride is therefore an endocrine disruptor in the broad sense of altering normal endocrine function or response, although probably not in the sense of mimicking a normal hormone. The mechanisms of action remain to be worked out and appear to include both direct and indirect mechanisms, for example, direct stimulation or inhibition of hormone secretion by interference with second messenger function, indirect stimulation or inhibition of hormone secretion by effects on things such as calcium balance, and inhibition of peripheral enzymes that are necessary for activation of the normal hormone."*

It has been hypothesized that the even-numbered carbon chain of the fluoroquinolone ring structure results in formation of a fluorofatty acid, which can be metabolized to fluoroacetate. Fluoroacetate is a chemical compound that is used as a pesticide that inhibits vital steps in the citric acid cycle.

An article published on Earth Clinic entitled LIKE ISRAEL, U.S. SHOULD BAN FLUORIDE AMID HEALTH CONCERNS: Thyroid Dysfunction, Fibromyalgia & Neurotoxicity Top List of Adverse Effects written by Jason Uttley notes that, "The popular fluoroquinolone antibiotics, which include Cipro and Levaquin, are among drugs linked by such groups to an extreme form of fluoride toxicity, known as organofluorine poisoning." Mr. Uttley's article asserts that organofluorine poisoning, which one can become afflicted from taking fluoroquinolone antibiotics, can lead to multi-symptom, chronic, illnesses like fibromyalgia.

Following is Mr. Uttley's article, LIKE ISRAEL, U.S. SHOULD BAN FLUORIDE AMID HEALTH CONCERNS: Thyroid Dysfunction, Fibromyalgia & Neurotoxicity Top List of Adverse Effects, which was originally published on www.earthclinic.com. It is republished with the author's permission.

> *"Nearly half a century after Minnesota passed legislation requiring the addition of fluoride to municipal water supplies, fluoride is under fire due to health concerns.[1] Evidence that the additive is not only a contributor to the epidemic of thyroid dysfunction, but also a likely neurotoxin linked to a range of conditions associated with cognitive impairment, has come as a shock, even to members of the scientific community who have reviewed the growing research.[2] On Aug. 26, 2014, faced with such disturbing evidence, Israel's Health Minister Yael German ordered an end to the practice of water fluoridation.[3] While German has been criticized for her decisive action, the move comes as little surprise to the handful of experts in the U.S. who have been aware of the dangers associated with fluoride for years.*
>
> ***Reversing course on water fluoridation***
>
> *Despite safety assurances from the American Dental Association (ADA) and Centers for Disease Control and Prevention (CDC), who have long advocated dumping fluoride into the water supply in the interest of dental health, new studies have made it hard to deny the evidence of long-term damage from fluoride ingestion.*
>
> *Studies that showed lower IQ levels in children exposed to too much fluoride received little attention initially, even as additional research demonstrated a gradual build-up of fluoride in specific areas of the brain.[4] [5] [6] That changed when the Head of Neurotoxicology at the one of America's most prestigious dental research facilities, the Harvard-affiliated Forsyth Institute, confirmed that cognitive impairment from fluoride appears very real indeed.[7]*
>
> *By the time investigative journalist Christopher Bryson brought the story of neurotoxicologist Dr. Phyllis Mullenix into the public eye, with his 2004 book The Fluoride Deception, U.S. scientists had already uncovered similar studies that pointed to the same disturbing conclusion.[8] [9] The EPA confirmed that even at the so-called "optimal" level of 1 part per million — a concentration widely accepted for water fluoridation programs in most states — the cumulative effect of fluoride on humans is deleterious, at times resulting in brain and kidney damage.[10]*
>
> *As with the majority of Americans, most officials failed to take the issue seriously at first due to decades of promotion that had convinced nearly everyone that fluoride had been proven safe to swallow. Massive marketing campaigns by the ADA, CDC and others equated fluoride opposition to quackery and conspiracy theories, which in-turn were messages reinforced by a media whose health stories have long been generated by a handful of journalists overly reliant on talking points provided by public health officials.*
>
> *Those charged with reviewing the emerging evidence were among the first to realize that both the scientific community and general public had been profoundly misled regarding the safety of fluoride. As health officials slowly began to accept the evidence presented by their own scientists,*

they faced the daunting task of overcoming public perception, which their predecessors and colleagues had helped shape.

Ending fluoridation with no reason would inevitably trigger an avalanche of criticism not only from the dental community with a vested interest in maintaining the status quo, but from the media and public as well. On the other hand, completely revealing the full extent of scientific concerns might not only trigger widespread outrage, but a profound loss of trust in the institutions responsible. Health officials on opposite sides of the Atlantic decided to address this catch-22 scenario in very different ways.

Israel's Health Minister German decided, in the fall of 2014, to be relatively forthcoming about some of the growing concerns when she implemented the recommendation of scientists by fully halting fluoridation. By contrast, U.S. Secretary of the Department of Health and Human Services Kathleen Sebelius decided, in the winter of 2011, on a much less transparent approach."

What the U.S. announcement failed to mention

In January of 2011, the U.S. Department of Health and Human Services (HHS) and the U.S. Environmental Protection Agency (EPA) made national headlines by issuing a joint recommendation to significantly lower the concentration of fluoride in water.[11] For Minnesota and some cold weather states, which maintain even higher levels in water, that proposal would cut the fluoride concentration by more than 40 percent, from 1.2 to 0.7 parts per million.

News of the Jan. 7, 2011, public announcement to draw down fluoride levels in the U.S. water supply was delivered to many by way of journalist, Mike Stobbe, whose articles on the subject appeared in newspapers across the United States, including both major newspapers in Minnesota.[12] [13] [14] Reports made it clear the ADA supported the decision to reduce fluoride levels. However, just four days later, the ADA informed HHS Secretary Sebelius that they were "very disturbed" to find out that the Dept of Health and Human Services was also quietly proposing to eliminate the CDC's Division of Oral Health.[15]

This was disturbing to them because the ADA has a long history of promoting water fluoridation alongside the CDC by using the Division of Oral Health as a mouthpiece to deride critics and echo the virtues of fluoride. In fact, it is the Division of Oral Health that is responsible for the CDC having gone so far as to extol water fluoridation as, "One of the 10 great public health achievements of the 20th century."[16]

In one motion, with nearly surgical precision, the Department of Health and Human Services and the Environmental Protection Agency had quietly proposed a move that would cut the cord linking fluoride promoters at the very moment they had launched their campaign to wind down water fluoridation. Surreptitiously they had convinced the ADA to publicly endorse their proposal to reduce fluoride levels, while simultaneously working to dismantle the part of the CDC that the ADA had used to convince the scientific community that fluoride was entirely safe.

Given that journalist Mike Stobbe is based in Atlanta and covers the CDC on behalf of the Associated Press, withholding news of the proposed elimination of the Division of Oral Health from one the few reporters charged with covering the very public announcement recommending the dramatic change to the water fluoridation program suggests a conscious effort by Secretary Sebelius and other officials to reduce Americans exposure to the proven neurotoxin while not casting a shadow over those responsible.

