PHARMACOVIGILANCE/POST MARKETING SURVEILLANCE NEWSLETTER

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Fluoroquinolones and the risk of disabling and potentially irreversible side effects

EDITOR'S

We express appreciation to our numerous stakeholders who are working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to making quarterly newsletters available to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of medicines and reporting of Adverse Drugs Reactions (ADRs). This edition of the newsletter focuses on Fluoroquinolones and the risk of disabling and potentially irreversible side effects

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions.

Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; pharmacovigilance@nafdac.gov.ng, fdic@nafdac.gov.ng) will be most appreciated.

Thank you for your relentless efforts towards strengthening Pharmacovigilance System in Nigeria.

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Text any DRUG RELATED PROBLEM to the SHORT CODE 20543 (For free on MTN, Glo, Etisalat and Airtel) for action by the Pharmacovigilance Centre.

Fluoroquinolones and the risk of disabling and potentially irreversible neurological and muscular (Neuromuscular) side effects.

Fluoroquinolones are some of the most commonly prescribed antibiotics worldwide. Their common use is due to their broad antibacterial spectrum of activity against Gram-positive, Gram-negative and mycobacterial pathogens as well as anaerobes. Fluoroquinolones contain a quinolone parent compound with a fluorine atom attached at the 6th position and often by a piperazinyl group attached at the 7th position.[1] They inhibit bacterial replication by blocking their DNA replication pathway. Their effectiveness against a broad range of bacterial infections is boosted by their good oral absorption and ability to penetrate tissues throughout the body, including the central nervous system.

Fluoroquinolones are available in both oral and parenteral formulations and are usually prescribed in short treatment courses. They are generally safe for most people but side effects include gastrointestinal disturbances, skin reactions, nervous system effects, bone, muscle and connective tissue effects.[2] In recent times, there has been grave concerns about the disabling and long-term impact of some adverse reactions induced by fluoroquinolone therapy. These disabling and potentially permanent side effects involve tendons, muscles, joints, and the nervous system. The side effects include tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders and impaired hearing, vision, taste and smell.

Tendon damage (especially damage to Achilles tendon) can occur within hours of starting fluoroquinolone treatment or up to 6 months after discontinuation of treatment. The risk for Achilles tendon rupture is increased within the first month following exposure to fluoroquinolones. Persons at increased risk for Fluoroquinolone-associated tendinopathy include those 60 years and older, non-obese persons, patients with kidney disease, lung, kidney, and heart transplant patients and patients with a history of concurrent use of glucocorticoids[3].

Generally, Fluoroquinolones should not be used in patients who have had serious adverse reactions associated with the use of quinolone or fluoroquinolone medicines. Patients should be advised to stop treatment with a fluoroquinolone antibiotic at the first sign of a side effect involving muscles, tendons or joints and the nervous system.

International Actions

United States Food and Drug Administration (USFDA)

The seriousness of fluoroquinolone antibiotics induced side effects became formally recognised when in 2008, the US (FDA) announced the first strong alert about the side effects of fluoroquinolone drugs, including tendon rupture and irreversible nerve damage.

This was just the first of a series of such strong alerts. A warning about nerve damage, specifically peripheral neuropathy, associated with the use of fluoroquinolone antibiotics was added in 2013. In 2016, the USFDA warned about the risk of disabling and potentially permanent side effects involving the tendons, muscles, joints, nerves and central nervous system. These side effects could occur together in the same patient; a syndrome recognised as Fluoroquinolone-Associated Disability (FQAD). A boxed warning (FDAs strongest warning) was revised to address these safety concerns[4].

In 2018, the FDA published a drug safety communication regarding hypoglycaemic coma and mental health side effects with fluoroquinolones. The safety communication was as a result of a comprehensive review of the FDA's adverse events reports and case reports published in medical literature. The FDA required class wide labelling changes to fluoroquinolone antibiotics. Mental health side effects including disturbance in attention, disorientation, agitation, nervousness, memory impairment and delirium were to be separately listed from other central nervous system effects. Additionally, the FDA required the blood glucose disturbances subsection of the labelling of all systemic fluoroquinolones to explicitly reflect the potential for risk of coma with hypoglycaemia.[5] Persons at increased risk for hypoglycaemia include older people and patients with diabetes who are taking medicines to reduce blood sugar. When considering a fluoroquinolone therapy, healthcare providers are required to find out if patients are taking a diabetic medicine and also if they have low blood sugar or symptoms of it while taking a fluoroquinolone[6].

