Adverse Reactions to Fluoroquinolones – Focus on Tendinopathy, QT Prolongation, and Neuropathy: A Review

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ABSTRACT

Fluoroquinolones are a widely prescribed class of antibiotics that have proven to be effective in treating a range of bacterial infections. However, the use of these drugs is associated with several adverse reactions that can cause significant harm to patients. This article aims to provide a comprehensive overview of the side effects of fluoroquinolones, with a particular focus on tendinopathy, QT prolongation, and neuropathy. Tendinopathy is a rare fluoroquinolone adverse reaction that can cause tendon rupture and significant disability. Patients who are older, taking steroids, and those who have a history of tendon disorders are more likely to develop this complication. Another serious side effect of fluoroquinolone use is QT prolongation. It has the potential to cause arrhythmias, in some cases fatal, and is more likely to occur in patients with pre-existing heart problems, electrolyte imbalances, and those taking drugs that prolong the QT interval. Finally, neuropathy is a less frequent but potentially debilitating adverse reaction affecting peripheral nerves that can manifest as numbness, tingling, muscle weakness, or even paresis. Given the potential for significant harm associated with fluoroquinolone use, clinicians must carefully consider the risks and benefits of prescribing these drugs, particularly in high-risk populations. Patients receiving them should be closely monitored for any signs and symptoms of these serious adverse reactions to allow for early intervention and appropriate management.

Key Words: *Fluoroquinolones, Tendinopathy, QT prolongation, Neuropathy, Antibiotic resistance*

eIJPPR 2024; 14(1):23-35

HOW TO CITE THIS ARTICLE: Suchy W, Buś Z, Król M, Dykas K. Adverse Reactions to Fluoroquinolones – Focus on Tendinopathy, QT Prolongation, and Neuropathy: A Review. Int J Pharm Phytopharmacol Res. 2024;14(1):23-35. https://doi.org/10.51847/HHoSB9BTtW

INTRODUCTION

Fluoroquinolones are potent antimicrobial agents derived from a wider group called quinolones, which were first introduced in the 1960s. Since then, they, as well as their younger brothers, have been gaining fame as powerful drugs prescribed to treat a wide range of infections [1]. Fluoroquinolones are generally well tolerated – their most common side effect is gastrointestinal distress with symptoms such as nausea, diarrhea, or stomach pain [2]. Nevertheless, some enthusiastically welcomed fluoroquinolones were forced to be taken off the market when after their introduction, some severe adverse reactions have been reported. Withdrawn drugs include temafloxacin, which caused serious hemolysis, hypoglycemia, or renal failure [3], trovafloxacin, after cases of liver failure following its use [4], and gatifloxacin, as it increased the risk of both hypo- and hyperglycemia [5]. There are also some more recent changes, as nalidixic acid, pipemidic acid, cinoxacin, and flumequine have been suspended in 2018 as a result of an investigation conducted by the European Medicines Agency (EMA) [6]. Therefore, there has been an ongoing debate regarding the safety of fluoroquinolones due to their ability to cause some serious adverse reactions. This review focuses on these less prevalent and significantly more severe side effects and discusses their mechanisms, risk factors, as well as possible ways of prevention and treatment.

Characteristics of quinolones

Based on their properties, quinolones are divided into four generations. The main differences between them and their

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Received: 11 December 2023; **Revised:** 23 February 2024; **Accepted:** 24 February 2024

most important members are depicted in **Table 1**. While older derivatives had a rather narrow spectrum, exhibiting activity primarily against gram-negative bacteria, newer ones, called fluoroquinolones, which contain fluorine in their structure, have a wider spectrum that includes both gram-positive and gram-negative bacteria [1]. Therefore, indications to use these agents, which initially involved only uncomplicated urinary tract infections (UTIs) caused by E. coli or other susceptible organisms, expanded significantly. Nowadays they also include community-acquired and nosocomial pneumonia, gastrointestinal and intraabdominal infections, prostatitis, sexually transmitted infections, as well as infections of the skin and soft tissue [7, 8]. Moreover, they exhibit activity against Mycobacterium tuberculosis, which can also be used to treat drug-resistant tuberculosis [9].

Table 1. Main characteristics of generations of quinolones based on refs. [1], and [10]

Generation	Members	Antimicrobial spectrum
I	Nalidixic acid, oxolinic acid, cinoxacin	Gram-negative bacteria (except *Pseudomonas* spp.)
II	Lomefloxacin, ciprofloxacin, ofloxacin	All gram-negative bacteria, some gram-positive bacteria, and some atypical pathogens
III	Levofloxacin, sparfloxacin, grepafloxacin	Enhanced activity against gram-positive and atypical pathogens
IV	Gemifloxacin, trovafloxacin, moxifloxacin	Additional anaerobic activity

