

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

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Ibnosina J Med Biomed Sci

## 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

DOI <https://doi.org/10.1055/s-0043-1777825>.  
ISSN 1947-489X.

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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.<sup>1</sup> In addition, FQs have shown some pleiotropic effects including antitubercular, antitumor, antimalarial, anti-human immunodeficiency virus (anti-HIV), and anti-Alzheimer activities.<sup>2</sup>

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.).<sup>3</sup>

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.<sup>4</sup>

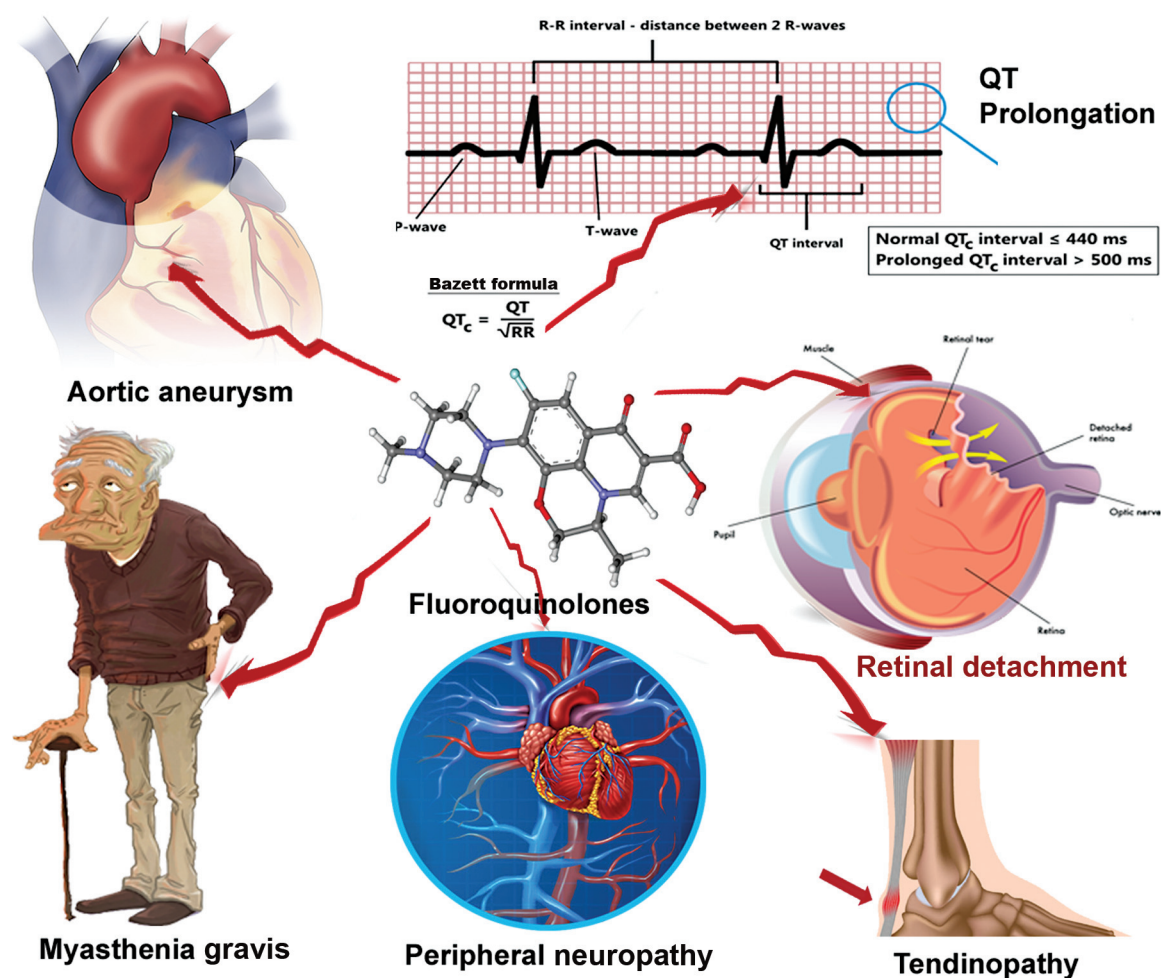
Common adverse effects of FQs include nausea, vomiting, anorexia, taste disturbance, abdominal discomfort, mild

elevation of aminotransferase levels, headache, dizziness, trouble sleeping, *Clostridium difficile* infection, and others.<sup>5</sup>