The USFDA advised that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.[7]

European Medicines Authority (EMA)

Subsequent to the US Food and Drug Administration (FDA) Drug Safety Communication published in July 2016, the EMA began a safety review of quinolone and fluoroquinolone antibiotics incorporating the views of patients, healthcare professionals and academics. The review, finalized on 15th November 2018 concluded that the marketing authorisation of medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended. The use of the remaining fluoroquinolone antibiotics should be restricted. Restrictions on the use of fluoroquinolone antibiotics mean that they should not be used to:

- treat infections that might get better without treatment or are not severe (such as throat infections);

- treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis; for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used

The European Union endorsed the recommendations of the EMA and issued a final decision on 14th February 2019 that is legally binding and applicable in all EU countries.

Health Canada

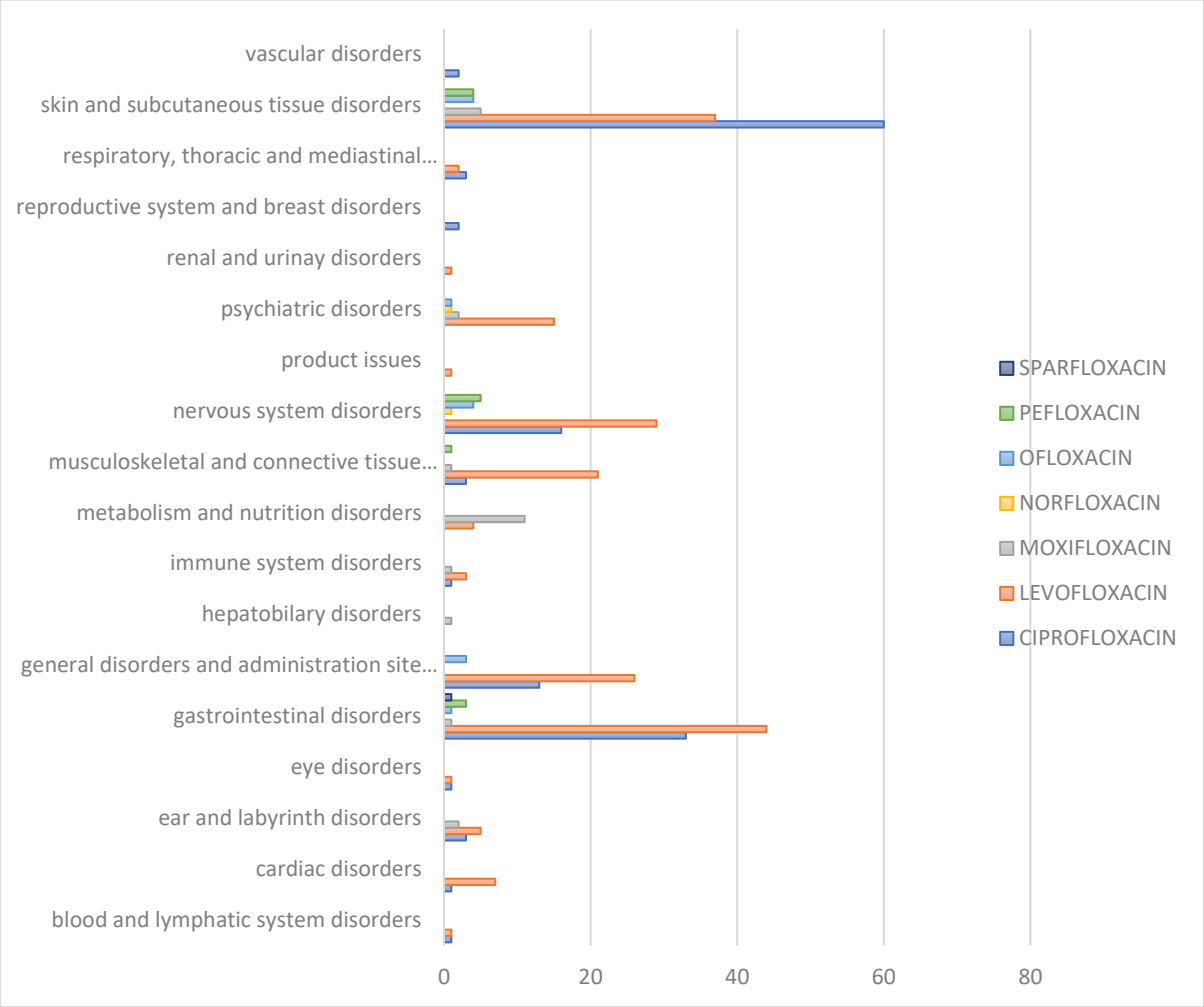
Health Canada in January 2017 similarly warned healthcare professionals of rare cases of disabling and persistent serious adverse reactions including tendinopathy, peripheral neuropathy, and central nervous system disorders reported for fluoroquinolones when used systemically (i.e. taken by mouth or by injection). Amongst other recommendations, healthcare professionals were reminded to consider the potential for disabling and persistent serious adverse events when choosing to prescribe a fluoroquinolone.[8]

