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An evaluation of reports of ciprofloxacin, levofloxacin, and moxifloxacin-association neuropsychiatric toxicities, long-term disability, and aortic aneurysms/dissections disseminated by the Food and Drug Administration and the European Medicines Agency

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Abstract

Introduction—Ciprofloxacin, levofloxacin, and moxifloxacin belong to the fluoroquinolone class of antibiotics and are amongst the most commonly prescribed antibiotics. In 2018 and 2019, Food and Drug Administration (FDA) and the European Medicine Agency (EMA) requested that manufacturers harmonize FQ safety information related to neuropsychiatric, aortic dissection, and long-term disability. The authors hypothesize that FDA and EMA epidemiologists support a strong association between these drugs and the three toxicities.

Areas covered—Studies of FQ-associated neuropsychiatric toxicity, long-term disability, and aortic ruptures/dissections. Clinical sources include FDA Advisory Committee documents, a 2014 Citizen Petition filed with the FDA requesting safety information additions to FQ labels for neuropsychiatric toxicities (partially granted in 2018), an under-review Citizen Petition under review by the FDA requesting a FQ Risk Evaluation and Mitigation Strategy, and safety notifications from the EMA.

Expert opinion—FDA and the EMA reports state that neuropsychiatric toxicity, long-term disability, and aortic dissections//aneurysms occur with all FQs. Disability and neuropsychiatric

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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toxicity can occur after one dose or several months after FQs. United States' and European' regulators warn physicians not to prescribe FQs for uncomplicated acute urinary tract infection, sinusitis, or bronchitis, unless other possible choices are tried first, as risks outweigh benefits in these settings.

Keywords

fluoroquinolones; adverse events; neuropsychiatric toxicity; restricted distribution; REMS (Risk Evaluation and Mitigation Strategy)

1 Introduction

Protecting patients from potentially life-threatening adverse drug effects is incumbent upon manufacturers, pharmaceutical companies, regulatory agencies, providers, and pharmacists. From Phase I studies through market approval and usage, adverse reactions that occur infrequently become evident as larger numbers of patients receive a drug. As fluoroquinolones (FQs) are administered to 22 million patients annually, adverse events including tendonitis and tendon ruptures, retinal detachment, peripheral neuropathy, neuropsychological impairment, prolongation of the QT interval, perforation of the tympanic membrane, aortic aneurysms/dissections have been observed.[1] Since 1996, regulatory agencies or advisory bodies in the United States (the Food and Drug Administration (FDA)) and the European Union (the European Medicines Agency (EMA))disseminated numerous public health communications and held Advisory Committees and manufacturers have disseminated Dear Health Care Letters, revised Medication Guides, and revised product labels in an effort to clearly disseminate new and harmonized FQ safety information. We review clinical findings associated with notifications disseminated by the EMA and the FDA since 2014.

2 Background for the study

Review papers of basic science studies that described the pathophysiology of FQ-associated neuropsychiatric toxicity, aortic aneurysms/dissections, or long-term disability that were published between 2013 and 2019 were reviewed. [1–7] These articles provide context for the primary study hypothesis. This hypothesis is that reports presented at FDA and EMA would identify strong statistical associations between use of the three FQs and neuropsychiatric toxicity, aortic aneurysms/dissections, or long-term disability, although empirical studies identifying causal relationships would not be found in the same data sources.

2.1 Fluoroquinolones and matrix metalloproteinases (2018)

In vivo and animal research show that FQs upregulate matrix metalloproteinase (MMP) enzymes that degrade collagen, especially collagen I and III. Cell biology and animal research identified mechanisms by which FQs lead to tendon rupture.[3,4] FQs upregulate MMP-1, MMP-2, and MMP-13, resulting in reduced diameter and amount of type I collagen fibrils. FQs cause degenerative changes in tendon cells with vacuole formation, organelle

dilatation, and apoptosis.[2] MMP-1, MMP-2, MMP-8 and MMP-9 expression occurs in corneal epithelium groups treated with topical FQs.[3]

Collagen and elastin are extracellular matrix components of aortic walls. In a human *in vitro* study, aortic myofibroblasts were isolated from nine patients with aortopathy undergoing elective aortic resection.[4] The study assessed extracellular matrix degradation in FQ exposed cells by multiplex analysis of secreted MMPs relative to tissue inhibitors of matrix metalloproteinases. Aortic cellular collagen-1 expression increased following FQ exposure as noted by immunoblotting, immunofluorescent staining, apoptosis, and necrosis.

2.2 Preclinical studies (2016)

Basic science hypothesis-generating findings for FQ toxicity were reported by Kaur et al. [5] Six- to eight-week-old C57BL/6 mice were treated with ciprofloxacin. Treatment groups received 10, 20, 30, 40, and 50 mg/kg of ciprofloxacin, respectively, and 1 control group received placebo. Limb strength was measured using grip strength meters every second day over 10 days. Rotarod experiments for evaluation of locomotion and balance were performed every other day. Elevated plus maze was used to measure anxiogenic effects, by comparing time spent by mice in the maze's closed and open arms during 5 minutes. Locomotory behaviour was analysed by counting number of squares crossed by mice in 5 minutes on the elevated plus maze. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and high-mobility group binding protein-1 immunochemistry on brain tissue slides quantified apoptosis and necrosis. Mice receiving 30, 40, and 50 mg/kg ciprofloxacin showed decreased numbers of successful rotations on the rotarod, compared with controls. For groups receiving 40 and 50 mg/kg ciprofloxacin, the number of successful rotations decreased significantly on Day 10 versus Day 0. There was a significant increase in percentage of closed arm entries on the elevated plus maze in treatment versus control groups, except for the 10 mg/kg ciprofloxacin group. The percentage of closed arm entries consistently increased with increasing ciprofloxacin dosage. There was significantly decreased locomotor activity on the open field apparatus among all treatment groups compared with control counterparts on days 5 and 10. Significant decreases in locomotor and exploratory behaviour alterations occurred for 10, 20, 30, and 40 mg/kg ciprofloxacin groups on Day 10 compared with Day 5 within the same group. Brain cortex tissue showed higher levels of apoptosis among all treatment groups compared with controls. Immunohistochemical studies on brain tissues revealed higher expression in levels of the high-mobility group protein-1 protein among ciprofloxacin-treated mice compared with controls and corresponded to ciprofloxacin dosage.

