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Stakeholders and Communication Division

## Public hearing on quinolone and fluoroquinolone medicines

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## General public (patient representatives, carers and families)

### *Speaker 1. Elizabeth Carmouche, Belgium*

I have been suffering severe adverse effects since taking a fluoroquinolone antibiotic two years ago and I have been asked to offer my views today on three separate issues.

#### First, regarding the role of quinolones and fluoroquinolones in the treatment of infections:

My response here is unequivocal. Quinolones and fluoroquinolones should be a treatment of last resort, i.e. they should be used only when all other (safer) treatment options have been exhausted. Under no circumstances should they be prescribed routinely for uncomplicated infections such as UTIs, which can normally be treated effectively with other medicines carrying fewer risks.

#### Second, regarding the risks associated with quinolone and fluoroquinolone use:

The risks are enormous. The consequences for my own health have been devastating. In March 2016 I was a very healthy, active 47 year-old woman, preparing to set off on a three week holiday. I was given a prescription for ciprofloxacin by a GP in my practice IN CASE I got a UTI or travellers' diarrhoea while abroad. I took the medication when I experienced what appeared to be symptoms of cystitis but only took two pills as they made me feel weak, nauseous and dizzy. A few short weeks later, I was suffering from severe joint, tendon, cartilage and bone pain in my thumbs, fingers, both wrists, the heels of both hands, both elbows, both knees, my right hip, both Achilles' tendons, both ankles, both shoulders, and crepitus in my neck. I also had numbness/pins and needles in my hands and feet. These debilitating symptoms didn't hit all at once: they started two to three weeks after I took the ciprofloxacin and they evolved progressively over the ensuing weeks and months.

Between May and July 2016, I consulted my GP, an orthopaedist, two rheumatologists and a neurologist. None of the doctors I saw thought it possible that what I was experiencing was caused by the ciprofloxacin. A few of them had heard of adverse effects on the Achilles tendons, but none had heard of or come across anyone with symptoms as extensive as mine.

One of the rheumatologists was convinced I must have a form of 'rheumatism' or an autoimmune condition and ordered blood tests, which showed that that was not the case. Ultrasound scans at a university hospital revealed anomalies in the bones of my hands/wrists (jagged rather than smooth edges), but the rheumatologist there was unable to advise me on what could be done to heal my bones and stop the pain.

Today, two years down the line, I have still not recovered. I am still in pain and I am physically incapable of doing many of the things I used to take for granted. I am a keen skier and walker and my skis and hiking boots are now gathering dust in the attic. I work full time but can only manage that because I work in an office environment. If my job was in any way physical, I would be unemployed.

#### Thirdly, and lastly, I have been asked to provide my views on further measures that could be taken to optimise the safe use of quinolones and fluoroquinolones

What I have realised in the two years since my health was damaged by ciprofloxacin is that doctors here in Belgium are completely unaware of the extent of the risks associated with fluoroquinolones and of their potential to cause permanent disability. Bayer outlines some of the potential adverse effects in its package insert for ciprofloxacin but omits to mention many of the symptoms and, crucially, does not make it clear that the adverse effects can be persistent and potentially permanent. Proper

transparency would hopefully lead doctors to modify their prescribing behaviour and equip them to deal more appropriately with patients who experience adverse effects.

I have FOUR key points to make here:

**FIRST: There needs to be official recognition of Fluoroquinolone Toxicity Syndrome and doctors need to be fully informed of what that syndrome entails.** When I have tried to explain to doctors that my problems are attributable to ciprofloxacin, the general reaction has been one of raised eyebrows. When I have pointed out that there are many thousands of people in the same boat as me and that there are forums all over the internet set up by patients suffering similar problems after taking fluoroquinolones, I have been told to beware of the internet and not to consult "Dr Google". Yet there are scores of serious studies and academic research papers available that document the problems that I have been experiencing. The problem is that none of the doctors I have consulted have read them. My GP has been sympathetic and acknowledges the reality of my suffering, but has told me she has no answers.

**SECOND: research needs to be carried out by the companies that manufacture fluoroquinolones to identify the mechanism of damage and find an antidote/effective treatment protocol.** In its package insert, Bayer, for example, tells patients to consult their doctor or pharmacist if they experience tendon problems. That is simply not good enough. The doctors I have consulted have no idea what to do to resolve the issue. If Bayer does not know how to reverse the damage caused by the medication it produces, then it owes it to patients to carry out research URGENTLY to identify a solution. And that solution needs to be COMMUNICATED TO MEDICAL PRACTITIONERS equally urgently so that patients like myself are not left to fend for themselves.

**THIRD: patients who are prescribed fluoroquinolones need to be monitored and offered appropriate and timely follow-up if side effects occur. They should have access to relevant tests, support and appropriate treatment to halt or reverse the damage caused and should receive guidance on what medicines and other substances they need to avoid.** For the record, I was refused comprehensive MRI testing by a rheumatologist in Belgium, apparently "because of the expense" of such tests, despite the fact that I have full medical insurance cover. That is unacceptable. I have had no option but to do my own research to try to work out how to relieve my symptoms. I have learned, for example, that repeated exposure to fluoroquinolones causes relapses. Unfortunately, certain animals are pumped full of these antibiotics and I have experienced serious setbacks on numerous occasions, particularly after eating pork. My most recent major setback was when I was prescribed a "Nasonex" nasal spray by my GP. It was only when I suffered a significant increase in bone and tendon pain that I realised that Nasonex is a corticosteroid – and corticosteroids are known to worsen the symptoms of people suffering from fluoroquinolone toxicity syndrome. I have been in chronic pain for two years now and when there is a flare up the pain gets worse and I limp badly and struggle to perform even simple tasks. Still, I am obliged to seek out my own solutions as no guidance has been forthcoming from the medical profession.

**FOURTH: a red flag system needs to be introduced in patient records to ensure that individuals who have already experienced serious adverse effects are NEVER prescribed fluoroquinolone drugs again unless it is a matter of life and death.** I have informed my family and my GP that under no circumstances am I ever to be given a fluoroquinolone again. But what guarantee do I have that doctors will even listen to me if I am hospitalised, or to my family if I am unable to express myself? The introduction of an official medical alert system is absolutely ESSENTIAL.

On a final note, I have no idea what my long term prognosis is. Am I now going to require knee and/or hip replacements a few years down the line? Even more worryingly, research papers show that mitochondrial damage caused by fluoroquinolones can also lead to neurodegenerative diseases such as

Parkinson's, Alzheimer's, and ALS/motor neurone disease. Is that what the future has in store for me? It is fair to say that I await and expect answers and proper follow-up on the part of both Bayer and the medical profession.

## **Speaker 2. Manex Bettan Arguinzoniz, Spain**

First of all I would like to thank the PRAC for this opportunity to be Heard.

My name is Bettan Arguinzoniz. I am an office pharmacist from Basque Country in the north of Spain with 15 years of experience. I have sold thousands of Fluoroquinolones under prescription.

My story is not different from many others: Two years ago I was prescribed a course of Ciprofloxacin 500mg, 2 pills a day, to treat a prostatitis that didn't even exist.

I didn't know my life was about to change...

Before, I was very healthy with no medical problems at all, I used to practice a lot of sports like football, running, crossfit, I had finished a Spartan race 3 months before and I was in the best shape I ever was in my life. I was a young healthy father of two lovely 2 and 4 year old children, and married to a great and beautiful wife and I had a good job that I loved. We were a very happy family.

Thanks to my experience as a pharmacist I told my wife right before taking the Ciprofloxacin that for some reason, I didn't really like this family of antibiotics but, after reading the leaflet I thought, "well, if I feel any side effects I will rapidly stop taking them and I will recover real fast since I am young and healthy". The leaflet says it is more common for old people to suffer from adverse side effects. Since I felt very young and I had taken antibiotics before for regular tonsils without any problems I didn't think it twice.

I took me 7 pills to realize this drug was hurting me. Of course I was prescribed antibiotics because I wasn't feeling good, but I started to feel much worse. I was experiencing the Ciprofloxacin side effects. The nightmare had just begun.

The next months after the treatment, I started experiencing the most strange and scary symptoms ever in my life. They would show up randomly. My health was progressively deteriorating, and everyone around could see it to the point that one day after 3 months, my mom hugged me and told me "oh my god you are going to die" and I answered " I know, mom, I am dying". I looked terrible. I was very fit and I lost 15 kg of muscle. I looked 20 years older.

Brain fog, head pressure, strong headaches, depersonalization, loss of memory, heart palpitations, arrhythmia, digestive problems, sore throat, swollen nodes, vision problems, eye pain, floaters, constant low fever and constant flu like symptoms, extreme fatigue, pain in joints, difficulties to walk, skin rushes all over my body, twitching in many muscles, especially in the eyelids and so on... the worst was my brain. I lost all capacity to function correctly. I was seeing life from other dimension if this makes sense to anyone. It is like living in an endless hangover. The worst you can remember.

These and more symptoms started to show up during the next months and today I carry many with me, specially the devastating brain damage, memory issues, brain fog and the pain in muscles, joints and ligaments, that are progressively deteriorating. Trying to exercise and going to work has become a torture.

I lost my capacity to manage regular daily situations, I couldn't work, I couldn't multitask, I couldn't play with my children, I couldn't keep normal conversations. I quit exercising, I quit football games, I couldn't go hang with friends, lost many of them, I was bedridden with a wheelchair in my brain.

Of course I visited more than 10 different doctors. I belong to a family of sanitary professionals and I got to visit the most prestigious doctors around. They test for everything.

All these physicians had no idea of what was wrong with me. I told them how things happened, I gave them all the information, but they never associated my symptoms to the CIPROFLOXACIN I took

before. After the worst 3 months of my life I visited the Head of Infectious Diseases and Microbiology of Navarra Clinic. He had worked in the USA in the Mayo clinic for 8 years and he was the only one that told me: "I think you are suffering from Fluoroquinolone Toxicity Syndrome". He had good information, the rest didn't.

All this happened almost 2 years ago. My life is not the same. I am still suffering many of these symptoms. Some are gone, some are debilitating and some are getting worse. If I had known all these could happen just for taking 7 pills of an antibiotic that was supposed to cure me, I would never ever had done it. I wish I had read about the serious, long lasting, chronic and the irreversible symptoms. I wish I had seen a Black box in the leaflet with this information. I think my father in law would never have prescribed me these antibiotics if he knew. Yes, it was my wife's dad who ruined our lives; he was trying to help me. He didn't know either. There is a big disinformation about the fatal risks behind them.

I am not here to convince anyone, I am not here to cry. But I think by now, we all know Fluoroquinolones hide very dangerous potential risks and we all know they can damage some people. I am not doing all this for fun. Trust me. I sell them every day in my pharmacy and I feel I am selling people guns to play the Russian roulette. Actually since I am aware, I have detected many victims in my own pharmacy and also between friends and family. Yes, more ruined lives.

All antibiotics can save lives, so do Fluoroquinolones, but we can avoid the potentially dangerous and disabling long lasting and sometimes irreversible side effects that accompany these antibiotic with some simple changes:

- Fluoroquinolones should be used as the **last option**, after other potentially useful antibiotics are discarded.
- Physicians should be **educated** about these powerful antibiotics and patients should be correctly warned about the possible side effects, so they can rapidly stop taking them and avoid further damage. A **Black Box** in the leaflet would be helpful.
- They should never be prescribed **unless strictly necessary** and they should be kept locked in hospitals like other antibiotics, instead of any pharmacy's drawers.

I am a pharmacist and a victim, my father in law is a doctor and a victim. We didn't know. We had no information. Now we do. It is too late for me. No one is going to cure me or give me back the happy live I had, but now, I can save other people from going through this hell. I do it every day in my pharmacy because now I do have the information I didn't have. The problem is that I can only reach few, just my customers, family and friends. And this is the reason I am here in front of the PRAC, because it is in your hands to reach more people to protect them.

### **Speaker 3. Richard Cooknell, UK**

For ease, throughout this statement, I will refer to both quinolones and fluoroquinolones as simply quinolones.

A few years ago I had a severe reaction to quinolones. I suffered from multiple side effects, which effected several body systems. These side effects continued to develop and worsen for months after stopping the drug. At my worst point I could barely walk, I was in constant agony, couldn't sleep at all and was close to suicide. This has had a devastating effect on mine and my family's lives.

Although my condition has improved, I still suffer several side effects to this day. Daily tasks are a struggle, I am still unable to perform my job as a firefighter and unable to take part in the sports or activities that I used to.

There are many thousands of others in various online groups, who have had severe, disabling and potentially permanent reactions to quinolones. I have been in contact with many of these people. From our experiences and from research I have done, I have these thoughts on quinolones.

I believe quinolones are used too often and too widely. I recognise these drugs save many lives and there is a place for them in medicine. However, because of the possibility of devastating side effects, their use should be severely restricted to extremely serious or life threatening infections, where no other treatment options exist. They should definitely NOT be used for minor infections, where a safer antibiotic could be used.

They should also not be prescribed so easily when an infection is only suspected. Where possible, proper testing for infection should always take place before prescribing a quinolone.

Quinolones should not be prescribed as a first option for conditions such as chronic prostatitis. Long courses of 6 weeks and more of Ciprofloxacin are regularly prescribed for this condition. But in the majority of cases this condition is not even caused by an infection.

There also needs to be much stronger warnings about the devastating side effects associated with quinolones. The current patient information leaflet does not explain how serious and persistent these side effects can be. There is no mention that a syndrome of multiple side effects can occur and can even develop long after finishing the drug. There is also no mention these side effects can last for years and may be permanent.

There seems to be a very limited awareness within the medical community of the tendon related side effects. But almost no awareness of other serious side effects. I know of many cases, including my own, where patients have reported side effects to their doctors. But because the doctors don't recognise these side effects, they have then instructed the patient to carry on taking the quinolone and to finish the course. This also means that the side effects never get reported. It was nearly a year later before I received a diagnosis of Fluoroquinolone Syndrome. Most patients never get this recognition.

This lack of awareness is particularly problematic when a patient presents with side effects of the central nervous system. Doctors do not believe these effects can be caused by quinolones. They therefore diagnose the patient with anxiety or depression. This can then even lead to doctors dismissing the patient's physical side effects as a manifestation of their anxiety/depression.

Doctors also regularly prescribe a NSAID or steroid with a quinolone. There seems to be no awareness that NSAIDs and steroids increase the risk of side effects from quinolones.

I also know of many cases, including my own, where people have partially recovered from their reaction to quinolones. Who have then taken a NSAID or steroid months later and it has caused a relapse of their quinolone reaction.

There is no treatment, help or support for people who suffer a reaction to quinolones. The majority of patients don't even get recognition they have suffered a reaction to quinolones. Treatment options should be explored and Quinolone Toxicity should become a recognised illness.

#### **Speaker 4. Markus Hamedinger, Austria**

I am not representing any organization or group of interest. I would like to bring to the PRAC the view of a patient that had multiple doses of fluoroquinolones (mainly Ciprofloxacin) during the last years for different reasons. Now I am strongly affected in my musculoskeletal system since about 2.5 years. I have a confirmed diagnosis from doctors and hospitals and other causes like rheumatism have been excluded by doctor's investigations.

I would like to answer the questions of the PRAC in the following way:

##### **1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?**

I think these antibiotics are used far too often because they work very efficiently. I made the experience that also another antibiotic did the same job after informing my doctor of heavy tendon and joint pain. In general quinolones should be used just when absolutely necessary to prevent irreversible and strong damage to patients.

##### **2. What is your view of the risks associated with quinolone and fluoroquinolone use?**

I was visiting several doctors for side effects of Ciprofloxacin during the last 2.5 years and found out that most of them knew about the possibility of these side effects on tendons. All of them underestimate the problems caused by this antibiotic class also because there has been a delay in the occurrence of these side effects. In my case it has changed my life completely. I am suffering constant musculoskeletal pain and disability. My daily walking distance is strongly limited and sports or work out activities are no longer possible. Up to now no therapy helped and I do not see any improvement for 2.5 years. I also feel that my body is not the same than before, healing is worsened, fluctuating pain in different areas of the body is present and I experience periods of severe fatigue.

##### **3. In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?**

Fluoroquinolones should be used only in rare cases when absolutely necessary. It would be important to give a clear guidance for Doctors in which cases these antibiotics can be used because they are the only choice. Furthermore, pharmacists and doctors should explicitly inform patients about the risks of possible side effects. For people that are already affected there should be research on how to cure from mentioned side effects. The veterinary use of these antibiotics should be completely forbidden to avoid humans taking quinolones through meat.

## **Speaker 5. Miriam Knight, Quinolone Toxicity Support UK**

My name is Miriam Knight and I represent both Quinolone Toxicity Support UK, which I co-founded three years ago, and also Fluoroquinolone Toxicity Victims in Europe. I first want to say thank you to all the affected speakers and observers from these groups and elsewhere for the huge, brave, effort they have made to be here. I also thank the Committee for giving us this opportunity to speak out and for giving us hope that the cause of this iatrogenic suffering is finally being acknowledged.

*In my answers to the three questions I use "Quinolone" to mean both quinolones and fluoroquinolones.*

*(Q1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?)*

Q1. My view is that Quinolones have NO role in the treatment of infections. All health professionals should know two things – 1. that when Quinolones were first being 'developed' as antibacterials in the 1960s, nothing was known about mitochondrial DNA; and 2. that around the year 2000, Quinolones were seen to be useful chemotherapy agents because of their bactericidal action of targeting topoisomerase II – which is also found in mitochondrial DNA. This review isn't about the antineoplastic nature of Quinolones but this is a big reason why the ADRs affect every cell in the body long after the drug is expected to have been eliminated. Oncologists later found they kill cells indiscriminately (rather than on target) which can only mean they're too dangerous to be used as an antibiotic.

Quinolone use varies greatly across Europe but has recently decreased in the UK for some infections because of the antimicrobial stewardship scheme. However most group members are still suffering today from being given a Quinolone many years ago because their doctor 'suspected' a simple infection. We've noticed that advice for Quinolone use is often confused, for example the Clinical Guidelines suggest 4-6 weeks of a Quinolone for 'suspected' chronic prostatitis. Further down the same page, the evidence for this treatment includes the conclusion of a 2012 meta-analysis which "found that antibiotics were no more effective than placebo for treating CP/CPPS" (1).

I've lost count of the harrowing stories I've heard from men and women who have had their lives destroyed by a Quinolone. Many have actually lost their lives – although recorded Quinolone deaths are comparatively low. Sadly, when victims can't stand the continuous pain any longer or when the failure of systems and organs brings about a premature demise, it doesn't count. Until a long-term follow-up study of Quinolone patients is made, those who die later from aortic aneurysms, cancers etc. just die. Please remember: absence of proof is not proof of absence.

*(Q2. What is your view of the risks associated with quinolone and fluoroquinolone use?)*

Q2. The risks associated with Quinolone use are not worth taking. Research from 1986 that proved Quinolones damage mammalian mitochondrial DNA along with their target of bacterial DNA is STILL ignored in licence applications and SmPCs(2). Susceptibility to the damage varies which probably depends on genetic or mitochondrial differences although more is being discovered all the time. Manufacturers and licence approvers have a duty of care to the public to be aware of the latest findings. The recent Clinical Trial Regulations should improve this situation in future.

Last September I sent the Committee a new paper (3) which explains how the metabolism of each cell is compromised by Quinolones in various ways - with many of the reactions becoming perpetual destructive loops. This paper discusses the mechanisms behind the known problems and especially details oxidative stress. This paper will have provided you with a greater understanding of the risks that my fellow speakers were given no choice about taking. This understanding must be passed on to the prescribers. It is arrogant beyond belief to assume everything is already known about the intricate

reactions that are taking place inside us, yet sufferers are regularly humiliated by their specialists who say because these drugs are licenced they can't possibly cause a problem.

*(Q3) In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?*

Q3. There will never be a safe use of Quinolones. They should never be used as they will always cause damage, observed or not. It is unacceptable for Quinolone use to threaten serious chronic illness when most target infections are not dangerous and safer alternatives could be used. If withdrawing them is unrealistic then the only way to achieve safer use is to implement severe restrictions with strict guidelines that must be adhered to, for example:

- a). Quinolones to be prescribed only in life or death situations where there are no alternatives left.
- b). Quinolones to be classified as schedule 2 controlled drugs with prescribing systems prompting for exclusion criteria such as patient age, history and genetic screening results.
- c). ALL prospective patients to be screened for genetic deficiency e.g. G6pd, and mitochondrial disease.
- d). All patients receiving Quinolones to be regularly monitored for ADRs including major organs, endocrine system, cancers and CNS problems for, say, 5 years.
- e). All prescribers to be notified immediately about the mechanism of action, severity of the risks, and importance of both genetic screening and follow-ups.
- f). Emergency staff to be prompted to ask about Quinolone history.
- g). SmPCs and PILs updated immediately plus visible warnings on packet label.
- h). Quinolone Toxicity to be recognised as a diagnosable Syndrome and to be given a diagnostic code under the ICD standard.

