Fluoroquinolones: are they all the same (or not) ?

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Disclosures and slides availability

• Research grants
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  – Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

• Decision-making and consultation bodies
  – General Assembly and steering committee of EUCAST
  – European Medicines Agency (external expert)
  – US National Institutes of Health (grant reviewing)

Slides: http://www.facm.ucl.ac.be ➔ Lectures
Belgium

10 millions inhabitants …

10 Nobel prizes (10/850)

• Peace
  - Institute of International Law, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)

• Literature
  - Maurice Maeterlinck, Ghent (1911)

• Medicine
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)

• Chemistry
  - Ilya Prigogyne, Brussels (1977)

• Physics
  - François Englert, Brussels (2013)
The **Catholic University of Louvain** in brief (1 of 4)

- originally founded in **1425** in the city of **Louvain** (in French and English; known as **Leuven** in Flemish)
The Catholic University of Louvain in brief (2 of 4)

- It was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's  
Erasmus  
Vesalius
The Catholic University of Louvain in brief (3 of 4)

- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities...

- in 1968, the University was divided into
  - a French-speaking Université catholique de Louvain
  - a Flemish-speaking Katholieke Universiteit Leuven…

Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("big bang")
(here in conversation with A. Einstein)

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…)
(here in front of a centrifuge)

The Catholic University of Louvain in brief (4 of 4)

- The Flemish-speaking *Katholieke Universiteit Leuven* has remained in Louvain (Leuven) and is named in English "Catholic Universiteit Leuven".

- The French-speaking *Université catholique de Louvain* has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwe)

- Together, the two Universities have about **55,000 students**
What do we do?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- novel antibiotics (and last studied)
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - kétolides (solithromycin…)
  - oxazolidinones (tedizolid …)

www.facm.ucl.ac.be

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

www.isap.org

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young ...
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young ...
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young ...


Cellular uptake, localization and activity of fluoroquinolones in uninfected and infected macrophages
Marie-Béatrice Carlier1, Bernard Scorneaux2, Andrée Zeneberg1, Jean-François Désnottes2 and Paul M. Tulkens1

1Laboratoire de Chimie Physiologique, and International Institute of Cellular and Molecular Pathology, Université Catholique de Louvain, Avenue Hippocrate 75, Bte 75.49, B-1200 Bruxelles, Belgium; 2Rhône-Poulenc Santé, Centre de Recherches de Vitry/Alfortville, 13, Quai Jules Guesde, B.P. 14, F-94403 Vitry s/Seine, France

REVIEW ARTICLE
Quinolones in 2005: an update
F. Van Bambeke1, J.-M. Michot1, J. Van Eldere2 and P. M. Tulkens1

1Unit of Cellular and Molecular Pharmacology, Catholic University of Louvain, Brussels and
2Department of Microbiology and Immunology, Rega Institute and Centre for Molecular Diagnostics, University Hospital, Catholic University of Leuven, Louvain, Belgium

Clin Microbiol Infect 2005; 11: 256–280

ORIGINAL RESEARCH ARTICLE
Moxifloxacin Safety
An Analysis of 14 Years of Clinical Data
Paul M. Tulkens,1 Pierre Arvis2 and Frank Kruesemann3

1 Pharmacie cellulaire et moléculaire & Centre de Pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany

PubMed
Tulkens AND (fluoroquinolone* OR quinolone*)
RSS Save search Advanced

Results: 1 to 20 of 54

Display Settings: Summary, 20 per page, Sorted by Recent

9-10/03/2015 Kuala-Lumpur & Penang, Malaysia
What shall we discuss?

• The basics: how were quinolones invented? (are they different by design?)

• The real life: microbiological properties… (or how to really differentiate them …)

• The first risk: resistance… (is there a difference) ?

• The next risk: toxicity… (what you need to know)

• Draw your own conclusions!
Mechanism of action of fluoroquinolones: the basics...
2 key enzymes in DNA replication:

- **DNA gyrase**
  - Stabilize positive node
  - Break back segment
  - Reseal break on front side

- **Topoisomerase IV**

**Bacterial DNA is supercoiled**
Ternary complex
DNA - enzyme - fluoroquinolone

COVALENTLY CLOSED CIRCULAR DNA

DNA GYRASE catalytic subunits

DNA GYRASE ATP binding subunits

FLUOROQUINOLONES:
4 stacked molecules

(Shen, *in* Quinolone Antimicrobial Agents, 1993)
Ternary complex
DNA - enzyme - fluoroquinolone

"GyraseCiproTop" by Fdardel - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:GyraseCiproTop.png#mediaviewer/File:GyraseCiproTop.png
Last accessed: 8/2/2015
Resistance to fluoroquinolones: the basics

- Decreased permeability
- Efflux pump
- Mutation of the enzymes and/or DNA protection
Fluoroquinolones are the first entirely man-made antibiotics: do we understand our molecule?