2.3 Neuropsychiatric toxicity- a genetic study (2017)

Another hypothesis generating study relates to whole genome sequencing studies from 24 persons with self-reported ciprofloxacin-associated neuropsychiatric toxicities. Persons were affiliated with the National Institutes of Health R01 funded SONAR project and a social network group.[1, 6,7] Individuals were mostly white (83%), female (65%), and < 40 years of age (61%), Sixteen patients experienced severe gastrointestinal distress, 9 patients experienced persistent headaches, and 18 experienced severe cognitive impairment. Thirteen patients (56%) had markers for one specific CYP450 gene related to pharmaceutical

metabolism. While information on cytochrome P450 metabolism is referenced on the product label for ciprofloxacin, our findings support this statement. Ongoing studies will evaluate levofloxacin and moxifloxacin and potentially identify additional genetic markers. Identification of this gene may lead to a diagnostic test that would facilitate recognition of high risk persons for FQ-associated neuropsychiatric toxicity.

2.4 Mitochondrial toxicity (2013)

Another FDA-proposed hypothesis generating investigation relates to FQ effects on mammalian topoisomerase II. *In vitro studies* in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin cause loss of mitochondrial DNA resulting in decreased mitochondrial respiration and arrested cell growth.[8] Mitochondrial conditions that are due to ATP insufficiency, especially in organs that rely on mitochondria for energy, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like Parkinson's, Alzheimer's and amyotrophic lateral sclerosis are associated with loss of neurons due to oxidative stress. *In vitro* studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin cause mitochondrial DNA (mtDNA) loss leading to decreased mitochondrial respiration and cell growth arrest. Protein-linked double-stranded DNA breaks in mtDNA from ciprofloxacin-treated cells suggest that ciprofloxacin targets mitochondrial topoisomerase II activity. [8]. An oxidative phosphorylation system lying on the mitochondrion's inner membrane provides 95% of the cell's ATP requirements. The mitochondrial respirator chain is a major producer of oxidative stress that occurs when there is greater production of reactive oxygen species than antioxidative processes. About 1–4% of oxygen reacting with the respiratory chain is incompletely reduced to the superoxide radical ion, hydrogen peroxide, lipid peroxides, and other free radicals. Under normal circumstances, reactive oxygen species are removed or do not build up and cellular damage such as lipid peroxidation, mtDNA mutations, and DNA strand breaks do not occur. If this does not happen, extensive oxidative damage can occur. Mitochondrial conditions resulting from insufficient ATP, especially in organs that rely on mitochondria for energy, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Phototoxic effects of FQs are due to mitochondrial formation of a singlet oxygen and superoxide anion. Because accumulation of DNA damage is a well-known factor that induces neurodegeneration, FQ-mediated neurotoxicity is consistent with its inhibitory effect on topoisomerase II. FQs also inhibit protein synthesis by inhibiting amino acyl-tRNA synthetases and prolonged inhibition of neuronal protein synthesis exacerbates oxidative stress and DNA damage-mediated neurotoxicity. Therefore, FQ's toxicity may have emerged from FQs promiscuous ability to target multiple organs vital to neuronal survival under stress conditions.

3 Data sources

All FQ -related safety notifications contained in FDA and the EMA databases for the years 2013 to 2019 were reviewed.[8–29] Keywords included ciprofloxacin, levofloxacin, moxifloxacin, fluoroquinonlones. Specific databases included Drugs@FDA and Medicines contained in the EMA database. Documents reporting on background and presentations at

FDA Advisory Committee and before the EMA Pharmacovigilance Risk Advisory were the primary data sources.

4 Specific clinical syndromes

4.1 Aortic dissection and aneurysm (2018)

Aortic dissection and aortic aneurysm are life-threatening diseases. In 2018, FDA reported on a FDA Adverse Event Report (FAERS) and a literature review of associations between FQ use and aortic aneurysm/dissection.[29] Lee et al described an increased risk of aortic aneurysm or dissection based on a rate ratio of 2.28 (95% confidence interval [CI]=1.67–3.13), after adjusting for individual confounders.[9] Patients older than 70 years appeared to have a higher risk. FDA noted that this study had design and analytical limitations. FAERS review of cases submitted through 2015 identified 15 cases of aortic aneurysm or dissection with FQ use. All patients had other risk factors including smoking, male gender, older age, hypertension, and atherosclerosis. FDA concluded that a causal association between aortic aneurysm or dissection with fluoroquinolones could not be determined. In 2018, FDA updated this review and included three epidemiological studies published between 2015 and 2018.[24] The studies found increased risks of aortic aneurysm or dissection with FQ. Each study had limitations including confounding by indications and small sample sizes.[10–12] FDA conducted another FAERS search from 2015 through 2018, identifying 56 cases of aortic aneurysm or dissection during or after FQs. All patients had at least one risk factor for aortic aneurysm or dissection, and most cases were submitted by litigation attorneys. FDA concluded that evidence on associations between FQ use and aortic aneurysm or dissection was consistent across epidemiological studies with an approximate two-fold increased risk over baseline risk of aortic aneurysm or dissection in each study.

