

Joint Meeting of the Antimicrobial Drugs Advisory Committee and
the Drug Safety and Risk Management Advisory Committee
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FDA's Adverse Event Reporting System (FAERS) Review:

**“Fluoroquinolone-Associated Disability” (FQAD) Cases
in Patients Being Treated for Uncomplicated Sinusitis,
Bronchitis, and/or Urinary Tract Infection**

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2013 Pharmacovigilance Review:

Disabling Peripheral Neuropathy Associated with Systemic Fluoroquinolone Exposure

- 2013 FDA review describing disabling peripheral neuropathy associated with fluoroquinolone use. This resulted in a labeling change describing the potential for irreversible peripheral neuropathy.
- 76% of patients with peripheral neuropathy also reported adverse events (AEs) involving other organ systems, including neuropsychiatric, musculoskeletal, vision, and cardiac events.
- The duration of many of these other adverse events also appeared to be prolonged and disabling.

“Fluoroquinolone-Associated Disability” (FQAD)

- This review was done to try to characterize the constellation of disabling symptoms that was seen in the previous review, which we will refer to as “fluoroquinolone-associated disability,” or FQAD.
 - Disability: A substantial disruption of a person's ability to conduct normal life functions. (CFR - Code of Federal Regulations Title 21, Sec. 314.80: Postmarketing reporting of adverse drug experiences)
- Must have adverse events reported from two or more of the following body systems:
 - Musculoskeletal
 - Neuropsychiatric
 - Peripheral Nervous System
 - Senses (vision, hearing, etc.)
 - Skin
 - Cardiovascular
- AEs had to last 30 days or longer after stopping the fluoroquinolone.

Few articles in peer-reviewed literature that describe this constellation of disabling symptoms

- Jay S. Cohen, MD (Cohen JS. Peripheral neuropathy associated with fluoroquinolones. *Ann Pharmacother* 2001;35:1540-7.)
 - Collected additional information on severe, long-term adverse events that affected other organ systems
- Beatrice A. Golomb, MD (Golomb BA, Koslik HJ, Redd AJ. Fluoroquinolone-induced serious, persistent, multisystem adverse effects. *BMJ Case Rep* 2015 Oct 5. pii: bcr2015209821. doi: 10.1136/bcr-2015-209821.)
 - UCSD Fluoroquinolone Effects Study
 - Currently enrolling patients online

Reports consistent with FQAD were more likely to be found in the lay press

- Newspapers: New York Times (9/10/12), USA Today (9/17/14), Washington Post (8/3/15)
- TV news reports
- Websites
- Social media

FAERS Benefits and Limitations

- Benefits
 - FAERS is a spontaneous (voluntary) reporting system
 - Clinical trials are usually done in hundreds of people; once a product goes to market, it is often used by millions of people
 - FAERS has the ability to detect rare and serious adverse events

FAERS Benefits and Limitations

- Limitations
 - There is underreporting
 - Causality may be difficult to determine
 - Reports must be reviewed and evaluated for:
 - Concomitant drugs
 - Medical history and co-morbid conditions
 - Temporal relationship of drug administration to the event
 - Not all reports contain enough detail to properly evaluate an event

FQAD Population

Goal: To identify FQAD cases reported to FAERS in a very specific population:

- Reported to be previously healthy before taking an oral FQ antibiotic
- Treated for uncomplicated sinusitis, bronchitis, and UTI
 - A “healthy patient” was a person able to perform all of the usual activities of daily living without significant restrictions prior to taking the FQ
 - Patients were included if they had controlled chronic diseases, such as hypertension, hypothyroidism, or hyperlipidemia

Search Criteria

Reports were searched in FAERS with the following criteria:

- Oral dosage forms for the 5 available fluoroquinolones
- US cases
- Outcome reported as disability
- Indications of uncomplicated sinusitis, bronchitis, and/or cystitis/UTI*
- Search from November 1, 1997 to May 30, 2015
- All MedDRA Preferred Terms (PT) (or adverse event terms) were searched