Don’t panic, we will travel together....
Chemistry and Activity

This is where all begins...
The pharmacophore common to all fluoroquinolones

BINDING TO DNA

BINDING TO THE ENZYME

AUTO-ASSEMBLING DOMAIN
(for stacking)
From chloroquine to nalidixic acid...

chloroquine

1939

7-chloroquinoline (synthesis intermediate found to display antibacterial activity)

1958

nalidixic acid

1962
Nalidixic acid *

- typical chemical features of fluoroquinolones (a, b, c)
  BUT a naphthyridone (N at position 8:)
- limited usefulness as drug
  - narrow antibacterial spectrum (Enterobacteriaceae only)
  - short half-life (1.5h)
  - high protein binding (90%)

* Belg. pat. 612,258 to Sterling Drugs, 1962
From nalidixic acid to the 1st fluoroquinolone

make 3 key modifications...

1978

broader Gram(-) activity
less protein binding (50%)
longer half-life (3-4h)

* 6-fluoro-7-pyrimidino-quinoleine

* Belgian patent 863,429, 1978 to Kyorin

* 6-fluoro-7-pyrimidino-quinoleine
From norfloxacin to ofloxacin via pefloxacin

* Eur. pat. Appl. 47,005 to Daiichi, 1982
From norfloxacin to ciprofloxacin

N
C
O
O-
N
H
N
CH3
F
F

norfloxacin

cyclopropyl to increase potency

ciprofloxacin *

* Ger. pat. 3,142,854 to Bayer AG, 1983
"1st generation" fluoroquinolones

norfloxacin

pefloxacin

methyl piperazine

methyl piperazine

methyl piperazine

morpholine
Ofloxacin is a racemic mixture

The active form of ofloxacin is the (-) S isomer

Levofloxacin is the pure (-) S isomer *

* Eur. pat. 206,283 to Daiichi, 1987
The present "first generation" of fluoroquinolones ...

- 1960
  - Nalidixic acid
  - Oxolinic acid
  - Flumequine
  - Pipemidic acid

- 1970
  - Norfloxacin
  - Pefloxacin
  - Ofloxacin
  - Ciprofloxacin
  - Fleroxacin
  - Rufloxacin

- 1980
  - Levofloxacin

<table>
<thead>
<tr>
<th>t_{1/2}</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 h</td>
<td>++</td>
</tr>
<tr>
<td>11 h</td>
<td>+</td>
</tr>
<tr>
<td>6 h</td>
<td>++</td>
</tr>
<tr>
<td>3-4 h</td>
<td>+++</td>
</tr>
<tr>
<td>6 h</td>
<td>++++</td>
</tr>
</tbody>
</table>

2 x more active than ofloxacin per g
How to improve the chemotherapeutic usefulness of the "first generation" fluoroquinolones

1. Maintain broad Gram(-) activity?

2. Further Improve Gram(+) activity?

3. Acquire activity against anaerobes?
The “second generation” fluoroquinolones

- Temafloxacin \(^a\)
- Sparfloxacin \(^b\)
- Grepafloxacin \(^c\)
- Gatifloxacin \(^d\)

- Gram (-);
- improved Gram (+)
- anti-anaerobe

---

\(^a\): Toyama, 1988 (?) ; \(^b\): Dainippon, 1985-1987; \(^c\): Otskuda, 1989; \(^d\): Kyorin, 1988
The “third / fourth generation” fluoroquinolones

- Clinafloxacin
- Trovafloxacin
- Moxifloxacin
- Gemifloxacin

anti-Gram (-)  anti-Gram (+)  anti-anaerobe

Activity against *S. pneumoniae*

- **I**
  - Ciprofloxacin: 0.5 - 2

- **II**
  - Moxifloxacin: 0.01 - 0.5

- **III / IV**
  - Levofloxacin: 0.5 - 2
Activity against *B. fragilis* (anaerobe)

<table>
<thead>
<tr>
<th>ciprofloxacin</th>
<th>moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 128</td>
<td>0.25 - 8</td>
</tr>
</tbody>
</table>
At this point …

Gram (-)  
- ciprofloxacin
- levofloxacin

Gram (+)  
- moxifloxacin

anaerobes

This is by design!
What shall we discuss?

- The basics: how were quinolones invented? (are they different by design?)

- The real life: microbiological properties... (or how to really differentiate them ...)

- The first risk: resistance... (is there a difference?)

- The next risk: toxicity... (what you need to know)

- Draw your own conclusions!
A unbiased estimation of antibiotic activity (in the absence of resistance)
Gram negative: *E. coli*

**Ciprofloxacin / Escherichia coli**
International MIC Distribution - Reference Database 2015-02-08

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

![Ciprofloxacin Graph]

**Levofloxacin / Escherichia coli**
International MIC Distribution - Reference Database 2015-02-08

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

![Levofloxacin Graph]

http://mic.eucast.org/Eucast2/regShow.jsp?id=1022
http://mic.eucast.org/Eucast2/regShow.jsp?id=1072
Last accessed: 8/2/2015
Gram positive: *S. pneumoniae*

**Moxifloxacin / Streptococcus pneumoniae**

International MIC Distribution - Reference Database 2015-02-08

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

**Levofloxacin / Streptococcus pneumoniae**

International MIC Distribution - Reference Database 2015-02-08

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

http://mic.eucast.org/Eucast2/regShow.jsp?Id=1099
http://mic.eucast.org/Eucast2/regShow.jsp?Id=1310
Last accessed: 8/2/2015
Anaerobes: *B. fragilis*

**Moxifloxacin / Bacteroides fragilis**

International MIC Distribution - Reference Database 2015-02-08

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

![Graph showing moxifloxacin and levofloxacin MIC distributions for B. fragilis](image)

- **Moxifloxacin**
- **Levofloxacin** (not recommended)

---

**B. fragilis**

- **Moxifloxacin**
- **Levofloxacin**

---

http://mic.eucast.org/Eucast2/regShow.jsp?id=1454

http://mic.eucast.org/Eucast2/regShow.jsp?id=1066

Last accessed: 8/2/2015
Killing abilities of fluoroquinolones: Are they all equal?

