

# Fluoroquinolone Safety Labeling Changes

FDA/CDER Drug Information Webinar  
April 4, 2017

# Fluoroquinolone Safety Labeling Changes

## Objectives

- Describe the disabling and potentially irreversible constellation of adverse events that have been associated with the use of systemic fluoroquinolones
- Recognize the importance of stopping the fluoroquinolone antibacterial drug at the first sign that a patient is experiencing a serious adverse reaction.
- Describe situations in which risks of fluoroquinolones outweigh benefits.
- Recognize the small treatment benefit of antibacterial drug therapy for ABS, ABECB, and uncomplicated UTI.
- Describe the clinician's difficulty in identifying the disabling and potentially irreversible adverse reactions associated with fluoroquinolones.

# Fluoroquinolone Safety Labeling Changes

## Outline

- November 5, 2015 Advisory Committee Presentations
  - Overview of treatment benefit for Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, uncomplicated Urinary Tract Infections
  - Review of Fluoroquinolone-Associated Disability Cases
- Advisory Committee Discussion
- Changes to the Fluoroquinolone Labeling

# ABS, ABECB, and uUTI

## Antibacterial Drug Treatment Effects

**The Antimicrobial Drugs Advisory Committee and the  
Drug Safety and Risk Management Advisory Committee  
November 5, 2015 Joint Meeting**

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# Regulatory Overview

## Landscape in the 1980s – 1990s

- Advances in pathophysiologic understanding of infectious diseases
  - Concentrations of drug at the site of infection
  - Different clinical outcome assessments for each site
- Adequate and well-controlled studies
  - §21 CFR 314.126
- Trials involve a particular body site
- Active control “equivalence trials”
  - Often smaller and were underpowered for an efficacy finding of “non-inferiority” (NI)

# Regulatory Overview

## Landscape in 2000s

- Advances in understanding NI trial design
  - Establish a degree of confidence that a test drug is not worse than an active control drug by a pre-specified amount
- Treatment effect of control drug needs to be established for NI trial
- NI margin justification
  - Guidance documents reflect work done to establish the treatment effect of an antibacterial drug for each body site infection for the NI trial design
  - Placebo-controlled trials provide the best source of data
    - ABS, ABECB, uUTI

# Treatment Effects

## General Approach ABS, ABECB, uUTI

- Reviewed trials published in the medical literature
- Randomized, prospective, placebo- or nonantibacterial-control
- Antibacterial drugs in general
  - Trials evaluated across all antibacterial drugs

# Treatment Effects

Acute Bacterial Sinusitis  
- ABS -



## ABS Treatment Effects

- FDA reviewed 20 placebo-controlled trials published in the literature
  - Enriched for “bacterial” etiology
  - Six showed a statistically significant difference
    - Pre-specified primary outcome measure
  - Outcome measures and timing of assessments differed, for example:
    - Proportion “much better” at day 10
    - Score of zero on pain scale at day 7
    - Absence of symptoms day 12

# ABS Treatment Effects

## Antibiotics for clinically diagnosed acute rhinosinusitis in adults (Review)

Lemiengre MB, van Driel ML, Merenstein D, Young J, De Sutter AIM



**THE COCHRANE  
COLLABORATION®**

“...no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis.”

Cochrane Database 2012, Issue 10

# ABS Treatment Effects

## Antibiotics for acute maxillary sinusitis in adults (Review)

Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, Liira H, Williams Jr JW, Mäkelä M



“There is moderate evidence that antibiotics provide a small benefit...”

“However, about 80%...improved within two weeks” with no antibacterial drug therapy.

Cochrane Database 2014, Issue 2

# ABS Treatment Effects

## IDSA GUIDELINES

### IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

- Viral etiology accounts for ~90% of acute sinusitis
- Difficult to differentiate between viral and bacterial
- Reserve antibacterial drug treatment for patients with greater severity of symptoms
  - Chow, et al, Clin Infect Dis 2012; DOI: 10.1093/cid/cir1043

# ABS Treatment Effects

- Meta-analysis of 9 randomized trials
  - Unable to identify the symptoms and their severity for whom antibacterial drug therapy would be warranted.
    - Young, et al, Lancet 2008; 371: 908-14

# ABS Treatment Effects

- **Summary**

- A treatment effect of antibacterial drugs was observed only in some trials
- Even in trials that attempt to enrich for bacterial etiology or a bacterial pathogen was identified, a large proportion of placebo recipients had favorable clinical outcomes
- Difficult to differentiate between viral and bacterial etiology on the basis of clinical signs and symptoms
- Current treatment guidelines recommend antibacterial drugs for patients with greater severity of ABS
- FDA guidance recommends superiority trial design
  - e.g., placebo-control

# Treatment Effects

Acute Bacterial Exacerbation of Chronic  
Bronchitis  
- ABECB -

## ABECB Treatment Effects

- FDA reviewed 15 placebo-controlled trials
  - Included patients with varying disease severity
  - Six showed a statistically significant difference
    - One study showed a reduction in mortality for hospitalized patients with severe ABECB
    - One study showed improved clinical assessments at day 14 in hospitalized patients
    - Four other studies enrolled outpatients with *milder* disease: outcome measure = symptom-based



