

Should Black Box Warnings for Fluoroquinolones be Revised: Is the Bar Set Too High?

**Pharmed Out Conference
June 12, 2015**

**Charles Bennett M.D. Ph.D. M.P.P.
University of South Carolina**

Fluoroquinolone Antibiotic Indications and Usage

- The three most common Fluoroquinolone (FQ) antibiotics
 - Levofloxacin (Levaquin)
 - Ciprofloxacin (Cipro)
 - Moxifloxacin (Avelox)

Fluoroquinolone Antibiotic Indications and Usage

- Nosocomial Pneumonia
- Community-Acquired Pneumonia
- Community-Acquired Pneumonia
- Acute Bacterial Sinusitis
- Acute Bacterial Exacerbation of Chronic Bronchitis
- Complicated Skin and Skin Structure Infections
- Uncomplicated Skin and Skin Structure Infections
- Chronic Bacterial Prostatitis
- Complicated Urinary Tract Infections
- Complicated Urinary Tract Infections
- Acute Pyelonephritis
- Uncomplicated Urinary Tract Infections
- Inhalational Anthrax (Post-Exposure)
- Plague

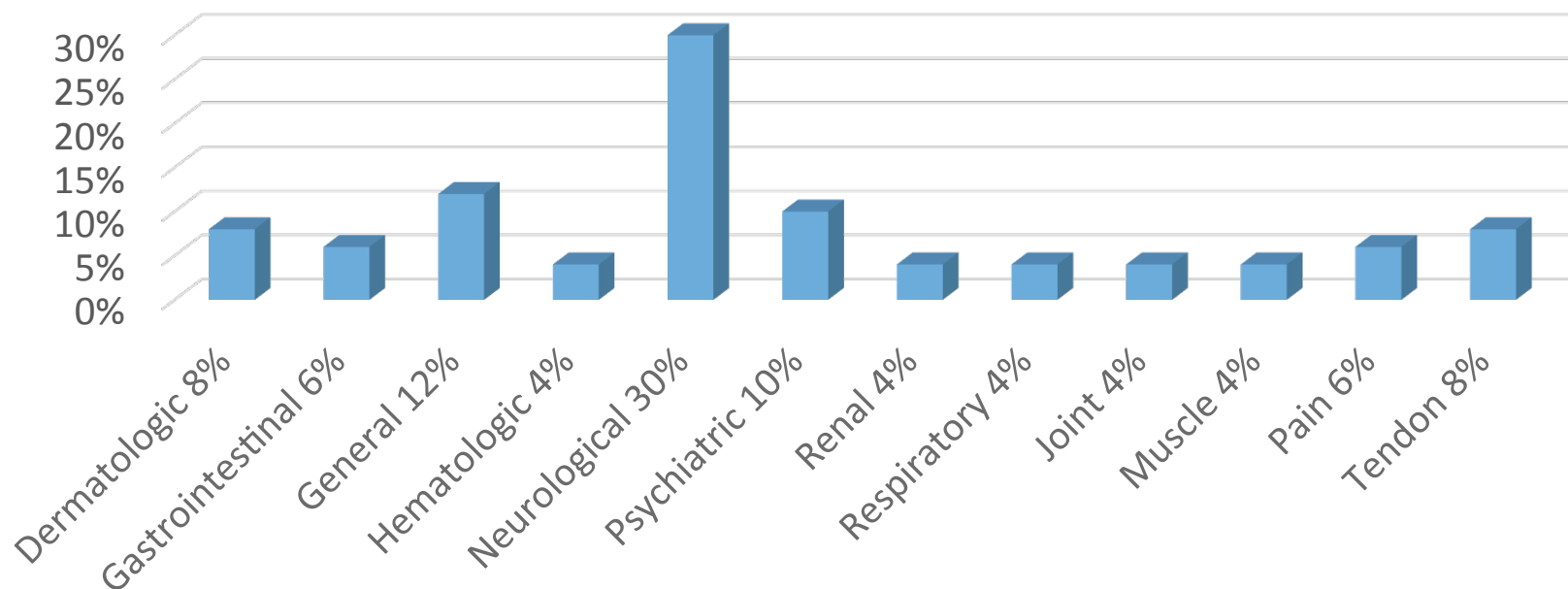
Fluoroquinolone Antibiotics Deaths/ Adverse Events

- FDA MedWatch data for Levaquin, Cipro, Avelox:
 - November 1, 1997 to February 3, 2011:
 - 210,705 AEs
 - 2,991 Death outcomes by case
- It is estimated that only 1% to 10% of actual Adverse Events (AEs) are reported to the FDA. Actual estimated FQ AEs/Death outcomes:
 - November 1, 1997 to February 3, 2011:
 - **2,000,000 to > 21,000,000 AEs**
 - **29,000 to > 299,000 Death outcomes by case**