This last point is actually the most important. The worst injury for all of the affected people is the fact that their suffering is ignored, denied and simply can't be treated. These are real, ordinary people who trusted their doctors – and ultimately their Health Agencies – to protect them, not to damage them beyond repair.

(1) <https://cks.nice.org.uk/prostatitis-chronic#!scenario>

quoting from: [<https://www.ncbi.nlm.nih.gov/pubmed/22870266> Cohen et al, 2012].

(2) SmPC Ciproxin Tablets 500mg, Bayer, Last updated on eMC: 28 Sep 2017

<https://www.medicines.org.uk/emc/medicine/20346/SPC/Ciproxin+Tablets+500mg/>

(3) Treatment of the Fluoroquinolone Associated Disability - the pathobiochemical implications

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5632915/>

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Ciprofloxacin Product Licence applications.

Shortly before the Public Hearing, I made an FOI request and subsequently received a heavily redacted copy of an application from 2010 (PL 32019/0023-26) This was granted to MAH Roger Oakes on 25th March 2010 then subsequently passed on to Tillomed Laboratories later that year and finally to Nexcape Pharmaceuticals on 5th June 2017 (PL42092/005-008).

According to the Lay Summary, the evidence given in the original application form is identical to an earlier application (PL11311/0185-88) first licensed to Tillomed Laboratories on 23rd June 2002/9th April 2003 (depending on size of tablet).

If I understand this information correctly, Ciprofloxacin available today (2018) has been licensed by MHRA/EMA using evidence that was provided by the applicant BEFORE June 2002.

In the Lay summary I frequently see statements such as “No new data were submitted, nor was it necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.”

Forgive me for asking but is accepting data from 16, possibly 26 years ago a satisfactory way to ensure a pharmaceutical drug is safe and has no risk attached? Is the MHRA/EMA not aware that science and drug research has moved on somewhat over the last two decades?

What I could read of the (redacted) evidence shocked me. Some of the studies used as evidence referred to Fluoroquinolone variants (as comparators to Ciprofloxacin) that were withdrawn before 2000. Presumably these studies were therefore published several years before 2000?

I could actually identify two studies as being published in 1985 and 1987, about 15 years before the application was written. These studies formed part of the evidence which was used to grant the licence application.

I challenge the statement I saw repeated in this application that “..Other information could not be found in the relevant literature”. By the year 2002 there would have been other studies, and certainly by the year 2010, the date this Oakes licence was granted, there was a wealth of information that would have suggested Ciprofloxacin was not the wonder drug it appeared to be.

I also challenge the statements made by the assessors that “No new data .. was .. necessary for these simple applications”. Or do the Guardians of the Public’s Health actually believe that no new information about the efficacy of these – or any drugs – will emerge after 20 years? No new discoveries about genetics or enzymes or the thousand and one amazing processes that occur in the human body and just might, by some chance, be affected by a drug? A drug that even in the 1990’s had molecular variants that were so dangerous to humans that they had to be withdrawn shortly after being licensed? Did it not occur to anyone in the Medicines Authority that more up to date evidence should be considered before the licence application was granted or passed on, unchallenged, right up until last year?

I set myself a challenge to see what FQ information I could find in half an hour from papers published around 2000 (not using any of the information I already have in my files). I found the following:

- a 1997 article stating that Epileptogenic neurotoxicity is a well known Central Nervous System side effect of quinolones that is often seen during chemotherapy.
- a 2001 paper stating that specific members of the Quinolone family display “high activity against eukaryotic type II topoisomerases, as well as cultured mammalian cells and in vivo tumor models”. It describes them as “antineoplastic” and says they “represent a potentially important source of new anticancer agents”.
- a 2003 study showing that Cipro induces morphological changes in the glands
- a 2005 study which concludes that T cells are involved in delayed immune reactions to quinolones and that cross-reactivity among the different quinolones is frequent.

It is frankly frightening to think that the Agency which has control over our drugs and health, the very people who instruct our medical professionals as to what best to prescribe for us, are so bound up with red tape that they can't do a quick internet search and think "This isn't right".

Fortunately those who have actually been damaged, probably irreversibly, by a Fluoroquinolone do have the ability to do these searches and we have found something like 7,000 studies of which only 10% have results in favour of FQs. This is something the EMA has to look at.

## ***Speaker 5. Raymond Miller, Quinolone Toxicity Support UK***

The theme of my presentation is that fluoroquinolones (FQs) probably cause mild or unnoticeable adverse drug reactions (ADRs) in many or even most patients, which will eventually lead to severe ADRs after further courses of them. I will explain this in the context of my own experience after three weeks of ciprofloxacin for a catheter acquired UTI. It is now three years since I took the cipro and I am not a severe case, but my neuropathic symptoms persist and fluctuate. I do not have a simple, linear improvement in them. I will describe my symptoms in my talk as concisely as possible, to put my condition in perspective.

I consider my symptoms to be a warning that I would become very ill with Quinolone Toxicity Syndrome (QTS) if I were to take cipro again or NSAIDs and substantial courses of corticosteroids. I suspect that many patients shrug off symptoms like mine as due to the target illness or to ageing or stress. This means that they could accept further treatment with FQs without quibble and then be affected badly.

The fundamental mechanism for QTS is the disruption of DNA replication in host-cell mitochondria, in a similar way to the intended DNA disruption in bacteria. I am very concerned that this could lead to chronic illness and disability that develops over several years, with signs and symptoms only appearing after such a period. I do not consider myself to be off the QTS hook just because my ADRs are relatively mild, especially as I still have them three years after treatment.

### Answers to the Hearing Questions

(Q1) What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?

(A1) I think FQs have become prescribed too commonly for non-life-threatening infections, because they are perceived as innocuous and low-risk to most patients. This is resulting in microbial resistance and commonplace ADRs.

(Q2) What is your view of the risks associated with quinolone and fluoroquinolone use?

(A2) I think the risks to patients from FQs far outweigh the benefits, especially as there are safer alternatives. There is a growing burden on health services from QTS conditions that could be avoided.

(Q3) In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?

(A3) I want FQs to be withdrawn for all but the most serious cases of infection. This is because it is unacceptable for them to disrupt host DNA and so threaten serious chronic illness where the target infections are not very dangerous. FQs should be reserved for life-threatening, tenacious infections and they should be controlled drugs. Even then, alternative drugs should be tried before resorting to FQs. If FQs do continue to be relatively commonplace then patients should be tested for tolerance to them, including for genetic mutations such G6PD, which can result in very severe QTS. Patients should be followed up for ADRs and developing QTS during and after a course of FQs.

## ***Speaker 5. Geoffrey Robinson, Fluoroquinolone Toxicity Victims in Europe***

1) FQs are powerful antibacterials (though implicated in antibiotic resistance) but are often used as first choice or second choice of ab. And are prescribed with contra indicated meds nsaid and benzos. And are prescribed (also in my case) when there is no infection identified. I was extremely athletic pre Cipro, then unable to work for almost six months post due to approx 20 documented ADRs and unwell for well over another year. Over seven and half years on I still have one clear Cipro induced harm to my neuro circulation

– intra cranial pressure. I had no infection – but experienced most of the ADRs listed in the packaging information and some that the regulatory agencies weren't aware of or omitted due to lack of pharmacovigilance data. Damage to my body covered a range of areas: Initially – incapacitating perineum pain, panic attacks (for first time my life), whole body electrical meltdown like being plugged into electric mains circuit, shocks up spine, face, teeth, eyes, legs. Tachycardia, bradycardia, palpitations. Nine weeks post Cipro multi systemic breakdown: severe pain in abdomen and back, dizziness, pressure in head, horrible sensations in body, spasms, felt as if water dripping onto head, throat closing up, needles into neck, strange head sensations, tinnitus, shocks/jolts around body eg spine, hands, legs, continual swallowing, pressure sound in ears, severe pain in joints: wrists, elbows, shoulders, knees, hips, ankles, ribs – crunching /clicking/hurting, burning lower spine pain, twitches in legs, fast heart beat, pain through body - fear/panic, back, knees, hips, ankles hurting and hips, knees, ankles, shoulders clicking, heavy crawling sensation in ears, sensation of something crawling in front of my throat, continual swallowing, alimentary canal felt weird, masses of digestive movements/sensations/bubbling from top to lower bowl (near anus), digestive system shut down for three weeks, loss of 15kg in muscle mass post, electricity sensations through body. Huge sleep disruption – sub four hours per night for weeks: night terrors, major pain in lower spine, all joints clicking, also audible clicks and pops in my face/nose area and in ears.

2) Risks are not assessed by GPs due to not running personalised testing to measure whether FQs are more likely to have serious adverse effects. Additionally adverse effects often begin after completing the drug. Sometimes weeks or even months later and GPs are unaware of this, hence genuine risk is misunderstood. I was not given any information about risks and was misprescribed diclofenac to take with the Ciprofloxacin. If I was told that I had an infection in future that could only be treated by quinolones I would choose not to take them.

3) Stop use in factory farming. FQs should be restricted and everyone prescribed them should be regularly assessed for several months afterwards. Genetic markers for risk should be included in decision making.

## ***Speaker 6. Julie Le Normand, France***

**1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?**

**2. What is your view of the risks associated with quinolone and fluoroquinolone use?**

**3. In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?**

My name is Julie Le Normand, I'm 37, I'm a French citizen and I am not representing any organization.

Back in November 2017, I had a terrible experience with levofloxacin (TAVANIC 500 mg, to be exact, twice a day for 10 days). That was the first time I ever took fluoroquinolones in my life, and it will certainly be the last.

Quinolones and fluoroquinolones (hereinafter referred to as Q & FQ) are far too broadly prescribed for cases where much less intense medicine would more than suffice for an efficient treatment. Having spoken with numerous people from across the world suffering from their adverse effects, I have learned that Q & FQ have been prescribed for everything from non-complicated urinary tract infections and sinusitis all the way to... anthrax exposure and the plague. I, for example, was prescribed a course of Levofloxacin by my general practitioner for a case of bronchitis/sinusitis at the end of November 2017. I would like the committee to know that I was never warned about the possible severe, long-lasting side-effects of this medication by the doctor, nor by any other medical staff. It only took me two days on Levofloxacin after which I had no choice but to stop the medication because of the sudden onset of its adverse effects.

The manufacturers' notice of the risks associated with Q & FQ is listed merely as "rare." My experience—and those numerous others who have suffered from them—can attest to the fact that the risks of use of Q & FQ are anything but rare, contrary to what all of us have been led to believe. Please allow me to kindly state to the Committee that I took merely 4 pills in total of levofloxacin over two days, 7 months ago. For some, the adverse effects affecting the musculoskeletal and/or nervous system occur weeks or even months afterwards, which makes it even more difficult to connect the delayed symptoms with a course of antibiotics taken several weeks/months before. For me, the onset was as immediate as it was intense. I started to feel an extreme weakness in my legs. It was so bad that I could neither stand up on my feet nor walk anymore. I cannot do justice to you in describing just how uncomfortable the sensations inside my legs were. It felt as if bugs were crawling on them. Both my ankles and my Achilles heels started to hurt and swell. I could hardly breathe. My blood pressure rose dramatically, and I was overcome with a feeling of confusion and agitation. The experience was so bad that afterwards, I was completely bedridden for more than 3 weeks and on sick leave from work for 6 weeks. I felt depressed. And 7 months out, I still feel weak emotionally. My face has aged suddenly though I'm 37. I did not used to be this way. I used to be a very healthy person. I loved hiking, skiing. I am still a mother to 2 children both under the age of 5. But now I am limited in my physical and emotional capacities, and this is extremely upsetting and unfair. I will say that there have been some concrete improvements since the episode, but a part of me still wonders whether I will ever be able to fully heal from this "toxicity syndrome." I have seen several doctors, each of whom have been helpless with the various symptoms I experienced. Long-lasting symptoms simply after a few pills of levofloxacin.

Please allow me to state for the record that I'm convinced Q & FQ should be limited only to life or death situations as their adverse side-effects far exceed what they can otherwise treat! In fact, I fear there is no such thing as a "safe use" of Q & FQ as the side-effects seem to be very common, almost the norm. Please allow me to reiterate that in my view Q & FQ should ONLY be prescribed at the

hospital in certain circumstances with very cautious care and a thorough monitoring of any possible side-effects. General practitioners should not be able to prescribe them anymore without identifying the bacteria to treat, and in any event, not as a secondary intention but rather as a last resort treatment.

If I may add a final remark, I believe that the topical Q/FQ (such as eyedrops, ear drops) should also be included in this safety review as they are known to cause adverse reactions as well, that can be as severe as those triggered by the oral or IV antibiotics.

I do hope that the outcome of this Public Hearing will lead to:

1. An acknowledgement of a so called FQ associated toxicity syndrome/disability within Europe. To my view, there is an urging need that the EMA acknowledges the existence of a so called FQ associated toxicity syndrome/disability (FQAD, like the US Food and Drug Administration did a couple of years ago).
2. If not a complete **BAN** of FQs, at least a **STRONG restriction** of their use within Europe

This would be for sure a historic choice (much stronger than the current "black box warnings" used in USA) and would give Europe the leadership in FQ toxicity awareness.

Thank you for your time and consideration and for the opportunity to present my experience to the Committee.

## **Speaker 7. Elsa Leitão, Germany**

My name is Elsa Leitao. I'm from Portugal and I'm currently living in Germany where I work as a scientist in the field of human epigenetics.

I'm 39 years-old and until three years ago I was fairly healthy. Then I was prescribed Ciprofloxacin to treat a regular urinary infection. I had no further warning from my physician about the special risks associated with this drug. After a few days I developed side effects: joint pain, muscle pain, difficulty in walking, lack of strength and general tiredness. It took me several months until I started feeling better but I never got back to my previous health state. I haven't been able to run longer distances again due to the fragility I still feel in certain tendons. Even after three years, I have sporadic episodes of severe joint pain that I believe are related to the ingestion of certain types of food that I became unable to tolerate.

I think quinolones and fluoroquinolones should only be used in life threatening conditions such as extremely severe infections. These drugs should be avoided when other treatments are possible. I believe that patients prescribed with these antibiotics are in great risk of becoming sicker than before the treatment. Moreover, the side effects take much longer to subside than the initial illness would take to disappear with other treatment and may even become permanently debilitating.

There are a few measures I think should be taken to optimise the safe use of these drugs: 1) Physicians should be better instructed about the severe long lasting side effects the administration of these drugs might have; these instructions should be clearly passed to medical school teachers, medical students and working physicians, so all links in the chain can simultaneously acquire this knowledge. 2) Physicians should inform the patients about the potential toxicity, so the patients can be alert to the appearance of potentially alarming signs. 3) Packages should contain clear warning labels. 4) The products information should be changed with regard to the use of these drugs to the treatment of non-severe infections.

Although this public hearing is more focused in trying to improve the future use of these drugs, I think the past shouldn't be forgotten nor the patients whose life was most severely and permanently affected. In this regard, efforts should also be taken in understanding how to treat these patients.

## **Speaker 8. Jarosław Linka, Poland**

### **1) What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?**

Fluoroquinolone (FQs) antibiotics are currently one of the most frequently prescribed drugs in Europe and play a very important role in treatment for bacterial infections, such as pneumonia, sinusitis, bronchitis, urinary tract infections, as well as for prostatitis. However, FQs are extremely toxic, have high potentials for adverse effects (AE) and associated with potentially long-lasting, frequently permanent, serious side effects. Adverse reactions (ADRs) are often delayed for some weeks or months after cessation of FQs drug therapy, which makes it extremely difficult to make a correct medical diagnosis and apply symptomatic treatment. They belong to the group of broad-spectrum antibiotics, effective for both gram-positive and gram-negative bacteria. FQs employ their antibacterial effect by preventing bacterial DNA from unwinding and duplicating through inhibition of their topoisomerase and gyrase, which differentiate them from other common antibacterial agents. This mechanism places them closer to chemotherapy drugs than other antibiotics, which mostly interfere with specific steps in homeostatic cell wall biosynthesis. As a result of this broad-spectrum and misunderstanding of their safety profile, doctors in Europe consider them as a safe treatment option and prescribe them even as an empirical first line antibiotics therapy. This is leading to an overuse of FQs, and in consequence tens of thousands of people suffer by them each year, yet nearly all those damages remain misdiagnosed or undiagnosed. Patients after FQs ADRs frequently are diagnosed as having Lyme disease, multiple sclerosis, neuropathies of every kind, lupus, rheumatoid diseases and most often fibromyalgia. Only a handful of doctors are aware of a devastating effects of FQs. The rest are uninformed and often deny the existence of fluoroquinolone associated disability (FQAD).

### **2) What is your view of the risks associated with quinolone and fluoroquinolone use?**

According to the latest research and available literature, FQs toxicity results from many causes, including the formation of reactive oxygen species, and generation of oxidative stress damage of the mitochondrial DNA, as well as from the chelation of metals and a change in gene expression. These mechanisms explain the reason why FQs are often reported, to cause permanent and serious side effects to: tendon, muscles, joints, nerves and other organs. Other long-lasting problems involve the cardiovascular system (QT interval prolongation), musculoskeletal system disorders (arthropathy, muscle weakness, joint pain and swelling), chronic fatigue and diabetes mellitus. Moreover, FQs have recently been discovered to induce delayed adverse neuropsychiatric effects including dizziness, sleep disturbance, anxiety, suicidal thoughts, hallucinations, psychosis, depression and recurrent mania. All the side effects should be mentioned on the patient info label, especially including psychiatric and potential delayed mitochondrial toxicity (like mitochondrial DNA depletion and mutations.)

### **3) In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?**

The overuse of FQs and the growing number of reports on ADRs often leading to the fluoroquinolone associated disability (FQAD) is the main reason to avoid FQs when other safer alternatives are available. FQs should only be used as the last resort, exclusively in a hospital, by a well trained specialist. Unfortunately routine blood and urine tests are generally non-contributory to diagnoses of FQ's ADR or FQAD, so specific molecular and genetic tests should be provided as quickly as possible. Special studies are necessary to find genetic factors underlying susceptibility and the genotypes predisposing to ADRs. Multicenter clinical trials on long-lasting FQAD in large groups of patients are also required. Immediately, the basic guidelines and standard treatment methods for ADR and FQAD should be developed. This can't be left to desperate patients and only several aware doctors who try to help them, like it was in my case. After one year of visiting numerous clinics in Poland, Germany,

China, and USA I have finally found doctors, who were willing to help me and are aware of the FQ toxicity syndrome. Based on published data analysis and subsequent empirical searching, an individualised treatment plan was developed, which significantly reduced or even reversed some of my damage caused by Levofloxacin. Although, after three years my quality of life is better, a lot of environmental factors can induce intermittent episodes of symptoms. I am still suffering from chronic fatigue, Achilles and other tendons tendinopathy, multilevel degenerative disc disease, peripheral and small fibre neuropathy, uncommon food sensitivities, muscle weakness and headaches. A Review of currently available knowledge of possible ways to treat of FQAD, inspired by my case, was published last year in the Oxidative Medicine and Cellular Longevity under the title: "Treatment of the Fluoroquinolone-Associated Disability: The Pathobiochemical Implications"

I hope that a PRAC meeting will set new restrictions for FQs and new procedures of their use only in hospitals, under long-term supervision and as a last resort treatment. Limited action from EMA such as just copying FDA's warning from June 26, 2016 will probably keep the current status quo for their use and spreading of their devastating delayed side effects, what we can still observe with the growing number of cases of FQAD from the United States.

<https://doi.org/10.1155/2017/8023935>

### ***Speaker 9. Andrea Noya, Italy***

As someone who's suffered and is still suffering serious side effects from a fluoroquinolone, prescribed to me more than a year ago, I'd like to share my experience, in the hope that more consciousness would be applied, when using these types of drugs and also in the hope of bringing these side effects to the attention of the many doctors, that still seem to ignore them.

Answering the questions:

1. I think quinolones and fluoroquinolones are powerful and effective drugs that should be only prescribed for serious or life threatening infections.
2. The risks, in my opinion, exceed the benefits. A patient shouldn't suffer serious or disabling side effects from a drug prescribed to treat or even prevent a common infection.
3. In my opinion, more restricting laws should be applied to this class of drugs and it should be mandatory for doctors to be better informed and trained on the use of quinolones and fluoroquinolones.

## **Speaker 10. Joshua Sutton, UK**

My name is Joshua Sutton and I am a business student at Sheffield Hallam University.

I would like to begin by saying that there is a place for Fluoroquinolones in modern medicine, and the use of them in a proper manner could be very effective. However, the current use of them is far too frivolous and exceptionally dangerous. These drugs have such strong capabilities of causing major damage, as two days after the treatment of Ciprofloxacin for an unconfirmed and nonurgent infection my neurological health greatly deteriorated. The impact that these drugs have had on my life is beyond belief.