The main mechanism in which fluoroquinolones act is the inhibition of gyrase – an enzyme responsible for basic processes such as replication or transcription of bacterial DNA [8]. It has a special ability to introduce negative supercoiling into DNA. Another molecular target is topoisomerase IV – an enzyme critical in supercoiled DNA relaxation [11]. Fluoroquinolones inhibit these enzymes by binding to their complex with DNA and stabilizing initially transient DNA breaks created by them. Inhibition of these two proteins leads to the suppression of DNA synthesis and therefore cell death [1]. However, the effect of the drug on these enzymes depends on the type of the affected bacteria since inhibition of gyrase is the main mechanism in gram-negative bacteria, while in gram-positive bacteria topoisomerase IV is usually the more susceptible enzyme, however, there are some exceptions [1]. Furthermore, some pathogens such as *Helicobacter pylori*, Mycobacterium tuberculosis, and Treponema pallidum lack the topoisomerase IV gene, implying that gyrase is the only fluoroquinolone target in these organisms [8].

Fluoroquinolones are characterized by high oral bioavailability as they are rapidly absorbed in the gastrointestinal tract [12]. Peak plasma concentration is achieved 1-2 hours following drug oral administration [13]. Also, newer derivatives reach higher serum concentrations and have longer elimination half-lives, which enables them to be administered once daily. Moreover, their bactericidal activity is concentration-dependent, and they exhibit post-antibiotic effects [1, 12]. They are widely distributed throughout the body, except cerebrospinal fluid, where the penetration is sufficient only during meningitis [12, 13]. The route of elimination can be either renal by glomerular filtration and tubular secretion, as in most fluoroquinolones, or hepatic. Therefore, the majority of these drugs require dosage adjustment in patients with impaired renal function [1, 13].

Fluoroquinolones are also prone to interact with other drugs. Their absorption is significantly decreased during the concomitant administration of antacids [12]. Fluoroquinolones are also able to markedly increase the serum concentration of methylxanthines, such as theophylline, due to a reduction in their metabolism by inhibiting isoenzyme 1A2 of the cytochrome P450 [12]. There have also been some concerns about the concurrent use of fluoroquinolones with non-steroidal anti-inflammatory drugs, as it has been associated with an increased risk of seizures due to interference with GABA receptors [12]. A study conducted on mice revealed that norfloxacin with either biphenylacetic acid or flurbiprofen is a combination that poses the greatest risk of this complication [14].

Furthermore, there are some states in which fluoroquinolone use is contraindicated. These include known hypersensitivity to the drug [15], myasthenia gravis due to possible exacerbation of the disease [16], concomitant administration of other drugs known to prolong QT interval or long QT syndrome (LQTS) [17], epilepsy, stroke [18]. Also, careful consideration should be given when prescribing them to individuals diagnosed with Marfan or Ehlers-Danlos syndrome since they are associated with a significantly greater risk of developing an aortic aneurysm or dissection, which might be furtherly increased by fluoroquinolone administration [19, 20]. Finally, they should also be cautiously prescribed to children and during pregnancy, and considered only if a safer alternative is not possible [1].

Tendinopathy

Tendons are structures that connect muscles to bones and transmit force, enabling movement. With specific properties and mechanical resistance, the tendon's white connective tissue is made up of collagen type I fibers

arranged parallel to the axis of the tendon [21]. Type I collagen and elastic fibers are produced by tenoblasts and tenocytes, which make up as much as 90% of the tendon's cells [22].

Tendon disorders can account for up to 30% of consultations with general practitioners caused by musculoskeletal conditions. This is a medical problem that can affect people of all ages [23]. Tendinopathy is a complex pathology of the tendon characterized by symptoms such as loss of function, pain, and difficulty in physical exertion. The terminology used to describe different tendon pathologies has been inconsistent in the past [24]. There are several different forms of tendinopathy. Tendinitis refers to tendon inflammation that responds to anti-inflammatory treatment such as steroids. Tendinosis is tendon degeneration, which can involve changes such as necrosis, neovascularization, or calcification, but not inflammatory characteristics. Paratendinosis, on the other hand, is inflammation caused by mechanical damage to the tendon rubbing against adjacent structures, such as bones [23].

Many potential factors contribute to tendinopathy, which is the subject of research. Many of them have weak evidence, and they also differ depending on the tendon's location. For example, the risk factors for rotator cuff tendinopathy were age over 50, diabetes, and overhead activities [25]. A different study listed nine potential risk factors for Achilles tendinopathy, including aspects related to mechanical injuries, abnormal gait, the use of ofloxacin and alcohol, and somatic diseases, for which there was limited evidence [26]. There was no strong evidence for the risk factors for patellar tendinopathy [27].

