Overview of Tendinopathy, Peripheral Neuropathy, Aortic Aneurysm, and Hypoglycemia Caused by Fluoroquinolones

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Abstract

Background Fluoroquinolones (FQs) are widely used in the management of several bacterial infections including urinary tract infections (UTIs), upper respiratory tract infections (URTIs), lower respiratory tract infections (LRTIs), skin and soft tissue, gastrointestinal tract infections (GITIs), and many other infections.

Objective This review article focuses on some serious side effects notified by United States Food and Drug Administration (US FDA) in different warning statements.

Methods The literature was searched, in databases such as Medline/PubMed/PMC, Google Scholar, Science Direct, Ebsco, Scopus, Web of science, Embase, and reference lists to identify publications relevant to the serious side effects associated with the use of FQs.

Results Several epidemiological studies and meta-analyses have documented the occurrence of serious side effects of FQs including tendinopathy, peripheral neuropathy, aortic aneurysm/dissection, hypoglycemia, QT prolongation, retinal detachment, and worsening of myasthenia gravis.

Conclusion The clinicians should be aware of serious side effects of FQs. The US FDA and European Medicines Agency recommend against the use of FQs as first-line therapies to treat infections such as acute sinusitis, acute bronchitis, and uncomplicated UTIs, as the risks outweigh the benefits. The risk of incidence of serious side effects of FQs is higher among patients with advanced age, renal insufficiency, and certain concomitant medications. To avoid occurrence of any serious side effects of FQs, the clinicians should prefer non-FQ antibacterial drugs to manage uncomplicated UTIs, respiratory tract infections, and other infections for which alternatives available.

Keywords
- fluoroquinolones
- tendinopathy
- tendinitis
- tendon disorders
- arthropathy
- aortic aneurysm
- aortic dissection
- QT prolongation
- Torsades de pointes
- retinal detachment
- myasthenia gravis

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Introduction

Fluoroquinolones (FQs) are broad-spectrum antibacterial drugs that are active against gram-positive, gram-negative, aerobic, and anaerobic organisms. FQs are widely used in the management of several bacterial infections including urinary tract infections (UTIs), upper respiratory tract infections, lower respiratory tract infections, skin and soft tissue, gastrointestinal tract infections, and many other infections.[1] In addition, FQs have shown some pleiotropic effects including antitubercular, antitumor, antimalarial, anti-human immunodeficiency virus (anti-HIV), and anti-Alzheimer activities.[2]

FQs are classified as first-generation quinolones (nalidixic acid, oxolinic acid, etc.), second-generation FQs (norfloxacin, ciprofloxacin, ofloxacin, enoxacin, etc.), third-generation FQs (levofloxacin, sparfloxacin, grepafloxacin, etc.), and fourth-generation FQs (moxifloxacin, gatifloxacin, gemifloxacin, etc.).[3]

FQs induce bactericidal effects via inhibition of deoxyribonucleic acid (DNA) gyrase and DNA topoisomerase IV, which are essential for the synthesis of messenger ribonucleic acid (mRNA) and DNA replication of bacteria.[4]

Common adverse effects of FQs include nausea, vomiting, anorexia, taste disturbance, abdominal discomfort, mild elevation of aminotransferase levels, headache, dizziness, trouble sleeping, *Clostridium difficile* infection, and others.[5]

In addition, use of FQs is associated with some serious adverse effects including nerve damage, tendinopathy, tendon rupture, tendinitis, tendon disorders, arthropathy, disability, QT Prolongation, torsades de pointes, and others. Our current review focuses on some serious side effects notified by United States Food and Drug Administration (US FDA) in different warning statements, which include tendinopathy, nerve damage, aortic aneurysm/dissection, hypoglycemia, QT prolongation, and worsening of myasthenia gravis (►**Fig. 1**).

Materials and Methods

The online databases such as Medline/PubMed/PMC, Google Scholar, Science Direct, Ebsco, Scopus, Web of science, Embase, and reference lists were searched using keywords like FQs, serious adverse events, tendinopathy, tendon rupture, tendinitis, tendon disorders, arthropathy, nerve damage, disability, aortic aneurysm, aortic dissection, QT prolongation, torsades de pointes, retinal detachment, and worsening of myasthenia gravis to identify relevant publications. The articles published in English are included in this review while discarding the duplicates.