Pasternak et al's retrospective cohort study evaluated risk of aortic aneurysm or dissection with oral FQ compared to amoxicillin use during the first 60 days after the start of treatment in patients aged 50 years or older.[11] To investigate timing, the 60-day risk period was divided into 10-day intervals. In the first 60-day risk period, FQ patients showed a 1.66-fold increased risk (95% CI=1.12–2.46) compared to amoxicillin patients. Secondary analysis by 10-day interval showed increase in risk mainly in the first 10 days. Secondary analyses investigated risk in days 61 to 120. There was no increased risk associated with FQs in this period (hazard ratio [HR]=0.67; 95% CI=0.40–1.11).

Daneman et al conducted a retrospective cohort study comparing the risk of severe collagen-associated adverse events, including aortic aneurysm, during periods of FQ use to periods of non-use in older patients turning 65 years old between 1997 and 2012.[10] Patients who received FQs were more likely to have baseline comorbidities, including hypertension, diabetes, atherosclerosis, and infections compared to those who never received FQs. After adjustment for baseline characteristics, the hazard of aortic aneurysm increased by 2.24-fold (95% CI=2.02–2.49) during a 30-day risk window following the treatment episode.

Howard et al. conducted self-controlled analyses to evaluate the association between FQs and aortic aneurysm or dissection in elderly patients (mean age, 71 years) [12] Each patient served as his/her own control to reduce or eliminate between-patient differences. The case

interval was a 60-day period before the diagnosis date of aortic aneurysm or dissection, and the control interval was one randomly selected 60-day period between 60 to 180 days before the event. This study found increased risk of aortic aneurysm or dissection associated with FQ exposure (odds ratio [OR]=2.71; 95% CI=1.14–6.46). Also, FQ exposure for longer than 14 days was associated with higher risks of aortic aneurysm or dissection (for 3–14 days of exposure, OR=2.41, 95% CI=1.25–4.65; for >14 days of exposure, OR=2.83, 95% CI=1.06–7.57).

Background risk of aortic aneurysm and dissection varies depending on the population at risk. One study reported an estimated annual risk for aortic aneurysm ranging from nine aortic aneurysm events per 100,000 persons in a general population to 300 aortic aneurysm events per 100,000 persons at highest risk (e.g., persons over the age of 85 years).[12]

4.2 Tendinopathy and cardiac arrythmia (2015)

FDA reviewers at the 2015 Advisory Committee meeting focused on six FQ-associated advents: acute kidney injury, anaphylaxis, tendinopathy, peripheral neuropathy, retinal detachment, and cardiac arrhythmias (the FDA reported that their review identified 722 articles in PubMed from 1996 to 2015).[15] Publications that were not epidemiologic studies, had no safety data, or only assessed pediatric populations were not reviewed. The result was 25 publications, all observational epidemiologic studies and one poster of FDA/Department of Defense Work. Eleven studies and the poster focused on tendinopathy. A consistently elevated risk of tendinopathy was observed, using healthcare claims or prescription event monitoring data. For arrhythmias, one study used infection-related diagnoses in the past year and focused on all-cause mortality.[13] Chou et al used diagnoses associated with the index prescription and focused on cardiovascular deaths.[14] For every 100,000 prescriptions or patients who received FQs, 12 to 57 patients experienced cardiac arrhythmias.[13,14] Underlying cardiovascular disease greatly increased serious arrhythmia risks. Peripheral neuropathy was evaluated based on review of two studies, including one FAERS analysis. Compared to controls, cases were 30% more likely to have used any FQ in the past year and 80% more likely to have an active FQ prescription.

4.3 Fluoroquinolone-associated disability (FQAD) (2013–2015)

A new toxicity, FQ-associated disability (FQAD), was first described in detail at FDA Advisory Committee meetings in April 2013 and November 2015.[8,15] Overall, 76% of FQAD patients reported other adverse events including prolonged and disabling neuropsychiatric toxicity, vision changes, cardiac events, and musculoskeletal events. The 2015 FDA update included a requirement that the FAERs report identify formal disability as a problem and that the AE lasted 30 days or longer after FQ discontinuation.[15] A FDA epidemiologist described at the 2015 Advisory Committee meeting 1,222 disability reports in the FAERS dataset with levofloxacin and ciprofloxacin having the highest numbers.[15] Excluded from analysis were 540 reports without documentation of multi-system toxicity and 15% more as the adverse event resolved less than 30 days after stopping the FQ. Overall, 178 FAERs reports for FQAD were described. The median age was 48 years (range, 13 to 84 years). Women accounted for 78% of the cases. Direct reports to the FDA were noted in 85% of the cases. A median of 3 days was for onset time (range, 1 hour to 3

months after FQ discontinuation). Onset was rapid in 50%, while in 12%, onset occurred more than 10 days after FQ discontinuation. In this time-limited data set, the longest FQAD duration was nine years after onset. One quarter of the FAERs reports described disabling findings for > 1 year. Musculoskeletal events (tendon, joint, and muscle) were reported in 97%, neuropsychiatric events in 68%, and peripheral venous events in 63%- occurring with a few days to a few weeks of each other. In the musculoskeletal group, joint pain was most commonly reported, followed by tendon pain or tendonitis, muscle pain, and muscle weakness. Pain was the most commonly reported symptom. With respect to neuropsychiatric toxicities, fatigue was followed by insomnia, anxiety, severe headaches, and dizziness. For peripheral nervous system toxicity, peripheral neuropathy was the most commonly reported. Also in the reports were episodes of diminished vision, tinnitus, and blurred vision. Overlap of symptoms occurred in the majority of patient reports.