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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup>

## 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,<sup>9</sup> whereas the first case of FQ-associated tendon rupture was reported in 1988.<sup>10</sup> Later, many cases of FQ-associated tendon rupture and pain reported.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13–16</sup>

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).<sup>17</sup>

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	<ul style="list-style-type: none"> <li>Advanced age</li> <li>Concurrent use of corticosteroids</li> <li>Renal pathological conditions</li> <li>Excessive physical activity</li> <li>Enhanced adiposity</li> <li>Diabetes mellitus</li> <li>Rheumatic disease</li> <li>Gout</li> <li>Hyperthyroidism</li> </ul>	<ul style="list-style-type: none"> <li>Decreased activity of cyclin B, cyclin dependent kinase-1 (CDK-1), checkpoint kinase-1 (CHK-1)</li> <li>Increased polo like kinase-1 (PLK-1)</li> <li>Decreased phosphorylation of focal adhesion kinase (FAK)</li> <li>Increased expression of matrix metalloproteinase-2 (MMP-2)</li> <li>Chelation of ions</li> <li>Production of fluoroquinolones (FQ)-induced reactive oxygen species (ROS) in mitochondria</li> </ul>	<ul style="list-style-type: none"> <li>The patients should consult their healthcare professionals once they experience tendon pain, swelling, or inflammation</li> <li>The healthcare professionals should discontinue FQs in patients with the symptoms of tendinopathy and to switch to non-FQ antibacterial medicines</li> </ul>	17, 18, 19
2	Peripheral neuropathy	<ul style="list-style-type: none"> <li>Concomitant use of drugs like theophylline, and nonsteroidal anti-inflammatory drugs (NSAIDs)</li> <li>Comorbid conditions including impaired renal function, diabetes mellitus, and lymphatic malignancy</li> </ul>	Unknown	<ul style="list-style-type: none"> <li>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.</li> <li>The healthcare professionals should stop FQs in patients developed any one of symptoms of peripheral neuropathy</li> <li>The healthcare professionals should switch to non-FQ antibacterial drug, unless the benefit outweighs the risk of continuing FQs</li> </ul>	26, 27
3	Aortic aneurysm/dissection	<ul style="list-style-type: none"> <li>History of aortic or other blood vessel aneurysm</li> <li>Hypertension</li> <li>Advanced age</li> <li>Female sex</li> <li>Prolonged use of FQs</li> </ul>	<ul style="list-style-type: none"> <li>Rapid degradation of extracellular matrix (ECM)</li> <li>Upregulation of MMP</li> <li>Downregulation of Lysyl oxidase (LOX)</li> <li>Suppression of collagen maturation</li> <li>Enhanced elastic fiber fragmentation and cell injury</li> <li>Significant reduction of expression of tissue inhibitor metalloproteinases (TIMP-1 and TIMP-2)</li> <li>Significant decrease in collagen-1 expression</li> <li>Reduction of collagen production in tenocytes and fibroblasts</li> <li>Inhibition of cell proliferation</li> <li>Promoted cell apoptosis</li> </ul>	<ul style="list-style-type: none"> <li>The patients with predisposing factors should never be prescribed with FQs unless there is no alternative treatment available<sup>4</sup></li> <li>The patients should be advised to seek emergency medical help if they experience sudden, severe, and constant pain in the stomach, chest, or back</li> </ul>	42, 43-47, 48
4	Hypoglycemia	<ul style="list-style-type: none"> <li>Type 2 diabetes mellitus</li> <li>Renal insufficiency</li> <li>Advanced age</li> <li>Sepsis</li> <li>Concomitant antidiabetic medications such as insulin, sulfonylureas, meglitinides</li> <li>Concurrent use of steroids</li> </ul>	<ul style="list-style-type: none"> <li>Sulfonylurea-like effect on pancreatic beta cells by blocking ATP-sensitive potassium channels and allowing calcium entry to release insulin</li> <li>Augmentation of activity of antidiabetic medications</li> </ul>	<ul style="list-style-type: none"> <li>The patients experiencing symptoms of hypoglycemia while using FQs and antidiabetic drugs concomitantly should seek immediate medical attention</li> </ul>	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	<ul style="list-style-type: none"> <li>• Prolonged QT syndrome</li> <li>• Torsades de pointes (TdP)</li> <li>• Renal insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Blockade of voltage-gated potassium channels</li> </ul>		83, 84
6	Worsening of myasthenia gravis	<ul style="list-style-type: none"> <li>• Myasthenia gravis</li> </ul>	<ul style="list-style-type: none"> <li>• FQs affect miniature endplate potential (MEPP) and miniature endplate current (MEPC) via presynaptic or postsynaptic mechanism</li> </ul>	<ul style="list-style-type: none"> <li>• Manufacturers required to add boxed warning regarding worsening of myasthenia gravis by FQs</li> </ul>	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.<sup>18</sup>