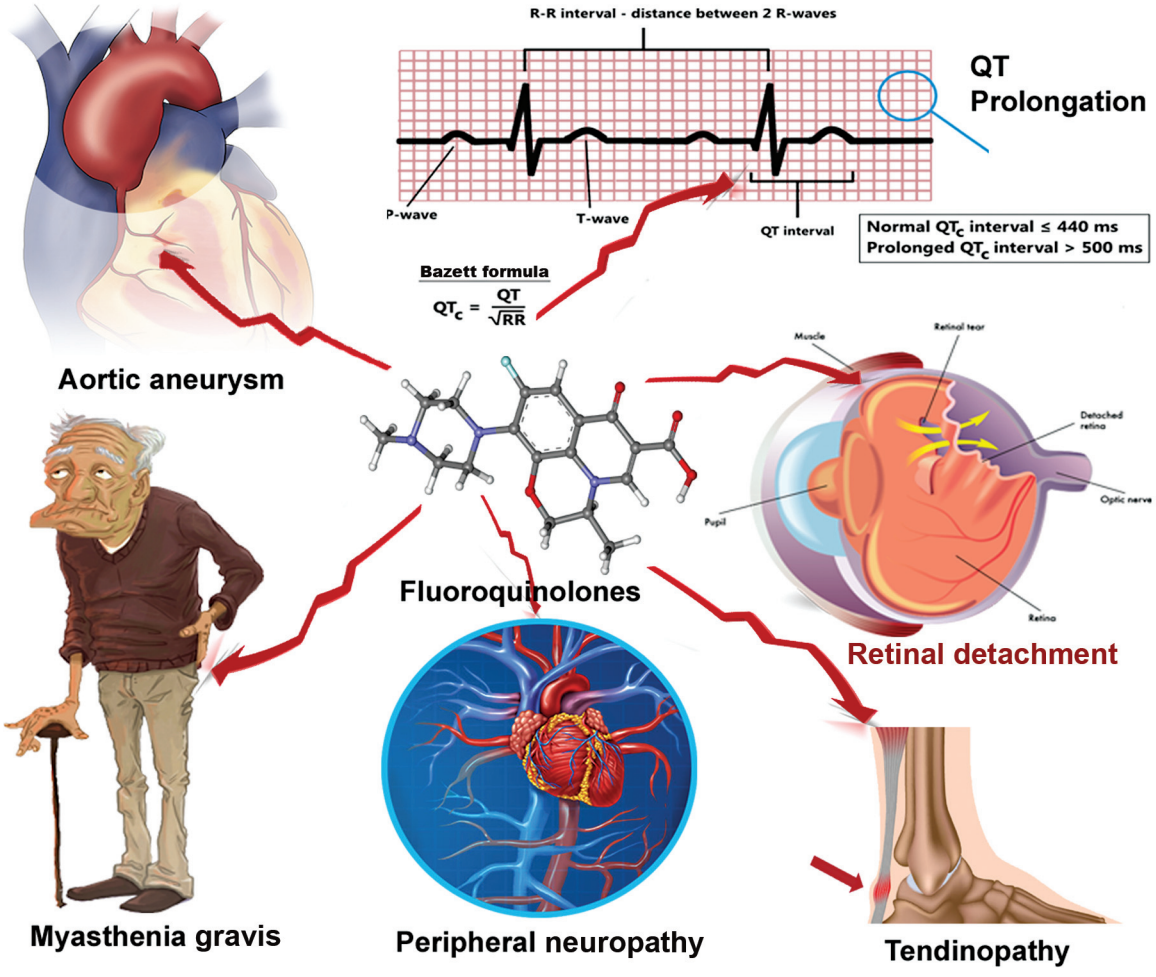

Fig. 1 Serious side effects of fluoroquinolones.

Results

The US FDA listed some serious side effects of systemic FQs, which include tendinitis, tendon rupture, numbness or tingling sensation in arms and legs, muscle weakness, muscle pain, joint pain, joint swelling, anxiety, depression, hallucinations, suicidal thoughts, confusion, worsening of myasthenia gravis, skin rash, sunburn, severe diarrhea, and abnormal heart beat.[6] Similarly, the European Medicines Agency (EMA) has also listed some serious side effects associated with FQS such as inflamed tendon, tendon rupture, muscle pain, joint pain, swelling of joint, feeling pins and needles, trouble sleeping, depression, tiredness, vision and hearing issues, memory problems, and altered taste and smell.[7] Moreover, a retrospective cohort study that was carried out in a tertiary care teaching hospital found that the incidence of adverse drug reactions was higher in patients taking FQs than that of other antibiotics prescribed for same conditions.[8]

