Fluoroquinolone-Associated Disability (FQAD) - Pathogenesis, Diagnostics, Therapy and Diagnostic Criteria

Side-effects of Fluoroquinolones

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Preface

The term 'Fluoroquinolone-Associated Disability', FQAD, has been an established entity at least since its use by the FDA at the Joint Meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, November 5, 2015 [1].

(However, others played a decisive role in its creation, above all Charles Bennett, University of South Carolina, Beatrice Alexandra Golomb and Jay Cohen, University of California, Krzysztof Michalak, University in Poznań, Poland, without whose fundamental work [2] this book would not have been possible, and Miriam J. van Staveren de Jonge, physician and patient, as well as Lisa Bloomquist with FloxieHope, David Melvin with MyQuinStory and numerous patients organized in self-help groups and forums, e.g. the fluorquinolone-forum.de.)

However, the FDA's definition with the associated diagnostic criteria is not suitable for the treating physician in everyday use [3].

This vade mecum is supposed to help the doctor and/or therapist to deal better and more adequately with affected patients and perhaps also be a guideline for the 'floxies' themselves.

At the beginning, the four major 'construction sites', which are caused as adverse effects of the fluoroquinolones and can lead to FQAD, are each discussed in compact form.

Special attention is paid to the pathogenesis, diagnostics and the limited therapeutic options which, from my point of view, may have a chance of success.

In the second part, I would like to propose diagnostic criteria for FQAD that achieve the most reliable and likewise time-saving containment of the new clinical picture and thus to attempt implementing them in everyday practice.

This book is also intended to pass on my experiences that I have made in our practice in recent years with about 500 FQAD patients, whose feedback has provided valuable suggestions for better understanding and treatment of this new disease.

Konstanz, Germany Stefan Pieper

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Contents

Introduction to FQAD

1

Since the exponential increase of new antibiotics in the second half of last century through focused research apart from the positive, life-saving effects, the uncritical and improper use has also increased enormously. Recent studies show that only 12.8% of prescriptions are indicated [1].

This circumstance is particularly problematic in the case of the so-called reserve antibiotics above all the fluoroquinolones (hereinafter FQs, for brevity) which are highly efficient to multiresistant germs.

The medical newspaper *Deutsches Ärzteblatt* writes in 2019: 'This substance group is a good example of how antibiotics can be "burned" by an unselected and often not indicated use. Increasing resistances in the range of 20-30 % make the use in hospital urinary tract infections a lottery game' [2].

Canadian research shows that almost every second patient has been treated with an FQ at least once in his lifetime [3].

An unimaginably large amount.

This figure is all the more credible when you consider that ciprofloxacin became the most frequently prescribed antibiotic in the USA between 1997 and 2002, with 22 million visits [4].

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FQs are the first fully synthetic antibiotic group ever. They were discovered accidentally in the 1960s through contamination during the production of the malaria drug chloroquine.

Their main representatives, ciprofloxacin, ofloxacin, norfloxacin, levofloxacin, gemifloxacin and moxifloxacin, were developed into the most effective but also the most toxic antibiotics of all, but their risks and adverse effects (AEs) were long downplayed in science and by the regulatory authorities.

For this reason, warnings were issued by the American regulatory authority FDA only after decades, and even much later by European and German authorities. It would go too far to explain the rocky road from petitions, hearings, threats of legal action, etc. to recognition of the problem and further to the hesitant action of the supervisory authorities.

Since 2016, FQs in the USA have only a very narrow range of indications, for example for the most severe bacterial infections such as anthrax and plague as well as pneumonia that cannot be treated in any other way [5].

Unfortunately, these reasonable restrictions as a reserve antibiotic were not followed so consistently at the European level.

In 2015, the FDA, in its Antimicrobial Drugs Advisory Committee, determined that of 14 antibiotics investigated, FQs have by far the highest risk of disability [6].

The FQ-AEs sometimes cause severe long-term damage and reach a previously unknown extent. Such serious, diverse, resistance to therapy and disabling are these side effects that the umbrella term of fluoroquinolone-associated disability, which is now also recognized by the FDA, has become established in Anglo-American studies.

Based on the cases reported to the FDA, Charles Bennett, Center for Medication Safety and Efficacy, University of South Carolina, calculated that between Nov. 1997 and Feb. 2011, the number of cases of FQ in the USA ranged from two million to over 21 million and between 29,000 and over 299,000 deaths [7].

By German standards, this amounts to about 40,000 to 400,000 affected persons and 150 to 1500 deaths per year. (These figures are surprisingly well in line with the very conservative calculations

of the AOK Scientific Institute 'Wido' in 2019, using a completely different calculation approach [8].)

Extrapolated over the last 30 years, this leads to at least 1.2 million victims only in Germany, most of whom are still alive due to their age distribution (83% under 60 years). Added to this are thousands, if not tens of thousands, of deaths since the introduction of the FQ in the 1980s.

With an invalidity rate of 15% [9], this means at least 180,000 severely disabled persons due to FQAD exist in Germany, and 6000 cases are added annually.

This corresponds roughly to the frequency of multiple sclerosis. Direct and indirect costs of MS patients in Germany amount to about 40,000 € per patient and year, a total of 8 billion € [10].

FQAD patients, whose disease is usually not diagnosed, not named and if so, not recognized but ignored, have nothing to expect from our health care system today. The majority of the costs spent on them concern unnecessary diagnostics, where no groundbreaking findings are made and which even ensures that these patients are at best misdiagnosed as psychosomatic or psychiatric, but are often stigmatized as hypochondriacs.

The economic damage is likely to be enormous, since 74% of these patients are in full-time employment (30–59 years) [9]. In this respect the situation is quite comparable to MS, where the indirect costs and thus the economic damage are €19,000 per patient per year. For the FQAD, this means total annual costs of €3.42 billion that is being placed on our health and social systems just because nobody is taking care of this serious disease! (These numbers are calculated for the German situation, but are fairly comparable to any country with similar standards in the health and economic system such as the EU countries, USA, Canada and so forth.)

These dimensions dwarf all previous medical or pharmaceutical scandals in the German health system, both in terms of the number of victims and the severity of the health restrictions, and above all the ignorance and blatant inaction of the supervisory authorities (EMA and BfArM). Because at the latest after the detailed and substantial statement of the FDA 2017 [9],

consequences for the German and European area should have been drawn immediately and not 2 years later.

The term FQAD for the severe, disabling syndrome-like adverse effects (AEs) of the FQ is now considered an established clinical picture.

The disease is comparatively new and yet it is likely to have enormous intersections and presumably also causal relationships with a variety of syndromes (see Fig. 1.1), whose etiopathogenesis is not known with certainty, such as CFS, PTSD, fibromyalgia, MCS and Gulf War syndrome. (In the 1990s, ciprofloxacin was administered to US soldiers during the Gulf War as a prophylactic measure against anthrax. Thousands of returnees developed symptoms of the 'Gulf War syndrome', which certainly have a variety of causes, but still read like a description of the Cipro leaflet.)

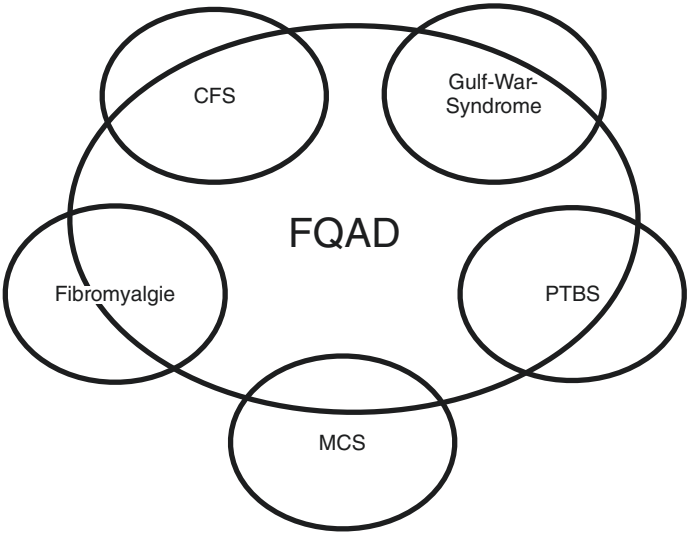

Fig. 1.1 Causal overlap of FQAD with related disorders

In view of the gigantic number of prescriptions, I consider the FQAD with its immense number of unreported cases to be the 'mother of all unclear syndromes'.

Golomb [11] rightly speaks of a serious, persistent, multi-symptom syndrome and FQ-induced mitochondrial neurogastro-intestinal encephalomyopathy.

Here, practically all manifestations are mentioned (mitochondrial, peripheral and autonomous neuropathic, central nervous and musculoskeletal).

It should not be confused with the fluoroquinolone toxicity syndrome, in which the patient develops one symptom (or several with the same organ manifestation) in an impressive form, for example an Achilles tendon rupture or aortic dissection, but otherwise no further AEs of the antibiotic can be obtained from other manifestations or the symptoms do not take invalidating proportions.

In all likelihood, the complete AEs spectrum is a class effect.

Although there are differences between the individual FQs in terms of their AE orientation, these are not qualitative.

Especially the R-7 group of the FQ seems to be an important determiner in this respect. For the AE frequency and intensity of tendon damage as well as genotoxicity and CNS-AEs it seems to be important whether an alkyl, piperazine or pyrrolidinyl group is attached to this side chain, sometimes the respective risk profile is even reciprocal [12].

However, data shows that the entire AE spectrum has been described in all FQs, and some have even been withdrawn shortly after market launch, in this frequency a rather unusual event.

In terms of pathogenesis and/or manifestation, we divide the FQ adverse effects into four groups:

- Oxidative stress and mitochondrial toxicity
- Musculoskeletal damage and collagen disorder
- Neurotoxicity
- Neuropsychiatric adverse effects

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2 FQAD and Oxidative Stress/ Mitochondrial Toxicity

Of all FQ-mediated damage, oxidative stress and mitochondrial damage is the first to be mentioned, as it always additionally compromises or even etiopathogenically triggers the damaging mechanisms of all other AEs at the cellular level.