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.<sup>19</sup>

## Peripheral Neuropathy

Many cases of FQs-associated peripheral nervous system toxicity have been reported<sup>20,21</sup> including in children.<sup>22</sup> Some nested case-control studies determined that the risk of peripheral neuropathy is enhanced in current users of FQs.<sup>23,24</sup> 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.<sup>25</sup> 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.<sup>26</sup>

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.<sup>26</sup> 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.<sup>27</sup>

## 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).<sup>28–32</sup> Several systematic meta-analyses found that the risk of aortic aneurysm and aortic dissection is significantly higher among the users of FQs.<sup>33–38</sup> 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.<sup>39</sup> 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,<sup>40</sup> 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.<sup>41</sup>

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.<sup>42</sup>

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.<sup>43–47</sup>

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.<sup>48</sup>

## 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.<sup>49</sup> Similarly, various other studies from Taiwan,<sup>50</sup> France,<sup>51</sup> and Korea<sup>52</sup> 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.<sup>53</sup>

Conversely, other studies including a nationwide, register-based cohort study from Denmark,<sup>54</sup> two case-control analyses from USA,<sup>55,56</sup> a retrospective cohort study using The Health Improvement Network database,<sup>57</sup> 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,<sup>58</sup> a nested case-control study of Korean National Health Insurance Service National Sample Cohort data,<sup>59</sup> and a nested case-control study of electronic health records<sup>60</sup> found no association between oral FQ use and retinal detachment. In addition, few systematic reviews and meta-analyses<sup>61–63</sup> 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.<sup>64,65</sup> 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,<sup>66</sup> levofloxacin,<sup>67–69</sup> and ciprofloxacin<sup>70</sup> were associated with the occurrence of hypoglycemia after their systemic administration. The occurrence of hypoglycemia has also been observed in nondiabetic patients.<sup>71</sup>

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).<sup>72</sup>

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.<sup>73</sup>

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.<sup>74</sup>

## 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 arrhythmias.<sup>75–78</sup> The risk of serious arrhythmias is found to be higher among the users of moxifloxacin and levofloxacin.<sup>79</sup>

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 arrhythmias.<sup>80</sup> However, a meta-analysis<sup>81</sup> and a nationwide cohort study from Korea<sup>82</sup> found that the risk of ventricular arrhythmia 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.<sup>83</sup>

The probable mechanism of pathogenesis of FQs-associated QT prolongation may include the blockade of voltage-gated potassium channels.<sup>84</sup>

## Worsening of Myasthenia Gravis

Multiple cases of myasthenia gravis exacerbation have been reported due to the systemic administration of FQs.<sup>85</sup> 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.<sup>86</sup>

FQs may exacerbate myasthenia gravis by affecting miniature endplate potential and miniature endplate current via presynaptic or postsynaptic mechanism.<sup>87,88</sup>

## 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.<sup>89</sup>

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.<sup>90</sup>

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.<sup>91</sup> 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.<sup>92</sup>

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.<sup>93</sup> FQs risk assessment should be implemented to minimize the occurrence of FQ associated disability.<sup>94,95</sup>

## 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

No ethical approval is required for review articles.