My view on the risks of Fluoroquinolones is that they very often outweigh the benefits, especially for unconfirmed and non-urgent infections. I was prescribed Ciprofloxacin on the 5th June 2017 by my GP. It was the 17th June when I first realised something was wrong, where my vision became very slurry and I felt very disorientated. This was accompanied by a horrible brain fog sensation that has never gone away, extreme light sensitivity and then walls of black snakes down the walls which ended up being the development of eye floaters.

Starting on the next day, the 18th June, I developed a terrible tremor and loss of sensation in my hands and feet where I quickly lost the ability to do even the most basic of tasks; tying my shoe laces, holding a knife and fork or even dressing myself. I would have excruciating deep rooted pains and aches down my glutes and hamstrings down into my feet, and the same down my arms into my hands that would refine me to my bed. The tops of my hands and feet would also be extremely sore, where moving my toes or fingers or clenching a fist would be agony.

I have burning and tingling pains and sensations all over my peripherals and head and face, and my limbs would consistently go numb. I couldn't hold my phone up to use it as my hands and arms would quickly go numb and I would awake every morning with both my arms hanging by my side completely dead. I would and still get burning sensations down my back and limbs that makes even the weight of a cotton t-shirt against my skin excruciating. In addition to this, I would also find it impossible to empty my bladder and would have to strain to do so even a little bit.

Onto the fatigue and weakness, I would be so weak to the point where I couldn't turn over a chicken breast in a frying pan or pick my feet up as I was walking so I would simply trip up over my own feet regularly. I would find it impossible to complete daily tasks. I was very reliant on my Mum to look after me and care for me during this period and I have had to make some major lifestyle adjustments in result of all of this. I am still very fatigued to this day and have great difficulty concentrating on anything. My cognitive abilities have been greatly affected by all this.

Alongside this, I have also been seeing a Cognitive Behavioural Psychotherapist to help me handle the anxiety involved with these symptoms.

Moving on, my opinion on further measures to optimise the safety of Fluoroquinolones should be to discontinue the use of them for unconfirmed and non-urgent infections, only allow GP's to use them as a last resort, perhaps if the patient has allergies or sensitivities to many other alternative antibiotics. Also, the use in hospitals should also be as a last resort, and any prescribing doctor should not only be fully aware of the adverse capabilities of Fluoroquinolones but also discuss any adverse reaction symptoms with the patient so they are well informed because if they begin to have adverse symptoms during their course and continue taking them they are going to be very unwell for a very long time.

Fundamentally, this is all an iatrogenic catastrophe and there needs to be immediate regulation to mitigate these risks involved.

Ciprofloxacin took away my health, my fitness and my sanity, and for that, its unforgivable.

## **Speaker 11. Miriam van Staveren, The Netherlands**

Dear EMA,

I am a physician from the Netherlands. I am also badly affected by the side effects of levofloxacin.

In July 2014 I went for a holiday on the Canary Islands. I was prescribed a 6 day course of levofloxacin for an inner ear infection and a sinusitis. During the treatment I noticed my Achilles tendons started hurting. I thought it was due to the fact that I had exercised too much: I took tennis lessons, I hiked and swam a lot, played ping pong, engaged in water aerobics, and dancing.

Travelling home, I felt all right. But after a week, my Achilles tendons started to hurt again, so severely, that I suddenly could not walk anymore. After yet another week my ankles started hurting as well. Followed by my knees, my left shoulder and both my thumbs. During the next 6 months I also developed (amongst others): muscle cramps and trembling (fasciculation's), neuropathy, joint pain and swelling, night sweats, severe itching, hair loss, intolerance against even the lightest exertion such as taking a shower, intolerance to light, profound insomnia and very painful dry eyes.

I became depended on a wheelchair and crutches. I was in pain day to day. I recently even lost my license as a physician due to the fact that I could not work anymore.

An MRI showed knee cartilage damage and a large meniscus tear, with fluid in both knees. My Achilles tendons were thickened as if I had been a Marathon skater. I had visible skin damage to my ankles and lower legs. My orthopedic surgeon was reluctant to operate me. Which, as you know, is rather remarkable for a surgeon.

Yet my surgeon wanted to explore what was going on in my body before he dared to operate on my knees. This is why he referred me to a professor in an University hospital in Amsterdam. This to perform a medical evaluation by a team of specialists: a toxicologist, a geneticist and internist and so on.

Unfortunately, after this rather optimistic beginning of my medical condition being believed, I could not find one single doctor who was familiar with the symptoms of the delayed and long lasting side effects of the fluoroquinolone antibiotics. The above mentioned professor told me he couldn't help me. Not even a clinical pharmacologist specialized in side effects of medication had heard of these severe and lasting side effects. I had to refer her to a professor from the university of California to convince her my symptoms were real and caused by levofloxacin.

In total I visited at least 7 specialist of 3 different top teaching hospitals in Amsterdam. None of them could help me, most could not believe my symptoms were due to taking levofloxacin. I remember once a GP asking me: "did you sprain your ankle?" This because my ankle was very swollen and painful.

No matter how much peer reviewed literature I showed, my doctors could not believe my symptoms were caused by levofloxacin nor were they able to help me. Even if believed, there hasn't been found a cure yet against the persistent and debilitating side effects of fluoroquinolones also called fluoroquinolone toxicity syndrome (FQT).

I have tried to warn various health care organizations in Holland involved in medication side effects. They all told me I was the first patient they ever met to have these persistent side effects. I tried to publish an article in a medical Dutch magazine. Sadly my article was refused because the editors deemed it not relevant for the Netherlands. As I agree, in the Netherlands antibiotics are prescribe quite reluctantly, however I got to know various other patients in my home country.

I performed a literature search and wrote a "Dear doctor" letter which I published online in August 2015. This letter was also sent to the FDA hearing about fluoroquinolones in November 5th 2015. My letter was meant for patients to show to their own doctors.

I learned there were many patients in various countries in the world desperately looking for knowledge, validation and help. They were gathered in Facebook groups. Some of those patients are also working in the medical field: medical doctors, nurses or pharmacists. They were all as astonished as I was that a few pills can cause such havoc. One medical doctor told me she thought the side effects of fluoroquinolones are much worse than the side effects of Chemo. On a certain moment she suffered so much she considered to go to a clinic in Switzerland to be euthanized.

Not being able to help other patients felt very frustrating for me. Up to this day I carry the stories of many of them with me in my heart. Some of those patients committed suicide in their despair. Almost all of them lost their previous active life and or jobs. I heard many of them were too ill to come to speak here today. Even too ill for a teleconference. I can understand this, as four years ago I would not have been able to be here myself, due to the side effects. I have been in contact with many patients. In Europe: Italy, Germany, Great Britain, Spain, Switzerland, Finland, the Netherlands, Sweden, Austria, Hungary and Belgium.

In the fall of 2017 I was approached by an author of Nature magazine. She was told I was a physician living in Europe who was knowledgeable about the side effects we are speaking about here today. She wrote an excellent article about the syndrome called fluoroquinolone associated disability (FOAD: name given by the FDA). Yet even after the article in Nature was published in the March 21st issue I was not able to get Dutch doctors interested. This detached attitude is no exception in the European medical field. I almost never heard of a patient being believed their symptoms are from taking the antibiotic this hearing is about.

This is why I am very grateful I was invited to speak at the EMA hearing. I know EMA is influential and I know you already put a lot of time in studying these side effects.

It is my strong belief that there is no safe use of fluoroquinolones. That is, until further in vivo human research can select those who will be harmed by taking them. It is very well possible that anyone can be affected, although some people are probably more vulnerable than others. Some patients are hit after having taken this antibiotics multiple times. Some are hit after just 2 pills. Obviously there is a personal threshold.

Further research should not only emphasize on safe use, - if at all possible -, but also on the exact mechanism of harm done. This to help those who are currently suffering from this complicated syndrome, which should get a diagnostic code. Firm upgraded warnings and full information about the debilitating side effects should be issued broadly in Europe as soon as possible. Possible mitochondrial toxicity should be included in the warnings.

Its use should be reserved for serious life threatening infections that do not respond to any other treatment. Any such infection should be cultured first. Patients should always be fully informed about the risk to become disabled after the use of a fluoroquinolone antibiotic.

## ***Speaker 12. John Crowley, Luxembourg***

My name is John Crowley, I'm Irish but living in Luxembourg and the story I'm about to tell you I would not have believed was possible if I had not experienced myself.

In 2009 I was in an accident which left me with a stricture of my urethra.

Over the next 5 years whenever I suffered from pain in penis my urologist put me on Ciprofloxacin as he told me it could be an infection and this would make my condition worse. He unfortunately never sent me for tests to verify if I had an infection.

In October 2014 (aged 38) while taking Ciprofloxacin I developed a sharp burning pain in my right Achilles tendon. The next day I felt the same in my left leg. At this point I was barely able to walk and went to the emergency room at my local hospital.

I was put on crutches and told this was a common side effect and would disappear in a few weeks.

Next up I developed pains in my arms and hands.

I went to an orthopaedic specialist and was diagnosed with Achilles tendonitis in both legs, golf and tennis elbow in both arms.

After months of physio I saw limited improvement and was sent for an MRI scan which confirmed the above diagnosis. 2 and a half years later the tendonitis is still visible via MRI.

Unfortunately the tendonitis remains and in the interim I also have developed tendonitis in both knees. I am no longer able to participate in sports and am in pain in my daily life constantly having to use ice to dull the pain. Even simple things like playing football with my children or bringing shopping bags into the house are no longer possible.

I work in an office and have had to change to a special ergonomic mouse as I can no longer use a standard mouse. I find it difficult but to date have been able to hold on to my job. If I was working in a manual profession such as a carpenter there is no doubt I would now be unemployed.

The next side effect I experienced was a pain in my arm which felt like an electric shock. This was followed by involuntary movement of my arm at night time which lasted for a period of several months and was very scary.

I went to see a Neurologist but by that time I got an appointment and took tests my symptoms had receded and my tests came back negative. The dr was unable to explain what might have happened.

Finally I have no evidence to link this to Ciprofloxacin but I have also developed the following over the past 3 years:

- i. Chronic dry eyes (I need to put drops in my eyes throughout the day and a special cream at night)
- ii. Eyes not focussing correctly
- iii. Dry skin
- iv. Dry ears
- v. Damage to my hearing
- vi. Stomach and digestion issues leading to acid reflux for which I'm now on PPI's
- vii. Insomnia
- viii. Less control over my bladder which requires me to urinate 1-2 per night

There is no history of any of the above in my family and my dr's are unable to explain the root cause. Perhaps just bad luck but I don't believe a healthy man at my age who always ate and exercised well could have so much bad luck in such a short space of time.

I have no doubt quinolones are a useful tool and have their place in the dr armoury but I believe it is used too frequently without a proper understanding of the side effects.

While some dr's have been very sympathetic to my plight the vast majority to be quite frank did not believe that it was possible that a quinolone could do this.

My recommendation would be for Dr's to be formally made aware of the dangers by the regulatory body, to be issued with a very strong recommendation that this only be used where alternatives were not available and finally for much enhanced warnings on the packaging.

I read that this medication could cause tendonitis on the label – it didn't say anywhere that this would last over 3 years (and at this point probably for the rest of my life). That's just not right and needs to be addressed.

#### Answers to 3 PRAC questions

I have no doubt quinolones are a useful tool and have their place in the dr armoury but I believe it is used too frequently without a proper understanding of how dangerous the side effects are One dr summed it up well when he said you dont use a bazooka to kill a mouse in your house. While you would no doubt get rid of the mouse the collateral damage would be too great and I believe a similar logic can be applied to quinilones.

While some dr's have been very sympathetic to my plight the vast majority to be quite frank did not believe that it was possible that a quinolone could do this.

My recommendation would be for Dr's to be formally made aware of the dangers by the regulatory body, to be issued with a very strong recommendation that this only be used where alternatives were not available (and if prescribed risks to be clearly explained to patients) and finally for much enhanced warnings on the packaging.

I read that this medication could cause tendonitis on the label – it didn't say anywhere that this would last over 3 years (and at this point probably for the rest of my life). That's just not right and the labelling needs to be addressed (for example in the US the packaging carries a black box warning).

### **Speaker 13. Enikő Pongrácz, Hungary**

Dear PRAC,

I was prescribed in October, 2014, ciprofloxacin 500mg 1/day for UTI, and in March, 2015, Ciloxan ear drops for Otitis media. After 5 weeks in both cases extreme high blood pressure and debilitating headache appeared, which very hardly could get back in control.

And the rest came after each...Gained +30 kg in 3 month, hypovolemia, sudden hair greying in 3 weeks, my hair can not be dyed ever since- low cardiopilin, low autophagy. My ears and nose are clogged, dry- Sjorgen Syndrome, Tinnitus loud ever since, sensorineural hearing damage, Myoclonus Tympani-Stapedius-Eustachian tubes-Palate, sleep apnea and insomnia. Carotid damage, Lymph nodes inflamed to double. Eye floaters, foggy vision, dry eyes, uveitis, vision worsened, frequent morning cornea bleedings due to high blood pressure during sleep reaching 200/150 and very high pulse, supratentorial flairs = mini stroke, shrinking frontal lobe, constricted hypothalamus arteries =release hormones problems leading all hormone problems, cortisol, estrogen, ovarian cysts several times, uterus myoma, GERD, SIBO, hiatus hernia, gallbladder blocked, colon pain, diarrhea, colon/fecal incontinence, urinary incontinence, tendonitis-capsulitis, insulin resistance, EHS (electro hyper sensitivity, or microwave sickness is due to mitochondrial damage), detox blocked still, not sweating for 2 years. Mitral insufficiency, LBBB, peripheral neuropathy (one hand and one leg), changed blood count, shifts in over range and under range. Reactivated EBV and HHV ever since, became chronic. Frey syndrome, teeth dentin browned, can not be cleaned and about 12 cavities ever since and 1 extraction. Multiple chemical sensitivity- to foods, smells, dust mites and suffocation from detergents and cleaning products. Several ER visits due to high blood pressure and angina. Continuous brain fog, ears and head pressure.

Since then I am half deaf, half heart and half limbs functioning.

I can not work anymore, previously I was business consultant, traveling for business and for private as well, doing all kind of dog-sports.

My life after cipro poisoning in sum its a total wrack: health-wise, financially and socially as well. I am disabled, several unrecoverable damages, however in Hungary there is no BNO code for fluoroquinolone toxicity and neither for electro hyper sensitivity - moreover doctors and healthcare deny both. All other symptoms I have are not subject to disability one by one. Misdiagnosed in row.

Can eat only bio, GMO free, no processed foods and take only additives free supplements to avoid side effects and diarrhea, with the significant extra costs of these products.

Natural and phisio-therapy and American doctor consultations are also significant costs.

Due to Electro-Hyper-Sensitivity can not go anywhere public (workplace included) only in nature and if 5G will be installed soon, I will have to move to a farm, in total isolation.

One hour shopping, a doctor visit, MRI/CT/ultrasound or any administrative sorting (bank, municipally, etc) is reactivating any virus I ever had (from contamination or from vaccine) - latest was shingles which I struggle since mid April.

Due to electrosmog (wifi, cell towers) following are also forbidden: public transportation, motorways, hotels, vacation, restaurant, shopping, café, cinema, theater,...

Due to peripheral neuropathy I can fall, can not held properly, I mistype.

I get tired very quickly, I can not run at all, I am not able to held my dog even for walking, while previously had done defense activity with him. Housework is limited to max one hour with protection mask and googles.

I lost connection to my friends- since can not meet them anywhere in public as before.

I vegetate and hope only, that PRAC will ask fuoroquinolone producers to research and develop the way by which we can expel this poison from our body, to stop further continuous damage occurring and repair damaged mitochondria. According to a research, ciprofloxacin stays forever, moves with exosomes at cell apoptosis so damage continues for lifelong -

[https://www.researchgate.net/publication/319129045\\_Antibiotic-induced\\_release\\_of\\_small\\_extracellular\\_vesicles\\_exosomes\\_with\\_surface-associated\\_DNA](https://www.researchgate.net/publication/319129045_Antibiotic-induced_release_of_small_extracellular_vesicles_exosomes_with_surface-associated_DNA)

Another research shows MRSA decreasing while stopping FQ use in hospitals:

<https://www.consumerreports.org/hospitals/surprising-remedy-deadly-hospital-infections/>

Post PRACs review all doctors, veterinarians and pharmacists should be noticed, and a health insurance protocol should be developed in each country for treating FQT.

Mitochondrial diseases' major cause are medications, patients are misdiagnosed and not too much is done for them in EU.

[https://mitochondrialdiseasenews.com/2018/05/11/multiple-consultations-tests-and-misdiagnosis-mark-mitochondrial-disease-odyssey-survey-finds/?utm\\_source=Mito+Disease&utm\\_campaign=ccfc61e1a8-RSS\\_EMAIL\\_CAMPAIGN&utm\\_medium=email&utm\\_term=0\\_fdcf314ce5-ccfc61e1a8-72144013](https://mitochondrialdiseasenews.com/2018/05/11/multiple-consultations-tests-and-misdiagnosis-mark-mitochondrial-disease-odyssey-survey-finds/?utm_source=Mito+Disease&utm_campaign=ccfc61e1a8-RSS_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_fdcf314ce5-ccfc61e1a8-72144013)

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Medication-induced+mitochondrial+damage+and+disease>

[https://mitochondrialdiseasenews.com/2018/05/17/ecrd2018-eu-must-do-more-for-rare-disease-patients-eurordis-leaders-say/?utm\\_source=Mito+Disease&utm\\_campaign=ccfc61e1a8-RSS\\_EMAIL\\_CAMPAIGN&utm\\_medium=email&utm\\_term=0\\_fdcf314ce5-ccfc61e1a8-72144013](https://mitochondrialdiseasenews.com/2018/05/17/ecrd2018-eu-must-do-more-for-rare-disease-patients-eurordis-leaders-say/?utm_source=Mito+Disease&utm_campaign=ccfc61e1a8-RSS_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_fdcf314ce5-ccfc61e1a8-72144013)

All severe adverse reactions must be black-boxed. I am confident that no disabling, debilitating (unrecoverable damage causing) medications should be on the market, until a recovery method is not found. Fluroquinolones should be withdrawn from public use, kept under lockers for Antrax or similar severe cases only, as misdiagnoses is very frequent ending in catastrophic consequences.

In Hungary pre- and postoperative always FQs are used. Since I've been affected, my mother was prescribed FQ in the ER, 2 days later by her doctor as well, and she had 'only' allergy, no conjunctivitis. My dog diagnosed with prostatitis was given FQ as first choice, which I denied, but soon turned out it was due to excess estrogen from chicken meat. These are 'only' 2 examples from my family, but could give many examples from my surroundings as well.

What do you think is compensating for all these suffering and ruined life?

Thanks a lot for this hearing opportunity !

2018. June. 01.

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Dear PRAC,

Please find below inserted my answers related to Fluoroquinolone and Quinolone EMA Public Hearing and please consider them.

Within the scope of this review and based on your experience with quinolone and fluoroquinolone treatment:

1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?

A chemotherapy drug should be the last choice given, not the first, therefore should be available only in hospital care. Should never ever be given as a pre or post -operatory medicine - now is the first choice. Should never-ever be given to kids or adults for simple otitis or conjunctivitis or any other usual disease - now its the first choice. Should be given only after a bactericidal test. Same valid for veterinary care as we do not want our pets dead, or do not want to eat FQ infested meat ( see the study with pray-birds dead in Spain, due to eating FQ infested animal corps).

2. What is your view of the risks associated with quinolone and fluoroquinolone use?

All side effects should be mentioned on the patient info label. Mitochondrial and DNA permanent grave damage and unknown elimination time should be mentioned as well, according to latest research available. ( in animal research after 520 days FQ was still present)

3. In your opinion, what further measures could be taken to optimize the safe use of quinolones and fluoroquinolones?

All countries should recognize and compensate the patients affected by FQ, FQAD should be recognized and compensated accordingly and all medical and pharmaceutical and veterinary staff should be retrained according to new restrictions ASAP in place. As a main unknown side effect, EHS/microwave sickness should be recognized as well by all countries.

Manufacturers must be made responsible to research remedies for counteracting the damages and finding ways for quick elimination from the cells.

Thanks for your consideration!

***Speaker applications not allocated a slot:***

***Malte Meinhardt, Germany***

1) Fluoroquinolones may be life saving, but they are far too often prescribed by doctors for minor infections in cases where other antibiotics might work.

2) Many doctors, pharmacists, and of course patients are not aware of the devastating risks and side effects of fluoroquinolones. In my case, the prescribing doctor did not warn me at all (rx were sent by mail) nor did the pharmacists. When speaking to other doctors after having been affected by side effects (polyneuropathy, tendon and joint problems, anxiety) they either did not know about it or would deny it. The warnings in the package insert are not clear enough or not accurate. For example, it is stated that especially people over 65 might be affected by tendon problems and that you should especially watch out for problems with the Achilles. I was in my 30s when I took the fluoroquinolones and got problems with my shoulders' tendons three years later.