*in vitro* kill curves: observations with *S. pneumoniae*

Fig. 1. Time kill curves of moxifloxacin versus levofloxacin against *S. pneumoniae* 7362 (average of 2 models).

Schafer et al. Diag Microb Infect Dis 2008; 60:155–161
Killing abilities of fluoroquinolones: Are they all equal?

Animal survival experiments (S. pneumonia i.p. inoculations)

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (mg/L) MXF</th>
<th>MIC (mg/L) LVX</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR33118</td>
<td>0.12</td>
<td>1</td>
</tr>
<tr>
<td>FL2812</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>FL5629</td>
<td>4</td>
<td>32</td>
</tr>
</tbody>
</table>

What shall we discuss?

• The basics: how were quinolones invented? (are they different by design?)

• The real life: microbiological properties... (or how to really differentiate them ...)

• The first risk: resistance... (is there a difference)?

• The next risk: toxicity... (what you need to know)

• Draw your own conclusions!
Resistance must first be assessed by MIC distributions

- Resistance of Gram-negative (ciprofloxacin/levofloxacin) is widespread and must be assessed locally (often ward by ward)

MIC distributions of fluoroquinolones against *P. aeruginosa* in the Academic Hospital of the University of Leuven, Belgium
Resistance must first be assessed by MIC distributions

- Conversely, resistance of Gram-positive is variable
  - High for MRSA (co-resistance frequent)
  - Low for *S. pneumonia* (especially for moxifloxacin; close to breakpoint for levofloxacin)

*MIC distributions of S. pneumonia* in Belgium for CAP (n=249)

Resistance must first be assessed by MIC distributions

- Conversely, resistance of Gram-positive is variable
  - High for MRSA (co-resistance frequent)
  - Low for *S. pneumonia* (especially for moxifloxacin; close to breakpoint for levofloxacin)

**MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)**
The risk for resistance to fluoroquinolones is to be “within the mutation selection window” ...

$C_{\text{max}}$ and "Mutant Prevention Concentration" (MPC) …

$\text{MIC}_{99} = 0.8 \text{ mg/L}$ (in this example)

"Classic" bactericidal effect

poorly sensitive organisms…

Elimination of resistant organisms

$\text{MPC}_{10} = 9$

Dong et al: AAC 1999; 43:1756-1758
"Mutant Prevention Concentration …"

Concentration that inhibits the majority of the organisms

Concentration needed to prevent the selection of resistant organisms (about 10 x the MIC)

Surviving bacteria vs. concentration

MIC\textsubscript{99} = 0.8

MPC\textsubscript{10} = 9

Dong et al; AAC 43:1756-1758
MPC: moxifloxacin vs levofloxacin

~10 x the median MIC (0.125 mg/L) for moxifloxacin.

~10 x the median MIC (1 mg/L) for levofloxacin.
Pharmacokinetics and “resistance” breakpoint vs. MIC

% of strains

MIC

Levofloxacin 500 mg 1X / day
• AUC [(mg/l)xh] 47
• peak [mg/l] 5
⇒ MIC\text{max} \sim 0.5

Moxifloxacin 400 mg 1X / day
• AUC [(mg/l)xh] 48
• peak [mg/l] 4.5
⇒ MIC\text{max} \sim 0.5

Maximal MIC to avoid selection of resistance

resistance breakpoint
➢ AUC/MIC = 100
➢ peak/MIC = 10

MIC data: EUCAST MIC distributions (wild type)
PK data: US and EU labelling (typical values)
A very recent paper...

Impact of poor compliance with levofloxacin and moxifloxacin on respiratory tract infection antimicrobial efficacy: A pharmacokinetic/pharmacodynamic simulation study

N. Carral\textsuperscript{a}, J.C. Lukas\textsuperscript{a,b}, I. Oteo\textsuperscript{a}, E. Suarez\textsuperscript{a,*}
A very recent paper...

Table 1
Interindividual variability of $fAUC_{0-24h}$ for levofloxacin (LFX) and moxifloxacin (MOX), estimated for various drug dosing regimens in simulated patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (S.D.)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24h}$ (mg h/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFX 500 mg q24 h</td>
<td>45.78 (3.72)</td>
<td>37.21–57.13</td>
</tr>
<tr>
<td>LFX 750 mg q24 h</td>
<td>68.68 (5.58)</td>
<td>55.82–85.69</td>
</tr>
<tr>
<td>LFX 500 mg q12 h</td>
<td>91.57 (7.34)</td>
<td>77.66–115.48</td>
</tr>
<tr>
<td>MOX 400 mg q24 h</td>
<td>43.63 (8.60)</td>
<td>26.43–72.20</td>
</tr>
</tbody>
</table>
A very recent paper...