## Funding and Sponsorship

No author received funds for the preparation of this manuscript.

## Conflict of Interest

None declared.

## References

- Majalekar PP, Shirote PJ. Fluoroquinolones: blessings or curses. *Curr Drug Targets* 2020;21(13):1354–1370
- Ezalarab HAA, Abbas SH, Hassan HA, Abuo-Rahma GEA. Recent updates of fluoroquinolones as antibacterial agents. *Arch Pharm (Weinheim)* 2018;351(09):e1800141
- Mimouni FZ, Belboukhari N, Sekkoum K. Mini review: is fluoroquinolone drug or poison? *J Complexity in Health Sci* 2019;2(02):70–76
- Fedorowicz J, Sączewski J. Modifications of quinolones and fluoroquinolones: hybrid compounds and dual-action molecules. *Monatsh Chem* 2018;149(07):1199–1245
- Baggio D, Ananda-Rajah MR. Fluoroquinolone antibiotics and adverse events. *Aust Prescr* 2021;44(05):161–164
- US Food and Drug Administration FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. December 20, 2018. Accessed December 7, 2023 at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics>
- European Medicines Agency Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. November 16, 2018. Accessed December 7, 2023 at: <https://www.ema.europa.eu/en/news/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone>
- Mathews B, Thalody AA, Miraj SS, Kunhikatta V, Rao M, Saravu K. Adverse effects of fluoroquinolones: a retrospective cohort study in a South Indian tertiary healthcare facility. *Antibiotics (Basel)* 2019;8(03):104
- Bailey RR, Kirk JA, Peddie BA. Norfloxacin-induced rheumatic disease. *N Z Med J* 1983;96(736):590
- McEwan SR, Davey PG. Ciprofloxacin and tenosynovitis. *Lancet* 1988;2(8616):900
- Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis* 2003;36(11):1404–1410
- Arabyat RM, Raisch DW, McKoy JM, Bennett CL. Fluoroquinolone-associated tendon-rupture: a summary of reports in the Food and Drug Administration's adverse event reporting system. *Expert Opin Drug Saf* 2015;14(11):1653–1660
- Berger I, Goodwin I, Buncke GM. Fluoroquinolone-associated tendinopathy of the hand and wrist: a systematic review and case report. *Hand (N Y)* 2017;12(05):NP121–NP126
- Godoy-Santos AL, Bruschini H, Cury J, et al. Fluoroquinolones and the risk of Achilles tendon disorders: update on a neglected complication. *Urology* 2018;113:20–25