3) Doctors and pharmacists should be informed about the potential devastating, long-term, and sometimes delayed side effects - in a clearer and more effective way than now (obviously, some issued warnings and informations did not reach the doctors). An antibiogram should be mandatory. An FQ rx should only be possible with additional approval by another medicine body or doctor. There should be warnings for the patient in the insert that are much clearer and more haunting than they are now and on the packaging (similar to the black box warning in the US).

## ***Gordon McIntyre, UK***

1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?

In my opinion, fluoroquinolones should only be used as a last line of defense in the treatment of infections. All other options should be exhausted, before fluoroquinolones are prescribed. Further, the patient should be made fully aware of the widespread and severe side effects associated with these drugs, so that they can make informed choices. Prescribers should also be made fully aware of the severe and persistent possible side effects of fluoroquinolones. There should be checks on the prescription. For example, a prescription should need to be signed off by a second practitioner before it is issued. Lastly, black box warnings should be routine for any fluoroquinolone drug.

2 What is your view of the risks associated with quinolone and fluoroquinolone use?

Antibiotics do save lives. That is clear. In the year 2000, they saved my life. I had pyelonephritis and probably would've died without antibiotics. However, the same antibiotics that saved my life, fluoroquinolones, also made my life intolerable in many ways. As soon as the treatment finished, I immediately began to suffer mental and physical issues that had not been there before taking fluoroquinolones. These included muscle tears, frozen shoulders, severe constipation, insomnia, migraines, kidney stones, anxiety, paranoia, depression, brain fog, food and drug intolerances, fatigue, tinnitus, visual abnormalities. These symptoms were not always co-present. Some of them came and went. Others, like migraines, depression and anxiety, were largely permanent.

The hard part was that I had no way of knowing what had caused all of these ailments. It was only when I was given fluoroquinolones for a second time in 2014, that I understood what happened to me in 2000. This time, I was given fluoroquinolone for a suspected prostatitis. The effect was immediate and devastating. I started to experience panic attacks, depersonalization, psychosis, heart arrhythmias, palpitations, fasciculation, tremors, severe brain fog, weaknesses in muscles, tendons and joint pain, loss of motivation, loss of libido, extreme fatigue, and several other debilitating symptoms.

I saw several doctors in the wake of this mal-prescription. In short, none of them believe that fluoroquinolones could be, or were responsible. No treatment was offered. No explanations were forthcoming. I was simply left to my own fate. My life since that point has been a constant battle. There are times when I have come very close to suicide. It is only my family and the support of fellow 'floxies' that kept me going through these terrible years. Without them, I would've certainly killed myself by now.

Doctors I talked to still refuse to believe that fluoroquinolone could be responsible for so much damage. This despite the numerous academic articles in humans learned journals. This despite the numerous newspaper articles. This despite the FDA ruling of May 2015. Such ignorance beggars belief to be frank. It is almost as if doctors do not wish to believe that the very medicine that they hand out can be so destructive. You will hear evidence to the contrary. Many people who have been damaged by these insidious programs will tell their story at this hearing. These people deserve to be listened to. Their lives of the damage, in some cases irreparably.

I can cite hundreds if not thousands of examples of people who have been damaged by fluoroquinolones. They have their own support groups. They have their own blogs. They have their own websites. You do not have to go far to find them. They even have their own name: Floxies. There are not many drugs whose victims have their own names. Even those who were the victims of thalidomide do not. But fluoroquinolone victims do. We do because there are so many of us. Because our experiences are so terrible and so unique.

3. In your opinion, what further measures could be taken to optimize the safe use of quinolones and fluoroquinolones?

Until proper, independent and unbiased studies are done on these drugs, then they should be removed from the market. This will not happen. Drug companies are simply too powerful.

A lesser demand would be for:

- Restriction on the prescription of these drugs.
- Black box warning
- Education of prescribers and other medical professionals as to the dangers of fluoroquinolone antibiotics.

***Gerald Ludwinski, Germany/South Africa***

Your question no 1: Fluoroquinolone are very efficient but the benefit/risk profile makes this drug only suitable for the most severe infections as a last option.

Your question no 2: The risk/benefit ratio in my case was, that I stopped counting at 39 side effects at the same time and after 21 month I still suffer from many of them. There is no known treatment worldwide to ease or heal the side effects. It is a life changing event where most of us FQ victims suffering from extreme physical and emotional pain and disabilities, from the loss of enjoyment of life, suffering financial losses in the past, present and most certainly in future earnings. Because there is no known treatment method, we also suffer from extreme monthly expenses for self helping measures, private medical care and treatment e.g. supplements, physio therapies and so much more. It is a tragedy and scandal that the Pharmaceutical Industry is preferring to suppress warnings and holding back information's about the full extent of the danger of the FQ from long-term extreme painfully multi-system disabilities, mitochondrial toxicity, degenerative diseases, change of DNA and RNA, Chromosomes, dysfunction of metabolic and immune system and so much more. I, as a M-chem and M-biochem have a good understanding how FQ works and destroys the body and I strongly believe, that in my life time there will be no cure for the side effected victims because the damage caused by FQ is too complex and effects every single cell in the body and will also have a life shortening effect.

Your question 3: FQ should only be given to patients that are stationary in hospital under strong supervision and no other Doctor should be allowed to prescribe FQ. If FQ are given as a last resort to a patient, these Doctors should have a special training and they should also make sure, that the patient is getting with his FQ intake Alpha Lipoic Acid R Form to protect the cells.

***Jason Piggott, UK***

I would like to inform the hearing of my personal experience of the use of these medicines for my 13 year olds post op infection. I wish to provide insight to a real world situation where I found my son was prescribed these medicines needlessly when alternative less damaging options were available. This subsequently left my son with tendinitis that has taken a number of months to heal. The experience put me in a position to have to undertake vast amounts of research of my own to understand the medicine and its side effects since it was evident that many of the medical professionals I was dealing with were generally unaware or unclear of the potential side effects. My ongoing experience when dealing with a number of doctors since, regarding my own health has highlighted to me an inherent lack of knowledge regarding these medicines and my concern is that they are being prescribed without full understanding of the potential consequences or when they are not necessary I.e. other antibiotics with milder side effects will work. I am not a medical professional but whenever I have questioned medical professionals on the use of these medicines I have a feeling I know more about there risks than they do. The hospital responsible for my sons treatment have completely reviewed their own practices following my engagement with them on the matter.

**Lyn How, UK**

1) I believe the role of Quinolones and Fluoroquinolones in the treatment of infections should be limited to last resort because the adverse reactions can be catastrophic and permanent.

2) my view of the risks associated with Q and F is that they are far wider than is generally accepted. In variety, severity and numbers of people affected. Any adverse reactions can be permanent. Because the side effects can appear days or even weeks after taking Quinolones the link is often missed by the medics. Also patients can take Quinolones on several occasions without adverse reaction until 'overload'. This leads doctors to falsely believe the symptoms presented cannot be caused by the Quinolones prescribed.

3) further measures should be taken to optimise the safe use of Q and F's by restricting their use to last resort situations and ensuring the risks are properly explained. More should be done to educate the medical profession regarding the devastating side effects and the need to recognise that symptoms can appear long after cessation and even after previous doses seem to have been taken without problem.

I was prescribed cipro in 2012 to take to India.....just in case I had any infections. With catastrophic consequences. From an active mature woman riding competition horses on a daily basis I was bedridden, then in a wheelchair then crutches. My post tibial tendons ruptured (at the Taj Mahal). I have had surgery but still have mobility problems, plus a host of other symptoms which a leading physician has attributed to adverse reactions to cipro. I am told further surgery will be necessary in the future and the replaced tendon has limited life. I took legal action against my GP to help with the costs of disability and to raise awareness and achieved an out of court settlement. This is a synopsis of the events that took place.

## **Jane Allan, UK**

1. These are toxic, chemotherapeutic drugs which should only be used in life + death situations where there is a confirmed bacterial infection sensitive to quins + no other treatment options are available.\*

Cipro has ruined my life + my family's unnecessarily. I was not hospitalised/ on a ventilator + my life was not in danger - there was no proof I had a bacterial infection sensitive to this poison when prescribed + there were safer treatments available.

I was a fit, healthy, sporty, hard working professional with a great family + social life before my body was sabotaged by cipro. I now live with widespread chronic neuromuscular pain, tinnitus, eye + dental problems and supersensitivity to medicines, supplements, therapies, foods and procedures (even minor ones).

2. The risks associated with quins are unacceptable because doctors (GPs, rheumatologists, neurologists, pharmacologists, pain management clinics, ENT consultants, ophthalmologists, neurogastroenterologists, urologists, psychiatrists) pharmacists, nurses + physios are: unaware of and not interested in them: do not recognise or acknowledge the severity, range + longevity of adverse reactions (ADRs) to quins which can be delayed and last weeks/months/ years plus they have no idea how to treat them.

I have: experienced disbelief, ignorance, arrogance + dismissiveness re ADRs to quins, had doctors try to convince me it isn't the drug causing my pain + imply the pain is all in my head; left appointments distraught, suffered severely from harmful, invasive, expensive, inconclusive procedures including an open muscle biopsy, lumbar puncture, hysterectomy, cystoscopy, nerve conduction studies plus many blood tests, x Rays, MRIs + CT scans.

After 5 years my quality of life is poor, my symptoms persist + my treatment is compromised.

3. Withdraw/ restrict (not simply update warnings) quins by using them on a named patient basis + classify them as schedule 2 controlled drugs.

Prescribe only when above applies.\*

Impose restrictions (that cant be overridden) on all prescribing + dispensing systems.

Inform patients verbally + in writing of the risks BEFORE prescribing + supplying - sign a consent form.

Issue warning cards.

Find ways to minimise development of ADRs.

Develop antidotes (and issue with all quins) + SAFE treatment pathways to ADRs.

Closely monitor patients affected by ADRs.

Update warnings in SPCs, PILs + labels to highlight the risks of causing permanent disabilities.

Review all national + local antibiotic guidelines + formularies + include a flow chart to restrict their use.

Educate all healthcare professionals (+ PHE, CCGs, NHS Trusts, private sector, regulatory bodies) of the dangers.

Independently review all pre + post marketing trial data.

Clarify the mechanism of action/s in humans + explain tolerance + thresholds

Investigate genetic links (cause /effect) with ADRs.

Investigate links with chronic fatigue, ME, SEID, fibromyalgia + unexplained chronic pain.

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In addition to my on line application please consider the information below during the EMA review on the safety of quinolones.

This class of drugs are restricted for specialist use in children, can treat anthrax infections, the plague and other life threatening infections yet are still being used for milder infections when much safer alternatives are available.

The current restrictions on quinolones are grossly inadequate and ineffective putting patients lives at risk unnecessarily.

All antimicrobial stewardship programmes should alert healthcare professionals to the risks and dangers of quinolones.

I strongly feel that many lessons can be learnt following my severe enduring adverse reaction to a short course of ciprofloxacin in 2013.

The NHS is ill equipped (even at the highest level) to recognise and treat the plethora of adverse reactions (ARs) associated with quinolones.

Doctors don't always believe doctors, pharmacists and nurses suffering ARs to quinolones let alone other patients - some patients even end up being labelled as trouble makers, blacklisted and told its all in your head!

I've lost count (150+) of the number of GP and hospital appointments I've had over the past 5 years and have a thick file of medical letters and test results post ciprofloxacin toxicity.

I have kept pain diaries and personal notes (carefully written prior to attending each appointment) in the hope that doctors would believe me, recognise and be able to treat my ARs to quinolones without making my symptoms worse.

Foolishly I was also hoping that doctors would be interested in trying to prevent this happening to others as the severity of my symptoms post ciprofloxacin has been life changing for me after losing my health, job, career plus a great family and social life. I've also had to battle with the authorities (DWP) to recognise my condition and now describe my life as an existence.

I do now have caring, empathetic, interested doctors treating me but this hasn't always been the case where scepticism, disbelief, ignorance, arrogance, dismissiveness and insensitivity have sometimes prevailed.

Some hospital appointments have been extremely stressful, upsetting and humiliating (for me and my family) and a complete waste of time causing more pain and suffering.

Comments from doctors along the lines of what do you expect me to do about it if it is an AR to a drug, almost demanding evidence/proof that my symptoms have been caused by ciprofloxacin, making contradictory statements about how there is more we don't know about the human body than we do know (then disbelieving/dismissing that my pain could be caused by ciprofloxacin) plus being criticised for sharing too much information are disrespectful.

Other less offensive but not particularly helpful comments from doctors who were indifferent and agnostic about ARs to quinolones were along the lines of that's interesting, you've taught me

something new today and apologising for not wanting to following this up as they have their own research interests.

It's only over the past couple of years that some doctors have acknowledged that I could be on to something regarding ARs to quinolones, that ciprofloxacin could be the cause of my pain and if it's good enough for the FDA it's good enough for me.

Most doctors, pharmacists, nurses and physiotherapists are unaware of the risks and dangers of ARs associated with quinolones including pain, gastric problems, joint/tendon/ligament/nerve/ muscle damage, anxiety, insomnia, acute psychiatric symptoms and fatigue even though these symptoms are already in the BNF, SPCs and PILs.

Healthcare professionals are unaware: that ARs to quinolones can be delayed, prolonged, disabling and permanent making it impossible for them to make the connection between cause (quinolones) and effect (symptoms); that many patients suffer with multiple ARs to quinolones.

The gravity, severity and complexity of this situation is not understood and there are no clear guidelines on how to minimise/ treat ARs to quinolones.

Having had a plethora of expensive, sometimes harmful investigative procedures over the past 5 years including blood tests, X-rays, scans, MRIs, multiple nerve conduction studies, a cystoscopy, lumbar puncture and an open muscle biopsy (which all came back normal ) some doctors still found it impossible to believe that ciprofloxacin could be the cause of my pain yet I recall exactly what happened to my body when I took it in 2013 and the enduring pain and suffering which has followed.

Absence of proof is not proof of absence when it comes to ARs to quinolones.

In 2013 I kept a detailed pain diary for 5 months post ciprofloxacin, which I shared with doctors, yet the most memorable comment made by a doctor was about how interesting it was that I'd called it my ciprofloxacin diary.

I also explained to many doctors that in 2009/2010 I'd suffered an undiagnosed painful condition in my feet (burning, stinging, tingling, numbness) which made it extremely difficult to walk and wear shoes/boots for a year. There was no injury sustained during this period yet my GP records show that I was prescribed ciprofloxacin (250mg BD) in 2008 for tonsillitis and again in 2009 for an ear infection. The type of pain I experienced in 2013 (whilst taking ciprofloxacin 500mg BD – with prednisolone introduced by my GP after a few days of ciprofloxacin alone) was the same but more intense and widespread than during 2009/2010 and hasn't gone away.

On one occasion a doctor who did not believe my pain was caused by ciprofloxacin described me as short (I'm 5'7" tall) to part justify undertaking an open muscle biopsy to look for underlying predisposing factors. I explained to the doctor in advance of this procedure how badly (pain wise) I'd reacted to physiotherapy and acupuncture post ciprofloxacin and the outcome of the biopsy was catastrophic (pain wise) for years plus the results were inconclusive.

One of my hospital clinic letters from 2014 refers to the number of cases reported **internationally** is probably **less than 100 over 20 years** in relation to the association of quinolones with sensory symptoms and neuropathies. I'm unsure where this information was sourced but these figures seem particularly low even just comparing with UK MHRA Interactive Drug Analysis Profiles (nervous system disorders) for quinolones.

Since taking ciprofloxacin in 2013 my body has become supersensitive (causes more pain) to nearly all medication (including most pain killers), procedures, interventions, examinations (including minor ones), supplements, physiotherapy, acupuncture and other treatments. The consequences for me are catastrophic.

My widespread (nerve, muscle and bone pain in my feet, legs, hands, arms, shoulders, eyes, ears, teeth, head, face, back, pelvis, abdomen) pain (burning, stinging, squeezing, throbbing, electric shocks, coldness, numbness, can feel like my circulation has been cut off in my hands, legs & feet and my legs are being pulled apart lengthways) can now be triggered by everyday normal activities like for example lifting a kettle/ saucepan, moving a plant pot, cleaning, using a hairdryer, texting, typing, mashing potatoes, walking, sitting, standing, sleeping, a dental check up, cold water, making it extremely difficult to function on a daily basis.

In addition to chronic pain I also suffer with constant tinnitus and dry eyes post ciprofloxacin.

After 5 years my symptoms persist, new ones continue to develop and my life is very much restricted and compromised.

My pain is extremely difficult to control because of my intolerance/ insensitivity to medicines post ciprofloxacin.

Suffering severe enduring ARs to a short course of an antibiotic prescribed by my GP without appropriate warnings, consultation, consent or advice is unacceptable.

I and many other sufferers like me throughout the uk and around the world have had similar frustrations and difficulties trying to get doctors, pharmacists and other healthcare professionals to recognise and acknowledge the severity of the risks associated with quinolones and for regulators to do something about this.

In 2015 I wrote to my local MP about this situation and received a disappointing, unhelpful reply from the then Minister of Life Sciences whose response told me nothing I didn't already know and didn't address my specific questions.

There are hundreds of published papers, some dating back to the 1990's highlighting the risks and dangers of drug induced neuropathies and other risks associated with quinolones yet doctors, pharmacists, nurses and physiotherapists are still unaware of these.

In the UK Drug Safety Updates on quinolones have been few and far between over the past 10 years (nothing I believe since 2012) yet in the US the FDA issued warning updates in 2013 (x1) and in 2016 (x2).

I am tortured and tormented by pain and suffering which has evolved over the past 5 years and it is impossible to portray the severity of this situation in just a few pages.

There is so much more which needs to be said about the devastation quinolones can cause and I sincerely hope that candour and transparency will prevail during this review process.

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I very recently received email notification of the article below (1) which has triggered me to share this, along with two other references (2 and 3), to try and put some kind of perspective and a time line on how little clinicians still know about the risks (particularly to the central and peripheral nervous system) associated with antibiotics even though the warnings have been out there for decades.

### **1. Clinicians do not recognise potential harm of antibiotics**

- Univadis Medical News
- Jun 8, 2018

**A new study of decision-making about the use of antibiotics in medicine has found the mistaken belief that antibiotics are harmless is widespread, with many clinicians influenced by the notion of 'why not take a risk' when it comes to prescribing antibiotics.**

For the study, 149 clinicians and 225 patients attending emergency departments at two large urban academic hospitals and 519 online nonpatient subjects were surveyed to determine whether providers share patients' rationales for antibiotic use.

The authors found that when comparing the status quo of remaining sick to the potential benefits of antibiotic use, patients are more likely to expect antibiotics, leading clinicians to prescribe them more, despite having a greater knowledge of the drugs and their side effects.

**"The problem is that patients, but more surprisingly clinicians, are not fully recognising the potential harms from antibiotic use,"** said Dr Eili Y Klein of the Center for Disease Dynamics, Economics & Policy (CDDEP) in the US. "Despite the fact that approximately 20 per cent of patients can get some sort of side effect, this does not seem to be as important a factor in decision-making as one would expect," Dr Klein added.

The findings are published in Medical Decision Making .

[https://www.univadis.org/medical-news/596/Clinicians-do-not-recognisepotential-harm-of-antibiotics?utm\\_source=newsletter+email&utm\\_medium=email&utm\\_campaign=medical+updates+-+daily&utm\\_content=2399746&utm\\_term=automated\\_daily](https://www.univadis.org/medical-news/596/Clinicians-do-not-recognisepotential-harm-of-antibiotics?utm_source=newsletter+email&utm_medium=email&utm_campaign=medical+updates+-+daily&utm_content=2399746&utm_term=automated_daily)

## **2. Neurotoxic effects associated with antibiotic use: management considerations**

Marie F. Grill (1) & Rama K. Maganti (2)

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British Journal of Clinical Pharmacology

Br J Clin Pharmacol / 72:3 / 381–393 / 381

2011

Antibiotics are among the most frequently used pharmaceuticals in both the inpatient and outpatient setting.

While these antimicrobial agents are generally well tolerated these drugs are not without their associated side effects, both dose-dependent and idiosyncratic in nature.

**While diarrhoea is a commonly associated adverse effect of many antibiotics, toxic effects on the central nervous system are perhaps much less recognised [1].**

**A danger for clinicians and patients alike, of not recognising neurotoxic effects of antibiotics is that the neurological manifestations of toxicity may be confused with a different neurological condition.**

Correspondingly, in cases of drug- induced encephalopathy, change in mental status may be ascribed to a metabolic abnormality especially in hospitalised patients.

**With greater education regarding these neurotoxic effects, medical care providers can learn to recognise toxic effects more readily and make medication adjustments as necessary since it is often a readily reversible process.**

**A high degree of suspicion is also essential for clinicians.**

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3175508/pdf/bcp0072-0381.pdf>

### **3. Prevention and management of drug-induced peripheral neuropathy.**

#### **Review article**

Olesen LL, et al. Drug Saf. 1991 Jul-Aug.

Authors

Olesen LL1, Jensen TS.

Author information

1 Department of Neurology, Aalborg Hospital, Denmark.

Citation

Drug Saf. 1991 Jul-Aug;6(4):302-14.