Impact of poor consolidation in a respiratory tract infection: A pharmacokinetic study

N. Carral, J.C. Lukas

Short Communication


Contents lists available at ScienceDirect

Target attainment rate for *S. pneumoniae*

- **MXF 400 mg q24h**
  - (MIC = 0.25 mg/L)
- **LVX 500 mg q12h**
  - (MIC = 1 mg/L)

90%
A very recent paper...
What differentiates fluoroquinolones?

Results with *S. pneumoniae*

Would this cause less emergence of resistance?
Moxifloxacin MIC's against *S. pneumoniae* in Belgium from 1999 to 2008 *

**S. pneumoniae susceptibility to moxifloxacin in Belgium**


- See also
  - Vanhoof et al Acta Clin Belg. 2006;61:49-57
  - Vanhoof et al Pathol Biol (Paris) 2010;58:147-151


* Moxifloxacin was introduced in 2001 and became the almost only fluoroquinolone used for RTI since 2004 in Belgium
Is there a molecular basis for a lesser emergence of resistance with moxifloxacin?

A C8-methoxy group lowers the MPC for an N-1-cyclopropyl-fluoroquinolone

FULL PRESCRIBING INFORMATION

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the NorA or pmrA genes seen in certain Gram-positive bacteria.

Last accessed: 8/2/2015
What shall we discuss?

• The basics: how were quinolones invented? (are they different by design?)

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• The first risk: resistance... (is there a difference?)

• The next risk: toxicity... (what you need to know)

• Draw your own conclusions!
We all agree about efficacy, but what about side effects…

therapy?

side effects?
# All antimicrobials have associated risks *

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Frequent or serious side effects</th>
</tr>
</thead>
</table>
| fluoroquinolones | levofloxacin | • Anaphylactic reactions and allergic skin reactions  
|               |            | • *Clostridium difficile*-associated colitis  
|               |            | • Hematologic toxicity  
|               |            | • **Hepatotoxicity** (ALT-AST elevation [common])  
|               |            | • Central nervous system effects: headache, insomnia, dizziness, convulsions  
|               |            | • **Musculoskeletal:** tendinopathies  
|               |            | • Peripheral neuropathy  
|               |            | • Prolongation of the QTc interval (cardiac disorders [rare])  
|               |            | • **Hypoglycaemia** (rare)  
|               |            | • Digestive tract: nausea, diarrhoea                                                                 |
|               | moxifloxacin | • Anaphylactic reactions and allergic skin reactions  
|               |            | • *Clostridium difficile*-associated colitis  
|               |            | • **Hepatotoxicity** (ALT-AST elevation [common])  
|               |            | • **Musculoskeletal:** Tendinopathies  
|               |            | • Peripheral neuropathy  
|               |            | • Prolongation of the QT interval (cardiac disorders [rare])  
|               |            | • Central nervous system effects: headache, insomnia, dizziness, convulsions  
|               |            | • Digestive tract: nausea, diarrhoea                                                                 |

* based on an analysis of the current respective labelling (European SmPC)  
- common: 1/10 to 1/100  
- rare: 1/1000-1/10000

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:  
- For [community-acquired pneumonia], TAVANICc should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.  
- Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.
A reasonable equilibrium for moxifloxacin?

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular
    (atypical pneumonia, tuberculosis)
- easy iv/po switch
- excellent oral bioavailability

- toxicity?
Side effects of moxifloxacin (clinical trials database)

Moxifloxacin Safety
An Analysis of 14 Years of Clinical Data

Paul M. Tulkens, Pierre Arvis and Frank Kruesemann

1 Pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany

Based on the analysis of 14,681 patients treated with moxifloxacin vs. 15,023 patients treated with comparators
Side effects of moxifloxacin
(clinical trials database)

Distribution of patients valid for the safety analysis, stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by comparator

<table>
<thead>
<tr>
<th>Study design and COMP</th>
<th>Treatment route [n]</th>
<th>IV/PO [n=6846]</th>
<th>IV only [n=1860]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO [n=21 298]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MXF [n=10 613]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>COMP [n=10 685]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV [n=34 31]</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>COMP [n=34 15]</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>IV only [n=9 37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>COMP [n=9 2]</td>
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</table>

**Double-blind studies**

<table>
<thead>
<tr>
<th>Category</th>
<th>PO [n=21 298]</th>
<th>IV/PO [n=6846]</th>
<th>IV only [n=1860]</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactam</td>
<td>2391</td>
<td>1077</td>
<td>408</td>
</tr>
<tr>
<td>β-lactam + macrolide</td>
<td>274</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>2246</td>
<td>444</td>
<td>0</td>
</tr>
<tr>
<td>Macrolide</td>
<td>3659</td>
<td>368</td>
<td>180</td>
</tr>
<tr>
<td>Other</td>
<td>1230</td>
<td>365d</td>
<td>181e</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8822</td>
<td>1889</td>
<td>588</td>
</tr>
</tbody>
</table>

**Open-label studies**

<table>
<thead>
<tr>
<th>Category</th>
<th>PO [n=21 298]</th>
<th>IV/PO [n=6846]</th>
<th>IV only [n=1860]</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactam</td>
<td>1318</td>
<td>554</td>
<td>0</td>
</tr>
<tr>
<td>β-lactam + macrolide</td>
<td>186</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>β-lactam ± macrolide</td>
<td>0</td>
<td>532</td>
<td>0</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>263</td>
<td>0</td>
<td>349</td>
</tr>
<tr>
<td>Macrolide</td>
<td>287</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>456</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1791</td>
<td>1542</td>
<td>349</td>
</tr>
</tbody>
</table>

PO= oral
IV = intravenous
MXF: moxifloxacin
COMP = comparator (see left column)

*Tulkens et al., Drugs R D (2012) 12: 71-100*
## Side effects of moxifloxacin
(clinical trials database)

**Table III.** Summary of safety data for patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by study design. An asterisk (*) indicates differences observed between treatment groups in disfavor of moxifloxacin that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups and for which the number of patients experiencing an event was ≥10 in either group.