- 15 Stephenson AL, Wu W, Cortes D, Rochon PA. Tendon injury and fluoroquinolone use: a systematic review. *Drug Saf* 2013;36(09):709–721
- 16 Alves C, Mendes D, Marques FB. Fluoroquinolones and the risk of tendon injury: a systematic review and meta-analysis. *Eur J Clin Pharmacol* 2019;75(10):1431–1443
- 17 Lewis T, Cook J. Fluoroquinolones and tendinopathy: a guide for athletes and sports clinicians and a systematic review of the literature. *J Athl Train* 2014;49(03):422–427
- 18 Bisaccia DR, Aicale R, Tarantino D, Peretti GM, Maffulli N. Biological and chemical changes in fluoroquinolone-associated tendinopathies: a systematic review. *Br Med Bull* 2019;130(01):39–49
- 19 Tanne JH. FDA adds “black box” warning label to fluoroquinolone antibiotics. *BMJ* 2008;337(7662):a816
- 20 Francis JK, Higgins E. Permanent peripheral neuropathy: a case report on a rare but serious debilitating side-effect of fluoroquinolone administration. *J Investig Med High Impact Case Rep* 2014;2(03):2324709614545225
- 21 Estofan LJF, Naydin S, Gliabus G. Quinolone-induced painful peripheral neuropathy: a case report and literature review. *J Investig Med High Impact Case Rep* 2018;6:2324709617752736
- 22 Morley C, Carvalho de Almeida C, Moloney S, Grimwood K. Ciprofloxacin-associated peripheral neuropathy in a child: a case report and review of the literature. *Pediatr Infect Dis J* 2022;41(02):121–122
- 23 Etminan M, Brophy JM, Samii A. Oral fluoroquinolone use and risk of peripheral neuropathy: a pharmacoepidemiologic study. *Neurology* 2014;83(14):1261–1263
- 24 Morales D, Pacurariu A, Slattery J, Pinheiro L, McGettigan P, Kurz X. Association between peripheral neuropathy and exposure to oral fluoroquinolone or amoxicillin-clavulanate therapy. *JAMA Neurol* 2019;76(07):827–833
- 25 Ali AK. Peripheral neuropathy and Guillain-Barré syndrome risks associated with exposure to systemic fluoroquinolones: a pharmacovigilance analysis. *Ann Epidemiol* 2014;24(04):279–285
- 26 Huruba M, Farcas A, Leucuta DC, Bucsa C, Mogosan C. A VigiBase descriptive study of fluoroquinolone-associated peripheral nervous system disorders. *Pharmaceuticals (Basel)* 2022;15(02):143
- 27 US Food and Drug Administration FDA Drug Safety Communication: FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection. August 15, 2013. Accessed December 7, 2023 at: <http://www.fda.gov/Drugs/DrugSafety/ucm365050.htm>
- 28 Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* 2015;5(11):e010077
- 29 Lee CC, Lee MT, Chen YS, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med* 2015;175(11):1839–1847
- 30 Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ* 2018;360:k678
- 31 Lee CC, Lee MG, Hsieh R, et al. Oral fluoroquinolone and the risk of aortic dissection. *J Am Coll Cardiol* 2018;72(12):1369–1378
- 32 Meng L, Huang J, Jia Y, Huang H, Qiu F, Sun S. Assessing fluoroquinolone-associated aortic aneurysm and dissection: data mining of the public version of the FDA adverse event reporting system. *Int J Clin Pract* 2019;73(05):e13331
- 33 Noman AT, Qazi AH, Alqasrawi M, et al. Fluoroquinolones and the risk of aortopathy: a systematic review and meta-analysis. *Int J Cardiol* 2019;274:299–302
- 34 Latif A, Ahsan MJ, Malik SU, et al. Fluoroquinolones and the Risk of Aortopathy: a systematic review and meta-Analysis. *Circulation* 2019;140:A15936
