FDA Introductory Remarks

Sumati Nambiar, MD, MPH
Director, Division of Anti-Infective Products, FDA

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

Purpose of Today's Meeting

- To discuss the benefits and risks of the systemic fluoroquinolone antibacterial drugs for the following indications given the scientific advances in clinical trials and the safety profile that has emerged over the lifecycle of these drugs:
  - Acute bacterial sinusitis (ABS)
  - Acute bacterial exacerbation of chronic bronchitis (ABECB)
  - Uncomplicated urinary tract infections (uUTI)

Background

Currently Available Systemic Fluoroquinolones

Drug	Initial Approval
Ciprofloxacin	1987
Ofloxacin	1990
Levofloxacin	1996
Moxifloxacin	1999
Ciprofloxacin ER	2002
Gemifloxacin	2003

Norfloxacin, initial approval in 1986 (NDA 19384), discontinued. NDA not yet withdrawn; ER=Extended-release.

Approved Indications to be Considered Today*

	ABS	ABECB	uUTI	Acute Uncomplicated Cystitis
Ciprofloxacin	√		√^	√
Ofloxacin		√		√
Levofloxacin	√	√	√	
Moxifloxacin	√	√		
Gemifloxacin		√		
Ciprofloxacin ER			√	

*Each of these fluoroquinolones is approved for one or more indications not listed in the table
^Labeled indication: UTI

Safety Labeling

- Boxed Warning
  - Tendinopathy and Tendon Rupture
  - Exacerbation of Myasthenia Gravis
- Warnings and Precautions Section
  - Hypersensitivity Reactions
  - Hepatotoxicity
  - Central Nervous System Effects
  - Peripheral Neuropathy
  - Prolongation of the QT Interval
  - Blood Glucose Disturbances
  - Photosensitivity/Phototoxicity
- Adverse Reactions Section
  - Clinical trials and postmarketing experience
- Medication Guide
  - Required under 21 CFR 208.1

Tendinitis and Tendon Rupture Safety Labeling

- Norfloxacin (1986) and ciprofloxacin (1987) labeling included nonclinical information on joint pathology in the Warnings and Precautions sections
- In 1996, labeling for all marketed fluoroquinolones were updated to include a warning of tendon rupture based on clinical evidence for tendon/joint toxicity associated with fluoroquinolone use
- Subsequently approved fluoroquinolones included warning for risk of tendon rupture (Class effect)
- In 2004, the warning was expanded to include information on the at-risk populations
- In 2008, a Boxed Warning was added to describe the risk and the at-risk populations

Safety Updates

- Central Nervous System:
  - Seizures, tremors and alterations of mental state included in ciprofloxacin labeling at the time of approval
  - In 1990, CNS adverse reactions including increased intracranial pressure and psychosis were added to Warnings/Precautions
  - In 2011, pseudotumor cerebri was added to the CNS toxicity warning
- Peripheral Neuropathy
  - In 2004, labeling updated to include a warning regarding peripheral neuropathy
  - In 2013, revised to add potential for neuropathy to be irreversible
- Exacerbation of Myasthenia Gravis
  - In 2010, included in Boxed Warning following review of cases with fatal outcome; prior to this was included in other sections of labeling

Safety Updates

- QT Prolongation and Torsades de Pointes
  - Since the 1990's information about proarrhythmic potential included in labeling
  - Cautionary statements regarding increased risk of QT prolongation resulting in TdP was included in most fluoroquinolone labels. Subsequent revisions for use in geriatric population inclusion of risk factors for QT prolongation
- Phototoxicity
  - In 2007, phototoxicity was included in the Warnings and Precautions section
- Hypersensitivity
  - Serious and sometimes fatal hypersensitivity reactions are included in the Warnings and Precautions section and continue to be updated based on postmarketing safety data

Emerging Safety Issues

- In the last few years, we have received an increasing number of postmarketing reports from patients describing signs and symptoms involving different body sites that often interfere with activities of daily living and can persist
- Recent publications describing increased risk of the following with fluoroquinolone use; these will not be discussed at today's meeting
  - Retinal detachment
  - Aortic aneursym rupture

Chang CC. JAMA Intern Med. Oct 2015
Chui CS. J Antimicrob Chemother Apr 2015

Overview of Treatment Benefit

- Prior discussions at advisory committee meetings on treatment benefit of antibacterial drugs for ABECB and ABS (2002, 2003)
  - Placebo-controlled trials acceptable for ABS and mild ABECB
- Discussion about risks and benefits of telithromycin (Ketek) at an advisory committee meeting in 2006 and subsequent removal of the indications for treatment of ABECB and ABS from telithromycin labeling
- Treatment benefits of antibacterial drugs for uUTI have not been discussed previously in an FDA public forum

http://www.fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective
http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective
http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective
http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3837t1.htm

Overview of Safety Data

- Drug utilization data for oral ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin
  - National estimates of patients and prescriptions from the U.S. outpatient retail pharmacy setting, 2010 through 2014
  - Office-based physician survey data, 2010 & 2014
    - diagnoses mentioned in association with a fluoroquinolone
    - drug molecules mentioned in association with a diagnosis
- Review of epidemiologic studies
  - Focusing on labeled events: tendinopathy, cardiac arrhythmia, and peripheral neuropathy
- Pharmacovigilance data
  - Review of the FDA Adverse Event Reporting System (FAERS) to characterize the constellation of symptoms associated with disability

Outline For the Day

- FDA Presentations
  - Joseph Toerner, MD MPH:
    - ABS, ABECB, and uUTI Antibacterial Drug Treatment Effect
  - Travis Ready, Pharm D:
    - Oral Fluoroquinolone Utilization Patterns
  - James Trinidad, MPH MS:
    - Epidemiology of Selected Fluoroquinolone-associated Adverse Reactions – A Literature Review
  - Debra Boxwell, Pharm D:
    - "Fluoroquinolone-Associated Disability" (FQAD) Cases in Patients Being Treated for Uncomplicated Sinusitis, Bronchitis, and/or Urinary Tract Infection

Outline For the Day

- Industry Presentations
- Lunch Break
- Open Public Hearing
- Discussion and Questions to the Committee

Question 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)?
  a. Following your vote, please provide specific recommendations, if any, concerning the indications for treatment of ABS and safety information discussed today, including the constellation of adverse reactions that were characterized as a fluoroquinolone-associated disability (FQAD)

Question 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 (ABECB)?
  a. Following your vote, please provide specific recommendations, if any, concerning the indications for treatment of ABECB and safety information discussed today, including the constellation of adverse reactions that were characterized as a fluoroquinolone-associated disability (FQAD)

Question 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 infections (uUTI)/acute uncomplicated cystitis?
  a. Following your vote, please provide specific recommendations, if any, concerning the indications for treatment of uUTI and safety information discussed today, including the constellation of adverse reactions that were characterized as a fluoroquinolone-associated disability (FQAD)

ABS, ABECB, and uUTI Antibacterial Drug Treatment Effects

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

Joseph G. Toerner, MD, MPH
Deputy Director for Safety
Division of Anti-Infective Products, CDER/FDA

Outline of the Presentation

- Regulatory Overview
- Treatment Effects
  - ABS
  - ABECB
  - uUTI
- Summary

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 for 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

THE COCHRANE COLLABORATION®

"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

THE COCHRANE COLLABORATION®

"…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

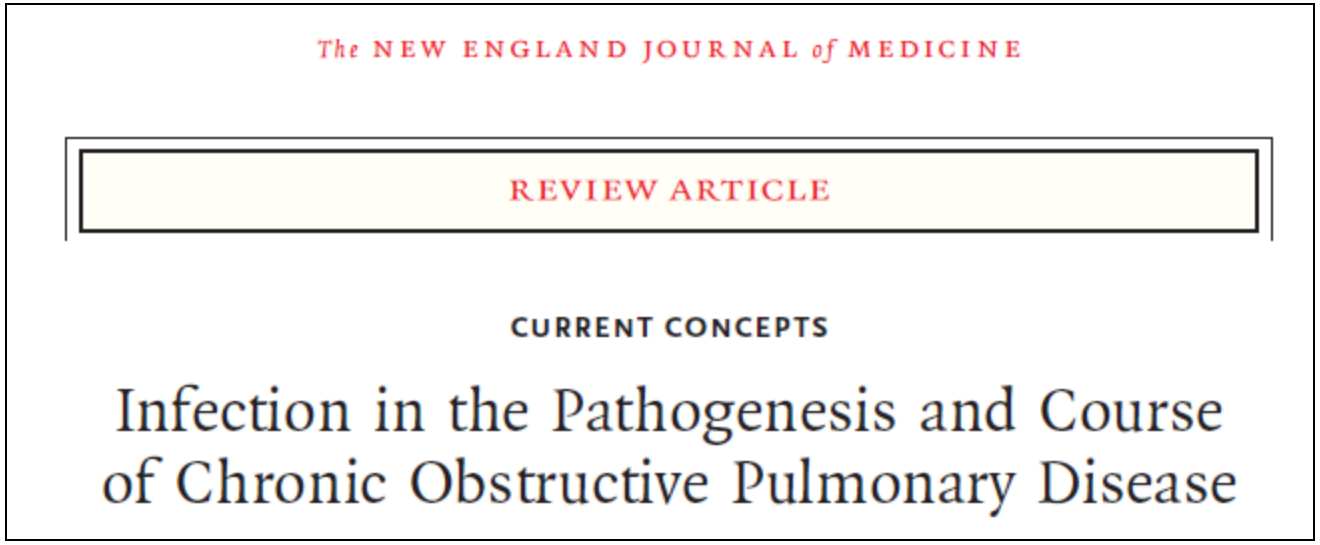
Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Summary and Appraisal of Published Evidence