# ABECB Treatment Effects

## Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)

Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC



“...supports antibiotics for patients ...who are moderately or severely ill”

Cochrane Database 2009, Issue 2

# ABECB Treatment Effects

## ATS/ERS TASK FORCE

**Standards for the diagnosis and treatment of patients with COPD:  
a summary of the ATS/ERS position paper**

CLINICAL PRACTICE GUIDELINE, PART 2



POSITION PAPER

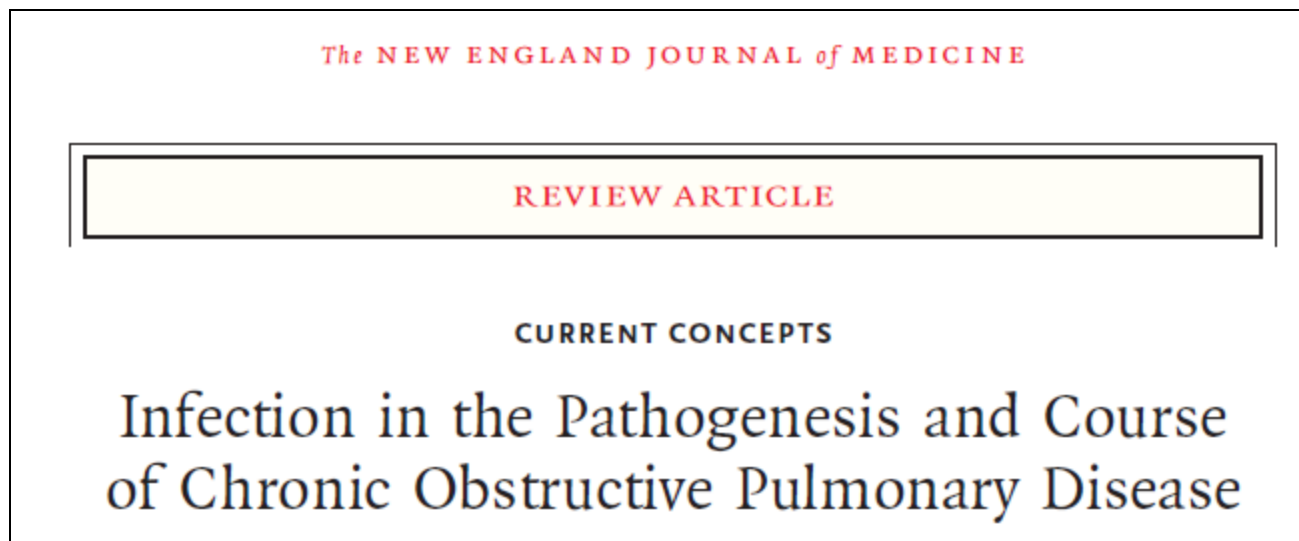
**Management of Acute Exacerbations of Chronic Obstructive  
Pulmonary Disease: A Summary and Appraisal of Published Evidence**

Treatment guidelines recommend antibacterial drug therapy for patients with moderate to severe disease

Celli, et al, Eur Respir J 2004; 23:932-946

Bach, et al, Ann Intern Med 2001; 134:600-20

# ABECB Treatment Effects



Review article also recommends antibacterial drugs for moderate-to-severe ABECB

- Sethi, Murphy, New Engl J Med 2008; 359:2355-65

## ABECB Treatment Effects

- “Mild” and “moderate-to-severe” ABECB
  - Clear definitions were not provided in the publications
- FDA considers the following definitions:
  - Patients who require hospitalization for treatment of ABECB have disease severity of “moderate-to-severe”
  - Patients who are being treated as outpatients have disease severity of “mild”

# ABECB Treatment Effects

- **Summary**

- Treatment effect for hospitalized patients
  - Treatment guidelines and review articles recommend antibacterial drug treatment for **moderate-to-severe** ABECB
- Treatment effect for patients with mild disease
  - A small treatment benefit in **mild** ABECB using an outcome measure from the patient's perspective
  - Generally antibacterial drug therapy is not recommended

# ABECB Treatment Effects

- **Summary**, cont.
  - FDA guidance document recommends superiority trials for outpatients with mild ABECB
    - Endpoint should be an outcome measure from the perspective of the patient (e.g., a PRO instrument)
    - Trial design options: treatment delay, placebo control, or superiority to active control.