Levaquin FDA FAERS Data

Top 50 Reported Adverse Events

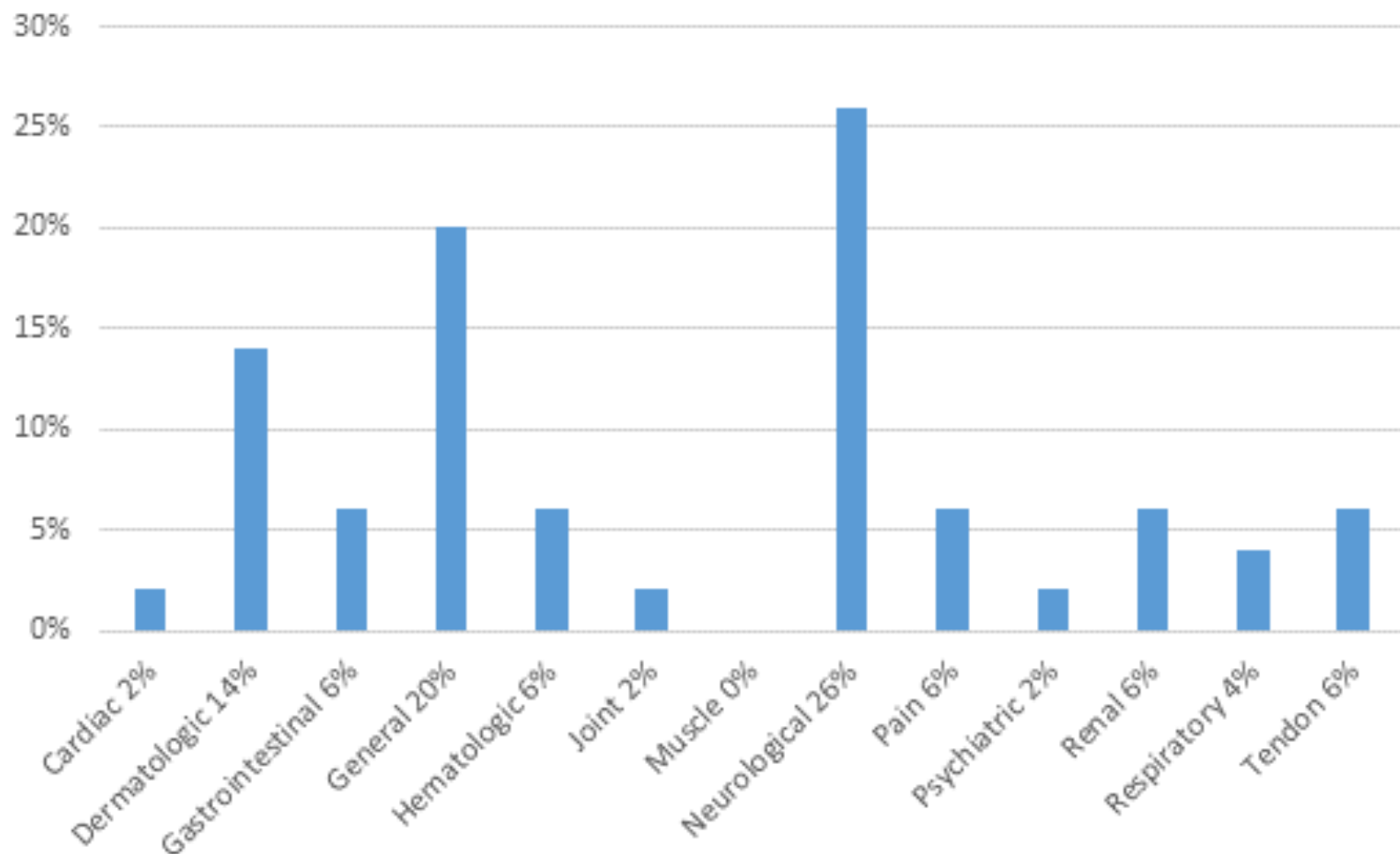
11/01/1997 - 1/20/2010



Cipro FDA FAERS Data

Top 50 Reported Adverse Events

11/01/1997 - 03/03/2011



Number of FQ Impacted Individuals

- According to FDA MedWatch data from November 1997 – May 2011, >51,000 FQ individual safety reports were submitted to the FDA.
- It is estimated that only 1% to 10% of actual reports are submitted to the FDA, so the actual estimated FQ individual safety reports are: **510,000 to > 5,100,000**

A Unique Collaboration

- About four years ago, representatives from an online Social Network (Floxed Network) of individuals reporting damage following consumption of FQ antibiotics contacted SONAR.
- Floxed Network representatives requested SONAR assistance in furthering FQ research.
- As a result, SONAR implemented basic science research on the FQ, Cipro.

