Fluoroquinolone-Associated Tendinopathy: Does Levofloxacin Pose the Greatest Risk?

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Fluoroquinolone antibiotics recently have gained increased national attention due to safety concerns. A well-described and serious adverse event associated with receipt of fluoroquinolones is tendinitis and tendon rupture. These tendon injuries can result in long-term sequelae, including chronic pain and mobility restrictions, and may warrant surgery. Due to the severity of these adverse events, a black box warning is included in the product labeling of all fluoroquinolones. In light of the mounting concerns surrounding fluoroquinolone-associated toxicities, the purpose of this clinical review is to provide a comprehensive summary of the risk of tendinopathy associated with levofloxacin, one of the most widely prescribed antibiotics in the United States, across in vitro, animal, and clinical studies, relative to other antibiotics. As part of this review, clinical presentation and onset, proposed mechanisms, patient-specific risk factors, and management of fluoroquinolone-induced tendon injury are summarized. Data were obtained from a comprehensive PubMed literature search and a review of U.S. Food and Drug Administration documents. Although tendinopathy is considered a fluoroquinolone class–wide toxicity, data from in vitro studies, animal studies, patient-level analyses, and large national and international surveillance reports suggest that levofloxacin, as well as its parent compound ofloxacin, possess higher propensities to cause tendon damage relative to other fluoroquinolones. Risk with ofloxacin and levofloxacin appears to be exposure dependent, with higher doses and longer durations being most commonly associated with tendinopathy. Other well-described patient risk factors for fluoroquinolone-associated tendinopathy include older age (older than 60 yrs), receipt of concomitant corticosteroid therapy, presence of renal dysfunction, and history of solid organ transplantation. Given widespread use of levofloxacin across patient care settings, knowledge of both patient- and drug-specific characteristics associated with increased risk of tendinitis and tendon rupture can promote safe use of levofloxacin and other fluoroquinolones.

Key Words levofloxacin, fluoroquinolone, tendinopathy, tendinitis, tendon rupture.
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Fluoroquinolone antibiotics recently gained increased national attention due to growing safety concerns. In November 2015, a joint meeting of the Antimicrobial Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee was conducted to review risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections.[1]

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Class-wide safety concerns, both new and established, were a major focus of this U.S. Food and Drug Administration (FDA) advisory meeting discussion. One of the most well-described and serious adverse events associated with receipt of fluoroquinolones is tendinitis and tendon rupture. These tendon injuries can result in long-term sequelae, including chronic pain and mobility restrictions, and may warrant surgery. Although the estimated incidence of fluoroquinolone-induced tendinopathy in the general population is low (0.14–0.4%),[2–4] all fluoroquinolones have a black box warning in the product labeling for tendinitis and tendon rupture due to the severity of this adverse event.

Levofloxacin is currently one of the most frequently prescribed antimicrobials in the United States.[5] U.S. outpatient prescription data from the IMS Health National Prescription Audit database indicate that 11.3 million levofloxacin prescriptions were dispensed in 2014 alone, an increase from 9.3 million in 2010.[1] In light of the increasing concerns surrounding fluoroquinolone-associated toxicities and the popularity of levofloxacin, the purpose of this clinical review is to provide a comprehensive summary of the risk of tendinopathy associated with levofloxacin, including its parent compound ofloxacin, across in vitro, animal, and clinical studies, relative to other antibiotics. As part of this review, clinical presentation and onset, proposed mechanisms, patient-specific risk factors, and management of fluoroquinolone-induced tendon injury are also summarized.

Literature Search

The PubMed database was searched for available reports related to levofloxacin-associated tendinopathy published between 1987 and October 2015. Evidence of tendinopathy associated with ofloxacin was also included given that this agent was in widespread use prior to levofloxacin availability and the chemical similarity between the two compounds (levofloxacin is the S-enantiomer of racemic ofloxacin).[6] Search terms included *levofloxacin* or *ofloxacin* in combination with *tendon*. A similar search was conducted using the Medical Subject Heading term *tendinopathy/chemically induced*. Clinical, animal, and in vitro studies were eligible for inclusion. Articles of interest retrieved in PubMed without abstracts and/or full texts were searched by author and title using Google Scholar. Only full-length articles were included. Documents, including FDA warning letters and prescribing information, and other possibly relevant public safety reports were also reviewed; relevant references from these sources were also reviewed and included. No formal assessment for methodologic quality was performed. Studies published in languages other than English were excluded. Sample populations restricted to pediatrics were also excluded; fluoroquinolone use in children is controversial given that observations of musculoskeletal injury in animal studies frequently involved juvenile species.[7]

Clinical Presentation

Fluoroquinolone-induced tendinopathy most commonly involves weightbearing tendons. The Achilles tendon appears to be the most susceptible to injury, although other body parts may also be affected (e.g., rotator cuff, biceps, hands, quadriceps).[8, 9] One study indicated that nearly 90% of fluoroquinolone-associated tendinitis and tendon rupture cases involved the Achilles tendon,[3] and bilateral involvement can occur in up to 50% of cases.[8] Achilles tendon disorders have been characterized by edema, tenderness, and swelling, and they are often accompanied by sharp pain with walking.[8, 10] Symptoms tend to occur acutely, and severity appears to correlate with the degree of edema.[11] Rupture is often preceded by tendinitis but may occur without forewarning.[8] Symptom onset varies considerably, and studies report an average onset of 9–13 days after fluoroquinolone therapy initiation (range 1–152 days).[8, 12–14] Most events occur within the first month[15]; however, tendon disorders can still occur up to 18 months following exposure.[16] Diagnosis of tendinitis or tendon rupture is commonly based on clinical presentation and physical examination, although imaging studies may also be used.[3] Clinical presentation does not appear to differ among individual fluoroquinolone class agents.