Quinolones and Fluoroquinolones induced ADRs in the NPC database

From 9th September, 2004 to 31st July, 2019, the NPC database has a total of three hundred and eighty- nine (389) (1.66%) suspected adverse events caused by fluoroquinolone reported and documented in the NPC ADR database. The reports cover seven fluoroquinolone antibiotics namely Ciprofloxacin (139 reports, (35.73%), Levofloxacin (197(50.64%), Moxifloxacin (24(6.17%), Norfloxacin (2(0.51%), Ofloxacin (13(3.34%), Pefloxacin (13(3.34%) and Sparfloxacin (1(0.26%).

The types of adverse events classified according to system organ classes were nervous system disorders, ear and labyrinth system disorders, musculoskeletal and connective tissue disorders, metabolism and nutrition disorders etc. as seen in figure 1.

Figure 1: system organ classes of reported events



Although fluoroquinolones were reported as the suspected drugs in these 389 ICSRs, 84.06% of the patients concomitantly took at least one other drug. Table 1 shows therapeutic categories of concomitant drugs taken with reported fluoroquinolones. The major therapeutic category of concomitant drugs taken was antituberculosis drugs reported in 173(44.47%) ICSRs. Majority of the antituberculosis drugs were taken concomitantly with levofloxacin (148) and Moxifloxacin (23). Levofloxacin is part of the recommended treatment regimen for tuberculosis in the National Tuberculosis Programme.

In fifty-seven (57(14.43%) ICSRs, the patients were reported to have taken concomitant medicines belonging to two (2) or more therapeutic categories. Therapeutic categories grouped as 'others' include antidiabetics, antipsychotics, anticonvulsants, antidepressants, electrolyte/ minerals, antifungals.

Table 1: Reported concomitant drugs

	reported suspected drugs							
concomitant drugs therapeutic category	**CIP N = 139 (35.7%)**	**LEV N =197 (50.6%)**	**MOX N = 24 (3.2)**	**NOR N= 2 (0.5%)**	**OFL N = 13 (3.3)**	**PEF N = 13 (3.3)**	**SPA N = 1 (0.30**	**Total ICSR N= 389 (100%)**
analgesics	15	5	0	1	0	4	0	**25 (6.4)**
antibacterials	18	5	0	0	0	2	0	**25 (6.4)**
antibacterials, analgesics	18	2	0	0	0	2	0	**22 (5.6)**
antituberculosis	2	148	23	0	0	0	0	**17 (4.4)**
antibacterials, others	9	2	1	0	0	1	0	**13 (3.3)**
antimalarials, analgesics	9	1	0	0	2	0	0	**12 (3.1)**
cardiovascular agents	3	5	0	0	2	1	0	**11 (2.8)**
antimalarials	3	4	0	0	2	1	0	**10 (2.6)**
others	5	4	0	0	0	0	0	**9 (2.3)**
vitamins	2	4	0	0	1	1	0	**8 (2.1)**
antibacterials, antimalarials	3	2	0	0	0	0	0	**5 (1.3)**
respiratory tract agents	3	1	0	0	0	0	1	**5 (1.3)**
antiretrovirals	2	1	0	0	1	0	0	**4 (1.0)**
antimalarials, others	2	1	0	0	0	0	0	**3 (0.8)**
Analgesics, others	1	1	0	0	0	0	0	**2 (0.5)**
non reported	44	11	0	1	5	1	0	**62 (15.9)**

CIP = Ciprofloxacin, LEV =Levofloxacin, MOX = Moxifloxacin, NOR = Norfloxacin, OFL = Ofloxacin, PEF = Pefloxacin,SPA = Sparfloxacin

Three hundred and twenty-nine (329) patients (84.58%), reportedly received their medication from hospital pharmacies. The reported indications for use included conditions for which fluoroquinolones are not recommended such as Cough/catarrh/sore throat (7(1.80%), fever 6(1.54%), malaria 4(1.03%). Table 2 shows reported indications for fluoroquinolones.