Tendinopathy

The first case of FQ-associated tendinopathy was reported in 1983. The patient was treated with norfloxacin for UTI and he has developed Achilles tendinopathy,[9] whereas the first case of FQ-associated tendon rupture was reported in 1988.[10] Later, many cases of FQ-associated tendon rupture and pain reported.[11] A summary of reports in the FDA's adverse event reporting system (FAERS) revealed that there were 2,495 reports of tendon rupture associated with the use of FQs, reported to till September 2012. Most of the reports of tendon rupture were associated with levofloxacin followed by ciprofloxacin and moxifloxacin.[12] In addition, several analyses have determined that the risk of Achilles tendon rupture, Achilles tendinitis, and any tendon disorders were observed to be enhanced by FQ administration.[13–16]

Exacerbation of FQs-associated tendinopathy has been observed in patients with certain risk factors including advanced age, concurrent use of corticosteroids, renal pathological conditions, excessive physical activity, enhanced adiposity, diabetes mellitus, rheumatic disease, gout, and hyperthyroidism (►**Table 1**).[17]

Various mechanisms have been proposed for the pathogenesis of FQs-associated tendinopathy that include decreased activity of cyclin B, cyclin dependent kinase-1, checkpoint kinase-1, and increased polo like kinase-1 resulting in arrest of proliferation (G2/M cell cycle arrest), decreased

Table 1 Fluoroquinolones-associated serious side effects

Sr. no	Serious side effects	Predisposing factors	Probable mechanism(s) of pathogenesis	Recommendations from regulatory agencies	References
1	Tendinopathy	• Advanced age • Concurrent use of corticosteroids • Renal pathological conditions • Excessive physical activity • Enhanced adiposity • Diabetes mellitus • Rheumatic disease • Gout • Hyperthyroidism	• Decreased activity of cyclin B, cyclin dependent kinase-1 (CDK-1), checkpoint kinase-1 (CHK-1) • Increased polo like kinase-1 (PLK-1) • Decreased phosphorylation of focal adhesion kinase (FAK) • Increased expression of matrix metalloproteinase-2 (MMP-2) • Chelation of ions • Production of fluoroquinolones (FQ)-induced reactive oxygen species (ROS) in mitochondria	• The patients should consult their healthcare professionals once they experience tendon pain, swelling, or inflammation • The healthcare professionals should discontinue FQs in patients with the symptoms of tendinopathy and to switch to non-FQ antibacterial medicines	17, 18, 19
2	Peripheral neuropathy	• Concomitant use of drugs like theophylline, and nonsteroidal anti-inflammatory drugs (NSAIDs) • Comorbid conditions including impaired renal function, diabetes mellitus, and lymphatic malignancy	Unknown	• The patients on FQs should consult their clinicians if they develop pain, tingling, numbness, weakness, burning, and change in sensation to pain, temperature, or touch. • The healthcare professionals should stop FQs in patients developed any one of symptoms of peripheral neuropathy • The healthcare professionals should switch to non-FQ antibacterial drug, unless the benefit outweighs the risk of continuing FQs	26, 27
3	Aortic aneurysm/ dissection	• History of aortic or other blood vessel aneurysm • Hypertension • Advanced age • Female sex • Prolonged use of FQs	• Rapid degradation of extracellular matrix (ECM) • Upregulation of MMP • Downregulation of Lysyl oxidase (LOX) • Suppression of collagen maturation • Enhanced elastic fiber fragmentation and cell injury • Significant reduction of expression of tissue Inhibitor metalloproteinases (TIMP-1 and TIMP-2) • Significant decrease in collagen-1 expression • Reduction of collagen production in tenocytes and fibroblasts • Inhibition of cell proliferation • Promoted cell apoptosis	• The patients with predisposing factors should never be prescribed with FQs unless there is no alternative treatment available4 • The patients should be advised to seek emergency medical help if they experience sudden, severe, and constant pain in the stomach, chest, or back	42, 43-47, 48
4	Hypoglycemia	• Type 2 diabetes mellitus • Renal insufficiency • Advanced age • Sepsis • Concomitant antidiabetic medications such as insulin, sulfonylureas, meglitinides • Concurrent use of steroids	• Sulfonylurea-like effect on pancreatic beta cells by blocking ATP-sensitive potassium channels and allowing calcium entry to release insulin • Augmentation of activity of antidiabetic medications	• The patients experiencing symptoms of hypoglycemia while using FQs and antidiabetic drugs concomitantly should seek immediate medical attention	72, 73, 74