2.1 Pathogenesis

This is mainly due to oxidative stress and the inhibition of the enzyme topoisomerase II. It is the human counterpart to bacterial topoisomerase or gyrase and is a mitochondrial enzyme that is of enormous importance for the maintenance of human mitochondrial DNA (mtDNA). This pronounced cytotoxicity of FQ, even in eukaryotic cells, puts it in direct proximity to chemotherapeutic agents in terms of structure and mode of action [1, 2].

In tendon tissue, for example, after FQ exposure, not only is clear mitochondrial damage and a glutathione deficiency detectable [3], but it also benefits from antioxidative and thus mitochondrial therapy, for example with MitoQ [4].

The attack on the mtDNA in the muscle cell disrupts proliferation and impairs the differentiation of skeletal muscle.

The fact that mitochondrial concentration of topoisomerase II is far higher in the CNS than in other tissues suggests that brain

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cells and presumably also peripheral nerves react correspondingly more sensitive to the inhibition [5].

FQs thereby have a dramatic effect on mtDNA topology, block replication and transcription, cause double-strand breaks and persistent protein-DNA adducts, and reduce DNA duplication and overall enzyme activity [5].

Michalak [6] impressively describes the harmful influence of the considerable oxidative stress generated by FQ, which in turn leads to a restricted mitochondrial performance and thus to a reduction in ATP production, among other things via weakened detoxification systems (SOD, GSH, Catalase, GPx). Mitochondria, the main source of free radicals anyway, are thus downright radical slingers in their damaged state and therefore maintain and multiply their own damage through oxidative stress, which can contribute to a chronification of the symptoms as described in FQAD. Once triggered, this disorder can lead to further symptoms in other cell systems via a negative cycle of oxidative stress and mitochondrial damage, as soon as a certain threshold has been exceeded in these systems ('mitochondrial threshold effects') [7].

This is aggravated by the assumption that quinolones may have an inhibitory effect on quinones, whose representative ubiquinone plays a central role in the respiratory chain and is one of the most important intracellular redox molecules [8, 9].

Furthermore, FQs form chelate complexes with bivalent cations (Mg, Mn, Ca, Cu, Zn, Fe, Co) and protein anions. Hence enormous amounts of cations are consumed and bound. This depletion disrupts cellular processes sensitively. It can be assumed that selenium also forms chelate complexes with FQ due to its bivalence, but this is currently the subject of further studies.

In addition to the extremely important redox and detoxification systems SOD2, GPx, Glutathione and Glutathione-S-transferase, these elements are involved in the formation and function of hundreds of mitochondrial enzyme systems.

Mg and Zn, for example, are additionally important cofactors for more than 300 cellular enzyme systems, and the lack of Ca signalling affects cell function [6, 10].

The magnesium deficit is also used as an explanatory model for FQ-induced diabetes mellitus type II, which in turn is likely to have a negative effect on mitochondrial function [6].

In our own patients we see a clear accumulation of diabetogenic findings such as an increased HOMA-Index as a sign of insulin resistance or prediabetic HbA1c values between 5.7% and 6.0%.

Finally, FQs induce changes in gene expression and epigenetics and the inhibition of the important detoxification enzyme cytochrome P-450 [11] and detoxification processes in general.

These complex damaging mechanisms lead to a situation in which the mitochondrial performance and thus the energy production of the cell and the entire organism is dramatically reduced, a state from which the cell often cannot save itself without help/therapy, since the antioxidative resources and the detoxification and repair system are also ATP-dependent.

In this respect, this connection casually explains the fatigue syndrome, which occurs in many patients and is usually associated with exertion-induced muscle pain.

2.2 Diagnostics

The diagnosis of mitochondrial function has made progress in recent years. Although measuring of ATP as the centrepiece remains very difficult to interpret because of the difficult preanalytics and the large number of different tests, the measurement of other direct or indirect parameters is already established. However, their quality still depends very much on the expertise of the respective medical lab.

Here are some examples:

Basic laboratory: CBC, LFT, RFT, LDH, Bili total, CRP, ESR, TSH, potassium, sodium, calcium, Fe, CK, BS.

Prediabetes: HbA1c, HOMA-Index,

Cell protection: Vit-D, Vit-E, homocysteine, holotranscobalamin, folic acid, omega-3 fatty acids, methylmalonic acid.

Free radicals: citrulline, nitrotyrosine, peroxides.

Oxidative damage: oxLDL, malondialdehyde.

Mitochondrial performance: bioenergetic health index (BHI), ATP test, possibly under stress, lactate/pyruvate, LDH isoenzymes, pregnenolone sulphate, mtDNA/nDNA, PGC-1alpha, rhodonase.

Mitochondrial protection: coenzyme Q10, glutathione oxidised/reduced, SOD, GPx, catalase, TAC, NRF2.

Chelation: iron, ferritin, Mg, Mn, Zn, Cu, Ca, Se and Co.

Silent inflammation: ESR, high-sens.-CRP, E-phoresis, possibly targeted Interleukins, NFkappaB, TNFalpha, IFNgamma

2.3 Therapy

Antioxidative therapy is the key point of FQAD treatment!

By the administration of the trace elements Mg, Mn, Zn, Cu, Co and Se, the most important redox systems are strengthened, especially the manganese-dependent SOD2, which prevents an excessive concentration of superoxide and the associated formation of peroxynitrite.

The hydrogen peroxide formed by the SOD is then detoxified to water by peroxidases such as catalases and especially GPx before increased lipid peroxidation by the hydroxyl radical can occur.

A prerequisite for this is the presence of selenium as the core metal of all peroxidases.

A major problem is the very stable chelate-protein complexes which FQs form with these bivalent cations.

Removing FQ from these complexes would be an ideal therapeutic option.

This seems to be possible by ozone therapy [12].

The administration of these metals (especially organic Mg) might be another option to displace FQ from the stable bonds. They are the natural FQ competitors at the protein-chelate complexes.

The administration should be continuous and rather low doses over a long period of time, as too much renal is lost when given in

high doses. (In principle, the administration of each cation should be preceded by a whole blood assay.)

Magnesium in particular causes the closure of the mPTP system (mitochondrial permeability transition pores) and thus an improvement of the membrane potential, which is reduced by FQ, oxidative stress and other factors in a vicious circle.

Glutathione, a sulphur-containing tripeptide thiol molecule and the most important cellular antioxidative system of the aqueous phase, suffers as an endogenous redox molecule especially from the attack of FQ.

It is not without reason that glutathione is described as the 'mother of all antioxidants, master of detoxification and maestro of the immune system' [13]. It occurs in high (millimolar!) concentrations in all mammalian cells [14].

It neutralizes reactive oxygen compounds and thus protects cells, DNA, lipids, membranes and mitochondria from oxidation. GSH itself is oxidized to the dimer GSSG, which is then regenerated by glutathione reductase.

It also recycles vitamin C and E back to its reduced form and has numerous other biological functions.

The non-enzymatic antioxidant capacity of the cell is largely based on glutathione [15], the ratio of reduced GSH to oxidized GSSG reflects the cellular redox balance.

It could be shown that even intracellular FQ concentrations, which are by a factor of 1000 (!) smaller than therapeutic doses, reduce the concentration of glutathione intracellularly by 20–50%! [3].

Although the body produces glutathione itself, it is constantly decimated by dietary mistakes, environmental toxins, medication, stress, trauma, ageing, infections, diseases and radiation (as well as in extreme form by therapeutic doses of FQ!), so that glutathione deficiency is not infrequent [16].

Therapeutically, the most important limiting component of glutathione should be given (N-acetyl-cysteine 600 mg/die). NAC also protects against toxic effects of oxygen radicals and acts against free radicals through various independent mechanisms [17].

The administration of glutathione, especially in high doses or intravenously, is not advisable, since for reasons that are as yet unclear, this often leads to sometimes severe relapses.

Alpha lipoic acid (ALA) also has a favourable effect in raising the intracellular glutathione level [18] and reduces lipid peroxidation in nerve cells by 50% [19].

However, care should also be taken when administering ALA, since in addition to heavy metals, ALA unfortunately also chelates manganese, zinc, iron, copper and cobalt, whose stores have already been emptied by the FQ anyway.

Vitamin B_{12} deficiency is associated with severe oxidative stress in animal models. Bito [20] was able to show that B_{12} deficiency significantly reduces glutathione levels as well as the activity of MnSOD, total SOD and catalase by up to 66%. At the same time, the ascorbic acid level of the cell decreases.

This, together with metalloproteinases activated by oxidative stress, in turn leads to the degradation of collagen protein [21], a mechanism very similar to that of FQs, which should certainly have negative synergistic effects.

The B_{12} deficiency also leads to memory disorders, most likely via the NMDA receptor system, which will be discussed below.

Therefore, we additionally treat with doses of hydroxocobalamin 1000 mcg s.c. on a weekly to monthly basis (see also Sect. 5.3).

In principle, with excessive oxidative stress, it appears sensible to minimize the 'hydrogen pressure' by way of fasting, since the mitochondrial system is already overtaxed with the nutrient supply. To this end, glycolysis activity should be restricted and the pentose phosphate pathway activated.

Long-term calorie restriction significantly reduces the peroxide load (by 45%) and oxidative damage to mtDNA (by 30%). The scene of action is exclusively complex I of the respiratory chain, the radical generator of the cell [22].

A change in diet in the form of a carbohydrate and calorie-reduced diet (low-carb, dinner cancelling, ketogenic diet) and above all fasting, e.g. as interval or intermittent fasting, is therefore an important therapeutic principle not only for the treatment of the frequently accompanying diabetic metabolic condition but

also for improving the energy situation in the cell. Due to long carbohydrate breaks, the insulin level drops and the cell can switch to β-oxidation, i.e. burning fat. Through the fasting state, various cell-protective measures are implemented, among other things through the formation of sirtuins.

A further important therapeutic goal is the stimulation of mitochondrial replication. Heavily damaged mitochondria are thereby driven into apoptosis in the natural selection process and eliminated, as they slowly lose their ability to replicate due to DNA damage. Less damaged mitochondria proliferate; the endpoint would be characterized by the healthiest mitochondrium in the cell.