- 35 Dai XC, Yang XX, Ma L, Tang GM, Pan YY, Hu HL. Relationship between fluoroquinolones and the risk of aortic diseases: a meta-analysis of observational studies. *BMC Cardiovasc Disord* 2020;20(01):49
- 36 Lai CC, Wang YH, Chen KH, Chen CH, Wang CY. The association between the risk of aortic aneurysm/aortic dissection and the use of fluoroquinolones: a systematic review and meta-analysis. *Antibiotics (Basel)* 2021;10(06):697
- 37 Vouga Ribeiro N, Gouveia Melo R, Guerra NC, et al. Fluoroquinolones are associated with increased risk of aortic aneurysm or dissection: systematic review and meta-analysis. *Semin Thorac Cardiovasc Surg* 2021;33(04):907–918
- 38 Chen C, Patterson B, Simpson R, et al. Do fluoroquinolones increase aortic aneurysm or dissection incidence and mortality? A systematic review and meta-analysis. *Front Cardiovasc Med* 2022;9:949538
- 39 Chen SW, Chan YH, Chien-Chia Wu V, et al. Effects of fluoroquinolones on outcomes of patients with aortic dissection or aneurysm. *J Am Coll Cardiol* 2021;77(15):1875–1887
- 40 Chen YY, Yang SF, Yeh HW, et al. Association between aortic aneurysm and aortic dissection with fluoroquinolones use in patients with urinary tract infections: a population-based cohort study. *J Am Heart Assoc* 2022;11(06):e023267
- 41 Son N, Choi E, Chung SY, Han SY, Kim B. Risk of aortic aneurysm and aortic dissection with the use of fluoroquinolones in Korea: a nested case-control study. *BMC Cardiovasc Disord* 2022;22(01):44
- 42 Leonova MV. Collagen-associated side effects of fluoroquinolones: aneurysm and aortic dissection (systematic review). *Consilium Medicum*. 2022;24(01):66–70
- 43 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;157(01):109–119.e2
- 44 Rawla P, El Helou ML, Vellipuram AR. Fluoroquinolones and the risk of aortic aneurysm or aortic dissection: a systematic review and meta-analysis. *Cardiovasc Hematol Agents Med Chem* 2019;17(01):3–10
- 45 Wee I, Chin B, Syn N, Lee KS, Ng JJ, Choong AMTL. The association between fluoroquinolones and aortic dissection and aortic aneurysms: a systematic review and meta-analysis. *Sci Rep* 2021;11(01):11073
- 46 Jun C, Fang B. Current progress of fluoroquinolones-increased risk of aortic aneurysm and dissection. *BMC Cardiovasc Disord* 2021;21(01):470
- 47 Zhang J, Zhang Z. Fluoroquinolones increase the risk of aortic aneurysm and dissection: a protocol for meta-analysis. *Medicine (Baltimore)* 2021;100(51):e28081
- 48 US Food and Drug Administration FDA Drug Safety Communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. December 20, 2018. Accessed December 7, 2023 at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics>
- 49 Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. *JAMA* 2012;307(13):1414–1419
- 50 Kuo SC, Chen YT, Lee YT, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis* 2014;58(02):197–203
- 51 Raguideau F, Lemaitre M, Dray-Spira R, Zureik M. Association between oral fluoroquinolone use and retinal detachment. *JAMA Ophthalmol* 2016;134(04):415–421
- 52 Baek YH, Park SJ, Jeong S, et al. Signal detection between fluoroquinolone use and the risk of rhegmatogenous retinal detachment: sequence symmetry analysis using nationwide South Korean healthcare database between 2004 and 2015. *Clin Drug Investig* 2018;38(12):1179–1188
- 53 Taher MK, Alami A, Gravel CA, et al. Systemic quinolones and risk of retinal detachment I: analysis of data from the US FDA adverse