The decision to ax the CDC's Division of Oral Health was not the only fluoride related news to surface following the Jan. 7 announcement. EPA officials also revealed around the same time that — after nine years of debate — they had suddenly been authorized to grant a petition to phase out sulfuryl fluoride insecticides.[17]

That piece of fluoride news also wasn't disclosed to journalists covering the proposed change to the water fluoridation program. Revealing the fact that concerns over the pesticide also related to fluoride would likely have triggered a barrage of questions and forced U.S. officials into a position to have to explain the full extent of scientific concerns.

Nevertheless, it's important to understand that the decision to phase out that fluoride-based pesticide validated the concern of scientists who had for years stated that the dangers of fluoride exposure extend well beyond water.

The cumulative effect

Although best known for its topical application to teeth through toothpaste, most of the fluoride that's ingested actually comes from other sources. Based on sheer volume, the leading source of fluoride in the diet stems from fluoridated tap water and the vast array of beverages (and to a lesser degree food) made with tap water. Based on relative toxicity, however, the leading sources of fluoride and related organofluorine compounds are pesticides and prescription drugs.

The concentration of fluoride in tap water has remained unchanged in most communities in the U.S. since water fluoridation programs first began (originating in the mid-1940's and becoming widely popular due to propaganda campaigns in the 1950's and 1960's). But fluoride, like lead, has long been known to accumulate in the human body. Thus, fluoride levels not only rise over the course of one's life, but also from generation to generation, as women unknowingly pass along higher and higher levels to their children. To make matters worse, new sources contribute to the total volume of fluoride consumed, which in turn makes the leading source of exposure — tap water — increasingly important.

Despite the fact that the alarm raised by scientists actually has little to do with the issue of dental fluorosis — the pitting and staining of teeth from excess fluoride exposure — the rapid growth of such a noticeable and widely acknowledged adverse health effect clearly illustrates the growing problem of overexposure to fluoride and organofluorine compounds. A report released by the CDC's National Center for Health Statistics on the prevalence of dental fluorosis showed that during a period when water fluoridation levels remained constant for much of the U.S., including

all of Minnesota, the total number of cases of dental fluorosis doubled in children (age 12-15), to more than 40 percent, while moderate to severe cases tripled.[18]

The growth of such a noticeable and widely accepted adverse effect has profound implications. Prolonged fluoride ingestion is now linked to neurotoxicity. There's also growing evidence linking it to thyroid dysfunction.[19] Tens of millions of Americans suffer from thyroid related conditions. Underactive thyroid disorders, which are associated with a slowdown in the body's metabolism and loss of cellular energy, are at epidemic proportions, particularly among women.

The fact that Israel's Health Minister acknowledged the risk fluoride poses to those with thyroid disease speaks volumes about just how seriously scientists now take this connection.

U.S. officials didn't touch on scientific concerns over thyroid disease or neurotoxicity in their 2011 public announcement. Instead Secretary Sebelius chose to cite a 2006 National Research Council report on fluoride toxicity as the primary motivation to dramatically cut fluoride levels in the water. That report was significant because, as experts have pointed out, the National Research Council had been specifically directed by U.S. health officials to base their conclusions only on widely accepted adverse effects, like dental fluorosis and bone fractures, and not on all the other, far more insidious effects that scientists can now reasonably conclude are also occurring. [20]

Dr. Hardy Limeback, the former President of the Canadian Association of Dental Research and one of the key authors of the National Research Council's 2006 report on fluoride, has since said that "Fluoridation could turn out to be one of the top 10 mistakes of the 21st century."[21] That statement, from a man who was once considered one of the top fluoride advocates and educators in Canada, isn't based simply on fluoride's known association to dental fluorosis and bone fractures.

Fibromyalgia: A theory of relativity

The issue of relative toxicity looms in the background of recent moves to stop water fluoridation. Fluoride and organofluorine based pesticides and prescription drugs may not contribute nearly the same volume of fluoride to the diet as tap water. However, such sources may be playing an even larger role in the development of certain rapidly emerging conditions.

Advocacy groups, such as Parents of Fluoride Poisoned Children, have long warned that some fluoride-based prescription drugs expose people to same level of toxicity as they would get from years of consuming fluoridated water.[22] [23] This toxicity often goes unchecked as it comes in the form of "side effects" that mirror the symptoms of chronic fluoride poisoning.

The popular fluoroquinolone antibiotics, which include Cipro and Levaquin, are among drugs linked by such groups to an extreme form of fluoride toxicity, known as organofluorine poisoning. A significant lag in the typical onset of symptoms makes organofluorines appear much less toxic than they really are. Only over the course of many months is the severe poisoning revealed, as comparatively mild symptoms slowly progress to become highly debilitating.

The small group of rheumatologists who defined "fibromyalgia" for the medical community in the mid-1980's, based on the symptom of greatest interest to their branch of medicine, had no idea what they were observing was a serious form of fluoride poisoning. Even as millions of women began to develop the vast array of symptoms following repeated exposure to such drugs, physicians were at a loss to explain the sudden emergence of the condition. Both the medical community and the pharmaceutical industry had been so badly deceived to think fluoride was safe that they have never been on the lookout for symptoms of chronic fluoride poisoning, much less to a form associated with a significant delayed reaction in the onset of symptoms.

In September of 2012, the New York Times revealed that the fluoroquinolone drug class was linked to the delayed onset of fibromyalgia-like symptoms.[24] For a drug overwhelmingly prescribed to women, the link of any drug class to such a debilitating condition should've garnered far more attention following this revelation. But to fluoride researchers, the news of a fluorinated drug linked to such symptoms should've come as no surprise.

Dr. George Waldbott, who was one of the first physicians to warn of the dangers of consuming fluoride, back when fluoridation first began, observed the very same symptoms in his patients. Of course, at that time, chronic fluoride poisoning was comparatively rare. Nevertheless, Waldbott tried unsuccessfully to bring attention to the fact that long-term fluoride poisoning was associated with a vast array of symptoms, including not only crippling musculoskeletal pain & stiffness, but also a debilitating form of cognitive impairment he described as, the "loss of mental acuity and ability to concentrate."[25]

Neurotoxicologist Phyllis Mullenix — whose work on the damage fluoride does to the brain triggered alarm among U.S. scientists — is among the researchers who have noticed the glaring similarities between advanced forms of chronic fluoride poisoning and what has come to be termed "fibromyalgia." Despite public perception, many fibromyalgia groups report that the condition's most paralyzing symptom isn't the excruciating musculoskeletal pain & stiffness, but rather the severe cognitive impairment. Memory and concentration problems can even progress to an extreme form of brain fog, known as "fibro fog"— a dementia-like condition.

More brain effects: Disrupting the thyroid and adrenals

As troubling as the connection to cognitive impairment is, what's garnered even more interest by some scientists is the degree to which fluoride's effect on the brain plays a major role in so many of its other devastating adverse effects.