# Treatment Effects

## Uncomplicated Urinary Tract Infections - uUTI -

## uUTI Treatment Effects

- FDA reviewed 5 prospective, randomized, controlled trials in outpatients with signs and symptoms of uUTI
  - 4 placebo control; 1 ibuprofen control
  - Mostly young adult women with signs and symptoms
  - Primary efficacy outcome measures:
    - Eradication of bacteria found at trial entry
    - Improvement or resolution of symptoms
    - Responder: eradication of bacteria and symptoms

Asbach, *Drugs* 1991;42 Suppl 4:10-13; Christiaens, et al, *Br J Gen Pract* 2002;52:729-34; Bleidorn, et al, *BMC Medicine* 2010;8:30; Ferry, et al, *Scan J Primary Health Care* 2007; 25:49-57; Dubi, et al, *Schweiz Med Wochenschr* 1982;112:90-2



# uUTI Treatment Effects

Table 1: Microbiologic eradication of bacteria in uUTI trials

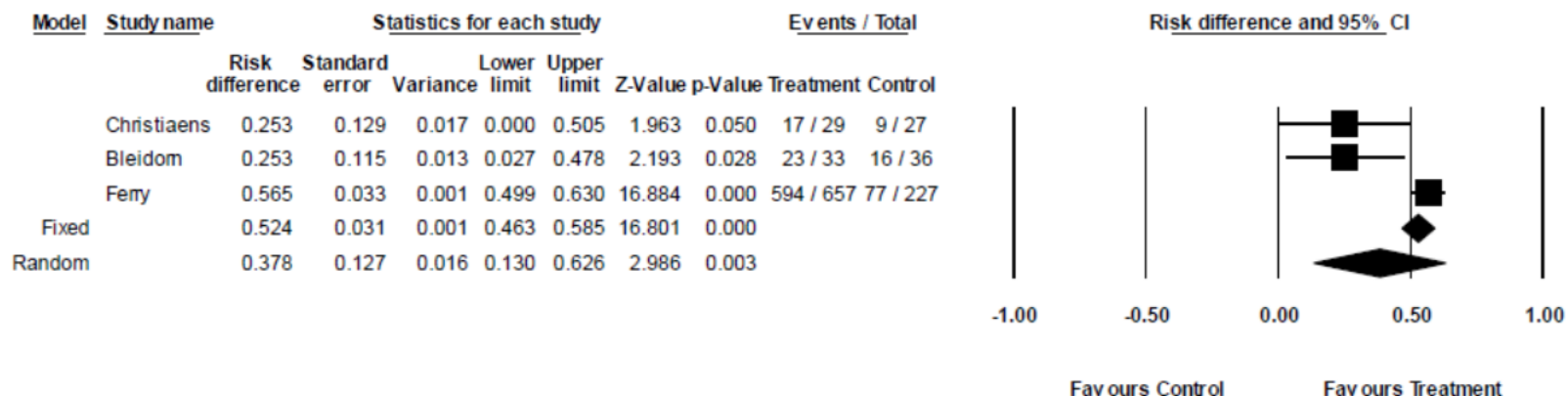
First author	Timing of follow up urine culture	Control	Antibacterial Drug
<b>Christiaens</b>	Day 4 post therapy	<b>33%</b> 9/27 Placebo	<b>59%</b> 17/29
<b>Bleidorn</b>	Day 4 post therapy	<b>44%</b> 16/36 Ibuprofen	<b>72%</b> 23/33
<b>Ferry</b>	Post therapy visits day 1 to 8	<b>34%</b> 77/227 Placebo	<b>90%</b> 594/657

Table 2: Clinical Response in uUTI trials

First author	Timing of assessment	Symptom assessment	Control	Antibacterial Drug
<b>Christiaens</b>	Day 4 post therapy	improved or no symptoms	<b>45%</b> 17/38 Placebo	<b>75%</b> 30/40
<b>Bleidorn</b>	Day 1 post therapy	Symptom resolution	<b>53%</b> 21/40 Ibuprofen	<b>43%</b> 17/40
<b>Ferry</b>	Post therapy visits day 1 to 8	no symptoms	<b>25%</b> 57/227 Placebo	<b>60%</b> 396/657

# uUTI Treatment Effects

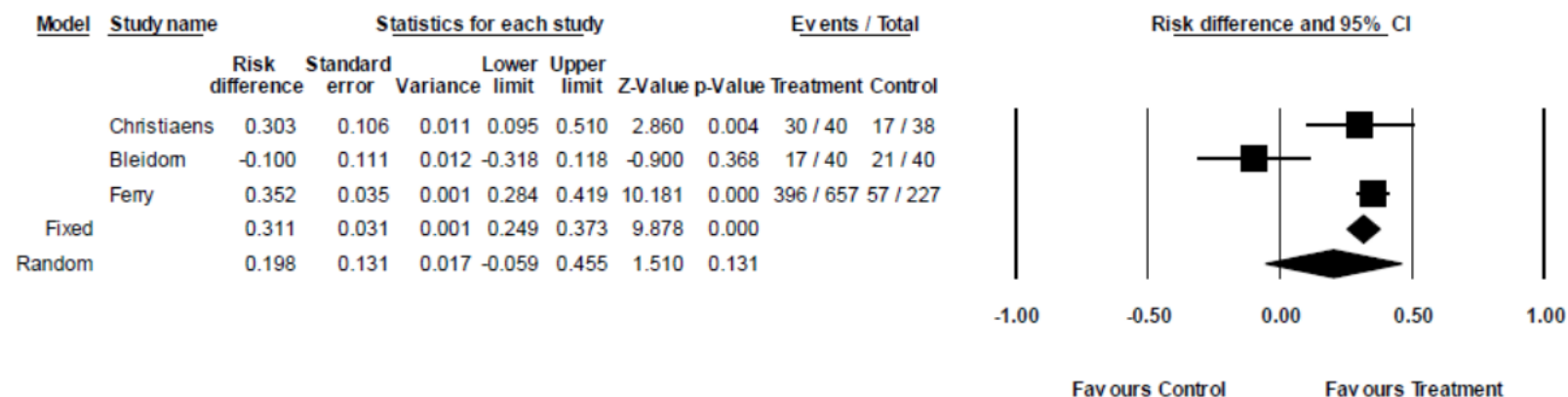
## Microbiological Eradication Outcome Assessment



