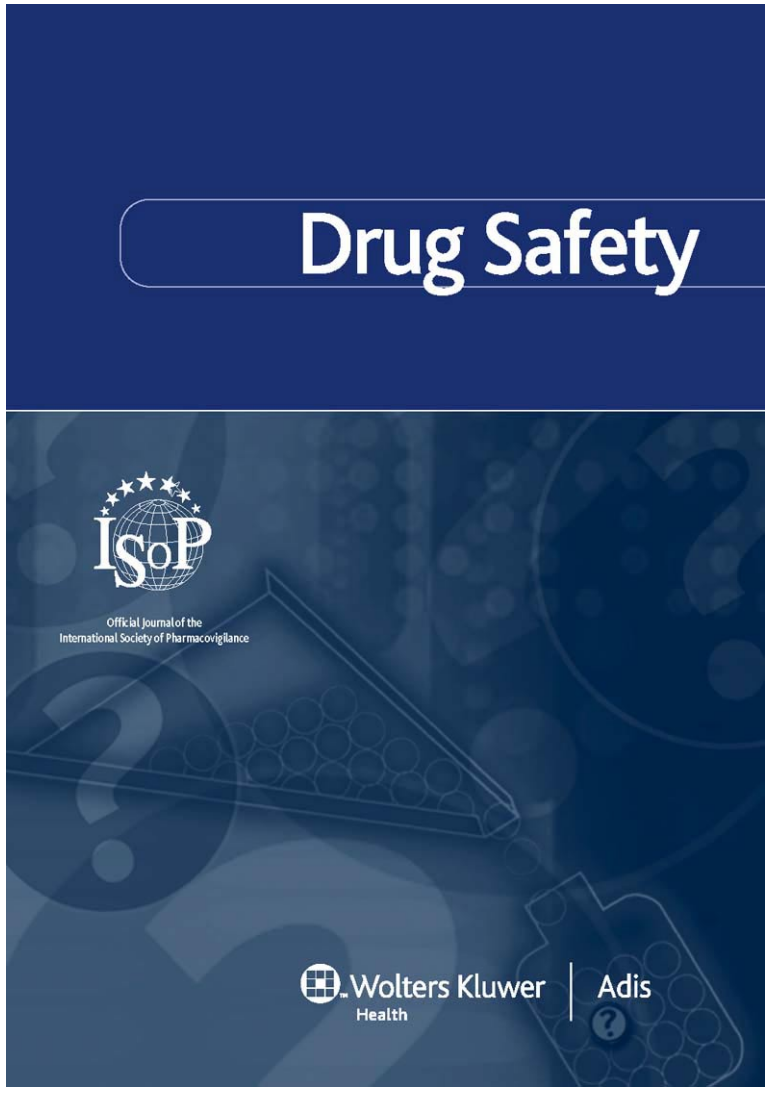

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Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin

Comparison with Other Fluoroquinolones and Other Antibacterial Classes

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Abstract

Moxifloxacin, a fluoroquinolone with potent activity against respiratory pathogens, is approved and considered as an alternative to β-lactams and macrolides for the treatment of acute bacterial sinusitis and lower respiratory tract infections. In this review, we critically examine its safety profile in comparison with other fluoroquinolones and other antibacterial classes sharing similar indications. Data were extracted from published clinical trials, meta-analyses, postmarketing studies, spontaneous report systems and case reports for rare effects.

Global analysis did not reveal significantly higher incidences of drug-related adverse effects than for comparators. Tendon rupture was infrequent with moxifloxacin, including when used in elderly patients with chronic obstructive pulmonary disease. Severe toxic cutaneous reactions and allergies were very rare. Phototoxicity and CNS adverse effects were less common than with other fluoroquinolones. Although causing a 4–7 msec corrected QT interval prolongation, severe cardiac toxicity was neither seen in large cohorts or clinical trials nor reported to pharmacovigilance systems. Hepatotoxicity was not different from what was observed for other fluoroquinolones (excluding trovafloxacin) and less frequent than reported for amoxicillin-clavulanic acid or telithromycin.

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.

Moxifloxacin is approved and used worldwide for three major respiratory tract infections, namely acute bacterial sinusitis, acute exacerbations of chronic obstructive pulmonary disease (COPD) and community-acquired pneumonia.[1,2] As with other fluoroquinolones with similar indications (e.g. levofloxacin), moxifloxacin presents many desirable antimicrobial and pharmacokinetic

properties (rapid bactericidal activity; spectrum covering the main pertinent pathogens, including those causing so-called atypical pneumonia, and, for moxifloxacin, anaerobes; excellent bioavailability after oral administration).[3] However, both American and European guidelines recommend these agents only as alternatives to either β-lactams or macrolides for outpatients[4,5] because of the following reasons: (i) the fear of rapid development of resistance; and (ii) the desire to minimize adverse effects often attributed to this whole class of antimicrobials.

The first concern (resistance) has not materialized so far for moxifloxacin. The minimum inhibitory concentrations of moxifloxacin against key respiratory pathogens (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) have remained almost unchanged since its commercialization in the late 1990s.[6-10] This is in contrast to what has been observed for levofloxacin,[11-13] which should now be used at higher dosages than originally recommended.[6,14,15] Therefore, moxifloxacin could be perceived as pharmacodynamically superior.[6,16-18] Yet, this advantage needs to be weighed against the risk of toxicity; several potent fluoroquinolones have been withdrawn or severely limited in their use because of unacceptable rates of severe adverse effects (e.g. temafloxacin, clinafloxacin, sparfloxacin, fleroxacin, grepafloxacin, trovafloxacin, gatifloxacin[3,19]).

