CASE REPORT

Fluoroquinolone-induced serious, persistent, multisymptom adverse effects

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SUMMARY

We present a case series of four previously healthy, employed adults without significant prior medical history in each of whom symptoms developed while on fluoroquinolones (FQs), with progression that continued following discontinuation evolving to a severe, disabling multisymptom profile variably involving tendinopathy, muscle weakness, peripheral neuropathy, autonomic dysfunction, sleep disorder, cognitive dysfunction and psychiatric disturbance. Physicians and patients should be alert to the potential for FQ-induced severe disabling multisymptom pathology that may persist and progress following FQ use. Known induction by FQs of delayed mitochondrial toxicity provides a compatible mechanism, with symptom profiles (and documented mechanisms of FQ toxicity) compatible with the hypothesis of an exposure-induced mitochondrial neurogastrointestinal encephalomyopathy.

BACKGROUND

Fluoroquinolones (FQs) are widely prescribed antibiotics (reportedly becoming the most common class of antibiotics prescribed to adults in 2002)[1] used to treat pneumonia,[2–4] sinusitis,[2–4] bronchitis[2–4] and urinary tract infections,[2 5] and also employed for prostate procedure prophylaxis,[6 7] among other indications.[8–11] As with all drugs, FQs have the potential for adverse effects (AEs).[8–15]

Tendinopathy is among the most distinctive and best recognised FQ AEs, and has been shown to entail mechanisms of oxidative stress and mitochondrial toxicity[16–20] (additional mechanisms may be involved[21]). These mechanisms explain other reported AE domains, including muscle, cognitive/central nervous system (CNS), psychiatric, peripheral nervous and gastroenterological AEs.[9 12 13 22–26] Delayed occurrence of tendinopathy and other symptoms such as cholestatic hepatitis have been reported.[27–29] 'A typical feature of FQ-induced tendinopathy is a considerable latency period in some cases between the commencement of treatment with an FQ and the onset of symptoms'.[30] FQs have been found to induce delayed mitochondrial toxicity (eg, mitochondrial depletion and mutation) and cytotoxicity,[31] providing a foundation for reported occurrence of delayed FQ AEs.[16 20]

Serious FQ AEs entailing each of the above symptom domains separately have been reported; instances of multiple AEs have been reported; persistent and delayed AEs are acknowledged; but little attention has gone to cases of serious multisymptom AEs entailing persistent and delayed FQ toxicity.

We present four cases involving serious multisymptom persistent and/or progressive FQ toxicity.

CASE PRESENTATION

Table 1 provides a précis of the participants' age/sex, body mass index, concurrent medications, purpose of FQ treatment(s), FQ(s) used and doses given, and domains of symptoms arising during and after FQ use. Table 2 provides results of tests conducted to which the authors had access. Not all test results were available to us. Elaboration on cases is given below.

Case 1

A 28-year-old woman, a professional educator, otherwise in good health, was given a 7-day course of 750 mg/day levofloxacin for a sinus infection, without noted problem, followed in several weeks by a 10-day course of 750 mg/day, as a precaution, after sinus surgery. During the second FQ course, symptoms emerged, including severe widespread tendon, muscle and joint pain, muscle weakness, peripheral nervous, somatic sensory, autonomic and special sense disturbances, cold extremities, gastrointestinal disturbances and CNS problems extending to cognition (including confusion), sleep and mood. Her physician advised that these were FQ AEs, and that she should discontinue the FQ immediately and inform all her physicians she should not receive FQs. Symptoms persisted and progressed after discontinuation, with emergence of new manifestations including fatigue, muscle atrophy, muscle spasms, fasciculations, shortness of breath and documented glucose dysregulation. The patient was bedridden throughout the year following levofloxacin use and unable to sit upright or bear weight on her feet unaided, with assistance required for feeding, bathing and toileting. Attempts at managing her pain were unsuccessful during the first year. She was referred to specialists including a rheumatologist, neurologist, orthopaedic surgeon, physical medicine and rehabilitation personnel, an internist, endocrinologist, podiatrist and physical therapist. Some but not all were familiar with FQ tendon AEs. None were aware of CNS or peripheral nervous system AEs associated with FQs.

Case 2

A 46-year-old man in vigorous good health, employed in a physically demanding, high responsibility job, was treated with 750 mg/day levofloxacin for 21 days for an unconfirmed diagnosis of epididymitis; during treatment, low-grade muscle aches and pains newly emerged. Muscle aches continued

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Table 1 Synopsis of FQ syndrome cases