4.4 FQ-associated suicides (2018)

The FAERS database is the source of data for this toxicity, a toxicity that has been described with variable estimates of incidence and risk factors in labels for ciprofloxacin, levofloxacin, and moxifloxacin.[30] Included cases had no psychiatric history or stable, controlled, psychiatric illness; had attempted or completed suicide; and were reported to the FDA listing the FQ as the suspected causal drug. Of 122 FQ associated suicide-related events in the FAERS database, 108 met inclusion criteria. One third of the reports were from physicians. Half of the cohort completed suicide; 61% were male, 18% were < 35 years old, and 42% had the event occur ≤ 2 weeks after FQ initiation. Characteristics of persons who attempted versus completed suicides were similar for age, gender, and event occurrence ≤ 2 weeks after FQ initiation. One third had received an FQ for UTI, 12% for sinusitis, and 12% for upper respiratory infection.

5 Assessments of FQ-associated neuropsychiatric toxicities, long-term disability, and aortic dissection/aneurysm reports contained in FDA and EMA databases

5.1 Assessment of FQ safety and toxicity updates by the Food and Drug Administration (2018–2019)

In July 2018, FDA’s Janet Woodcock, Director of FDA’s Center for Drug Evaluation and Research, reviewed FDA’s information on neuropsychiatric toxicities in her response to Bennett’s Citizen Petition.[16] FDA review found that the terms “agitation, delirium, disturbance in attention, memory impairment, disorientation, and nervousness” were frequently included in FAERS reports and therefore, FDA requested that FQ manufacturers add these terms to the “Warnings and Precautions: sections of all three FQ labels. FDA reviewers reported a reasonable evidence of a causal association between these drugs and the identified neuropsychiatric toxicities. Woodcock reported that based on this review, FDA required manufacturers to add a new subcategory to the Central Nervous System Effects section of all FQ labels to include a subsection called “Psychiatric Effects” that outlines toxicities of “toxic psychoses, hallucinations, or paranoia; depression or suicidal thoughts; anxiety; agitation, restlessness, or nervousness; confusion, delirium,

disorientation or disturbances in attention; lightheadedness; insomnia or nightmares; and memory impairment. Attempted or completed suicide have been reported, especially in patients with a medical history of depression or an underlying risk factor for depression. These reactions may occur following a first dose." This information is referred to in Boxed Warnings, indicating that they are serious adverse drug reactions. FDA also warned of risks of hypoglycemic coma. FDA noted that mental health side effects and serious blood disturbances are now consistent across FQ product labels. The labeling changes were made based on FAERs and published case reports.

Health care professionals were advised that FQs should not be prescribed to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections because the risks outweigh the benefits. In 2018, a FDA review found that FQs can increase occurrence of rare but serious aortic dissections or aortic aneurysm ruptures that could lead to hemorrhage or death. [29] FDA concluded that epidemiological studies and FAERS cases provided evidence of an association between FQ use and risk of aortic aneurysm or dissection, but they could not determine a causal association due to study limitations.

5.2 Assessments of toxicities by the European Medicines Agency (2018–2019)

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) held a public hearing in June 2018 to review FQ adverse events.[17] This was only the second such public meeting ever convened by the PRAC. PRAC recommended that certain FQs be taken off the market and has recommended that the use of other FQs be restricted. The Committee for Medicines for Human Products (CHMP) accepted the PRAC recommendations in November 2018. In 2019, the EMA made a final legal determination regarding FQ changes that has been adopted by all 29 member states. These recommendation parallel those that have been made in the United States in 2018.

In 2018, the European Committee on Human Medicines Product (CHMP) confirmed that the use of FQs should be restricted. Also, prescribing information for healthcare professionals and information for patients now describe disabling and potentially permanent side effects and advise patients to stop treatment with FQs at the first sign of side effects involving muscles, tendons or joints and the nervous system.[21] Restrictions will mean that FQs should not be used: to treat infections that might get better without treatment or are not severe (such as throat infections); to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;; for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder); to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used. Importantly, FQs should generally be avoided in patients who have previously had serious side effects with FQs. They should be used with special caution in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a FQ also increases this risk, combined use of these medicines should be avoided. The benefits and risks of FQs will be monitored continuously in Europe and a drug utilisation

study will evaluate the effectiveness of the new measures to reduce inappropriate use of FQs by investigating changes in prescribing behaviour.

6 Assessments of FQ-associated toxicities by other regulatory agencies

6.1 Assessments of rare FQ-associated cases of aortic dissection/aneurysm by the Australian Therapeutic Goods Administration (TGA) (2019)

On April 10, 2019, the TGA announced that they were investigating rare but serious adverse event of aortic dissection/aneurysm based on reports of this toxicity that were disseminated in FDA's 2018 Drug Safety Communication and EMA's 2018 PRAC recommendations to update FQ safety information to include warnings of this risk.[21,25,29] TGA has not received any Australian adverse event reports of this toxicity but is monitoring its adverse event reports closely. Other FQ toxicities including neuropsychiatric toxicities, disability, and tendon ruptures are listed in product labels according to organ systems, but no Black Box warnings are included in these labels.

6.2. Assessments of FQ-associated permanent serious adverse reactions including tendinopathy, peripheral neuropathy, and central nervous system disorders by Health Canada (2017) and Alberta Health Services (2018)

In 2017, Health Canada reported in a Safety Review that healthcare professionals were reminded to consider the potential for disabling and persistent serious adverse events when choosing to prescribe FQs, avoid FQs in patients who have previously experienced serious adverse reactions associated with them; stop FQ treatment if a patient reports any serious adverse reaction.[26,27] Health Canada is currently working with manufacturers to strengthen the prescribing information for these drugs. Health Canada identified 115 reports of persistent and disabling FQ side effects. In 29 reports, the causal link was probable and in 49 reports it was possible. Canada Health noted that available published literature supported a link between FQs and permanent disability, particularly for side effects such as tendinopathy and peripheral neuropathy. Health Canada noted that FQs are associated with a two-fold to three-fold increased risk of tendon rupture and aortic dissection.

