# Safety of antibiotics with special reference to moxifloxacin and its benefit-risk ratio


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# Contents of the Presentation

- Safety
  - overview
  - hepatic
  - QTc
- "Respiratory" Fluoroquinolones in todays' epidemiological situation

# Overview: treatment emergent adverse events in comparative clinical studies (oral form; all indications)

| | Moxifloxacin | Comparator |
|---|---|---|
| **Total** | **9394 (100)** | **9359 (100)** |
| **AE** | 4057 (43.2) | 3950 (42.2) |
| **ADR *** | 2257 (24.0) | 2059 (22.0) |
| **SAE** | 369 (3.9) | 361 (3.9) |
| **SADR *** | 56 (0.6) | 50 (0.5) |
| **Fatal AE** | 33 (0.4) | 44 (0.5) |
| **Fatal ADR** | 3 (<0.1) | 4 (<0.1) |

AE: adverse event; ADR: adverse drug reaction;
SAE: serious AE; SADR: serious ADR

Comments:

- similar moxifloxacin/comparator ADR, SADR, and Fatal ADR ratios for sequential or IV
- Similar findings in published studies (see next slide)

**Data from** Bayer HealthCare
Bayer Schering Pharma

# Safety data from published * clinical trials

6270 patients moxifloxacin
5961 patients comparator

- amoxicillin/clavulanic acid, cefuroxime, cefixime,
- clarithromycin, azithromycin,
- trovafloxacin, levofloxacin,
- sulfamethoxazole

Overal conclusion: no significant difference for

- Side effects
- Serious side effects

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** Andriole et al. (2005) Drug Safety 28:443-53*

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# Patients with possible drug-related hepatic disorders in comparative clinical trials (oral moxifloxacin)

| | Moxifloxacin (N=9394) | | | Comparators (N=9359) | | |
|---|---|---|---|---|---|---|
| | AE [ADR] | | | | | |
| (Sub-)SMQ | Total | Serious | Fatal | Total | Serious | Fatal |
| **Comprehensive search All cases** | 219 (2.3%) [153 (1.6%)] | 6 (<0.1) [3 (<0.1)] | 0 (-) | 223 (2.4%) [139 (1.5%)] | 8 (<0.1%) [3 (<0.1%)] | 2 (< 0.1%) [0 (–)] |
| **Liver related investigations, signs and symptoms *** | 180 [120] | 4 [2] | 0 [0] | 198 [124] | 4 [1] | 0 [0] |
| **Cholestasis and jaundice of hepatic origin** | 13 [9] | 0 [0] | 0 [0] | 6 [4] | 1 [1] | 0 [0] |
| **Possible liver-related coagulation and bleeding disturbances** | 17 [15] | 0 [0] | 0 [0] | 13 [8] | 1 [1] | 0 [0] |
| **Possible drug related hepatic disorders - severe events only** | **19 [16]** | **2 [1]** | 0 [0] | **17 [7]** | **3 [0]** | 0 [0] |
| Hepatitis, non-infectious | 7 [7] | 1 [1] | 0 [0] | 6 [3] | 0 [0] | 0 [0] |
| Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions | 12 [9] | 1 [0] | 0 [0] | 9 [4] | 1 [0] | 0 [0] |
| Liver neoplasms, benign | 0 [0] | 0 [0] | 0 [0] | 0 [0] | 0 [0] | 0 [0] |
| Liver neoplasms, malignant and unspecified | 0 [0] | 0 [0] | 0 [0] | 2 [0] | 2 [0] | 0 [0] |

AE: adverse event; ADR: adverse drug reaction; SMQ: Standard MedDRA Query
The allocation of a liver related adverse event to any of the sub-SMQs is not mutually exclusive. One patient can have one event allocated to several sub-SMQs, or several events located to different sub-SMQs. In consequence, the overall number of patients identified with the "comprehensive search" is smaller than the sum of all patients allocated to the sub-SQMs.