	Sex	Age	BMI	Concurrent medications	Diagnosis leading to FQ	FQ	Dose/days	AEs during	AEs after	Current health status
1	Female	28	Not provided	Hydrocodone taken prn pain (postsurgery)	Sinus surgery preoperative +postoperative	L	750×7 days 750×10 days	A1, A2, B, C1, C2, CS, F, M, PN, S, T, M, V, W	In addition to those listed as during, also D, G, N/O, Sl	Disabled
2	Male	46	29.2	Lansoprazole 30 mg once a day Cetirizine 10 mg once a day	Epididymitis	L	750×21 days		A1, C1, C2, F, G, M, PN, T, V, W,	Limited work
3	Female	55	19.7	Alendronate (for osteoporosis)	Sinus infections×3 Urinary tract infection×1	L	(500×10 days)×3 750×5 days	F, M, T	C1, C2, F, O, PN, Sl, T, W, C1, C2, H, M, PN, S, V, W	Disabled
4	Female	23	19.7	Pantoprazole (initiated after/due to onset of symptoms—ie, nausea—on M) Birth control pills (details not provided)	Diarrhoea Throat infection	C M	(500 two times a day ×10 days) ×2 400×5 days	A1, C1, G A1, A2, B, C1, F, G, M, N, PN, S, Sl, W	C1, CS, F, G, O In addition to those listed as during, also CS, O, T	Disabled

AE, adverse event; BMI, body mass index; FQ, fluoroquinolone; prn, as needed.
FQs: C, ciprofloxacin; L, levofloxacin; M, moxifloxacin.
Symptom classes (not mutually exclusive): A1, autonomic cardiovascular; A2, autonomic other (eg, dry eyes); B, breathing; C1, cognitive; C2, psychiatric; CS, chemical and/or food sensitivity; D, dysglycemia; F, fatigue; G, gastroenterological; H, hearing or tinnitus; M, muscle; N, other neurological; O, other (headache; hair loss); PN, peripheral neuropathy; S, sensory; Sl, sleep; T, tendinopathy; V, vision; W, weakness including bulbar, respiratory muscle, urinary muscle.

following FQ discontinuation, with progression and emergence of symptoms including fatigue, muscle weakness and atrophy, peripheral neuropathic and autonomic disturbances (tachycardia, bradycardia), CNS manifestations (cognition and mood), vision abnormalities, with gastrointestinal manifestations and intestinal motility issues. Initially, after FQ use, he experienced what he termed an 'autonomic storm' comprising tachycardia, accompanied by very low energy, depression and anxiety. His symptoms evolved with tendinopathy emerging at 9 months affecting the Achilles tendons, feet and knees, and producing tendon pain with exercise in an athlete who previously ran or biked 10 miles a day. Limitations due to pain, and later fatigue, progressed, necessitating progressive curtailing of his cycling from 10 to 6, 4, 3 then 0 miles/day. He switched to walking, which then also became difficult. He purchased an exercise cycle in an effort to remain active, but discontinued use, as aerobic exercise produced delayed fatigue and pain. He stated, "I would expend energy and then pay for it later." Bilateral patellar and foot tendon as well as knee pain with walking emerged, requiring him to stop and sit after walking 100 feet. Muscle strength seemed initially relatively preserved (compared to sustained activities—eg, he could open jars that his wife found problematic), but 15–30 min after application of effort he would experience significant fatigue, and muscle strength deteriorated with time. He was referred to specialists including neurologists, orthopaedists, endocrinologists and gastroenterologists, and referred to a teaching hospital where he underwent testing for a number of autoimmune conditions; questions were asked to screen for possible heritable conditions, and toxic exposures were assessed (all tests were reportedly negative). He underwent CT of the chest and abdomen, to screen for possible endocrine tumours or a paraneoplastic syndrome; results were unremarkable beyond non-specific hepatosplenomegaly. Over a period of approximately 3 years, multiple electromyography/nerve conduction velocity (EMG/NCV) studies were performed, which were unremarkable (2 were available for view, but as many as 8 were reportedly conducted). Biopsies of the thigh and calf to examine epidermal nerve fibre density revealed marked reductions in small nerve fibres (thigh value 4.8, normal ≥6.8; calf 4.0, normal ≥5.4—values are fibres per mm length of epidermis), with no indication of microinflammation, consistent with small fibre neuropathy. Other testing (table 2) was non-contributory. When the patient relayed the history of events starting with the FQ, an academic centre specialist reportedly told him that it could not be the FQ because the specialist had not come across this connection in the literature he had read. However, a local doctor did record this as possibly due to the FQ. The patient received a diagnosis of polyneuropathy of unknown origin and/or fibromyalgia. He initially received a prescription for pregabalin (which he discontinued), and two abortive trials of (different) benzodiazepines, which led to paradoxical adverse reactions (including anxiety). He remains on 10 mg of citalopram (without material relief), and several supplements, including zinc, for the peripheral neuropathy. More than 5 years after FQ use, this previously physically robust man remains affected with atrophy, profound muscle weakness, fatigue (recently evolving into a chronic fatigue-like condition), chronic gastrointestinal problems, mood disturbance, recurring muscle pain and tendinopathy, and painful peripheral neuropathy. Formerly vigorous, his problems necessitated limiting work in his physically demanding profession, and ultimately led to his early retirement. Notably, a brother had previously received an FQ for a prostate problem, which was followed by chronic fatigue syndrome that persisted for 5 years and then gradually abated.