Proposed Mechanisms

Although several theories exist, the exact mechanism of fluoroquinolone-induced tendon toxicity remains undefined. Given that many theories involve tendon injury at the cellular level, an understanding of a functional tendon system is needed to appreciate the proposed mechanisms and their toxicity implications. Tendons are complex, poorly vascularized tissues that connect muscle to bony structures, and

their primary function is to transmit mechanical forces from muscle to bone.[17] They are composed mainly of collagen, which provides tensile strength against mechanical forces.[17, 18] Collagen is arranged in a series of hierarchical structures within the tendon. Collagen bundles (primary, secondary, and tertiary) are the largest structures, which are organizations of fibers that in turn are made up of fibrils (i.e., aggregations of collagen molecules).[17, 19] Collagen is synthesized by tendon cells, or tenocytes, within the tendon extracellular matrix (ECM), which ultimately leads to the formation of collagen fibrils, fibers, and bundles.[19] The ECM is a conglomerate of numerous substances including a gel-like proteoglycan complex that acts as a scaffold for surrounding cells.[11, 18] The ECM communicates with surrounding cells via transmembrane integrin receptors to signal initiation of adaptive functions to support optimal transmission of mechanical forces along the tendon.[18] Integrin receptor activation stimulates numerous intracellular pathways including the mitogen-activated protein (MAP) kinase pathway that is responsible for tenocyte proliferation.[11, 20–22] Of note, these integrins require trivalent and divalent cations such as magnesium for appropriate functioning.[20] Tenocyte synthetic and proliferative processes are balanced by degenerative processes, the latter of which involve matrix metalloproteinases. These enzymes degrade collagen in response to tissue inflammation and damage.[23] Balance of collagen synthesis and degradation under normal physiologic conditions is key for appropriate tendon tissue remodeling and repair after injury.[18, 23]

Fluoroquinolones have been postulated to compromise tendon function and increase risk of injury, particularly in weightbearing joints most subject to mechanical force,[11] via several proposed mechanisms. Fluoroquinolones may cause direct tissue injury including necrosis or exposure-dependent cellular apoptosis.[20] They may also induce toxicity indirectly by stimulating local release of tissue-damaging substances including nitric oxide and oxygen-derived species.[10, 24] Fluoroquinolones may inhibit mammalian (rather than solely bacterial) topoisomerase II, resulting in cellular mitochondrial toxicity.[11] These agents may also stimulate activity of matrix metalloproteinases and other enzymes that degrade collagen and components of the ECM including proteoglycan.[23] Fluoroquinolones, which are known chelators of cations, may deplete divalent ions (e.g., magnesium) essential for appropriate integrin receptor signaling.[11, 20] Disruption of integrin function and related pathways (e.g., MAP kinase) has been associated with numerous deleterious effects including cellular apoptosis and formation of damaging free radicals.[20, 25] To complicate matters, repletion of essential ions needed for appropriate integrin function secondary to fluoroquinolone chelation may be delayed given poor local vascularization.[17] Fluoroquinolones have also demonstrated toxicity potential in proximal tissues such as cartilage (i.e., chondrotoxicity) that could contribute to local injury.[11, 20]

Proposed mechanisms of fluoroquinolone-associated tendinopathy are considered to apply class-wide. Although not well described, chemical structure differences among class agents may contribute to variable toxicity risk potential. In rats, higher rates of tendon lesions were observed with agents possessing a methylpiperadinyl substituent at the seventh position of the fluoroquinolone structure (e.g., ofloxacin, levofloxacin), whereas agents with a piperadinyl substituent (e.g., norfloxacin, ciprofloxacin) demonstrated little to no toxicity.[26] The specific role that these structures serve in tendon injury, if any, is unknown. Ultimately, when considering the numerous potential mechanisms, fluoroquinolone-associated tendinopathy may be precipitated by a complex set of physiologic and chemical factors rather than a singular process.

In Vitro Data

Levofloxacin- and ofloxacin-induced tendon toxicity has each been well described by in vitro studies, particularly in cartilage cells, or chondrocytes (Table 1). One study with ofloxacin found that after 72 hours of exposure, integrin expression in chondrocyte cells derived from fetal mouse epiphyseal cartilage decreased with increasing concentrations (10, 30, and 100 mg/L).[27] Collagen formation and matrix integrity were also substantially decreased in the ofloxacin-treated versus control cultures. In juvenile rabbit chondrocytes, ofloxacin demonstrated interference with integrin receptor function and the MAP kinase pathway (concentration 10 μg/ml) as well as concentration- and time-dependent apoptosis (2–10 μg/ml), with up to 96 hours of drug exposure.[25] Decreased cellular viability was also observed with 10 μg/ml, a concentration considered achievable in human plasma. Another study demonstrated a concentration- and time-

Table 1. In Vitro Studies Describing Levofloxacin- and Ofloxacin-Associated Tendon and Cartilage Toxicity

Model	Drug concentration	Human concentration	Exposure	Findings
Fetal mouse chondrocytes[27]	OFX 10, 30, and 100 mg/L	OFX 10 μg/ml[25]	72 hrs	Concentration-dependent decrease in integrin expression; decreased collagen formation and matrix integrity
Juvenile rabbit chondrocytes[25]	OFX 2–10 μg/ml		≤96 hrs	Concentration- and time-dependent apoptosis (2–10 μg/ml); integrin receptor function and MAP kinase pathway interference (10 μg/ml)
Rabbit chondrocytes[28]	OFX 5, 10, 20, 40, and 80 μg/ml		≤96 hrs	Concentration- and time-dependent decreased cell viability; concentration-dependent increase in reactive oxygen species production and DNA damage
Rat annulus fibrosus cells[29]	LVX 30, 60, and 90 μg/ml	LVX 3–10 mg/L[21, 22]	24–48 hrs	Dose-dependent decreased cell viability, increased apoptosis (caspase-3), increased expression of metalloproteinases ($p<0.05$ for all)
Human tenocytes[22]	LVX 3, 10, and 30 mg/L		≤96 hrs	Concentration- and time-dependent cellular matrix structural changes including less matrix production and increased matrix metalloproteinase expression; apoptosis with all concentrations
Human tenocytes[21]	LVX 3 and 10 mg/L		≤96 hrs	Concentration-dependent increases in metalloproteinase expression and the apoptosis marker caspase-3; degenerative changes in the extracellular matrix at both concentrations
	LVX ± DEX 0.1–1.0 nM			LVX + DEX: Time-dependent, synergistic degeneration and apoptosis

DEX = dexamethasone; DNA = deoxyribonucleic acid; LVX = levofloxacin; MAP = mitogen-activated protein; OFX = ofloxacin.

dependent trend in decreased cell viability in rabbit chondrocytes exposed to ofloxacin 5, 10, 20, 40, or 80 μg/ml for up to 96 hours.[28] Interestingly, a concentration-dependent increase in intracellular reactive oxygen species production and DNA damage was also observed.