Fluoride has long been suspected of interfering with thyroid function by replacing iodine, an essential component of the thyroid hormones. That said, new evidence suggests that fluoride's primary mode of interference — not only with the thyroid, but also the adrenals — relates to the damage fluoride does to the parts of the brain that regulate the body's neuroendocrine system.

The thyroid and adrenal glands produce hormones that control an astonishing array of bodily functions, including cellular energy production and inflammatory response. Signals sent and

received by the brain regulate how much of these critical hormones to produce. Even relatively small disruptions in this cyclical pathway, known as the hypothalamus-pituitary axis, can have devastating consequences.

Too much or too little of the powerful hormones, or how the body uses the hormones, can trigger an onslaught of symptoms. While this breakdown may involve the thyroid, the adrenals are now thought to be more universally affected. As a result, clinical tests only reveal measurable thyroid impairment in some patients.

Well-known fibromyalgia researchers, including Dr. John Lowe and Dr. Jacob Teitelbaum, have concluded that the tests for thyroid dysfunction are simply inaccurate. To them, the empirical evidence points to the conclusion that fibromyalgia is essentially an extreme form of thyroid dysfunction.

Those with the distinct advantage of understanding how fluoride poisoning affects the brain, however, see things a bit differently. From their point of view, all conditions related to long-term fluoride poisoning, including thyroid dysfunction and fibromyalgia, are associated with a common breakdown in the brain's ability to properly regulate hormones.

The fact that fibromyalgia research has recently shifted its attention to this area is of no surprise to fluoride experts, like Phyllis Mullenix.

The stages of long-term fluoride poisoning

The fibromyalgia connection is particularly important because from the vantage of severe long-term fluoride poisoning it becomes easier to understand why it's linked to many other conditions.

Take for instance one of the most misunderstood conditions in all of modern medicine — chronic fatigue syndrome — a condition now referred to by many as myalgic encephalomyelitis, or ME, which means "muscle pain with inflammation of the central nervous system." Since fibromyalgia also means "muscle pain" and is also known to involve central nervous system inflammation, the connection to ME might seem obvious, even to those who may not be aware of the astonishing degree of overlap across the entire array of symptoms, including cognitive impairment.

Naturally, without knowing that both conditions represent widely varying stages of organofluorine poisoning likely caused by highly toxic fluorinated prescription drugs, it's been difficult to understand the connection between the two conditions. So dramatically do the symptoms ramp up in the most advanced forms of poisoning that in many ways the vast differences in the quantity and severity of symptoms make ME/CFS & fibromyalgia almost appear unrelated.

Nevertheless, in Minnesota, one of the nation's first patient advocacy organizations for ME/CFS joined forces with a fibromyalgia support group in 2003 to form the Chronic Fatigue Syndrome/Fibromyalgia Association of Minnesota. Unfortunately, this short-lived partnership

ultimately destroyed both organizations, as member support began to erode following this alliance.

While some clearly understood that there was an important connection between the conditions, with no knowledge of the common cause, mismanagement of the nonprofit proved fatal in the face of dwindling support. ME/CFS patients had difficulty identifying with the more excruciating symptoms, while fibromyalgia sufferers wanted to distance themselves from ME not only because the symptoms tend to be far less crippling, but also because of the stigma associated with its original, seemingly harmless sounding name.

Ironically, while few took the illness seriously because of its label, perhaps the most stunning aspect of the CFS connection is that "chronic fatigue" is far and away the best known of all the early symptoms of fluoride poisoning.

Even in the early days of the fluoridation debate, fluoride was suspected of dramatically slowing cellular energy production. This is why the critics of fluoridation, like Dr. Waldbott, listed "chronic fatigue not relieved by sleep or rest" as one of the first symptoms of chronic fluoride poisoning.[26] It is no coincidence that when Stanley Kubrick made a mockery of the issue in 1964, with Dr. Strangelove, the movie's lead character pointed to "a profound sense of fatigue" as the reason for sparking his concerns about fluoridation.

But as experts know only too well, chronic fatigue really only scratches the surface in terms of fluoride's adverse effects. Disrupting cellular energy production by impairing the area of the brain that controls the thyroid and adrenal glands causes a cascade of ensuing symptoms. The more severe the poisoning, the more advanced the symptoms become.

For physicians, the label "stress and anxiety disorder" is often used for a myriad of early symptoms (i.e. cold hands & feet, headaches, dry mouth, weight gain, etc.), unless clinical tests reveal thyroid impairment. As the quantity and severity of symptoms progress most of those affected tend to be treated like hypochondriacs. With each new symptom comes a new diagnosis. Urinary frequency is commonly labeled "incontinence" or "polyuria"; gastrointestinal disturbances, "irritable bowel syndrome"; numbness, "peripheral neuropathy"; joint pain, "osteoarthritis"; and so on.

Noticeable memory and concentration problems, as well as isolated muscle pain are also familiar initial symptoms. However, because muscle and brain cells are among the most densely packed cells in the body with energy producing mitochondria, such cells tend to be most profoundly affected when the fluoride poisoning becomes relatively severe. Debilitating cognitive impairment often precedes the excruciating widespread muscle pain that is a hallmark of the more advanced stages of long-term fluoride poisoning.

By the time patients advance to the "fibromyalgia" diagnosis, where a breakdown in energy production approaches its punishing zenith, the complete list of symptoms is often brutally long, incredibly agonizing and extremely difficult to cope with.

The gender factor

Although fluoride is an equal opportunity toxin, which can affect both men and women, most related conditions disproportionately affect women. Despite claims that there are many factors for this, it is very possible that the simplest explanation is correct: the most toxic fluorinated prescription drugs, which have primarily been directed at women, are largely responsible.

If the New York Times is right and the widely popular fluoroquinolone antibiotics are linked to fibromyalgia, and fluoride experts are right and fibromyalgia represents an extreme form of fluoride poisoning, then the drug class is likely linked to all fluoride related conditions.

Thyroid dysfunction, ME/CFS, fibromyalgia and every one of the conditions that now appear to correspond to the various symptoms or stages of fluoride poisoning, are all disorders that predominantly affect women. Statistics vary, but in general roughly four out of five of those battling such conditions are women.

While the fluoroquinolones are not the only type of fluorinated drug linked to fibromyalgia, they appear to deserve special attention for several reasons: (1) they gained widespread use in the early 1980's, just as ME/CFS and fibromyalgia emerged out of nowhere (2) they're overwhelmingly prescribed to women for common ailments, like urinary tract infections, (3) fluoride and organofluorines are cumulative in nature, so repeated exposure to highly toxic drugs matter greatly, (4) the medical community has an exceedingly poor track record when it comes to issues of women's health.

Due to the delayed onset of symptoms associated with organofluorine poisoning, those who are diagnosed with related conditions often report that doctors treat them as hypochondriacs, as they slowly develop one symptom after the next. This slow progression of symptoms has also undoubtedly played a major role in how the medical community defined the conditions in the mid-to-late 1980's.

In 1988, the CDC made a mockery of the women who had developed the early, and yet serious form of fluoride poisoning, when it endorsed the "chronic fatigue syndrome" label. So poorly was the condition defined — in spite of a name that corresponds to the most well-known symptom of early fluoride poisoning — that not even the CDC itself took the condition seriously at first.