Case 3

A 55-year-old woman in good health, without significant medical history, was treated with levofloxacin 500 mg/day for 10 days, with treatment repeated two additional times over several years, for presumed sinus infections. A fourth course entailed levofloxacin 750 mg for 5 days for a confirmed urinary tract infection. During the first course, the patient developed fatigue, muscle aches, and tendon and joint pain, initially attributed to the underlying infection. Her symptoms persisted following treatment and progressed, with continued fatigue and tendon symptoms, and emergence of muscle weakness and CNS manifestations (sleep, mood/anxiety). Following the fourth

Table 2 Laboratory findings*

	Test given	Results
1	NA†	NA
2	**Nerve punch biopsy**	A. *Right thigh:* Significantly reduced epidermal nerve fibre density (4.84 fibres per mm length of epidermis, normal ≥6.8), **consistent with small fibre neuropathy** B. *Right calf:* Significantly reduced epidermal nerve fibre density (4.03 fibres per mm length of epidermis, normal ≥5.4), **consistent with small fibre neuropathy**
	Peripheral & Autonomic Nerve Tests	
	Sural sensory nerve potentials	Normal
	Sympathetic skin response	Normal
	Q-sweat test	Normal
	EMG/NCV	Normal
	EMG/NCV repeat	Normal
	CT of the chest and abdomen	Non-specific hepatosplenomegaly
	Blood tests	
	Autoimmune panel	
	Rheumatoid factor	Negative
	ANA Scr	Normal: <1:40 titre
	Double-stranded DNA	Normal: 1.45 IU (<25 is negative)
	SM antibody	Normal: 0.11 EU (<20 is negative)
	SM RNP	Normal: 10.01 EU (<20 is negative)
	SSA/Ro	Normal: 2.89 EU (<20 is negative)
	SSB/La	Normal: 0.06 EU (<20 is negative)
	SCL 70	Normal: 0.31 EU (<20 is negative)
	Jo-1	Normal: 0.70 EU (<20 is negative)
	CK	Normal: 80 U/L (ref range 55–170)
	ESR	Normal: 5 mm/h (ref range 0–10)
	CRP	Normal: <0.5 mg/dL (ref range 0.01–0.82)
	Monospot	Normal (from doctor's note)
	Lyme titre	Normal (from doctor's note)
	Neurotransmitter levels	
	Serotonin	Normal
	Dopamine	Normal
	Norepinephrine	Normal
	Epinephrine	Normal
	Norepinephrine/epinephrine ratio	Normal
	Glutamate	Low normal: 15.0 μg/g Cr (ref range 15–35)
	GABA	Low: 291.9 μg/g Cr (ref range 550–750)
	Adrenal hormones	
	Cortisol	Normal (each of 4 times)
	DHEA	Normal (each of 2 times)
3	**EEG**	Abnormal EEG due to left intermittent temporal focal θ slowing and excessive β.
	EEG repeat	Disordered EEG due to generalised θ slow activity, which is sometimes sharply featured, left > right.
	EMG	Right > left median neuropathy of the wrist.
	MRI of the brain (no contrast)×3	Aborted, rescheduled Punctate white matter hyperintensities Bihemispheric punctate white matter hyperintensities 'again seen'
	MRI of the shoulder, left (no contrast)	Moderate tendinosis of the supraspinatus and mild tendinosis of the infraspinatus tendon with bursal surface fraying of supraspinatus tendon
	MRI of the shoulder, right (no contrast)	Bicipital tendinopathy. Small full-thickness rotator cuff tear of the infraspinatus. Acromioclavicular osteoarthritis
	MRI of the knee, left (no contrast)	Peripheral displacement of the lateral meniscal body due to loss of hoop fibre strength. Joint effusion. Grade 2 articular cartilage irregularity
	MRI of the lower extremity (no contrast)	Focal intertarsal and tarsometatarsal osteoarthritis. Small tibiotalar joint effusion
	MRI of the ankle, right (no contrast)	Mild inframalleolar posterior tibialis tenosynovitis. Trace retro-Achilles and retrocalcaneal bursitis. Small tibiotalar joint effusion
	Laboratory tests	
	Sodium	Normal: 142 mmol/L (ref range 135–145)
	Potassium	Normal: 4.2 mmol/L (ref range 3.8–5.0)
	Chloride	Normal: 104 mmol/L (ref range 100–108)
	Bicarbonate	Normal: 27 mmol/L (ref range 22–29)
	Anion gap	Normal: 11
	Creatinine	Normal: 0.7 mg/dL (ref range 0.6–1.1)
	Blood urea nitrogen	Low: 4.8 mg/dL (ref range 6.0–21.0)
	Glucose	Normal: 86 mg/dL (ref range 70–100)
	Calcium	Normal: 9.5 mg/dL (ref range 8.9–10.1)
	Magnesium	Normal: 2.1 mg/dL (ref range 1.8–2.3)
	Total protein	Normal: 6.8 g/dL (ref range 6.3–7.9)
	Albumin	Normal: 4.2 g/dL (ref range 3.5–5.0)
	Alkaline Phosphatase	Normal: 73 IU/L (ref range 41–108)
	Bilirubin, total	High (trace): 1.2 mg/dL (ref range 0.1–1.1)
	Bilirubin, direct	Normal: 0.2 mg/dL (ref range 0–0.3)