<table>
<thead>
<tr>
<th>Study design and event</th>
<th>Treatment route [n (%)]</th>
<th>PO [n= 17465]</th>
<th>IV/PO [n= 3745]</th>
<th>IV [n= 1159]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td></td>
<td>3782 (42.9)</td>
<td>3711 (42.9)</td>
<td>1202 (63.6)</td>
</tr>
<tr>
<td>Any ADR</td>
<td></td>
<td>2211 (25.1)</td>
<td>2026 (23.4)</td>
<td>455 (24.1)</td>
</tr>
<tr>
<td>SAE</td>
<td></td>
<td>318 (3.6)</td>
<td>316 (3.7)</td>
<td>315 (16.7)</td>
</tr>
<tr>
<td>SADR</td>
<td></td>
<td>47 (0.5)</td>
<td>48 (0.6)</td>
<td>53 (2.8)</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td></td>
<td>366 (4.1)</td>
<td>337 (3.9)</td>
<td>144 (7.6)</td>
</tr>
<tr>
<td>Premature discontinuation due to ADR</td>
<td></td>
<td>261 (3.0)</td>
<td>251 (2.9)</td>
<td>74 (3.9)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td></td>
<td>28 (0.3)</td>
<td>36 (0.4)</td>
<td>66 (3.5)</td>
</tr>
<tr>
<td>ADR with fatal outcome&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td></td>
<td>3 (&lt;0.1)</td>
<td>4 (&lt;0.1)</td>
<td>3 (0.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Open-label studies</th>
<th></th>
<th>PO [n= 3833]</th>
<th>IV/PO [n= 3101]</th>
<th>IV [n= 701]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td></td>
<td>764 (42.7)*</td>
<td>766 (37.5)</td>
<td>891 (57.8)</td>
</tr>
<tr>
<td>Any ADR</td>
<td></td>
<td>330 (18.4)*</td>
<td>325 (15.9)</td>
<td>348 (22.6)</td>
</tr>
<tr>
<td>SAE</td>
<td></td>
<td>104 (5.8)</td>
<td>96 (4.7)</td>
<td>280 (18.2)</td>
</tr>
<tr>
<td>SADR</td>
<td></td>
<td>12 (0.7)*</td>
<td>5 (0.2)</td>
<td>**42 (2.7)*</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td></td>
<td>70 (3.9)</td>
<td>67 (3.3)</td>
<td>137 (8.9)</td>
</tr>
<tr>
<td>Premature discontinuation due to ADR</td>
<td></td>
<td>51 (2.8)</td>
<td>49 (2.4)</td>
<td>66 (4.3)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td></td>
<td>10 (0.6)</td>
<td>15 (0.7)</td>
<td>64 (4.2)</td>
</tr>
<tr>
<td>ADR with fatal outcome&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (&lt;0.1)</td>
</tr>
</tbody>
</table>
Side effects of moxifloxacin (clinical trials database)

- AE, ADR and SADR were mainly gastrointestinal disorders and "changes observed during investigations" such as asymptomatic QT prolongation.
- Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated diarrhoea were similar with moxifloxacin and comparators.

<table>
<thead>
<tr>
<th>Study design and event</th>
<th>Treatment route [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO [n= 17465]</td>
</tr>
<tr>
<td>Any AE</td>
<td>3782 (42.9)</td>
</tr>
<tr>
<td>Any ADR</td>
<td>2211 (25.1)</td>
</tr>
<tr>
<td>SAE</td>
<td>318 (3.6)</td>
</tr>
<tr>
<td>SADR</td>
<td>47 (0.5)</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td>366 (4.1)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td>28 (0.3)</td>
</tr>
<tr>
<td>ADR with fatal outcome</td>
<td>3 (&lt;0.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Open-label studies</th>
<th>Treatment route [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO [n= 3833]</td>
</tr>
<tr>
<td>Any AE</td>
<td>764 (42.7)*</td>
</tr>
<tr>
<td>Any ADR</td>
<td>330 (18.4)*</td>
</tr>
<tr>
<td>SAE</td>
<td>104 (5.8)</td>
</tr>
<tr>
<td>SADR</td>
<td>12 (0.7)*</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td>70 (3.9)</td>
</tr>
<tr>
<td>Premature discontinuation due to ADR</td>
<td>51 (2.8)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>ADR with fatal outcome</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