It is recommended that fluoroquinolone antibiotics use should be limited to serious bacterial infections where their benefits outweigh the risks, and to which there is no better alternative antibiotic. 'Table 2 shows the indications of various reported classes of fluroquinolones. Tuberculosis was the most common indication 169(43.4%), this was followed by bacterial infections 48 (12.3%), enteric (Salmonelosis)fever 32 (8.23%), Prophylactic use 13 (3.34%), and urinary tractions 13 (3.34%). However, 24 (6.13) cases were reported without indication of use.

Table 2. Reported indications for fluoroquinolone use

Number of ICSRs	**Suspected drugs**							
Indications	**CIP N= 139 (35.7%)**	**LEV N =197 (50.6%)**	**MOX N = 24 (3.2)**	**NOR N= 2 (0.5%)**	**OFL N = 13 (3.3)**	**PEF N = 13 (3.3)**	**SPA N = 1 (0.30**	**Total ICSR N= 389 (100%)**
Tuberculosis	0	147	21	0	1	0	0	**169 (43.4)**
Bacterial Infections	25	18	0	0	2	3	0	**48 (12.34)**
Enteric (salmonellosis)fever	28	2	0	0	1	1	0	**32 (8.23)**
Others	20	2	0	2	0	0	0	**24(6.13)**
Prophylaxis	7	4	0	0	0	2	0	**13 (3.34)**
Urinary Tract Infection	6	2	1	0	4	0	0	**13 (3.34)**
Respiratory tract infections	7	3	0	0	0	0	0	**10 (2.57)**
Gastroenteritis/ Diarrhoea	8	1	0	0	0	0	0	**9 (2.31)**
Cough/catarrh/sore throat	6	1	0	0	0	0	0	**7 (1.80)**
Septicaemia	7	0	0	0	0	0	0	**7 (1.80)**
Fever	6	0	0	0	0	0	0	**6 (1.54)**
Bone Infection	0	1	0	0	0	3	0	**4 (1.03)**
Malaria	4	0	0	0	0	0	0	**4 1.03)**
Diabetic Foot Ulcer	0	1	0	0	0	2	0	**3 (0.77)**
ear infections	0	1	0	0	0	0	1	**2 (0.51)**
eye infections	1	0	0	0	1	0	0	**2**
No indications reported	14	14	2	0	4	2	0	**36 (9.25)**

CIP = Ciprofloxacin, LEV =Levofloxacin, MOX = Moxifloxacin, NOR = Norfloxacin, OFL = Ofloxacin, PEF = Pefloxacin,SPA = Sparfloxacin

The reported adverse events were reviewed to bring out those that pertain to the organs said to be implicated in the potentially permanent and disabling side effects viz tendons, muscles, joints, and the nervous system. Specific events considered in the review were tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste and smell. In a total of eighty-five (85) ICSRs, at least one of these events was reported (table 3). Levofloxacin was reported as the suspected drug in 60 of these 85 cases and ciprofloxacin in 17.

Table 3. Reported Adverse Events of Interest

number of ICSRs	Suspected drugs					
Adverse events of interest	**CIP N = 17 (20)**	**LEV N = 60 (70.6)**	**MOX N = 4 (4.7)**	**OFL N = 2 (2.4)**	**PEF N = 2 (2.4)**	**Total ICSR N = 85**(100.00%)
arthralgia	0	23	0	0	0	23(27.06%)
depression	0	2	2	0	0	4(4.71%)
depression, sleep disorder	0	5	0	0	0	5(5.88%)
fatigue	1	2	0	0	0	3(3.53%)
gait disturbance	1	0	0	0	0	1(1.18%)
impaired hearing	2	6	2	0	0	10(11.76%)
impaired hearing and vision	1	0	0	0	0	1(1.18%)
impaired vision	1	0	0	0	1	2(2.35%)
paresthesia	4	5	0	0	0	9(10.59%)
peripheral neuropathy	0	1	0	0	0	1(1.18%)
peripheral neuropathy, impaired hearing	0	1	0	0	0	1(1.18%)
sleep disorders	6	15	0	2	1	24(28.24%)
tendinitis	1	0	0	0	0	1(1.18%)
Total ICSR	**17**	**60**	**4**	**2**	**2**	**85**(100.00%)