When symptoms of peripheral neuropathy appear, the possibility that they have been induced by drugs should be considered. A large number of drugs of all kinds, several of which are considered indispensable, have been implicated in peripheral neuropathy. A list of some of these drugs is provided. Neuropathy is a universal and dose-limiting factor during treatment with vinca alkaloids, but is otherwise a rare complication of drug therapy. Drug-induced peripheral neuropathy is almost always due to a dose-dependent primary axonal degeneration caused either by toxic reactions or by metabolic changes in neurons or their surroundings. The use of drugs should be restricted, especially in patients with a risk for development of neuropathy or with already existing neuropathy, e.g. patients with hepatic or renal failure, diabetes mellitus, or malnutrition. Patients should be given vitamins, prophylactically or therapeutically, which will sometimes allow a treatment to be continued. In other cases of drug-induced neuropathy the drug should be stopped. Reversal depends on the severity of the neuropathy, intensity and duration of the treatment and existence of causative cofactors, but generally the prognosis is good. While waiting for recovery physiotherapy is of importance, and when paraesthesia and pain are troublesome the patient should be treated with carbamazepine, imipramine or lidocaine (lignocaine).

PMID 1653573 [Indexed for MEDLINE]

I have read the full article and there are many drugs implicated. I have extracted what I feel is extremely important information from page 307 on the prevention of drug induced peripheral neuropathy:

First aim should be to improve knowledge about peripheral neuropathies and their causes.

Secondly we should improve the use of already available knowledge.

No drug should be used in the treatment of humans until it has passed experimental investigation without serious side effects. Even then late and unexpected adverse effects cannot be precluded.

<https://www.ncbi.nlm.nih.gov/m/pubmed/1653573/>

The examples above clearly speak for themselves and demonstrate that very little progress has been made in 27 years to protect patients from harmful, potentially permanent neurotoxic effects of antibiotics including quinolones.

**The warnings are not getting through to clinicians and hence to patients whose lives are often at risk unnecessarily.**

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As part of the review process please note the following:

**Having worked as a registered pharmacist for 27 years I guarantee that in 2013 none of my colleagues (many of whom are experienced pharmacists) and doctors that I saw (many) new that ciprofloxacin and other quinolones could cause such pain and suffering.**

#### **PIL discrepancies**

The patient information leaflet for levofloxacin warns against taking with NSAIDs and steroids whilst ciprofloxacin doesn't yet this is a class effect?

Copied from a levofloxacin PIL:

Non-steroidal anti-inflammatory drugs (NSAIDs)-used for pain and inflammation such as aspirin, ibuprofen, fenbufen, ketoprofen and indomethacin. **You are more likely to have a fit (seizure) if taken with Levofloxacin tablets**

Corticosteroids, sometimes called steroids—used for inflammation. You may be more likely to have inflammation.

<https://www.medicines.org.uk/emc/files/pil.4624.pdf>

<https://www.medicines.org.uk/emc/files/pil.3484.pdf>

**One consultant I met in 2014 thought that because I was given prednisolone (at the same time as ciprofloxacin) this was ok (and beneficial) - I quote from his clinic letter 'and she was on steroids anyway!' Doctors do not understand that giving steroids such as prednisolone can actually INCREASE inflammation and make a very bad clinical situation much worse. This was the same ill informed doctor who requested an open muscle biopsy and didn't appreciate how badly I had reacted to physiotherapy and acupuncture- the consequences of the biopsy were horrific.**

#### **NICE discrepancies**

There is a discrepancy between the use of quinolones and NSAIDs in NICE guidelines for the treatment of prostatitis and epididymo-orchitis as follows which has previously been pointed out to NICE and the MHRA by the Quinolone Toxicity Support UK group yet nothing has changed :

<https://cks.nice.org.uk/prostatitis-acute#!scenario>

Treat the pain:

Paracetamol and/or **ibuprofen (taken regularly) is recommended first-line.**

<https://cks.nice.org.uk/scrotal-swellings#!scenario:4>

Avoid quinolones in people with a history of tendon disorders related to quinolones, or a history of seizures or conditions that predispose to seizures.

Quinolones — **increased risk of convulsions with an NSAID.** Concurrent use should be avoided in people with epilepsy or with conditions that predispose to seizures.

#### **Adverse drug reactions vs side effects**

Most clinicians believe that once a quinolone antibiotic is discontinued adverse reactions/ side effects will disappear once the treatment is out of your system which is not the case as documented in SPCs and the BNF.

Clinicians do not understand the difference between a side effect and an adverse reaction and do not appreciate there are different types of adverse reactions which is extremely important when trying to understand the adverse reaction profile of quinolones which fit into many of the sub categories below. They're not just all type A!

**Type A - augmented**

Exaggeration of medicines normal effects at usual doses.

Includes unwanted reactions that are predictable and dose dependent.

May reduce in severity with time.

**Type B- bizarre/ idiosyncratic**

Not predictable.

Rare but cause serious illness & death

Susceptible individuals.

Often lead to withdrawal of drugs.

**Type C- continuing**

Dose and time related

Adrenal suppression by steroids.

**Type D- delayed**

Some time after use.

Leucopenia up to 6 weeks after lomustine

**Type E- end of use**

Withdrawal effects

B blockers, opiates, Z drugs, antidepressants.

**Type F- failure**

Unexpected failure of therapy.

Drug interactions.

St Johns Wort with COCs.

**Type G- genetic/ genomic**

Irreversible genetic damage.

Thalidomide and phocomelia.

**Type H- hypersensitivity**

Immune mediated

Response to a drug in sensitised patients.

Anaphylaxis (IgE mediated)- penicillins, Interstitial nephritis- amoxicillin

**Yellow Card Reporting System and quinolones (MHRA)**

Not fit for purpose particularly with complex situations like long term adverse reactions to quinolones.

App and website don't interlink.

Website doesn't include information sent separately via email regarding updates.

Too many different 'code numbers' used by the MHRA when reporting/ updating about the same primary issue.

No follow up from the MHRA even when symptoms are ongoing and multiple updates are sent in.

Unable to update original entries as prompted on the website- have to repeat a lengthy on line process or send separate emails. When people are unwell and in pain this reporting system is a complete turn off.

GPs are not keen to report adverse reactions involving drugs that they have prescribed and specialists won't do it if they haven't prescribed the drug- they tell you to go back to your GP and ask them to report it so in the end it doesn't always get reported by a clinician!

Extremely difficult to speak to senior staff members at the MHRA about real safety concerns regarding quinolones.

ADRs are massively under reported yet the MHRA don't make it easy to report/ update events.

They never give you a direct response to a direct question- evasive and sit on the fence.

When a new drug is licensed it's probably only been taken by a few thousand people and of those only a few hundred would have taken it for more than a year,

This is why post marketing pharmacovigilance is vital for detecting adverse reactions to quinolones so it should be made much easier for patients to report concerns, clinicians should be more willing to do this and the MHRA should follow them up.

### **Genetic testing**

This was discussed at the hearing and I would like to share my personal results which could be relevant to other sufferers and have a potential causal/ effect/ contributory link with adverse reaction to quinolones.

Having been seen by so many specialists over the past 5 years I've ended up under the care of a professor at the John Radcliffe Hospital who undertook gene testing which revealed a variant in NAV1.9 (encoded by the gene SCN11a). My case is being taken forward on a research basis so it may be something that the review could follow up with other victims who have suffered chronic pain with quinolones.

### **Final personal comments**

Please stop this crime against humanity and restrict quinolones which kill, maim, torture and ruin lives unnecessarily.

Many quinolones have been withdrawn from the market because of their side effect profile yet we still have licensed quinolones available with similar toxicity issues?

Quinolones work similarly to anthracyclines (chemotherapy drugs such as doxorubicin, daunorubicin and epirubicin) which interfere with DNA replication within bacterial and human cells.

Chemotherapy should never be used for mild infections/ suspected infections treatable with safer antibiotics.

No words can ever describe the pain and suffering ciprofloxacin has caused (and still does after 5 years) me and my family- only close family and friends who see my daily struggle for survival really understand.

Out of sheer desperation when traditional medicine hasn't worked (and sometimes made things worse) I foolishly and regrettably tried several alternative therapies which have had catastrophic consequences on my pain and mobility issues- Chinese herbal remedies (horrific), acupuncture, massage, homeopathy, many supplements.

We urgently need clear treatment protocols that do not cause more pain and suffering.

Risk is a function of **SEVERITY** and **FREQUENCY** and if drugs such as quinolones can cause permanent disability and death they are **HIGH RISK** and must be restricted.

I cannot tolerate medicines and foods which I could pre ciprofloxacin, I cannot sleep properly, I cannot exercise without severe consequences and I cannot live my life as I should at the age of 53.

I was a very active person 5 years ago who worked and lived a full on life pre ciprofloxacin - now I exist and struggle physically, mentally and emotionally.

Stop using these drugs unless there are absolutely no alternatives, educate healthcare professionals about the dangers and WARN patients about the devastating life changing consequences these drugs can cause.

Informed consent must be obtained prior to issuing these toxic drugs,

Put patient safety first not profits.

## **David Hallows, UK**

### Question 1

Not everyone who has been prescribed fluoroquinolones would have had an infection. I was prescribed these drugs for a suspected prostatitis infection in 2000.

Ciproxin was like an explosion going off inside my body. It quickly brought on Nerve damage, Joint pain, Tendon ruptures and Gastric problems. This has worsened over time.

My medical records list 5 other antibiotics that could have been prescribed.

In my particular case fluoroquinolones would never have been of any use. If this had been known at the time my life would have been very different.

In 2000 I worked full time as a factory operative. In 2001 I had to stop work as I had become a liability. What if I had fallen into a machine. Nowadays I need help with everyday chores.

### Question 2

For me there was no risk assessment about the use of ciproxin. At the time it was known that there was some risks.

I was told the side effects would stop 6 weeks after taking the tablets. What they did not tell me was the side effects could be permanent.

This risk was not assessed or explained.

### Question 3

Medical professionals recognizing side effects of fluoroquinolones.

Not to over prescribe. Guidelines state 4 to 6 weeks for prostatitis.

I was prescribed ciproxin for 19 weeks and told to take an NSAID.

As an unhappy spokesperson for the dangers of fluoroquinolones. My message is that we must take every measure possible to only prescribe safely.

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### My Story

I have also experienced devastating effects from taking Ciproxin. I started to suffer from severe pelvic pain after a routine investigation. I was told that this could be a suspected prostatitis and in November 2000 I was prescribed long term ciproxin.

I had a full health check before taking this drug and was in reasonably good health, in full time employment and taking regular exercise on a daily basis. I was 30 years old.

I was told I would need to take this drug long term 6 weeks at 2 x 500mg and 13 weeks at 1 x 500mg. The consultant also told me to take ibuprofen but I was unable to tolerate this painkiller as well as cipro.

There was no proven infection for prostatitis. Ciproxin did not help with my water works problem but it has left me with a number of other complaints. I have listed a few below

Peripheral Neuropathy – Moderately severe

Ulcerative colitis – with marked inflammation

Erosive Duodenitis with ulceration

Hiatus hernia

Thyroid problems

Joint pain

Ruptured Tendons

ringing in the ears

Jaundice

Oedema

Panic Attacks

Eye/vision disturbances

Headaches

Fluctuating blood-sugar levels

I lost quite a lot of weight. My coordination and concentration was very poor I stumbled on a daily basis and was only able to leave the house in a wheelchair.

My life was devastated and had become so restricted due to the side effects.

I had to stop work as I became so ill and wheelchair bound I was unable to look after myself at this point my partner was having to take care of me.

Although my symptoms started whilst taking ciproxin The Sheffield National Health Service turn a blind eye to this and told me cipro was a safe antibiotic. In January 2011 the NHS tried to section me under the mental health act stating that my poor health was due to self neglect.

The last 18 years have been very difficult my relationship broke down because of the severe impact these side effects was having on my quality of life I was unable to go on holidays or out for a meal.

I have tried to stay strong and with determination I managed to get out of the wheelchair and on to crutches and in 2010 I was able to walk short distances independently.

My diet is to eat plain bland food like boiled potatoes, carrots, cauliflower and poached cod. I take a liquid multivitamin as this is easy for me to digest.

My recovery started when I was referred to see a rheumatologists. I was tested for autoimmune diseases as my condition indicated that I could be suffering from one of these. All test came back clear but showed a number of vitamin deficiencies I was commenced on B12 injections and started to take a liquid multivitamin. Nerve conduction studies was only done on the peripheral nerves by the NHS. They showed a moderately severe peripheral nerve damage and a bone scan showed osteoporosis further blood test ruled out pernicious anaemia and there was no metabolic bone disorders causing the osteoporosis.

Recently I decided to see a neurologist and gastroenterologist in Germany. The results were unbelievable my stomach flora was still positive with bad bacteria I have type C gastritis, multiple vitamin deficiencies and food intolerances The comprehensive nerve conduction studies was showing moderately severe systemic nerve damage and the peripheral nerve damage is still progressive.

## **Marco Cardosi, Italy**

Il sottoscritto Marco Cardosi di anni 52, impiegato, a causa dei forti dolori per Calcoli renali iniziati dal mese di agosto 2016 e protrattisi fino al mese di ottobre 2016, si rivolgeva al medico responsabile dei ricoveri di una Clinica di Roma al fine di ottenere un ricovero.

Durante la degenza, iniziata in data 14 ottobre 2016, veniva sottoposto alle analisi ematiche e successivamente a "Urotac" che evidenziava la presenza di un Calcolo disceso in vescica e una Colite.

Le analisi effettuate non evidenziavano nessuna grave infezione in atto dovuta ai Calcoli né tantomeno alla Colite.

Anche le analisi precedenti il ricovero riportavano valori normali fatta eccezione per la presenza di "ossalati di calcio" nelle urine.

Le visite specialistiche effettuate dal Gastroenterologo e dall'Urologo refertavano le patologie diagnosticate.

Il medico responsabile, "Oncologo", decideva, **di sua iniziativa e senza che lo scrivente ne fosse a conoscenza**, di attuare una cura antibiotica per flebo a base del fluorochinolone "**Levoxacin**" ("**Levofloxacin**") e del farmaco **Metronidazolo**.

Al sottoscritto **non è stato fatto firmare nessun "consenso informato" sulla terapia prescelta** durante il periodo di permanenza in Clinica, in concomitanza delle infusioni dei predetti antibiotici, **cominciava ad avvertire forte debolezza e senso di disequilibrio in deambulazione** tanto che interveniva prontamente una dottoressa controllando la pressione e il battito cardiaco del tutto normali ma decideva di non interrompere la somministrazione dei citati antibiotici in questione.

Il giorno 21 ottobre 2016 veniva dimesso dalla Clinica con la prescrizione contenuta nel relativo "foglio di dimissioni" **di continuare ad assumere il "Levoxacin" ("Levofloxacin") anche a domicilio e senza nessuna indicazione della durata della cura.**

Lo scrivente però **continuava ad accusare forte debolezza e senso di disequilibrio in deambulazione** e per tale motivo si sottoponeva ad ulteriori accertamenti ematici, cardiologici, e doppler completi, tutti negativi, la visita otorina era senza evidenze di patologie in atto.

Visto il perdurare dei sintomi, il 19 dicembre 2016, era a visita da un neurologo dell'ospedale Santa Lucia di Roma.

A causa di ciò era costretto ad assentarsi dal lavoro per lungo periodo per tutti i mesi di novembre e dicembre 2016 soffrendo notevoli disagi che si ripercuotevano sulla vita sociale quotidiana.

Attualmente il sottoscritto continua a seguire la cura del neurologo ed uno dei 2 sintomi, la debolezza, è pressoché scomparsa; il senso di disequilibrio invece, seppur attenuato, è ancora presente in deambulazione.

### Risposte alle 3 domande:

1) La mia opinione sul ruolo di questi antibiotici è condizionata dalla esperienza vissuta da paziente e pertanto ritengo che questi farmaci debbano essere somministrati solo quando ci sia un comprovato pericolo di vita del paziente e non per i casi di infezioni di minore gravità.

2) I rischi associati, a mio parere, così come descritti in diverse fonti della letteratura medica, possono invalidare la vita dei pazienti in modo anche permanente sia a livello muscolo-scheletrico con la "rottura dei tendini" sia a livello neurologico con le patologie "neuropatiche"; peraltro ci sono anche da

considerare le tante "reazioni avverse" segnalate "a lungo termine", la mia opinione è che l'impiego terapeutico deve essere limitato fortemente.

3) Per l'uso sicuro, secondo me, dovrebbe essere ben compreso il meccanismo farmacodinamico in modo tale che si possano studiare valide contromisure atte ad eliminare il benché minimo rischio sia degli effetti collaterali sia delle cosiddette "reazioni avverse".

***Donato Iacovazzo, UK***

I am an Italian clinician working in London. I would like to attend the Public Hearing as a patient, having developed myself a peripheral neuropathy following a course of ciprofloxacin 4 months ago. I was not aware of this serious adverse event, and I was not warned about this neither by the prescribing physician nor the pharmacist. Despite having stopped the medication at the first signs of the disease, my symptoms evolved and have persisted to this day, significantly affecting my quality of life. I think the serious and debilitating adverse events associated with the use of fluoroquinolones outweigh their benefits in the setting of the treatment of non life-threatening infections. I do believe that these antibiotics should be reserved for use in case of severe and life-threatening infections and their use should be limited for in-patients. It would be important to raise awareness among physicians and pharmacists about the importance to warn and inform patients about these severe adverse events and how to recognize their early signs and symptoms.

## ***Sylvia Schmenk, Germany***

My name is Sylvia Schmenk. I am 43 years old and come from Hamburg, Germany. My story began on 30<sup>th</sup> October 2017 when I was prescribed Ciprofloxacin for diverticulitis. After only 3 days of taking the medication my symptoms already improved.

5 days after taking the first dose I experienced a seizure and collapsed (paralysis of the tongue, whole body trembling). I was taken into hospital and admitted for a week of tests. Further symptoms began appearing; neurological, cardiovascular, pulmonary, muscular, rheumatic, hormonal, metabolic, gastrointestinal. I suffered panic attacks and also hallucinations. My liver and kidney values were also negatively impacted. In total I can list almost 50 individual symptoms. My body was totally out of whack. I can provide an excel spreadsheet detailing all symptoms and their intensity over the last 6 months.

During the next 2 – 5 months the psychological symptoms began to improve but it was like a rollercoaster with the other symptoms. After eating chicken or red meat from animals treated with preventative antibiotics (used in industrial livestock farming) certain neurological symptoms incl. paralysis of the tongue returned. I changed by diet to exclude all meat other than strictly organic meat. After this step it still took 8 – 10 weeks to begin to feel better. It was impossible to predict how I would feel day-to-day. On bad days my body's reactions to the toxins were so extreme that I feared that they would kill me. I needed to be supported 24/7 by my family just to get through the day. Some nights were particularly frightening due to hallucinations, nightmares and shortness of breath.

All appointments that I had with doctors of traditional medicine failed to return any conclusive test results and I felt like my symptoms were not being taken seriously. Being ignored and not believed by those who should normally be able to help was an additional psychological burden. The breakthrough came when I visited a blood performance diagnostician and was diagnosed with a mitochondrial disorder.

It was only after 6 months that I slowly began to feel part of the real world again. By this time I had lost my job (I got sick during the probation period of a new job) and have been on sick pay since December 2017. Needless to say, the financial impact is also a great worry. The prospect of starting a new job, and the related stress potentially setting off the symptoms again, is a constant fear.

Due to this experience I am a shadow of my former self. I was always very sporty (captain of the handball team for 30 years), sociable and outgoing. I had a global sales role travelling all over the world, managing large teams of colleagues. The effects of this drug have been hugely devastating to all aspects of my life. Given the chance, and knowing what I know now, I would have taken a less intensive antibiotic instead of a drug of the fluorquinolone group. We must raise awareness of the dangers of this group of drugs.