**age (> 65 y)**  
PO: n = 2551 vs. 2403  
sequential: n = 1373 vs. 1334  
IV: n = 170 vs. 191

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>1050 / 1021</td>
<td>929 / 900</td>
<td>83 / 81</td>
</tr>
<tr>
<td>ADR</td>
<td>440 / 448</td>
<td>348 / 307</td>
<td>27 / 31</td>
</tr>
<tr>
<td>SAE</td>
<td>207 / 184</td>
<td>298 / 290</td>
<td>32 / 24</td>
</tr>
<tr>
<td>SADR</td>
<td>16 / 18</td>
<td>49 / 30</td>
<td>4 / 6</td>
</tr>
<tr>
<td>discont. AE</td>
<td>116 / 109</td>
<td>131 / 104</td>
<td>10 / 10</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>78 / 74</td>
<td>62 / 42</td>
<td>4 / 6</td>
</tr>
<tr>
<td>death AE</td>
<td>29 / 32</td>
<td>100 / 98</td>
<td>13 / 10</td>
</tr>
<tr>
<td>death ADR</td>
<td>3 / 1</td>
<td>2 / 3</td>
<td>0 / 1</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

**diabetes**  
PO: n = 777 vs. 717  
sequential: n = 926 vs. 917  
IV: n = 80 vs. 72

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>355 - 310</td>
<td>587 / 565</td>
<td>42 - 35</td>
</tr>
<tr>
<td>ADR</td>
<td>158 - 126</td>
<td>196 / 174</td>
<td>13 - 14</td>
</tr>
<tr>
<td>SAE</td>
<td>78 - 56</td>
<td>198 / 182</td>
<td>16 - 11</td>
</tr>
<tr>
<td>SADR</td>
<td>11 - 3</td>
<td>22 / 11</td>
<td>2 - 2</td>
</tr>
<tr>
<td>discont. AE</td>
<td>34 - 26</td>
<td>78 / 64</td>
<td>6 - 6</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>22 - 14</td>
<td>38 / 20</td>
<td>1 - 4</td>
</tr>
<tr>
<td>death AE</td>
<td>10 - 6</td>
<td>46 / 23</td>
<td>9 - 4</td>
</tr>
<tr>
<td>death ADR</td>
<td>0 - 0</td>
<td>2 / 2</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

renal impairment

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>1283 - 1229</td>
<td>572 - 549</td>
<td>102 - 92</td>
</tr>
<tr>
<td>ADR</td>
<td>259 - 229</td>
<td>196 - 181</td>
<td>31 - 32</td>
</tr>
<tr>
<td>SAE</td>
<td>94 - 80</td>
<td>202 - 180</td>
<td>26 - 22</td>
</tr>
<tr>
<td>SADR</td>
<td>9 - 9</td>
<td>30 - 23</td>
<td>2 - 1</td>
</tr>
<tr>
<td>discont. AE</td>
<td>49 - 53</td>
<td>75 - 78</td>
<td>11 - 7</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>27 - 33</td>
<td>28 - 25</td>
<td>2 - 3</td>
</tr>
<tr>
<td>death AE</td>
<td>12 - 14</td>
<td>58 - 67</td>
<td>10 - 7</td>
</tr>
<tr>
<td>death ADR</td>
<td>0 - 3</td>
<td>3 - 3</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

hepatic impairment

<table>
<thead>
<tr>
<th></th>
<th>n = 146 vs. 163</th>
<th>n = 183 vs. 196</th>
<th>n = 46 vs. 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>69 - 70</td>
<td>183 - 196</td>
<td>23 - 18</td>
</tr>
<tr>
<td>ADR</td>
<td>37 - 32</td>
<td>43 - 43</td>
<td>7 - 6</td>
</tr>
<tr>
<td>SAE</td>
<td>5 - 7</td>
<td>60 - 53</td>
<td>7 - 7</td>
</tr>
<tr>
<td>SADR</td>
<td>1 - 1</td>
<td>10 - 7</td>
<td>1 - 0</td>
</tr>
<tr>
<td>discont. AE</td>
<td>6 - 7</td>
<td>24 - 24</td>
<td>1 - 1</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>6 - 3</td>
<td>11 - 7</td>
<td>1 - 0</td>
</tr>
<tr>
<td>death AE</td>
<td>2 - 4</td>
<td>14 - 24</td>
<td>2 - 0</td>
</tr>
<tr>
<td>death ADR</td>
<td>0 - 1</td>
<td>1 - 2</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

cardiac disorders

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>sequential</th>
<th>JVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>707 - 655</td>
<td>804 - 804</td>
<td>63 - 57</td>
</tr>
<tr>
<td>ADR</td>
<td>340 - 297</td>
<td>315 - 293</td>
<td>16 - 25</td>
</tr>
<tr>
<td>SAE</td>
<td>132 - 110</td>
<td>251 - 246</td>
<td>23 - 11</td>
</tr>
<tr>
<td>SADR</td>
<td>14 - 8</td>
<td>43 - 35</td>
<td>3 - 2</td>
</tr>
<tr>
<td>discont. AE</td>
<td>70 - 64</td>
<td>119 - 96</td>
<td>7 - 3</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>43 - 45</td>
<td>59 - 43</td>
<td>1 - 1</td>
</tr>
<tr>
<td>death AE</td>
<td>11 - 25</td>
<td>69 - 75</td>
<td>11 - 8</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 2</td>
<td>3 - 4</td>
<td>0 - 1</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