Continued

Table 2 Continued

Test given	Results
γ-glutamyl transferase	Normal: 16 u/L (ref range 6–29)
Alanine aminotransferase	Normal: 11 u/L (ref range 4–24)
Aspartate aminotransferase	Normal: 27 u/L (ref range 18–43)
Creatine kinase	Normal: 55 u/L (ref range 38–176)
Ceruloplasmin, serum	Normal: 36.7 mg/dL (ref range 14.0–47.8)
CRP, high sensitivity	'Average risk': 1.60 mg/L (average risk 1.0–3.0)
α1 Antitrypsin genotype	Normal: Neither the S nor the Z allele was detected
Urinalysis	Unremarkable
Endocrine	
Thyroid-stimulating hormone	Normal: 4.36 mIU/L (ref range 0.30–5.0)
Cell blood count	
White blood cell count	Normal: 5.0×10(9)/L (ref range 3.4–10.6)
Differential	Normal
Platelets	Normal: 309×10(9)/L (ref range 149–375)
Haemoglobin	Normal: 13.7 g/dL (ref range 11.5–15.3)
Haematocrit	Normal: 40.8% (ref range 33.3–43.3)
Red blood cell count	High: 5.43×10(12)/L (ref range: 3.68–4.88)
Mean cell volume	Low: 75.2 fL (ref range: 82.7–96.8)
Red blood cell distribution width	Normal: 14.1 (ref range: 11.9–15.5)
Iron-related tests	Iron % Sat normal: 33 (ref range 14–50)
	Ferritin normal: 54 μg/L (ref range11–307)
	Transferrin normal: 264 mg/dL (ref range 170–340)
Antibody tests‡	
HBc	Normal: negative
HbsAg	Normal: negative
HCV	Normal: negative
HIV	Normal: negative
N-type calcium channel Ab, S	Normal: 0.00 nmol/L (ref range <0.1)
P/Q type calcium channel Ab, S	Normal: 0.00 nmol/L (ref range 0.00–0.02)
AchR muscle binding Ab	Normal: 0.00 nmol/L (ref range 0.00–0.19)
AchR ganglionic neuronal Ab, S	Normal: 0.00 nmol/L (ref range 0.00–0.02)
ANNA-1, serum	Normal: titre negative
ANNA-2, serum	Normal: titre negative
AGNA-1, serum	Normal: titre negative
PCA-1, serum	Normal: titre negative
PCA-2, serum	Normal: titre negative
PCA-Tr, S	Normal: titre negative
Amphiphysin, S	Normal: titre negative
CRMP-5, S	Normal: titre negative
ASMA	Normal: titre negative
CRP Quant	Normal: 1.50 mg/L (low, ref range 3–8)
c-ANCA	Normal: negative
p-ANCA	Normal: negative
ENA Screen	Normal: 11 (<20)
Endomysial	Normal: negative
IgA	Normal: 179 mg/dL (ref range 50–400)
Intrinsic factor blocking Ab, S	Normal: negative
Striated Muscle Ab	Normal: titre negative
Tissue trans glutamyl IgA Ab	Normal: 3.2 U/mL (ref range <4)
TPO	Normal: 3.1 IU/mL (ref range <4)
Neuronal (V-G) K+channel Ab	Normal: 0.00
α-1 Antitrypsin	Normal: 132 mg/dL (ref range 100–190)
Metabolic and methylation profile	**Result (common metabolic association)**
Fatty acid metabolism	
Adipate	'Very high' (abnormal fatty acid oxidation)
Suberate	'High' (abnormal fatty acid oxidation)
Ethylmalonate	'High' (abnormal fatty acid oxidation)
Energy production markers	
Citrate	'High' (renal ammonia loading)
Cis-aconitate	'Very high' (renal ammonia loading)
Isocitrate	'High' (renal ammonia loading)
α-Ketoglutarate	'Very high' (renal ammonia loading)
Succinate	'Very high' (renal ammonia loading)
Fumarate	'High' (renal ammonia loading)
Malate	'Very high' (renal ammonia loading)
Methylation cofactor markers	
Methylmalonate	'High' (adenosylcobalamin insufficiency)
Neuropsychological report	Intelligence in the bright normal range. No underlying language impairment. 'She has unequivocal difficulties, however, with concentration'

Continued

Table 2 Continued

	Test given	Results
4	**Oesophagogastroduodenoscopy**	Chronic non-specific inflammation and focal intestinal metaplasia of stomach lining
	Autonomic testing	
	Gastric emptying	Abnormal: prolonged gastric emptying. No evidence of gastro-oesophageal reflux
	Parasympathetic testing	Normal: consecutive difference of heart rate variability, coefficient of variance, heart rate range is normal for age. Valsalva ratio is normal for age
	Sympathetic testing	
	Sympathetic portions Valsalva	Large phase II decline but a significant and nearly full recovery and a significant but not excessive phase IV overshoot
	Tilt table testing	Abnormal: Moderate tilt-induced tachycardia. Various symptoms induced. No evidence of neurogenic orthostatic hypotension or presyncope. 'There is a large increase in heart rate despite the baseline tachycardia'. 'The findings are consistent with a form of orthostatic intolerance based on the HR responses'. Consistent with POTS-type syndrome.
	Sudomotor testing	Normal
	Doctor's diagnosis	Autonomic polyneuropathy