Random-effects meta-analysis treatment effect was **13%**, the lower bound of the two-sided 95% CI (ibuprofen was used as the control in one study)

# uUTI Treatment Effects

## Clinical Symptom Resolution Outcome Assessment



Random-effects meta-analysis treatment effect crossed zero (ibuprofen was used as the control in one study)

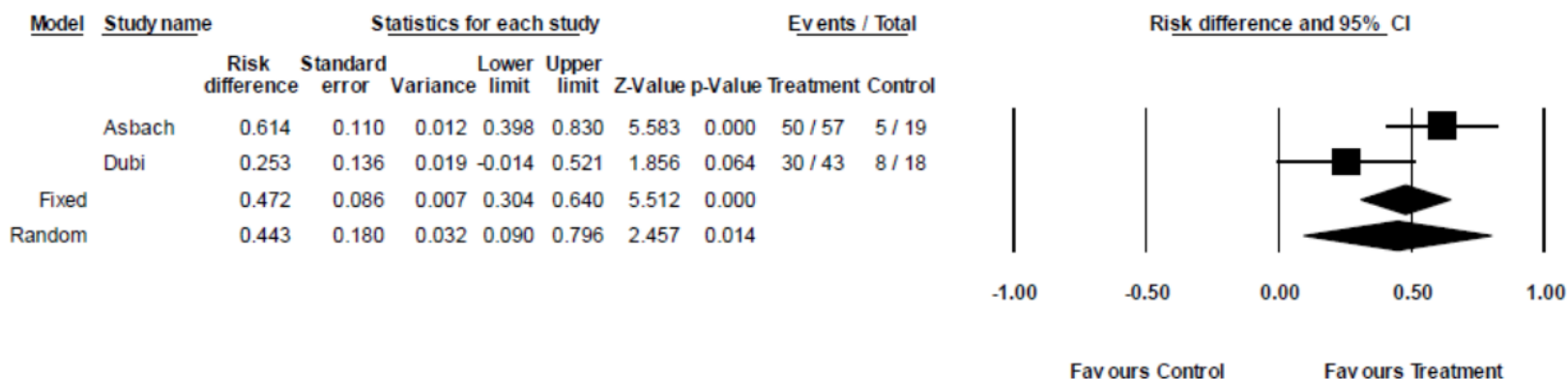
# uUTI Treatment Effects

Table 3: Clinical Symptom Resolution + Micro Eradication Responder Assessment

First author	Timing of assessment	Control	Antibacterial Drug
Asbach	Day 14-17 post therapy	<b>26%</b> 5/19 Placebo	<b>88%</b> 50/57
Dubi	End of treatment	<b>44%</b> 8/18 Placebo	<b>70%</b> 30/43

# uUTI Treatment Effects

## Clinical Symptom Resolution + Micro Eradication Responder Assessment



Random-effects meta-analysis treatment effect was **9%**, the lower bound of the two-sided 95% CI

# uUTI Treatment Effects

- **Summary of literature review and meta-analysis**
  - Treatment effect versus control (placebo or ibuprofen) on microbiological eradication
  - Treatment effect versus placebo control on responder assessment
  - Treatment effect versus placebo control on resolution of symptoms
  - Uncertain if there is any treatment effect versus ibuprofen on resolution of symptoms
- **Strengths**
  - Clinical microbiology laboratory assessments for urine culture are standardized and well-characterized
  - Symptom outcome assessments are straightforward
- **Limitations**
  - Variability in the timing of the outcome assessments
  - Symptom relief with ibuprofen

# uUTI Treatment Effects

## Other summary observations:

- Approx. 34% - 44% of patients randomized to receive placebo achieved microbiological eradication
- One trial reported rescue antibacterial therapy
  - 33% (12/36) randomized to ibuprofen
  - 18% (6/33) randomized to antibacterial drug therapy
- Among the 5 trials, 3 patients treated for pyelonephritis: 2 on placebo; 1 on antibacterial