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

Table1: Microbiologic eradication of bacteria in uUTI trials

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

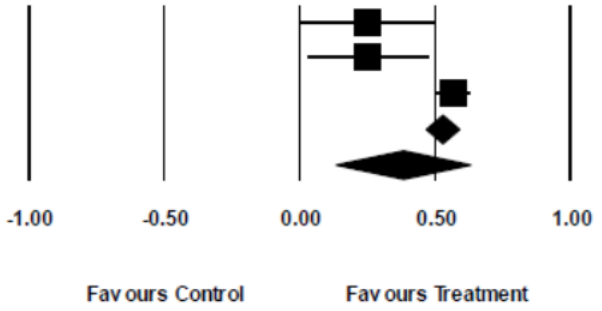
Table 2: Clinical Response in uUTI trials

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

uUTI Treatment Effects

Microbiological Eradication Outcome Assessment

Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Treatment	Events / Total Control
	Christiaens	0.253	0.129	0.017	0.000	0.505	1.963	0.050	17 / 29	9 / 27
	Bleidorn	0.253	0.115	0.013	0.027	0.478	2.193	0.028	23 / 33	16 / 36
	Ferry	0.565	0.033	0.001	0.499	0.630	16.884	0.000	594 / 657	77 / 227
Fixed		0.524	0.031	0.001	0.463	0.585	16.801	0.000		
Random		0.378	0.127	0.016	0.130	0.626	2.986	0.003		

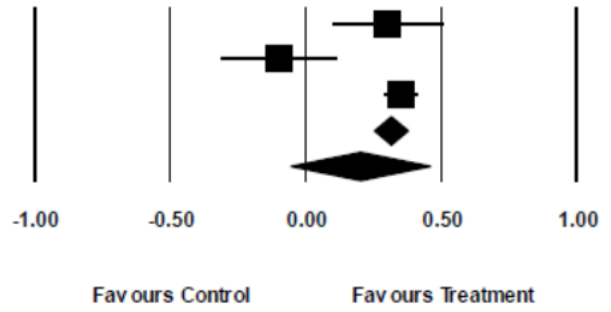


Random-effects meta-analysis treatment effect was **13%**, the lower bound of the two-sided 95% CI (ibuprofen was used as the control in one study)

uUTI Treatment Effects

Clinical Symptom Resolution Outcome Assessment

Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Treatment	Events / Total Control
	Christiaens	0.303	0.106	0.011	0.095	0.510	2.860	0.004	30 / 40	17 / 38
	Bleidorn	-0.100	0.111	0.012	-0.318	0.118	-0.900	0.368	17 / 40	21 / 40
	Ferry	0.352	0.035	0.001	0.284	0.419	10.181	0.000	396 / 657	57 / 227
Fixed		0.311	0.031	0.001	0.249	0.373	9.878	0.000		
Random		0.198	0.131	0.017	-0.059	0.455	1.510	0.131		



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

uUTI Treatment Effects

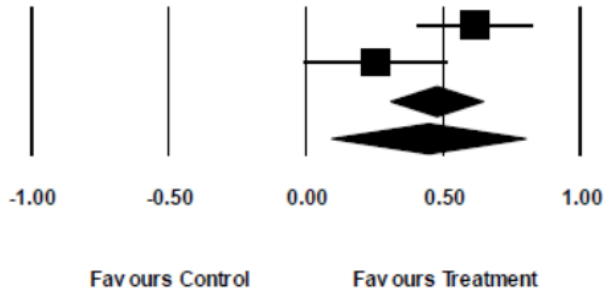
Table 3: Clinical Symptom Resolution + Micro Eradication Responder Assessment

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

uUTI Treatment Effects

Clinical Symptom Resolution + Micro Eradication Responder Assessment

Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Treatment	Events / Total Control
	Asbach	0.614	0.110	0.012	0.398	0.830	5.583	0.000	50 / 57	5 / 19
	Dubi	0.253	0.136	0.019	-0.014	0.521	1.856	0.064	30 / 43	8 / 18
Fixed		0.472	0.086	0.007	0.304	0.640	5.512	0.000		
Random		0.443	0.180	0.032	0.090	0.796	2.457	0.014		



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 Dis1994;169:1390-2

uUTI Treatment Effects

Antimicrobial agents for treating uncomplicated urinary tract infection in women (Review)

Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L

THE COCHRANE COLLABORATION®

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

Oral Fluoroquinolone Utilization Patterns

Travis Ready, Pharm.D.
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration
November 5, 2015

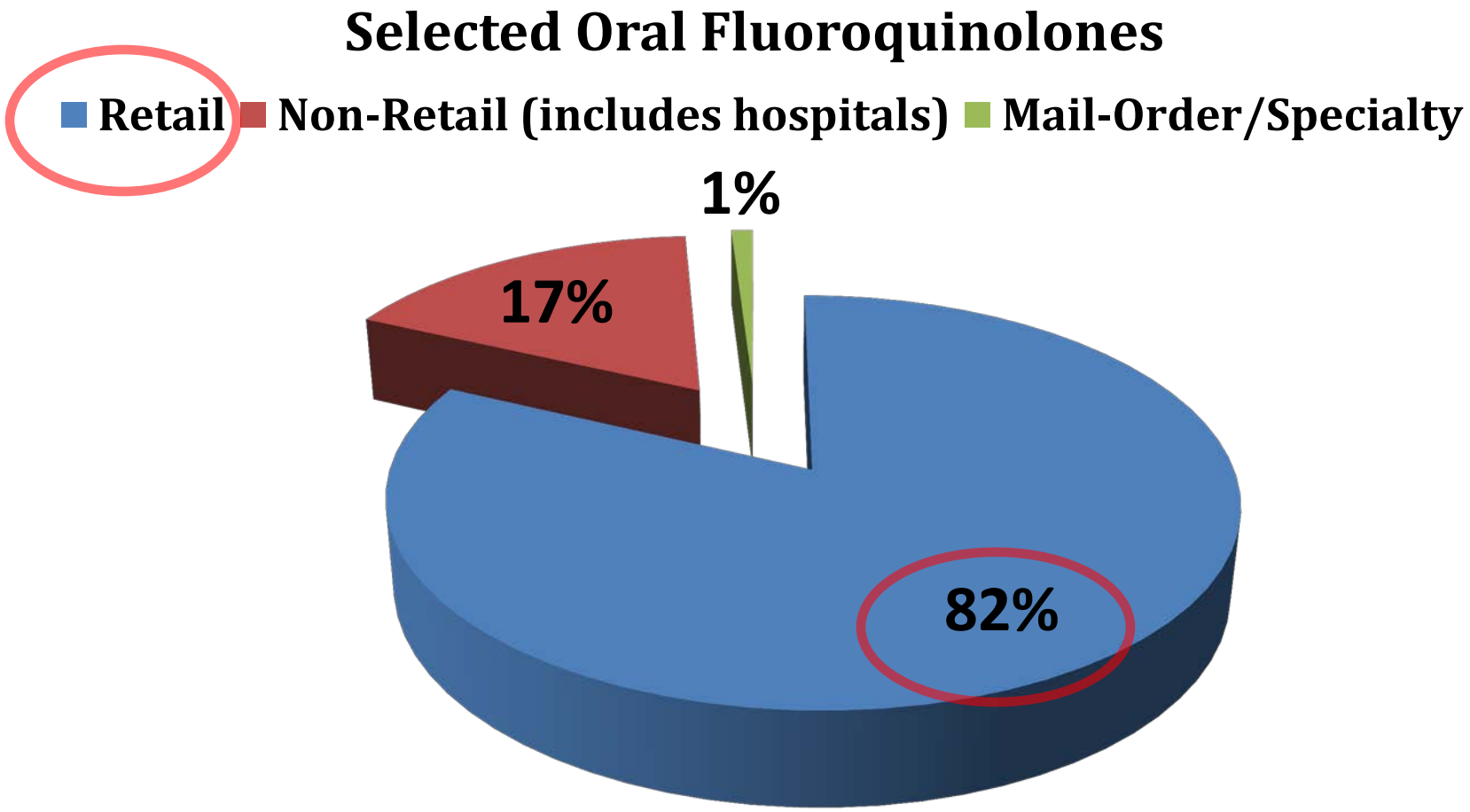
Selected Oral Fluoroquinolones

- Ciprofloxacin
- Levofloxacin
- Moxifloxacin
- Gemifloxacin
- Ofloxacin

Outline

- U.S. sales distribution data
- U.S. outpatient retail pharmacy utilization data
  - Prescription and patient level data
  - Top prescriber specialties
- U.S. office-based physician surveys
  - Top diagnoses
  - Top drugs
- Limitations
- Key Findings

U.S. Sales Distribution for 2014



Source: IMS Health, National Sales Perspectives™. Year 2014. Data extracted August 2015.