*Laboratory findings to which the authors had access. Results were not successfully accessed for all tests for all participants.
†Case 1 stated: "to be honest, other than blood work, I didn't feel well enough for a lot of tests. I didn't have any biopsies or skin punch tests for nerve damage because my pain was so off the charts I couldn't bear it. I'd also heard others who had been injured by quinolones say that it took them a very long time to heal after such tests so I avoided them…"
‡Tests for antibody unless antigen is specified.
Ab, antibody; AChR, acetylcholine receptor; Ag, antigen; ANA, antinuclear antibody; c-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibody; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; ASMA, anti-smooth muscle antibody; CK, creatine kinase; CRP, C reactive protein; CT, computerized axial tomography; CRMP-5, collapsin response mediator protein 5 (regulates dendritic development and synaptic plasticity in the cerebellar Purkinje cells); DHEA, dehydroepiandrosterone; EEG, electroencephalogram; EMG/NCV, electromyography/nerve conduction velocity; ENA, extra nuclear antigen antibody; GABA, γ-aminobutyric acid; HBc, hepatitis B core antibody; HbsAg, hepatitis B surface antigen; IgA, immunoglobulin A; NA, not applicable; p-ANCA, ANAC—perinuclear; POTS, postural orthostatic tachycardia syndrome; TPO, thyroid peroxidase antibody; V-G, voltage-gated.
Paraneoplastic autoantibody evaluation: AGNA-1, antiglial/neuronal nuclear antibody type 1; ANNA-1, antineuronal nuclear antibody, type 1; ANNA-2, antineuronal nuclear antibody, type 2; PCA-1, Purkinje cell cytoplasmic antibody 1; PCA-2, Purkinje cell cytoplasmic antibody type 2; PCA-Tr, Purkinje cell cytoplasmic antibody type Tr.

course of levofloxacin, peripheral neuropathy and widespread pain developed within 48 h of the last dose. Fatigue, tendinopathy and the previous CNS and psychiatric symptoms persisted, with emergence of significant cognitive impairment manifested by confusion and memory loss, followed by further mood, muscle (including bulbar), somatic and special sensory disturbances.

Work up included joint MRIs, repeat EEGs, repeat brain MRI, EMG, neuropsychological function testing and many laboratory tests, including assessments of chemistry, blood counts, thyroid function, an extensive autoimmune panel, and tests assessing fatty acid metabolism and energy production markers (table 2). MRIs and EMG confirmed tendon as well as joint and muscle pathology in this woman with no material antecedent musculoskeletal history. Brain MRI showed white matter hyperintensities. Neuropsychological impairment was documented, primarily related to concentration, more striking in the context of a previously high functioning individual with a doctoral degree. EEG showed slowed θ activity. Routine blood and urine tests were largely non-contributory. Blood tests were, however, notable for significant abnormalities across the range of assessed markers of fatty acid metabolism and energy production. (This is consistent with a hypothesis of mitochondrial/metabolic derangement.)

Case 4

A 23-year-old woman, in excellent health with no material medical history, was treated with ciprofloxacin 500 mg two times a day for 10 days for traveller's diarrhoea. During treatment, she experienced nausea, dizziness, light-headedness, tachycardia and cognitive symptoms described as 'brain fog' (memory loss and severe difficulty concentrating). The memory problems and brain fog continued after FQ discontinuation. New symptoms emerged within a month of treatment and persisted, including diarrhoea, designated as irritable bowel syndrome, new food intolerances resulting in gastrointestinal pain, unilateral migraines, chronic fatigue and new development of frequent upper respiratory and sinus infections. Despite persistence of symptoms, she continued to work as an engineer. Following 7 years with symptoms, she was prescribed moxifloxacin 400 mg daily for 5 days for sore throat with fever. New symptoms during this FQ course included convulsions, gastroenterological (severe acid reflux, nausea, vomiting, abdominal pain, appetite loss, presumed gastroparesis), autonomic (tachycardia episodes with heart rates into the 140s lasting for hours, orthostatic intolerance, hypotension, mydriasis, dry eyes, mouth and sinuses), muscle (extreme weakness, fasciculations), debilitating fatigue, sleep (insomnia), cognitive and somatic sensory symptoms (burning, stabbing, tingling, numbness, vibrating), difficulty breathing and urinary urgency. Owing to the severe symptoms, the moxifloxacin was discontinued after the third day. The symptoms persisted, leading to a 16-pound weight loss during the month post-moxifloxacin, leaving the patient at a weight of 96 pounds, ascertained by home measurements (body mass index (BMI) ~15–16). Symptoms following discontinuation evolved to encompass mood swings, cluster migraines, 'brain fog', significant hair loss (described as 'several handfuls' per day, consistent with telogen effluvium) and new onset of multiple chemical sensitivities. New chronic dry eye resulted in a corneal ulcer 3 months post-moxifloxacin. Three to four months after treatment, joint and muscle pain in the neck, shoulders, hands, knees and ankles developed. Achilles tendonitis emerged 9 months post-moxifloxacin.