Fluoroquinolones can cause rare but serious complications in the form of tendinopathy, regardless of the route of administration and the dosage used [28]. The incidence of that AE is estimated to be 0.14-0.4% [29, 30]. The mean age of patients suffering from this complication is 59 years [30]. After starting the therapy with fluoroquinolones, the median latency period for tendinopathy to occur is about 6-10 days [22, 31]. The first cases of tendinopathy have been noted 20 years after fluoroquinolones were introduced to the market (in the 80s) [22]. Patients taking fluoroquinolones who have additional risk factors, such as older age (over 60 years), steroid therapy, previous tendinopathy, or kidney transplantation, are more susceptible to this adverse reaction [28]. One retrospective study showed that Achilles tendonitis associated with fluoroquinolones was more common in non-obese individuals over 60 years of age who were taking oral glucocorticosteroids. A slight increase in risk was also observed in women, diabetics, and individuals with renal failure or undergoing hemodialysis [32]. Weight-bearing tendons are the most commonly affected tendons following fluoroquinolone administration. The Achilles tendon seems to be the most susceptible to damage, accounting for about 90% of cases of tendinopathy [30]. However, other tendons such as the rotator cuff, biceps brachii, quadriceps, and hand tendons may also be affected. The injury is bilateral in up to 50% of the patients and tendon rupture complicates about 40% of cases [30]. The mechanism of this toxicity is not fully understood [33]. It is suggested that the toxicity of fluoroquinolones results from increased expression of metalloproteinases, inhibition of fibroblast proliferation, and induction of oxidative stress. Some studies also indicate the possibility of the chelating activity of fluoroquinolones and antagonistic effects on magnesium [28].

In studies on rats, many complex tendon pathologies were found, which can be induced by various fluoroquinolones. The most common changes noted in these studies were: swelling with infiltration of mononuclear cells, disruption of collagen deposition in the matrix of synovial membranes and tendon sheaths, mucoid degeneration, fragmentation of tenocyte nuclei, detachment of tenocytes from the extracellular matrix, swelling of cellular organelles such as mitochondria and endoplasmic reticulum. Ciprofloxacin caused a reduction in the synthesis of certain proteins such as type I collagen, elastin, proteoglycans, and fibronectin. An important component of fluoroquinolone action on tendon tissue is the increased expression of matrix metalloproteinases (MMP-1, MMP-2, MMP-13). There is also an increase in the expression of caspase-3 and apoptosis markers [34].

Pefloxacin is indicated as the riskiest fluoroquinolone in terms of tendinopathy. Adding drugs such as ofloxacin, norfloxacin, or ciprofloxacin to treatment with pefloxacin was associated with an increased risk of tendon inflammation [35].

The first meta-analysis in 2019 regarding the risk of tendinopathy after fluoroquinolones, which included 15 studies, showed that therapy using fluoroquinolones increased the risk of Achilles tendon damage and inflammation. They also increased the risk of any tendon disorder [28]. A case-control study showed that current exposure to fluoroquinolones increases the risk of any tendon rupture (aIRR 1.61, 95% CI 1.25-2.09) and Achilles tendon rupture (aIRR 3.14, 95% CI 2.11–4.65), which persists for 60 days. Simultaneous use of fluoroquinolones and oral glucocorticosteroids was particularly dangerous (aIRR 19.36, 95% CI 7.78-48.19 for Achilles tendon). There was no association with factors such as exposure to co-amoxiclav or statins [36]. Other drugs that increase the risk of tendinopathy include statins, glucocorticosteroids, aromatase inhibitors, anabolic steroids, isotretinoin, and antiviral drugs (mainly indinavir) [22].

Some case reports reveal tendon damage in unusual sites associated with the use of fluoroquinolones. A 43-year-old Hispanic man suffered a bilateral patellar tendon rupture

while lifting a television. His medical history revealed that 3 months before the injury, the patient underwent a 10-day course of ciprofloxacin for an upper respiratory tract infection [37]. Another patient, a 44-year-old African American woman, presented to an ophthalmology clinic with swelling and eversion of the right lower eyelid. The patient did not report any trauma in her history. Three weeks before the onset of symptoms, she was hospitalized for pneumonia and acute kidney injury. She was treated with intravenous ciprofloxacin and oral levofloxacin and also received inhaled fluticasone. The patient was diagnosed with a lateral canthal tendon rupture [38]. Cases of hand and wrist tendon damage following previous fluoroquinolone use have also been documented [39].

Some preventive measures can be undertaken to decrease the risk of this side effect in patients. The most important issue is to avoid prescribing fluoroquinolones in high-risk groups mentioned above, as well as avoiding concomitant use of other drugs that may cause tendinopathy as an AE. If it is not possible, the patient should be informed about the risk of this complication and advised to stop taking the medication and seek medical attention if any alarming symptoms occur [40]. Moreover, there are some more specific ways of preventing fluoroquinolone-induced tendinopathy. Since oxidative stress is supposed to play a role in tendon impairment, a reduction in the formation of reactive oxygen species (ROS) should decrease the risk of this AE [41]. This can be obtained in various ways. The first arises from the photosensitizing effect of fluoroquinolones. When under exposure to ultraviolet, fluoroquinolones become photoactivated, leading to increased production of ROS [42]. Therefore, sun protection is highly advised in patients taking these antibiotics and was shown to reduce the incidence of phototoxic reactions [34]. Another way is the use of antioxidants. Studies revealed that agents such as N-acetylcysteine [43] or anethole dithiolethione [44] decrease the toxic effect exerted on tendon cells by fluoroquinolones. A different suggested therapy is the use of platelet-rich plasma as a source of growth factors, which was shown to protect the viability of cells exposed to ciprofloxacin [45]. Nevertheless, all of the mentioned studies have been conducted on cell lines or in an animal model, therefore there is a lack of reliable, clinical evidence validating their use in patients.