The two most important therapeutic options for this are again fasting, but also altitude training, for example through Interval-Hypoxia-Hyperoxia Therapy® (IHHT).

In addition, the active ingredient pyrroloquinoline quinone (PQQ 10–40 mg/die) has been shown to be an ideal substance for improving mitochondrial regeneration, and it also protects against oxidative stress [23, 24].

In food, PQQ is found in parsley, carrots, cabbage, spinach, kiwi, papaya, green tea, tofu and especially concentrated in natto [25].

In addition to the natural antioxidant coenzyme Q10 100 mg p.o., the mitochondrial-selective antioxidant MitoQ (5 mg/die) has proven to be effective. A study with human Achilles tendon cells showed that it is able to protect the mitochondria against FQ-induced oxidative stress and membrane damage and to stabilize the mitochondrial membrane potential [11].

Other promising antioxidants are resveratrol [26], but in principle also all other polyphenols such as curcumin and quercetin, as well as selenium, vitamin C with flavonoids and vitamin E [27], preferably with tocotrienols, and vitamin D [28].

Metformin could play an important role as an antidiabetic as it is apparently able to close the mPTPs (mitochondrial permeability transition pores) and thus offer protection against oxidative stress [29].

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3 FQAD and Musculoskeletal Damage/Collagen Disorder

The collagen disorder with the 'quinolone-induced tendinopathy' is probably the best known and most recognized side effect, which was already reported in the late 1980s and early 1990s [1–6].

The toxicity of this side effect appears to correlate with the methyl-piperidinyl side groups in position 7, so that in this respect pefloxacin, fleroxacin, levofloxacin and ofloxacin have a higher risk than, for example, ciprofloxacin [7].

In addition to tendon involvement with tendon ruptures and tendinitis (for years the literature only referred to 'Fluoroquinolone-Associated Tendinopathy'), all other collagen-containing tissues are also at risk (skin, subcutis, joints, capsules, ligaments, vascular walls, cartilage, muscles, etc.) and can be damaged.

Thus, besides the impressive Achilles tendon ruptures (seven times higher risk!) [8], practically all other collagen-associated damage is conceivable and/or already documented, for example aortic aneurysms and dissections [9], vasculitis, retinal detachment [10], corneal damage [11], uveitis [12], arthralgias/arthritides, infantile arthropathies [13–15], rheumatic disease [1], low back pain [16] and multiple other tendon damage such as tendinitis, tendovaginitis, tendon ruptures, torn ligaments and muscles, inguinal hernias, penis fractures, wound healing disorders, suture and anastomosis insufficiencies, but also myalgias, muscle spasms and damage to muscle cells up to rhabdomyolysis.

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One of the most threatening collagen damages is certainly aortic aneurysms and dissections. The data situation in this regard is robust [9, 17–19]; only two studies published in 2020 showed divergent results [20, 21]. In a recently published retrospective observational study, we were also able to confirm the association between the administration of FQ in pneumonia and the development of aortic aneurysms for Germany [22].

A very large study from January 2021 [23] provides evidence that there is an increase in risk for patients even without other vascular risk factors ('47 596 545 antibiotic prescription fills among US adults aged 18 to 64 years found an increased rate of aortic aneurysms within 90 days after fluoroquinolone use').

3.1 Pathogenesis

Tendon complaints occur on average 18 days after the start of FQ therapy and even as soon as 6 days in half of the patients. Tendon ruptures are common and happen to 40% of patients (half of them were given corticosteroids simultaneously, which makes it a risk factor). They occur with a latency of about 1 month. However, tendon damage is documented within a period of 2 hours (!) up to 6 months after the start of treatment; the recovery phase extends over 2–600 days (on average 2 months) and has been described as 'delayed' in many cases [24].

In his review [25], Michalak emphasized that the protracted, sometimes years-long processes can be explained [26] by a crystalline and thus very poorly soluble molecular structure of the FQs, which allows them to survive for a very long time in the cell and leads to the agonizing, chronic and in some cases even irreversible long-term effects [27].

But how can such a robust bradytrophic tissue, trimmed for longevity and tear resistance, such as the Achilles tendon, be damaged in such a severe way within hours to days that it ruptures without adequate trauma?

This requires a number of pathogenetic factors, and the course of the damage is now reasonably well documented.

The onset of damage within hours suggests a direct cytotoxic effect [28, 29].

The first step is probably the activation of certain proteolytic enzymes, so-called matrix metalloproteinases or gelatinases (especially MMP-2 and MMP-9), with concomitant degradation of type I collagen within the tendon cells, which accounts for 90% of the collagen in the tendon. In other words, the induction of this group of enzymes by FQ leads to healthy tendon tissue or collagen tissue as a whole being practically digested. Consequently this results in rapid damage [28, 29].

This initially compromises the integrity of the tendon, which now reacts with multiple inflammatory, regenerative and remodelling processes. These, however, are now clearly hindered by the swelling and expansion of the mitochondria as an expression of mitochondrial damage, cell shrinkage followed by phagocytosis, thus reduction of cytoskeletal structures, reduced fibrillar diameters, cell detachment from the extracellular matrix, hyalinization of the collagen bundles, reduction of signal proteins and cytoskeletal proteins with subsequent inhibition of collagen and proteoglycan synthesis and elastin and fibronectin atrophy, induction of the apoptosis marker caspase-3 (apoptosis was already observed at the lowest doses of levofloxacin) [30], down-regulation and inhibition of important enzyme systems (Cycli B, CDK-1, CHK-1, focal adhesion kinase phosphorylation), thereby restricted tenocyte migration and destruction of the extracellular matrix [7].

Chelation with magnesium and iron ions and the inability of the tendon tissue to quickly rebalance electrolyte fluctuations favour the tendotoxic effects.

Furthermore, chelate complexes lead to deficient collagen-proline hydroxylation of the amino acid proline to hydroxyproline [31] and thus reduced provision of hydroxyproline, one of the three most important structural proteins of collagen metabolism, which significantly worsens the mechanical properties of collagen (see Sect. 3.4).

Magnesium depletion and nitric oxide flooding are likely to have an additional negative effect on chondrocytes [25].

In addition to the mitochondrial damage, FQs also lead to disturbances in cell fusion in the structure and differentiation of skeletal muscle fibres due to their specific inhibition of topoisomerase 2. This explains the frequently occurring muscle tears [32].

3.2 Diagnostics

Even after low FQ doses, electron microscopic changes in the tendon tissue [33] become apparent, but these are often not detectable with conventional imaging techniques. Depending on the degree of damage, typical changes can be seen in the further course of the disease using ultrasound and MRI, but these are not obligatory.

The reduced elasticity of the tendon tissue as a result of the hydroxyproline deficiency is usually perceived very clearly by the patient; corresponding clinical tests such as elastography of the Achilles tendon would be desirable and meaningful, but unfortunately are hardly ever carried out [34].

The measurement of hydroxyproline in serum or urine often shows dramatic results; the amino acid is sometimes no longer detectable at all in the measurements, further evidence that the hydroxylation of proline in the tendon cell is interrupted. Moreover the Proline-Hydroxyproline Ratio is strongly increased as a sign of substrate accumulation.

In addition, there are also unspecific laboratory changes such as the increase in ESR and high-sensitive CRP as an expression of silent inflammation.

3.3 Therapy

The therapeutic possibilities are unfortunately very limited.

Causally, we give withania somnifera (= ashwagandha), curcumin and resveratrol to inhibit the activity of the MMPs. Synthetic inhibitors such as doxycycline or the ‘TIMPs’ (Tissue Inhibitors of Metalloproteinases) known in oncology would be a therapeutic option, but again with many adverse effects and are cost intensive

[35–37]. Caffeic acid phenethyl ester (CAPE) derived from honeybee propolis appears to effectively inhibit the gene expression of MMPs (MMP-2, MMP-9, MT1-MMP) and tissue inhibitor of metalloproteinase-2 (TIMP-2) through downregulation [38, 39].

The limited hydroxylation of proline leads to hydroxyproline deficiency; therefore the administration is a therapeutic option.

We give L-Hydroxyproline 600 mg/d in a collagen-strengthening amino acid combination with glycine 180 mg and L-proline 600 mg, among others. This corresponds to the sequence motif glycine-proline-hydroxyproline, which is most frequently repeated in the primary structure (amino acid sequence) of collagen. Proline is given under the idea of increasing substrate pressure and facilitating hydroxylation together with a retardant vitamin C 1000 mg plus flavonoids, vitamin C being the most important co-factor in hydroxylation.

For this purpose, a retardant vitamin C 1000 mg plus flavonoids is added. It is the most important co-factor in hydroxylation.

Balneo-physically, transcutaneous electrical nerve stimulation (TENS) with high-frequency or even galvanic currents, the sensomotoric body therapy according to Dr. Pohl, osteopathy, lymphatic drainage and careful fascia therapy have proven to be useful.

Shock wave therapy (ESWT) is rather not recommended.

3.4 Hydroxyproline

The formation of chelate complexes by FQ leads to a deficient collagen-proline hydroxylation of the amino acid proline to hydroxyproline (prolyl-4-hydroxylase) [31] via inhibition of dioxygenases (DOXG) and thus reduced provision of hydroxyproline, one of the three most important structural proteins of collagen metabolism, which significantly worsens the mechanical properties of collagen.

Hydroxyproline strengthens the adjacent collagen polypeptide chains within a collagen molecule by forming hydrogen bonds and strengthens the covalent cross-links between collagen molecules. A lack of hydroxylation leads to damaged collagen molecules, and the associated functional impairment of the structural

protein leads to damage to any collagen-containing connective tissue.

For this reason, we routinely substitute hydroxyproline in patients with collagen problems. However, it is unclear to what extent circulating hydroxyproline can be used in order to improve collagen synthesis respectively collagen regeneration in the first place (see Sect. 3.3 above).

A measurement of proline and hydroxyproline on our own patient cohort yielded impressive results: A total of 77 measurements were carried out on 65 patients.

In 50 measurements before the start of therapy, hydroxyproline was not detectable at all in the serum of 39 patients (78%), and in another 5 patients the level was in the lower fifth. Only six patients had a normal hydroxyproline level initially.