In fact, so little did the CDC think of the condition that, in the late 1990's, they were caught diverting millions of dollars in research funds intended to get to the bottom of the rapidly emerging condition to other programs and then, ultimately, lying to Congress about it. [27] [28] The CDC then led the medical community on a long and futile effort to find a virus responsible for the condition. Time and again announcements of breakthroughs in identifying the virus turned out to be misguided, wrong, or even manufactured. [29] [30] [31]

The fact that the CDC did all of this while their Division of Oral Health was aggressively promoting the actual cause – fluoride – on behalf of the ADA represents a degree of incompetence that is almost unfathomable, even for a federal agency.

Not to be outdone, the leading rheumatologists who defined "fibromyalgia" in the mid-1980's decided to not only ignore the early symptoms of the condition, and therefore treat the ME/CFS connection as if it were unrelated, but the connection to the vast array of other symptoms — including the devastating cognitive impairment — by labeling the emerging condition based solely on one symptom of interest to their particular branch of medicine.

In 1990, they compounded this astonishing oversimplification by recommending that the criteria to be used by the medical community to diagnose the illness would also center on that same, lone symptom. To make matters worse, Dr. Fredrick Wolfe, one of the nation's preeminent rheumatologists who played a major role defining the new condition, later suggested (under tremendous pressure to explain where it came from) that its rapid growth could only be explained if it were entirely psychosomatic.

Although Wolfe's explanation was largely dismissed by other prominent fibromyalgia researchers, it is a notion that many physicians actually still believe, in part because of how poorly the condition was defined. Despite the label, the diagnostic criteria and even the corresponding marketing of pharmaceuticals that, not coincidentally, all center around that same symptom, those who develop "fibromyalgia" don't strictly complain of severe widespread muscle pain as one would expect if the condition were some sort of social or marketing generated phenomenon. For the vast majority of sufferers who are properly diagnosed, the list of common symptoms is not only long and harsh, but also unrelenting and highly progressive.

Incredibly, the controversial end point of fibromyalgia —the conspicuous symptom of spinal and cranial calcification, which affects those with the very worst conditions — is also an end point of chronic fluoride poisoning.[32] [33] In fact, if there is one symptom of long-term fluoride poisoning that is the most well-known beyond the very early symptom of chronic fatigue, it is almost certainly spinal stenosis. That particular symptom was highlighted as far back as 1937, in one of the most comprehensive fluoride toxicity books ever written, Fluorine Intoxication. And yet, by the time the deluge of cases of chronic fluoride poisoning surfaced in the early-to-mid 1980's, that connection had long since been forgotten by all but a handful of experts.

The gender bias that has contributed to women being treated like hypochondriacs by physicians has been compounded by a lack of understanding of the relative toxicity of certain fluoride based pharmaceuticals as well as a complete disregard for the symptoms and stages of chronic fluoride & organofluorine poisoning. For an illness whose sudden rise predated the (mid-1990's) popularization of the internet and affects women at a rate approaching 9-to-1, the notion that millions of members of "the weaker sex" are still being accused of concocting the debilitating symptoms of fibromyalgia speaks volumes for just how much issues of women's health have been misguided and marginalized.

Turn of the tide

With one of America's closest allies recently ending water fluoridation due to health concerns, the time has come for federal officials in the U.S. to immediately halt the practice of adding the

fluoride to the American diet. Unlike Health Minster German who courageously acted to protect the citizens of Israel, Secretary Sebelius and her successor, Secretary Sylvia Burwell, have moved far too slow responding to concerns raised by the scientific community.

For a proven neurotoxin linked to thyroid and other endocrine maladies, the implications of such significant excess fluoride exposure among younger and younger age groups are staggering. Tens of millions of Americans suffer from thyroid dysfunction.[34] Millions more suffer from fibromyalgia, a condition whose symptoms are identical to an extreme form of chronic fluoride poisoning. To deny those patients and their doctors the knowledge that fluoride not only causes such conditions, but almost universally worsens symptoms regardless of how the condition originated is of profound importance.

When Minster Yael German announced the end to the practice of water fluoridation in Israel, she specifically cited the health implications for those suffering from thyroid dysfunction, pregnant women and the elderly.[35] Scientists in the United States who have been working to bring the adverse effects of fluoride to light admit that those are only a few of the most obvious at-risk groups. Those who have been working to uncover the full measure of fluoride's harmful effects now understand that the link to thyroid dysfunction and cognitive impairment is only the beginning.

America has a long road ahead. As it stands, consuming fluoride from fluoridated water is largely unavoidable, especially since most water filters don't remove it. For those with related conditions who will see a vast improvement in their symptoms when daily dietary fluoride consumption begins to fall, the end to water fluoridation cannot come soon enough. But while ending water fluoridation is an important step, stopping drug fluorination and revealing all of the damage that fluoride has done to human health is even more important. Thanks to the bravery of scientists and others who are sharing the evidence of harm, that day is slowly approaching.

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Fluoroquinolones and Mast Cell Activation

What is the connection between fluoroquinolone toxicity and mast cell activation/histamine intolerance? Can fluoroquinolones trigger mast cell activation and histamine intolerance?

The symptoms of mast cell activation are similar to those of fluoroquinolone toxicity. According to Mastocytosis Society Canada, the symptoms of mast cell activation are:

> *"skin lesions or sores, skin rash, spots, redness, hives, persistent fatigue, itching, flushing & severe sweating, joint, bone pain, headaches, tachycardia (racing heartrate), eyes tearing/dry, eye pain, persistent body/tissue pain, difficulty exercising, vertigo, episodes of low body temperature, unexplained Vitamin B1 2 deficiency, scents/odors/chemical reactions, difficult menses (females), numbness & tingling in face and extremities, skin feels on fire, unexplained anxiety, sudden drops in blood pressure, fainting, persistent diarrhea, vomiting, unexplained weight loss, cognitive impairment, sinus problems, chest pain, vision problems, hair loss, mouth sores, nausea, swelling & inflammation, odd reactions to insect stings, anesthesia difficulties, anemia, thyroid problems, decreased bone density, unexplained weakness, shortness of breath, sunlight sensitivity, temperature (hot/cold) sensitivity, difficulty with foods, drinks, anaphylactoid reactions, anaphylaxis, gastrointestinal pain, bloating, unexplained medication reactions, enlarged liver/spleen, liver/spleen/bladder/kidney pain, enlarged lymph nodes, frequent urination, recurring infections, neuropathic pain, constipation, iron deficiency, unexplained bruising, bleeding, malabsorption, intermittent tinnitus or hearing problems."*

That's a pretty comprehensive list of fluoroquinolone toxicity symptoms too. (Though, as I discussed with Dr. Wahls in episode 14 of The Floxie Hope Podcast, all of the multi-symptom, chronic diseases of modernity have more in common with each other than they don't, and should probably all just be categorized as cellular dysfunction disorders and treated similarly.)