Management of this AE is mainly symptomatic since the precise mechanism underlying this complication is not well elucidated. Therefore, the treatment includes discontinuation of the drug, pain control, and rehabilitation, which consists of two parts. The first of them includes rest and immobilization of the affected tendon, while the second comprises progressive loading physical therapy. Sometimes, especially in the case of a tendon rupture, surgical intervention is required [30, 31, 46].

Tendinopathy caused by fluoroquinolones also carries other problems, such as high costs of treatment. One retrospective study evaluated the costs of fluoroquinolone-related tendinopathy treatment in Finland between 2002 and 2012. 145 people seeking compensation for this condition were included. It was estimated that direct treatment costs amounted to 14,800 EUR per claimant. A significant proportion of patients (51%) were hospitalized (average stay of 21 days), which was the costliest medical service, averaging 9,915 EUR per hospitalization episode [47].

To conclude, tendinopathy is a complication of fluoroquinolones that can manifest in many forms [23]. It most commonly affects the Achilles tendon but can also occur in less typical locations such as the patellar tendon or eye muscle tendon [30, 37, 38]. It is associated with risk factors such as older age, diabetes, or steroid therapy [28, 32]. The potential mechanism may involve the accumulation of ROS and damage to mitochondria [28, 34]. In addition to medical issues, this complication carries significant systemic costs and is a burdensome problem for the healthcare system [47].

QT prolongation

The QT interval reflects depolarization and repolarization of the action potential of cardiac ventricles. Typically, it lasts 420–440 ms in males and 440–460 ms in females, and its prolongation (inherited or acquired LQTS) represents changes in repolarization. The acquired LQTS may result from electrolyte or metabolic abnormalities, or anomalies of heart structure, or it may be a drug-induced adverse effect (AE) [48].

One of the most important groups of agents causing this side effect is fluoroquinolones. Although they are useful in the treatment of various diseases, they should be cautiously prescribed to patients who are predisposed to torsade de pointes (TdP) [48]. This is a potentially fatal polymorphic ventricular tachycardia often appearing due to the prolongation of QT interval [49]. Clinically, it may manifest as syncope, dizziness, palpitations, seizures, and sudden death but it also may be asymptomatic [48]. Fluoroquinolones, such as levofloxacin or moxifloxacin, may lead to TdP by blocking voltage-gated potassium channels, especially the rapid component of the delayed rectifier potassium current (I Kr) in ventricular cardiomyocytes encoded by the human ether-a-go-go-related gene (hERG) [48, 50]. This phenomenon results in an accumulation of potassium ions and delayed cardiac repolarization [17].

Noel [51] conducted a clinical trial on healthy adult volunteers to evaluate the impact of levofloxacin, moxifloxacin, and ciprofloxacin on QT and corrected QT

(QTc) interval. This study presented that even a single high dose of antibiotic leads to the change in QTc interval and achievement of approximately 1.5 times the maximum plasma concentration of medication that is found after recommended doses which are 800 mg of moxifloxacin, 1000 mg of levofloxacin, and 1500 mg of ciprofloxacin.

Briasoulis *et al*. [48] conducted a retrospective analysis of TdP in patients who received fluoroquinolones in the USA in the period 1996-2001 which revealed that 25 cases of TdP were associated with the administration of these drugs. Nevertheless, various members of this group demonstrate different proarrhythmic potential. Previous clinical studies and case reports indicate that moxifloxacin is associated with the greatest risk of QT interval prolongation conducive to TdP, whereas oral ciprofloxacin seems to carry the lowest risk of this AE [17, 49].

One of the most important nonmodifiable risk factors of drug-induced TdP is aging. Probably, it is associated with frequent abnormalities of heart structure, polypharmacy resulting in drug interactions, and reduced drug clearance [49]. The next risk factor of drug-induced TdP is the female sex, as women generally have a longer duration of QTc. This phenomenon probably is multifactorial, but the main cause seems to be an effect of sex hormones on cardiac ion channels resulting in sex differences in the cardiac repolarization process [52]. The confirmation of this was reported by Jonsson *et al*. [53] who observed that estrogen reduces the expression of both rapid (I Kr) and slow (I Ks) delayed rectifier potassium current while progesterone enhances I Ks and testosterone enhances both I Kr and I Ks. Täubel *et al*. [52] conducted a study to determine differences in cardiac electrophysiology between moxifloxacin and levofloxacin in men and women. This study showed that the increase in the duration of early repolarization in women was greater with moxifloxacin than with levofloxacin. Probably it results from the dual block – both IKs and IKr are caused by moxifloxacin. What is more, it suggests the involvement of sex hormone-dependent differences in IKs leading to differences in QT intervals between moxifloxacin and levofloxacin.