Similar exposure-response trends have been observed with levofloxacin. One study evaluated changes in tendon-like intervertebral disk-derived rat annulus fibrosus cells after exposure to various levofloxacin concentrations for 24–48 hours.[29] Levofloxacin induced cellular shrinking and degenerative changes at concentrations of 30, 60, and 90 μg/ml, whereas control cells grew normally. Dose-dependent cellular apoptosis was observed at rates of 6.38%, 9.20%, and 13.06% with each respective incremental concentration increase. Decreased cell viability, increased apoptosis as indicated by caspase-3, and increased expression of metalloproteinases involved in tissue and matrix degradation were all observed in a statistically significant dose-dependent manner ($p<0.05$ for all).

Perhaps the most notable findings from in vitro studies come from those using human tenocytes. One study involving tenocytes treated with levofloxacin concentrations of 3, 10, and 30 mg/L for up to 4 days demonstrated cellular matrix structural changes, including less matrix production, in a concentration- and time-dependent manner.[22] Levels of matrix metalloproteinases increased in the same fashion. Apoptosis was observed even at the lowest levofloxacin concentration. Levofloxacin concentrations of 3 and 10 mg/L are reflective of those achievable in plasma and tendons during therapeutic treatment.[21, 22] A subsequent study in human tenocytes demonstrated similar findings, including degenerative changes in the ECM, with both of these concentrations (3 and 10 mg/L).[21] Increases in metalloproteinase expression and the apoptosis marker caspase-3 were more pronounced at the higher levofloxacin concentration. Effects of concurrent dexamethasone (0.1–1.0 nM) and levofloxacin exposure were also studied, given that both drugs can independently induce tendon damage. Cells treated concurrently with levofloxacin and dexamethasone exhibited synergistic toxicity, with more pronounced degeneration and apoptosis occurring with combined drug exposure than with either drug alone. Cellular toxicity was time dependent over the 4-day exposure period and generally detectable earlier with combined drug exposure.

Animal Data

Tendon toxicity in animals has been observed with levofloxacin and ofloxacin doses that produce similar drug exposure profiles in humans.

Studies mainly involved observation of tissue lesions or clinical musculoskeletal toxicity. Similar to in vitro studies, both dosage and duration appear to drive the extent of tendon toxicity. Higher doses were associated with an increased risk, supporting a dose-response relationship. Longer durations of exposures have also been associated with ofloxacin- and levofloxacin-associated tendon toxicity.

The dose dependency of levofloxacin-induced tendinopathy was well described in a juvenile rat study.[26] Achilles tendon lesions occurred in 7 of 17 rats (41%) and 6 of 8 rats (75%) after single doses of levofloxacin 300 mg/kg and 900 mg/kg, respectively. The identified 50% toxic dose was 419 mg/kg (95% confidence interval [CI] 268–849) for levofloxacin and 616 mg/kg (95% CI 455–1177) for ofloxacin. These levofloxacin doses would correspond to supratherapeutic concentrations in humans; 50 mg/kg/24 hours and 100 mg/kg/24 hours in rats appear to achieve comparable areas under the curve (AUCs) for therapeutic doses of 500 mg/day and 750 mg/day, respectively.[30]

In rats, administration of oral levofloxacin 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced considerable arthropathy.[6] Arthrotoxicity has also been described in young beagles administered therapeutic levofloxacin doses for 8–9 consecutive days.[7] Clinical toxicity was demonstrated at the lowest dose of 2.5 mg/kg/day (0.2-fold or higher of the estimated AUC of therapeutic levofloxacin 500 mg every 24 hrs), whereas synovitis and articular lesions were observed at 10 mg/kg and 40 mg/kg doses (equivalent to and 3-fold higher than estimated therapeutic doses, respectively). For higher doses, lesions persisted until the end of the 18-week recovery period. These findings are supported by a similar study in which young dogs developed arthropathic lesions after receiving oral levofloxacin 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days.[6]

The exposure-dependent risk of toxicity with ofloxacin and levofloxacin has not been observed with other common fluoroquinolones. In juvenile rats, both ofloxacin- and levofloxacin-induced Achilles tendon lesions after single doses started at 300 mg/kg, whereas no lesions were observed with norfloxacin or ciprofloxacin even at the highest dose of 900 mg/kg.[26] Increased toxicity with ofloxacin and levofloxacin was attributed to achievement of higher drug concentrations or chemical structure features. Similar findings were demonstrated in nonhuman primates, in which arthropathy was seen with administration of ofloxacin 200 mg/kg twice/day for 5 days[31] but not with more aggressive dosing of norfloxacin 500 mg/kg for 7 days.[32] Although ofloxacin and norfloxacin were studied in different primate species, findings from these and other studies may still suggest an increased risk of toxicity with ofloxacin and levofloxacin compared with other class agents (Table 2).

Clinical Data: What Is the Risk?

Numerous surveillance and safety studies from both the United States. and Europe have been published describing the risk of ofloxacin- and levofloxacin-associated tendinopathy (Table 3). Initially, risk of tendon toxicity with levofloxacin was suspected to be quite low; only one case of possible drug-related tendinitis and no cases of tendon rupture were reported from phase II and phase III clinical trials with 5388 patients.[13] Although limited evidence existed for levofloxacin-associated tendinopathy on licensure in the United States. in December 1996, the risk of tendon disorders with its parent compound ofloxacin had been well described by large foreign surveillance studies. Consistent with in vitro and animal studies, many of these surveillance studies documented increased tendon toxicity with ofloxacin relative to other fluoroquinolones.[2, 4, 8, 36]

One United Kingdom prescription monitoring study published in 1996 assessed postmarketing tendon disorder (i.e., tendinitis, tenosynovitis, or tendon rupture) reporting rates for the fluoroquinolones ciprofloxacin, norfloxacin, and ofloxacin in comparison with azithromycin and cefixime.[4] Whereas the time frame varied slightly for each agent, all prescriptions were written between November 1988 and December 1991, and all events were reported within 2 months of therapy initiation. Of ~11,000 patients, tendinopathy was reported for 20 adults. Tendon disorder rates were highest with ofloxacin (11 per ~11,000 patients) compared with those observed with other fluoroquinolones (1 and 3 per ~11,000 for ciprofloxacin and norfloxacin, respectively) and other antibiotics (2 and 3 per ~11,000 for azithromycin and cefixime, respectively). Published the same year, one of the largest retrospective studies of fluoroquinolone (pefloxacin, ofloxacin, norfloxacin, and ciprofloxacin)-associated

Table 2. Animal Studies Describing Levofloxacin- and Ofloxacin-Associated Musculoskeletal Toxicity