In 2018, the Alberta province issued a backgrounder indicating with a Boxed Warning that FQs are associated with rare but persistent and disabling adverse effects.[28] Physicians were advised to avoid FQ use in treatment of uncomplicated urinary tract infections, acute bronchitis, and acute sinusitis as the risks (adverse, resistance) outweighed the benefits.

7 FQ-related safety litigation

Additional information on FQ-associated neuropathy, disability, and aortic aneurysms/dissection has been described in litigation that has been filed in several state courts in the United States.

7.1 Multi-District Litigation (MDL) for FQ-associated neuropathy (2018)

A MDL consists of a large number of cases pending before state courts and that are consolidated in a single court-room where a judge and a jury can rule on each case in

a one-by-one manner. This is different than class-action lawsuits where a judge and jury rules on one case that represents concerns that apply to an entire legally certified class of individuals. MDL # 15—MDL-2642 is an MDL where plaintiffs claim that they have suffered FQ-associated neuropathy.[31] Of note, peripheral neuropathy was added to FQ labels in 2004. Product labels noted that nerve damage was a rare toxicity that would reverse when levofloxacin was discontinued. Studies from 2001 noted that symptoms developed within one week of FQ initiation and in most cases persisted for > 1 year. In 2013, FDA required that an update to the levofloxacin label including strong warnings, removal of the word “rare,” and emphasis on rapid symptom onset and in most cases, persisted for > 1 year even if levofloxacin were discontinued.

Defendants deny that FQs are defective or unreasonably dangerous and that they failed to provide adequate warnings. The defendants are Bayer Pharmaceuticals, Merch, Johnson and Johnson, Janssen Pharmaceuticals, McKesson Corporation, Schering Pharmaceuticals, and Bayer Corporation. A MDL Judicial Panel determined that centralizing the FQ neuropathy cases was appropriate. The Honorable John R Tunheim in Minnesota coordinates discovery and pretrial matters. Follow-on FQ neuropathy cases filed in federal court will be transferred to the District of Minnesota and become part of the MDL as “tag-a-long” cases. After discovery and pretrial matters conclude, cases that make up MDL # 15–2642, unless otherwise resolved, will be transferred back to districts in which they were originally filed for trial or other proceedings. [30] In 2016, *o*f nearly 400 peripheral neuropathy cases, 383 cases were pending in federal litigation and 39 claims were filed in the Philadelphia Court of Common Pleas. In 2018, Judge Tunheim stayed proceedings for defendants Bayer Incorporated and Merck and Company.

By 2018, 750 cases were in the MDL. As part of pretrial proceedings, small groups of FQ-associated peripheral neuropathy lawsuits were prepared for trial. The first round of these “bellwether” cases began in 2018 and a second one was scheduled for in January 2019; a ciprofloxacin trial in March 2019, and two more moxifloxacin trials in 2019. Another 18 cases make up the second phase of “bellwether trials, with eight cases to be selected by defense attorneys and eight by plaintiffs attorneys. All cases must have been filed after April 21, 2016 and must not include claims where defendants received more than one FQ product. Litigation began after FDA required manufacturers to update warning labels in 2013 adding text about permanent FQ-associated nerve damage and Bennett filed a 2014 Citizen Petition describing potential for permanent levofloxacin-associated nerve damage. Prior warnings indicated that some FQ users developed temporary nerve damage in rare cases. Plaintiffs allege that manufacturers should have provided stronger warnings disclosing permanent neuropathy risks. Plaintiffs and the Bennett Citizen Petition filed with the FDA in 2014 argue that the first signal of a possible permanent nerve damage was published in 2001. If adequate warnings had been provided, plaintiffs claimed that they may have avoided painful debilitating injuries. In 2016, FDA issued a Drug Safety Communication advising clinicians not to prescribe FQs for common uncomplicated infections of the urinary tract, sinus, and lung unless other antibiotics were not available- as risks outweighed the benefits. Available information at the FDA 2015 Advisory Committee meeting reviewed risks of peripheral neuropathy, tendon ruptures, retinal detachments, and other safety concerns. As of 2019, 513 federal court cases of FQ-associated peripheral neuropathy were pending

against Bayer, Merck, Johnson and Johnson, Janssen, and Bayer alleging failure to warn. In 2015, the US Judicial Panel on MDL ordered all federal cases of FQ-associated neuropathy transferred to US District Judge John R Tunheim in the District of Minnesota. As of 2018, there were 1,212 actions- although several cases were settled for confidential amounts. Lawsuits involving levofloxacin were settled by Johnson and Johnson, while cases involving moxifloxacin and ciprofloxacin did not.

7.2 Multi-District Litigation (MDL) for FQ-associated tendon rupture (2018)

Judge John Tunheim also presided over MDL # 08–1943, which consisted of plaintiff's allegations that levofloxacin cases tendon ruptures.[32] Defendants were Johnson and Johnson and Ortho-McNeil. In 2008, the FDA required FQ manufacturers to increase their warnings of tendon rupture. Plaintiff's attorneys claimed that destroyed an adverse clinical study about levofloxacin and tendon rupture and physicians were not warned of this risk. In 2010, a Minnesota Federal jury awarded a plaintiff in the first levofloxacin bellwether case $1.8 million. In 2013, of the 1,879 pending claims for 1,892 plaintiffs on levofloxacin-associated tendon rupture, Johnson and Johnson had settled claims for 1182 plaintiffs and 153 more were in settlement negotiations. In August 2015, the U.S. Judicial Panel on MDL ordered all ciprofloxacin- and moxifloxacin- -associated neuropathy cases consolidated for pretrial proceedings to US District Judge John R Tunheim. By September 2018, the federal MDL had reached 1212 actions, although several had been settled for confidential amounts. As of April 2019, 513 of these cases were pending in federal court, alleging failure to warn.