Specialist referrals occurred, with tests conducted including gastric emptying (affirming gastroparesis), oesophagogastroduodenoscopy (chronic non-specific inflammation and focal intestinal metaplasia of stomach lining) and tilt table testing (contributing to a diagnosis of autonomic polyneuropathy/dysautonomia/postural orthostatic tachycardia syndrome). C reactive protein (CRP), ammonia level and candida antibodies were elevated; leucopaenia and anaemia were identified.

INVESTIGATIONS

These individuals with symptoms arising in association with FQ use completed a UC San Diego Human Research Protections Program (IRB)-approved survey, which inquired about the individual's FQ use (including the specific drug, dose, condition for which treatment was provided) and associated AEs (symptom

characteristics, time course in relation to drug use, severity and impact on quality of life and function). The results were collated.

OUTCOME AND FOLLOW-UP

Table 1 provides, for the four cases, a synopsis of serious multisymptom persistent/progressive AEs on FQ antibiotics, including health status.

DISCUSSION

These cases highlight the potential occurrence of serious, persistent and delayed multisymptom AEs apparently triggered by FQ use—causing severe functional compromise and disability in previously vigorous, healthy individuals. The cases developed new-onset symptoms during and following FQ use; there were no identified alternative exposures, including other medications, to which the changes were attributable. Domains of serious and persistent sequelae included the better recognised tendon and muscle issues, but extended to the well-reported but still often unappreciated potential for cognitive, psychiatric, peripheral nervous and gastrointestinal as well as endocrine issues.[9 12 13 22–24 32–40] Of note, CNS, musculoskeletal and psychiatric symptoms are materially more frequent with FQs than with other antibiotic classes.[41] Indeed, each of the classes of problem described in these cases, extending also to domains of cytopenias and dysglycemias, are documented in the literature and reflected in FQ package inserts.

The FQ literature entails cases not only encompassing specific reported symptoms, but also those reporting multisymptom problems, persistent problems,[22 42 43] delayed problems (arising up to months or longer after FQ use)[44–49] and severe and/or disabling problems with FQs;[17 22 32 33 50–60] yet there is a relative dearth of examples in which these are united. A feature in these cases is the continued evolution of the profile of pathology, continuing after FQ discontinuation and extending to emergence of new problems following FQ usage, with resulting widespread serious pathology leading to significant disability in previously healthy, highly functional individuals.

These findings buttress and extend prior reports involving FQ-induced tendon, muscle, central nervous, psychiatric, peripheral nervous, gastrointestinal, autonomic and endocrine FQ-induced serious and persistent AEs. They provide a bridge to delayed pathology extending beyond tendinopathy. Widespread occurrence of new tendinopathy, due to its characteristic and distinctive nature, has had readier ascription to the FQ class, even when onset has been delayed. The linking of other AEs following FQs to tendon pathology, the linking of tendon pathology (and FQ effects) to mitochondrial dysfunction in the literature,[16 20 31 61–64] delayed mitochondrial dysfunction following FQ exposure (cell culture),[31] delayed and widely variable latency to the onset of symptoms in mitochondrial dysfunction in humans (including those with heritable defects in the same kindred)[65] and the known relation of mitochondrial dysfunction to the other FQ-affected domains, provide a strong case for causal occurrence. Moreover, principles have been outlined by which these processes may be expected to produce problems with a compatible profile, entailing variable latency of onset following exposure to a significant mitochondrial toxin, manifest in vulnerable individuals, affecting domains involving muscle–tendon, CNS, peripheral nervous system, gastrointestinal, autonomic, special sensory and other domains observed here.[66 67]

As we have outlined elsewhere, mitochondrial injury may engender further oxidative stress (mitochondria are the leading source as well as target of intracellular free radicals); oxidative stress (also linked to FQs)[16 68 69] in turn may produce more mitochondrial damage. Once triggered, this can, in some instances, create a cycle of oxidative stress and mitochondrial injury that can be self-sustaining or progressive, leading to the emergence of new symptoms as clinical detection thresholds (mitochondrial 'threshold effects') are reached.[70]

The widespread FQ tendon-related AEs described in these case studies are acknowledged in the literature, on the drug labels and in the FDA Adverse Event Reporting System MedWatch report data. The CNS, psychiatric and peripheral nervous system adverse drug reactions described in these case studies are also identified in the literature,[9 12 13 22–24] as well as on the drug labels.