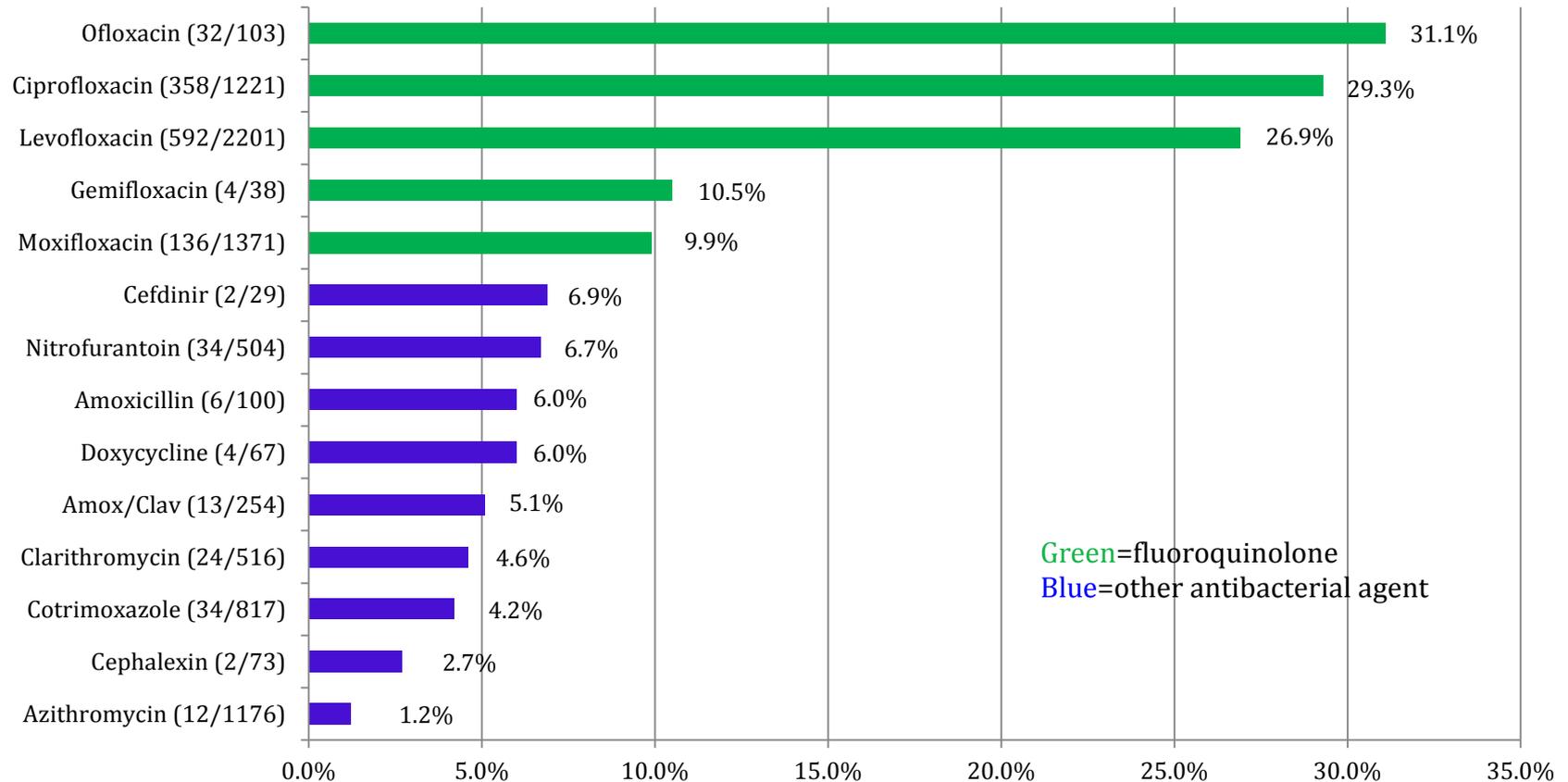
*Indications PT: Sinusitis acute, Sinusitis bacterial, Sinusitis, Bronchitis acute, Bronchitis, Bronchitis bacterial, Cystitis, Acute cystitis, Cystitis bacterial, Urinary tract infection, UTI-urinary tract infection, Urinary tract infection bacterial

Disability Search Results

Fluoroquinolone	Number of Reports
Levofloxacin	592
Ciprofloxacin	358
Moxifloxacin	136
Ofloxacin	32
Gemifloxacin	4
TOTAL	1,122

May include duplicate reports.