7.3 Litigation for FQ-associated aortic aneurysm and aortic dissection (2018–2019)

In October 2015, a JAMA Internal Medicine study reported increased risks of aortic dissection/ aortic aneurysm with FQ use. According to allegations raised in lawsuits involving ciprofloxacin, levofloxacin, and moxifloxacin, FQ users may face more than two-fold increased risk of aortic dissection/rupture. As noted above, FQs may decrease the strength of extracellular matrix proteins, that are regulate by proteolytic enzymes, including MMPs. The working theory is that FQs decrease production of MMPS which leads to extracellular matrix degradation and then tendon rupture and aortic dissection/rupture. In December 2018, FDA issued a safety alert of risks of aortic ruptures/dissections with FQs. No MDL exists, while individual cases may have been filed.

8 Conclusions

Since 2013, a dizzying array of serious adverse drug reactions associated with fluoroquinolones have been identified and are now described in the same format in product labels for ciprofloxacin, levofloxacin, and moxifloxacin in the United States and in European Union countries. In Europe and the United States, FDA and EMA advised that FQs should be prescribed for uncomplicated urinary tract infections, sinus infections, or bronchitis when all other antibiotic options are not available. The newest serious adverse drug reactions were fluoroquinolone-associated disability (described by Deborah Boxwell of the Office of Surveillance and Epidemiology of the FDA (2013 and 2015)), serious neuropsychiatric toxicities, as described in a Citizen Petition from Charles Bennett in 2014 and responded to affirmatively by Janet Woodcock, Deputy Director of the FDA

in 2018 and aortic dissections.[16,18] An important aspect is collaboration of a social network who experienced severe FQ-associated toxicities and an National Cancer Institute R01 funded SONAR pharmacovigilance at the University of South Carolina. Because it has been empirically documented for some serious adverse events that only 1% of these serious adverse events are reported to the FDA.[33] Using this estimate, the estimated average number of individuals with FQ-associated deaths during the years December 1996 to May 2016 can be estimated at 102,000 for ciprofloxacin; 147,000 for levofloxacin; and 63,000 for moxifloxacin (based on the actual annual number of FAERS reports for ciprofloxacin, levofloxacin, and moxifloxacin-associated adverse events reported between January 1, 1990 and June 30, 2019 as noted in the FAERS database and multiplying by the 100-fold underreporting rate that was empirically derived in reference 33).[33,34]

9 Expert opinion

Regulatory agencies in the United States, Europe, Canada, and Australia have each evaluated the association between use of ciprofloxacin, levofloxacin, and moxifloxacin and subsequent development of neuropsychiatric toxicities, aortic aneurysms/dissections, and long-term disability.(Table I) These toxicities were not recognized until 2013 and then have been described extensively by regulatory agencies as well as the manufactures of these three drugs. The data supporting these changes are primarily statistical associations, while causal investigations are ongoing. In an important development for safety evaluations conducted by the EMA and the FDA, patients have been included in formal presentations held by Advisory Committees to the FDA and to the EMA. The neuropsychiatric toxicities include attempted or completed suicide that has reportedly occurred within one or two days of initiation of ciprofloxacin, levofloxacin, and moxifloxacin. The long-term disability is an entirely new syndrome that is now known in the medical literature as FQ-associated disability (FQAD), where disability can persist for years and can begin within days of initiation of ciprofloxacin, levofloxacin, and moxifloxacin or even months after discontinuing one of these medications. These toxicities have been described among patients who had previously received ciprofloxacin, levofloxacin, or moxifloxacin and had not developed toxicity. Studies are ongoing related to genetic risk factors, causality, and therapeutic approaches to eradication of these toxicities. Patients who develop these toxicities and their pharmacists and medical providers should report the events to the relevant regulatory agency and to the pharmaceutical manufacturers, as these toxicities are being actively investigated. In the future, it is hoped that centers of excellence for ciprofloxacin, levofloxacin, and moxifloxacin associated toxicities are developed. A key limitation to developing these centers and to conducting research on ciprofloxacin, levofloxacin, and moxifloxacin associated neuropsychiatric toxicity, long-term disability, and aortic aneurysms/dissections is the absence of a specific laboratory test for these diagnoses. Key areas for future study are further evaluation of the genetic risk factors for these toxicities, identification and validation of diagnostic approaches, and consensus opinions on optimal medical therapies. It is hoped that in five to ten years from now, the annual number of persons receiving inappropriate prescriptions for ciprofloxacin, levofloxacin, and moxifloxacin has declined to almost zero and the burden of related illness is almost zero. Optimally, a global fund to support the long-term costs of these toxicities

should be established as thousands of persons are currently disabled by ciprofloxacin, levofloxacin, or moxifloxacin.

Based on extensive safety reporting by clinicians, epidemiologists, patients, and medical personnel employed by manufacturers of fluoroquinolones, and recommendations from advisory committees to regulatory agencies in the United States, Europe, Canada, and Australia, a marked change in the recommended use of FQs for treatment of uncomplicated urinary tract infection, sinusitis, or bronchitis has occurred. In general, in these settings, FQs should not be prescribed unless all other options have been tried. Inpatient and outpatient antimicrobial Stewardship Programs would be ideal change agents here.[35,36]

If Antimicrobial Stewardship programs are successful, noticeable outcomes would be a large decrease in the number of persons who receive these three drugs for diagnoses that are unlikely to be bacterial and secondly, a large decrease in the number of persons who develop ciprofloxacin, levofloxacin, or moxifloxacin associated neuropsychiatric toxicities, aortic aneurysms/dissections, or long-term disability annually. Major barriers to this occurring has been long-standing practice patterns where FQs are prescribed empirically to large numbers of patients who do not have bacterial infections.