Under therapy (23 patients) with 600 mg hydroxyproline/die orally, the level of measured hydroxyproline was significantly higher in 14 patients, sometimes above normal. However, in 9 patients the hydroxyproline level remained unmeasurably low.

Further interesting is a follow-up of the hydroxyproline level in a female patient over several years. The baseline in 2010 was 8 nmol/ml (normal range 0–19) *before* FQ administration. In Dec 2013 FQ antibiotics were given. In 2014, no hydroxyproline was detectable in the measurement (<1), in 2015 and 2016 normal values with 16 and 7 nmol/ml, and in 2020 after a relapse only 3.5 nmol/ml. The proline levels were always in the upper half of normal range.

I would like to emphasize that these data do not claim to be scientific, but could at least point the way to the discovery of pathological cell processes.

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4 FQAD and Neurotoxicity/ Peripheral Neuropathy (PN)/ Autonomic Neuropathy/Small Fibre Neuropathy

FQ-induced damage to peripheral nerves has been proven beyond doubt [1–5].

About 65% of the reported AEs in FQ involves the peripheral nervous system. Of the top 50 reported AEs by far the most, namely about 30%, are neurological [6, 7]. Recent studies show a significantly increased risk (depending on cumulative dose and treatment period) that increases by 3% per day of treatment and persists for up to 180 days after exposure [8]. Patients had the highest risk at first use [3]. The FDA sees no dose dependence [2, 5].

Clinically, patients show typical symptoms of peripheral neuropathy, but these are usually neither detectable by relevant neurological diagnostics nor respond to conventional therapy [9, 10]. Exceptions are listed below [11].

In addition to PNP, two case reports report on FQ-induced autonomic neuropathy [9, 12], and our patient file also includes five cases secured by gastric scintigraphy and numerous suspected cases. Four of the five cases are gastroparesis; one case shows a clear dumping syndrome. Gastrointestinal symptoms such as nausea, vomiting, feeling of fullness, burping and pain in the upper abdomen may too often be dismissed as normal gastrointestinal

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antibiotic side effects, but are nevertheless an expression of an autonomic neuropathy.

Kelentey was able to demonstrate such FQ-induced changes in autonomic and sensory nerve cells in an animal model. Sjögren-like autonomic nerve alterations in salivary and sweat glands were also found, which could also explain the frequent symptoms of dry mucous membranes in FQ patients. In addition, there are several case reports of FQ-associated nerve damage such as optic nerve [13], Tourette's [14], Guillain-Barré [15] or carpal tunnel syndrome [16].

4.1 Pathogenesis

It is astonishing that no model for the pathogenesis of these severe AEs can be found in the entire literature. In the absence of this, in accordance with the FDA [2, 5] oxidative stress and mitochondrial damage-induced neurotoxic mechanisms seem to me the most likely approach, possibly in connection with direct neurotoxic effects of FQ [17].

The FDA also proposes a harmful mechanism associated with nucleoside reverse transcriptase inhibitor (NRTI) (since a pharmacogenetic association for the development of PN has been established and may also apply to FQs), but without submitting studies on this [4].

In autonomic neuropathy there is still an interesting approach, whether gastrointestinal symptoms are induced by inhibited effector GABAergic neurons projecting into the periphery or by the FQ blockade of primary peripheral GABA neurons in the enteral nervous system.

4.2 Diagnostics

Conventional diagnostic measures are practically always fruitless; only the skin biopsy for small fibre neuropathy shows positive results more often [9, 18, 19] (see Sect. 4.4).

The same applies to gastric emptying scintigraphy for the detection of an autonomic gastric emptying disorder. It is extremely meaningful, frequently indicated, but is rarely scheduled.

The clinical picture therefore remains decisive.

4.3 Therapy

The fact that in connection with FQAD the term 'irreversible symptoms' is often used is mainly due to neuropathic symptoms. Only 10% of the cases showed an improvement during the observation period [10]; of 108 observed cases none showed a complete recovery after 10 years [5]. Nowhere is the despair of the 'floxed' patient as great as in neuropathic pain.

All relevant analgesics (NSAIDs, novalgin, opioids, etc.), anticonvulsants (lamotrigine, carbamazepine, but also pregabalin or gabapentin), SNRI (such as duloxetine and venlafaxine), tricyclics of the amitriptyline type as well as local application of lidocaine and capsaicin have little or no effect.

In our practice, we have had good experience with the freely available 5% CBD oil. However, cannabis therapy works much better, ideally starting with hybrid varieties via vaporization. Oral administration, for example as dronabinol drops, has not proved to be as effective. Unfortunately, despite clear indications, cannabis therapy is refused and withheld from almost all FQAD patients, even by pain therapists and pain ambulances. Do not ask me why.

In one case report the administration of immunoglobulins [20] was effective, and in another folic acid [11].

In comparable studies—as in our practice—ALA has proven to be a valuable therapeutic option [21]. Compared to conventional therapeutics, it is better tolerated, has a faster onset of action and improves paresthesias, numbness, sensory deficits, muscle strength and, above all, neuropathic pain [22]. The NATHAN study and many other data make us very confident about the neuroprotective effect. However, ALA doses of less than 1200 mg per day p.o. do not seem to have any significant effects [23].

In addition, ALA is an effective mitochondrial and antioxidant agent (see Sect. 2.3).

For neuroprotection, we give benfotiamine 300 mg p.o. p.d. and hydroxycobalamin 1000 mcg s.c. p.d. p.d. and the mitochondrial therapy described above.

Other promising approaches are acetyl L-carnitine [24], vitamin E [25], omega-3 fatty acids [26] and uridine monophosphate [27].

The overexpression of sirtuins in neurons can also prevent and reverse neuropathies in the mouse model [28]. Cellular sirtuin induction has also been described for resveratrol [29] and calorie restriction [13, 30].

A novel approach could in future be the anti-epileptic drug lacosamide; it has been indeed recommended recently from the 'Deutsche Gesellschaft für Neurologie' for SFN (see Sect. 4.4).

With regard to autonomic neuropathy, an attempt at therapy with domperidone is justified, but rarely successful. Metoclopramide does not help. In gastroparesis, solid food should be avoided or distributed in small units.

4.4 Small Fibre Neuropathy

There is no doubt about the neurotoxicity of fluoroquinolones. The sometimes irreversible polyneuropathic symptoms and the most severe neuropathic pain are also sufficiently documented.

However, it is only possible in exceptional cases to arrive at a groundbreaking finding with conventional neurological diagnostics including imaging, lumbar puncture, nerve biopsy and, of course, neurological and standard neurophysiological examination.

Small fibre neuropathy is often considered as a differential diagnosis.

Only two case reports have been published on this [18, 31].

Unfortunately, attending neurologists are very reluctant to initiate diagnostics in this regard. This may be due to the fact that such a diagnosis, which is usually invasive, can only take place at selected neurological centres, and on the other hand, knowledge

about the rare clinical picture and its association with fluoroquinolones is not very widespread. Patients therefore encounter enormous difficulties when such a diagnostic measure is desired.

In the absence of published figures, I can only refer to my own unadjusted and as yet unpublished statistics. These are FQAD patients who fulfilled the clinical criteria for SFN and were referred for appropriate diagnosis. Neurological and standard neurophysiological examination was normal in all patients, excluding large fibre polyneuropathy.

In a total of 25 measurements (20 skin biopsies, 5 QST, 1 confocal corneal microscopy, one patient was examined twice) carried out on my own patients (aged between 28 and 59 years, 20 female and 5 male), 20 tested positive at 17 different neurological centres, 13 of them university hospitals in Germany or Switzerland.

The presence of SFN could therefore be confirmed in 80% of the patients, there were three borderline findings (12%), including one patient who was positive in QST but tested negative at another neurological centre using confocal corneal microscopy, and only 2 negative results (8%).

These rather impressive figures, mind you without any claim in the scientific processing of the raw data, allow the cautious conclusion that SFN should be regarded as the leading cause of neuropathic complaints in FQAD patients.

Therefore, the option of a therapy trial with lacosamide would make sense. This drug is recommended by the German Society of Neurology for the treatment of SFN, so there is the possibility of off-licence treatment in certain cases.

Considering these results, albeit at a statistically irrelevant level, a controlled study would definitely be desirable and much needed to arrive at robust data.

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5 FQAD and Neuropsychiatric Adverse Effects

What is downright perfidious about FQAD is that in addition to the symptoms in the tendon apparatus, nerves or even fatigue, which are clearly perceived by the patient as physical, there are usually psychiatric symptoms [1] which the patient himself cannot classify and which further reduce his acceptance by the consulting doctor.

This acceptance is dramatically reduced anyway, as only 40% of those patients affected state that a doctor would have taken their complaints seriously [2].

The neuropsychiatric disorders are described by the FDA and in studies [2, 3] as follows:

Nervousness, agitation, anxiety and panic attacks [4], psychosis, hallucinations, paranoia, depersonalization, sleep disorders with nightmares, paresthesia, tinnitus, hypersensitivity to light and noise, tremor, convulsions, epileptic seizures [5, 6], clouding up to unconsciousness, memory disorders with amnesia, delirium, depression and suicidal thoughts. Suicides under FQ influence are documented. [7].

In addition, there are often cognitive limitations ('brain fog'), a disorder with a lack of mental clarity and limited concentration and focusing ability.

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The incidence is as high as 11% [8], in our patient population even significantly higher. This discrepancy is probably due to the fact that especially mild psychological symptoms are not taken seriously by the patients themselves. And if so, they are certainly not associated with the previous intake of the antibiotic. Only more detailed interviews will give a corresponding picture. The symptoms can occur within hours after the first tablet.

5.1 Pathogenesis

It is probably mainly based on the excitatory effect by inhibition of the GABA system (psychiatric symptoms) [9] and the activation of the NMDA receptors (brain fog). [10, 11].

GABA is one of the most important inhibitory neurotransmitters in the human brain and has, among other things, a stress-regulating role in the amygdala system of the CNS. Benzodiazepines, for example, enhance its effect in the brain by interacting with the GABA-A receptor. FQs are also able to bind to this receptor [12], but this has the opposite effect of benzodiazepines, as FQs antagonize it [13].