Moreover, the harmful effect of fluoroquinolones may be intensified by electrolyte abnormalities and other medicaments with TdP risk [49, 50]. First of all, these drugs include antipsychotics, amiodarone, and certain macrolides such as erythromycin. The background of these interactions relates to the inhibition of drug metabolism and pharmacodynamic interactions facilitating the action of the drug at the channel site (for example the metabolism of erythromycin and clarithromycin by cytochrome P450 system in the liver and active Ikr blockers which are their metabolites) [49]. However, as far as electrolyte abnormalities are concerned, hypokalemia and hypomagnesemia have been related to 28% of case reports of drug-induced TdP [49].

Another risk factor was tested by Assimon *et al*. [50] and it concerned patients with hemodialysis-dependent kidney failure. Their study showed that patients treated with respiratory fluoroquinolones were more predisposed to QT interval prolongation conducive to sudden cardiac death in comparison to amoxicillin-based therapy. This phenomenon seems to be associated with structural heart disease often diagnosed among the hemodialysis population such as left ventricular hypertrophy or heart failure with subsequent cardiac remodeling and downregulation of hERG and other ion channels. This study indicated the importance of medication review and identification of possible pharmacodynamic drug interactions before prescribing new drugs as a crucial method of prevention of drug-induced TdP [50].

Another strategy concerns avoiding fluoroquinolones among the patients diagnosed with congenital LQTS and taking antiarrhythmic agents of class Ia and III or other agents prolonging the QT interval. In these cases, a careful assessment of risks and benefits should be conducted to select an antibiotic with the lowest QT prolongation potential [48, 54].

What is more, fluoroquinolones should be prescribed cautiously or even avoided among patients with other risk factors for arrhythmias including medications interfering with the metabolism of fluoroquinolones [55]. Additionally, patients with cardiac conditions such as heart failure or ischemic heart disease should be administered fluoroquinolones under ECG monitoring [54].

In summary, fluoroquinolones may lead to a potentially fatal AE – the prolongation of QT interval. This consequence is related to the occurrence of TdP with syncope, dizziness, and even sudden cardiac death as a clinical manifestation [48, 49]. The reason for that phenomenon is a blockage of voltage-gated potassium channels [48, 50]. Moxifloxacin is associated with the greatest potential of QT interval prolongation conducive to TdP, whereas oral ciprofloxacin seems to carry the lowest one [52]. The risk factors of that adverse reaction are both nonmodifiable and modifiable. The predisposition is related to aging, female sex, electrolyte abnormalities, and other medicaments with TdP risk such as antipsychotics or certain macrolides [49, 50]. What is more, it is crucial to remember that a particular group of patients at risk of fluoroquinolone-induced TdP are patients with hemodialysis-dependent kidney failure [50]. The experts indicate some strategies for prevention including precise medical review, identification of possible drug interactions, and avoiding fluoroquinolones among patients diagnosed with congenital LQTS [50, 54, 55].

Neuropathy

Neuropathy is defined as any disease that affects peripheral nerves (excluding the brain and spinal cord) [56]. It gives

many various signs and symptoms, but in the case of fluoroquinolone-induced neuropathy, the most characteristic is weakness, numbness, changes in pain and temperature sensitivity [57], hyperesthesia, hypoesthesia, allodynia, or even peripheral paresis [58]. There are also some reports indicating the possibility of optic nerve neuropathy related to the use of fluoroquinolones [59] that manifests with reduced visual acuity, reduced visual field, and color vision disturbances that resolve completely after discontinuation of the therapy. Furthermore, there are also case reports disclosing the correlation between fluoroquinolones and the appearance of Guillain-Barré syndrome (GBS) [60] or demyelinating neuropathy [61].

It is believed that these side effects are related to the ability to bind with mammalian mitochondrial topoisomerase II. Loss of mitochondrial DNA and associated mitochondrial toxicity could play a major role in the development of neuropathy in vulnerable patients as neurons relay their metabolism mainly on mitochondria. Other mechanisms involved in the neurotoxicity of fluoroquinolones are increased oxidative stress and reduction in protein synthesis via inhibition of aminoacyl-tRNA synthetases [62].