Percentage of Disability Reports* Among all Serious Outcome Reports with Selected Antibiotics for Treatment of Uncomplicated Sinusitis, Bronchitis, and UTI



*Number of US reports reporting disability divided by the total number of US serious adverse event reports for oral dosage forms, from November 1, 1997 to May 30, 2015

FQAD Cases

After retrieving the 1,122 reports, individual review of each report was needed to further identify cases of FQAD:

- To identify that the patient had adverse events reported from two or more of the following body systems:
 - Musculoskeletal
 - Neuropsychiatric
 - Peripheral Nervous System
 - Senses (vision, hearing, etc.)
 - Skin
 - Cardiovascular
- That the AEs lasted 30 days or longer after stopping the fluoroquinolone

Exclusions

Reports meeting FAERS search criteria (n=1,122)

Excluded Reports (n=944)

- Reported a disabling AE, but from less than two of the selected body systems: n= 540 (57%)
- Events lasted for less than 30 days after stopping the FQ: n=139 (15%)
- Complicated or confounded drugs or medical history: n= 102 (11%)
- Diagnosed with an indication other than uncomplicated sinusitis, bronchitis, or UTI: n= 101 (11%)
- Duplicate report: n= 33 (3%)
- Case found in another FQ report: n=17 (2%)
- Not enough information to clinically evaluate: n=12 (1%)

FQAD Case Series (n=178)

US Disability Reports Associated with Oral Fluoroquinolones and FQAD Cases

	Total Disability Reports*	Total FQAD Cases [†]	Percentage of Cases
Levofloxacin	592	91	15%
Ciprofloxacin	358	65	18%
Moxifloxacin	136	19	15%
Ofloxacin	32	2	--
Gemifloxacin	4	1	--
TOTAL	1,122 reports	178 cases	

*Reports: All individual reports coming into FAERS, including duplicate reports

†Cases: Reports have been de-duplicated, assessed for clinical relevance, did not meet the exclusion criteria

FAERS Search Results

Descriptive Characteristics of FQAD Cases Reported to FDA from November 1, 1997 – May 30, 2015 (N=178)

Age (n=173)	Mean: 48.1 years Median: 48 years Range: 13-84 years	0-29 years: n=15 (9%) 30-59 years: n=128 (74%) ≥ 60 years: n=30 (17%) < 18 years: n=2 (1%)
Sex	Female: 138 (78%) Male: 40 (22%)	After removing all UTI cases (n=93): Female: 74%; Male: 26%
Reported Indication for FQ Therapy	Cystitis/UTI—84 (47%) Sinusitis—59 (33%) Bronchitis—26 (15%) Sinusitis/bronchitis—7 (4%) Bronchitis/UTI—1 (<1%) Sinusitis/bronchitis/UTI—1 (<1%)	
Report type	Direct: 152 (85%) Expedited: 18 (10%) Non-expedited: 8 (5%)	

FAERS Search Results

Descriptive Characteristics of FQAD Cases Reported to FDA from November 1, 1997 - May 30, 2015 (N=178)

<p>Onset of AEs from start of FQ therapy (n=102)</p>	<p>Mean: 5.4 days Median: 3 days Range: 1 hour—3 months Onset 1—2 days of starting FQ: n=49 (48%) Onset 3-4 days of starting FQ: n=20 (20%) Onset 5-10 days of starting FQ: n=21 (20%) Onset >10 days of starting FQ: n=12 (12%)</p>
<p>Duration of AEs <i>at the time the report was received by the FDA</i> (n=166)</p>	<p>Mean: 61.2 weeks (14 months) Median: 30 weeks (7 months) Range: 30 days—9 years ≥ 1 year: n=39 (23%)</p>

Body Systems in FQAD Cases (n=178)

Organ Systems	Percentage of Cases Involved
Musculoskeletal (tendon/joint/muscle)	97%
Neuropsychiatric	68%
Peripheral Nervous System	63%
Senses (vision, hearing, etc.)	32%
Skin	15%
Cardiovascular	12%

Reported Musculoskeletal Events* [tendon/joint/muscle] (n=173)

- Joint pain (113)
- Tendon pain/tendonitis (66)
- Muscle pain (52)
- Muscle weakness (39)
- Joint swelling (20)
- Muscle cramps or spasms (17)
- Tendon rupture (14)
- Joint popping or cracking (13)
- Limb pain and swelling (11)
- Joint stiffness (11)

Unlabeled events
are underlined

*Patients may have reported more than 1 event in each body system

Reported Neuropsychiatric Events* (n=121)