Floxed Network Survey Incorporated with Basic Science

- Concurrent to SONAR basic science research, the Floxed Network posted a one-question survey online asking if Floxed individuals experienced neuropsychiatric AEs.
- Answers from 94 online survey Floxed respondents were analyzed (<http://www.myquinstory.info/>).
- The online Floxed survey results were incorporated with the SONAR basic science research:
“Investigating fluoroquinolone neuropsychiatric toxicity by scientists and a social network,” (Fayad, et.al. Final Revision. J. Supportive Care in Oncology. 2015)

Fluoroquinolone Neuropsychiatric Toxicity

- SONAR's Cipro basic science research documented:
 - Brain damage
 - Liver damage
 - Tendon damage
- This basic science “reveals effects of FQs associated with NP toxicity. Recent changes in product labels for FQs describe neurologic toxicity, but not psychiatric toxicity. Our findings support a recommendation that the FDA should consider a product label change that would include more prominent descriptions of FQ-associated NP toxicity.” (Fayad, et.al. Final Revision. J. Supportive Care in Oncology. 2015)

2013 FQ FDA Pharmacovigilance Review

“Fluoroquinolones have been found to affect mammalian topoisomerase II, especially in mitochondria.”

2013 FQ FDA

Pharmacovigilance Review

- “Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis.”
- “Neurodegenerative diseases, like Parkinson’s, Alzheimer’s and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress generated by reactive oxygen species (ROS) related to Mitochondrial Toxicity.”

2013 FDA FQ Pharmacovigilance Review, cont.

Other FQs already removed from the market due to mitochondrial toxicity:

- “Trovafloracin was withdrawn from the market in 2001 due to cases of liver failure. Studies in cultured hepatocytes identified the mitochondria as the source of trovafloracin’s hepatotoxicity. (FDA, 2013, page 25)
- “Gatifloracin was withdrawn from the market in 2006 because of severe glucose disturbances.” (FDA, 2013, page 25)

FQ Research

- SONAR basic science research and Floxed Network survey results
 - “Investigating fluoroquinolone neuropsychiatric toxicity by scientists and a social network” (Fayad, et.al. Final Revision. J. Supportive Care in Oncology. 2015)
- 2013 FDA FQ Pharmacovigilance Review
- > 40 segments on TV Stations with interviews with SONAR Investigators on FQ AE research
- 2013 FAERs Review

FDA has Clear Legal Responsibilities for Drug Safety

CHAPTER 9—FEDERAL FOOD, DRUG, AND COSMETIC ACT, Section 393, the FDA “**shall—** (1) Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;....”

FDA has Clear Legal Requirements for Black Box Warnings

Title 21 - FOOD AND DRUGS, CHAPTER I

“1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.”

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57>

FDA Non-Binding Black Box Warning Guidance for Industry

- “There is an adverse reaction so serious in proportion to the potential benefit from the drug ...” **OR**
- “There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug”... **OR**
- “FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted....”

June 23, 2014 Mitochondrial Toxicity Citizen Petition

As a result of four years of investigation, SONAR submitted a Citizen Petition June 18, 2014 to the FDA asking for the following Black Box Warning:

WARNING: POSSIBLE MITOCHONDRIAL TOXICITY

Fluoroquinolones may cause Mitochondrial Toxicity.

Mitochondrial Toxicity has been implicated in conditions such as peripheral neuropathy, hepatotoxicity, glucose disturbances, phototoxicity, developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, lactic acidosis, Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS).

Citizen Petition

This Citizen Petition is *unique* because it is based on the FDA's own 2013 Pharmacovigilance Review, the FDA's own research, the FDA's own conclusions; it asks the FDA to place its own words on the FQ labels.

September 11, 2014 Psychiatric Citizen Petition

The decision to submit this Citizen Petition was based on the seriousness of psychiatric events, including suicidal thoughts or acts.

WARNING: SERIOUS PSYCHIATRIC EVENTS

Serious psychiatric events including, toxic psychoses, hallucinations, paranoia, suicidal thoughts or acts, loss of consciousness, delirium, depressed level of consciousness, amnesia, coma, and memory impairment have been reported in patients receiving fluoroquinolones, including Levaquin. These events may start during treatment or may be delayed and start days, weeks, or months after the last dose.