The loss of GABA activity then has an over-stimulating effect on the CNS.

NSAIDs can synergistically potentiate this effect [14]. Although they themselves have no antagonistic influence, they increase the FQ effect at the receptor 33,000-fold! [15].

This means an enormously increased risk for psychiatric AEs in patients who, for example, take Ibuprofen or Diclofenac at the same time because of musculoskeletal respectively neuropathic problems caused by the FQ or for the treatment of the underlying disease (sinusitis, cystitis, etc.). Several seizures have been observed under this combination [8].

CNS-AEs are apparently dose-dependent. In a double-blind study with Fleroxacin, for example, high doses of Fleroxacin resulted in severe sleep disturbance in 60% of patients [16].

The chelation of magnesium by the FQ seems to increase these excitatory effects enormously. In vitro, only a small drop in Mg concentration already has a very strong influence (investigations

with clinafloxacin). The activation of NMDA receptors by a lower Mg blockade in the ion channel also seems to play a role here [17].

To make matters worse, by inhibiting the liver enzyme CYPIA2, certain FQs such as ciprofloxacin reduce the liver detoxification of coffee and tea, thus contributing to the stimulating CNS effect; some FQs reduce caffeine clearance by 84% [18].

In addition, FQs induce oxidative stress in the brain, while antioxidant systems such as GSH and catalase are compromised, and serotonin and GABA levels decrease [19]. Via increased NO load ('nitrosative stress') cognition and learning processes are impaired; NO acts as a retrograde messenger in the NMDA system.

5.2 Diagnostics

A saliva and urine analysis (nor/adrenalin, dopamine, serotonin, glutamate, GABA, cortisol and DHEA daily profile) [20] provides important information on the central storage of the most important neurotransmitters and the neuroendocrine stress axis. Furthermore, we determine pregnenolone sulphate as a neuroprotective and mitochondrial marker.

In the case of neurogenic damage and barrier disorders, the determination of the neuron-specific enolase (NSE) and the protein S100b may also be used in the laboratory. In the case of nitrosative stress, the determination of citrulline in urine (NO detection) may be used.

5.3 Therapy

GABA, γ-aminobutyric acid, is the biogenic amine of glutamic acid. It is synthesized from glutamate with the help of the enzyme glutamate decarboxylase. Although a GABA transport system for the blood-brain barrier was already proven several years ago, it is hardly therapeutically useful (the yield is a brain-GABA-increase of only 33%). In animal models, however, a more than 380% increase in brain GABA was measured when administered

together with L-arginine [21], suggesting a relationship with nitric oxide (NO).

Data also show central GABAergic effects by vagus stimulation via lacto- and bifidobacterial strains in terms of induction via the gut-brain axis [21].

Since the therapeutic aim is primarily to strengthen the central GABA system, we should make use of these mechanisms.

We give either GABA itself or L-glutamine, which can easily pass the blood-brain barrier and serve as a precursor of GABA in the brain. L-glutamine also plays a key role in the mucous membrane function of the gastrointestinal tract and its immune system. Also taurine, which modulates the activity of attenuating neurotransmitters (e.g. GABA), and L-theanine, which increases the concentration of the neurotransmitters serotonin, dopamine, GABA and glycine in the brain, are useful tools.

Due to the almost obligatory dysbiosis, we give probiotics with lacto- and bifido strains as well as dextrorotatory lactic acid to every FQ patient anyway.

We treat memory disorders/brain fog (frequent central nervous symptoms) with hydroxycobalamin or allicin as NOS inhibitors or NO scavengers, since there is usually NMDA overactivation with excessive NO flooding.

For this reason (high NO load) we do not combine GABA with L-arginine (because: arginine + O_2 ≫ citrulline + NO), because with existing NO overexpression the administration of L-arginine is superfluous anyway, even contraindicated. However, if citrulline is not increased, the administration of L-arginine should be considered. In this respect, for the leading symptomatology 'GABA disorder' only the GABA system should be treated first and only in the second step the nitrosative stress, as otherwise the 'transport effect' of NO described above cannot be used.

A promising approach is the administration of Pregnenolone or Allopregnanolone, both neurosteroids which have a CNS-protective effect [22]; endogenous Allopregnanolone can also favourably influence CNS neurotoxicity by reducing oxidative stress [23].

It acts as a positive allosteric modulator at the GABA-A receptor with similar anxiolytic and sedative effects as benzodiazepines and plays an important role in fine-tuning the GABA-A receptor.

The administration of pregnenolone, actually a GABA-A blocker, leads to increased allopregnanolone levels and to a reduction in amygdala-associated activity in negative emotions and anxiety [24].

Melatonin has been shown to be protective with regard to mitochondrial oxidative stress due to its good brain permeability [25] and also has a sleep-promoting effect.

In the brain bivalent zinc, the most common metal, plays an essential role in many proteins involved in the defence mechanism against oxidative stress [26].

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Diagnostic Criteria of the FQAD

6

The second part of this book is intended to help develop diagnostic criteria suitable for practical use.

Anyone who is currently working on the topic of FQ-induced side effects, and in particular FQAD, is doing pioneering work.

This also applies to the diagnostic criteria. In view of the intensive work (and numerous changes) that has been done, for example, in the development of diagnostic criteria for CFS, this first version can only be a proposal for the FQAD.

It has yet to prove its effectiveness in everyday practice and will be subject to testing there. It is to be expected that after a period of revision there will be proposals for changes in many places—especially in the selection of cardinal symptoms—which will then be incorporated into the present version within the framework of a consensus process.

Our classification is binary, i.e. we want to know whether the patient is suffering from FQAD or not.

6.1 Preliminary Considerations and Requirements

There are many imponderables in the diagnosis of FQAD. To name but a few:

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- the period between the administration of antibiotics and the development of symptoms could be extremely long (more than 6–12 months), which may lead to overlooking the cause-and-effect relationship,
- the patient's complex of symptoms is so 'blurred', unspecific and unclear that the keyword or idea 'fluoroquinolones' does not even come up,
- the resistance of the consulted physician, especially if he has prescribed the FQ himself or even out of ignorance, may be so great that he will not consider such a differential diagnosis,
- another suspected diagnosis, such as 'somatization disorder', will put the doctor's diagnostic inquisitiveness at a standstill,
- the diagnosis is not pursued further because of a defeatist attitude ('there is nothing we could do about it anyway'),
- a mixed form with overlapping diseases (such as diabetes mellitus, MS, fibromyalgia, CFS, depression or cancer with chemotherapy/radiation),
- the patient simply gives up after many months or even years of frustrated searching and stigmatization.

In these and many other cases, an established 'FQAD checklist' would be helpful; ideally, it should also be used by the patient himself without the help of the doctor.

Diagnostic criteria for a disease should be formulated according to need. For example, at the scientific or institutional level, they should be reasonably comprehensive, on the other hand simple and practical for a pension specialist, and as effective as possible for medical work with the patient. There, in practice, they should help to make the diagnosis as certain as possible or exclude it within a manageable time frame. The test should therefore have a high sensitivity and specificity. This is precisely what the FDA's diagnostic criteria lack (see Sect. 6.2).

6.2 The FDA's Diagnostic Criteria

In 2017 [1], the FDA provides the following three diagnostic criteria for the clinical picture of FQAD:

- Disability: A substantial disruption of a person's ability to conduct normal life functions.
- Must have adverse events (AEs) reported from two or more of the following body systems:
  - Musculoskeletal
  - Neuropsychiatric
  - Peripheral nervous system
  - Senses (vision, hearing, etc.)
  - Skin
  - Cardiovascular
- AEs had to last 30 days or longer after stopping the fluoroquinolone.

For everyday practise these criteria are not specific nor sensitive enough.

Here are some examples:

- A patient who was given FQ in the context of an influenza, who is still on sick leave after 30 days and still complains of body ache, arthralgia in the legs and a subsiding viral exanthema, would have a diagnosed FQAD according to these criteria.
- At the same time, a patient would fall through the net with sleep disturbance and a severe exhaustion syndrome.
- Anyone who uses FDA criteria to exclude FQAD at this stage (30 days after stopping the FQ) might miss a symptom that would occur later, for example the diagnosis of an aortic aneurysm or a torn tendon after 6 weeks or even many months.
- The entire area of mitochondrial dysfunction and also large parts of central nervous AEs, which go far beyond the neuropsychiatric area, are not sufficiently mentioned by the FDA. The same applies to the autonomic neuropathies.

6.3 The Synoptic Diagnostic Criteria

The following diagnostic criteria are a fairly complete summary and mostly literal collection from publications of the FDA, EMA and Rote-Hand-Briefe (e.g. black-box-warnings), from the package inserts and technical information of the corresponding FQ, from scientific publications and case reports as well as from our own experiences in our practice. This is why it sometimes comes to meaningful repetitions.

If we were to list and compare them, we would have a questionnaire of 8 DIN A4 pages (see Table 6.1):

6.4 Diagnostic Criteria with the Cardinal Symptoms for Practice

A compressed version of these 8 pages (see Table 6.1) obviously won't have the same accuracy. For practical purposes, some symptoms have been generalized, summarized into headings, some have been reformulated, and many have been deleted.

I have correlated these changes with the frequency of symptoms in publications and literature and also with my experience with FQAD patients in order to obtain a condensate that has a sufficiently high sensitivity and specificity for everyday practice.

A catalogue of cardinal symptoms should be developed, which would ideally be pathognomonic for FQAD. For example, rare symptoms (such as creaking or cracking noises near the joints, depersonalization, rapidly ageing and thin skin) are common in patient descriptions, although they are rarely mentioned in the literature. They thus come very close to a pathognomonic symptom. For example, one mother once told me that she could hear the creaking in the joints of her little daughter who was contaminated with FQ through breast feeding; another patient had found several fellow patients in a forum who all saw 'grimaces or gargoyles' during the excitatory CNS phase, a symptom which I have otherwise only found in connection with benzodiazepine withdrawal (apparently a typical GABA symptom).