However, if Antimicrobial Stewardship programs in the inpatient and outpatient settings fail to lead to meaningful changes in medical practice, some consideration should be considered to placing these drugs under a Risk Evaluation and Mitigation Strategy whereby a fluoroquinolone can not be prescribed unless the patient signs an informed consent agreement that risks and benefits have been described, the physician who prescribes the drug has participated in a formal regulatory agency approved education session and co-signs the informed consent agreement, and the pharmacy that distributes the fluoroquinolone also has registered with the regulatory agency that it will comply with the formal safety notification efforts are designed as part of the REMS- similar to REMS that were established for erythropoietin and darbepoetin in 2010 (these REMS were removed in 2017).[19] Finally, policy makers could consider supporting a patient assistance compensation fund for persons who have experienced long-term fluoroquinolone-associated toxicity and for basic science investigation of fluoroquinolone-associated toxicity.

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References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Marchant J When antibiotics turn toxic. Nature 2018; 555: 431–433. **This paper provides a concise overview of the most recent FQ-associated toxicities and the genetic testing findings that are the basis for the Provisional Patent Application by SONAR.

2. Tsai WC, Hsu CC, Chen CP, et al. Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen. J Orthop Res 2011;29:67–73. [PubMed: 20602464]

3. Reviglio VE, Hakim MA, Song JK et al. Effect of topical fluoroquinolones on the expression of matrix metalloproteinases in the cornea. BMC Ophthalmol. 2003 Oct 6;3:10. [PubMed: 14529574]

4. Guzzardi DG, Teng G, Kang S et al. Induction of human aortic myofibroblast-mediated extracellular matrix dysregulation: A potential mechanism of fluoroquinolone-associated aortopathy. J Thorac Cardiovasc Surg. 2019 Jan;157(1):109–119.e2. doi: 10.1016/j.jtcvs.2018.08.079. Epub 2018 Sep 21. [PubMed: 30528439]

5. Kaur K, Fayad R, Saxena A et al. Fluoroquinolone-related neuropsychiatric and mitochondrial toxicity: a collaborative investigation by scientists and members of a social network. J Community Support Oncol. 2016;14(2):54–65. [PubMed: 26955658] **This manuscript includes basic science findings for FQ-associated toxicity, FDA Adverse Event Report System (FAERS) data, and background information that supported the 2014 Citizen Petition by Dr. Bennett and the 2018 FDA Response by Janet Woodcock MD from the FDA.

6. Bennett A, Qureshi ZP, Bennett CL. A novel genetic marker has been identified in patients with fluoroquinolone-associated neuropyschiatric toxicity: Preliminary findings. Federal Practitioner 2017; S30 (abstract). [PubMed: 30766308] **This abstract includes the findings that underly the Provisional Patent Application for genetic testing for ciprofloxacin-associated neuropsychiatric toxicity.

7. Schroeder MO. Could taking that antibiotic have serious long-term consequences? US News and World Report. August 30, 2018. https://www.msn.com/en-us/health/medical/could-taking-that-antibiotic-have-serious-long-term-consequences/ar-BBMEvqy (accessed 02/18/2019)

8. FDA Pharmacovigilance Review. April 17, 2013. https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm467383.pdf. Accessed 2/18/2019.

9. Lee CC, Lee MT, Chen YS et al. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. JAMA Intern Med. 2015 Nov 1;175(11):1839–47. [PubMed: 26436523]

10. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open. 2015 Nov 18;5(11):e010077.

11. Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ 2018 Mar 8;360:k678. doi: 10.1136/bmj.k678. [PubMed: 29519881]

12. Howard DPJ, Banerjee A, Fairchild JF et al. Age-specific incidence, risk factors and outcome of acute abdominal aortic aneurysms in a defined population. British Journal of Surgery 2015; 102:907–915. [PubMed: 25955556]

13. Rao GA JR Mann A Shoaibi, et al. , 2014, Azithromycin and Levofloxacin Use and Increased Risk of Cardiac Arrhythmia and Death, Ann Fam Med 2014; 12:121–127. [PubMed: 24615307]

14. Chou HW, Wang JL, Chang CH et al. Risks of Cardiac Arrhythmia and Mortality Among Patients Using New-generation Macrolides, Fluoroquinolones, and Betalactam/Beta-lactamase Inhibitors: a Taiwanese Nationwide Study, Clin Infect Dis 2015, 60:566–577. [PubMed: 25409476]

15. FDA Briefing Document - Joint Meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. 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). November 5, 2015. https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm467383.pdf. Accessed June 25, 2019.

16. Woodcock J FDA. Partial approval and partial denial response from FDA to the Southern Network on Adverse Reactions (SONAR) regarding levaquin. https://www.regulations.gov/document?D=FDA-2014-P-1611-0005. Accessed 2/18/2019.

17. European Medicines Agency. Review of quinolone and fluoroquinolone-containing medicinal products. https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products. Accessed 2/18/2019