## ***Axel Dastig, Germany***

Sehr geehrte Damen und Herren,

mein Name ist Axel Dastig und ich habe seit mehreren Jahren immer wieder Medikamente aus der Gruppe der Fluorchinolone von einem Urologen verschrieben bekommen. Der ausführliche Arztbericht liegt der EMA vor. In jener Zeit wurde ich immer kranker, habe immer öfter Hilfe bei Ärzten gesucht und musste feststellen, dass diese sich mit vielerlei Krankheiten auskannten, jedoch über keinerlei Kenntnisse von Medikamenten- Nebenwirkungen der o. g. Gruppe verfügten und auch nicht Willens waren sich ursächlich mit der breiten Palette meiner Beschwerden auseinander zu setzen. Erst viel später im Verlauf konnten mein Hausarzt sowie der Apotheker kausal feststellen, dass meine Behinderungen auf die wiederholte Einnahme von Fluorchinolonen mit schweren Nebenwirkungen zurückzuführen waren. Die Tatsache, dass für mich als Patient dieses Risiko weder von meinem behandelnden Arzt noch durch ausreichende Hinweise in den Packungsbeilagen für mich ersichtlich war, nahm mir die Möglichkeit selbst darüber zu entscheiden, ob ich dieses Medikament nehme oder nicht. Es wird nämlich nicht darauf hingewiesen, dass mögliche Schäden langwierig oder dauerhaft bestehen, wie es bei zehntausend Anderen und mir der Fall ist. Ich will nicht abstreiten, dass es in Zeiten von Resistenzbildung wichtig ist Antibiotika zur Verfügung zu haben. Allerdings werden Fluorchinolone, obwohl empfohlen, in der Praxis nicht als Reserveantibiotika verwendet. Es ist ein unhaltbarer Zustand, dass allein in Deutschland 33 Millionen Tagesdosen wie Hühnerfutter über die Bevölkerung verstreut werden. Obwohl man weiß, dass in den USA die Indikationen schon längst wesentlich einschränkt wurde und das Gefahrenpotential nicht überschaubar ist. Betroffene Patienten, wie wir, werden allein gelassen in einer Welt aus Schmerzen ohne Hoffnung auf ärztlichen Beistand, denn die Ärzte haben in der Regel keinen Behandlungsansatz. Junge, gesunde Menschen werden einfach krank, verlieren ihre Arbeit, ihr Haus, ihre Familie, ihr Leben. Ich kann nur für das Gesundheitssystem in Deutschland sprechen und dieses hat im Umgang mit diesen gefährlichen Medikamenten auf ganzer Linie versagt. Deshalb ist nun die EMA gefragt neue Richtlinien für den Einsatz von Fluorchinolonen auszugeben. Es muss dafür gesorgt werden, dass verantwortungsvoll mit diesen Medikamenten umgegangen wird. Es ist auch notwendig, die geschädigten Menschen ausfindig zu machen und ihre Erkrankung anzuerkennen, wie es in den Vereinigten Staaten schon völlig normal ist. Dort wird die Behinderung durch den Einsatz von Fluorchinolonen offiziell anerkannt und die Geschädigten können einen Schadensersatz erklagen, um ihre Pflege- und Therapiekosten zu finanzieren.

## ***Declan Waugh, Ireland***

Thank you for contacting me regarding the upcoming EMA public hearing for quinolone and fluoroquinolone medicines on 13 June 2018. In your correspondence you note that I have until the 1st June to make a modification to my statement. In light of this I wish to make the following amendment.

In my original statement, I mentioned the study by Pradhan et al (1995) which reported that the mean serum F levels was 11 µM, within 12h after an initial dose of ciprofloxacin [1]. However, if one examines the data for all subjects in this study it was reported that one individual (subject 19) had a baseline serum fluoride level of 1.3 µM and within 12h post treatment their serum fluoride level increased to 131µM, which is highly significant. Moreover, on day 7 post administration their urine fluoride level had increased to 14.8ppm. Among three other subject's urinary fluoride levels had increased to 7.6, 9.3 and 9.8 ppm respectively on day 7. Unfortunately, however, serum F levels were not measured in subjects for the same period, but clearly based on the urinary F concentrations serum F levels would have been significantly elevated.

It is well known that there exist genetic differences in individuals in how they metabolize drugs and they relate to the cytochrome P450 (CYP450) enzyme system. Of the CYP450 group of enzymes CYP2E1 is recognized as a key metabolic enzyme involved in the biotransformation and defluorination of fluoride-containing medications [2-3] including ciprofloxacin [4]. Legus et al (2002) reported that a high level of CYP2E1 activity will increase the biotransformation of drugs or compounds that undergo biotransformation [5]. Wandel et al (1997) reported that the biotransformation or liberation of F ions is related to the administered dose in the drug and the CYP2E1 level activity [6]. Stephans et al (1994) reported a 50-fold variability in CYP2E1 enzyme activity in humans has been observed [7]. It has been reported that CYP2E1 polymorphisms can cause the differences of interindividual drug metabolism and liver injury, or even severe adverse drug reaction [8].

One of the clinical implications of this is that interindividual difference in the susceptibility to fluoroquinolone adverse reactions may be directly related to the difference in the catalytic activity of CYP2E1. For example; a standard dose of ciprofloxacin may contain in the region of 36 mg of incorporated F. If just 10% of this is metabolised it will release 3.61 mg F per day in a 75kg person. However, for high metabolizers, the amount of F released will be significantly higher and may result in significantly elevated serum F levels as reported by Pradhan et al (1995). However, it is important to note that the age of the subjects in this latter study varied from 8 months to 13 years. CYP2E1 activity is low in infants and increases with age [2]. This may explain the high variability in serum F levels reported in this study. Pharmacogenomic variations in drug metabolism resulting in elevated plasma F levels and skeletal fluorosis in adults have also been reported with fluoride-containing medications such as voriconazole [9].

Overall, this highlights the urgent need to determine the pharmacokinetics and biotransformation products of fluoroquinolone medications and other fluorine-containing drugs, as well as the risk of acute or chronic F exposure.

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## ***Elizabeth Aitkenhead, UK***

In my view, fluoroquinolones have an important role to play in the treatment of infection, particularly as there is the growing issue of antibiotic resistance. However, due to the potentially very serious and ongoing nature of the side effects associated with this class of antibiotic, they should be reserved for cases where no other safe treatment options exist, and the risks should be carefully explained to the patient. There should also be research into why some people are susceptible to damage and others are not, so that both medical professionals and patients can make a more informed choice.

I have first-hand experience of the risks associated with fluoroquinolones, specifically Ciprofloxacin. I was prescribed it several times for urinary tract infections which persisted after treatment with Trimethoprim, and had no adverse effects. I was then prescribed it in September 2017 and suffered an adverse reaction which currently persists. My primary symptoms have been damage to my right knee and elbow tendons, middle-ear issues (fluid in the middle ear and retracted eardrums) and tinnitus, severe anxiety and depression, pains in my extremities and fatigue. I have lost a substantial amount of weight. This has had the broader effect of leaving me unable to work with the attendant financial impact. My views on the risks are that the potential severity is far too great to prescribe them where there are equally effective treatment options. For instance, from prior experience a course of Cephalexin would have resolved my UTI and allowed me to retain my life and health.

The key thing that would optimise the safe use of fluoroquinolones is increased awareness among general practitioners. After I became unwell and sought help, I was shocked to realise that none of the gps at my surgery were aware of any serious risks apart from perhaps tendon rupture in the over sixties group. None were aware of the updated US FDA black box warnings. The word "rare" was also used a lot. As far as I am aware, none of them reported my adverse reaction via the yellow card reporting scheme. My experience appears to have repeated itself across gp surgeries over the country as everyone similarly affected who I have interacted with has had much the same experience. With gps disbelief and reluctance to report, no wonder the prevalence of adverse reactions is still considered rare. Although I did manage to get my surgery to state an allergic reaction on my notes after contacting my practice manager, I have in the main been faced with disbelief and the consensus appears to be that I am simply suffering from anxiety. I have no reason to believe that there will be any hesitation on any of their parts in prescribing quinolones or fluoroquinolones in the future. This is why I think that this public hearing and its outcome are vital, in order to safeguard patients at future risk as well as making it easier for those already affected to receive appropriate help and support.

## **Mauro Saitta, Italy**

1) i think that they are used too much even for minor infections when less dangerous antibiotics could be used.

2)I think that the risk/benefit ratio is unfavorable. the fact that many people are not affected by this syndrome the first time they took a quinolone does not mean that they will not be affected the next time they take a quinolone. in my case, due to a trivial infection that could be treated with antibiotics of equal effectiveness but with zero risks, i was prescribed a quinolone which ruined my life, causing pathologies that will last for the rest of my life. i will never accept that my life ended thanks to some pills. following the assumption of the antibiotic, I began to suffer of:

- fibromyalgia
- peripheral neuropathy
- back pain especially in the lumbar with crackling and popping in the low back
- blurred vision
- dry eyes (i had to put punctal plugs)
- brain fog
- migrant joint pain
- chronic fatigue
- anxiety
- depression
- slow recovery after physical effort
- drowsiness
- herniated disk
- shortness of breath
- cartilage erosion
- low stamina
- tendon erosion
- cognitive impairment

even worse is that the post-fluoroquinolone disability is not a recognized syndrome neither by the health system nor by the doctors, who are not trained on this syndrome, so we are not recognized any help, no exemption, no facilitation , no invalidity pension.

3) i think that these antibiotics must be banned from the market, but i know that will never happen. One measure should be that these antibiotics must be prescribed only when there aren't no other safe alternatives. An other one should be informing consumers through clear and visible warnings on the packaging of the drug of the risk of incurring in serious and permanent side effects from which it will never be possible to heal.

## **Rosemary Venner, UK**

I would like to videoconference to tell the meeting of my disabilities caused by the administration of Ciprofloxacin in November 2015. One 500mg dose for cystitis caused intense pain below bottom left rib resulting in me being admitted to hospital and subsequently being wrongly diagnosed and treated with intravenous Ciprofloxacin for pneumonia. Blurred vision and tinnitus occurred on day two and remained for twenty-five months. Loss of balance remains and severe disability in not being able to board and travel by public transport to visit museums, cinema and shops in London as well as locally in Cambridge, Bedford and Milton Keynes. I am limited to local town centre and park by mobility scooter.

The previous day I had been shopping in Bluewater with my sister, wearing my high heels as usual for my high insteps. When I left hospital 22 days later I was in a wheelchair and when I arrived home I fell in the hall and realised I had no balance. Recovery is still incomplete. It took me three months to be able to walk without a frame, four months to be able to dress myself with underwear and some top clothing, and thirteen months to wear shoes with a small heel which cause back and instep pain. I still have no balance and cannot walk even slowly without aid. Having visited my dentist for six-monthly checks for a decade, he is shocked and concerned that tooth roots have been affected as for cases of mouth cancer treatment after I had the Ciprofloxacin, and he has removed nine teeth and prescribed two dentures since.

Doctors should be informed of life-changing side effects in some patients and only prescribe quinolones and fluoroquinolones for severe infection and with consideration and discussion with each patient.

-

Yellow Card Report Overview submission GB-MHRA-EYC 00140168

Although I was not fortunate enough to be selected to speak or attend the public hearing next week on this subject, I am told that I may submit further information on my devastating adverse reactions to Ciprofloxacin which have been ongoing since November 2015. My Yellow Card submission in May 2016 was followed up by ADR 23489689 subsequent update request in January 2017.

I am still seriously disabled by peripheral neuropathy causing loss of balance and lack of strength in limbs to support and save myself when falling. I still have to use a mobility scooter, a tri-walker for short distances and several walking sticks situated in various parts of the house to aid balance. I can walk up to ten yards unaccompanied but not unaided, and generally have someone with me to get me up if I do fall. Whilst the tinnitus and blurred vision did not reveal on any tests, both were in fact successfully removed by an ENT consultant in January 2018 while conducting investigations on my lack of balance: he performed the Epsley manoeuvre which did not reveal the problem but he was astounded that it instantly removed both tinnitus and blurred vision. He had never heard of that effect before and I am eternally grateful. My dentist says he has only seen my type of tooth root damage once before and that was in a patient who had chemotherapy for mouth cancer.

I still cannot wear my 3" heels which perfectly supported my high insteps for more than 50 years, cannot climb stairs, get on to public transport, visit all the galleries, museums and historic houses, travel to see grandchildren, go to shopping centres like Bluewater, Kent, as I did before having Ciprofloxacin administered first by one tablet and then intravenously in November 2015.

I remain optimistic and determined to live as successfully as possible but it would seem that no further improvement can be expected. This week I gave up £3,000 of the money saved for years for my funeral to adapt my ensuite shower which has been in a cubicle 8" above floor level for 24 years; despite having someone to help me out safely, I have twice fallen this year whilst descending from it so the work had to be done.

Thank you for your time and attention. Please, please take the adverse effects of this dreadful drug seriously and ensure that it is only prescribed to patients with serious infection and who are made aware of the potential side effects. I react to all medication prescribed and was an obvious case for avoiding it totally. Thank you for arranging the public hearing.

## ***Ursel Nowotny, Germany***

I'm a 59Years old woman. I've got Levofloxacin in October 2016 and a second time in September 2017. After the first time (10 Tabl, 1/day) I've got a Bizeps- and supraspintus tendinitis. Two month later I could't walk more than 200 - 300 meters, then I got heavy calf pain in both legs. I also got problems with my eyes, I needed new glasses. And I got panic attacks and a depression, extra systols and massiv brain fog. Until today I could not work. Next month I have an operation, where I get a prothesis for my knee. For this, I cannot come myself to the public hearing.

If I had knewed, from this medicine I can got persistent trouble, I've never, never have take them. But I did'nt know. I am very afraid, how my life will go on.

Please, will you take care, that not any person could get this horrible disability. In Germany there is no ICD 10 Code like they have in America. Why in Europe there ist no Flourchinolne assoziated disability? What shall I and other People do? We've got no benefit at all, what shall we live from?

1. I've got FC for a normal bronchitis, it does'nt help. I only got the side effechts. If I'm ill between live or death, I never will take FC one more time!
- 2: I never believed, that I coul be the one from 1000, who got this persistent side effects.
3. Only give FC when there ist no other option!!

## **Richard Pyne, UK**

1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?

Vital for severe infections, but not for CPPS/Prostatitis, which in 95% of cases is non-bacterial and does not lead to further/life-threatening complications.

I have come to this view due to the continuing, and severely disabling, adverse drug reaction, that I have suffered, since I took Cipro in early 2016 for Prostatitis.

They are being overused casually, with needlessly catastrophic effects in a significant number of cases.

Unfortunately, neither patients, nor prescribing medical professionals, in large number, seem to be aware of this.

2. What is your view of the risks associated with quinolone and fluoroquinolone use?

They are substantive and greatly underappreciated by medical professionals. Patients and their families are not being given informed consent. Both I and my family were not.

I have Autistic Spectrum Disorder. We now have research that leads us to believe that people with this are particularly vulnerable to Fluoroquinolones.

The National Institute for Clinical Excellence, NICE, state in their Clinical Knowledge Summaries, with regards to the treatment of Chronic Prostatitis with ciprofloxacin, levofloxacin, and tetracycline:

"Both guidelines identified a meta-analysis that pooled data from three RCTs (n = 215) that assessed the effectiveness of ciprofloxacin, levofloxacin, and tetracycline. A second more recently published meta-analysis, which pooled data from two trials included in the first meta-analysis discussed above, found that antibiotics were no more effective than placebo for treating CP/CPPS [Cohen et al, 2012]."

If, as the FDA has said, Ciprofloxacin is not safe to be prescribed for a few days, to patients with acute bacterial sinusitis, acute exacerbation of chronic bronchitis and uncomplicated urinary tract infections, "because the risk of these serious side effects generally outweighs the benefits", then how is it safe to be prescribed for 4-6 weeks for Prostatitis, a condition less severe than those/at little risk of life threatening complications, when it is no better than a placebo, according to said clinical research quoted by NICE, and where no evidence of infection is found in 95% of cases.

Even if we are missing something here, informed consent must surely be given.

I quote my test results here, "Microscopy is not suggestive of infection. Routine culture not performed"

Yet Cipro was still prescribed without any warning of any potential ADR's, in the written words of the urology consultant, "to cover any underlying prostatitis".

The Cipro did not even help with the prostatitis.

I now have a multiple ongoing, life-changing and debilitating symptomatology.

My family and I find this unacceptable.

After suffering my severe ADR I found out that there were many other people who had also suffered a similar reaction. Many of these people were also in the United Kingdom. The commonality between these people and the overlapping symptomatology, speaks of a real, serious and severe medical syndrome/condition. However it appears to be hiding in plain sight.

Personal evidence of the more than substantial under-reporting of adverse drug reactions to fluoroquinolones, is found in the fact that my family is aware of at least three men who have had an

adverse drug reaction to ciprofloxacin, who were prescribed it for prostatitis, by the very same urology department, at the very same hospital, in the east of England. One of them was myself, another one has had a severe and life denuding reaction, and the third is a family acquaintance who spoke to us after hearing about my story. He only reported it to his doctor, the hospital and the MHRA Yellow Card Scheme after finding out about what had happened to me. If he hadn't heard my story, he would never have reported his reaction. If you extrapolate this for the whole country then it may give you an idea of the kind of numbers we could potentially be dealing with. This is just one department in one hospital. Consider also, all of those people who have had an insidious and slowly unfolding reaction to ciprofloxacin, who have not realised what the cause of their health problems is. Their numbers will appear in no governmental statistics. Also please factor in those who have had a reaction and didn't/haven't actually reported it.

3. In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?

Medical professionals need urgent notification/education on the severe risks involved. There appears to be a severe vacuum of knowledge here.

They should be restricted to cases of life-threatening infections only. Not used for CPPS/Chronic Prostatitis, under any circumstances.

Patients must be given informed consent of the risks involved by medical professionals. Whenever they are used.

More research is urgently needed into why some people react so badly.

People with ASD may be particularly vulnerable to this class of drug and they must not be prescribed it unless their life is at risk.

Recognition of the reality of Fluoroquinolone Toxicity syndrome/Fluoroquinolone Adverse Reaction Disease/Fluoroquinolone Acquired Disability

Treatment modalities/pathways to be developed for people suffering with it.

Urgent alteration of NICE Clinical Guidelines for fluoroquinolones and prostatitis. They are currently failing patients with catastrophic results.

## **Elizabeth Pyne, UK**

1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?

Quinolones and fluoroquinolones are vital 'in extremis', but must not be used for less serious, non-life threatening conditions such as CPPS/Prostatitis. The risks of serious, long lasting side effects from the drugs clearly outweigh the benefits. They are being overused casually with needless and catastrophic effects. It is in all stakeholders' interests that they are targeted carefully and appropriately.

2. What is your view of the risks associated with quinolone and fluoroquinolone use?

The risks are greatly underestimated by medical professionals. There is little or no discussion about the nature of these drugs with patients and their families and thus no informed consent.

How can a drug which may result in permanent nerve and musculoskeletal damage (and more) be prescribed so casually for non-serious conditions? The FDA has said that Cipro should not be prescribed to patients with acute bacterial sinusitis, acute exacerbation of chronic bronchitis and uncomplicated urinary tract infections 'because the risks outweigh the risk of serious side-effects generally outweigh the benefits'.

I quote my son's MSU test results, "Microscopy is not suggestive of infection. Routine culture not performed"

Yet Cipro was still prescribed with no warning of any potential ADR's, in the written words of the urology consultant, "to cover any underlying prostatitis".

My son has ASD and it is the case that those on the spectrum are often more sensitive to drugs. The medical profession seems largely unaware of this.

My son's ongoing symptoms include, CNS/ANS symptoms, dreadful insomnia, breathing difficulties, aches, muscle weakness, difficulty walking, nerve pain, skin damage, vision damage, muscle fasciculations, involuntary spasms, twitches and photo toxicity.

Cipro has had a severe and traumatic effect on his physical and psychological health. He now stays with me and has weekly support from Social Services. He has changed from an active person who regularly walked several miles a day and went swimming to someone who rarely leaves the house. He has felt suicidal and has been a very serious concern to his family. Our lives have been shattered.

His father passed away in 2016. My son had to be pushed in a wheelchair to his father's hospital room over six months after he took Cipro because he could only walk a few yards.

I am also aware of at least three men who have had an adverse drug reaction to ciprofloxacin, who were prescribed it for prostatitis, by the same urology department at the same hospital, in the east of England. One of them is my son, the second has had a severe and life changing reaction to it, and the third is a family acquaintance, who spoke to me after hearing about my son's story. If he hadn't heard my son's story, he said, he would never have reported his adverse reaction.

Even if patients report their severe adverse drug reaction to the hospital, as my son and I did in March of 2016, the hospitals don't appear to be acting appropriately, or taking patients seriously enough. We were told by the hospital that they had discussed my son's case in their clinical governance meeting. However, despite this, they appear to have made no alteration to their prescribing procedure, with regards to giving patients informed consent of any potential ADR's. This, we believe, is happening all over the United Kingdom. Patients who do report adverse drug reactions are being treated as little more than statistical outliers. They are not.

We quote below from our family acquaintance. Please note the dates:

"Regarding our other conversation, I have looked back at my notes and I was prescribed Ciprofloxacin on 18/10/16, 500mg twice daily for 4 weeks. It was probably the 19th before I took the first one. I stopped taking it on the 23rd, in my notes I have written:

"Stopped taking Ciprofloxacin because of side effects – Indigestion / reflux, Joint pains and pins and needles (ankles & knees), dry eyes, general lethargy and feeling of being unwell / depressed".

I also remember this issue of twitching in my feet and hands which was the final trigger for me to stop. When I saw the consultant at the end of October we discussed Trimethoprim as a possible alternative to Ciprofloxacin in the future but it was not prescribed. I.e. the course of antibiotics was just abandoned."

Our family acquaintance has told us that no mention was made to him of any potential side effects, just as in our case. We can only presume that our case was not seen as relevant enough to the hospital to consider informing patients of any potential ADR's going forward.