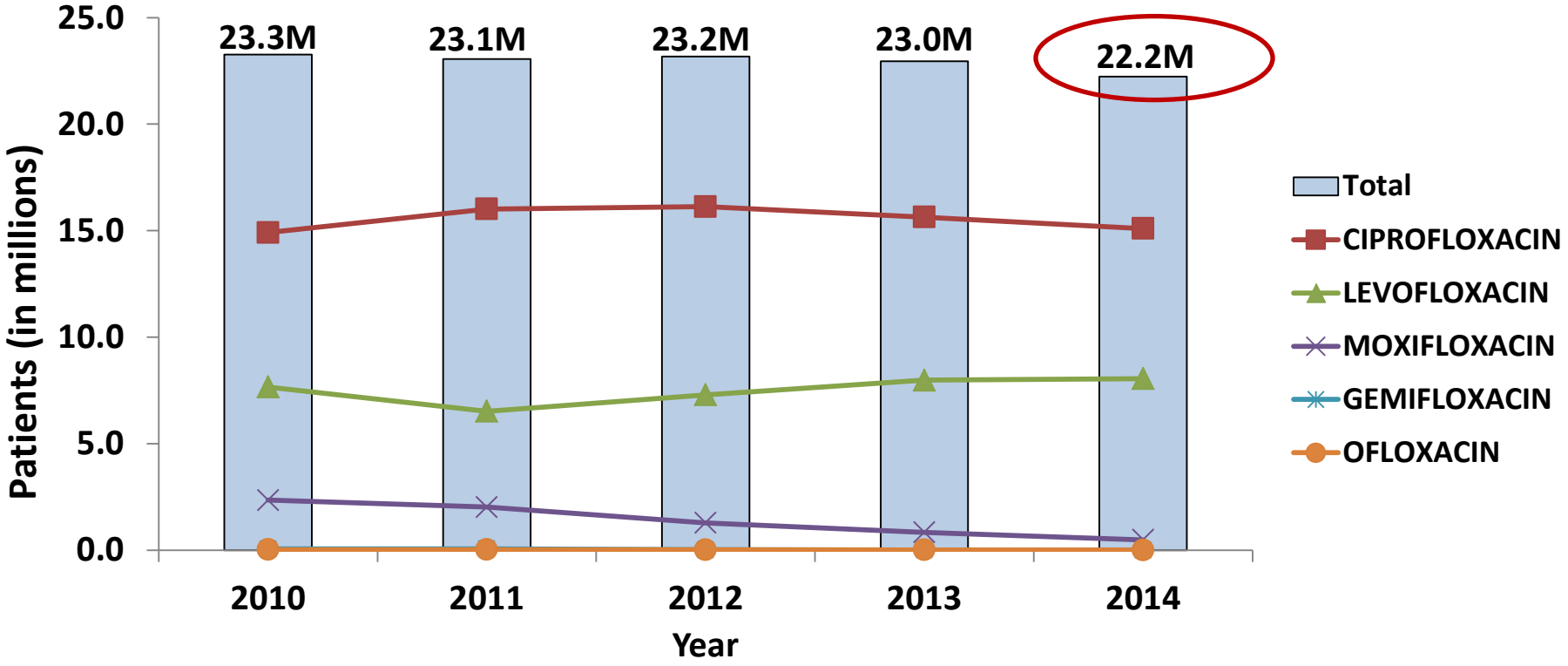
U.S. Outpatient Retail Pharmacy Utilization of Oral Fluoroquinolones

2010-2014

IMS Health, Vector One®: Total Patient Tracker (TPT)

IMS Health: National Prescription Audit® (NPA)

Patient Data

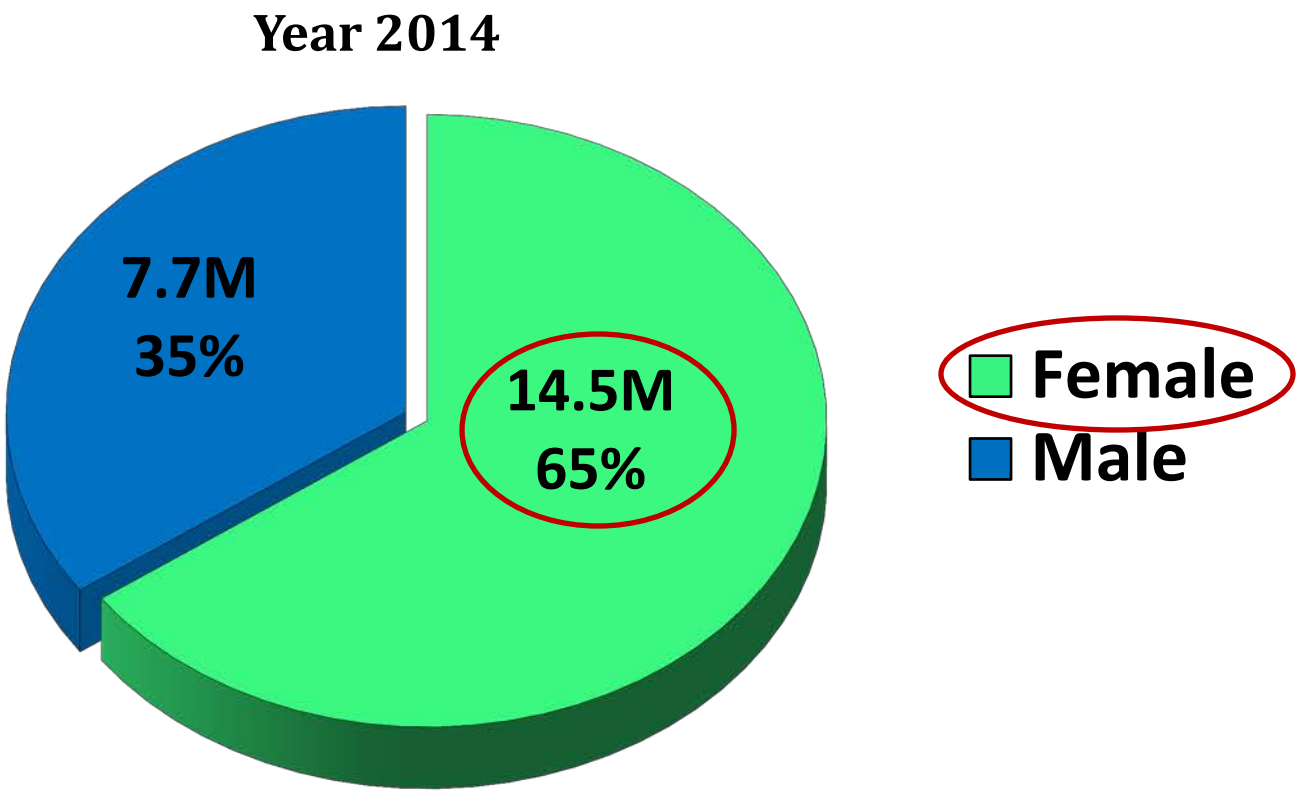


Nationally estimated number of unique patients* who received dispensed prescriptions for selected oral fluoroquinolones from U.S. outpatient retail pharmacies

Summing patients across products or time periods will result in double counting and overestimates of patient counts, and a total percentage >100%.

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010 through 2014. Data extracted AUG 2015.