*** similar to published studies**

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**Could this be a signal ?**

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# SMQ-search for "severe events": Hepatic overview by event type/diagnosis

| | Moxifloxacin AE [ADR] | Comparator AE [ADR] |
|---|---|---|
| **Total** | **19 [16]** | **17 [7]** |
| Hepatitis | | |
| CTC grade ≥3 (severe) | 3 [2] | 1 [0] |
| CTC grade <3 (non-severe) | 4 [4] | 5 [3] |
| Hepatic failure | | |
| CTC grade ≥3 (severe) | 1 [0] | 0 |
| CTC grade <3 (non-severe) | 2 [2] | 1 [1] |
| Liver disorder | | |
| CTC grade ≥3 (severe) | 0 | 3 [1] |
| CTC grade <3 (non-severe) | 9 [8] | 5 [2] |
| Liver neoplasm | 0 | 2 [0] |
| Outcomes | | |
| Resolved/improved | 17 | 10 |
| Unchanged | 1 | 2 |
| Worsened/death | 0 | 1 |
| Unknown | 1 | 4 |

AE: adverse event; ADR: adverse drug reaction

Common Terminology Criteria for Adverse Events v3.0:

- AP, GGT, AST, ALT: Grade 1 (mild), >ULN – 2.5x ULN; Grade 2 (moderate), >2.5 – 5.0x ULN; Grade 3 (severe), >5.0 – 20.0x ULN; Grade 4 (life-threatening), >20.0x ULN
- Total bilirubin: Grade 1 (mild), >ULN – 1.5x ULN; Grade 2 (moderate), >1.5 – 3.0x ULN; Grade 3 (severe), >3.0 – 10.0x ULN; Grade 5 (life-threatening), >10.0x ULN

# Crude incidence rates of acute liver injury caused by non-fluoroquinolone antibiotics (observational studies)

**(endpoint: international consensus *)**

| Antibiotic | population | Incidence rate / 100,000 users (CI 95 %) |
|---|---|---|
| cotrimoxazole | Saskatchewan Health Plan, Canada (1982-1986) | 1.0 (0.2-5.7) |
| erythromycin | Saskatchewan Health Plan, Canada (1982-1986) | 2.0 (0.7-5.9) |
| macrolides [a] | General practice research database, United Kingdom (1994-1999) | 2.5 (0.9-5.4) |
| amoxicillin-clavulanic acid [b] | General practice research database, United Kingdom (1994-1999) | 8.6 (2.4-14.6) |

***** AAT/Alk. phos. ratio (hepatocellular: $\geq 5$; cholestatic: $\leq 2$ ; mixed: $> 2$ and $< 5$)

[a] clarithromycin similar to erythromycin; mostly short term and cholestatic; AOR = 6.1 [0.8-45.9]

[b] cholestatic or mixed, short and long-term (clavulanic acid main culprit); AOR = 94.8 [27.8-323]

De Valle et al (2006) Aliment. Pharmacol. Ther. 24:1187-95
Garcia Rodriguez (1996) 156:1327-32
Perez et al (1993) Epidemiology 4:496-501
de Abajo et al. (2004) Br. J. Clin. Pharmacol. 58:71-80

**Our independent analysis**

# Relative risk of hepatic adverse event * of fluoroquinolones *vs.* macrolides and telithromycin in observational studies

**(incidence calculated based on data from reporting systems)**

| Antibiotic class | Case patients | Non-case patients | Relative risk (CI 95 %) |
|---|---|---|---|
| fluoroquinolones | 34 / 1069 | 865 / 22869 | 0.8 (0.6-1.2) |
| macrolides | 46 / 1069 | 587 / 22869 | 1.7 (1.25 – 23) |
| telithromycin | 20 / 2219 | 98 / 20667 | 1.82 (1.12 – 2.96) |

* elevated liver function tests, jaundice, hepatocellular damage, liver failure

Motola et al (2007) Eur. J. Clin. Pharmacol. 63:73-9
Fluoroquinolones in Italy at the time of the survey and included in the analysis: levofloxacin, ciprofloxacin, moxifloxacin, lomefloxacin, norfloxacin, pefloxacin, rufloxacin, ofloxacin

Dore (2007) Drug Saf. 30:697-703

**Our independent analysis**

# FDA reporting rate per 10,000,000 prescriptions (spontaneous reports)

| Antibiotic class | Acute liver failure [a] |
|---|---|
| Levofloxacin | 2.1 * |
| Moxifloxacin | 6.6 |
| Telithromycin | 23 |
| Trovafloxacin | 58 |

[a] Empiric Bayes Geometric Mean (EBGM) study
www.fda.gov/ohrms/dockets/AC/06/slides/2006-4266s1-01-07-FDA-Brinker.ppt
presented December 2006 to FDA Advisory Committee

Liver failure was defined as "acute or severe liver injury with encephalopathy, liver transplant following acute illness, death in the setting of acute liver injury (hospital. with transam. elev., or hyperbilirubin., or clin jaund.)"