(*Continued*)

Table 1 (*Continued*)

Sr. no	Serious side effects	Predisposing factors	Probable mechanism(s) of pathogenesis	Recommendations from regulatory agencies	References
5	QT prolongation	• Prolonged QT syndrome • Torsades de pointes (TdP) • Renal insufficiency	• Blockade of voltage-gated potassium channels		83, 84
6	Worsening of myasthenia gravis	• Myasthenia gravis	• FQs affect miniature endplate potential (MEPP) and miniature endplate current (MEPC) via presynaptic or postsynaptic mechanism	• Manufacturers required to add boxed warning regarding worsening of myasthenia gravis by FQs	87, 88, 86

phosphorylation of focal adhesion kinase leading to diminished cell migration (tenocytes), increased expression of matrix metalloproteinase-2 (MMP-2) causing reduction of type I collagen metabolism, chelation of ions, which influence epigenetics and enzymes, and production of FQ-induced radical oxygen species in mitochondria.[18]

The US FDA has issued safety alerts regarding tendinitis and tendon rupture associated with the use of FQs, in July 2008. The risk of FQs-associated tendinitis and tendon rupture is higher among individuals over 60 years, persons using concomitant steroids, and the recipients of kidney, heart, and lung transplants. Moreover, the US FDA has advised the patients to consult their healthcare professionals once they experience tendon pain, swelling, or inflammation. In addition, the US FDA has recommended the healthcare professionals to discontinue FQs in patients with the symptoms of tendinopathy and to switch to non-FQ antibacterial medicines.[19]

Peripheral Neuropathy

Many cases of FQs-associated peripheral nervous system toxicity have been reported[20,21] including in children.[22] Some nested case–control studies determined that the risk of peripheral neuropathy is enhanced in current users of FQs.[23,24] In addition, a pharmacovigilance analysis of cases reported to FAERS until 2012 determined that systemic administration of FQs potentially was associated with peripheral neuropathy, nerve damage including Guillain-Barre syndrome.[25] Moreover, a VigiBase descriptive analysis revealed that FQs were associated 4,374 reports of peripheral nervous system disorders such as peripheral neuropathy, neuralgia, polyneuropathy, sensory loss, and peripheral sensorimotor neuropathy. Among them 3,531 reports have been considered as serious.[26]

Possible predisposing factors of FQs-associated neuropathy may include concomitant use of certain drugs such as theophylline, nonsteroidal anti-inflammatory drugs, and comorbid conditions including impaired renal function, diabetes mellitus, and lymphatic malignancy.[26] The pathogenesis of FQs-associated peripheral neuropathy is unknown.

In August 2013, the US FDA has alerted the patients and healthcare professionals about the risk of permanent nerve damage and required the manufacturers for label changes. The US FDA has advised the patients on FQs to consult their clinicians if they develop any one of symptoms of peripheral neuropathy such as pain, tingling, numbness, weakness, burning, and change in sensation to pain, temperature, or touch. The US FDA has also recommended the healthcare professionals to stop FQs in patients developed any one of symptoms of peripheral neuropathy and switch to non-FQ antibacterial drug, unless the benefit outweighs the risk of continuing FQs.[27]

Aortic Aneurysm

Various population-based observational studies of large administrative datasets have determined that recent exposure to FQs increased the risk of aortopathy (aortic aneurysm, aortic dissection, and aortic rupture).[28–32] Several systematic meta-analyses found that the risk of aortic aneurysm and aortic dissection is significantly higher among the users of FQs.[33–38] Moreover, a retrospective cohort study of Taiwan National Health Insurance Research Database determined that the risk of all-cause mortality, aortic death, and later aortic surgery was found to be higher among the patients with aortic aneurysm or aortic dissection, who are exposed to systemic FQs.[39] Similarly, another retrospective cohort study of Taiwan National Health Insurance Research Database revealed that the mortality was increased in patients who took FQs to treat UTIs compared to the users of cephalosporins,[40] and a nested case–control study of Korea National Health Insurance data stressed on higher incidence of aortic aneurysm or aortic dissection among the users of systemic FQs.[41]

The risk of FQs-associated is higher among patients with a history of aortic or other blood vessel aneurysm, hypertension, advanced age, female sex, and prolonged use of FQs.[42]