A small case series is not the best setting for identification of AE risk factors, but some information is available from the literature. For many drugs, there is dose/potency influence on risk of AEs. Assessment of a dose relation with FQs is hindered by the fact that each FQ agent has one adult dosing schedule recommended across conditions. Some evidence supports the possibility of potency-related effects: AE occurrence in the setting of overdose has been described.[71] Higher blood levels at a given dose are expected in the setting of renal dysfunction, and FQ AEs are well reported in the setting of dialysis or renal insufficiency,[72–75] and in the elderly—with diminished renal clearance.[76–79] FQs can also cause renal dysfunction or failure,[80–89] which could possibly magnify the risk of other FQ AEs. Beyond renal dysfunction[90 91] and older age,[90 91] FQ AEs are reported to be increased with use of steroids,[44 90 91] with strenuous physical activity (where increased energy demand magnifies any damage associated with mitochondrial dysfunction and impaired energy supply),[91 92] use of renin-angiotensin blockers,[93] and settings of concurrent mitochondrially toxic agents—such as chemotherapy,[88] HIV protease inhibitors,[87 94 95] statins[92] and amiodarone[45 90 96–98] (or class III antiarrhythmics, more generally). Impaired mitochondrial function more commonly might amplify risk, but routine assessments are not available.

This study bears the limitations attending all case series. There is no defined base population or control group, so rates and risk ratios cannot be defined, but they are not meant to be here. (We do not presume that problems of this severity and chronicity are common.) AE causality criteria commonly entail features such as resolution with dechallenge, and time course of onset relative to the drug, to accrue points favouring causality; these are problematic for AEs that persist or progress following the initial triggering insult. We suggest an amendment to those criteria: when a symptom occurs in the context of occurrence of one or more other symptoms already established to relate to the drug, in the presence of compatible mechanisms known to be shared by both symptoms, this boosts the causality points for that/those symptoms. Not every symptom experienced by these individuals need have the FQs as the origin. But these individuals' marked change in health state, with development of numerous symptoms, each known from other evidence to arise with FQs, as part of an evolution originating with use of FQs, suggests FQs as a common foundation for most of the symptoms reported.

FQs are a strong weapon in the battle against serious bacterial infections. We suggest extending, to adults, an attitude/approach advocated by others in the setting of paediatric use: 'Fluoroquinolone use should be restricted to situations in which there is no safe and effective alternative to treat an infection caused by multidrug-resistant bacteria or to provide oral therapy when parenteral therapy is not feasible and no other effective oral agent is available'.[99] Concerns about increased risk of retinal detachment have recently been raised.[100] Use has been

Patients' perspectives

- **Patient 1**: The severe adverse reactions associated with my consumption of the FQ levofloxacin (L) have drastically affected every aspect of my life. I am no longer the vibrant, outgoing, independent, productive person that I once was. I continue to endure chronic, crippling pain and devastating illness as a result of taking FQs 5 years ago. The debilitating symptom expression leaves me in large part housebound, bed-ridden and dependent upon others for around-the-clock care. I have lost so much as a result of having taken L. I've lost a teaching career that I loved, my mobility, my quality of life, being able to eat a normal diet, my independence, relationships with family members and friends, hobbies, time, the ability to be the type of active parent that my son deserves, memories, our hopes and dreams for the future as a family. No one should ever have to suffer as I have, as my family has, as so many others have from similar reactions to these drugs. I took this medication as a preventative measure after a routine sinus surgery, and it prevented more than a potential infection…it prevented me from living. Existing in this state isn't living.
- **Patient 2**: Living life after the FQ levofloxacin (L) has been challenging to say the least. {After L was} prescribed in 2007 for an unconfirmed infection, I had to retire early at the end of 2012, a full decade earlier than I had anticipated. This impacted our family greatly, forcing my wife to return to menial work and having to accept occasional financial assistance from two adult children, while still raising three children at home, one of whom is disabled. To meet our financial needs, our nest egg had to be depleted in order to pay current financial obligations, get out from under debt and pay medical bills.
- We now, with my meagre retirement and my wife's part time work, fall within the federal poverty guidelines. I estimated I have lost over seven figures due to retiring a decade early. I had to push myself to an early retirement date in order to gain basic healthcare for myself and for my family. To achieve this, I had to push myself while in the throes of an adverse drug response and it took a heavy toll on my body. It was one of the hardest things I ever faced, much worse than any challenges I faced as a law enforcement official. Each day is challenging from a health perspective.
- Today, I have progressing severe and debilitating fatigue, body-wide degenerative joint disease and several neurological pathologies. Earlier, I was employed in law enforcement and had the physique of an athlete. Now, every day is filled with pain—both physical and emotional. I have become separated from friends and some family, of whom some are unable to grasp that an antibiotic could cause such devastation. I am unable to participate in, or attend, social activities such as church services, funerals or weddings. Never warned of any risks, even though safer alternatives were available, I would have chosen not to take FQs for a non-life threatening health condition. My story is not unique. I hear from people daily whose lives, like mine, have been utterly destroyed by this class of drugs.
- **Patient 3**: {Adverse effects from the FQ levofloxacin (L)} have had a devastating impact on my life, both professionally and personally. Professionally, I am no longerable to work due to ongoing health issues that began 7 years ago after taking L for a simple sinus infection. Personally, I have lost connection with friends and family members, who do not understand the changes they have witnessed in me after I took this antibiotic for a simple sinus infection.
- I feel like I have lost everything that was important to me including family, friends, cognitive sharpness, sound sleep, food I enjoy, executive level employment, and a six-figure income. Due to post-FQ challenges, I am unable to travel, spend extended time with my grandchildren or enjoy life as I once did.
- I am unable to live a single day without extensive pain and discomfort. If my physician had been aware of the actual long term, permanent damage that can be caused by FQs, I believe he would not have prescribed it for a simple infection. If adequate and accurate warnings had been on the L label, I would not have agreed to take this drug for a simple infection. I was not allowed to provide informed consent. My life has literally been destroyed.
- **Patient 4**: {Contributed with the patient's consent by the spouse of the affected person} I fortunately never took a FQ, but I witnessed, first hand, the devastation they cause. I watched my young, healthy, beautiful, intelligent wife go from being an {type omitted} engineer with one of the top engineering firms in the world, and an active woman with a busy social life, to being almost entirely bedridden almost overnight. This was all due to three doses of a drug she shouldn't have been prescribed anyway. I have been asked to tell her story. I am only doing so because she is too sick to tell her own story (she is in bed with the flu, and we wanted to respond in a timely fashion).
- She was given the FQ moxifloxacin (M) in August 2010, for a sore throat of unconfirmed origin (it was likely viral). She was given no warning as to potential side effects. I personally witnessed her having convulsions after taking just a few doses. She described it as feeling like 'burning' and like 'her organs were melting'.
- For the past 3½ years, I have watched her suffer from intense nausea, gastroparesis, neuropathy, tachycardia, impaired immune function and a host of other symptoms. I have been with her when she wakes up in the middle of the night shaking. Just last night, she was unable to sleep because of the tremors in her legs. She often has stabbing and burning sensations, usually in her foot and lower leg, but at times all throughout her body. She is unable to fight off any infection, and she catches every germ that goes around. The frequent infections compound her suffering and linger for weeks, much longer than they would were her immune system not depressed. She frequently has nausea, and for a period of time she was unable to eat due to the gastroparesis. She also has to deal with almost constant 'brain fog'; she has difficulty remembering things and is unable to focus on activities happening around her. On a daily basis, she has to deal with extreme exhaustion and fatigue. She used to walk at least two miles a day to and from the train. Now, walking across the apartment is an ordeal. Many days she is confined to bed and sometimes she has to sit on a stool in order to shower.
- This has caused our family financial damage. Between lost wages and medical treatment after medical treatment, we have lost hundreds of thousands of dollars. We still hope to own our own home someday, but right now our reality is