BMI < 18

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>sequential</th>
<th>JVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>113 - 171</td>
<td>89 - 83</td>
<td>17 - 10</td>
</tr>
<tr>
<td>ADR</td>
<td>70 - 96</td>
<td>26 - 27</td>
<td>5 - 3</td>
</tr>
<tr>
<td>SAE</td>
<td>11 - 28</td>
<td>36 - 30</td>
<td>3 - 3</td>
</tr>
<tr>
<td>SADR</td>
<td>0 - 5</td>
<td>5 - 4</td>
<td>0 - 0</td>
</tr>
<tr>
<td>discont. AE</td>
<td>14 - 27</td>
<td>10 - 11</td>
<td>1 - 0</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>12 - 20</td>
<td>6 - 9</td>
<td>1 - 0</td>
</tr>
<tr>
<td>death AE</td>
<td>3 - 5</td>
<td>15 - 15</td>
<td>1 - 0</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 0</td>
<td>0 - 0</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin (clinical trials database)

Comparison with other drugs

A. oral therapy

1. moxifloxacin vs β-lactams

risk factor: age > 65 y (n=909 vs 788)

2. moxifloxacin vs macrolides

risk factor: age > 65 y (n=1232 vs 942)

Tulkens et al., Drugs R D (2012) 12: 71-100

NO difference!
# Hepatotoxicity

Crude incidence rates of acute liver injury caused by antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>population</th>
<th>Incidence rate (CI)</th>
<th>Incidence rate (CI)</th>
<th>endpoint</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoroquinolones (w/o moxifloxacin)</td>
<td>Outpatient clinic, Sweden (1995-2005)</td>
<td>0.7 (0.5-1.1)</td>
<td></td>
<td>International consensus</td>
<td>[1]</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>Outpatient clinic, Sweden (1995-2005)</td>
<td>0.08 (0.0-0.5)</td>
<td></td>
<td>International consensus</td>
<td>[1]</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>Saskatchewan Health Plan, Canada (1982-1986)</td>
<td>1.0 (0.2-5.7)</td>
<td>4.9 (0.9-27.6)</td>
<td>International consensus, hospitalisation</td>
<td>[2]</td>
</tr>
<tr>
<td>erythromycin</td>
<td>Saskatchewan Health Plan, Canada (1982-1986)</td>
<td>2.0 (0.7-5.9)</td>
<td>14.0 (4.8-41.2)</td>
<td>International consensus, hospitalisation</td>
<td>[2]</td>
</tr>
<tr>
<td>amoxicillin-clavulanic acid</td>
<td>General practice research database, United Kingdom (1991-1992)</td>
<td>22.5 (14.7-34.4)</td>
<td>17.4 (11.4-26.5)</td>
<td>International consensus</td>
<td>[3]</td>
</tr>
</tbody>
</table>


*Van Bambeke & Tulkens, Drug Safety (2009) 32:359-78*
Hepatotoxicity

Hepatotoxicity risk of antibiotics
(percentage of prescriptions for antibiotics with main indications for use in the community setting)

Andrade & Tulkens, JAC (2011) 66: 1431–46
QTc prolongation

Genetics
- LGTS-1-LQTS-7
- Unknown ion channel mutations

Underlying cardiac disease
- Ischemia
- CHF
- Bradycardia
- Atrial fibrillation

Electrolyte derangements
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

Organ impairment
- Renal insufficiency
- Severe hepatic disease

\( \text{i}_{\text{k}} \)-blocking comedictions or CYP3A4 inhibitors
- www.torsades.org

Prescription of QT-prolonging drug (antimicrobials listed)
- Macrolides/kinetics
- Quinolones
- Azoles
- Penicillins
- TMF-SMZ

Owens & Ambrose CID (2005) 41:S144-157
EMA position

... the risk of arrhythmias appears to increase with the extent of QT/QTc prolongation.
- Drugs [with] QT/QTc interval by around 5 ms or less do not appear to cause TdP.
- ...data on drugs [with] QT/QTc interval by... 5 to < 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk.*

... decisions about [drug] development and approval will depend upon the morbidity and mortality associated with the untreated disease or disorder and the demonstrated clinical benefits of the drug, especially as they compare with available therapeutic modalities.

* this includes erythromycin and clarithromycin (Balardinelli et al, TIPS (2003) 24:619-625)
### Torsade de pointe: comparison of risk

*reporting rate of Torsades de pointe induced by antibiotics*

<table>
<thead>
<tr>
<th>drug</th>
<th>No. of U.S. Cases Reported to the FDA</th>
<th>No. of Estimated Total U.S. Prescriptions (millions)</th>
<th>No. of Cases /10 Millions Prescriptions (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>moxifloxacin</td>
<td>0</td>
<td>1.4</td>
<td>0 (0-26)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>2</td>
<td>66</td>
<td>0.3 (0.0-1.1)</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>2</td>
<td>9.5</td>
<td>2.1 (0.3-7.6)</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>13</td>
<td>24</td>
<td>5.4 (2.9-9.3)</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>8</td>
<td>3</td>
<td>27 (12-53)</td>
</tr>
<tr>
<td>erythromycin</td>
<td>11 –17</td>
<td>151</td>
<td>0.7 -1.1</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>16 –31</td>
<td>90</td>
<td>1.8 -3.4</td>
</tr>
<tr>
<td>azithromycin</td>
<td>7 –10</td>
<td>124</td>
<td>0.6–1</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>1 -1</td>
<td>42</td>
<td>0.2 –1</td>
</tr>
</tbody>
</table>