Table 6.1 Synopsis of diagnostic criteria for fluoroquinolone-associated disability (FQAD)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
1	**Which fluoroquinolone did you take?**	
	Ciprofloxacin (Cipro, Ciproxin, Ciloxan)	
	Levofloxacin (Levaquin)	
	Moxifloxacin (Avelox)	
	Ofloxacin (Floxin, Exocin, Tarivid)	
	Gemifloxacin (Factive)	
	Enoxacin (Enoxor)	
	Norfloxacin (Noroxin, Tavanic)	
	Lomefloxacin (Maxaquin)	
	Another fluoroquinolone:	
2	**When did the first complaints appear? (after starting to take the fluoroquinolone)**	
	Within hours	
	Within weeks	
	Within 6 months	
	Later than 6 months	
3	**These complaints already exist after discontinuation of the product**	
	For several days	
	For 30 days or more	
	For at least 3 months	
	For at least 6 months	
	Since at least 1 year	
	For over 1 year	
4	**By the existing complaints your physical performance is**	
	Not affected	
	Little reduced	
	Greatly reduced	
	Over 50% reduced	
	Very strongly (over 70–90%) reduced	
5	**This disease has caused or is causing**	
a	A significant restriction in the normal way of life	

(continued)

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
a	A clear to dramatic impairment of the quality of life	
a	A hazard or the loss of employment	
a	Financial difficulties	
a	Increasing tensions within the family	
a	Metamorphosis of life	
6	**Predisposing factors**	
a	Problems with previous treatments with fluoroquinolones	
a	Female	
a	Older than 60 years	
a	Concurrent cortisone therapy	
b	Concurrent NSAR therapy	
a	Heart disease/cardiac insufficiency	
a	Glucose-6-phosphate dehydrogenase deficiency	
a	Potassium or magnesium deficiency	
a	Diabetes	
a	Epilepsy	
a	Stroke/cerebral ischemia	
a	Depression/psychosis	
a	Liver dysfunction	
a	Renal dysfunction	
a	Myasthenia gravis	
a	Marcumar intake	
a	Vascular aneurysm	
a	Aortic dissection	
a	Hypertension	
a	Atherosclerosis/vascular changes	
a	Marfan syndrome	
a	Ehlers-Danlos syndrome	
a	Behcet's disease	
7	**General symptoms/fatigue-associated complaints (mitochondrial disorders)**	
a	Weakness/asthenia/fatigue	
a	General indisposition/feeling ill	

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
a	Tiredness	
a	Fever/sweating	
a	Muscular weakness	
a	Pain including pain in the back, chest, pelvis and limbs	
a	Muscle and bone pain	
a	Chronic pain (long-term pain)	
a	Reduced appetite/reduced food intake	
a	Reduced resistance to infections	
a	Serious deterioration of the general condition in febrile infections	
a	Local symptoms such as sore throat, pharynx and mouth or pain when urinating in the case of febrile infections	
8	**Collagen disorder**	
8a	Tendons/muscles/joints	
a	Muscle pain/myalgia	
a	Increased muscle tone	
a	Muscle cramps/muscle twitches	
a	Muscle reactions with damage to the muscle cells	
a	Rhabdomyolysis	
a	Joint pain/arthralgia	
a	Pain and swelling of the joints, joint inflammation, arthritis	
a	Tendon complaints	
a	Pain and swelling of the tendons, tendon inflammation/ tendonitis	
a	Tenosynovitis	
a	Rupture of tendons/ligaments/ muscles	
a	Achilles tendon complaints/rupture	
b	Lumbago/lumbar spine complaints (low back pain)	
c	Creaking and cracking noises in tendons and joints	
8b	Heart and vascular diseases	
	Valvular heart disease (regurgitation, insufficiency)	
a	Aortic dissection	

(continued)

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
a	Aortic aneurysm or ektasia	
a	Inflammation of the blood vessels (vasculitis)/ leukocytoclastic vasculitis	
8c	Other collagen disorders	
b	Retinal detachment, uveitis, floaters, corneal damage	
	Cataract	
c	Inguinal hernia	
c	Penis fracture	
c	Wound healing disorder	
c	Anastomosis insufficiency	
b	Arthropathy in children	
c	Rapidly ageing or sunken skin, thin skin, hair loss	
9	**Nerve symptoms (neurotoxicity)**	
9a	Peripheral neuropathy	
a	Pain, burning, tingling, numbness, decreased or altered sensation (electric, electric shock or other)	
a	Limb weakness	
a	Increased or reduced sensitivity of the skin to pain, temperature and touch stimuli	
a	Peripheral sensory or sensorimotor neuropathy	
b	Guillain-Barré syndrome	
9b	Nerve symptoms (neurotoxicity) of the cranial nerves	
a	Visual disturbances/vision loss/blurred vision/double vision	
a	Hearing disorders/deafness/tinnitus/vertigo	
a	Flavour disturbances/loss of taste	
a	Odour disturbance/loss of odour	
9c	Nerve symptoms (neurotoxicity) of the autonomic nerves	
a	Abdominal pain	
a	Nausea/feeling of fullness	
a	Swallowing difficulties	
a	Vomiting	
a	Diarrhoea	
a	Constipation	

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
a	Flatulence/meteorism	
a	Heartburn/dyspepsia	
a	Dizziness when getting up/feeling of impending unconsciousness	
a	Tachycardia/abnormally fast heart rhythm/change in heart rhythm	
a	Dilatation of blood vessels (vasodilation)/low blood pressure	
a	Hypertension	
a	Sweating/excessive perspiration/hyperhidrosis	
a	Skin dryness	
9d	Central nervous and cognitive symptoms (neurotoxicity)	
a	Headaches	
a	Dizziness	
a	Concentration disorder	
a	Impairment of the ability to react	
a	Limited memory	
a	Drowsiness	
a	Coordination disorders	
a	Gait insecurity/gait disorder	
a	Disturbed attention	
a	Speech disorder	
a	Partial or total loss of memory	
a	Shaking/tremor	
a	Migraine	
a	Increase of the cerebral pressure	
a	Colour vision disorder	
10	**Psychological symptoms (GABA receptor disorder)**	
a	Restlessness	
a	Overactivity/agitation	
a	Psychomotoric hyperactivity	
a	Nervousness	
a	Confusion	
b	Brain fog (clouded thinking)	

(continued)

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
a	Faint/syncope/temporary unconsciousness	
a	Disorientation	
a	Anxiety or panic attack	
a	Mood swings	
a	Unusually increased reaction to sensory stimuli/light sensitivity	
a	Extrapyramidal disorders/dyskinesias	
a	Insomnia	
a	Nightmares/abnormal dreams	
a	Hallucinations/paranoia	
c	Hallucinations with vision of grimaces	
a	Depersonalization	
a	Mental disorders/psychotic reactions	
a	Depression	
a	Suicidal thoughts	
a	Psychotic reactions with self-endangering behaviour/suicide attempts or completed suicide	
a	Seizures	
11	**Gastrointestinal symptoms (dysbiosis)**	
a	Loss of appetite/anorexia	
a	Nausea	
a	Abdominal pain	
a	Vomiting	
a	Diarrhoea	
a	Feeling of fullness	
a	Heartburn/dyspepsia	
a	Flatulence	
a	Upset stomach	
a	Digestive disorders	
a	Constipation	
a	Gastrointestinal inflammations	

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
a	Haemorrhagic diarrhoea/enterocolitis/very severe diarrhoea with blood or mucus/pseudomembranous colitis/colitis with fatal outcome	
12	**Other symptoms and diseases**	
12a	Skin and mucous membranes	
a	Mucocutaneous reactions	
a	Skin rash/itching/hives/urticaria	
a	Skin is more sensitive to sunlight and/or UV light	
a	Toxic epidermal necrolysis/Stevens-Johnson syndrome/ erythema multiforme/photosensitivity reaction	
a	Small, punctiform skin bleedings/petechiae	
a	Stomatitis/oral mucosa inflammation	
a	Oral thrush	
a	Painful blistering in mouth/nose, penis or vagina	
a	Fungal disease of the vagina (Candida)	
a	Infections with other bacteria or fungi	
a	Candida infections	
a	Vesicular rash with fever	
12b	Kidney	
a	Urinary tract inflammation	
a	Fluid retention	
a	Dehydration	
a	Increased serum creatinine and urea levels/kidney dysfunction	
a	Blood and crystals in urine	
a	Renal failure/acute renal failure	
a	Interstitial nephritis	
b	Necrotizing renal vasculitis	
12c	Allergic reaction	
a	Swelling of hands, feet, ankles, mouth and neck	
a	Allergic reaction, angioedema, anaphylactic reaction and death	

(continued)

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
a	Respiratory distress, including asthmatic symptoms/ bronchospasm	
a	Allergic pneumonitis	
12d	Liver/bile	
a	Increase in liver values bilirubin, ALT/AST, GGT, AP, LDH	
a	Liver dysfunction/inflammation of the liver/jaundice	
a	Bile flow	
a	Severe, rapidly progressing liver inflammation up to life-threatening liver failure including death/death of liver cells (liver necrosis) up to life-threatening liver failure	
12e	Pancreas	
a	Increase of the enzyme amylase	
a	Inflammation of the pancreas (pancreatitis)	
12f	Blood count	
a	Blood picture changes, leukocytopenia, leukocytosis, neutropenia, anaemia, reduction or increase of a blood clotting factor (thrombocytes), eosinophilia	
a	Haemolytic anaemia	
a	Agranulocytosis	
a	Pancytopenia	
a	Reduced function of the bone marrow, which can be life-threatening	
12g	Metabolism/laboratory values	
a	Increase in blood sugar (hyperglycaemia)	
a	Hypoglycaemia/hypoglycaemic coma	
a	Elevated blood lipid level	
a	Elevated uric acid level	
a	Elevated calcium blood level	
a	Elevated sodium blood level	
12h	Heart/circulation	
a	Life-threatening irregular heartbeat	
a	Ventricular arrhythmia/torsade de pointes	
a	Cardiac arrest	
a	Angina pectoris	

Table 6.1 (continued)

	Synopsis of the diagnostic criteria for fluoroquinolone-associated disability (FQAD)	Tick off
13	**Revision after**	
	3 months	
	6 months	
	12 months	

a-symptoms—symptoms that are either included in the patient information leaflet or in the package insert of the fluoroquinolones provided by the manufacturer or mentioned in the official warnings or information of the FDA/EMA/BfArM/Rote-Hand-Briefe (black box warning)
b-symptoms—symptoms collected and identified through other data (publications, case reports, studies in animals, etc.)
c-symptoms—symptoms which, according to own experience/patient experience, are significantly more frequent
Evaluation: FQAD is confirmed if:

- at least one criteria from each of the headings 1–5 is ticked, which is not greyed out
- from headings 7–10, at least two of the headings symptoms were ticked
- if these criteria are not met, however, they will be met in the case of a revision after 3, 6 or 12 months

(Such a questionnaire would be well suited for a scientific study or an accompanying patient survey in its completeness, but certainly not for the diagnosis in patients)

Further requirements are that the test should be short and concise (I do not consider a length of more than two A4 pages to be feasible in practice), the patient should quickly find himself in the symptoms, and the test should be simple and as self-explanatory as possible, with only questions or statements to be ticked.