The inflammatory process is believed to play an important role in the pathophysiology of the discussed neuropathy. During an antibiotic, an increase in serotonergic nerve endings was observed after the third day of treatment and was related to the accumulation of mast cells in their vicinity. However, on the seventh day, the density of nerve endings was reduced, probably due to the release of inflammatory mediators, such as histamine, from mast cells. The mediators could contribute to the development of neurogenic inflammation that damages nerve endings and could even lead to their atrophy [63]. The drawback of this proposed mechanism is the fact that it was established in rats and investigated innervated organs were salivary glands, so the direct transfer to some symptoms in humans could not be certain. Some clinical and neurophysiological findings suggest a small fiber neuropathy pattern of toxicity [58, 64], which is consistent with the work previously cited. Furthermore, axonal degeneration and demyelination patterns were also observed [65].

It is worth mentioning that discontinuation of therapy is often sufficient to resolve symptoms [59, 64] but on the other hand, there were also reports indicating irreversible neuropathy [57, 66] or even that the majority of cases are persistent [67]. Even the local formulation of the drug is not potentially free from this side effect, as the authors suggest [68], due to the individual threshold of sensitivity to blood concentration achieved by this route of administration.

Most studies show an increased risk of neuropathy induced by fluoroquinolones [69-72] but there are also works indicating no increase in the incidence of this AE in a specific group of patients [73]. The most important facts are discussed in the next paragraphs.

One of the largest studies related to the problem of fluoroquinolone-induced neuropathy [69] revealed a significantly increased risk compared to controls - aIRR for fluoroquinolones was 1.47; 95% CI, 1.13-1.92. Interestingly, the risk increased during the antibiotic course, and each day of current exposure was associated with about a 3% increase in risk. The risk persists up to 180 days after discontinuation of the therapy. The authors also included analysis indicating an estimated absolute risk of neuropathy - it was established as 2,4 users/10000 patients per year of current drug use. NNH fluctuated depending on the length of the treatment course and was estimated as 152083 (95% CI, 117742-202778) for 10-day therapy, and NNH was proportional to the length of the course.

Carpal tunnel syndrome (CTS) was revealed to be associated with the use of fluoroquinolones [70]. The authors show that the use of any drug from this class in the previous year increases the relative risk of the occurrence of CTS (RR = 1,36, 95% CI 1,32- 1,38). What is highlighted here is that even a delayed response to the drug is possible, similar to the study discussed above.

The next study on the topic of fluoroquinolone-induced neuropathy focused on a comparison between new and prevalent users of drugs [71]. Both groups had a higher risk of this AE, but the current new users were at a greater risk of its development (RR = 2,07, 95% CI 1,56- 2,74).

Other interesting findings on this topic were disclosed by Ali [72]. He showed not only an increased risk of neuropathy after fluoroquinolone therapy but also a risk of GBS, which is an even more dangerous form of peripheral nervous system damage.

In opposition to the previous results, observation is made that in children with acute lymphoblastic leukemia, fluoroquinolones in combination with vinca-alkaloids do not increase the risk of neuropathy induced by cytotoxic drugs [73]. The reason why these two groups of drugs that can induce neuropathy do not show a synergistic effect is unknown. In the case of vincristine-induced peripheral neuropathy, local inflammation is one of the suggested mechanisms of its development, similar to that induced by fluoroquinolones. It is speculated that the probably stronger neurotoxic effect of vincristine can mask the weaker AE of antibiotics, which is confirmed by the high incidence (79%) of neuropathy in the study cited.

In general, there is a correlation between fluoroquinolone use and an increased risk of neuropathy, but the knowledge about this phenomenon needs to be augmented with more large observational studies.

Amyloidosis, Lyme disease, Sjögren syndrome, shingles, alcohol abuse, current smoking, as well as therapy with phenytoin and nitrofurantoin within 90 days were established as risk factors for this AE [69]. The same article

also highlights that age ≥ 60 years and male gender are significant risk factors. Marginally higher risk in patients with high BMI is also indicated, as well as the influence of the high score in the Charlson comorbidity index. The age group at risk seems to be confirmed by another study [74]. Some reports show that previous neuropathy, such as complex regional pain syndrome (CRPS) [75], diabetes mellitus [65, 76], or Charcot-Marie-Tooth syndrome [77] could also be considered as risk factors for neuropathy. Also, the combination with other drugs used in the treatment of HIV infection and tuberculosis (like ethionamide and streptomycin) is believed to increase the risk of this AE, but in this case, it is difficult to establish the exact contribution of fluoroquinolones in its development. As mentioned above, new users [71] of fluoroquinolones are also in the higher-risk group. However, there also are reports indicating that female sex and age 16-65 are risk factors, but the authors admit that this phenomenon could be biased by some aspects [67].