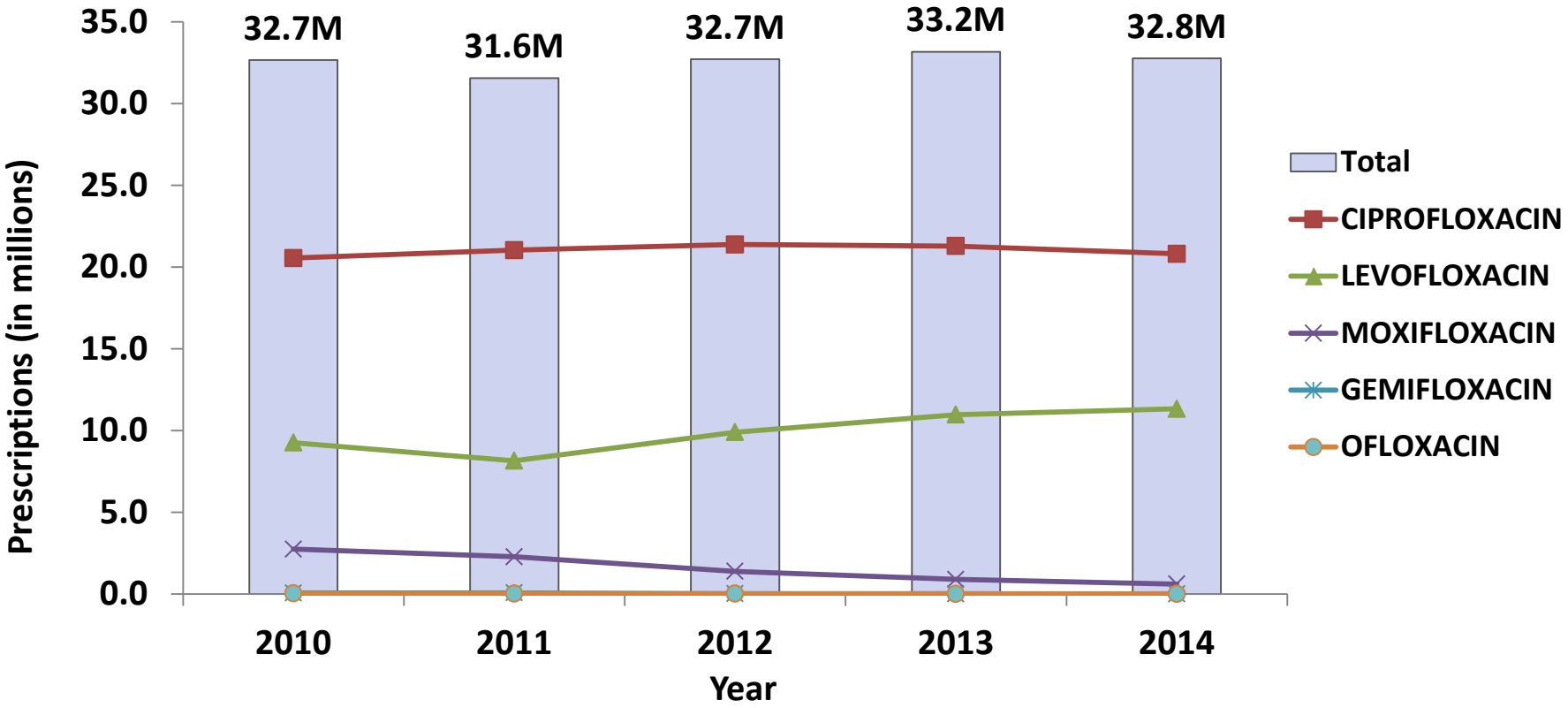
Patients Demographics



Nationally estimated number of unique patients, by patient sex, who received dispensed prescriptions for selected oral fluoroquinolones from U.S. outpatient retail pharmacies in 2014

Source: IMS Health, Vector One®: Total Patient Tracker. Year 2014. Data extracted AUG 2015.

Dispensed Prescriptions



Nationally estimated number of prescriptions for selected oral fluoroquinolones dispensed from U.S. outpatient retail pharmacies

Source: IMS Health, National Prescription Audit™. Years 2010 through 2014. Data extracted August 2015.

Top Prescriber Specialties

Top prescribing specialties of selected oral fluoroquinolones by number of prescriptions dispensed from U.S. outpatient retail pharmacies, 2014

	TRx (N)	*Share %*
Total Prescriptions	**32,768,680**	***100.0%***
Family Practice	**6,706,881**	***20.5%***
Internal Medicine	**6,287,868**	***19.2%***
Nurse Practitioner	**3,209,545**	***9.8%***
Osteopathic Medicine	**3,172,033**	***9.7%***
Physician Assistant	**2,676,992**	***8.2%***
Urology	**2,186,872**	***6.7%***
Emergency Medicine	**1,685,179**	***5.1%***
Specialty Unspecified	**770,250**	***2.4%***
Obstetrics/Gynecology	**768,209**	***2.3%***
General Surgery	**487,293**	***1.5%***
All Other Specialties	**4,817,558**	***14.7%***

Source: IMS Health, National Prescription Audit™. Year 2014. Data extracted August 2015.

Diagnoses Associated with Utilization of Selected Oral Fluoroquinolones

Encuity Research, LLC., TreatmentAnswers™ Database

The term "drug use mention" refers to mentions of a drug in association with a diagnosis (ICD-9 codes) during a patient visit to an office-based physician. More than one diagnosis may be mentioned during a visit. A "drug use mention" does not necessarily result in a prescription being generated; rather, the term indicates the drug or product was mentioned during an office visit. Due to small sample size and wide confidence intervals, counts below 100,000 do not provide reliable national estimates of use.

Top Diagnoses in 2014

Top diagnoses expressed as "drug use mentions" associated with selected oral fluoroquinolones in descending order

1. **Ciprofloxacin (N = 17.9 million drug use mentions)**
   - **Urinary Tract Infection, NOS*: 43%**
   - **Prostatitis, NOS: 4%**
2. **Levofloxacin (N = 9.5 million drug use mentions)**
   - **Pneumonia, NOS: 22%**
   - **Urinary Tract Infection, NOS: 13%**
3. **Moxifloxacin (N = 1.8 million drug use mentions)**
   - **Bronchitis NOS: 22%**
   - **Pneumonia, NOS: 19%**
4. **Gemifloxacin (N = 119,000 drug use mentions)**
   - **Acute bronchitis: 90%**
5. **Ofloxacin** *(numbers too low for reliable national estimates)*

*NOS: not otherwise specified

Source: Encuity Research, LLC., TreatmentAnswers™. Year 2014. Data extracted August 2015.

Selected Diagnoses by Drug

- **ABECB broadly defined as:**
  - **COPD with exacerbation (ICD9: 491.212)**
  - **Obstructive chronic bronchitis with exacerbation (ICD9: 491.210)**
  - **Obstructive chronic bronchitis with acute bronchitis (ICD9: 491.220)**

- **uUTI broadly defined as:**
  - **Acute cystitis (ICD9: 595.000)**
  - **Cystitis NEC (ICD9: 595.890)**
  - **Cystitis NOS (ICD9: 595.900)**
  - **Urinary tract infection NOS (ICD9: 599.000)**

- **AS (acute sinusitis*): ICD9 461.x**

ICD9 codes describing the etiology, such as viral or bacterial, are not available

Top Antibiotics for Selected Diagnoses, 2014

- **Top antibiotics* associated with broadly defined** <u>ABECB</u>
  (N= 594,000 drug use mentions)
  - Azithromycin: **27%**
  - Levofloxacin: **23%**
- **Top antibiotics* associated with acute sinusitis (ICD9 461.x)**
  (N= 8.9M drug use mentions)
  - Amoxicillin/clavulanic acid: **28%**
  - Amoxicillin: **26%**
  - Azithromycin: **20%**
  - Levofloxacin: **6%**

systemic, oral forms only

****diagnoses include: COPD with exacerbation (ICD9: 491.212), obstructive chronic bronchitis with exacerbation (ICD9: 491.210), and obstructive chronic bronchitis with acute bronchitis (ICD9: 491.220)***

Source: Encuity Research, LLC., TreatmentAnswers™. Year 2014. Data extracted August 2015.

Top Drugs for Selected Diagnoses for 2014

- **Top drug molecules* associated with broadly defined** uUTI (N=25.2M drug use mentions)**
  - Ciprofloxacin: **32%**
  - Nitrofurantoin: **23%**
  - Sulfamethoxazole/trimethoprim: **22%**
  - Phenazopyridine: **8%**
  - Levofloxacin: **5%**

systemic, oral forms only

****diagnoses include: acute cystitis (ICD9: 595.000), cystitis NEC (ICD9: 595.890), cystitis NOS (ICD9: 595.900), and urinary tract infection NOS (ICD9 599.000)***

Source: Encuity Research, LLC., TreatmentAnswers™. Year 2014. Data extracted August 2015.

