CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES
&
HEALTH INFORMATION DESIGNS

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Fluoroquinolones (FQs) are a frequently prescribed class of broad spectrum antibiotics that cover a wide range of bacterial infections. This class of antibiotics exert their antimicrobial activity by inhibiting DNA gyrase and topoisomerase IV, two enzymes used for bacterial DNA replication, which leads to bacterial cell death.[1,2] There are four generations of FQs, each subsequent generation increasing in spectrum of activity.[2]

The first generation agents cinoxacin and nalidixic acid were the first quinolones to come to market, covering gram-negative organisms with the exception of Pseudomonas.[3] First generation agents are classified as quinolones. The addition of fluoride to the original quinolone structure created the next generations of the class, known as FQs.[3] Second generation agents such as ciprofloxacin and ofloxacin cover gram-negative organisms (including Pseudomonas), some gram-positive and some atypical pathogens.[3] Third generation agents such as levofloxacin have similar coverage against gram-negative organisms as the second generation agents, but also have expanded gram-positive and atypical pathogen coverage.[3] Fourth generation agents such as gemifloxacin and moxifloxacin have similar coverage when compared to third generation agents plus broad anaerobic coverage.[3]

Systemic FQs (Table 1) are used to treat a wide range of bacterial infections including, but not limited to, urinary tract infections, skin and soft tissue infections, community and hospital acquired pneumonia, osteomyelitis, and sexually transmitted diseases. Not only do FQs have multiple indications for use and broad spectrum coverage, they also possess excellent tissue penetration and oral bioavailability, as well as favorable safety and tolerability characteristics.[2,3] It is no surprise that approximately 23.1 million unique patients in the United States received a prescription for an oral fluoroquinolone medication from a retail pharmacy during 2011,[4] making FQs the third most commonly prescribed outpatient antibiotic class in adults that year.[5]

Taking a closer look at the Connecticut Medical Assistance Program population, graph 1 depicts the trend of outpatient systemic fluoroquinolone prescriptions dispensed from 2014 through 2018. During 2018, there were 22,453 unique patients who received 28,759 outpatient systemic fluoroquinolone prescriptions, 523 patients were less than 18 years of age (FQ use in the pediatric population is not recommended for general use due to arthropathy with erosions of cartilage in weight bearing joints found in studies of juvenile animals.[6]) FQs made up 0.27% of the total prescriptions dispensed during 2018 under the Connecticut Medical Assistance Program benefit.

Over the past decade, the FDA has released multiple warnings and precautions regarding the use of FQs. Below are summaries of the FDA warnings associated with the class since the late 2000's.

During July 2008, the FDA required a *black box warning* to be added to the drug label and medication guides of fluoroquinolone antibiotics regarding the increased risk of tendinitis and tendon rupture in patients who receive a prescription for a fluoroquinolone.[7] Although the increased risk of tendinitis and tendon rupture was previously added to the prescribing information, there continued to be serious reports of cases which pushed the FDA to increase the warning to a *boxed warning*. The achilles tendon is the most common tendon associated with FQ tendinitis and tendon rupture, although tendons of the shoulder, hand, biceps, and thumb have also been reported.[2] There are certain factors that increase the risk of this adverse event: patient greater than 60 years of age, patients who are receiving concurrent corticosteroids, and transplant patients. Tendon rupture has been reported to occur either during treatment with FQs or even occurring up to months after discontinuation of the medication.[7] Taking a closer look at the Connecticut Medical Assistance Program population, there were 20 adult patients who received a FQ and received a subsequent diagnosis of tendon rupture during 2018, 5 of those patients received concurrent corticosteroids and 3 of the 20 patients were 60 years of age or older.

During February 2011, the FDA required a *black box warning* to be added to FQ drug labels and medication guides to inform prescribers of worsening symptoms of myasthenia gravis, including muscle weakness and breathing difficulty, associated with FQ utilization. Taking a closer look at the Connecticut Medical Assistance program, there were 7 adult patients who received a FQ during 2018 with a concurrent diagnosis or history of myasthenia gravis.