Model	Drug dosage and route	Human concentration	Exposure	Outcomes	Findings
Juvenile rats[26]	10 oral fluoroquinolones administered at 100, 300, and 900 mg/kg	LVX doses achieving comparable AUCs for therapeutic doses in humans: 50 mg/kg/24 hrs in rats approximates 500 mg/day in humans; 100 mg/kg/24 hrs in rats approximates 750 mg/day in humans[30]	Single dose	Achilles tendon lesions	
				LVX 300 mg/kg	7/17 (41%)
				900 mg/kg	6/8 (75%)
					TD_{50}: LVX 419 mg/kg (95% CI 268–849)
				OFX 300 mg/kg	5/33 (15%)
				900 mg/kg	7/10 (70%)
					TD_{50}: OFX 616 mg/kg (95% CI 455–1177)
				CIP, NOR (300 mg/kg, 900 mg/kg)	No lesions
Juvenile rats[6]	Oral LVX 300 mg/kg/day; i.v. LVX 60 mg/kg/day		Oral: 7 days i.v.: 4 wks	Arthropathy	Observed
Young beagles[7]	Oral LVX 2.5, 10, 40 mg/kg/day	Estimated AUC comparison for therapeutic dose of LVX 500 mg/24 hrs	8–9 days	Clinical musculoskeletal toxicity	2.5 mg/kg/day
				Synovitis	10 mg/kg/day, 40 mg/kg/day
				Articular lesions	Lesions persisted for 18 wks
Young dogs[6]	Oral LVX 10 mg/kg/day; i.v. LVX 4 mg/kg/day	2.5 mg/kg/day, ≥ 0.2-fold higher; 10 mg/kg/day, equivalent; 40 mg/kg/day, 3-fold higher[7]	Oral: 7 days i.v.: 14 days	Arthropathy	Lesions observed
Juvenile marmosets[31]	Oral OFX 200 mg/kg twice/day	NS	5 days	Joint cartilage damage	Loosening and loss of matrix, chondrocyte necrosis

AUC = area under the curve; CI = confidence interval; CIP = ciprofloxacin; i.v. = intravenous; LVX = levofloxacin; NOR = norfloxacin; NS = not specified; OFX = ofloxacin; TD_{50} = 50% toxic dose.

tendon disorders described 421 case reports (340 tendinitis, 81 tendon rupture) in France between August 1992 and December 1993.[8] Ofloxacin was implicated in 18% (77/421) of cases, with an associated rate of 1 case/173,600 daily doses defined (DDD). Similar to findings from other studies, these rates were higher than those reported for norfloxacin (35/421; 1 case/799,600 DDD) and ciprofloxacin (22/421; 1 case/325,860 DDD).

Another retrospective study conducted in the Netherlands compared rates of tendinitis with fluoroquinolones (ofloxacin, ciprofloxacin, and norfloxacin) to those of other antibiotics (amoxicillin, trimethoprim-sulfamethoxazole, trimethoprim, and nitrofurantoin) among a cohort of primary care patients.[2] Patients were 15 years or older and received a reference antibiotic between January 1995 and December 1996 with a documented tendon disorder occurring within 1 month of prescription. The incidence of fluoroquinolone tendinitis was 7.74 per 100,000 days compared with 3.27 per 100,000 days for the nonfluoroquinolone antibiotics, with a relative risk (RR) of 2.4 (95% CI 0.96–5.80). Ofloxacin demonstrated a crude RR of 6.5 (95% CI 2.14–19.45) and adjusted RR of 4.9 (95% CI 1.57–15.06) for tendinitis, whereas no association was found with ciprofloxacin or norfloxacin. This risk increased upon stratification for Achilles tendinitis, with an RR of 10.1 (95% CI 2.20–46.04) with ofloxacin compared with an RR of 4.4 (95% CI 1.27–20.27) for the class agents collectively. Ofloxacin was associated with a risk increase of 15 cases of tendinopathy per 100,000 days compared with 4 cases per 100,000 for all fluoroquinolones.

Levofloxacin, the pure *S*-enantiomer of racemic ofloxacin,[6] was first introduced into the Asian market in 1993 followed by the U.S. market in December 1996. The first case report of levofloxacin-induced tendinitis was published in 1999,[44]

Table 3. Studies Describing Tendon Disorder Findings with Levofloxacin or Ofloxacin

Study type (study period)	Population	Subjects	Observation period	Outcome	Findings
Pharmacovigilance (1988–1991)[4]	General population	33,620 FQ users, 22,525 non-FQ users	2 mo	Tendon disorders	Cases per 11,000 patients: OFX 11, NOR 3, CIP 1
Pharmacovigilance (1992–1993)[8]	Case reports	421 case reports (340 tendinitis, 81 tendon rupture)	Mean onset 9.3 days (range 1–152 days) from Rx	Tendon disorders	OFX 1 case/173,600 DDD, CIP 1 case/325,860 DDD, NOR 1 case/799,600 DDD
Cohort study (1995–1996)[2]	General practice	97 tendinitis or tendon rupture cases over 548,919 days	Rx duration + 1 mo; mean onset 9 days	Tendinitis	OFX RR[a] 4.9 (95% CI 1.57–15.06), no association with NOR or CIP
				Tendon rupture	OFX 15 cases/100,000 days, all FQs 4 cases/100,000 days
Pharmacovigilance (1/1999–6/1999)[33]	Case reports	8 tendinopathy reports	Mean onset 5 days (range 2–11 days)	Tendinopathy	LVX 7/8 cases, NOR 1/8 cases
Postmarketing surveillance (1997–2000)[34]	General population	15 million LVX Rx	39 mo	Tendon rupture	< 4 ruptures/million LVX Rx
Pharmacovigilance (NS)[35]	General population	5388 LVX patient Rx in Europe, 130 million LVX patient Rx worldwide	NS	Tendinitis	LVX 1/500,000 patient Rx
				Tendon rupture	LVX 1/1.6 million patient Rx
Pharmacovigilance (1988–1998)[36]	Case reports	42 tendon disorder reports	≤1 mo for 93% of cases	Tendon disorders	OFX 38% (16/42), CIP 31% (13/42), NOR 19% (8/42)
Pharmacovigilance; case series (1994–2002)[37]	Hospital medical records	7 patients with tendon disorder or tendon rupture	16 mo	Achilles tendon rupture or disorder	LVX 5/7 cases, CIP 2/7 cases LVX 1 patient/350,000 people/3 mo
Pharmacovigilance (1999–2001)[38]	Case reports	10,011 FQ ADE reports for 18 million inhabitants	NS	Serious tendinitis	LVX 11.4 reports/DDD/100 inhabitants/day, CIP and NOR < 4 reports/DDD/100 inhabitants/day
Pharmacovigilance (1997–2002)[39]	Case reports	78 patients with FQ musculoskeletal ADEs	Mean onset 7 days	FQ musculoskeletal ADE cases	LVX 35/78 (44.9%), CIP 30/78 (38.5%), NOR 10/78 (12.8%)
Case-control (1/1997–6/2001)[40]	Insurance claims, medical records	947 Achilles rupture, 18,940 controls	6 mo	Achilles tendon rupture	Any FQ OR[a] 1.2 (95% CI 0.9–1.7), OFX OR[a] 1.4 (95% CI 0.6–3.6), LVX OR[a] 0.6 (95% CI 0.3–1.4)
Pharmacovigilance (2005–2006)[41]	Case reports	272 FQ ADE reports for 18 million inhabitants	NS	Achilles tendinitis and rupture	LVX 24/32 (75%)
				Other tendinitis and rupture	LVX 10/14 (71.4%)
Cohort study (4/1996–12/2009)[42]	Hospital database inpatients and outpatients	17,147 FQ users, 38,517 cephalosporin users	Rx duration + 30 days	Tendon disorders	OFX RR 80.24 (95% CI 9.46–680.47), LVX RR 5.20 (95% CI 1.74–15.51), CIP and NOR no cases LVX 9 cases/13,334 Rx, OFX 1 case/96 Rx
Pharmacovigilance (FQ approval date September 2012)[43]	FAERS	2,495 FAERs reports	NS	Tendon rupture	LVX EBGM = 20.0 (95% CI 18.2–21.6), MOX EBGM = 13.3 (95% CI 11.7–15.1), NOR EBGM = 9.6 (95% CI 6.5–13.5), OFX EBGM = 8.2 (95% CI 6.3–10.2), GEM EBGM = 1.9 (95% CI 0.7–4.5)