Limitations

- Data are from outpatient retail pharmacy settings
  - Not applicable to other settings of care, e.g. hospitals or mail-order/specialty setting
- Diagnoses data indicate that a given drug was mentioned during an office visit
  - Prescriptions are not necessarily generated
- No specific ICD-9 codes for indications of interest
  - Broadened definitions for uUTI and ABECB may include more severe disease states

Key Findings

- Widely used and total use has remained steady over recent years
- Ciprofloxacin is the most commonly used, followed by levofloxacin and moxifloxacin
- Majority of patients were female
- Primary care and mid-level practitioners are the primary prescribers
- According to an office-based physician survey database, fluoroquinolones were associated with possible acute sinusitis, uUTI (broadly defined), and ABECB (broadly defined)

Joint Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

Epidemiology of Selected Fluoroquinolone-Associated Adverse Reactions – A Literature Review

Presenter: James Phillip Trinidad, M.P.H., M.S., LCDR-USPHS
Chih-Ying (Natasha) Chen, Ph.D.
Veronica Sansing-Foster, Ph.D., M.S.
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration

November 5, 2015

Outline

- Literature search
- Studies of tendinopathy
- Studies of serious cardiac arrhythmia
- Studies of peripheral neuropathy
- Conclusion

Literature Search Methods

PubMed search
Publications on fluoroquinolones and adverse events* in humans, English-only, published from January 1, 1986 to May 15, 2015
(N=722 Citations)

*Adverse events
Acute kidney injury
Anaphylaxis/Hypersensitivity
Tendinopathy
Peripheral neuropathy
Retinal detachment
Cardiac arrhythmia

Exclude:
Case reports/ series, Commentaries/reviews
Methods development, No safety data
Pediatric populations only
Non-systemic exposures only (ophthalmic, optic, or topical)
Inpatient setting only

11 studies of tendinopathy + 1 study (poster)

12 studies of serious cardiac arrhythmia

2 studies of peripheral neuropathy

TENDINOPATHY

Fluoroquinolone Labeling: Tendinopathy

- Class-wide boxed warning for tendinitis and tendon rupture

- Increased risk among patients with the following characteristics:
  - Over 60 years of age
  - Taking corticosteroids
  - Have kidney, heart, or lung transplants

Out of twelve studies, four were of higher quality

- Twelve studies identified

- Quality criteria for in-depth review
  - Adjudication of tendinopathy cases
  - No restriction to transplant recipients only

→ Four studies selected for in-depth review

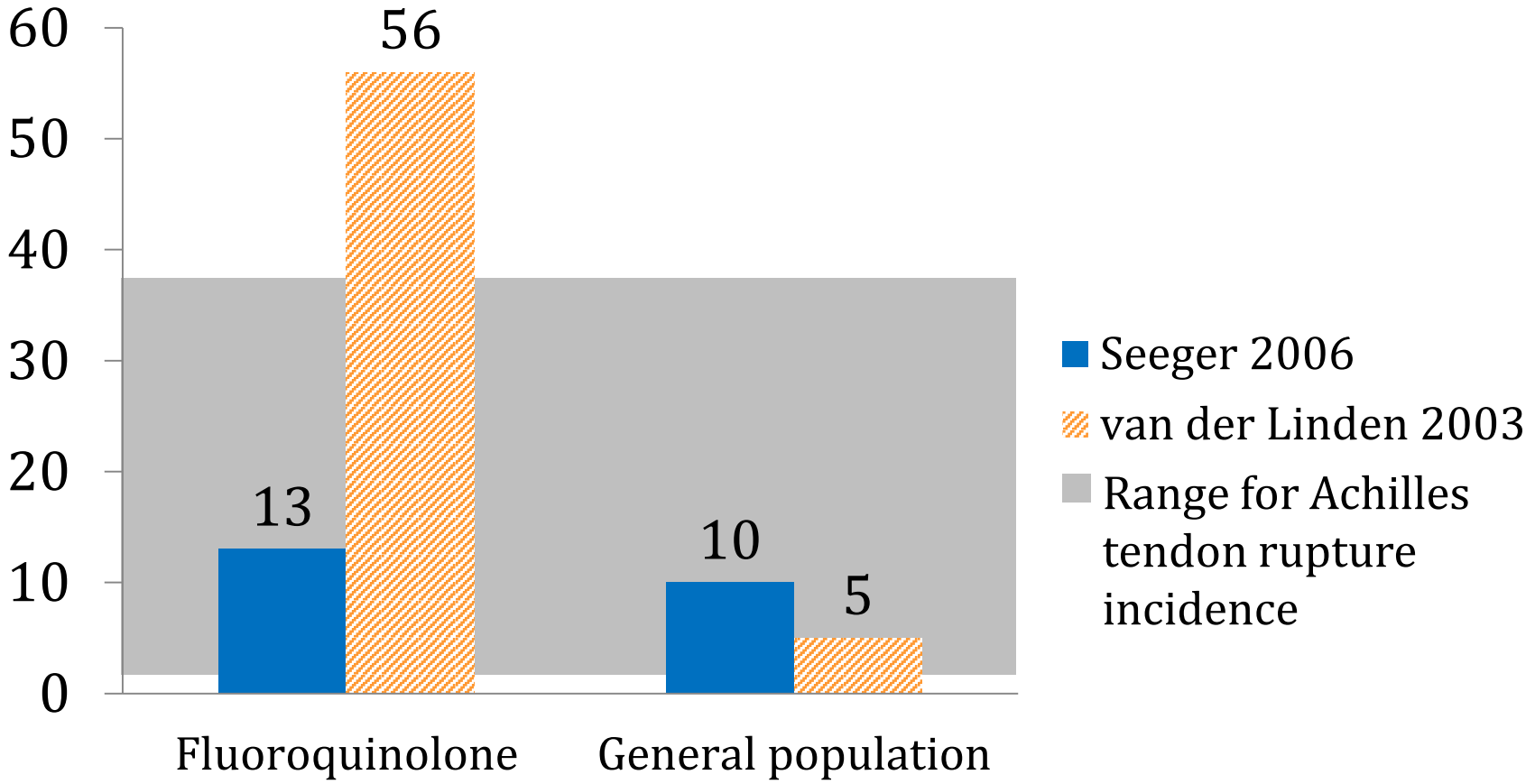
Different methods found consistently increased tendinopathy risk in patients taking fluoroquinolones (1)

- Designs: Case-control or cohort
- Data: Health care claims or prescription-event monitoring
- Comparator: Other antibiotics and/or no exposure
- Outcomes: Tendinopathy, Achilles tendon rupture (ATR), and/or tendinitis
- Risk windows: 6 months, 2 months, or 1 month
- Confounder adjustment: Multivariate, univariate, age restriction

Different methods found consistently increased tendinopathy risk in patients taking fluoroquinolones (2)

- Seeger (2006): aOR = 1.2, 95% CI [0.9, 1.7]
- Wilton (1996): cRR = 2.7, 95% CI [0.8, 9.5]
- van der Linden (1999): aRR = 2.1, 95% CI [0.8, 5.1]
- van der Linden (2003): cRR = 11.0, 95% CI [5.8, 20.8]
  - Restricted to elderly (≥60) patients

Achilles Tendon Rupture (per 100,000 person-years)



Degree of evidence for effect modification by age, corticosteroid use, and transplant status

- Two studies found increased risk of tendinopathy among elderly (≥60) among corticosteroid users
  - Seeger and van der Linden (2003): Increased association with fluoroquinolones or quinolones among elderly using corticosteroids
  - van der Linden (2003): High risk when restricting to elderly, regardless of corticosteroid use

- No study stratified by transplant recipient status
  - Corticosteroid use could increase risk among transplant recipients

Most of boxed warning supported by epidemiological data

- Supported: Increased risk of tendinitis and tendon rupture
- Moderate support: Further increased risk in elderly (≥60) patients and patients taking corticosteroid drugs
- No comment can be made from the epidemiological data regarding tendinopathy risk among transplant recipient status
- Achilles tendon rupture is rare, but disabling.

SERIOUS CARDIAC ARRHYTHMIA

Fluoroquinolone Labeling: QT Prolongation, Arrhythmia, and Torsades de Pointes

- QT prolongation and infrequent cases of arrhythmia, or isolated (rare) cases of Torsades de pointes

- Recommends avoidance/caution in use of fluoroquinolones among patients with the following characteristics:
  - Selected cardiovascular or proarrhythmic conditions
  - Use of antiarrhythmic agents or other drugs that prolong the QT interval
  - Susceptible elderly patients

Among 12 studies, 2 selected for in-depth review

- 12 articles examined cardiac adverse events
  - Quality criteria for in-depth review
    - a short risk window
    - active comparator and capture indication for antibiotic use
    - adjustment for risk factors of drug-induced arrhythmia
    - evidence of outcome measure validity
    - captured serious clinical consequences of QT prolongation like death