FDA Citizen Petition Responses

Dec 17, 2014 Mitochondrial Toxicity Citizen Petition:

“FDA has been unable to reach a decision on you petition because it raises complex issues requiring extensive review and analysis by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your request.”

March 9, 2015 Psychiatric Citizen Petition:

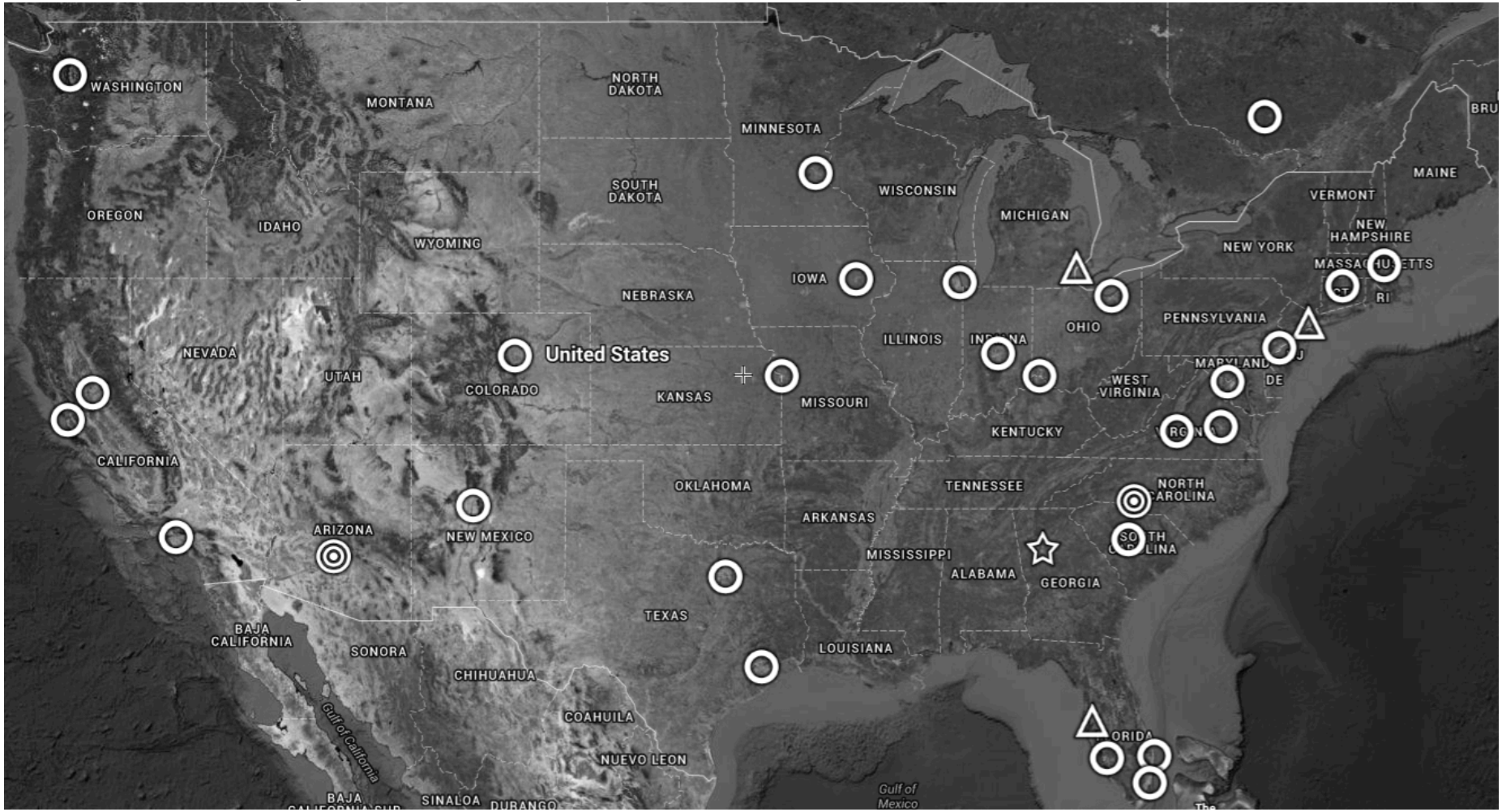
“FDA has been unable to reach a decision on you petition because it raises complex issues requiring extensive review and analysis by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your request.”