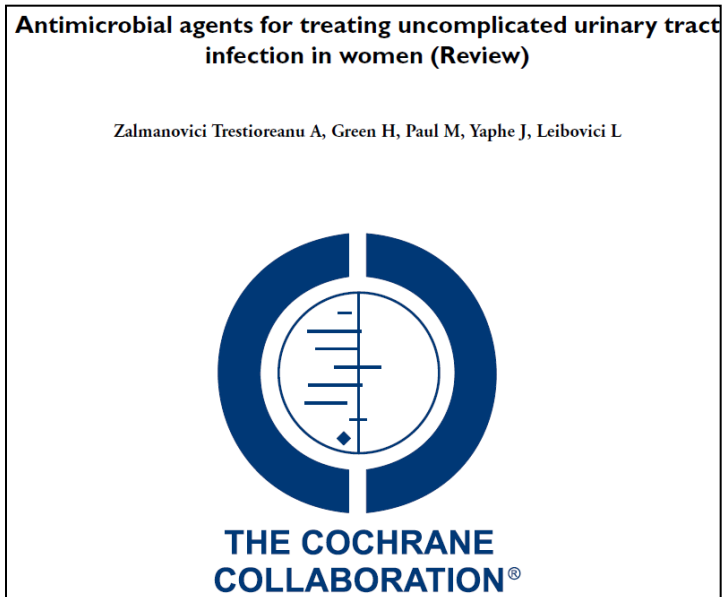
# uUTI Treatment Effects

## Other summary observations, cont.:

- The clinical course of untreated uUTI has not been well-characterized
- The clinical course of untreated asymptomatic bacteriuria in pregnancy has been clearly characterized: relative risk of pyelonephritis is 3.37
  - Gratacos, et al J Infect Dis 1994;169:1390-2



# uUTI Treatment Effects



Cochrane Database 2010, Issue 10

Comparative effectiveness

IDSA GUIDELINES

Executive Summary: International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Gupta, et al, Clin Infect Dis 2011;52:561-4

Treatment with antibacterial drugs  
- there are no options for non-antibacterial therapy

## Treatment Effects: Overall Summary

- **ABS:** treatment effect observed only in a small number of trials
- **ABECB:** treatment effect for hospitalized patients with moderate-to-severe disease; treatment effect based on symptom improvement for outpatients with mild disease
- **uUTI:** treatment effect over control for microbiological eradication; treatment effect over placebo control for symptom resolution; treatment effect over placebo for responder assessment

Joint Meeting of the Antimicrobial Drugs Advisory Committee and  
the Drug Safety and Risk Management Advisory Committee  
November 5, 2015

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

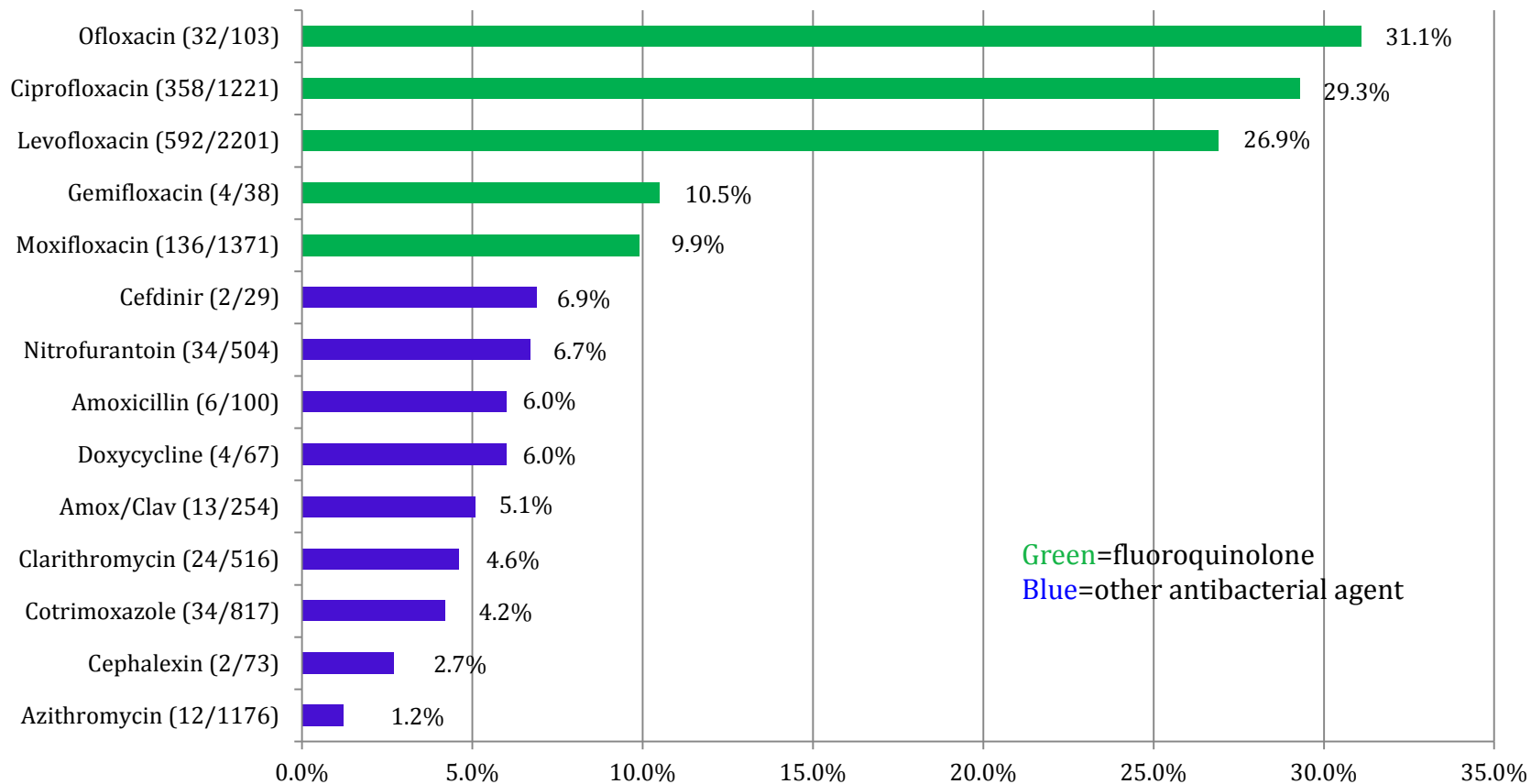
\*Indications PT: Sinusitis acute, Sinusitis bacterial, Sinusitis, Bronchitis acute, Bronchitis, Bronchitis bacterial, Cystitis, Acute cystitis, Cystitis bacterial, Urinary tract infection, UTI-urinary tract infection, Urinary tract infection bacterial