18. Bennett CL for SONAR. Citizen petition from Southern Network on Adverse Reactions (SONAR) [for label change to include 'possible FO-associated mitochondrial toxicity']. http://www.regulations.gov/#!documentDetail;D=FDA-2014-P-0856-0001. Dated June 18, 2014; posted July 17, 2014. Accessed July 28, 2015.
19. Bennett CL for SONAR. Citizen petition from Southern Network on Adverse Reactions (SONAR) [for Risk Evaluation and Mitigation Strategy] Dated June 21, 2018.
20. European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC): 9–12. July 9– 12, 2018 Accessed https://www.ema.europa.eu/en/events/pharmacovigilance-risk-assessment-committee-prac-9-12-july-2018 (accessed June 25, 2019)
21. European Commission Final Decision: Disabling and potentially permanent side effects lead to suspension or restrictions on use of FQs. https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-disabling-potentially-permanent-side-effects-lead_en.pdf. Marcjh 11, 2019. Accessed June 21, 2018.
22. Request by German medicine authority (BFArM) under Article 31 of Directive 2001/83/EC. Initiiated February 9, 2017. Timetable established July 12, 2018. https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-timetable-procedure_en.pdf (accessed June 25, 2019)
23. PRAC Recommendations on FQs by the European Union Pharmacovigialance Risk Assessment Committee. October 5, 2018. https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-prac-recommends-restrictions-use_en.pdf (access June 21, 2018)
24. FDA Drug Safety Communication. FDA reinforces safety information about serious low blood sugar side effects and mental health side effects with FQs; requires label changes. July 10, 2018. https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side (accessed June 21, 2109)
25. Therapeutics Goods Administration. FQ antibiotics and risk of aortic aneurysm/dissection. https://www.tga.gov.au/publication-issue/fluoroquinolone-antibiotics-and-risk-aortic-aneurysmdissection. April 12, 2019. Accessed June 21, 2019.
26. Health Canada. Summary Safety Review: FQs- assessing the potential risk of persistent and disabling side effects. January 23, 2017. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/61900a-eng.php (accessed June 21, 2019).
27. Health Care Professional Letter. FQs- risk of disabling and persistent serous adverse reactions including tendinopathy, peripheral neuropathy, and central nervous system disorders. January 23, 2017. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/61900a-eng.php Accessed June 25, 2019.
28. Alberta Health Services. Antimicrobial Stewardship Backgrounder- FQs not a first line choice. Issue 16: June - November 2018. https://www.albertahealthservices.ca/assets/info/hp/as/if-hp-asb-2018-11-issue-16.pdf (accessed June 21, 2019)
29. FDA Drug Safety Communication. FDA warns about increased risk of ruptures or tears in the aortal blood vessel with FQs antibiotics in certain patients. December 12, 2018. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics (accessed June 21, 2019)
30. Kommalapati A, Wallem S, Qureshi ZP et al. Fluoroquinolone-associated suicide. Eur J of Internal Medicine 2018- epub Jluy 18.
31. United States District Court, District of Minnesota. Description of MDL # 15-MD-2642 https://www.mnd.uscourts.gov/MDL-Fluoroquinolone/introduction.shtml (accessed June 22, 2019)
32. United States District Court, District of Minnesota. Description of MDL #08–1943. https://www.mnd.uscourts.gov/MDL-Levaquin/introduction.shtml (accessed June 22, 2019)
33. Moore TJ, Bennett CL. Underreporting of hemorrhagic and thrombotic complications of pharmaceuticals to the U.S. Food and Drug Administration: empirical findings for warfarin, clopidogrel, ticlopidine, and thalidomide from the Southern Network on Adverse Reactions (SONAR). Semin Thromb Hemost 2012 Nov;38(8):905–7. doi: 10.1055/s-0032-1328890. Epub 2012 Oct 21. [PubMed: 23086541]

34. FDA Adverse Events Reporting System Dashboard. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis (accessed September 3, 2019)

35. Core Elements of Outpatient Antibiotic Stewardship. Centers for Disease Control and Prevention. https://www.cdc.gov/antibiotic-use/core-elements/outpatient.html (accessed September 3, 2019)

36. Core Elements of Hospital Antibiotic Stewardship Programs. Centers for Disease Control and Prevention. https://www.cdc.gov/antibiotic-use/core-elements/hospital.html (accessed September 3, 2019)

Article highlights

- Three fluoroquinolones, ciprofloxacin, levofloxacin, and moxifloxacin, have been identified by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as being strongly associated with neuropsychiatric toxicity including suicide, aortic dissections/aneurysms, and long-term disability.
- These associations have been reported at Advisory Committee meetings held in 2013, 2015, and 2018 by the FDA and by one Advisory Committee held by the EMA in 2018
- Safety warnings describing these toxicities have been disseminated by the FDA, EMA, Canada Health, the Therapeutic Goods Administration in Australia and the manufacturers of ciprofloxacin, levofloxacin, and ciprofloxacin between 2013 and 2019.
- The most recent safety announcements on ciprofloxacin, levofloxacin, and moxifloxacin from the FDA, EMA, Canada Health, and the Therapeutic Goods Administration in Australia now state that these agents should not be considered as first line therapies for acute sinusitis, bacterial infections among persons with chronic obstructive pulmonary disease, or urinary tract infections as the risks outweigh the benefits in these settings.
- Antimicrobial stewardship programs are ideal change agents to ensure that the most recent safety advisories are implemented in practice.
- If clinically meaningful changes in use of these three FQs do not occur, consideration should be given to implementing a Risk Evaluation and Mitigation Strategy that includes registration of patients and providers.

Table I.

Drug summary box.

Drug names (generic)	**Ciprofloxacin, levofloxacin, and moxifloxacin**
Phase (for indication under discussion)	Regulatory agency assessments of FQs associated toxicity by the FDA, the EMA, Canada Health, and Australia's Therapeutics Goods Administration. The EMA review was undertaken after German regulators requested assistance with understanding FQ safety. [20–29]
Indication	Treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infection (in European Union Countries, United States, Canada, Australia)- when other antibiotics are not available.
Pharmacology description/mechanism of action	This information is not known at the present time, although several basic science theories have been postulated.
Chemical structure	Ciprofloxacin, levofloxacin, and moxifloxacin belong to the fluoroquinolone class of antibiotics.
Pivotal safety findings	Fluoroquinolone-associated disability (FDA 2013, FDA 2015, and EMA 2018) [8,12] Fluoroquinolone-associated neuropsychiatric toxicity (Bennett C 2014, Bennett A 2016, FDA 2015, FDA 2017, FDA 2018, EMA 2018) [12, 19, 20] Fluoroquinolone-associated suicide (Kommallapati 2018)[32] Genetic predisposition to ciprofloxacin-associated neurotoxicity (Bennett A 2017) [1,6] Fluoroquinolone-associated aortic dissection (FDA 2018) [29]