Various mechanisms have been proposed for the pathogenesis of aortic aneurysm or aortic dissection linked to the use of FQs, which include rapid degradation of extracellular matrix, upregulation of MMP, downregulation of Lysyl oxidase (LOX), FQ-mediated iron chelation inhibits Prolyl 4-hydroxylase (P4H) and LOX resulting in suppression of collagen maturation, enhanced elastic fiber fragmentation and cell injury, significant reduction in expression of tissue inhibitor metalloproteinases (TIMP-1 and TIMP-2), significant decrease in collagen-1 expression, reduction in collagen production in tenocytes and fibroblasts, and inhibition of cell proliferation and promoted cell apoptosis.[43–47]

Moreover, in December 2018, the US FDA warned about the risk of aortic aneurysm and aortic dissection linked to the use of FQs. The patients with a history of aortic or other blood vessel aneurysms, peripheral atherosclerotic vascular diseases, hypertension, certain genetic blood vessel disorders (Marfan syndrome, Ehlers-Danlos syndrome), and the elderly are at heightened risk of developing FQs-associated aortic

aneurysm or aortic dissection, and such patients should never be prescribed with FQs unless there are no alternative treatment available. The patients should be advised to seek emergency medical help if they experience sudden, severe, and constant pain in the stomach, chest, or back.[48]

Retinal Detachment

Many epidemiological studies determined that the risk of retinal detachment is elevated due to the administration of systemic FQs. The first study reporting the risk of FQ-associated rhegmatogenous retinal detachment (RRD) was reported in 2012, from Canada.[49] Similarly, various other studies from Taiwan,[50] France,[51] and Korea[52] have determined the link between FQ use and RRD. Moreover, a study examining the adverse drug event reports submitted to FAERS found a positive association of Moxifloxacin with RRD.[53]

Conversely, other studies including a nationwide, register-based cohort study from Denmark,[54] two case–control analyses from USA,[55,56] a retrospective cohort study using The Health Improvement Network database,[57] a self-controlled case series study of data from Hong Kong Clinical Data Analysis and Reporting System Database and Taiwan National Health Insurance Research Database,[58] a nested case–control study of Korean National Health Insurance Service National Sample Cohort data,[59] and a nested case-control study of electronic health records[60] found no association between oral FQ use and retinal detachment. In addition, few systematic reviews and meta-analyses[61–63] did not also find any association of development of RRD with the use of systemic FQs.

Hypoglycemia

The use of FQs has been found to be associated with the occurrence of both hypoglycemia and hyperglycemia and the risk of adverse drug interaction resulting in severe hypoglycemia was higher among diabetic patients taking antidiabetic medications and a FQ concurrently.[64,65] Several population-based studies observed that systemic FQ is linked to higher incidence of hypoglycemia especially in patients with diabetes. The FQs such as moxifloxacin,[66] levofloxacin,[67–69] and ciprofloxacin[70] were associated with the occurrence of hypoglycemia after their systemic administration. The occurrence of hypoglycemia has also been observed in nondiabetic patients.[71]

The predisposing factors of FQ-associated hypoglycemia may include type 2 diabetes mellitus, renal insufficiency, advanced age, sepsis, concomitant antidiabetic medications such as insulin, sulfonylureas, meglitinides, and concurrent use of steroids (►**Table 1**).[72]

Multiple mechanisms have been proposed for the development of FQ-associated hypoglycemia, which may include sulfonylurea-like effect on pancreatic beta cells by blocking ATP-sensitive potassium channels and allowing calcium entry to release insulin, and augmentation of activity of antidiabetic medications.[73]

In October 2018, the US FDA reinforced that FQs may reduce blood sugar levels (hypoglycemia) significantly, which may result in serious problems including coma, especially in patients taking antidiabetic drugs. FQs may also induce additional mental health side effects such as nervousness, memory impairment, agitation, delirium, disturbances in attention, and disorientation. The US FDA required changes in drug labels and medication guides of FQs with these updates. The patients experiencing symptoms of hypoglycemia like confusion, blurred vision, dizziness, unusual hunger, headaches, irritability, shaky feeling, trembling, sweating, weakness, and pounding heart while using FQs and antidiabetic drugs concomitantly should seek immediate medical attention.[74]

QT Prolongation

Different population-based studies have determined that the administration of FQs is associated with heightened risk of prolongation of QT interval and cardiac arrythmias.[75–78] The risk of serious arrythmias is found to be higher among the users of moxifloxacin and levofloxacin.[79]

On the contrary, a binational cohort study of Danish and Swedish adult population revealed that the use of oral ciprofloxacin was not associated with an enhanced risk of serious arrythmias.[80] However, a meta-analysis[81] and a nationwide cohort study from Korea[82] found that the risk of ventricular arrythmia and cardiovascular mortality has been elevated by the use FQs especially moxifloxacin.