Several floxies who have been able to get a diagnosis from a doctor have come back with a diagnosis of mast cell activation, or a disease that is related to mast cells. For example, one floxie friend's doctors have diagnosed him with eosinophilia, a disorder that is related to mast cells and histamine intolerance. Other floxies have been diagnosed as histamine intolerant, and instructed to go on a low-histamine diet. As noted above, many floxies have symptoms of mastocytosis, and it is possible that fluoroquinolones activate mast cells and trigger mastocytosis.

Mast cell disorders are considered to be rare, but, according to Mastocytosis Society Canada:

> *"escalation in the prevalence of these patients worldwide has resulted in a flurry of medical research ongoing in numerous countries. This indicates that these disorders may not be rare, but rather have been commonly misidentified and unfortunately for patients worldwide, commonly undiagnosed. Since approximately 2005, every year there are new theories, classifications, and*

adjustments to the mastocytosis definitions due to escalation of patients presenting with these disorders worldwide."

I found the following information connecting fluoroquinolones and mast cell activation / mastocytosis:

- From the International Journal of Tissue Reaction's article, Effect of levofloxacin and ciprofloxacin injection on permeability of the tail vein in mice and skin microvasculature in rats, "These results suggest that LVFX and CPFX increase vascular permeability through the induction of histamine release from mast cells in rodents." (LVFX is levofloxacin and CPFX is ciprofloxacin.)
- From the Journal of Pharmacy and Pharmacology's article, Characterization of Histamine Release Induced by Fluoroquinolone Antibacterial Agents In-vivo and In-vitro, "Intravenous injection of levofloxacin and ciprofloxacin at 1–10 mg kg−1 produced dose-related elevations in plasma histamine level in anaesthetized dogs. In contrast, levofloxacin was devoid of plasma histamine increment in anaesthetized rats at 100 mg kg−1, whereas ciprofloxacin at the same dose caused endogenous histamine release. Levofloxacin and ciprofloxacin induced non-cytotoxic secretion of histamine from all mast cells tested in a concentration-dependent manner, whereas rat skin and peritoneal mast cells were thirty- to one-hundred-times less sensitive to the effect of fluoroquinolones as compared with the canine skin mast cells." Note that in studies beagle puppies have been made lame by fluoroquinolones.
- From the Archives of Toxicology's article, Differential response of mast cells separated from various organs and basophils of dogs to the fluoroquinolone antimicrobial levofloxacin, "Histamine releases induced by the fluoroquinolone antimicrobial levofloxacin (LVFX) were investigated using mast cells separated from various organs and peripheral basophils of dogs, being the most susceptible species to quinolone derivatives, in both in vivo and in vitro systems. An intravenous infusion of LVFX at 30 mg/kg over a 30-min period produced endogenous histamine release from 5 min, and a maximum at 30 min, in which the plasma LVFX concentration was approximately 50 μM. A close correlation (r=0.87, n=20) between histamine and LVFX concentrations in plasma during the infusion was observed. In the in vitro study, LVFX at 30 μM or more caused histamine release from mast cells separated from the liver and skin, but not from the gastric mucosa, lung, and peripheral basophils. More exactly, the liver mast cells were most susceptible to LVFX among the organs tested. On the other hand, compound 48/80, a prototype histamine liberator, elicited the histamine release from the liver or skin mast cells at 10 μg/ml, and the calcium ionophore A23187 at 1 μM exhibited the histamine release from the mast cells derived from all organs examined. Histochemical analysis revealed that the liver and skin mast cells had positive reaction for both alcian blue and safranin staining, but the gastric mucosa and lung mast cells were only positive for alcian blue staining, indicating that LVFX preferably activated the connective tissue-type mast cells rather than the mucosal-type mast cells. The degranulation

> of the liver and skin mast cells brought about by either LVFX or compound 48/80, unlike the calcium ionophore A23187, was blocked by pretreatment with pertussis toxin, suggesting the involvement of pertussis toxin-sensitive G proteins. The results obtained from the canine experiments strongly suggest that LVFX induces histamine release from the connective tissue-type mast cells distributed mainly in the liver, somewhat in the cutaneous tissue, through the activation of pertussis toxin-sensitive G proteins."

The articles noted above are all from animal studies, not human studies, but they show that fluoroquinolones can activate mast cells and histamine release in mammals, and it's reasonable to think that they may do the same things to humans that they do to dogs. Also, the similarity between fluoroquinolone toxicity symptoms and mastocytosis symptoms, though not a smoking gun, indicate that further studies of the affects of fluoroquinolones on mast cells should be done.
A few good resources for people with mastocytosis, and it's possible that floxies are in that category, are:

1. Dr. Theoharides web site
2. Mastocytosis Society Canada web site
3. The Low Histamine Chef web site
4. Alison Vickery's web site

I suspect that mast cells are profoundly affected by fluoroquinolones and that mast cell activation is a big part of fluoroquinolone toxicity. The potential options, and mechanisms for fluoroquinolone toxicity, are mind-boggling. Add mast cell activation to the list.

Fluoroquinolones and the Vagus Nerve

The vagus nerve is a huge nerve that connects the brain to the various organs throughout the body. Our autonomic nervous system (ANS) is controlled via the vagus nerve. It connects the digestive tract to the brain and when you feel butterflies in your stomach, that feeling is traveling from your stomach to your brain via your vagus nerve. Breathing and heart rate, as well as other ANS functions, are controlled through the vagus nerve.

The brain coordinates ANS functions using the vagus nerve, and how smoothly those functions are being coordinated is referred to as the "tone" of the vagus nerve.

The article, Hacking the Nervous System, goes over the hypothesis that inflammation is related to vagal nerve tone, and that vagal nerve tone has a lot to do with chronic, multi-symptom illnesses, like autoimmune diseases.

I wonder if vagal nerve damage has something to do with fluoroquinolone toxicity, and I wonder if things that improve vagal tone can help floxies to heal. I suspect so on both counts.

Vagal nerve tone is important, and "Research shows that a high vagal tone makes your body better at regulating blood glucose levels, reducing the likelihood of diabetes, stroke and cardiovascular disease. Low vagal tone, however, has been associated with chronic inflammation."

Little is known about how vagal tone relates to health. One of the scientists interviewed for Hacking the Nervous System stated, "We don't even know yet what a healthy vagal tone looks like." They are looking into it though, and vagal nerve stimulating implants are being used in clinical trials. (Read Hacking the Nervous System for more information about the implants.)

Improving Vagal Tone

Things that are less drastic and invasive than a vagal nerve stimulating implant can improve vagal tone. For example, meditation can improve vagal tone. "Those who meditated showed a significant rise in vagal tone, which was associated with reported increases in positive emotions. 'That was the first experimental evidence that if you increased positive emotions and that led to increased social closeness, then vagal tone changed,' Kok says."

To drastically oversimplify a complex process, things that make you feel good, socially connected, happy, relaxed, etc. improve vagal tone. Conversely, stress and trauma decrease vagal tone. Many things that helped me through my fluoroquinolone toxicity journey were things that are purported to improve vagal tone – meditation, healing arts

(e.g. dancing and music), mindfulness, acupuncture, chiropractic, and eliminating stressful stimuli from my life (e.g. getting off the internet).