- Fatigue (43)
- Insomnia (38)
- Anxiety (33)
- Headaches (24)
- Dizziness (23)
- Depression (19)
- 'Brain fog' (18)
- Nightmares (15)
- Memory impairment (12)
- Confusion (10)
- Lightheadedness (9)
- Panic attacks (8)
- Impaired concentration (8)
- Loss of balance (8)
- Vertigo (8)
- Hallucinations (6)
- Disorientation (5)
- Feeling like something crawling on/under skin (4)
- Malaise (4)

Unlabeled events
are underlined

*Patients may have reported more than 1 event in each body system; only AEs with ≥ 4 reports were displayed

Reported Peripheral Nervous System Events* (n=113)

- Peripheral neuropathy (50)
- Numbness (41)
- Tingling (35)
- Burning pain (36)
- Electrical or shooting pain (19)
- Twitching (17)
- Tremors (15)
- Pins & needles sensation (5)
- Paresthesias (3)
- Prickling (1)

Unlabeled events
are underlined

*Patients may have reported more than 1 event in each body system

Reported Senses Events* (n=57)

- Eye pain (16)
- Diminished vision (15)
- Tinnitus (14)
- Blurred vision (11)
- Hearing impairment (5)
- Pressure in ears (2)
- Loss or altered taste (2)
- Sensitivity to light (1)
- Double vision (1)
- Retinal tear (1)
- Ear pain (1)
- Loss of smell (1)

Unlabeled events
are underlined

*Patients may have reported more than 1 event in each body system

Reported Cardiovascular Events* (n=22)

- Palpitations (16)
- Tachycardia (10)
- Chest pain/discomfort (4)

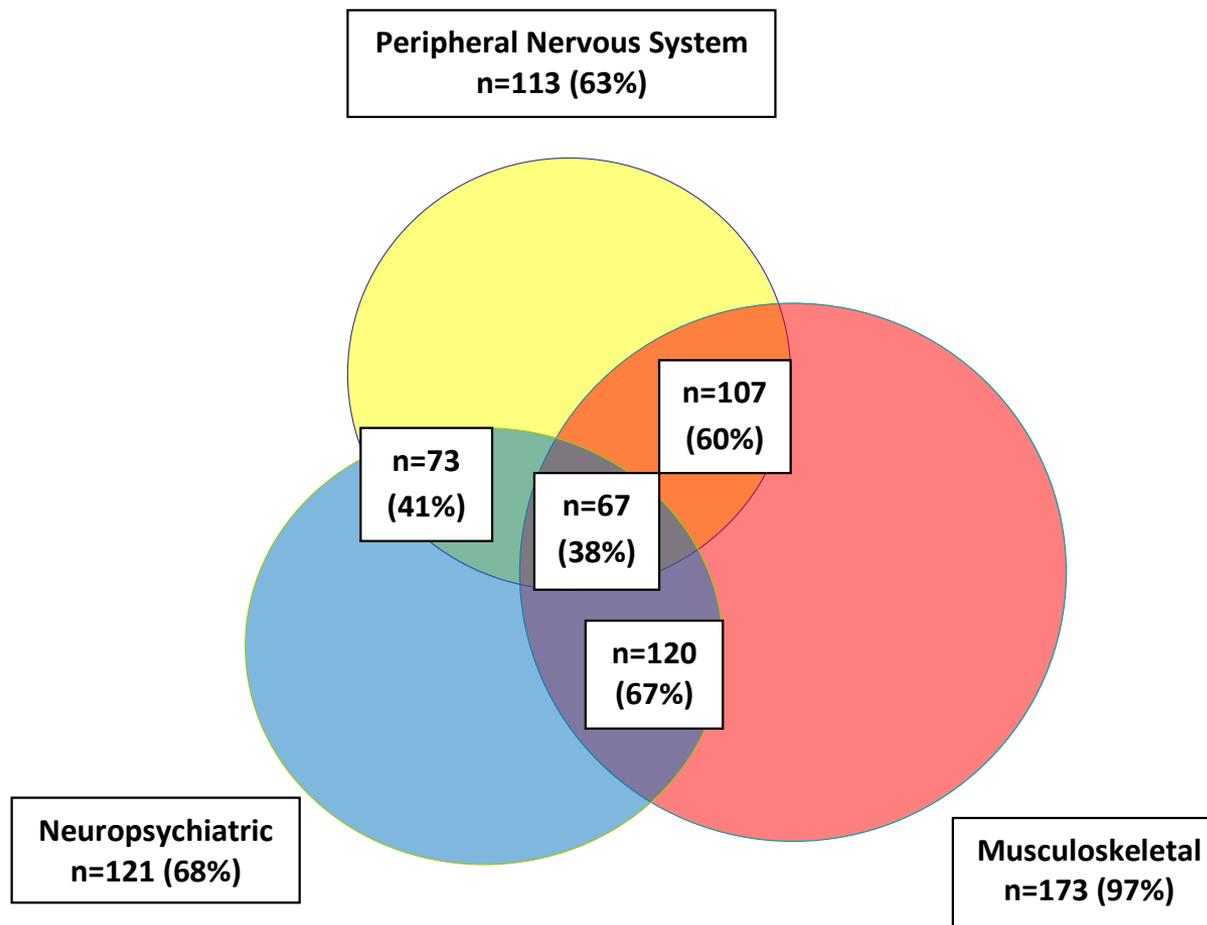
Reported Skin Events* (n=27)