- event reporting system. *Expert Opin Drug Saf* 2022;21(02):269–276
- 54 Pasternak B, Svanström H, Melbye M, Hviid A. Association between oral fluoroquinolone use and retinal detachment. *JAMA* 2013;310(20):2184–2190
  - 55 Fife D, Zhu V, Voss E, Levy-Clarke G, Ryan P. Exposure to oral fluoroquinolones and the risk of retinal detachment: retrospective analyses of two large healthcare databases. *Drug Saf* 2014;37(03):171–182
  - 56 Kapoor KG, Hodge DO, St Sauver JL, Barkmeier AJ. Oral fluoroquinolones and the incidence of rhegmatogenous retinal detachment and symptomatic retinal breaks: a population-based study. *Ophthalmology* 2014;121(06):1269–1273
  - 57 Eftekhari K, Ghodasra DH, Haynes K, Chen J, Kempen JH, VanderBeek BL. Risk of retinal tear or detachment with oral fluoroquinolone use: a cohort study. *Pharmacoepidemiol Drug Saf* 2014;23(07):745–752
  - 58 Chui CS, Man KK, Cheng CL, et al. An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study. *J Antimicrob Chemother* 2014;69(09):2563–2567
  - 59 Choi SY, Lim HA, Yim HW, Park YH. Administration of oral fluoroquinolone and the risk of rhegmatogenous retinal detachment: a nationwide population-based study in Korea. *PLoS One* 2018;13(04):e0195563
  - 60 Taher MK, Crispo JAG, Fortin Y, et al. Systemic quinolones and risk of retinal detachment III: a nested case-control study using a US electronic health records database. *Eur J Clin Pharmacol* 2022;78(06):1019–1028
  - 61 Chui CS, Wong IC, Wong LY, Chan EW. Association between oral fluoroquinolone use and the development of retinal detachment: a systematic review and meta-analysis of observational studies. *J Antimicrob Chemother* 2015;70(04):971–978
  - 62 Alves C, Penedones A, Mendes D, Batel Marques F. A systematic review and meta-analysis of the association between systemic fluoroquinolones and retinal detachment. *Acta Ophthalmol* 2016;94(05):e251–e259
  - 63 Taher MK, Habsah M, Bjerre L, Momoli F, Mattison D, Krewski D. Systemic quinolones and risk of retinal detachment II: systematic review of clinical trials. *Clin Med Rev Case Rep* 2021;8:369
  - 64 Granados J, Ceballos M, Amariles P. [Hypo or hyperglycemia associated with fluoroquinolone use]. *Rev Med Chil* 2018;146(05):618–626
  - 65 Pakkir Maideen NM. Pharmacokinetic and pharmacodynamic interactions of sulfonylurea antidiabetics. *Eur J Med* 2018;6:83–96
  - 66 Chou HW, Wang JL, Chang CH, Lee JJ, Shau WY, Lai MS. Risk of severe dysglycemia among diabetic patients receiving levofloxacin, ciprofloxacin, or moxifloxacin in Taiwan. *Clin Infect Dis* 2013;57(07):971–980
  - 67 Aspinall SL, Good CB, Jiang R, McCarren M, Dong D, Cunningham FE. Severe dysglycemia with the fluoroquinolones: a class effect? *Clin Infect Dis* 2009;49(03):402–408
  - 68 Saad NA, Elberry AA, Samy Matar H, Hussein RRS. Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients. *Int J Clin Pract* 2021;75(05):e14072
  - 69 Liao SH, Hu SY, How CK, et al. Risk for hypoglycemic emergency with levofloxacin use, a population-based propensity score matched nested case-control study. *PLoS One* 2022;17(04):e0266471
  - 70 Kabbara WK, Ramadan WH, Rahbany P, Al-Natour S. Evaluation of the appropriate use of commonly prescribed fluoroquinolones and the risk of dysglycemia. *Ther Clin Risk Manag* 2015;11:639–647
  - 71 Berhe A, Russom M, Bahran F, Hagos G. Ciprofloxacin and risk of hypoglycemia in non-diabetic patients. *J Med Case Rep* 2019;13(01):1–6
  - 72 Althaqafi A, Ali M, Alzahrani Y, Ming LC, Hussain Z. How safe are fluoroquinolones for diabetic patients? A systematic review of dysglycemic and neuropathic effects of fluoroquinolones. *Ther Clin Risk Manag* 2021;17:1083–1090
  - 73 El Ghandour S, Azar ST. Dysglycemia associated with quinolones. *Prim Care Diabetes* 2015;9(03):168–171
  - 74 US Food and Drug Administration FDA Drug Safety Communication: FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label; changes. July 10, 2018. Accessed December 7, 2023 at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side>
  - 75 Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. *Int J Antimicrob Agents* 2007;29(04):374–379
  - 76 Zambon A, Polo Friz H, Contiero P, Corrao G. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Saf* 2009;32(02):159–167
  - 77 Lapi F, Wilchesky M, Kezouh A, Benisty JJ, Ernst P, Suissa S. Fluoroquinolones and the risk of serious arrhythmia: a population-based study. *Clin Infect Dis* 2012;55(11):1457–1465
  - 78 Chou HW, Wang JL, Chang CH, Lai CL, Lai MS, Chan KA. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and  $\beta$ -lactam/ $\beta$ -lactamase inhibitors: a Taiwanese nationwide study. *Clin Infect Dis* 2015;60(04):566–577
  - 79 Liu X, Ma J, Huang L, et al. Fluoroquinolones increase the risk of serious arrhythmias: a systematic review and meta-analysis. *Medicine (Baltimore)* 2017;96(44):e8273
  - 80 Inghammar M, Svanström H, Melbye M, Pasternak B, Hviid A. Oral fluoroquinolone use and serious arrhythmia: bi-national cohort study. *BMJ* 2016;352:i843
  - 81 Gorelik E, Masarwa R, Perlman A, et al. Fluoroquinolones and cardiovascular risk: a systematic review, meta-analysis and network meta-analysis. *Drug Saf* 2019;42(04):529–538
  - 82 Cho Y, Park HS. Association of oral ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin with the risk of serious ventricular arrhythmia: a nationwide cohort study in Korea. *BMJ Open* 2018;8(09):e020974
  - 83 Assimon MM, Pun PH, Wang LC, et al. Analysis of respiratory fluoroquinolones and the risk of sudden cardiac death among patients receiving hemodialysis. *JAMA Cardiol* 2022;7(01):75–83
  - 84 Briasoulis A, Agarwal V, Pierce WJ. QT prolongation and torsade de pointes induced by fluoroquinolones: infrequent side effects from commonly used medications. *Cardiology* 2011;120(02):103–110
  - 85 Wang SH, Xie YC, Jiang B, et al. [Fluoroquinolone associated myasthenia gravis exacerbation: clinical analysis of 9 cases]. *Zhonghua Yi Xue Za Zhi* 2013;93(17):1283–1286
  - 86 Jones SC, Sorbello A, Boucher RM. Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review. *Drug Saf* 2011;34(10):839–847
  - 87 Krenn M, Grisold A, Wohlfarth P, et al. Pathomechanisms and clinical implications of myasthenic syndromes exacerbated and induced by medical treatments. *Front Mol Neurosci* 2020;13:156
  - 88 Sheikh S, Alvi U, Soliven B, Rezanian K. Drugs that induce or cause deterioration of myasthenia gravis: an update. *J Clin Med* 2021;10(07):1537
  - 89 US Food and Drug Administration FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. May 12, 2016. Accessed