An article in Psychology Today, "How Does the Vagus Nerve Convey Gut Instincts to the Brain?" notes that, "Using positive self-talk and taking deep breaths is a quick and easy way to engage the vagus nerve and parasympathetic nervous system to calm yourself from both the top-down and from the bottom-up."

Additionally, exercise also improves vagal tone. Playful exercise is best, but regardless, movement is good for vagal tone.

Vagal Tone and GABA Neurotransmitters

A decrease in vagal tone may be connected to damage to GABA neurotransmitters. The article in Psychology Today, "How Does the Vagus Nerve Convey Gut Instincts to the Brain?" notes that, "The most exciting discovery of this study is that under closer scrutiny of the rats' brains, the researchers found that the loss of signals coming up from the abdomen via the vagus nerve altered the production of both adrenaline and GABA in the brain."

The ANS dysfunction that many floxies experience is likely connected to vagal nerve health, as the ANS is controlled via the vagus nerve.

A Hypothesis for Fluoroquinolone Toxicity

A possible hypothesis for fluoroquinolone toxicity is that people who get floxed have an underlying, dormant hiatal hernia (they're pretty common) that is exacerbated by the FQ and the massive amount of oxidative stress induced in the gut by the FQ. The hiatal hernia irritates the vagus nerve and triggers ANS dysfunction that is self-perpetuating. The damage to the vagus nerve also alters the production of neurotransmitters, especially GABA, and hormones.

It's possible, and I believe that the vagus nerve is a big part of the FQ toxicity puzzle. However, please know that I have not found much scientific research to support this hypothesis. Also, other possible causes for fluoroquinolone toxicity mentioned in the post, What is Fluoroquinolone Toxicity? have more supporting evidence supporting. However, all of these causes are not mutually exclusive, and may all play a role.

Measuring Vagal Tone

In Hacking the Nervous System it is noted that:

> *"The strength of your vagus response is known as your vagal tone and it can be determined by using an electrocardiogram to measure heart rate. Every time you breathe in, your heart beats*

faster in order to speed the flow of oxygenated blood around your body. Breathe out and your heart rate slows. This variability is one of many things regulated by the vagus nerve, which is active when you breathe out but suppressed when you breathe in, so the bigger your difference in heart rate when breathing in and out, the higher your vagal tone."

Another term for the relationship between breath and heart rate is respiratory sinus arrhythmia breathing (RSA breathing). I found the following passage from A Headache in the Pelvis to be interesting:

> *"RSA breathing is a description of the relationship between heart rate and breathing and refers to the heart rate varying in response to respiration. RSA is a phenomenon that occurs in all vertebrates. You can experience the phenomenon of RSA by taking your pulse and noting that when you breathe in, the heart rate increases slightly and when you breathe out the heart rate decreases slightly. There is considerable research that indicates that when there is balance and health, the heart rate and the breath move robustly together as inhalation occurs, heart rate increases as exhalation occurs, heart rate drops.*
>
> *Under circumstances of mental or physical disease the relationship between breathing and heart rate is disturbed. When individuals suffer panic attacks for instance, RSA is lower and disturbed. When they recover from panic disorders their RSA breathing becomes stronger, more balanced, and robust. The higher and stronger the heart rate variability is in relationship to appropriate respiration, the higher is the general level of health and well being. For example healthy children generally have very robust RSA breathing in which the heart rate can sometimes vary 40 beats or more between inhalation and exhalation.*
>
> *Reduced RSA is thought to be an indicator of an adverse prognosis for people with heart disease. Generally disturbed RSA is indicative of early problems in the healthy functioning of the autonomic nervous system as it relates to a number of diseases.* ***It has been suggested that one measure of the therapeutic effect or safety of a drug is whether it positively or negatively affects RSA.****" (emphasis added).*

Vagal tone and RSA breathing are either one and the same, or, at the very least, highly related. As doctors Wise and Anderson note in A Headache in the Pelvis, the effects of pharmaceuticals on RSA (or vagal tone) should be measured and noted, and those drugs that have deleterious effects on RSA should only be taken in extreme circumstances. The effects of fluoroquinolones on RSA breathing and vagal tone are unknown.

Coordinating Breathing with Heart Rate

I'm a huge fan of breathing exercises for health. The post Breathing Exercises for Health goes over some thoughts on breathing exercises for floxies. The easiest breathing exercise that I use is just saying, "OM" – take a deep breath in and let it out slowly while singing/chanting/groaning "OM."

To get my heart and breath regulated, I took a Chinese herb called Suxiao Jiuxin Wan. It's supposed to improve heart qi. (Heart qi? What? I'm not sure of this, but I suspect that "heart qi" is related to vagal nerve tone, but people who know more about this can either prove or disprove this notion.) Suxiao_Jiuxin_Wan has been shown to help people with angina and it calmed my racing heart dramatically. I'm not a doctor or Chinese herb specialist, so please do your own research, but it helped me immensely.

Fluoroquinolone toxicity is an incredibly complex disease with many facets. Is the nervous system involved? Absolutely. Is the vagus nerve involved? Almost certainly. But, unfortunately, not much research has been done on how fluoroquinolones relate to either the vagus nerve specifically or the nervous system generally.

Improving vagal tone has multiple health benefits for floxies and non-floxies alike. Most of the things that can be done to improve vagal tone are pretty simple and inexpensive. Meditate – be socially connected – exercise – do breathing exercises – minimize stress – think positively. None of those are magic bullets, they're all processes and practices. They're all good for you, free, and certainly worth a try.

Fluoroquinolones are Chemo Drugs

When I first heard people referring to fluoroquinolone antibiotics (Cipro, Levaquin, Avelox, Floxin and a few others) as "chemotherapy drugs," I thought that they were exaggerating or incorrect. After all, fluoroquinolones are used to treat urinary tract infections, traveler's diarrhea, anthrax, and other bacterial infections, not cancer. But then I started to do some research into how fluoroquinolones work and I discovered that they cause mitochondrial damage, which leads to oxidative stress and cell death (1, 2), they interfere with the DNA replication process of mitochondria (3), they disrupt tubulin assembly (4) and that they are being investigated for their tumor killing abilities (5, 6). I also found that all other drugs that have the same mechanism for action as fluoroquinolones – topoisomerase interrupters (FDA warning label, 7) (topoisomerases are necessary for proper DNA replication) – are used as chemotherapy drugs – topotecan, amsacrine, etoposide, etc. Fluoroquinolones are, truly, chemotherapy drugs – they just happen to be used as popular antibiotics. They can kill cancerous tumor cells because, in addition to killing bacterial cells, they also kill eukaryotic cells (8, 9).