- Ongoing skin rash or acne (13)
- Sweating (7)
- Photosensitivity (7)
- Skin sensitivity to touch (6)
- Hair loss (5)
- Flushing (4)

Unlabeled events
are underlined

*Patients may have reported more than 1 event in each body system

Venn Diagram of FQAD Cases that Reported an Adverse Event in the Top 3 Body Systems (n=178)



Percentage of FQAD Cases for Each Fluoroquinolone by Body System

	Musculo-skeletal	Peripheral nervous system	Neuro-psychiatric	Senses	Cardio-vascular	Skin
Levofloxacin (n=91)	98%	52%	74%	30%	10%	10%
Ciprofloxacin (n=65)	94%	78%	66%	31%	12%	15%
Moxifloxacin (n=19)	95%	79%	65%	30%	10%	15%
Ofloxacin (n=2)	--	--	--	--	--	--
Gemifloxacin (n=1)	--	--	--	--	--	--



Case Report

Case report: 49-year-old woman, 2004

This patient received a 10-day supply of levofloxacin 500 mg to treat a sinus infection. The symptoms began 2 days after starting the drug.

“Prior to taking this drug, I was a healthy 49-year-old, an advanced downhill skier, with NO medical problems. I could barely walk, had to crawl up my staircase. I had severe muscle weakness, muscle burning and joint pain in all my limbs...I ached and burned in what seemed every tendon and muscle in my body...I continue to suffer 22 months later with the following disabling conditions: Severe tendon/muscle pain and tightness, tendonitis, tingling, numbness, prickling, pins and needles sensations in my extremities. Electrical sensations. Feeling of worms crawling under my skin. Severe arm and leg weakness. Muscle twitching, spasms and contractions. Severe muscle tenderness. To poke my muscles feels like a bee sting! Inability to sleep due to pain 24 hours per day, 7 days per week. Inability to work due to pain and weakness. Difficulty thinking clearly, confusion. Chronic fatigue.”

Observations

- No one fluoroquinolone appeared to have a greater association with FQAD than another.
- Direct reports: 85% is an unusually high number
 - Over past 10 years, the percentage of direct reports for all drugs has ranged from approximately 2-6%.
 - The unusually large number of direct reports coming from patients who described similar experiences after taking a FQ was very beneficial in describing these disability cases.

Observations

- The current Box Warning states that tendonitis and tendon rupture can occur in all ages, but that there is an increased risk in older patients, usually over 60 years of age.
 - In this case series, only 17% of all patients were found to be 60 years of age or older.
 - In addition, the percentage of tendonitis/tendon rupture cases were the same in both the younger and older age groups.
- Majority (74%) of cases were reported in patients 30-59 years old.

Observations

- Many of the patient's clinicians were reported to be at a loss as to what was causing these symptoms.
- Some patients reported extensive medical testing to try to diagnose the cause of their disability symptoms, but test results were frequently negative.
- Effective treatments were not identified.

Observations

- Most of the individual AEs that exist within FQAD are currently described in fluoroquinolone labels. However, the constellation of disabling symptoms described here is not in the label.
- The decrease in quality of life was described as being profound, and it affected both the patient and his/her family.

Thank you for your attention

MedWatch website--<http://www.fda.gov/Safety/MedWatch>