During August 2013, the FDA required drug

Table 1: List of FDA Approved Systemic Fluoroquinolones[12]

Brand Name	Generic Name
Avelox	moxifloxacin
Baxdela	delafloxacin
Cipro / Cipro extended release	ciprofloxacin/ciprofloxacin extended release
Factive	gemifloxacin+
Levaquin	levofloxacin+
Ofloxacin	ofloxacin

labels and medication guides for all FQs to be updated to better describe the serious side effect of peripheral neuropathy.[8] Although peripheral neuropathy was added to the *Warnings/Warnings and Precautions* sections of all systemic fluoroquinolone drugs in 2004,[8] the 2013 warning was updated to provide a better description that FQ associated peripheral neuropathy can have a rapid onset and carries the risk of being permanent. The more recent upgraded warning in 2013 resulted in the need to describe the potential rapid onset and risk of permanent peripheral neuropathy associated with FQs.

During May 2016, the FDA advised that the risk of disabling and potentially permanent side effects associated with fluoroquinolone antibiotics (involving the tendons, muscles, joints, nerves and central nervous system (CNS)) generally outweigh the benefits in patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections where other treatment options are available.[9] It was advised that FQs be reserved for patients that have no other treatment options.

During July 2016, the FDA followed up with the advisories issued earlier that year and approved label changes for systemic FQs to include a *black box warning* to address the disabling and potentially permanent side effects on tendons, muscles, joints, nerves, and the CNS that can occur together in the same patient. Adding a class warning that FQs are not recommended for use in patients with acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risks outweigh the benefits.[10]

During July 2018, the FDA again added to the *Warnings/Warnings and Precautions* sections of the labeling for FQs regarding the risk that FQ associated hypoglycemia can lead to coma. Additionally, labeling changes across the class were also made to address the mental health adverse events associated with FQs including: agitation, nervousness, delirium, and memory impairment.[11]

During December 2018, the FDA required a new warning regarding the rare but serious risk of aortic aneurysm be added to the *Warnings/Warnings and Precautions* sections of prescribing information for all fluoroquinolone antibiotics. FQ use can increase the occurrence of aortic tears, dissections, or ruptures which can lead to internal bleeding and death.[12] FQs are not recommended for use in patients at increased risk unless there are no other treatment options available.

Patients who are at an increased risk of fluoroquinolone associated aortic tears or rupture include patients with the following[12]:

- History of aortic aneurysms
- Peripheral atherosclerotic vascular disease
- Hypertension
- Genetic disorders that involve blood vessels (Marfan syndrome, Ehlers-Danlos Syndrome)
- Elderly

There are currently four observational studies published between 2015 and 2018 that show an increased risk of aortic aneurysm or dissection associated with fluoroquinolone utilization[13-16] as well as case reports submitted to the FDA. The mechanism for the risk of aortic aneurysm or dissection has not been determined and although there appears to be evidence of an association between fluoroquinolone use and an increased risk of aortic aneurysm or dissection, the FDA did not determine a definite causal association due to the limitations of the studies.[12]

The estimated background risk of aortic aneurysm is 9 events per 100,000 people per year in the general population and 300 events per 100,000 people per year in the highest risk population. Some of the studies showed rates of about twice the risk of aortic aneurysm rupture and dissection in patients taking FQs.[12] Taking a closer look at the Connecticut Medical Assistance program, there were 11 adult patients who received a FQ prescription and received a subsequent diagnosis (within 60 days of the FQ prescription) of aortic tear, rupture, or dissection during 2018. This places the Connecticut Medical Assistance population at 11 events per 21,930 people per year, or 37 events per 100,000 people per year.

While there have been many documented warnings, precautions, and boxed warnings associated with the FQ antibiotic class within the last 10 years, these medications continue to have a relevant place in treating certain bacterial infections. The FQs have a wide range of bacterial coverage and treat many indications. They have excellent tissue penetration and oral bioavailability and are generally safe and tolerable. As always, it is important when selecting any medication to review the entire clinical picture and take into account the risk versus benefit of using the selected agent.

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