ADE = adverse drug event; CI = confidence interval; CIP = ciprofloxacin; DDD =defined daily dose; EBGM = empirical Bayes geometric mean; FAERS = U.S. Food and Drug Administration Adverse Event Reporting System; FQ = fluoroquinolone; GEM = gemifloxacin; LVX = levofloxacin; MOX = moxifloxacin; NOR = norfloxacin; NS = not specified; OFX = ofloxacin; OR = odds ratio; RR = relative risk; Rx = prescription.
[a]Adjusted value.

although several reports of tendon disorders had been reported to the manufacturer prior to this. The first postmarketing data from the United States. were published in 2001, reflecting safety data from the 39 months following levofloxacin launch.[34] Using data from more than 15 million U.S. prescriptions, the rate of levofloxacin-associated tendon rupture was reported to be less than 4 per million prescriptions.

Although few postmarketing reports for tendinopathy were filed in the United States., evidence was increasing in Europe for tendon toxicity with levofloxacin. One Swiss study assessed reports of fluoroquinolone-associated Achilles tendon disorder or rupture from five departments at Lund University Hospital between January 1994 and March 2002.[37] Five of seven patients received levofloxacin, with all events occurring within 16 months of prescription. This corresponded to an associated tendinopathy rate of one patient every 3 months in an area with 350,000 inhabitants. Similar reports of increased tendinopathy with levofloxacin prompted a toxicity surveillance study by the Swiss Drug Monitoring Center, SANZ, published in 2000.[33] From 1986 to June 1999, 4.1% (19/460) of adverse reaction reports to SANZ for fluoroquinolones involved tendinopathy. Between January and June 1999, levofloxacin was implicated in seven of eight tendinopathy cases reported. This reflected higher toxicity reporting rates despite shorter clinical use of this agent compared with other fluoroquinolones. Similarly, in Sweden, 78 reports of fluoroquinolone-associated musculoskeletal toxicity were made to the Swedish spontaneous adverse drug event reporting system at Uppsala University Hospital between 1997 and 2002.[39] The highest number of reports (35/78 [45%]) were with levofloxacin (Achilles tendinitis 57%, rupture 26%), despite its national launch in 2000.

Several other studies emerged out of Europe describing levofloxacin-induced tendinopathy, including large surveillance reports.. One vigilance study published in 2001 assessed data from ~130 million levofloxacin prescriptions in Europe and other countries.[35] Tendinitis occurred in 1 in 500,000 prescriptions, whereas tendon rupture occurred in 1 in 1.6 million prescriptions. A study in Italy described spontaneous adverse event reporting from three regions comprising 18 million people (~32% of the Italian population) between January 1999 and December 2001.[38] Levofloxacin was associated with the highest reporting rate for tendinitis, expressed as 11.4 reports/DDD/100 inhabitants/day. Interestingly, during the same time frame as the Italian study,[38] levofloxacin was associated with the highest tendinitis report rate in the World Health Organization Collaborating Center database (522 reports of tendon disorder including rupture).[38] As of February 2002, this number had increased to 586 reports of tendinitis and tendon rupture with levofloxacin, compared with 120 cases of tendon rupture reported with ciprofloxacin.[37]

Several years after the study from Italy just cited,[38] a similar surveillance study was conducted using a comparable population.[41] Notably, fluoroquinolone prescribing in Italy had increased by 4% in the years following the first national study (from 2004–2007). Fluoroquinolone safety data from January 2005 to December 2006 were reviewed for four Italian regions comprising 18 million inhabitants, or 33% of the Italian population; in this study, 272 adverse drug reactions were reported for fluoroquinolones. For both study years, levofloxacin was associated with the highest rate of adverse drug reactions, including tendinopathy. Of the 32 total cases of fluoroquinolone-associated Achilles tendinitis or tendon rupture and 14 cases of other tendinitis or rupture, levofloxacin use was implicated in 24 (75%) and 10 (71.4%) cases, respectively.

Similarly, in the most recent published review of the FDA's Adverse Event Reporting System (FAERS) through September 2012, most reports for fluoroquinolone-associated tendon rupture were associated with levofloxacin (1555/2495 [62.3%] total reports).[43] Signal detection results were also highest for levofloxacin (empirical Bayes geometric mean [EBGM] = 55.2, 95% CI 52.3–58.0) compared with other fluoroquinolones. These findings are consistent with a hospital database study from 2012 of more than 17,000 inpatients and outpatients prescribed fluoroquinolones in Japan, which noted the highest number of tendon disorder cases to be associated with levofloxacin (9 cases in 13,334 patients).[10]

Although these large-scale analyses are informative, they are associated with numerous limitations. Many studies used adverse event reporting databases that rely on voluntary submissions. Events may be underreported, or reports may contain insufficient patient-level detail to establish true causality. Reports may also be subject to reporter or temporal bias. In addition, the previously mentioned studies reported event occurrence in variable terms (e.g., events/DDD, events/prescription, events/persons/time frame), which

make risk characterization challenging. However, several studies clearly demonstrate a higher event rate with ofloxacin and levofloxacin compared with other class agents and comparators. For levofloxacin, events seemed to occur at higher rates compared with other fluoroquinolones despite less time on the clinical market.