## Disability Search Results

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

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
<b>Levofloxacin</b>	592	91	15%
<b>Ciprofloxacin</b>	358	65	18%
<b>Moxifloxacin</b>	136	19	15%
<b>Ofloxacin</b>	32	2	--
<b>Gemifloxacin</b>	4	1	--
<b>TOTAL</b>	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)

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

**Onset of AEs from start of FQ  
therapy  
(n=102)**

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%)

**Duration of AEs *at the time  
the report was received by  
the FDA*  
(n=166)**

Mean: 61.2 weeks (14 months)

Median: 30 weeks (7 months)

Range: 30 days—9 years

≥ 1 year: n=39 (23%)

## 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  $\geq 4$  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)

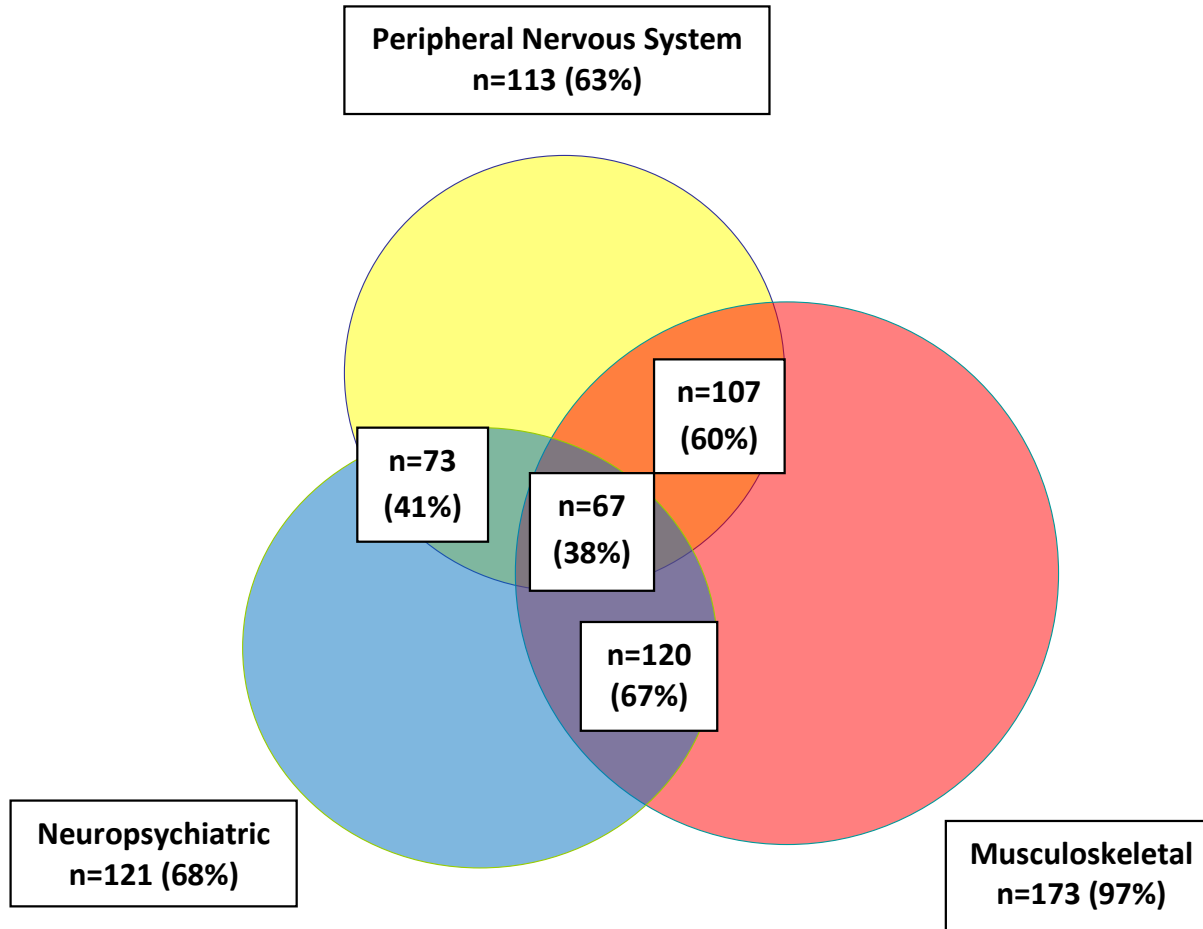
- Ongoing skin rash or acne (13)
- Sweating (7)
- Photosensitivity (7)
- Skin sensitivity to touch (6)
- Hair loss (5)
- Flushing (4)