* The US labelling of levofloxacin includes warning against "potentially severe hepatotoxicity" (http://www.levaquin.com/levaquin/isi_index.html)

**Our independent analysis**

# Hepatotoxicity: Conclusions

- There is no evidence from currently available data that reactions are more frequent than with comparators
  - Clinical trials:
    - Apparent imbalance in drug-related “severe events” as per MSSO SMQ (see slides 7-9) is based on clinically non-severe, non-serious events; the number of serious, or clinically severe ADRs is too small for meaningful conclusions
  - Spontaneous data:
    - No comparative statement possible from company data
    - Value of comparative analyses of spontaneous data from different companies is considered to be limited
    - No signal in EBGM analysis conducted by FDA

**Our independent analysis**

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# QTc interval: observations and clinical impact

**Moxifloxacin is known to cause modest QTc prolongation**

➔ 6 – 7 msec in healthy volunteers, Phase II/III – po and Phase II/III – iv

**but without true clinical impact**

| Agent | Serious cardiac events * (no. per 10 millions patients treated or as indicated) |
|---|---|
| Moxifloxacin | 4 [a] (in 13 millions) |
| Ciprofloxacin | 8 |
| Ofloxacin | 18 |
| Levofloxacin | 18 |
| Gatifloxacin | 27 (in 3 millions) |
| Sparfloxacin | > 100 |
| Grepafloxacin | > 150 |

*** Torsades de Pointes, ventricular tachycardia, or bradycardia**

**[a] current observed rate is 5.8 per 10 millions**

Ianini (2004) Drug Benefit Trends (suppl) 34-41

PSUR Bridging Report July 18, 2008

See also: Owens & Ambrose (2005) CID 41S2: S144-57

Falagas et al (2007) Int. J. Antimicrob. Ag. 29:374-9

Veyssier et al. (2006) Med. Mal. Infect. 36:505-12

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# Respiratory fluroquinolones in todays' epidemiological situation: what if ?

# What if fluoroquinolones are made "impossible to prescribe" ?

➔ **significant problems in several EU countries because of resistance to other, often recommended antibiotics**

| | Resistance of *S. pneumoniae* (%) in 2005 * | | | |
|---|---|---|---|---|
| **Country** | **Penicillins [1]** | **Macrolides [2]** | **Tetracyclines [2]** | **MDR [3]** |
| **France** | 49.2 | 50.1 | 41.1 | 40.8 |
| **Spain** | 40.1 | 30.1 | 27.6 | 26.7 |
| **Italy** | 24.5 | 48.1 | 37.5 | 18.8 |
| **Mean EU** | 24.0 | 24.6 | 19.8 | 15.8 |

* Pneumococcal isolates (n = 1974) recovered from patients with community-acquired respiratory tract infections in 15 European countries (Eur J. Clin. Microbiol. Infect. Dis., 2007;26:485-490)

[1] intermediates and full-resistant (intermediates require high doses)

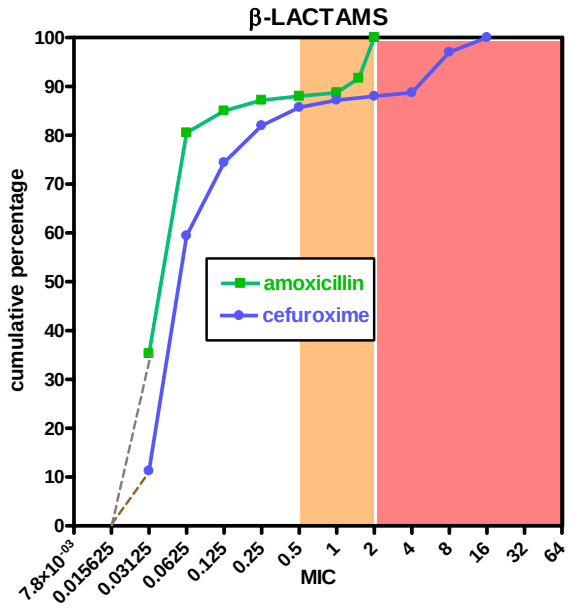
[2] full and crossed resistance to all macrolides except telithromycin