Clinical Data: Who Is at Risk?

Several patient populations have been identified to be at greater risk for fluoroquinolone-induced tendinopathy based on surveillance and other studies (Table 4). Risk factors are largely described at the class level. The most well-described at-risk populations are the elderly[8, 16, 36, 46–48, 51] and patients receiving concomitant corticosteroid use.[8, 16, 46, 47, 51, 52] These risk factors were first suggested in one of the earliest fluoroquinolone pharmacovigilance studies conducted in France comprising 100 patients who experienced tendinitis (69 patients) or tendon rupture (31 patients) from pefloxacin, norfloxacin, ciprofloxacin, or ofloxacin between 1985 and July 1992.[14] Given that the mean patient age was 63 years (range 25–84 yrs), age older than 60 was suggested to increase risk of tendinopathy with fluoroquinolone use. Concomitant corticosteroid therapy was noted in 17 patients.

In 1996, the same authors published a continuation of this analysis including tendinopathy cases in France between August 1992 and December 1993.[8] As discussed earlier, it was one of the largest analyses of fluoroquinolone-associated (pefloxacin, ofloxacin, norfloxacin, and ciprofloxacin) tendon disorders at the time, reporting 340 cases of tendinitis and 81 cases of tendon rupture. Most of the reported cases (70%) involved patients older than 60 years, with a mean age of 62 years. Concomitant corticosteroid use was reported in 10% of patients with tendinitis and 30% with tendon rupture. Of those patients who experienced tendinitis while receiving a fluoroquinolone and concomitant corticosteroid, most cases (18%) involved ofloxacin. A higher percentage of tendon ruptures relative to tendinitis were reported for all fluoroquinolones in the setting of concomitant steroid use. Considering these findings, authors suggested the risk of fluoroquinolone-associated tendon injury to be increased in both patients 60 years or older and those receiving corticosteroid therapy.

Subsequent studies produced similar findings and further characterized these risk factors. One large population-based case-control study conducted in the United Kingdom compared patients aged 18–95 years with a first-time reporting of Achilles tendon rupture between 1988 and 1998 to a control group of 50,000 randomly sampled patients.[16] All cases were obtained from the General Practice Research Database containing data for ~8 million individuals. Fluoroquinolone exposure was classified as current (rupture during prescription course plus 30 days), recent (rupture less than 180 days following prescription course), and past (rupture less than 18 months following prescription course). For the 1367 cases identified, the adjusted odds ratio (OR) for Achilles tendon rupture was 4.3 (95% CI 2.4–7.8), 2.4 (95% CI 1.5–3.7), and 1.4 (95% CI 0.9–2.1) for current, recent, and past fluoroquinolone exposure, respectively. In patients with current fluoroquinolone exposure, the OR was 5.3 (95% CI 1.8–15.2) for patients not receiving oral corticosteroids but 17.5 (95% CI 5.0–60.9) and 18.4 (95% CI 1.4–240.2) with current and recent steroid exposure, respectively. Age was also identified to be a significant risk factor for tendon rupture, with an OR of 6.4 (95% CI 3.0–13.7) for patients aged 60–79 years and 20.4 (95% CI, 4.6–90.1) for those 80 years or older. Risk analysis with specific agents in patients older than 60 years demonstrated a higher OR of 28.4 with current ofloxacin use (95% CI 7.0–115.3) compared with norfloxacin (OR 14.2 [95% CI 1.6–128.6]) and ciprofloxacin (OR 3.6 [95% CI 1.4–9.1]).

These risk factors have been further substantiated by comprehensive literature reviews. One review published in 2003 assessed 98 case reports and multiple surveillance studies of tendinopathy and tendon rupture with pefloxacin, ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, fleroxacin, and enoxacin occurring between 1966 and 2001.[3] The mean ± SD patient age was 59.0 ± 16.0 years (range 28–92 yrs). Tendinitis and tendon rupture were reported in 83.7% and 40.8% of patients, respectively. Steroid use (systemic or inhaled) before and during fluoroquinolone therapy was reported in 32.7% of all cases and in 52.5% of tendon ruptures. Several years later, a 2013 review of 16 observational studies published between 1996 and 2012 involving tendinitis and rupture with 12 fluoroquinolones (e.g., ofloxacin, levofloxacin, norfloxacin, and ciprofloxacin) described similar trends for increased toxicity risk in these patient populations.[15] For many studies, ORs were increased by several-fold among patients with

Table 4. Risk Factors for Fluoroquinolone-Associated Tendon Disorders

Outcome	Fluoroquinolone[a]	Risk factors[a]				
		Age	Corticosteroid use	Renal dysfunction	Transplant	Dose
Tendinitis[2]	All FQs: RR 3.7 (0.9–15.1) OFX: RR 4.9 (1.57–15.06)	NS	No association	NS	NS	NS
Achilles tendinitis	All FQs: RR 1.3 (0.4–4.7) OFX: RR 10.1 (2.2–46.0)					
Tendon disorder cases[36]	All FQs: 4 cases/100,000 Rx OFX: 38% (16/42) CIP: 31% (13/42) NOR: 19% (8/42)	> 60 yrs: 71% (30/42) with tendon disorders	24% (10/42) of cases	5% (2/42) of cases	NS	37% of OFX cases involved twice the recommended daily dose
Achilles tendinitis or rupture[45]	CIP only ($p<0.05$)	No association	NS	No association with serum creatinine levels	21.8% in lung transplant recipients vs. 0.4% general population	NS
Achilles tendon disorders[46]	All FQs: RR 1.9 (1.3–2.6)	≥60 yrs: RR 3.2 (2.1–4.9) < 60 yrs: RR 0.9 (0.5–1.6)	≥60 yrs old + steroid: RR 6.2 (3.0–12.8)	NS	NS	NS
Achilles tendon rupture[16]	Current FQ use All FQs: OR 4.3 (2.4–7.8) OFX + ≥60 yrs old: OR 28.4 (7.0–115.3) NOR: OR 14.2 (1.6–128.6) CIP: OR 3.6 (1.4–9.1)	60–79 yrs: OR 6.4 (3.0–13.7) ≥80 yrs: OR 20.4 (4.6–90.1)	Current FQ and steroid use: OR 17.5 (5.0–60.9) Current FQ, recent steroid use: OR 18.4 (1.4–240.2)	NS	No association	0.76–1.25 DDD_e[b]: OR 6.7 (3.8–11.7) > 1.25 DDD_e[b]: OR 12.5 (2.3–68.3)
Achilles tendon rupture[42]	Any FQ: OR 1.2 (0.9–1.7) OFX: OR 1.4 (0.6–3.6) LVX: OR 0.6 (0.3–1.4) FQ + ≥60 yrs old + any oral steroid: OR 5.8 (0.9–38.6)	≥60 yrs: OR 1.1 (0.5–2.3)	FQ + Any oral steroid: OR 1.1 (0.8–1.6) Any oral steroid: OR 1.4 (1.0–1.8) High cumulative steroid dose (≥301 mg): OR 1.7 (1.1–2.7)	No association	NS	Cumulative FQ dose ≥8000 mg: OR 1.5 (1.0–2.3)