Many of the strange things about fluoroquinolone toxicity that don't make sense when thinking of fluoroquinolones as antibiotics make perfect sense when fluoroquinolones are thought of as chemo drugs. They are, indeed, chemo drugs. Like all chemo drugs, adverse effects are long-lasting and cumulative. Adverse reactions can be delayed. One can tolerate the drug well at one time, then react horribly to it another time. If doctors and patients alike would start realizing that fluoroquinolones are chemo drugs, perhaps they would recognize fluoroquinolone toxicity and prescribe fluoroquinolones more appropriately.

This following was originally published on www.collective-evolution.com as "FDA Allows Chemo Drugs to be Prescribed as Antibiotics:"

> *"A few popular antibiotics affect DNA, similar to some chemotherapy agents. If you're sensitive to them, you could pay a neurological price that causes sudden and serious neuropathy and degrees of brain damage. The Food and Drug Administration is concerned about drugs in the fluoroquinolone class, and these already have a black box warning for an increased risk of tendon ruptures. But I'm telling you that more reports have come in with accusations of neurological damage. Personally, I would only use these for life-threatening infections that were unresponsive to older, regular antibiotics."* –Suzy Cohen, RPh

It is not appropriate to give people cell-destroying chemotherapy drugs when they don't have cancer. That should be obvious. It shouldn't even need to be said. But it's happening every day when people are prescribed fluoroquinolone antibiotics – Cipro/ciprofloxacin, Levaquin/levofloxacin, Floxin/ofloxacin and Avelox/moxifloxacin – to treat ear, bladder, prostate, sinus and other infections. Fluoroquinolones are chemotherapy drugs. They have just been mass marketed as antibiotics by the FDA.

You may be thinking something along the lines of, "WHAT? Cipro isn't a chemo drug, it's an antibiotic. Everyone knows that."

Here are several reasons why Cipro, Levaquin, Floxin, Avelox and all other fluoroquinolones should be recognized as cell-destroying chemotherapy drugs:

1. In an article published in the journal Urology, it was noted that, "Ciprofloxacin and ofloxacin exhibit significant time and dose-dependent cytotoxicity against transitional carcinoma cells." That's great – excellent, actually – if you happen to have carcinoma cells in your bladder. But if you just happen to have a bladder infection, chemo drugs that exhibit toxicity toward human cells – cancer or otherwise – are inappropriate for use (1).
2. The mechanism for action for fluoroquinolones is that they are topoisomerase interrupters (2).Topoisomerases are enzymes that are necessary for DNA replication and reproduction. All of the other drugs that are topoisomerase interrupters are approved only for use as chemotherapeutic agents. It is only appropriate to use drugs that disrupt the process of DNA replication and reproduction when someone's cells are already so messed up that they have cancer.
3. Fluoroquinolones have been found to interfere with the DNA replication process for human mitochondria (3, 4, 5). Mitochondria are vital parts of our cells, (cellular energy is produced in our mitochondria), and disrupting the process through which mitochondrial DNA replicates causes cellular destruction, oxidative stress and disease.
4. Fluoroquinolones have been shown to be genotoxic and to lead to chromosomal abnormalities in immune system cells (6). Hmmm… perhaps the uptick in autoimmune diseases can be explained by the destruction of immune system cells by fluoroquinolone antibiotics. Even if not, destruction of immune system cells is not an appropriate response to an ear infection.
5. Fluoroquinolones disrupt cellular tubulin assembly (7). All of the other drugs that disrupt tubulin assembly are chemotherapeutic drugs. Again, it is only appropriate to use drugs that profoundly damage cells in extreme cases, and it's never appropriate to use them on healthy people.
6. Drugs that are derived from fluoroquinolones are chemotherapeutic drugs. Qinprezo/vosaroxin is an anti-cancer drug that is derived from quinolones (fluoroquinolones without the added fluorine atom).

I could go on. There are many, probably hundreds, of journal articles noting the deleterious effects of fluoroquinolones on human cells. The biochem in them is daunting though, so rather than going further with a list with terms such as "topoisomerase interrupter" and "tubulin assembly," I'll point you toward this video that describes how fluoroquinolones work –

https://www.youtube.com/watch?v=IkKZ_gxAOXI

Fluoroquinolones do the same thing to human mitochondria that they do to bacteria. Mitochondria are structurally very similar to bacteria and it is generally accepted that mitochondria are ancient bacteria that adapted to live symbiotically within eukaryotic cells a few billion years ago. Mitochondrial destruction leads to oxidative stress which leads to all sorts of chronic diseases – including the diseases of modernity such as fibromyalgia, chronic fatigue syndrome / M.E. , autism, Gulf War Syndrome, Alzheimer's Disease,Parkinson's, diabetes, cancer and others.

The FDA Knows How Dangerous These Drugs Are

The FDA knows that fluoroquinolones are dangerous drugs that cause mitochondrial dysfunction and cellular destruction, but they turn the other cheek and do NOTHING to curb the use of these dangerous drugs.

In their April 27, 2013 Pharmacovigilance Review, "Disabling Peripheral Neuropathy Associated with Systemic Fluoroquinolone Exposure," (8) the FDA notes that the mechanism for action through which fluoroquinolones induce peripheral neuropathy is mitochondrial toxicity. The report states:

> *"Ciprofloxacin has been found to affect mammalian topoisomerase II, especially in mitochondria. In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin cause a loss of motichondrial DNA (mtDNA) , resulting in a decrease of mitochondrial respiration and an arrest in cell growth. Further analysis found protein-linked double-stranded DNA breaks in the mtDNA from ciprofloxacin-treated cells, suggesting that ciprofloxacin was targeting topoisomerase II activity in the mitochondria."*

The FDA approved the clinical trial for Qinprezo/vosaroxin, so THEY KNOW that quinolone derivative drugs are chemotherapeutic agents.

Disregard of the Hippocratic Oath

But the FDA won't change their prescribing guidelines based on the large amount of evidence that fluoroquinolones are cell-destroying chemo drugs. Instead, they let doctors prescribe these dangerous drugs to people who are healthy other than an infection. Cancer drugs – drugs that hurt people – are being given to formerly healthy people to get rid of prostate and sinus infections.

It's a ridiculous and obscene violation of the Hippocratic Oath.

Because both doctors and the FDA refuse to acknowledge that fluoroquinolones are chemo drugs, not "just" antibiotics, the adverse effects of these dangerous drugs aren't recognized. Like all cell-destroying chemo drugs, fluoroquinolone induced cellular destruction leads to increased oxidative stress which causes multi-symptom, often chronic, illnesses. Fluoroquinolone toxicity syndrome looks and feels a lot like rheumatoid arthritis,

lupus, fibromyalgia, chronic fatigue syndrome/M.E., etc. The damage done to a person's cardiovascular system (9) by fluoroquinolones can lead to heart attacks long after exposure to the drug has stopped. The depletion of magnesium from cells by fluoroquinolones can lead to type-2 diabetes (10). Most ironically, drug induced cellular destruction can cause cancer.

Ignorance Isn't Bliss

Cellular destruction by drugs leads to illness. When it's recognized that fluoroquinolones destroy cells, the connection between them and the multi-symptom, chronic illnesses that fluoroquinolone toxicity mimics, isn't that hard to recognize.