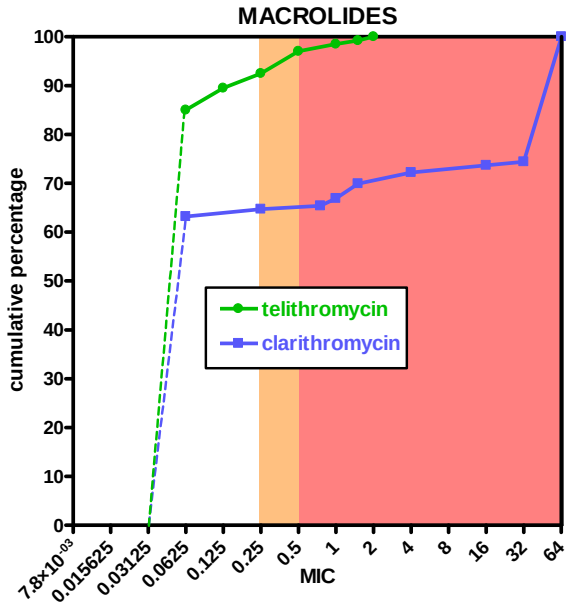
[3] penicillin (I or R) plus resistance to 2 or more other classes of antibiotics

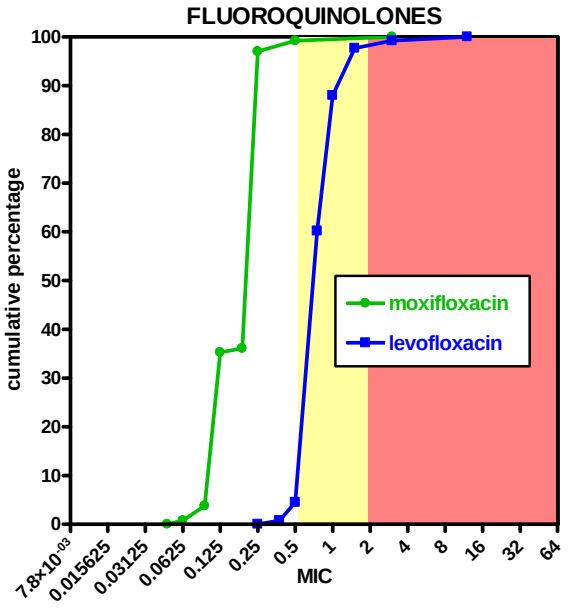
**Our independent analysis**

# An example for community *S. pneumoniae* in Belgium

Cumulative MIC distribution in 133 cases of confirmed infection against EUCAST breakpoints (http://www.eucast.org)




- amoxicillin: 0 % > R
  but at high dose
- cefuroxime: 13 % > R

- telithromycin: 8 % >R
- clarithromycin: 35 > R

- levofloxacin: 1 % > R
  bur at high dose
- moxifloxacin: 0 % R

Lismond et al (2008) ECCMID P1747
(Similar observations in two other Belgian independent centres [Louvain - Pasteur Institute])

**Our independent analysis**

# Conclusions

- The safety profile of "respiratory" fluoroquinolones remains largely acceptable and not worse than that of several other comparators if SmPC (labelling) warnings are taken in due consideration
  - Hepatic events, bullous skin, and clinical cardiac events are not different from comparators (incl. levofloxacin)
  - ➔ Consistent with peer-reviewed published literature
- Restricting moxifloxacin specifically is, in my view, counter-productive and against Public Health interest because it will drive use of the remaining antibacterials with their own risks
  - ➔ safety profiles of high doses of beta-lactams and levofloxacin are potentially worse than that of moxifloxacin;
  - ➔ macrolides or tetracyclines are no longer an option in many EU countries and are not free from toxicities.

**Our independent analysis**

# Disclosures

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- the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics
- the Belgian Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Pharmaceutical Industry for specific drug-related studies

Note:

- all work, irrespective the source of funding, is published in peer-reviewed journals and is available from our web site
- P.M. Tulkens is member of the Committee organizing public campaigns for appropriate use of antibiotics in Belgium since 2000 *

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* Bauraind et al. JAMA. 2004 Nov 24;292(20):2468-70.