*Van Bambeke & Tulkens, Drug Safety (2009) 32:359-78*
# Tendinopathies: main features and incidence

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>OBSERVATIONS/FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative quinolones reported[^6,9,10]</td>
<td>Ciprofloxacin (most commonly reported), norfloxacin, pefloxacin, ofloxacin, levofloxacin</td>
</tr>
<tr>
<td>Associated risk factors[^11,31,33–37]</td>
<td>Age &gt;60 years, corticosteroid therapy, renal failure, diabetes mellitus, history of tendon rupture</td>
</tr>
</tbody>
</table>
| Relative risk of tendon disorders[^3,16,31]                              | 1.7-fold increase for all tendinopathies  
1.3-fold increase for tendon rupture  
4.1-fold increase of Achilles tendon rupture  
46-fold increase of tendon rupture with concurrent corticosteroid exposure  
1.5-fold increase in tendon disorders if age > 60 years  
2.7-fold increase in tendon rupture if age > 60 years                                                                 |
| Affected tendons[^11,33,44]                                             | Achilles tendon most commonly affected (89.8% of cases)  
Multiple other tendons reported  
Up to 50% of cases with bilateral involvement  
Symptoms of tendinitis often precede tendon rupture by up to 2 weeks                                                                 |
| Latency period of tendinopathy[^3,4,6,15]                               | Median onset of 6 days (85% of cases within first month)  
Up to 50% of cases after fluoroquinolone discontinued                                                                 |

Tendinopathies…

• In 2005, all fluoroquinolones marketed in the US have received a black box label about tendinopathies.

WARNING:
Fluoroquinolones, including AVELOX®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, and in patients with kidney, heart or lung transplants. [see Warnings and Precautions (5.1)]

Fluoroquinolones, including AVELOX, may exacerbate weakness in persons with myasthenia gravis. Avoid AVELOX in patients with known history of myasthenia gravis [see Warnings and Precautions (5.2)].

Noroxin® (NORFLOXACIN) TABLETS

WARNING:
Fluoroquinolones, including Noroxin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see WARNINGS).

Fluoroquinolones, including Noroxin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Noroxin in patients with known history of myasthenia gravis (see WARNINGS).
Tendinopathies…

- But this is what we found for moxifloxacin in our survey of the whole clinical trial database

**Table VII.** Incidence of selected treatment-emergent adverse events presented by Standard MedDRA Queries/Bayer MedDRA Queries and preferred terms in patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only).

<table>
<thead>
<tr>
<th>SMQ/BMQ and preferred term</th>
<th>Treatment route [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>MXF</td>
</tr>
<tr>
<td></td>
<td>[n=10613]</td>
</tr>
<tr>
<td>Tendinopathies</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td></td>
<td>very rare and no difference</td>
</tr>
<tr>
<td></td>
<td>no case</td>
</tr>
</tbody>
</table>

PO= oral
IV = intravenous
MXF: moxifloxacin
COMP = comparator

*Tulkens et al., Drugs R D (2012) 12: 71-100*
Tendinopathies: incidences (revisited)...

In 2011, the Institute for Safe Medication Practices (ISMP) published a report titled "QuarterWatch: 2010 Quarter 2". This report monitored MedWatch reports and highlighted signals for Varenicline, Levofloxacin, and Fentanyl. The report can be accessed at [ISMP's QuarterWatch](http://www.ismp.org/quarterwatch/2010Q2.pdf) and was last accessed on 20/02/2015.

Levofloxacin (LEVAQUIN) Cases Lead Antibiotics

While antibiotics rank among the safest drugs we monitor, levofloxacin (LEVAQUIN) was suspect in more reports of serious injury than any other antibiotic. Most cases involved tendon rupture and other muscle, tendon, and ligament injuries. Case reports of this problem substantially outnumbered those for two chemically similar drugs—ciprofloxacin (CIPRO), with greater volume of prescriptions, and moxifloxacin (AVELOX), with somewhat less frequent medical use.
Tendinopathies: incidences (revisited)...
Moxifloxacin safety: a conclusion…

Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin
Comparison with Other Fluoroquinolones and Other Antibacterial Classes

Françoise Van Bambeke and Paul M. Tulkens

Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

The data show that using moxifloxacin, in its accepted indications and following the corresponding guidelines, should not be associated with an excessive incidence of drug-related adverse reactions, provided the clinician takes care in identifying patients with known risk factors and pays due attention to the contraindications and warnings mentioned in the labelling.
Thank you for your attention!

And ask questions
The "first generation" of fluoroquinolones

- Nalidixic acid
- Oxolinic acid
- Cinoxacin
- Pipemidic acid

- Norfloxacin
- Pefloxacin
- Ofloxacin
- Ciprofloxacin
- Fleroxacin
- Rufloxacin

improved anti Gram (-) activity

<table>
<thead>
<tr>
<th>$t_{1/2}$</th>
<th>activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 h</td>
<td>++</td>
</tr>
<tr>
<td>11 h</td>
<td>+</td>
</tr>
<tr>
<td>6 h</td>
<td>++</td>
</tr>
<tr>
<td>3-4 h</td>
<td>+++</td>
</tr>
</tbody>
</table>