Only the intake modalities of the respective fluoroquinolone (dose, frequency, length of time) should be entered directly in writing. A long FQ history would have to be listed on an extra sheet, whereas the questionnaire only contains the names and cumulative doses of the respective FQ.

My suggestion for a condensed, practice-oriented form of the diagnostic criteria would then be as follows (see Table 6.2).

Table 6.2 FQAD—Diagnostic criteria according to Pieper

	FQAD **Diagnostic criteria according to Pieper**	Tick off
1	**Which fluoroquinolone was taken? When was it taken? What dose was taken? For how long?**	
	Please provide detailed information! Use separate sheet or back page	
2	**When did the first complaints appear? (after starting to take the fluoroquinolone)**	
	Within hours or days	
	Within weeks or months	
	Later than 6 months	
3	**These complaints already exist after discontinuation of the product**	
	For 30 days or more	
	For at least 6 months	
4	**By these complaints your physical performance is**	
	Greatly reduced	
	Over 50% reduced	
	Very strongly (over 70–90%) reduced	
5	**The disease has caused or is causing**	
	A significant restriction in the normal way of life	
	Significant to dramatic impairment of the quality of life	
	A hazard or the loss of employment	
	Financial difficulties	
	Increasing tension within the family	
	Metamorphosis of life	
6	**General symptoms/fatigue-associated complaints (mitochondrial disorders)**	
	Weakness/powerlessness/fatigue/efficiency drop	
	General indisposition/feeling ill	
	Fever/sweating/night sweats	
	Reduced resistance to infections	
	Pain, including pain in the back, chest, pelvis and limbs, muscle and bone pain	
7	**Musculoskeletal/collagen adverse effects**	
	Muscle pain, weakness, cramps or twitching	

Table 6.2 (continued)

	FQAD **Diagnostic criteria according to Pieper**	Tick off
	Pain, swelling, inflammation of the joints, tendons, tendon sheaths, fasciae, ligaments, muscle attachments	
	Rupture of tendons, ligaments and/or muscles/hernias	
	Lumbago/lumbar spine complaints/low back pain	
	Vascular aneurysm, aortic aneurysm, aortic dissection, valvular heart disease	
	Retinal detachment/mouches volantes/vitreous clouding/floaters	
	Rapidly ageing or sunken skin, thin skin, hair loss	
	Creaking and cracking noises in tendons and joints	
8	**Nerve symptoms (neurotoxicity)**	
	Tingling, pain, also electrifying, burning, stinging	
	Increased or reduced or painful sensitivity of the skin to pain, temperature or touch stimuli	
	Disturbances of sight, hearing, taste or smell	
	Tinnitus/spinning sensation/gait or coordination disorders	
	Gastrointestinal symptoms, autonomic nervous system	
	Feeling of fullness, burping, nausea and/or vomiting	
	Stomach or abdominal pain, heartburn	
	Flatulence/constipation/diarrhoea	
	Dizziness—Fainting feeling when getting up	
	Tachycardia/low or high blood pressure	
	Dryness of the skin or mucous membranes	
9	**Central nervous and psychological symptoms**	
	Headaches/dizziness	
	Concentration disorder/memory impairment	
	Restlessness/nervousness/trembling/agitation	
	Anxiety or panic attacks/mood swings	
	Confusion/disorientation/brain fog/speech disorder	
	Hypersensitivity of the senses (light, noise, etc.)	
	Insomnia, nightmares, abnormal dreams	
	Depression, suicidal thoughts, attempted suicide	
	Hallucinations/paranoia/depersonalization	
	Mental disorders/psychotic reactions	

(continued)

Table 6.2 (continued)

	FQAD Diagnostic criteria according to Pieper	Tick off
10	**Skin and mucous membranes**	
	Reactions of the skin and mucous membranes	
	Sensitivity to light/sunlight, also UV light	

FQAD is confirmed when

- at least one criterion from each of the headings 1–5 is ticked
- from headings 6–10, at least two of the headings symptoms were ticked
- if these criteria are not met, they will be met in the event of a revision after 3, 6 or 12 months

6.5 The Bell's Disability Scale

This scale has proven to be useful for representing the degree of disability, i.e. the extent of the complaints limiting the patient's life. It has long been used for this purpose in chronic fatigue syndrome, including by the Charité, for example [2].

I would also recommend this scale for the FQAD; it would look like this (see Table 6.3).

6.6 FQAD, Acute and Chronic Form

For practical reasons, I propose here a further subdivision of the FQAD, which is of far-reaching importance from a prognostic point of view as well as sociomedically (incapacity to work, reduction in earning capacity, disability, pension claims, etc.), namely the division of the FQAD into an acute and a chronic form.

The only criteria for this would be the time course of the illness. The acute form of the disease should have healed within 6 months at the latest or be below the threshold of the diagnostic criteria mentioned above, whereas in the chronic form the diagnostic criteria of the FQAD still apply after 6 months.

Table 6.3 FQAD disability scale (adopted from Bell)

	FQAD disability scale (adopted from Bell)
100	No symptoms at rest; no symptoms with exercise; normal overall activity level; able to work full-time without difficulty
90	No symptoms at rest; mild symptoms with activity; normal overall activity level; able to work full-time without difficulty
80	Mild symptoms at rest; symptoms worsened by exertion; minimal activity restriction noted for activities requiring exertion only; able to work full-time with difficulty in jobs requiring exertion
70	Mild symptoms at rest; some daily activity limitation clearly noted. Overall functioning close to 90% of expected except for activities requiring exertion. Able to work full-time with difficulty
60	Mild to moderate symptoms at rest; daily activity limitation clearly noted. Overall functioning 70–90%. Unable to work full-time in jobs requiring physical labour, but able to work full-time in light activity if hours flexible
50	Moderate symptoms at rest. Moderate to severe symptoms with exercise or activity; overall activity level reduced to 70% of expected. Unable to perform strenuous duties, but able to perform light duty or desk work 4–5 hours a day, but requires rest periods
40	Moderate symptoms at rest. Moderate to severe symptoms with exercise or activity; overall activity level reduced to 50–70% of expected. Not confined to house. Unable to perform strenuous duties; able to perform light duty or desk work 3–4 hours a day, but requires rest periods
30	Moderate to severe symptoms at rest. Severe symptoms with any exercise; overall activity level reduced to 50% of expected. Usually confined to house. Unable to perform any strenuous tasks. Able to perform desk work 2–3 hours a day, but requires rest periods
20	Moderate to severe symptoms at rest. Unable to perform strenuous activity; overall activity 30–50% of expected. Unable to leave house except rarely; confined to bed most of day; unable to concentrate for more than 1 hour a day
10	Severe symptoms at rest; bedridden the majority of the time. No travel outside of the house. Marked cognitive symptoms preventing concentration
0	Severe symptoms on a continuous basis; bedridden constantly; unable to care for self

I suggest *aFQAD* (*a*cute) for the acute form and *cFQAD* (*c*hronic Fluoroquinolone-Associated Disability) for the chronic form.

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7 Inside Story: Practical Experience with FQAD Patients

Here it goes from the scientific part to the field of experience, which I have made with the treatment of more than 500 patients.

Dose Dependence

FQ-AEs can occur hours after the first tablet.

In this respect I, like many other authors, consider a direct dose dependence to be rather unlikely. At the same time, however, I have observed a cumulative effect in many patients. The first treatment cycles with FQ are still virtually free of adverse effects and then comes a point where FQ treatment suddenly triggers the most severe symptoms. This cumulative dose, however, lies in a very wide range; it can be in the low milligram range, but in some patients it can also be well over 100 grams!

A possible explanation could be a non-uniform, genetically determined metabolism (see below), which could explain the presence of (a) a wild type or (b) a heterozygous and (c) a homozygous type of a poor metabolizer in three groups of patients, whose dose tolerance could be correspondingly different.

Furthermore the dose dependence is probably different within the different groups of AE. For example there is with high probability no dose dependence in neurotoxic AEs [1, 2]. However, in

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the collagen group many patients develop more severe symptoms with increasing dose.

GABA

The question of whether FQ receptor inhibition is competitive or not has not yet been clarified. The marked improvement in many patients after a few weeks could be due to a central reactive over-expression of GABA (in the case of competitive inhibition) or to a new formation of GABA receptors (for non-competitive) or both. The good response to GABA and glutamine preparations would rather speak for competitive inhibition.

Pain Therapy

Analgesia in FQAD is challenging; conventional pain therapy usually fails (peripheral analgesics, opiates, antineuropathic drugs) and/or is contraindicated like NSAIDs. Lacosamide seems to be acting rather more effective in regard to small fibre neuropathy, but still, there are the usual precautions to be taken, e.g. from my point of view small fibre neuropathy has to be accurately diagnosed by skin punch biopsy before starting the regime.

The over-the-counter CBD oil 5% often helps, but cannabis preparations, especially hybrid varieties, are more effective.

Local rubbing with magnesium oil can be helpful.

Course of the FQAD Disease

The courses are very uneven. Initially, the neuropsychiatric aspect often predominates, but all 'FQ construction sites' can occur within hours after the first administration of FQ.

If one wants to establish a chronological sequence of symptom groups at all, it would look like this:

neuropsychiatric > mitochondrial > neurotoxic > musculoskeletal

This sequence also usually corresponds to the subsiding of the symptoms.