  → 2 articles for in-depth review

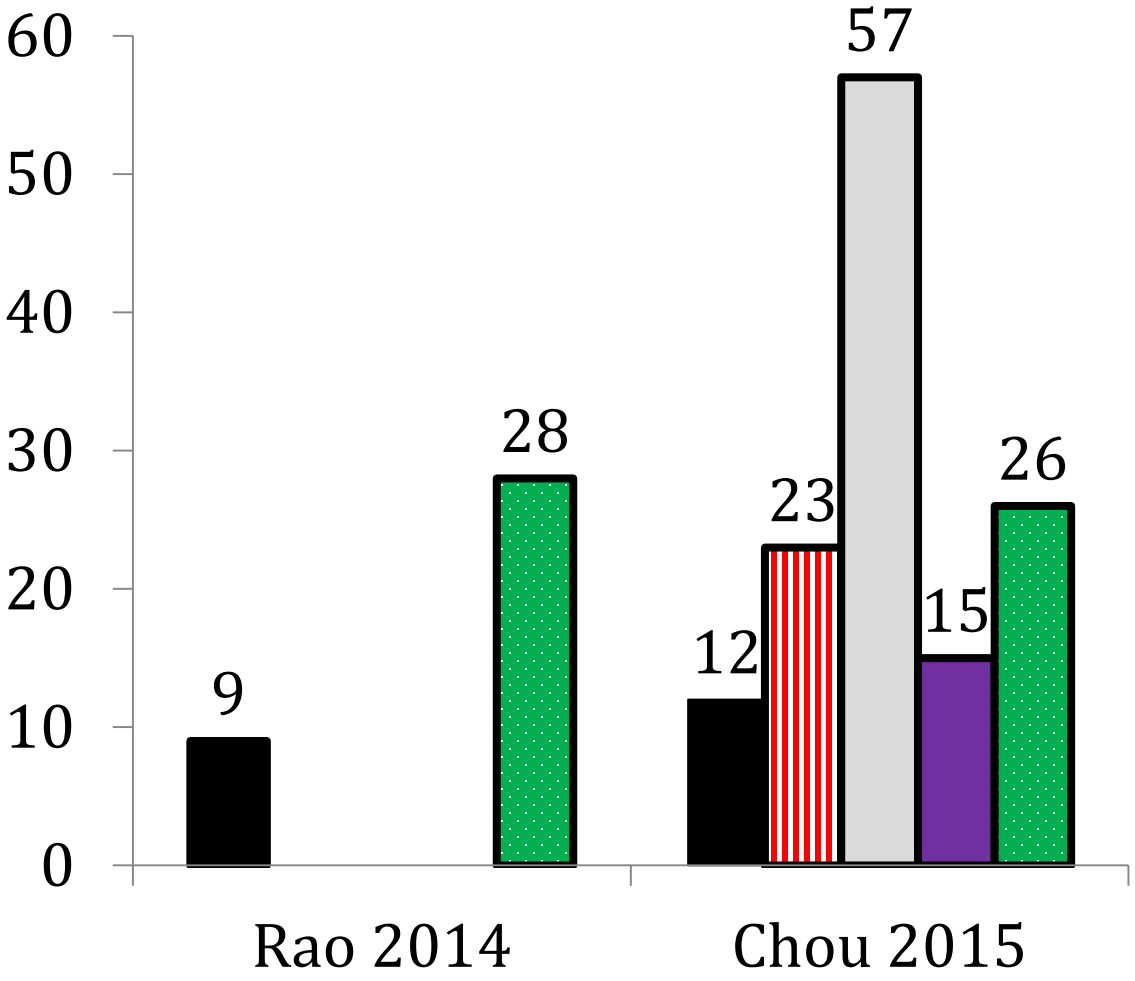
Similar Study Designs

	Rao 2014	Chou 2015
Study design	Retrospective, claims-based cohort	Retrospective, claims-based cohort
Fluoroquinolones	Levofloxacin	Moxifloxacin, ciprofloxacin, levofloxacin
Comparator	Amoxicillin & amoxicillin-clavulanate	Amoxicillin-clavulanate
Outcome	All-cause mortality Serious ventricular arrhythmia	Cardiovascular death Severe ventricular arrhythmia
Risk window	5 days after exposure	7 days after exposure
Indication for use	Diagnosis of infection within 1 year prior to exposure	Diagnosis of the index prescription (no info. on determination of diagnosis)
Confounding adjustment	Inverse probability weighting accounting for indication of antibiotic use, comorbidities, other medications, health resource utilization	Propensity score adjustment accounting for indication of antibiotic use, comorbidities, other medications, healthcare resource utilization

Study limitations make relative risks difficult to interpret

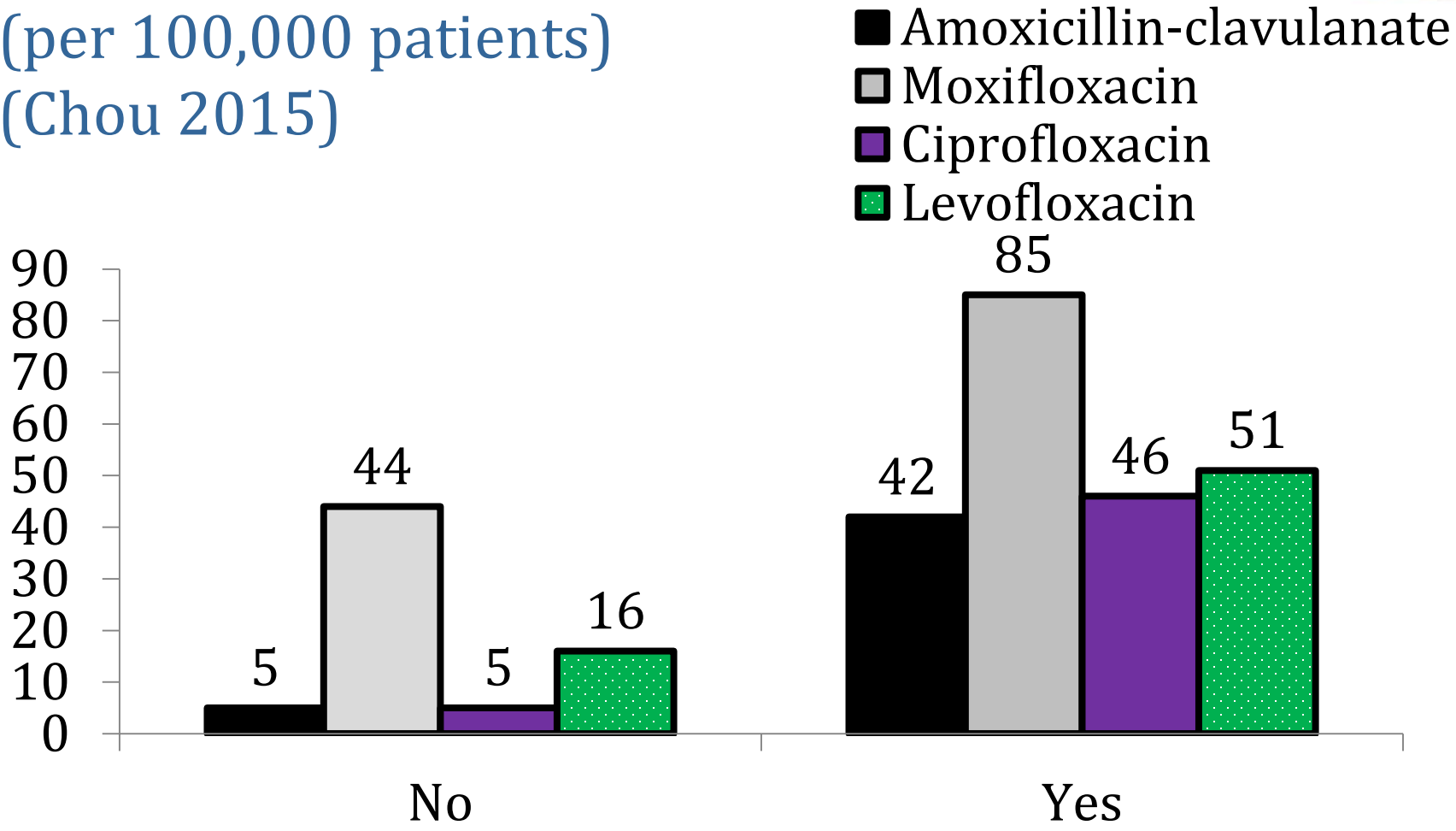
- Inadequate control for indication for antibiotic use
  - Rao 2014 : Indications defined within **1 year prior to exposure**
  - Chou 2015:
    - Unclear definition of indication
    - Broad indication categories
- Some outcome events not likely due to QT prolongation
  - Rao 2014: **All-cause mortality**
  - Chou 2015: **Cardiovascular deaths**
- Some outcome events include **outpatient-diagnosed arrhythmia** (Chou 2015)

Serious Arrhythmia (per 100,000 Rx or patients)



*Reference:
Amoxicillin and/or Amoxicillin-clavulanate

Serious Arrhythmia by Baseline Cardiovascular Diseases (per 100,000 patients) (Chou 2015)



ICD 9-CM: 250.7, 401-405, 410-414, 425-428, 429.1-429.3, 441, 442, 458

Cannot draw conclusions on relative risk, but absolute risk is low

- Definitive conclusion on **relative risk** cannot be made due to limitations of the existing evidence
  - Inadequate control for indication for antibiotic use
  - Measurement errors in capturing outcome event

- The **absolute risk of serious arrhythmia events** is likely low
  - Observed risk of serious arrhythmia events was higher among users with underlying cardiovascular disease, which is consistent with label warnings

PERIPHERAL NEUROPATHY

Fluoroquinolone Labeling: Peripheral Neuropathy

- Labeling warn of risk of peripheral neuropathy
  - Quick onset
  - Possibly irreversible