The hospital also told our complaints advocate that there had been no reports of issues with ciprofloxacin currently in the UK. Considering what we now know, we are baffled as to why they would make this statement.

Consider also, all of those who have had an insidious and slowly unfolding reaction to ciprofloxacin, who have not realised, both as we speak, and in the past. Their numbers will appear in no MHRA statistics. Also please factor in those who have had an ADR, know it, but have never reported it. The iceberg sits mainly below the surface here.

3. In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?

Medical professionals need urgent notification/education of the risks involved.

Fluoroquinolones restricted to serious life-threatening conditions.

When prescribed, the risks should be clearly discussed with patients.

Patients should be asked if they have taken the drug previously as side effects can be cumulative. Medical records should be checked.

Patients with Autistic Spectrum Disorder may be vulnerable to this class of drug. They should not be used unless life is at risk.

Full recognition of Fluoroquinolone Toxicity Syndrome.

Treatment modalities and pathways to be developed for FTS.

Urgent alteration of NICE clinical guidelines as they are currently completely inadequate.

**Daniel Fine, UK**

1. *What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?*

2. *What is your view of the risks associated with quinolone and fluoroquinolone use?*

3. *In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?"*

1) *My view is that while quinolones may have a role in treating serious conditions, they are currently massively overprescribed and misunderstood.*

My experience with them started in October last year when I went to the doctor after suffering some mild groin pain for around five weeks. After around thirty seconds consultation she diagnosed me with 'suspected epididymitis' and prescribed me ciprofloxacin 500 mg twice a day for one week.

I believe further tests should have been done to determine whether epididymitis was likely before prescribing the drug, as I hadn't presented with other symptoms and didn't have any risk factors for this disease. Researching after the fact, it's become clear to me that the pain was most probably stress related yet I was given a powerful antibiotic which, I only found out later, is supposed to be a last-line of defence. Even if this infection was probable, other antibiotics should have been prescribed first, like doxycycline, an antibiotic I had taken before that is associated with far less risks.

Regardless I took the ciprofloxacin for six days before realising I was experiencing the side effects which I have detailed in my answer to the second question. I think my experiences with this drug, and many others like me, could and should have been avoided. When quinolones are given in cases like mine, where the infection is either, not proven or not serious, the risks far outweigh the benefits and other avenues need to be considered first.

2. I think the risks are too often underestimated by medical professionals. When I was prescribed ciprofloxacin neither the doctor nor the pharmacists warned me of any of the side effects. The drug caused tendonitis, muscle weakness and nerve damage mainly in my legs. I went from being a fit and healthy 25 year old and a strong hiker, to essentially unable to walk within two weeks of taking Cipro. For four months I was housebound and struggled to even go upstairs and answer the door. My parents had to essentially become my carers putting a huge strain on my relationship with them, my mental health and my career.

I would never have imagined that antibiotics could cause these side effects that so drastically reduced my mobility, so despite waking up on the second night after starting the course with pain in my ankle, I rationalised the pain (I thought I kicked a wall) and kept taking them. I believe with greater awareness of the risks associated with quinolones, cases like mine can be greatly ameliorated or avoided altogether. Over the last few months I've often thought back to that moment and how much damage I could have prevented had I been warned about the possibility of tendonitis. The doctor told me that she was aware of the risk but thought it was so unlikely in under-60s that it wasn't even worth mentioning.

This has to change! Had the doctor been more aware of the risks she might not have prescribed them to me and likely would have warned me of the risks.

3. In order to optimise their safe use, I think at the very least the risks need to be properly flagged for doctors and pharmacists. I know that in America they have a black box warning on these drugs, I think we should have something similar, and I hope you will also consider changing the rules so they are not available to General Practitioners without referral and subsequent monitoring by a hospital.

Either way we need greater awareness of the side effects so that doctors can better weigh up the benefits and risks to using them and can properly warn patients when prescribing. Since suffering adverse reactions, I've spoken to many doctors who had heard of ciprofloxacin causing these kinds of side effects, but all talked about it as a hypothetical, none of them seemed to really consider that this could happen to one of their patients.

When responding to my complaint, the doctor stated that she didn't think it was necessary to warn me as I am under 60. I think this idea needs to be challenged, patients of all ages can and have suffered serious ADRs from quinolones. So if there is greater awareness of their risks, and we could have some way of limiting them to serious conditions, then I believe they could be used much more safely.

## ***Fekete Zoltán, Hungary***

I ate Cifran 500mg, 2+5 pieces. These are only SINCE the Cifran:

- strong joint problems: i can't eat:
- purin-include foods as all of meats/all of zoolite: fat, etc. = all ache
- all of legumes = mainly fingers ache
- all of dairy products (caseine?) = neck- and knee ache or fingers
- arachidon acid-include foods as egg or offals = all ache, mainly what i use for moving
- natrium-nitrit / natrium glutamat (preserved foods)
- i can't ejaculate fully mainly on the left side (after the first piece of Cifran) - left spermatic deferent?  
= frustrated life in every minute and ache in left ball
- strongly probably i have IR: darker eyesight after every sugar include food, mainly pear or melone or "too many" carb
- strong tinnitus on right side - i cant sleep and live! and worse hearing at the same time already
- worse eyesight basically (less sharpness for example)

I can't eat withouth self-destruct, please help. I can't do the IR diet and these others together - i don't want goin to be diabetes! The doctors don't help, they don't believe to me, but see me to stupid.

i can't buttoning my shirt or use the shoe lace withouth ache. Things are going from bad to worse.

***Nicholas Rohlfes, Germany***

1. Fluorquinolones can be very dangerous, it is prescribed way too often. It should only be prescribed if no other medication helps
2. Very high, your life can be ruined from this medication just after 2 tablets my life has changed and now, half a year later it is still there. My visual abilities decreased a lot.
3. better warning notes! only prescribe quinolones if they are really necessary.

**Robert Reinbach, UK**

1. My view is that quinolones and fluoroquinolones have an important role in treating patients with infections associated with this antibiotic, and that they remain a useful drug at the 'controlled' disposal of the practitioner.

2. My view of the risks are laid out from first-hand experience of the adverse effects this drug can bring. From musculoskeletal issues, damage of the nervous system, associated impact on mental health and sensory processing.

3. I believe the damage, both permanent and temporary (some symptoms have lifted), can be mitigated through a better understanding of the drug within the practise and its associated drug interactions. As an example, it took over 6 months for my GP to slowly conclude, and only through process of elimination, that the antibiotics may have had some part in my decline of health. In the meantime, one symptom (painful cracking joints) was attempted to be alleviated through prescribing me steroids. Before I took the drug, my new found vigilance saw me research any potential interactions and I easily uncovered that many people report steroids can cause as much damage as NSAIDs when interacted with fluoroquinolones. Also through the 6 month period, I was sent to psychiatrists to be put on SSRI's as I was told it was a bout of severe anxiety that was causing these symptoms. Again, I am very grateful I chose not to start the treatment.

I really would like to stress the importance of an inclusive and genuine understanding of the patient's anxieties and concerns. A dismissive approach to the patient's suspicions of this drugs role in their health can be influential, particularly if they are suffering from any mental health disorders that this drug is temporarily inducing. This is step one.

## ***Charlotte Kanon, The Netherlands***

### question 1

In April 2017, my non-life-threatening bacterial infection was treated with Levofloxacin with a course of 6 weeks.

The infection is gone but my normal life now as well.

So many bizarre symptoms appeared after that cure where I still camp with them today.

It has destroyed my life.

It started with weakness in my legs; I almost could not walk. And quickly spread in symptoms such as;

Huge hair loss, burning muscles, muscle pain, loss of strength, brainfog, loss of balance, eye problems, tremors, Fatigue, exhaustion, chest tightness, chest pain. Skin rash.

And to this day, new symptoms still appear that are worse than the previous ones.

### question 2

The risks you run with the use of FQ's are horrible and unusually insignificant.

I have also never been warned about the risks.

When I knew what to expect, I kindly thanked.

I regret every day that I have taken those pills and that my life now consists of pain, exhaustion and fear.

Fear of the future.

Fear that it gets worse.

I am a single mother and I take care of my 8 year old daughter.

Every day I have to disappoint myself and her in my abilities.

I can not bring her to school by bike.

I can be happy that I can dress myself.

The normal things that I did until a year ago are still a vague memory.

Everything costs so much power, effort and disappointment and that of a prescribed drugs.

### question 3

I think the risk is so great that it is never safe to use FQ's.

Also in cases of life and death not.

Because if you have survived a life-threatening illness after a treatment of fq, then there is the risk of a lifelong disability.

Medication must be safe at all times.

# Pharmaceutical companies

## ***Speaker 14. Leo Plouffe, Bayer AG***

Bayer AG appreciates the opportunity to contribute to the discussion initiated by PRAC on the use of fluoroquinolone antibiotics.

### Question 1

The development of fluoroquinolones in the 1980's offered highly effective new treatment options to patients and physicians for potentially life-threatening bacterial infections.

The safety and efficacy of Bayer's ciprofloxacin and moxifloxacin have been demonstrated in clinical trials involving more than 90 000 patients and extensive experience in clinical practice among an estimated 800 million patients. Ciprofloxacin and moxifloxacin are now generic and are manufactured and supplied in Europe by hundreds of companies.

In Europe, ciprofloxacin is indicated for 22 different types of infections that range from life-threatening to less severe. The prescribing information states that official guidance should be considered and these do generally not recommend ciprofloxacin for less severe infections if there are treatment alternatives. Moxifloxacin is indicated for 5 different types of infections if other initial treatment options are not considered appropriate.

When used according to approved information for prescribers and established medical treatment guidelines, ciprofloxacin and moxifloxacin meet a significant medical need for patients and their healthcare professionals, who rely on these medications as an option for the treatment of specific bacterial infections.

### Question 2

The safety profiles of ciprofloxacin and moxifloxacin are well described and reflect experience gained through the treatment of an estimated 800 million patients.

When used in line with the approved prescribing information, which references medical treatment guidelines, the benefits of treatment outweigh the risks for the vast majority of patients. However, treatment with fluoroquinolones may result in severe adverse drug reactions. These are described in the prescriber information and in the patient information leaflet ("PIL").

Bayer has been in continuous scientific dialog with health authorities and medical communities to ensure that safety information is up to date. The aim of this joint effort is to provide the necessary guidance for the assessment of the benefit and risk of treatment for the individual patient. This dialogue is improved by including the patient perspective.

Bayer is open to further clarifying the nature and duration of some of the adverse drug reactions in the prescriber information and the PIL.

### Question 3

Bayer continuously monitors the benefit-risk profile of ciprofloxacin and moxifloxacin, taking into account all adverse events reported from patients, healthcare professionals, clinical trials, and scientific literature.

Clear communication about benefit and risk of treatment is essential to optimize the safe use of these products for the individual patient. Bayer has been and continues to be supportive of enhancing this communication. This includes potential updates to the prescriber information and the PIL, and a communication to healthcare professionals (DHPC).

Bayer sees an opportunity to collaborate with PRAC in working with patient groups and academic centers specializing in patient safety communication, to further improve the content and format of the PIL, and to identify novel ways to distribute it.

Bayer is open to discuss with PRAC further measures that may be generated following this public hearing.

## Healthcare professionals and academia

### **Speaker 15. Jamie Wilkinson, Pharmaceutical Group of the European Union (PGEU)**

1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?

They are an important class in an increasingly resistant environment. They should be used according to indication / diagnosis / sensitivity and not as first-line if not indicated for it, unless risk-benefits are outlined to patients and appropriate measures / cautions adhered to.

2. What is your view of the risks associated with quinolone and fluoroquinolone use?

The perceived benefits should outweigh the risks. However, we have a preference for retaining access / option to dispense quinolones/fluoroquinolones in primary care with additional measures so as not to restrict the supply of potentially useful / helpful medicines from patients who would benefit from them. If additional measures are needed, their design and implementation should be subject to meaningful end-user testing / consultation, and not constitute an unnecessary a restriction or withdrawal.

3. In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?

- Guidelines / protocols / (locally) agreed formularies
- Pop-up messages on dispensing software
- Medication review in addition to counselling
- Indication on the prescription / access to indication / shared access to records
- Rapid diagnostic tests
- Patient card on the outside of packaging

For more information on how pharmacists can contribute to the safe, effective and rational use of medicines please see PGEU's Best Practice Paper on Pharmacovigilance and Risk

Minimisation: <https://pgeu.eu/en/policy/15:pharmacovigilance.html>

## **Speaker 16. Graham Bothamley, European Respiratory Society (ERS)**

Question 1: view on the role

Important antibiotic in respiratory infections

Longer term use in multi drug resistant (MDR)tuberculosis

An essential drug in MDR TB

Question 2: risks

Reported risk of cardiac ion channels (QTC) prolongation

Risk of tendinitis (especially in the elderly)

General risks

Question 3: further measures

Drug companies should report on denominator

Are the data sufficient to black box drug for reporting?

Follow-up of patients (standard 2 year treatment plus a minimum of a 2 year follow-up for MDR-TB)

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In terms of antibiotic stewardship and evidence-based use, I will refer to the following ERS guidelines:

1. Management of COPD exacerbations (<https://doi.org/10.1183/13993003.00791-2016> and <https://doi.org/10.1183/13993003.02265-2016>)
2. Management of adult bronchiectasis (<https://doi.org/10.1183/13993003.00629-2017>)
3. Management of hospital-acquired pneumonia and ventilator-associated pneumonia (<https://doi.org/10.1183/13993003.00582-2017>) with ESICM, ESCMID and ALAT
4. Guidelines for the management of adult lower respiratory tract infections (including community acquired pneumonia) (Clin Microbiol Infect 2011; 17 (Suppl. 6): 1–24)

Concerns about masking TB with empirical use of fluoroquinolones for respiratory infections:

Change KC et al. Eur Respir J 2010; 35: 606-13. doi: 10.1183/09031936.00104209.

Wang J-Y et al. Thorax 2006; 61: 903-8. doi: 10.1136/thx.2005.056887

TB

Long-term outcomes of patients with extensively drug resistant TB (resistance to fluoroquinolones and injectable drugs as well as rifampicin and isoniazid):

Pietersen E et al. Lancet 2014; 383: 1230-39 only 16% favourable outcome cf. Mitnick CD, et al. NEJM 2008; 359:563-74 - the dangers of anecdotal evidence.

In terms of risks:

Cochrane Database Syst Rev 2013; 6:CD004795. doi 10.1002/14651858.CD004795.pub4

QTc: <http://www.ingentaconnect.com/content/iuatld/ijtlid/2012/00000016/00000002/art00002#>  
(Torsade des pointe (cardiac arrhythmie) 5 case reports of 117 million patients treated with

moxifloxacin) and about 6 ms QTc prolongation (ECG measurement); importance of other drugs used simultaneously

REMOX trial and its publications

Tendinitis: <https://www.ncbi.nlm.nih.gov/pubmed/24762232> (89 case reports, by 2014)

Stephenson AL et al: Drug Saf 2013; 36(9): 709-21. doi: 10.1007/s40264-013-0089-8 (one report regarding age >60 [Wise BL, et al. Am J Med 125(12): e23-1228.e28. doi: 10.1016/j.amjmed.2012.05.027.]); role of concomitant steroids)

ERS survey: order of adverse effects for grade 3 or above - tendinitis (most common), QTc, photosensitivity; rare seizures, motor co-ordination, anxiety

General considerations:

Due to drug, due to condition for which drug was given or non-causative association (role of randomised controlled trials vs. anecdotal evidence)

Drug levels variations (Weiner M et al. Antimicrob Ag Chemother 2018; 62: e01802-17. <http://aac.asm.org/content/62/5/e01802-17.full.pdf+html> and genetic marker of drug transporter gene, also affecting rifampin levels)

**Speaker 17. Mary McCarthy, European Union of General Practitioners (UEMO)**

1. What is your view on the role of quinolone/fluoroquinolone in the treatment of infections?

As a general rule, broad spectrum antibiotics should not be prescribed as first-line treatment in the management of infections. In general practice quinolones are avoided because of the risk of increasing antibiotic resistance and because in many cases, antibiotics may not be needed.

2. What is your view of the risks associated with quinolones and fluoroquinolone use?

Quinolones and in particular ciprofloxacin, are associated with an increased risk of C Diff infection which is becoming increasingly common in frail, elderly and hospitalised patients.

There are also significant side effects including joint pains and nausea, tendon damage, which may be permanent, and neuropathies.

3. In your opinion what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?

Avoid use of these antibiotics as first-line treatments because of increased risk of MRSA and C Diff infection

Reserve use for isolates where sensitivity is confirmed and there are no lower-risk alternatives

Avoid use with

- duloxetine (increased drug levels)
- Clozapine (neutropenia)
- Phenothiazine (arrhythmia)

Avoid in pregnancy and in Paediatrics

There are few indications for quinolones/fluoroquinolones in primary care. There may be an argument for restricting their use to specialised care

**Speaker 18. Neal L Millar, Institute of Infection, Immunity and Inflammation, University of Glasgow, UK**

What is your view of the risks associated with quinolone and fluoroquinolone use?

I am an academic orthopaedic surgeon based at The university of Glasgow , Scotland and an international expert on tendon injuries and the basic science of tendinopathy. It is well recognised within the clinical tendon communities that fluoroquinolone use can result in significant clinical injuries to human tendons with an increasing burden of disease on the EU health care system.

Tendinopathy and the concurrent tendon ruptures have been linked to the use of certain fluoroquinolone medications such as ciprofloxacin (CPX) with a reported incidence of approximately 10-15 cases per 100,000 fluoroquinolone prescriptions. Risk factors for fluoroquinolone-induced tendinitis and tendon rupture are renal failure, corticosteroid use, diabetes mellitus, older age and hyperparathyroidism.

CPX has been shown in laboratory studies to lead to tendon cell hypercellularity, irregularly arranged fibres and glycosaminoglycan content. It induces extracellular matrix changes and increased fibre distance, decreased diameter and changes in the tendon structure.

This is a hugely debilitating conditions for patents exposed to fluoroquinolone induced tendon disease which in many cases is life changing.

I have treated many such patients and my insight into the clinical and basic science of how this condition may be mitigated would provide useful insights to the committee and how strategies should be put in place to warn patients of tendon issues and hopefully understand how to treat fluoroquinolone induced tendon disease.

## **Speaker 19. Ber Oomen, European Specialist Nurses Organisations (ESNO)**

### **I - GENERAL**

#### **Introduction to antimicrobial resistance (AMR) as a global public health issue and how nurses take the responsibility on this matter:**

Antibiotic resistance is now a major threat to public health; without urgent, coordinated action, the world faces the prospect of a post-antibiotic era in which common infections which have been treatable for decades are fatal again. As outlined in the UK Review on AMR, it is predicted that without policies to stop the worrying spread of AMR, today's already large 700,000 deaths every year would become an extremely disturbing 10 million every year by 2050, more people than currently die from cancer. Fluoroquinolones are among the most widely used oral antibacterial drugs however resistance to fluoroquinolones is extremely widespread. According to the WHO 2014 report, there are countries in many parts of the world where treatment of urinary tract infections caused by E. coli with fluoroquinolones is now ineffective in more than 50% of patients.

#### **The need to introduce stricter measures on the use of all antibiotics, including quinolone and fluoroquinolone antibiotics:**

Antibiotics need to be used more sparingly in both humans and animals in order to reduce the unnecessary use that fuels drug resistance. Currently, huge quantities of antimicrobials are wasted globally on patients who do not need them. A transformation is needed in the way antibiotics are consumed and prescription. By conserving antibiotics, the development of resistance could be slowed and the usefulness of existing products could be preserved for longer. Rapid diagnostic testing would help tremendously in the reduction of unnecessary prescription of antibiotics. The introduction of rapid diagnostic tools to identify the strain of bacterial infection would allow the implementation of stricter measures on the use of antibiotics. Legislation could be introduced to ensure antibiotics are only administered when needed.

#### **The importance of raising awareness on this issue among nurses related to quinolones and fluoroquinolones:**

- Global public awareness of AMR must be improved across the board to ensure prudent use of antibiotics. Awareness is necessary to guarantee patients and farmers do not demand antibiotics unless necessary and that clinicians and veterinarians do not prescribe antibiotics unnecessarily.
- Clearly, raising awareness and setting goals can be very effective. In NHS England, the introduction of national reduction targets for MRSA was associated with a 56% decline in cases between 2004-2008.
- Nurses are pivotal in tackling resistance as they can enhance infection prevention and control in hospitals.
- Furthermore, by establishing positive relationships with patients, nurses can encourage the responsible use of antibiotics and educate patients on the dangers of AMR.