(continued)

Table 4 (continued)

Outcome	Fluoroquinolone[a]	Risk factors[a]				
		Age	Corticosteroid use	Renal dysfunction	Transplant	Dose
Any tendon disorder[47]	Current FQ use: OR 1.7 (1.4–2.0)	No association	Recent FQ + steroids: OR: 1.8 (1.1–2.9)	NS	NS	NS
Any tendon rupture	Current FQ use: OR 1.3 (1.0–1.8)	No association	Recent FQ + steroids: OR 3.1 (1.5–6.3)			
Achilles tendon rupture	Current FQ use: OR 4.1 (1.8–9.6); 1 case/5958 FQ patients/year	Higher risk for ≥60 yrs (p=0.009); FQ + > 60 yrs: NNH 1638	Recent FQ + steroids: OR 43.2 (5.5–341.1); FQ + steroids NNH 979			
Achilles tendon rupture[48]	Incidence FQ 17.7/100,000; general population 12.0/100,000	Standardized incidence ratio (derived from general population) ≥60 yrs: 4.0 (0.5–14.4) < 60 yrs: 2.5 (0.5–7.4)	NS	NS	NS	NS
Muscle pain[49]	LVX only	NS	NS	NS	NS	Muscle pain observed with higher daily doses of LVX/body weight (509.6 mg/kg vs 468.9 mg/kg, p=0.03)
Tendinitis						All cases (4/84) with LVX 500 mg twice/day[d]
Achilles tendinopathy[50,c]	No association with individual agents	No association	NS	Cl_{cr} < 60 ml/min: OR 6.14 (1.23–30.64)	Higher risk with longer time since heart transplantation (p=0.03)	No association
Achilles tendinitis[51]	All FQs: OR 4.3 (3.2–5.7)	≥60 yrs: OR 8.3 (5.4–12.8) < 60 yrs: OR 1.6 (1.1–2.5)	Steroids: OR 9.1 (4.6–18.0) No steroids: OR 3.2 (2.3–4.4)	Renal failure/hemodialysis: OR 20.0 (2.7–149) No renal failure/hemodialysis: OR 3.9 (2.9–5.2)	NS	NS

CIP = ciprofloxacin; Cl_{cr} = creatinine clearance; DDD_e = defined daily dose equivalents; FQ = fluoroquinolone; LVX = levofloxacin; NNH = number needed to harm; NOR = norfloxacin; NS = not specified; OFX = ofloxacin; OR = odds ratio; RR = relative risk; Rx = prescription.

[a]All ORs, RRs, and incidence ratios are adjusted and expressed with 95% confidence intervals.

[b]DDD: ofloxacin 400 mg, ciprofloxacin 1000 mg, norfloxacin 800 mg, nalidixic acid 4000 mg; 0.75–1.25 DDD: ofloxacin 300–500 mg, ciprofloxacin 750–1250 mg, norfloxacin 600–1000 mg, nalidixic acid 3000–5000 mg; > 1.25 DDD: ofloxacin > 500 mg, ciprofloxacin > 1250 mg, norfloxacin > 1000 mg, nalidixic acid > 5000 mg.

[c]Study population consisted of heart transplant recipients.

[d]Study groups were LVX 500 mg twice/day for the entire treatment period (group 1), LVX 500 mg twice/day for 3 wks then 750 mg/day for the remaining treatment (group 2), and 750 mg/day for entire treatment period (group 3). The median treatment period was 12 wks.

concurrent steroid use and older age (60 yrs or older).

In addition to age and steroid use, renal dysfunction has also been suggested to increase risk of fluoroquinolone-associated tendinopathy. In the previously mentioned review from 2003, tendinopathy in the setting of hemodialysis or renal dysfunction was described in 14 case reports.[3] In a large analysis of 28,907 fluoroquinolone-induced tendinitis cases and 7685 associated rupture cases in the United Kingdom, 1.4% and 2.2% of patients had renal failure or received dialysis, respectively.[51] Although not statistically significant, the association with Achilles tendinitis was stronger among those characterized as "renal failure/dialysis" compared with those with normal renal function (OR 20.0 vs 3.9). However, the significance of renal dysfunction has been described elsewhere, with one study comprising 149 heart transplant recipients finding creatinine clearance lower than 60 ml/min to be an independent risk factor for fluoroquinolone-induced Achilles tendinopathy with an OR of 6.14 (95% CI 1.23–30.64).[50]

History of solid organ transplantation has also been associated with increased tendinopathy risk. Fluoroquinolone-associated tendon toxicity studies in the renal, lung, and heart transplant populations have suggested higher incidences of tendon toxicity in these populations compared with those not receiving transplants. In the 2003 review of 98 tendinopathy case reports, renal transplantation was identified as a risk factor in 12 case reports.[3] In an analysis of 101 lung transplant recipients, the overall incidence of Achilles tendon disease was 21.8% compared with the estimated 0.4% risk described for the general population.[2, 45] Although the rationale behind this population trend is unclear, the possible role of corticosteroid exposure should not be overlooked, given that these agents are often used posttransplantation.