But rather than recognizing how fluoroquinolones work (it says right on the label that their mechanism for action is interruption of topoisomerases), they are thought of as "just" antibiotics and thus the only adverse reactions that are recognized as connected with them are allergic reactions that send people to the emergency room.

Chemo drugs have long-lasting adverse effects. Often, adverse reactions to chemo drugs are delayed. There is a tolerance threshold for chemo drugs. Adverse reactions to chemo drugs are systemic. All of these things are true for fluoroquinolones (11).

If you suffer from disabling peripheral neuropathy, or brain fog, or destroyed cartilage, or any of the other adverse effects of fluoroquinolones that can be explained by the fact that they are chemo drugs, you may think that justice and retribution for your pain and suffering may be gained through suing the doctor that inappropriately gave you a chemotherapeutic drug when you didn't have cancer. Unfortunately, success with a lawsuit is unlikely because doctors are prescribing dangerous chemo drugs to generally healthy people who have infections (and even prophylactically for traveler's diarrhea) because fluoroquinolones are approved for those uses. The FDA negligently allows cell-destroying drugs to be given to people to treat simple infections and traveler's diarrhea. The FDA allows fluoroquinolone chemo drugs to be given to KIDS (ciprodex ear drops are approved for children as young as 6 months old).

The FDA Isn't Protecting You From Cell-Destroying Drugs

Do you want to take a cell destroying chemo drug when a relatively benign antibiotic in the cephalosporin or penicillin class could get rid of your infection? Do you want to give your child a chemo drug? Of course not – that's ridiculous.

But the FDA isn't keeping it from happening. They are looking the other way while more than 20 million prescriptions for fluoroquinolones are written each year. They aren't making the connection between cell-destroying drugs (fluoroquinolones are a big culprit, but they're not the only dangerous, cell-destroying drug) and the chronic diseases that plague us. They are not protecting the people from the pharmaceutical companies that

want REO for their investors, not health for the world's citizens. They are allowing the absurd situation of an acute problem – an infection – being converted into a chronic illness (fluoroquinolone toxicity syndrome and all the other diseases related to cellular destruction) by a chemo drug masquerading as an antibiotic.

Sources:

1. Urology, "Quinolone antibiotics: a potential adjunct to intravesical chemotherapy for bladder cancer."
2. FDA Warning Label for Cipro/Ciprofloxacin
3. Science Translational Medicine, "Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells"
4. Mutation Research, "Ciprofloxacin: mammalian DNA topoisomerase type II poison in vivo"
5. Molecular Pharmacology, "Delayed cytotoxicity and cleavage of mitochondrial DNA in ciprofloxacin-treated mammalian cells"
6. Nepal Medical College Journal, "Genotoxic and cytotoxic effects of antibacterial drug, ciprofloxacin, on human lymphocytes in vitro"
7. Current Medicinal Chemistry, "Recent Advances in the Discovery and Development of Quinolones and Analogs as Antitumor Agents."
8. Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology, Pharmacovigilance Review, April 17, 2013, "Disabling Peripheral Neuropathy Associated with Systemic Fluoroquinolone Exposure"
9. Journal of Antimicrobial Chemotherapy, "Quinolone-induced QT interval prolongation: a not-so-unexpected class effect"
10. Medical Hypotheses, "Fluoroquinolone antibiotics and type 2 diabetes mellitus"
11. Journal of Investigative Medicine HIGH IMPACT CASE REPORTS, "Permanent Peripheral Neuropathy: A Case Report on a Rare but Serious Debilitating Side-Effect of Fluoroquinolone Administration"

Conclusion

How could a commonly-used drug do all that damage? How could an ANTIBIOTIC do so much damage? Could a class of commonly-used antibiotics really cause mitochondrial dysfunction, oxidative stress, mineral depletion, downgrading of GABA neurotransmitters, microbiome destruction, epigenetic changes, thyroid malfunctions, fluoride toxicity, mast cell activation, decrease in vagal nerve tone, and more?

Seriously? How could a drug do all that?

Honestly, I'm not a biochemist and I'm not sure how fluoroquinolones can do all the damage that they have been shown to do. There are undoubtedly complex interactions involved in creating the multi-symptom syndrome of fluoroquinolone toxicity. There are surely feedback and feedforward loops between the many biological systems that are damaged. There are likely genetic factors that make some people more susceptible to fluoroquinolone toxicity than others. Human bodies are complex, and how a drug reacts in a human body is difficult to predict.

Any one of the documented effects of fluoroquinolones on cells could account for it causing a multi-symptom, chronic illness. For a drug to do all the damage that fluoroquinolones do to multiple bodily systems makes it an extraordinarily dangerous class of drugs.

I think that it's best to realize—truly realize—that fluoroquinolones are chemotherapy drugs that severely damage cells of all types. Fluoroquinolones are, indeed, being used as chemotherapeutic agents to help fight cancer. Like all cancer-fighting chemotherapies they can save lives, but they are also dangerous drugs that should be used with caution.

Fluoroquinolones should only be used in life-or-death situations. It is not appropriate to use dangerous drugs to treat benign infections that are not life-threatening. The consequences of fluoroquinolone use are serious, and adverse reactions are severe.

I hope that the dangers of fluoroquinolones are recognized someday, and that their use is strictly curtailed. The victims of fluoroquinolones deserve recognition. More than recognition, most victims of fluoroquinolones want to prevent others from being hurt. Prudent, appropriate use of these dangerous drugs is necessary, and it is the right thing for the medical establishment to do.

Even with all the damage that fluoroquinolones do, people recover from fluoroquinolone toxicity. There are stories of hope and healing on www.floxiehope.com. Life goes on after fluoroquinolone toxicity—cells heal, mitochondria are replaced, energy returns, health returns, struggles end and happiness renews.

It's true that not everyone recovers from fluoroquinolone toxicity, but many do. It's possible that most do. Time, proper nutrition, supplements, pharmaceuticals, alternative health practices (like acupuncture and chiropractic), movement, physical therapy, and more, have helped people through fluoroquinolone toxicity.

As a wise friend once said, "No side-effect can be proven permanent until you're dead." It's true.

For my "floxie" friends reading this—though the fluoroquinolone you ingested hurt you, it didn't kill you. Try to believe that you're going to be okay. Hope and optimism are helpful and healing, they really are. There are recovery stories and helpful hints available through many sources on www.floxiehope.com. Many people have found the e-book, The Fluoroquinolone Toxicity Solution to be helpful and informative. It is available through www.floxiehope.com as well.

I wish all "floxies" healing. May your body heal and may you find health and happiness again.

Thank you to everyone who signed up for the Floxie Hope email list, read this ebook, and is interested in learning about fluoroquinolone toxicity! Adverse drug reactions aren't easy or fun topics, so I'm assuming that your interest stems from either wanting to know what happened in your body, or wanting to help a loved one. I hope that the assertions and hypotheses in this ebook help you to understand the problem, so you can be closer to the solution.

I'm available to answer questions or address concerns. Please don't hesitate to reach out to me through the "Contact" link on www.floxiehope.com.