Since fear, panic and agitation are often the main symptoms in neuropsychiatric AEs, in the acute phase we are dealing with

very anxious patients who have also obtained information about the disease from various sources that are not always helpful at this stage. They long for the fastest possible treatment. Nevertheless, even in these cases one should try to arrange for as comprehensive a diagnosis as possible in advance, as the therapy is then based on this.

Unfortunately, an initially very fast and broad therapy does not make such a difference for the further course of the disease. On the contrary, a therapeutic 'broadside' often leads to an initial worsening.

Three groups of patients can be roughly described prognostically:

- one third get better very quickly, i.e. within weeks to 3 months a considerable progress of >30 points on the Bell scale can be seen.
- one third improves slowly with about 10 points every 3 month.
- in one third, little or no progress can be seen, at least in the observation period to date. These are often patients who initially rated themselves very low (0–20) on the Bell scale. Here the cellular conditions for a healing process seem to be so bad that the cell cannot sufficiently free itself from the vicious circle. In this group there is again a very small proportion of mostly male and rather younger patients with a dramatic course of disease, severe symptoms and an almost life-threatening progress.

Otherwise, neither age, sex, the start of therapy nor other factors seem to play a decisive role in prognosis.

Charles Bennett, however, postulated a genetic predisposition which, in the sense of a mutation, compromises the quinolone metabolism and thus leads to a high FQ accumulation in the cells including the CNS [3] and thus determines the risk of FQ-AEs. Should this be confirmed, it would be very interesting to compare these data with the three patient groups in order to identify possible correlations at the genetic level.

In this context, I also suspect the Gilbert-Meulengracht syndrome, whose phenotype is a slow detoxifier. The affected enzyme

UDP-glucuronosyltransferase-1A is involved in the metabolism of FQ, so it is obvious that this polymorphism could also play a role in the accumulation and expression of FQAD [4].

Relapses

FQAD takes its course with relapses. A large proportion of patients experience this.

These exacerbations or flare-ups can sometimes be very difficult, so that the patient has the feeling of starting from scratch. For this reason, they are also associated with considerable psychological stress. A relapse of this kind can suddenly destroy all the cautious optimism that has been built up during a recovery phase. The patient then has the feeling that he cannot escape from this vicious circle at all. This is why the feedback from patients after a relapse is much more desperate and shocking than at the initial presentation.

The triggers for such a relapse are manifold and/or often cannot be determined at all. In the approximate order of occurrence, these are:

- Overstrain: The patient wants too much (of his old life back) or too much is demanded of him. He overstrains his mitochondrial system, which responds with a complete collapse according to the house-of-cards principle. Warning signs are subtle or non-existent.
- Viral infections of any kind (especially EBV, influenza) and Covid-19 almost inevitably lead to a relapse, which, however, can be gradual.
- Antibiotic treatments can very often lead to a relapse, even if no FQ has been given repeatedly. This is related to the specific mitochondrial toxicity of practically all antibiotics and is, so to speak, inherent in the system (according to the endosymbiotic hypothesis mitochondria originated as separate bacteria-like organisms).
- Extraordinary efforts, even those of very limited duration like travel, lengthy diagnostic examinations or medical assessments as well as any form of psychological stress.
- Therapeutic (and diagnostic) overzealousness, see below.

Therapeutic Over-Eagerness

It is urgent to stress once again how counterproductive uncalculated therapeutic zeal can be. Any specific treatments (e.g. glutathione infusions) as well as therapy attempts in other directions (heavy metal detox, tooth restoration, vaccinations, elective procedures, etc.) should be well considered!

Floxed Patients are Fragile!

In this connection, another important aspect should be emphasized, which should actually be a warning at the very beginning of this book:

FQAD patients are almost mimosa-like sensitive!

They are blown away by the slightest breeze and are sent into relapse, sometimes they do not even tolerate natural and herbal remedies in normal therapeutic doses, and they react enormously to environmental stimuli from noise to electrosmog (most likely in terms of a multiple chemical sensitivity syndrome), to food (e.g. potentially FQ-contaminated meat and farmed fish products) or food containing gluten, to all kinds of stressors and are extremely susceptible to infections similar to a chronic fatigue immune deficiency (CFIDS).

Any invasive measure, be it a diagnostic lumbar puncture or a well-meant infusion therapy, has to be well deliberated and substantiated.

Of course, this does not apply to every patient and every stimulus or trigger, but it is essential to be aware of this constellation!

Psychoses

Severe psychoses as a result of fluoroquinolone treatment have been well documented since the 1990s [5] and are also topic of recent studies [6].

These may range from dizziness, headache, and sleep disturbances being the frequent ones to depression, anxiety, confusion, agitation and paranoia [7] and furthermore to manic episodes [8], insomnia, and hallucination [9], visual hallucinations [10], delusional parasitosis [11] and delirium [12], suicidal ideations and catatonia [13]. Mind you, even 108 FQ-associated suicide or suicide attempt events have been reported to the FDA

between 1994 and 2015. Half of the events described completed suicides [14].

These severe adverse effects are mediated by GABA antagonism and probably also NMDA agonism [15].

However, I have not come across a single case in which a treating psychiatrist would have taken into account the adverse effects of previously prescribed antibiotics in his diagnostic considerations, even if it was pointed out to him.

Instead, I am aware of cases in which patients were discharged with a fivefold combination of psychotropic drugs or even interned in closed wards against their will. It is precisely in this area that disastrous individual fates are revealed.

Disregard and Psychosocial Isolation

FQAD patients do not experience their environment as empathetic, but quite the contrary, as rude, even hostile. They feel left alone.

Not taken seriously by their general practitioners, smiled at and dismissed by specialists, they are forced in their desperation to go on a causative investigation themselves. If they eventually have an idea about the context of their sufferings, their odyssey really begins.

Young or middle-aged people, who suddenly out of the blue develop symptoms like a seriously ill person without even knowing why, who are immediately confronted with frightening and untreatable pain, with an inexplicable exhaustion and previously unknown psychological problems, panic attacks, sleep disorder and suicidal thoughts, are, to make matters worse, virtually on their own in respect of coping with the disease.

Above all, doctors are of no help; their behaviour is shameful, humiliating and counterproductive instead. Unfortunately, there are only a few exceptions to this. This ranges from doubts about the patient's description or a harsh 'there's no such thing' to smug and disparaging downplaying of a chief physician in front of the assembled team during chief rounds ('yes, this is just such a fad') to the complete negation of the clinical picture (the diagnosis in the discharge report is then called 'doctor-hopping' and 'clinic-

hopping', if patients in their desperation have visited the same or different emergency rooms several times).

Even a seriously ill FQAD patient whom I had personally announced in writing at an anthroposophical clinic prior to admission and urged the consultant on the phone to check for this clinical picture could not escape this fate. In his discharge report it said 'somatization disorder' and 'non-compliance'.

These reactions were very impressively documented in a recent study [16], but believe me, what I have heard from my patients is often so much worse that you are on the verge of tears yourself (you just don't know whether it is out of anger, shame or pity…).

In direct conversation, medical colleagues suddenly develop a completely unscientific attitude towards this clinical picture (this cannot be because 'I have already taken the remedy myself', 'this is something rare' or 'I've been prescribing it for years, nothing ever happened') or are searching doggedly for a diagnosis within their own horizon of experience. A colleague once made bitter reproaches to me because I would ruin his psychotherapeutic efforts by telling the patient that it was all due to AEs of an antibiotic.

For the FQAD patients, this disregard means above all increasing social isolation, the gradual turning away from their circle of friends and acquaintances and a progressive disintegration of the family structure. (A patient once thanked me, because his father called him after 2 years of silence (!) to apologize. Watching my youtube video he had realized finally that his son had a 'real' illness after all.)

Hardly anyone still believes in them and still stands by them.

Those who do so regardless, usually parents or spouses, make great emotional, temporal and financial sacrifices; they fall into a stressful and dangerous comorbidity.

From a sociomedical point of view, practically all FQAD patients face the existentially threatening situation that health insurance companies, health care providers and pension insurance institutions negate them in the most scandalous way. Neither diagnostic nor therapeutic measures are provided or reimbursed, there are no clinics or at least specialized physicians to turn to, no

rehabs either, no pensions are paid, well, you can't even write a sick note for these patients!

And this despite the fact that the Scientific Institute (WIDO) of the biggest health insurer in Germany, AOK, has invested a great deal of effort in publishing a 15-page extremely critical essay on the fluoroquinolone topic, in which the sentence appears: 'Patients must be intensively informed about the dangers and alternatives of these drugs and receive targeted support in the event of damage' [17].

Final Remark

FQAD is a very serious disease. I would like it to be perceived as such and not as a political issue.

Those affected have a right to be perceived. Doctors, therapists, but also experts and judges should no longer have to operate in a twilight zone.

The path to this is actually clearly mapped out. Carried by a great commitment of the affected people and therapists, flanked by official bodies such as the FDA, EMA or the Wido, and documented by a surprising amount of scientific work and studies, the conceptual idea of this disorder and the disease itself is about to become an adult.

I hope this book can make a contribution to this.

7.1 Epilogue

According to Wikipedia, Trojans, or rather Trojan horses, are programs that are deliberately infiltrated into other people's computers and perform functions not specified to the user.

They secretly start an installation routine and install malware on the system.

They are disguised as useful programs, for example by actually having a useful function in addition to their hidden function. They are therefore a combination of two independent programs. By starting the first program, the hidden malware is thus started unnoticed.

It uses the possibilities of the operating system, influences its programs and opens invisible windows.

Trojan horses also succeed in deactivating the antivirus software or manipulating the system in such a way that they are no longer detected by the software.

The malicious routine can independently carry out all actions undetected. Data is blocked, modified, and deleted, and network performance is restricted.

These malicious programs then run independently, which means that they cannot be deactivated by deleting the Trojan program. The Trojan horse is no longer required in this system for the malware to continue running.

Weak points are sometimes exploited as soon as they become known, even at the very day of exposure.

There is hardly a better way to describe the perfidious mechanism of the (side) effects of Fluoroquinolones.

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