Deaths/AEs While the FDA Fails to Act on Petitions

- **An additional 126,000 to >1,260,000 AEs during the past 10 months**
- **An additional 1,700 to >17,000 Death outcomes during the past 10 months**
- The majority were most likely preventable since the majority of FQ prescriptions are for routine infections.
- Because the FDA has knowledge of these AEs/Death outcomes; and the FDA has knowledge of possible Mitochondrial Toxicity, FDA staff are directly responsible for the preventable AEs/Death outcomes.

Stories and News Coverage of Fluoroquinolone Death/AEs

Fluoroquinolonestories.com



Stories and News Coverage of Fluoroquinolone Death/AEs

- Charlotte, NC:
- Atlanta, GA

Congressional Communication

- During the past year since the Citizen Petitions (June and September 2014) were submitted, the following discussions were held:
 - Meeting with Senate Health Committee staff
 - Meetings with numerous individual Senate offices
 - Phone conversations with Senate and House Committee healthcare staff members
 - Presentation to FDA staff by Floxed individuals

Timeline for FDA Action/Inaction

- **April 17, 2013** the FDA wrote a Pharmacovigilance Review which describes possible FQ Mitochondrial Toxicity associated with serious, life-ending neurodegenerative diseases, including ALS, Alzheimer's, and Parkinson's.
- **April 2013 the FDA failed** to place warnings of possible FQ Mitochondrial Toxicity and associated ALS, Alzheimer's, and Parkinson's on the FQ labels.
- **June 2014** SONAR submitted a Citizen Petition to the FDA asking for warnings of possible FQ Mitochondrial Toxicity and associated ALS, Alzheimer's, and Parkinson's on the FQ labels.
- **September 2014** SONAR submitted a Citizen Petition for neuropsychiatric toxicity.

Timeline for FDA Action/Inaction

- **December 2014** the FDA responds that its too **complex** to place warnings of possible FQ Mitochondrial Toxicity.
- **March 2015** the FDA responds that its too **complex** to place warnings of possible FQ Neuropsychiatric Adverse Events.
- **As of June 2015**, the FDA has **still not** placed warnings of possible FQ Mitochondrial Toxicity and associated ALS, Alzheimer's, and Parkinson's on the FQ labels.

Is the Bar Set Too High Conceptually?

- 1) The FDA's legal bar related to Black Box Warnings is not too high.
 - CHAPTER 9, the FDA shall ensure that drugs are safe.
 - Title 21, AEs that “may lead to death or serious injury, may be required” to be in a Black Box.
- 2) The Industry Guidance bar related to Black Box Warnings is not too high.
 - Black Boxes may be needed if “there is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug.”
- 3) The bar related to the FDA acting, however, is a significant problem which, in the case of the SONAR FQ Citizen Petitions, has had a devastating impact on thousands of individuals.

Is the Bar Set Too High for FQs?

- 1) The FDA's legal bar related to Black Box Warnings is not too high to address FQ AEs.
 - FQ possible mitochondrial toxicity and psychiatric AEs, including suicide, “may lead to death or serious injury” so they require a Black Box.
- 2) The Industry Guidance bar related to Black Box Warnings is not too high to address FQ AEs.
 - FQ possible mitochondrial toxicity and psychiatric AEs, including suicide, are AEs “so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug” and, therefore, require a Black Box.
- 3) The bar related to the FDA acting has been a significant problem in that the FDA has failed to act on the Citizen Petitions which has had a devastating impact on thousands of individuals.

Request to the FDA for Immediate Action

- The average time it takes, historically, for a Citizen Petition to the FDA to be acted upon is 2.6 years.
- Even so, as described in the Mitochondrial Toxicity Citizen Petition, SONAR requests that the FDA ***immediately*** place on the Levaquin label in a Black Box, its own words, based on its own research, from its own April 17, 2013 Pharmacovigilance Review.

Request to the FDA for Immediate Action

WARNING: POSSIBLE MITOCHONDRIAL TOXICITY

Fluoroquinolones may cause Mitochondrial Toxicity. Mitochondrial Toxicity has been implicated in conditions such as peripheral neuropathy, hepatotoxicity, glucose disturbances, phototoxicity, developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, lactic acidosis, Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS).

This is a unique opportunity for the FDA, SONAR, and patients to work together to establish a model for stakeholder collaboration to successfully address drug safety issues related to FQ antibiotics.

Thank you

Charles Bennett, M.D., Ph.D., M.P.P.

Center for Medication Safety and Efficacy
Southern Network on Adverse Reactions (SONAR),
South Carolina College of Pharmacy/USC Campus
715 Sumter Street, Suite 311-L
Columbia SC 29208
803-777-2289-office
803-777-2820-fax