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
<b>Levofloxacin (n=91)</b>	98%	52%	74%	30%	10%	10%
<b>Ciprofloxacin (n=65)</b>	94%	78%	66%	31%	12%	15%
<b>Moxifloxacin (n=19)</b>	95%	79%	65%	30%	10%	15%
<b>Ofloxacin (n=2)</b>	--	--	--	--	--	--
<b>Gemifloxacin (n=1)</b>	--	--	--	--	--	--

# 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

- The decrease in quality of life was described as being profound, and it affected both the patient and his/her family.



# November 5, 2015 Advisory Committee

Joint meeting of two committees:

- Anti-Infective Drugs Advisory Committee
- Drug Safety and Risk Management Advisory Committee

# Advisory Committee Votes

1. VOTE: Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial sinusitis (ABS)?

**NO: 21** YES: 0 ABSTAIN: 0

2. VOTE: Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease (ABECB-COPD)?

**NO: 18** YES: 2 ABSTAIN: 1

3. VOTE: Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of uncomplicated urinary tract infection (uUTI)?

**NO: 20** YES: 1 ABSTAIN: 0

## Advisory Committee Discussion

- ABS, ABECB, and uUTI: fluoroquinolones should not be used as first-line therapy
- New safety information should be included in labeling
- Better communication to health care professionals

# Drug Safety Communications

## Labeling Changes for Fluoroquinolones

May 12, 2016: FDA announces Safety Labeling Change notification letters to applicants of systemic fluoroquinolones

<http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm>

July 26, 2016: FDA announces approval of the updated safety labeling information for systemic fluoroquinolones

<http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm>

The newly approved changes to the drug labels can be found at the Drugs@FDA

# Fluoroquinolone Class Labeling Changes

## **BOXED WARNING**

Updated to include new warning that serious adverse reactions can occur together and be potentially irreversible; reserve for use in patients who have no alternative treatment options for ABS, ABECB, uUTI.

## **INDICATIONS AND USAGE**

Reserve for use in patients who have no alternative treatment options for ABS, ABECB, uUTI.

## **WARNINGS AND PRECAUTIONS**

Updated to include new warning that serious adverse reactions can occur together and be potentially irreversible

## **INFORMATION FOR PATIENTS AND MEDICATION GUIDE**

Revised accordingly to inform patients about risk of disabling and potentially irreversible serious adverse reactions

# Fluoroquinolone Class Labeling Changes

**WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS**

*See full prescribing information for complete boxed warning.*

- Fluoroquinolones, including CIPRO<sup>®</sup>, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:
    - Tendinitis and tendon rupture (5.2)
    - Peripheral neuropathy (5.3)
    - Central nervous system effects (5.4)
- Discontinue CIPRO immediately and avoid the use of fluoroquinolones, including CIPRO, in patients who experience any of these serious adverse reactions (5.1)
- Fluoroquinolones, including CIPRO, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid CIPRO in patients with known history of myasthenia gravis. (5.5)
  - Because fluoroquinolones, including CIPRO, have been associated with serious adverse reactions (5.1-5.15), reserve CIPRO for use in patients who have no alternative treatment options for the following indications:
    - Acute exacerbation of chronic bronchitis (1.10)
    - Acute uncomplicated cystitis (1.11)
    - Acute sinusitis (1.12)

# Fluoroquinolone Class Labeling Changes

## 1.12 Uncomplicated Urinary Tract Infections

LEVAQUIN<sup>®</sup> is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus*.

Because fluoroquinolones, including LEVAQUIN, have been associated with serious adverse reactions [see *Warnings and Precautions (5.1-5.14)*] and for some patients uncomplicated urinary tract infection is self-limiting, reserve LEVAQUIN for treatment of uncomplicated urinary tract infections in patients who have no alternative treatment options.

# Fluoroquinolone Class Labeling Changes

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects

Fluoroquinolones, including LEVAQUIN, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting LEVAQUIN. Patients of any age or without pre-existing risk factors have experienced these adverse reactions [*see Warnings and Precautions (5.2, 5.3, 5.4)*].

Discontinue LEVAQUIN immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including LEVAQUIN, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.