that most months we just make ends meet and are stuck in an unstable housing situation.

- But by far, the most damaging aspect of this drug has been the psychological toll it has taken. My wife cannot live a normal life. She has to decide between a doctor's appointment and visiting her 90-year-old grandmother because she typically isn't strong enough to leave the house twice in 1 week. She cannot just go see a friend. Often, she cannot even just pick up the phone and call a friend because the energy she exerts during a phone call might leave her wiped out. She has had to miss numerous family functions. If we invite her mother and brother over for Christmas, we have to 'take a survey' to see if anyone has been sick lately. If anybody is getting over a cold, my wife either has to decide to ask them not to come, or she needs to sit on the other side of the room. Usually, she catches the cold anyway, despite all precautions, and ends up in bed for weeks. She cannot enjoy an afternoon apple picking with her niece and nephews. She can ride to the orchard, but after a few minutes, she needs to go back to the car and sit down until it is time to leave. She can't eat the foods she loves. She can't travel. She can't just hang out with her friends. We both dreamed of a family when we were married about a year before she took M. We would need a miracle to realise that dream now; my wife is much too sick for pregnancy, childbirth and motherhood right now. She can't devote the time and energy to things that she used to enjoy. Her life has been completely torn apart by these drugs. All she can do is just try to warn others about the dangers of FQs.

urged against in athletes 'unless no alternative is available';[21 101] but all people should engage athletically when able, and FQ compromise to function may be even more problematic in those who are unable (due to existing compromise to function). Caution has also been urged in the elderly, in whom functional compromise may add to existing compromise, having a particularly great impact. There is the added complication that FQ AEs may be misconstrued as problems related to ageing.[90] (Fortunately, formulary restrictions to limit FQ use have been shown to be implemented without compromise to patient safety.)[102] We suggest that patients and physicians be educated regarding these serious FQ side effects; that patients be cautioned to alert physicians should any adverse reaction emerge (since continued use might increase risk of a serious outcome—and sometimes has);[103] and that FQs be avoided for non-life-threatening, mild, moderate and uncomplicated infections. The risk of persistent widespread serious multisystem disability from FQs, even if rare, underscores the importance of carefully weighing alternatives, and perhaps reserving these agents for settings in which the necessity clearly warrants the risks.

Learning points

- Fluoroquinolone (FQ) antibiotics can, rarely, produce severe, disabling, multisystem problems with symptoms that are persistent, progressive and/or delayed.
- Oxidative and mitochondrial mechanisms may contribute to or underlie these problems.
- Physicians should be educated regarding the possibility of these adverse effects.
- Patients should be charged to promptly report any adverse effects that arise on FQ use to their physician, to limit risk of progression.
- FQs should be reserved for conditions for which other effective antibiotics are not available, until means are available to identify vulnerable individuals.

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