- December 7, 2023 at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-advises-restricting-fluoroquinolone-antibiotic-use-certain>
- 90 European Medicines Agency Quinolone- and Fluoroquinolone-Containing Medicinal Products. March 19, 2019. Accessed December 7, 2023 at: <https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products>
  - 91 Bratsman A, Mathias K, Laubscher R, Grigoryan L, Rose S. Outpatient fluoroquinolone prescribing patterns before and after US FDA boxed warning. *Pharmacoepidemiol Drug Saf* 2020;29(06):701–707
  - 92 Sankar A, Swanson KM, Zhou J, et al. Association of fluoroquinolone prescribing rates with black box warnings from the US food and drug administration. *JAMA Netw Open* 2021;4(12):e2136662
  - 93 Bonkat G, Wagenlehner F. In the line of fire: should urologists stop prescribing fluoroquinolones as default? *Eur Urol* 2019;75(02):205–207
  - 94 Pietruszyński R, Pietruszyńska-Reszetarska A, Sokal J, Domżałski M. Antioxidant therapy in the management of fluoroquinolone-associated disability. *Arch Med Sci* 2020;16(06):1483–1486
  - 95 Gatti M, Bianchin M, Raschi E, De Ponti F. Assessing the association between fluoroquinolones and emerging adverse drug reactions raised by regulatory agencies: an umbrella review. *Eur J Intern Med* 2020;75:60–70