Because the precise mechanism of neuropathy is not yet established, casual treatment is barely possible. Based on laboratory studies on this topic, only directions that could be translated into clinical practice might be proposed and included the reduction of oxidative stress, the restoration of reduced mitochondrial potential, the supplementation of cations chelated by fluoroquinolones (e.g., Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, Fe^{2+}, Co^{2+}, Mn^{2+}, and K^{+}), supporting mitochondrial proliferation in the cell, the removal of permanently accumulated fluoroquinolones in cells (the mechanism is not confirmed) and regulation of disturbed epigenetics and enzyme activity [78]. If AE is present, discontinuation of fluoroquinolone treatment and symptomatic treatment is proposed [79] as a significant part of cases resolves over time [64, 76].

Neurotoxicity associated with CNS caused by fluoroquinolones (e.g. headache, lowered seizure threshold, psychoses) is caused by their property to inhibit GABA receptors. Therefore, benzodiazepines, which enhance signaling via this receptor, were proposed as a possible treatment option [80]. Probably newer drugs acting through a similar mechanism (gabapentin, pregabalin) might be the best choice in symptomatic treatment.

The new possible method of similar AE treatment (but for now far from being accepted and recommended), especially in case of overdosage, is dialysis. Although prescribing information negates such a possibility, pharmacokinetic studies showed its efficacy in lowering levofloxacin blood plasma concentration [81].

Although fluoroquinolones can induce neuropathy, they are not the only antibiotics with such properties. Other antibacterial agents such as metronidazole, linezolid, and nitrofurantoin are also related to this AE [72] and were shown to increase its risk to a greater extent than fluoroquinolones. In the case of metronidazole, these results were not confirmed by a meta-analysis published by the Cochrane Library that discusses the treatment and prevention of pouchitis [82], since it does not show a significant difference between the AEs of ciprofloxacin and metronidazole. The comparison of fluoroquinolones and amoxicillin-clavulanate confirmed a lower incidence of neuropathy in the case of the latter drug [69].

Some in-group analyses are also available. Levofloxacin and ciprofloxacin are believed to have the most significant risk of neuropathy induction, while moxifloxacin is the safest drug considering this AE [72, 80]. Besides that, both norfloxacin and ofloxacin have an indirect risk. This study also highlights that ciprofloxacin has the highest ability to induce GBS [72].

In conclusion, fluoroquinolone-induced neuropathy manifests itself as various symptoms that affect both sensory and motor neurons [57, 58]. There are several hypotheses explaining the possible pathophysiology of this AE [62, 63, 65], but none of them is certain, and probably more than one mechanism is responsible for the full spectrum of observed neuropathies. It is difficult to accurately estimate the incidence of this neuropathy, due to many risk factors that are not yet fully understood. However, studies show that it is a real concern and indicates caution, especially when they are used often on the same patient. Symptomatic treatment is recommended mainly because there is no obvious causal treatment for this AE, but some laboratory studies indicate some potential targets [78]. To improve symptoms, discontinuation of therapy is needed, but cases are showing irreversible neuropathy. It is believed that levofloxacin and ciprofloxacin have the highest risk of induction of neuropathy [72, 80]. However, other fluoroquinolones are also able to induce it, as well as many other groups of antibiotics.

The current issue with fluoroquinolone use – antibiotic resistance

Despite the undeniable potency of fluoroquinolones, their overuse and misuse have led to the emergence of resistant bacterial strains, which are currently a serious threat to the general public's health. Noteworthy, some multidrug-resistant bacteria, including vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA), predominantly exert cross-resistance to fluoroquinolones [8].

Resistance can occur in three different mechanisms, shown in **Figure 1**. The most common of them is a mutation in the subunits of one or both of the target enzymes (1), resulting in a significantly decreased ability of fluoroquinolones to bind to the enzyme-DNA complex. This mutation may occur in serine residue, which does not negatively impact the activity of the enzyme, or acidic residues of amino

acids, which decreases its activity 5-10 times. This might be the reason why serine changes encompass > 90% of the mutant pool [7]. Alteration in one of the enzymes results in < 10-fold resistance, while mutations in both enzymes may confer resistance of up to 100-fold [7, 8]. Another possibility is plasmid-mediated resistance (2), carrying the genes responsible for decreasing the binding of the target enzymes to DNA, which lowers the number of enzyme-DNA complexes, crucial for fluoroquinolone action (2a), altering drug metabolism (2b) and increasing fluoroquinolone efflux from the cell (2c). It usually causes low-level resistance (up to 10-fold), but significantly higher resistance, reaching even 125-fold, has also been noted. Moreover, plasmids can also be transferred horizontally, which can lead to their rapid spread [83]. The last type is chromosome-mediated resistance (3), able to decrease the drug influx into the cell by downregulating the porins (3a), as well as, similarly to plasmid-mediated resistance, increasing the drug efflux (3b). It usually causes low-level resistance, although its ability to decrease the fluoroquinolone concentration within the cell makes it easier for other types of resistance to emerge [7, 8].