Predisposing factors of FQs-associated QT prolongation may include patients with prolonged QT syndrome, Torsades de pointes, and renal insufficiency.[83]

The probable mechanism of pathogenesis of FQs-associated QT prolongation may include the blockade of voltage-gated potassium channels.[84]

Worsening of Myasthenia Gravis

Multiple cases of myasthenia gravis exacerbation have been reported due to the systemic administration of FQs.[85] In addition, a study analyzing FAERS data revealed that there were many cases of FQ-associated myasthenia gravis exacerbation reported. Moreover, the US FDA has required the manufacturers to add boxed warning regarding enhanced risk of worsening of myasthenia gravis in patients taking FQs, in February 2011.[86]

FQs may exacerbate myasthenia gravis by affecting miniature endplate potential and miniature endplate current via presynaptic or postsynaptic mechanism.[87,88]

FDA and EMA Recommendations

In May 2016, the US FDA advised against the use of FQs to treat acute sinusitis, acute bronchitis, and uncomplicated UTIs, where other treatment options are available, as FQs-associated serious adverse effects (tendinopathy, peripheral neuropathy, aortic aneurysm/dissection, retinal detachment, hypoglycemia, QT prolongation, etc.) outweigh the benefits. FQs should

be reserved for patients who do not have alternative treatment options. The US FDA urged the manufacturers to update drug labels and medication guides of FQs. The patients are advised to contact their healthcare professionals if they develop any symptoms of serious adverse effects associated with FQs and the healthcare professionals should stop FQ and switch to non-FQ antibacterial drug.[89]

Similarly, the EMA notified the healthcare professionals as well as the consumers regarding FQ-associated serious side effects. EMA restricted the use of FQs to treat nonsevere throat infections, nonbacterial infections, and uncomplicated UTIs and other infections for which alternatives are available. EMA has also stressed that FQs should be avoided in patients who developed serious side effects in prior use, and who are on steroids. Caution should be exercised while using FQs in patients with renal insufficiency.[90]

Despite the FDA and EMA recommendations and black boxed warnings, no significant reduction in the rate of FQ prescriptions to treat acute sinusitis, acute bronchitis, and uncomplicated UTIs was observed in a retrospective review of antibiotics prescribed at a single, large, academic outpatient center.[91] On the contrary, a cross-sectional study that used Medicare administrative claims data on Medicare fee-for-service beneficiaries and OneKey data on physicians and their organizations found overall decline in FQs prescriptions after the release of FDA warnings. The level of FQs prescribing in post-warning period 2 (2016) was decreased significantly from post-warning period 1 (2013) by −0.77 percentage points. The prescribing trend of FQs was declined only from physicians at teaching hospitals.[92]

Common aspects of poor prescriptions of FQs may include inappropriate coverage of organisms, inappropriate dosage, unnecessary extension of treatment duration, and inappropriate use of antimicrobial prophylaxis.[93] FQs risk assessment should be implemented to minimize the occurrence of FQ associated disability.[94,95]

Conclusion

The clinicians should be aware of serious side effects of FQs that include tendinopathy, peripheral neuropathy, aortic aneurysm/dissection, retinal detachment, hypoglycemia, QT prolongation, and worsening of myasthenia gravis. The US FDA and EMA recommend against the use of FQs as first-line therapies to treat infections such as acute sinusitis, acute bronchitis, and uncomplicated UTIs, as the risks outweigh the benefits. FQs should be reserved for the patients who have no alternative treatment options. The patients who are prescribed with FQs should be advised to monitor for signs and symptoms of FQs-associated serious side effects and should contact their healthcare professionals right away. The risk of incidence of serious side effects of FQs is higher among patients with advanced age, renal insufficiency, and certain concomitant medications. To avoid occurrence of any serious side effects of FQs, the clinicians should prefer non-FQ antibacterial drugs to manage uncomplicated UTIs, respiratory tract infections, and other infections for which alternatives are available.

Authors' Contributions

R.B. contributed substantially to conception and design and acquisition of data; N.M.P.M. helped in conception and design, data analysis, and interpretation of data; H.N. drafted the article and revised it critically for important contents.

Compliance with Ethical Principles

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Conflict of Interest

None declared.

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