Among 2 studies, 1 selected for in-depth review

- 2 studies examined peripheral neuropathy
  - 1 passive surveillance of FAERS data
  - 1 case-control study

→ Case-control study selected for in-depth review

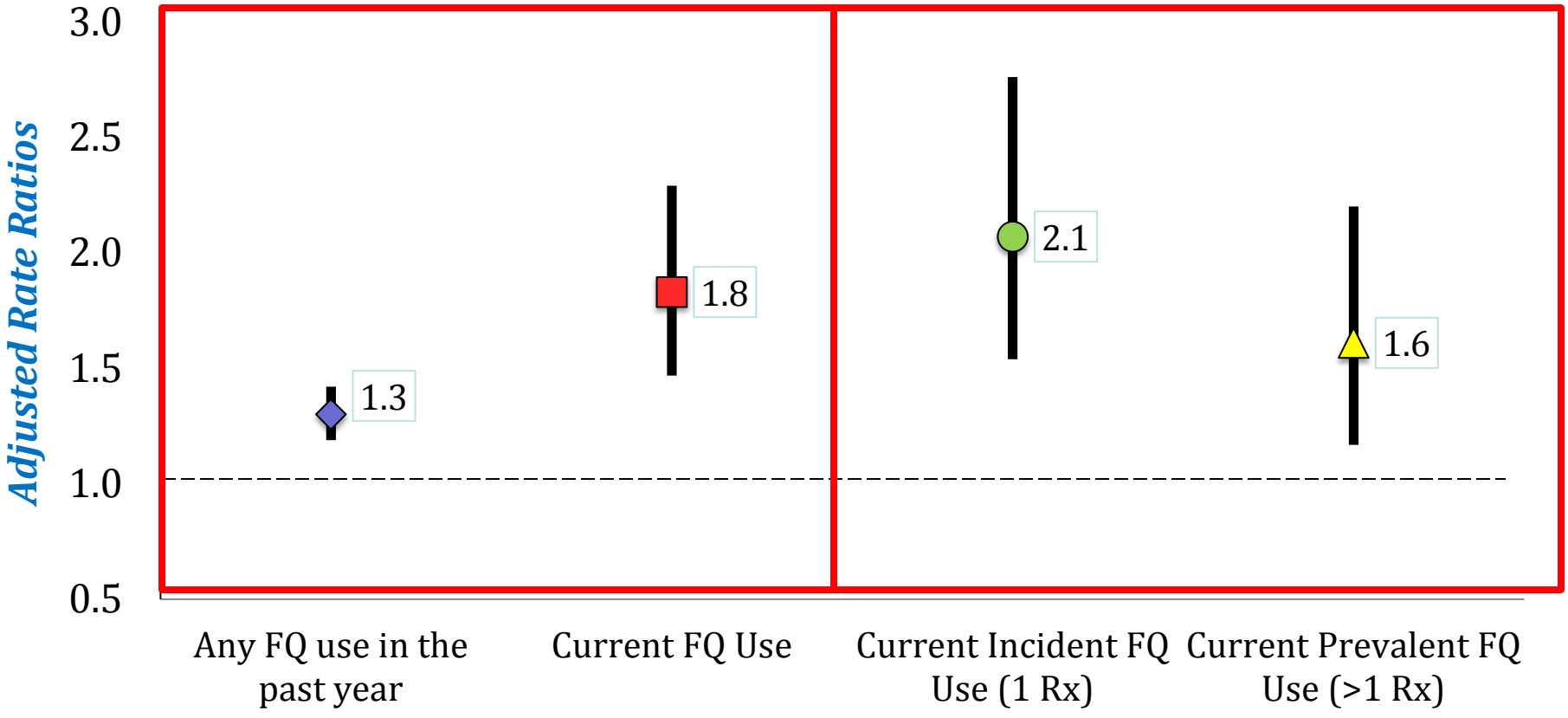
Case-Control Study of Peripheral Neuropathy

	Etminan 2014
Study design	Retrospective, matched case-control (1:4)
Population	Male patients 45-80 years without diabetes from Lifelink commercial claims database
Cases	Incident idiopathic or drug-induced peripheral neuropathy (ICD-9-CM 356.4, 356.8, 357.6) (n = 6,226)
Controls	Matched on age, calendar time and follow-up (n=24,904)
Exposures	Oral fluoroquinolones vs. no use
Risk window	Past year and current use
Confounder adjustment	Chronic renal failure, chronic liver disease, hypothyroidism, postherpetic neuralgia, the use of nitrofurantoin and metronidazole

Study limitations make findings difficult to interpret

- No incidence reported
- Estimates of relative risk may be inaccurate
  - Algorithms used to detect outcomes were not validated
  - No adjustment for other possible risk factors
  - Guillain-Barré not identified
- Limited generalizability: All male subjects, aged 45-80

Adjusted rate ratios show increased risk of peripheral neuropathy with fluoroquinolone use



Level of support for labeled information based on epidemiological data is weak

- Increased risk of peripheral neuropathy
  - Methods and results of the study were unclear
  - Magnitude of increased risk may not be accurate

- Did not assess onset or irreversibility of peripheral neuropathy
  - There is no information regarding the timing, severity, or duration of peripheral neuropathy.

CONCLUSIONS

Overall Conclusions

- Tendinopathy
  - Supported: Increased risk of tendinitis and tendon rupture
  - Moderate support: Further increased risk in elderly (≥60) patients and patients taking corticosteroid drugs
- Cardiac arrhythmia
  - Definitive conclusion on relative risk cannot be made due to limitations of the existing evidence
- Peripheral neuropathy
  - Weak support from epidemiological data
- Absolute risk of tendinopathy, serious cardiac arrhythmia, and peripheral neuropathy is low.

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

Debra Boxwell, PharmD
Division of Pharmacovigilance II
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration

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 <u>two</u> or <u>more</u> of the following body systems:
  - Musculoskeletal
  - Neuropsychiatric
  - Peripheral Nervous System
  - Senses (vision, hearing, etc.)
  - Skin
  - Cardiovascular

- AEs had to last 30 days or longer <u>after</u> 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

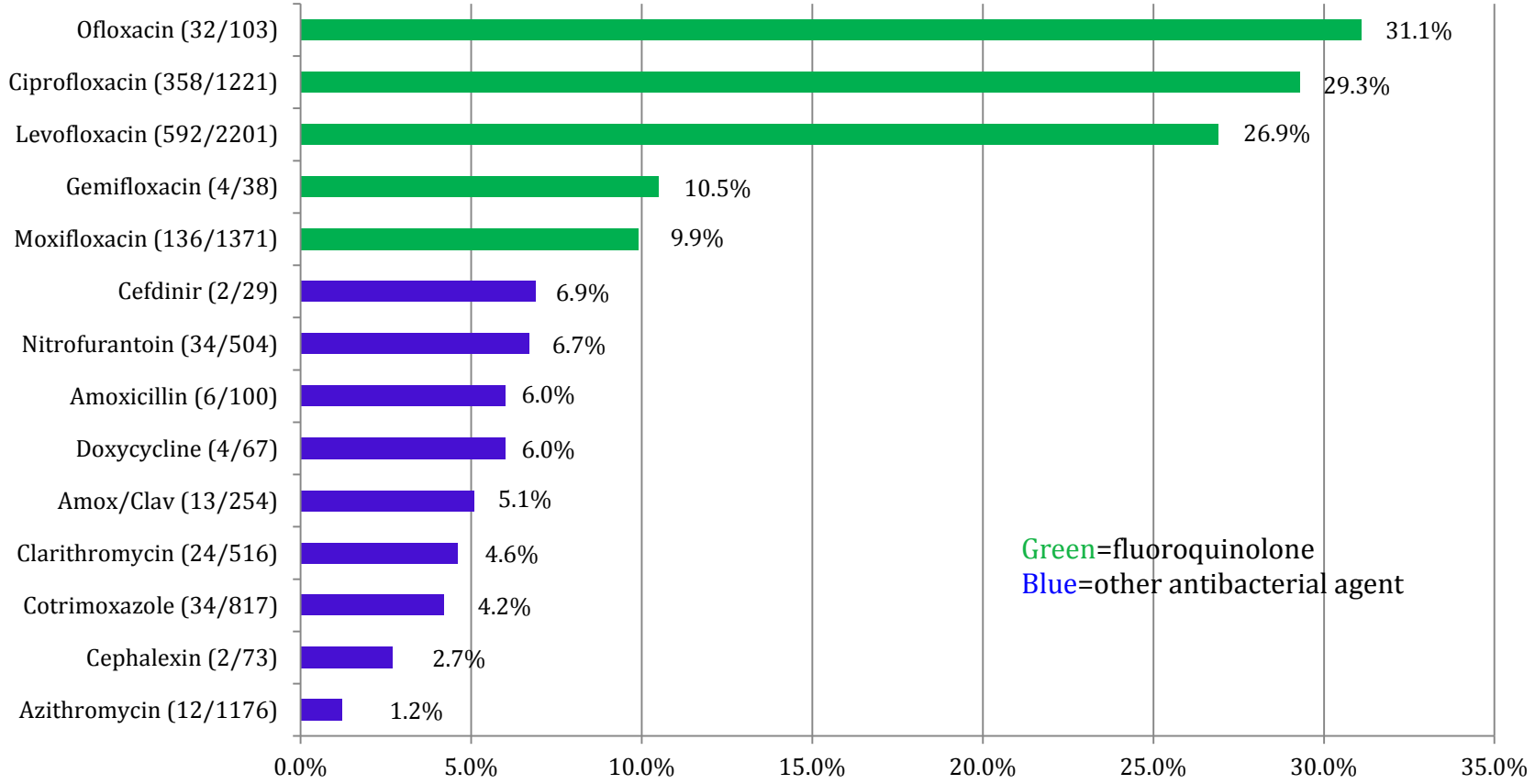
*Indications PT: Sinusitis acute, Sinusitis bacterial, Sinusitis, Bronchitis acute, Bronchitis, Bronchitis bacterial, Cystitis, Acute cystitis, Cystitis bacterial, Urinary tract infection, UTI-urinary tract infection, Urinary tract infection bacterial

