

# Safety limitations of fluoroquinolones' use

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## Introduction

Fluoroquinolones are class synthetic antibacterial medicines in use since 1961. First representatives had a rather narrow antibacterial spectrum. With the inclusion of the fluorine atom in the molecule the spectrum of antibacterial activity had significantly broaden. Nowadays fluoroquinolones are separated in four generations: first and second generations are mostly active against Gr(-) microorganisms and third and fourth generation are effective against Gr(+) as well. Fluoroquinolones play a significant part in the treatment of respiratory, gastrointestinal and urological infections and are mostly used *per os*.

This makes them accessible and preferable therapeutic option but also brings up questions about control of use, overuse and abuse. Aside from the growing problem of microbiological resistance, a lot of severe adverse drug reactions have been linked to fluoroquinolones treatment recently.

## Materials and methods

For the purpose of the current study, a review of the referral procedure of the safety of quinolones and fluoroquinolones has been done. The official assessment report of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) and the documents of the procedure were analyzed. The data shown by the PRAC was amended with a literature search on the topic of safety limitations of fluoroquinolones use. The main safety concerns were outlined and both the

non-clinical and clinical aspects of their development were studied. Along with the regulatory point of view of the PRAC assessment we also used a practical approach to point out the biggest issues related to fluoroquinolones therapy as well as a brief guidance on therapeutic behavior in cases where quinolone therapy is no longer the best option based on the latest safety information.

## Results and discussion

The procedure of safety assessment and PRAC referral of quinolones and fluoroquinolones was conducted in 2018. For the purpose of the referral the EudraVigilance database was searched. All ADRs reported to the system in the period 1998-2016 which included quinolones or fluoroquinolones as suspected drug were extracted. Other criteria of the search were serious ADR which led to long term complications, ADR with duration more than 30 days or ADR with result "recovered with sequels". The total number of cases that met the criteria was 2141. 393 of them were marked as leading to disability. The analysis showed that the most frequently reported medicines were levofloxacin, ciprofloxacin, moxifloxacin, ofloxacin and norfloxacin. The majority of the cases referred to impairment of musculoskeletal system, nervous system and general disorders with 37% of the cases including ADRs in more than one system. Most numerous ADR cases were tendon inflammation, tendon rupture, arthralgia and tendon disorder.

Non-clinical, clinical studies and scientific publications present enough data to consider that

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there is drug-reaction relatedness between use of fluoroquinolones and potentially disabling ADR of the musculoskeletal system (Lewis & Cook, 2014). 46% of the analyzed cases represented problems with muscles and mainly tendons. 15 % of the analyzed cases were ADRs from the nervous system and most frequently reported ADRs were sense and memory impairments. Central nervous system damage such as sleep disorders, depression and anxiety were also frequently reported ones, and 5% of them were marked as resulting in disability (Doussau de Bazignan et al., 2006; Tome & Filipe, 2011).

Over 100 indications for use of fluoroquinolones were present in the EU at the start of the referral. During the safety assessment they were classified in four categories based on data on the risk/benefit ratio. In the first category were put those indications where no change in treatment behavior is needed. This group includes chronic sinusitis, cervicitis, orchitis, gastrointestinal infections, intraabdominal infections etc. In these indications PRAC considers that the benefit outweighs the potential risk of disabling ADRs (EMA, 2018).

The second group of indications includes acute sinusitis, uncomplicated cystitis, otitis media and COPD exacerbations. For those conditions PRAC considers there are other medicines present in the EU that have a greater benefit for the patient and should serve as first line treatment choice. For this reason, uncontrolled use of fluoroquinolones in this subset of indications carry risk of development of microbial resistance.

For the third group indications PRAC's recommendation is to suspend use of fluoroquinolones because of a negative benefit/risk ratio. In pharyngitis, tonsillitis, laryngitis, vaginal infections, septicemia and endocarditis etc. fluoroquinolones are not recommended as treatment option. The majority of the cases of pharyngitis, tonsillitis and laryngitis are of a viral nature rather than a bacterial pathogen and this makes treatment with quinolones unnecessary (Revez & Cardona, 2015). In cases of septicemia PRAC recommends start treatment of the underlying cause for septicemia which usually requires antibiotic treatment.

In the fourth group are put some indications which are considered too vast and unspecified. Rewording should be done and the product information should be corrected in order to include the updated guidance for use of fluoroquinolones.

As a result of the PRAC safety referral procedure the benefit/risk ratio is considered to be negative for piperidic acid, nalidixic acid, flumequine and cinoxacin. Their marketing authorizations in the EU should be suspended. The benefit/risk ratio remains positive for ciprofloxacin, levofloxacin, perfloracin, moxifloxacin, ofloxacin, norfloxacin, lomefloxacin, prulifloxacin and rufloxacin.

## Conclusion

The conducted analysis showed that fluoroquinolones should not be used as a first line therapy for infections, especially when the condition is self-limiting or uncomplicated. Quinolones remain important treatment option but in cases meeting certain criteria and in case of quinolones sensitive pathogen. Overall safety profile of the quinolones pharmacological class is considered to be well known, with the majority of frequent ADRs being non serious. However, recent assessment of safety data shows that rare ADRs are linked to long duration and risk of disability. Limiting the indications for use of fluoroquinolones is an important measure to minimize risk of serious disabling ADRs and development of microbiological resistance.

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