Studies have also described certain drug usage practices to increase the risk of tendinopathy. A number of studies have suggested an increased risk of tendinopathy with higher fluoroquinolone doses including both ofloxacin and levofloxacin.[36, 40] One study of 42 cases of fluoroquinolone-associated tendon disorders between January 1988 and January 1998 in the Netherlands identified ofloxacin as the most frequently implicated fluoroquinolone in 38% of cases; notably, about a third (37%) of these involved twice the recommended ofloxacin daily dose.[36] Dose-dependent toxicity has also been suggested with levofloxacin, as demonstrated by one retrospective analysis of 84 patients treated for bone infections.[49] Patients received various dosing strategies (500 mg twice/day; 500 mg twice/day for 3 wks, then 750 mg once/day; 750 mg once/day) for a median of 12 weeks (mean ± SD 13.7 ± 3.9 wks; range 2–54 wks). Tendinitis and muscular pain were reported in 19 patients (22.6%) and affected more patients receiving levofloxacin 500 mg twice/day in comparison with other dosing regimens. Of the 12 patients requiring a switch of therapy due to muscular pain, 11 received 500 mg twice/day. Six patients (7.2%) discontinued therapy due to these toxicities. Given these findings, the authors suggested an increased risk of toxicity with higher daily doses (i.e., 1000 mg) of levofloxacin, particularly for longer durations. The 16 patients who reported muscle pain had a significantly higher mean cumulative dose to body weight ratio (mg/kg) compared with the 68 patients who did not experience pain (509.6 ± 15.4 vs 468.9 ± 59.8, respectively; p=0.03).[49]

For many patients, the risk of levofloxacin-induced tendinopathy is likely compounded by the presence of multiple risk factors. For example, the presence of renal dysfunction and failure with the intake of larger fluoroquinolone doses increases the risk of tendinopathy.[16] This is of particular concern with levofloxacin and ofloxacin use because these agents are highly dependent on renal elimination. Levofloxacin undergoes nearly 90% renal elimination as unchanged drug, with the mean half-life considerably prolonged in the setting of lower creatinine clearances (~24 hrs for lower than 50 ml/min) compared with higher clearances (~9 hrs for 50 ml/min or higher).[9] Therefore, patients with renal dysfunction may be at higher risk for tendon toxicity given the propensity for increased levofloxacin exposure with elevated concentrations for extended periods, particularly when the recommended dosage adjustment is not made. Overall concern for decreased drug clearance and relative renal impairment is also pertinent for elderly patients, with creatinine clearance declining by an average of 40% between middle and very old age (older than 80 yrs).[53] This age-associated renal impairment, in conjunction with a tendency toward decreased muscle mass, is suggested to predispose elderly patients to a higher maximum concentration and plasma AUC with fluoroquinolones in comparison with younger patients.[53]

Considering these drug and patient factors collectively, both ofloxacin and levofloxacin should be considered high risk for tendinopathy in the elderly population.

Prescription Labeling Warnings

Several of the previously mentioned risk factors for fluoroquinolone-induced tendinopathy have been incorporated into prescription labeling to warn clinicians. The black box warning for tendinitis and tendon rupture for fluoroquinolones, introduced in 2008, indicates increased risk in patients older than 60 years; in those taking concomitant corticosteroids; and in kidney, heart, or lung transplant recipients. Other factors noted to possibly increase risk of tendinopathy are strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis.[9] Although not included in prescribing information, additional risk factors described in the literature include trauma,[40] gout, diabetes mellitus, hyperparathyroidism, sports activity, hypothyroidism,[3] history of tendinopathy, magnesium deficiency, diuretic use, peripheral vascular disease,[54] respiratory disease (e.g., asthma, chronic obstructive pulmonary disorder, chronic bronchitis),[33] ulcerative colitis, Crohn disease,[16] low muscle mass,[37] and obesity.[40] Some analyses have also suggested sex of the patient to be a risk factor, although data are conflicting.[3, 14, 16, 33, 46, 51] Although it is important for clinicians to be knowledgeable about patient characteristics and drug properties possibly associated with fluoroquinolone tendinopathy, no patient is exempt from risk, as demonstrated in one case report describing Achilles tendinitis in a 20-year-old man without history of disease or concurrent medication use.[55]

Management and Sequelae

Fluoroquinolone product labeling advises patients to rest and contact their health care provider at the first signs of tendinitis or tendon rupture. Drug discontinuation is recommended if pain, swelling, inflammation, or tendon rupture occur.[9] Safety of therapy continuation at a decreased dose, switching to another class agent with possibly less tendinopathy risk, or fluoroquinolone rechallenge after injury are limited to case reports.[3] Tendinopathy management strategies may involve nonsurgical or surgical intervention, depending on severity. Nonsurgical strategies, which appear to be appropriate for most patients, include use of analgesics, physical therapy, casts, and/or immobilization. Surgical intervention may be required for those with more severe tendon injury. In one review of 98 cases of tendinitis or tendon rupture, nine required surgery.[3] Another analysis of only tendon rupture cases indicated that surgery was performed for 7 of 31 patients.[14]

Fortunately, many patients recover from tendinopathy or rupture without consequence. In one retrospective study of 421 cases of tendinopathy, 66% of patients had favorable recovery (outcome unknown for 24%), generally by 15–30 days after therapy discontinuation.[8] However, time to recovery may be prolonged for some individuals. In one review of 98 tendon injury cases, recovery occurred in a mean $\pm$ SD of 59.9 $\pm$ 101.2 days, ranging from 2–600 days, with a median time of 38.5 days.[3] In rare cases, symptoms have persisted for longer than 6 months after therapy discontinuation.[56] Long-term complications (e.g., swelling, bruising, difficulty walking, decreased flexion, movement restrictions, and pain) are estimated to occur in ~10% of cases.[3, 8]

Conclusion

Tendinitis and tendon rupture, in addition to other musculoskeletal toxicities, can be serious consequences of fluoroquinolone use. The exact mechanism of these toxicities is unknown. Although the precise incidence of tendinopathy varies by study, numerous factors associated with elevated risk of injury have been consistently described in the literature. Patients who are older than 60 years, are receiving concomitant corticosteroids, are solid organ transplant recipients, or have renal insufficiency appear to be at greatest risk of fluoroquinolone-induced tendinitis and tendon rupture. Several reports have suggested increased risk of injury with levofloxacin and ofloxacin use in comparison with other commonly prescribed class agents. Toxicity risk appears to increase with administration of higher doses for longer durations. Higher tendinopathy rates with these two agents may be associated with achievement of high systemic drug concentrations, reliance on renal elimination, and/or toxic chemical structure substituents. To promote safe use of levofloxacin, particularly given its widespread use across care settings, clinicians should be aware of patient-specific factors associated with increased risk of tendon injury.

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