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

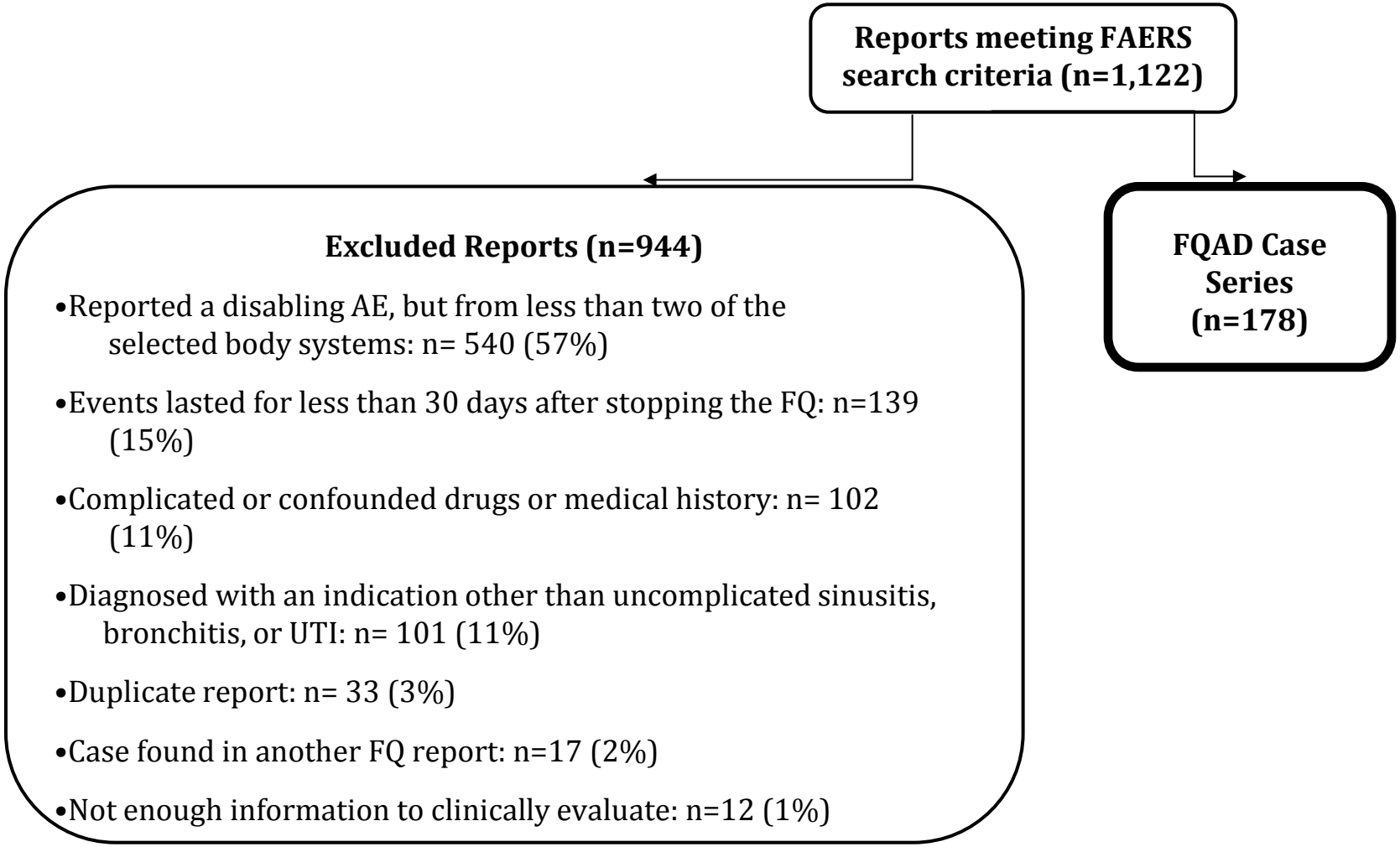
FQAD Cases

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)	
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 ≥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)

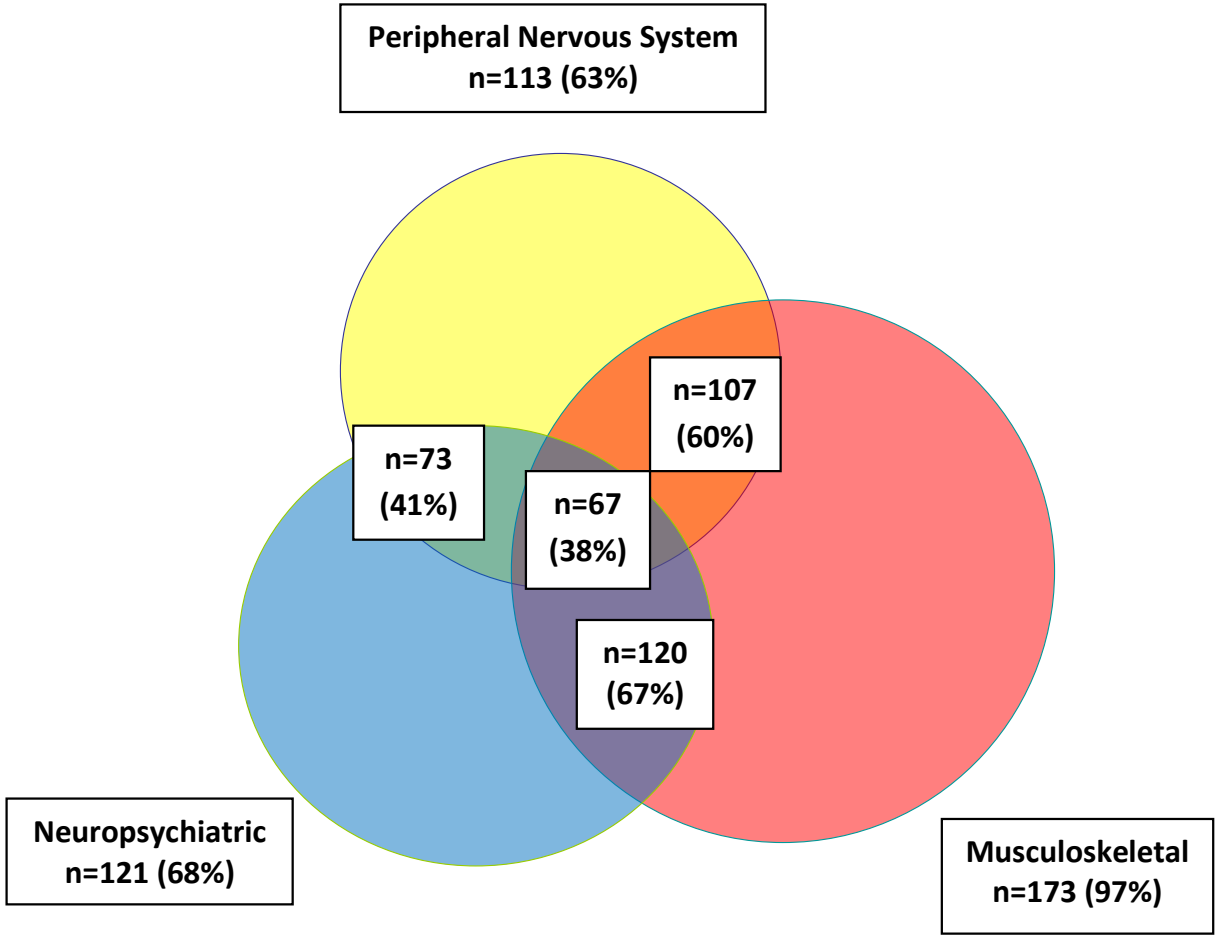
Reported Skin Events* (n=27)

- 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