CIP = Ciprofloxacin, LEV =Levofloxacin, MOX = Moxifloxacin, NOR = Norfloxacin, OFL = Ofloxacin, PEF = Pefloxacin,

The time between the commencement of fluoroquinolone antibiotics therapy to the onset of the Adverse Events of interest was determined from the ICSRs. The determined TTOs ranged from hours (events reported to have started same day drug started) to several months. The longest TTO reported was eight (8) months with a median TTO of 4 weeks

The possible role of concomitant medicines in these cases of interest cannot be downplayed. 91.76% of the 85 patients who reported one or more of the events under review concomitantly took other medications belonging to different therapeutic categories. In seven (7) cases, there were no concomitant medicines reported. The concomitant medicines in the 85 cases are reflective of the general data(table1.) with antituberculosis drugs as the main therapeutic category (50 ICSRs)

At the time of reporting, 30(35.29%) of the events had resolved, 5(5.88%) resolved with disability of which impaired hearing 4 cases and impaired vision 1 case. Table 4 shows reported outcome of adverse events of interest.

Table 4: Reported outcome for adverse events of interest

Number of ICSRs	Reported outcome

Adverse events of interest	Ongoing N=10(11.76%)	Recovered/ Resolved N=30(35.29%)	Resolved with disability N=5(5.88%)	Unknown N= 40(47.06%)	Total ICSRs N=85(100%)
arthralgia	4	6	0	13	23
depression	0	2	0	2	4
depression, sleep disorder	0	0	0	5	5
fatigue	0	2	0	1	3
gait disturbance	0	1	0	0	1
impaired hearing	1	0	4	5	10
impaired hearing and vision	0	1	0	0	1
impaired vision	1	0	1	0	2
paraesthesia	1	5	0	3	9
peripheral neuropathy	0	0	0	1	1
peripheral neuropathy/ impaired hearing	0	1	0	0	1
sleep disorders	3	11	0	10	24
tendinitis	0	1	0	0	1
Total ICSR	**10**	**30**	**5**	**40**	**85**

Conclusion

The National Agency for Food and Drugs Administration and control (NAFDAC) has a mandate to ensure the safety and quality of medicines used in Nigeria. This mandate empowers NAFDAC to take regulatory decisions based on safety and quality data generated from medicine use after approval. The safety data may be generated internally within Nigeria from reports of ADRs. NAFDAC may also leverage on safety information generated by other NMRAs such as the US FDA EMA, Ghana FDA and MCA Zimbabwe.

Healthcare providers have the responsibility to ensure the safety of patients. This responsibility requires them to as much as possible use medicines in line with standard treatment guidelines. They are to observe patients for occurrence of adverse events. Such adverse events should be properly documented and submitted to National Pharmacovigilance Centre, NAFDAC Corporate Headquarters, Abuja.

Healthcare providers are implored to collaborate with NAFDAC to improve safety monitoring of medicines so as to improve reporting of Adverse Drug Reactions and also improve treatment outcomes.

[1] Emdex vol.1 June 2016- May 2017 edition

[2] BNF 71 March- December 2016

[3] **Fluoroquinolone-Associated Tendinopathy: An Achilles Heel for Clinicians**
Mary K. Donnelly-Strozzo, and Roseann Velez available at:
https://contemporaryclinic.pharmacytimes.com/journals/issue/2016/june2016/fluoroquinolone-associated-tendinopathy-an-achilles-heel-for-clinicians
Assessed 09/07/19

[4] (https://www.medsafe.govt.nz/committees/marc/reports/172-Fluoroquinolones_Redacted.pdf)

[5]FDA Updates Warnings for Fluoroquinolones on Risks of Mental Health and Low Blood Sugar Adverse Reactions https://www.infectioncontroltoday.com/fda/fda-updates-warnings-fluoroquinolones-risks-mental-health-and-low-blood-sugar-adverse-reactions

[6] FDA. (2018). FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. Drug Safety Communications, 0-1.

Walker, M. (2018, July 10). FDA: New Warnings for Fluoroquinolones: Class-wide label changes address mental health side effects, hypoglycemic coma risk. Medpage Today.

[7] FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together
https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-advises-restricting-fluoroquinolone-antibiotic-use-certain

[8]FLUOROQUINOLONES - Risk of Disabling and Persistent Serious Adverse Reactions
https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/61900a-eng.php