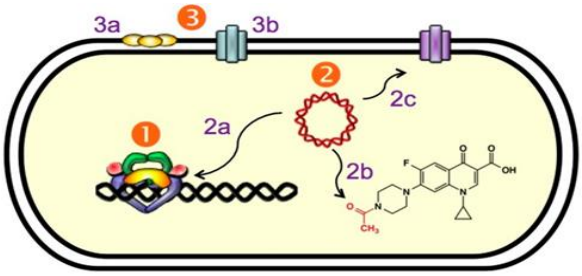

Figure 1. Mechanisms of fluoroquinolone resistance (Image from ref. [7]).

RESULTS AND DISCUSSION

There are still some significant concerns regarding the safety of fluoroquinolones. Due to their great efficacy and convenient dosing, they have been administered liberally and occasionally recklessly [84]. Medical practitioners had to temper their optimism, though, as the number of reported adverse reactions has been rising alarmingly. The majority of the side effects were minor, but some of them had the potential to be fatal [50, 85]. This resulted in the restriction of the use of these powerful drugs and the discontinuation of some fluoroquinolones. Some of the side effects not mentioned in the previous part of the review are shown in **Table 2**.

Table 2. Other side effects associated with fluoroquinolone use based on refs. [2], [15], [20], and [86-91]

Side effect	Description
Photosensitivity	While taking fluoroquinolones, some individuals may develop an increased sensitivity to sunlight or UV radiation, which can cause a rash or skin blistering. Patients using these drugs are advised to avoid prolonged sun exposure, dress protectively, and use sunscreen whenever they are outside.
Hepatotoxicity	Rarely, fluoroquinolone-using patients have experienced liver failure with jaundice, black urine, and abdominal pain as possible symptoms. Patients taking other drugs that impact liver function or those with pre-existing liver disorders should be thoroughly monitored while using these antibiotics.
Aortic aneurysm or dissection	Fluoroquinolones have been associated with the development of aortic aneurysm rupture or aortic dissection, which are potentially fatal.
Musculoskeletal effects	Rare incidences of arthralgia and myalgia have been linked to fluoroquinolones, and in some cases, these symptoms may persist for months or even years after discontinuation of the drug.
Hematologic effects	Agranulocytosis, hemolytic anemia, and thrombocytopenia can all be caused by fluoroquinolones. Patients using them need to have close monitoring for any symptoms of hematologic disorders.
Dysglycemia	In some cases, fluoroquinolones have been linked to both hypo- and hyperglycemia. Although the precise mechanism underlying this association is unclear, it is believed to be connected to how fluoroquinolones alter the body's insulin production and glucose metabolism.
Hypersensitivity reactions	Fluoroquinolones may cause a variety of hypersensitivity reactions ranging from mild skin rashes to potentially life-threatening systemic (anaphylaxis) or cutaneous reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis).
***Clostridioides difficile* infection**	Fluoroquinolones, as broad-spectrum antibiotics, pose the risk of causing gut dysbiosis, which creates a favorable environment for *Clostridioides difficile* overgrowth.

Trends in fluoroquinolone prescribing have been changing throughout the years. After their introduction in the 1980s, their utilization in the United States has been increasing systematically from 1991-2010, with stabilization from 2011-2015 [92]. This has led to fluoroquinolones overtaking the lead as the class of antibiotics accounting

for the most antibiotic expenditure in 2009 [93] and being the number three most-prescribed antibiotic group in adults in 2011 [94]. They have been frequently misused as they have been routinely prescribed for uncomplicated UTIs, acute sinusitis, and acute bronchitis – diagnoses that do not require fluoroquinolones [95]. A study revealed that 25% of prescribed fluoroquinolones are for conditions that do not require antibiotics or for which fluoroquinolones are not recommended as a first-line therapy [84]. It is a serious concern since antibiotics are the second group of drugs causing AEs requiring admission to the emergency department, with fluoroquinolones being the most likely class to lead to hospitalization [96]. As a result of that, the FDA has issued several safety warnings regarding these drugs [97]. A study investigating their impact on fluoroquinolone prescribing revealed that it significantly decreased from 35,616,786 fills in 2015 to 21,100,050 in 2019. An intriguing finding is that the number of fills increased in two groups, one of them being infectious diseases specialists. This might indicate the shift of prescribing from general practitioners to specialists, ensuring the appropriate use of these potent drugs. The second group was nurse practitioners, which might be due to their growing importance in the US healthcare system [97].

CONCLUSION

Due to growing interest in fluoroquinolones, their utilization has been snowballing in the 1990s and 2000s. Moreover, they were often prescribed for indications that did not require their usage. These phenomena gave rise to the development of bacterial resistance to these drugs. As a result of these circumstances, accompanied by reports of various adverse reactions in their users, a series of FDA black box warnings regarding fluoroquinolones have appeared. After that, their utilization in the US decreased substantially. This data raises hopes for more responsible fluoroquinolone prescribing in the future, resulting in better treatment results and fewer adverse reactions.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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ISSN (Online) 2249-6084 (Print) 2250-1029