# Fluoroquinolone Class Labeling Changes

**MEDICATION GUIDE**  
**AVELOX<sup>®</sup> (AV-eh-locks)**  
**(moxifloxacin hydrochloride)**  
**Tablets**

**AVELOX<sup>®</sup> (AV-eh-locks)**  
**(moxifloxacin hydrochloride)**  
**Injection Solution for Intravenous use**

Read the Medication Guide that comes with AVELOX<sup>®</sup> before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

## **What is the most important information I should know about AVELOX?**

AVELOX belongs to a class of antibiotics called fluoroquinolones. AVELOX can cause serious side effects that can happen at the same time and could result in death. If you get any of the following serious side effects, you should stop taking AVELOX and get medical help right away. Talk with your healthcare provider about whether you should continue to take AVELOX.

# Challenge Question 1

Which of the following adverse reactions have been described to be disabling and potentially irreversible and occur together in the same patient?

- a. Peripheral neuropathy, central nervous system effects, tendinitis/tendon rupture
- b. Hemolytic anemia, liver failure, peripheral neuropathy
- c. Tendinitis/tendon rupture, thrombocytopenia, orthostatic hypotension

# Challenge Question 1

Which of the following adverse reactions have been described to be disabling and potentially irreversible and occur together in the same patient?

- a. Peripheral neuropathy, central nervous system effects, tendinitis/tendon rupture**
- b. Hemolytic anemia, liver failure, peripheral neuropathy
- c. Tendinitis/tendon rupture, thrombocytopenia, orthostatic hypotension

Answer “a” describes the disabling and potentially irreversible serious adverse reactions that were observed to occur in the same patient

## Challenge Question 2

You are seeing a patient in an urgent care center who complains about numbness and tingling in the lower legs, tenderness of the ankles, and new feelings of anxiety for the past 12 hours. You prescribed ciprofloxacin 250 mg BID x 3 days for treatment of uncomplicated urinary tract infection 2 days ago, and she has taken a total of 3 ciprofloxacin tablets. Tenderness in her Achilles tendons subsided but on exam she has moderate tenderness of her thumb tendons on both hands, and no neurological abnormalities. Her symptoms of urinary tract infection have resolved. What is the most appropriate next step?

- a. Continue ciprofloxacin for another day
- b. Stop ciprofloxacin and switch to nitrofurantoin and complete a 7 day course of therapy
- c. Stop ciprofloxacin and tell her that these symptoms will promptly resolve
- d. Stop ciprofloxacin and arrange for her to establish care with a primary care clinician for management of her symptoms that may become permanent
- e. Continue ciprofloxacin for another day and begin treatment for de Quervain's tenosynovitis with naproxen and physical therapy

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- e. Continue ciprofloxacin for another day and begin treatment for de Quervain's tenosynovitis with naproxen and physical therapy

“d” is the correct answer –stop the fluoroquinolone and offer follow up care for management of her adverse reactions; uUTI symptoms have resolved and she probably doesn't need additional antibacterial therapy

## Challenge Question 3

Which of the following infectious disease indications for levofloxacin has no limitation of use statements and the benefit remains highly favorable when considering the risks?

- a. Uncomplicated urinary tract infections
- b. Community-acquired bacterial pneumonia
- c. Acute bacterial sinusitis
- d. Acute bacterial exacerbation of chronic bronchitis

## Challenge Question 3

Which of the following infectious disease indications for levofloxacin has no limitation of use statements and the benefit remains highly favorable when considering the risks?

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- b. Community-acquired bacterial pneumonia**
- c. Acute bacterial sinusitis
- d. Acute bacterial exacerbation of chronic bronchitis

The benefits of antibacterial drugs such as systemic fluoroquinolones for bacterial pneumonia (answer “b”) outweigh the risks, but always be mindful of the potential adverse reactions when prescribing a fluoroquinolone drug.

# Challenge Questions 4

What is the best therapeutic option for a patient with a two day history of sinus headache, sinus congestion, and low-grade temperature elevation of 99 degrees F?

- a. Levofloxacin
- b. Amoxicillin - clavulanate
- c. Over-the-counter decongestant therapy and analgesia
- d. Both "a" and "c"



# Challenge Questions 4

What is the best therapeutic option for a patient with a two day history of sinus headache, sinus congestion, and low-grade temperature elevation of 99 degrees F?

- a. Levofloxacin
- b. Amoxicillin - clavulanate
- c. Over-the-counter decongestant therapy and analgesia**
- d. Both "a" and "c"

Symptoms of acute sinusitis are infrequently caused by a bacterial infection, and answer "c" is the best answer. Most cases of acute sinusitis are caused by a viral infection and respond well to therapy directed to the patient's symptoms.

# Challenge Question 5

True or False Question

Clinicians can easily identify and confirm the adverse events associated with disabling and potentially irreversible serious adverse reactions associated with fluoroquinolones.

True

False

# Challenge Question 5

## True or False Question

Clinicians can easily identify and confirm the adverse events that can be disabling and potentially irreversible serious adverse reactions associated with fluoroquinolones.

True

**False**

Not every clinician has encountered a patient who experienced the disabling and potentially irreversible adverse reactions and this unusual constellation of adverse reaction may not be easily identified. Furthermore, with the exception of tendon rupture, clinical testing related to the adverse reaction might not readily document the findings.