#### **The need for centralised reporting of incidences of AMR in hospitals and share a proposal:**

Surveillance is crucial to provide the information on which to base policies. Without a standardized system for recording the prevalence of AMR infections and AMR deaths, the full scale of the problem cannot be properly understood and therefore cannot properly be responded to. For example, the European Centre for Disease Prevention and Control estimated that there were 25,000 deaths directly caused by multi-drug resistant bacteria in Europe every year. Whilst this figure is shockingly high, it is likely to be a gross underestimate since the estimation was made by looking at the figures for just five

multi-drug-resistant bacteria. The report itself stated that the figure of 25,000 was an underestimate. Given how closely they work with patients, nurses are best positioned to register the incidence of AMR in hospitals and to provide a better understanding of the seriousness of this public health problem.

ESNO is calling for Europe-wide register in which every case of an antibiotic resistant infection is recorded, with details of the bacteria which caused it and which antibiotics the bacteria was resistant to. The register would also include information on whether the patient died due to this infection.

The majority of people who die from a bacterial infection die from sepsis so even if simply every case of sepsis was recorded, it would record the majority of the AMR-related deaths.

This centralised reporting system could be based on the Datix incident reporting software currently used by the NHS in the UK. This electronic reporting system can be used by a range of healthcare professionals including nurses, healthcare assistants, clinicians, paramedics.

### **How overuse of antibiotics, particularly quinolones and fluoroquinolones in husbandry can threaten applicability in human health:**

There is a continuing threat to human health from imprudent use of antibiotics in animals: it is therefore absolutely vital that the extensive and unnecessary use of antibiotics in agriculture is reduced. In particular, fast progress is needed on banning or restricting the use in animals of antibiotics that are vital for human health. Since the publication of a report on AMR in 1998 by the House of Lords Science and Technology Committee, the ban of fluoroquinolones in veterinary medicine has been recommended. The report states "potent agents important to human medicine, such as the fluoroquinolones, deserve extreme economy of use in veterinary practice."

In order to implement appropriate laws banning the use of antibiotics in husbandry to any other purpose than to combat disease, investment into effective non-antibiotic alternatives is required.

## **II - NURSES RELATION AND IMPACT**

### **How nurses are currently using quinolones and fluoroquinolones:**

Nurses see that quinolones and fluoroquinolones as broad-spectrum antibiotics are often used in the health practice and widely prescribed to treat respiratory tract, urinary tract, gastrointestinal tract, bone, joint and skin infections and they are used as a last-resort antibiotic due to increasing resistance. They at one hand see that the medication is often described with the experience that it also triggers further cases of AMR and have an extra concern on this aspect such as monitoring side effects.

### **The nurses view on the risks associated with these specific antibiotics:**

These antibiotics can induce adverse events and this is a major concern to nurses because of great impact on the health status. With addition side effects nurses need to monitor not only the disease the patients treatment for but also has to monitor the effect of the medication, it is a double issue to address and tripled by handling if side effects occur due to the medication. Such as the gastrointestinal tract (nausea and diarrhoea) and central nervous system (headache and dizziness) as most common and extra as cardiovascular system (QT interval prolongation), musculoskeletal system (tendinitis and tendon rupture), endocrine system (glucose homeostasis dysregulation), renal system (acute renal failure) and the CNS (seizures)

This make it for the nurse, who is the first line professional in relation to the patient and the disease, to explore of deterioration of a change in the overall health status of a patient is due to the disease or the medication. With the use of quinolones and fluoroquinolones nurses are extra alert on this or should be very alert and educated.

So far we have not found publications on this from the nurses practice and we wonder if this included in Continued Professional Development (CPD) program but we believe it is in pockets but not enough researched yet because Fluoroquinolones have also been strongly associated with MRSA acquisition. Nurses need to be aware of the following aspects:

- Since they are broad-spectrum antibiotics, they should be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective;
- indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant to last-resort broad-spectrum agents, and also kills normal commensal flora, increasing the risk of Clostridium difficile infection.
- England achieved substantial reductions in C. difficile infection after introduction of a national programme to improve infection control measures and reduce use of high-risk antibiotics, particularly fluoroquinolones;
- Exposure to levofloxacin or ciprofloxacin has been found to be a significant risk factor for the isolation of MRSA;

In addition, we should not forget that changing a medication, one to another is not such a thing like a single activity on a switch board. If you look at the great concerns on the special designed Facebook groups on quinolone and fluoroquinolone, these are the same reflection nurses have to deal with in daily practice, "Have you been Floxed"

#### **How nurses support minimization of adverse reactions with quinolones and fluoroquinolones:**

- Nurses should be aware and if possible with those with prescribing authority, avoid use of quinolones and fluoroquinolones unless there are no alternative treatment options;
- Ensure patients with infections requiring quinolone and fluoroquinolone antibiotics are isolated to prevent outbreaks of infection in the hospital;
- Ensure patients are educated on the risks of adverse reactions of these antibiotics;
- Support the doctors in ensuring the use of interacting medications is avoided – for example, co-administration of certain nonsteroidal anti-inflammatory drugs with quinolones increases the likelihood of seizures;
- Inform the doctor about the doses and timings of other medications;
- Ensure they are familiar with the patient's pre-existing symptoms, for example;
  - Seizures usually involve a susceptible population with underlying CNS disorders, such as epilepsy hence patients with a history of a seizure disorder should receive quinolones with caution;
  - Overexposure to quinolones should be avoided in patients with type 2 diabetes;
  - Quinolones should be used with caution among elderly patients receiving corticosteroid therapy due to risk of tendinitis;
  - Alert other health professionals if an adverse reaction is suspected, taking into account the temporal relationship between antibiotic initiation and symptom onset – since nurses are most closely involved in direct patient care, they are best placed to identify adverse drug reactions;

**Current practices in nursing that are intended to support patients who are prescribed with these antibiotics:**

- Immediately informing patients and relatives about the infection with bacteria that is either resistant to other antibiotics or is unknown and hence explaining the need for the patient to take quinolone or fluoroquinolone antibiotics;
- Nurses should ensure patients are aware of the possible consequences of taking quinolones and fluoroquinolones;
- Patients should be advised to stay informed on those bacteria were it is proven they have developed a resistance system;
- Maintaining a trusting relationship with the patient to ensure patients voice their concerns about possible adverse reactions such as tendon pain;
- Carrying out safety monitoring, for example electrocardiograms (ECGs) and blood glucose level monitoring;

**Measures in place in nursing guidelines and hospital protocols that can contribute to more specific risk minimisation measures:**

Nurses, and especially those in advanced positions, should take a lead or be involved with educational interventions such as mandatory training which covers adverse events for these antibiotics. Implementation of standardised monitoring systems for patients receiving quinolones and fluoroquinolones and a reporting adverse events to monitor the incidence and identify further action required to minimise incidence and by preference a overarching European system because the issue is not limited to one nation.

*Angelica Lindsey-Clark, Research Consultant, PA International Europe and Ber Oomen Executive Director ESNO, 04-4-2018*

## **Speaker 20. Paul Tulkens, Louvain Drug Research Institute, Belgium**

As an academic person, involved in the assessment of activity and toxicity of antibiotics since many years, I'd like to present a balanced view on the current situation with the fluoroquinolones.

1. What is your view on the role of quinolones and fluoroquinolones in the treatment of infections?

Fluoroquinolones [ciprofloxacin, levofloxacin, moxifloxacin, and to a lesser extent ofloxacin [racemic mixture] and norfloxacin [weaker activity]] are an important part in our armamentarium for the treatment of infectious diseases. Being highly bactericidal, they possess a spectrum of activity well suited for the treatment of many severe infections (ciprofloxacin is more oriented towards Gram-negative organisms and moxifloxacin towards Gram-positive organisms). They are often the only alternative for an oral administration and/or early parenteral to oral switch. They may often be used in monotherapy. While resistance cannot be ignored, (i) it varies between organisms and the fluoroquinolones preferentially directed against them; (ii) it is not unique to fluoroquinolones. Using fluoroquinolones for treatment of mild infections is more debatable but using any antibiotic (thus even "first line" ones) in any infection carries also its own risk of selecting resistant organisms.

2. What is your view of the risks associated with quinolone and fluoroquinolone use?

Fluoroquinolones have well known toxicity risks described in details (with incidences) in the corresponding SmPCs. It is essential for the prescriber (i) to take into account the contraindications and warnings (some are specific) before prescribing any fluoroquinolone; (ii) to warn the patient about potential (but rare) long term toxicities. Many of the adverse effects of fluoroquinolones can be minimized (or mitigated) by taking contra-indications into full account and by avoiding their use in patients with known risk factors. Adverse reactions (sometimes severe and limiting) are also seen with many other antibiotics recommended as "first line" for the same indications that those for which fluoroquinolones may be prescribed

3. In your opinion, what further measures could be taken to optimise the safe use of quinolones and fluoroquinolones?

The prescriber and the patients must be clearly informed of the potential risks of each fluoroquinolone, including its contraindications, in order to prospectively detect patients for which toxicity risk would exceed the expected benefit.

->Rewording and strengthening the warnings about side effects in the SmPC may be one way to go.

Fluoroquinolones could be restricted to indications where they have a clear role (such as severe infections) and warn against (or remove their indications) for mild infections.

->The SmPC could better indicate more clearly that the use of a fluoroquinolone should be reserved for severe infections and/or situations where first line antibiotics cannot be used.

## **Speaker 21. Florian Wagenlehner, European Association of Urology (EAU)**

1. Quinolones and fluoroquinolones have unique pharmacokinetic and pharmacodynamic properties that are advantageous in the treatment of various infections, such as complicated urinary tract infections and genital infections. High bactericidal activity, a high volume of distribution and a high bioavailability characterizes their pharmacological properties. In certain infections, such as chronic bacterial prostatitis they are the most appropriate agents for treatment. For oral treatment of uncomplicated pyelonephritis they are also important, as comparator agents would only be oral cephalosporines, exhibiting a high risk of underdosing. Quinolones and fluoroquinolones no longer should play a role in the treatment of benign uncomplicated cystitis or for prophylaxis. Empiric treatment is significantly limited by the increasing resistance rates against fluoroquinolones.

2. There are three definite risks of quinolones and fluoroquinolones that need to be addressed:

- 1.) Toxicity for the individual host.
- 2.) Collateral damage on the microbiome of the individual host.
- 3.) Emergence of resistance against quinolones and fluoroquinolones and cross-resistance against unrelated antibiotics in the society and the environment.

3. The use of quinolones and fluoroquinolones need to be restricted to severe and complicated infections. This needs to be implemented in guidelines, but also probably regulated by authorities. If administered for treatment in complicated cases, the dosage needs to be sufficiently high, to decrease emergence of resistance. To investigate parameters or biomarkers that could help identify patients at risk for toxicity would be important.

***Speaker applications not allocated a slot:***

***Arturo Di Girolamo, Italy (Infection Control Infectivologist)***

Quinolones and fluoroquinolones are widely used for the treatment of different infections, especially for respiratory and urinary ones.

Besides the known risk of adverse events associated with their use, e.g. tendinopathies, there is currently a major risk for the diffusion of antimicrobial resistance that, in some Countries, like Italy, Greece, East European, represents a major concern.

In (not only) my opinion, the safe use of such antimicrobials should be better implemented in terms of prevention of ATB resistance, by strenghtening the information about this risk and by limiting their inappropriate use, even by sharing information to the great public.

***Beatrice Golomb, US (University of California)***

We have heard by email, and survey, from more than a thousand individuals who have experienced fluoroquinolone (FQ) adverse effects (AEs), and I have published on potential for serious, persistent and progressive multisymptom FQ AEs.

Based on vast experience with potential life-changing side effects:

1. FQ use should be restricted to life-threatening or organ threatening illness where there is no viable alternative. Although many people tolerate FQs, the extreme and life-altering nature of severe adverse effects, in absence of a test to reliably determine who is at risk, occurring even in people who have tolerated the drug previously, underscores that these drugs should be reserved for settings in which there is no alternative.
2. Studies to ascertain whether genetic or other markers can reliably distinguish who is at risk might allow broadened use of these agents, with greater safety; but for many adverse effects that operate through shared mechanisms, there are many pathways to vulnerability.

**Damaris Pfeiffer-Boehme, Germany (Heilpraktikerin, zert. GAPS-Therapeutin)**

1. My patient, born 1950, was given Tarivid for prostatitis over 20 yrs. ago which did nothing to heal his condition, rather ruined his health and life until today despite all the measures he's been taking by going to doctors and health care professionals all over Germany. He has spent all his money looking for cures and because of his ill health has not been able to hold any job for long over a decade. Before taking Tarivid he was a very active, slim, athletic and clever person, fluent in German and English – after Tarivid he's a wreck:

His immune system is compromised and he suffers from high nitrosative stress as shown by blood works, his brain has been badly damaged with lots of consequences (as shown by a PET scan) and he has taken on a lot of weight being unable to control it. Some more effects Tarivid had on him: His mental activity, thinking process, sleep-wake cycle and memory are severely impaired, he suffers from anomia, excruciating pain from muscle spasms, back pain, insomnia, drowsiness/stupor, constipation, hormonal imbalances etc. etc. etc.

He reacts paradoxically to many therapeutic interventions – many measures proven to powerfully help „normal“ patients will do the opposite for him (i.e. Vitamin-C-intravenous drip will make his pain worse – for days and weeks etc.).

Another patient (elderly lady over 80yrs.) of mine was twice given Ofloxacin for a „trivial“ bladder infection as the FIRST course of intervention, which, considering the risks, is simply incredible and goes to show that many doctors (the ones describing it in this case were in ER on a weekend) don't have a clue what they are doing. This lady had the sensation she was crazy and going to die, so the first time she stopped taking the medication after 2 pills and the next time (I'd told her NEVER to take that stuff again, but the next time, not being aware it was a „flox“ again, she took it once more) had those sensations after only one pill. In her case we were able to contain the side effects and restore her to her former self, thanks to the fact she stopped taking this stuff at once.

2. My patients' and my own view are that this kind of medication is far too toxic and dangerous to be given to any patient. The risks far outweigh the benefits from what I can see in my patients and from others affected. Since the conditions this unreasonably hazardous drugs were prescribed for could have been alleviated or cured with the help of natural therapies or at least antibiotics with far less dangers of such immense side effects, the possible harm and harm done stands in no relation whatsoever to the expected usefulness of the drug.

3. How, please tell, can such a toxic drug ever be safe??? As long as there is no proven remedy for the terrible side effects that let affected people suffer horribly for the rest of their lives this toxic stuff needs to be banned. If not, the use has to be SEVERELY restricted and skulls printed on the package and insert.

I'd like to include some more details about my patient's history:

H. G., born in Febr. 1950, was treated with Tarivid (Oxofloxacin) in 1987 for prostatitis. This treatment did not do anything to cure his original disease but started ruining his health right away up to this day for over 30 years now, in a manner that's hard to imagine.

What's even harder to believe is the fact that though at the time he was able to connect with numerous other victims (he posted advertisements over weeks, paying them himself), who also suffered immensely, he/they were not able to get any compensation/reparation payments from the distributor HOECHST even after writing to the BGA (Bundesgesundheitsamt) in 1987 and by taking the matter to court.

Alas he is not in possession of his documents of the trial any more since he felt he had no chance that justice would prevail and he felt cheated by what may have happened behind closed doors (bribes? In whatever form...).

Since he finds it very hard to remember details and his memory is very impaired by the drug, it's very difficult to reconstruct what really happened around the trial more than 20 years ago.

Also he no longer has any contact to the other victims and years ago he told me that many of them have died meanwhile.

How can drugs as dangerous as fluoquinolone still be on the market after so many years – and that without a drastic warning – after having wrecked and destroyed so many people's health and lives, even killing them.

Back to my patient: Having been a very clever, fit and athletic kind of person, bilingual in German and English, he now found himself unable to hold a job any longer due to the side effects he suffered beginning with the treatment in 1987.

Now over 30 yrs. later he has tried every conceivable treatment – mainstream and alternative – with no lasting positive effect whatsoever. He is still suffering on an permanent basis, has no money and in a desolate state altogether.

Symptoms my patient has been experiencing for the last 31 years:

- Impaired blood circulation, especially in the head and brain region though not confined to this area
- Impaired brain activity in many regions of the brain (as shown by PET scan – which he had to pay for himself from his meager means!!!) – this is a scandal if I ever saw one!
- Excruciating spasms in his muscles (mostly neck and back, but not only there)
- His thyroid is malfunctioning since that time,
- His sleep pattern is a mess – he cannot fall asleep in the evening, rather in the early morning hours, and then his sleep is far from refreshing or regenerating.
- He cannot concentrate, gets lost in his thoughts, cannot remember, is searching for words etc.
- Though having been fit and athletic as a young man he is grossly overweight and simply cannot lose weight whatever he attempts to do.

He's been telling me, that this is a phenomenon he has seen quite often with victims of Tarivid: Men taking on a lot of weight while women lost weight – both groups at a very unhealthy level

- His blood pressure is all over the place with no way to control it.
- He is suffering from impaired function of his kidneys and liver
- And of course he is in a very sorry state mentally and psychologically.
- He suffers from nausea and bouts of dizziness as well as disturbed consciousness
- I'm sure I've forgotten some points...

It's unbelievable that a patient in such a sorry state is left to fend for himself without any compensation from the manufacturer.

Another elderly lady patient of mine has twice been given a flouquinolone for a simple UTI as a first choice(!!!), the first time she felt like she was going to die after only 2 or 3 pills, the second time she had the sensation of going mad after just one or two pills. Each time she came to me right afterwards and we were able to alleviate her discomfort.

What I just cannot fathom is the fact, that such dangerous stuff is given like candy endangering unsuspecting patients and not warning them that they could suffer from horrible side effects for the rest of their lives and that after more than 30!!! years no one so far has seen the necessity for banning such a poisonous drug or even putting an effective warning label on it.

I recommend to take such dangerous drugs off the market immediately and to use less antibiotics in general, since we have a problem with resistance coming our way already at present and I feel it´s a scandal that still AB´s are given like candies though there are lots of alternatives out there – though maybe not patentable...

Please add these few notes to my statement already made. Thank you so much!

***Nuno Pereira, Portugal (Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos, Direção-Geral da Saúde)***

1. In our view quinolones and fluoroquinolones role in the treatment of infections is very restricted and they should not be used for treatment of common community or hospital acquired infections.
2. There is accumulated evidence that quinolones are associated to myriad of side effects and FDA already issued an alert related with this subject. Additionally quinolones and fluoroquinolones have a big impact on antimicrobial resistance being one of the classes with a bigger ecological impact. Also the risk of C.diff infection associated with the use of quinolones is known and a matter of concern in several countries

**David Healy, UK**

1. The quinolones and fluoroquinolones can be effective anti-infectives but can also cause considerable physical and mental difficulties. The academic case for both the benefits and harms is compelling.

2. In my capacity as a mental health professional I have treated a number of patients with mental reactions to fluoroquinolones that have been misdiagnosed leading to inappropriate treatment that aggravated their problems. I have a colleague, a senior academic in family medicine, who has also been badly affected.

3. I believe these drugs should come with appropriate warnings so that at the first hint of problems treatment can be switched to something else, and treatment would be restricted to conditions where the use of these drugs can be better supported. In daily practice I see fluoroquinolones being used as first line treatments for trivial conditions in a manner that should not be happening. I routinely tell anyone I know who is likely to end up on an antibiotic they should declare an allergy to fluoroquinolones, as otherwise they are likely to be put on them.

As an active participant in RxISK.org we regularly get reports of individuals affected by quinolones. But linked into this it is worth noting that we get a large number of problematic reactions to doxycycline also.

The broader problem is educating doctors and others to the idea that problems do happen and patient efforts to alert them to this should be heeded.

## **Charles Bennett, US (Southern Network on Adverse Reactions (SONAR))**

Revised product labels for the quinolones disseminated in the United States, and the FDA's Drug Safety Communication (<https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm>), state that serious side effects associated with fluoroquinolones outweigh benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections. Safety warnings were added as Boxed Warnings (the strongest FDA warnings) to labels for fluoroquinolones in 2016.

[<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm513183.htm>] FDA review ad found that fluoroquinolones when used systemically are associated with disabling and potentially permanent serious side effects that can occur together. SONAR identified fluoroquinolone association with severe neuropsychiatric toxicity, including depression, inability to perform activities of daily living, suicidal thoughts, suicidal actions, completed suicides, confusion, clouded thinking, and severe and diffuse pain. [Kaur K J Community Support Oncol. 2016 14(2):54-65]. Neurotoxicity can occur shortly after or months after fluoroquinolone use. Neurotoxicity, psychiatric toxicity, muscle pain, and disability can persist for years. These toxicities are described in 210,000 FDA event reports. [Kaur K et al, JCSO 2016] Over 120 fluoroquinolone-associated suicide attempts or completed suicides associated with fluoroquinolones are reported, with 45% occurring within 2 weeks of drug initiation. [under review] Our research identified certain genes associated with neuropsychiatric syndromes.

[<https://www.sciencedirect.com/science/article/pii/S095362051830284X?via%3Dihub>]. All patients, providers, and pharmacists who dispense fluoroquinolones should be registered. Revised labels should include Boxed Warning information from the United States, and that severe persistent neuropsychiatric toxicity can occur.