The aim of this review is to critically examine the safety profile of moxifloxacin, not only in comparison with other fluoroquinolones,[1] but also with other antibacterials often recommended for the treatment of respiratory tract infections, thereby providing the clinician with comprehensive information that may help in correctly positioning moxifloxacin among the various available drugs.

The following public sources of information were used for this review: (a) a systematic survey of the literature published in the English language and referenced in PubMed using as keywords the name of the drug combined with the words 'safety', 'side effect', 'adverse effect' or 'toxicity', or the name of the specific adverse effect examined;[2] (b) the US Prescriber Information (US labelling) of each drug;[3] (c) the documents available on the website of the US FDA. We made a systematic distinction between (a) clinical studies (having led to registration or undertaken after commercialization); (b) postmarketing studies (initiated by the registration holder); (c) case reports; (d) spontaneous pharmacovigilance reports; and (e) 'case/non-case' studies.

1. Global Safety Profile

1.1 Published Comparative Clinical Trials and Postmarketing Studies

Safety data from published clinical trials included 6270 patients treated with oral moxifloxacin versus 5961 patients receiving a comparator, which was either a β-lactam (amoxicillin, amoxicillin-clavulanic acid, cefuroxime axetil, cefalexin, cefixime), a macrolide (clarithromycin, azithromycin), a fluoroquinolone (trovafloxacin, ofloxacin, levofloxacin) or cotrimoxazole (trimethoprim/sulfamethoxazole).[19-21] No difference could be

1 The structural formulae of all fluoroquinolones mentioned in this review, together with general considerations on structure-toxicity relationships, can be found elsewhere (see Van Bambeke et al.[3])

2 The original search was performed in April 2008 with no date limit, and repeated in November 2008 to capture additional references; at manuscript proof stage (21 March 2009) a new search covering the whole of 2008 to March 2009 was again performed using '(moxifloxacin OR levofloxacin) AND (adverse effect OR safety OR cardiac OR hepatic OR toxicity OR QTc OR tendon* OR photoxicity OR death)' as boolean operators to retrieve the very last publications relevant to moxifloxacin and levofloxacin.

3 Moxifloxacin and levofloxacin, as well as all other fluoroquinolones currently approved in Europe, have been registered through decentralized or national procedures, making it difficult to compare and analyze the individual drug labels. An analysis of recent decisions of the European Medicines Agency about moxifloxacin and an update of its labeling, which will apply to countries of the EU, is presented in section 3 in this review.

evidenced between the two arms, with about 45% of patients demonstrating adverse effects during treatment, approximately half of which were considered to be possibly drug-related. Among these, nausea and diarrhoea were observed at a frequency >5%, dizziness was reported in 2.5–3.6% of patients (depending on age but without significant difference between age groups), and liver function test disturbances were seen in about 1.1% of the patients treated with moxifloxacin. Serious drug-related adverse effects were uncommon (0.1–1%) or rare (0.01–0.1%) no matter which drug was administered.

Postmarketing studies and meta-analyses of randomized controlled trials in acute sinusitis,[22-29] acute exacerbation of chronic bronchitis,[25-27,30-37] community-acquired pneumonia[25-27,38-48] or hospital-acquired pneumonia[49] globally confirm this safety profile for moxifloxacin versus comparators. However, the number of patients enrolled in all these studies (<100 000[19]) does not allow assessment of the incidence of very rare adverse effects (occurring in <0.01% of patients).

1.2 Data from Reporting Systems

Spontaneous pharmacovigilance reports, although informative, do not allow the incidence of adverse effects to be determined or to compare safety profiles of different drugs, because the number of reports is highly dependent on the number of prescriptions and the attention paid to each drug by the reporter.[50] A better insight into the risk of developing adverse effects can be obtained from the 'case/non-case' approach. Table I shows the relative odds ratios of a series of well known adverse effects of fluoroquinolones obtained in such studies. Two are clearly associated with the use of all fluoroquinolones, namely tendon rupture (now with a 'warning box' in the agents' respective US labelling) and toxic skin reactions (also seen with sulfonamides, cephalosporins and tetracyclines). Dysglycaemia is mainly observed for gatifloxacin. No specific hepatotoxicity risk is associated with fluoroquinolones as a class (see section 2.6 for analysis by agent), in contrast with macrolides and telithromycin, for which a larger risk of hepatotoxicity is clearly evidenced.

2. Main Reported Toxicities

2.1 Tendon Rupture

Fluoroquinolone-related tendon rupture affects preferentially but not exclusively, the Achilles tendon. The mechanism remains uncertain, although current hypotheses include direct toxicity on collagen fibres, formation of reactive oxygen species,[56,57] increased expression of matrix metalloproteinases[42,58] and complexation of magnesium ions in joints and cartilages.[59,60] The overall estimated incidence ranges from 0.14% to 0.4%.[56] Risk factors include age, concomitant use of corticosteroids, renal failure, diabetes mellitus, gout, hyperparathyroidism, peripheral vascular disease, sporting activities and rheumatic disease.[51,61] No truly comparative study of fluoroquinolones is available; however, tendon rupture is more frequently mentioned in spontaneous reporting systems for levofloxacin than for ciprofloxacin or norfloxacin.[50,51] For COPD patients, tendon rupture is usually ascribed to age and to corticosteroid administration, two known aggravating factors.[62,63] Although isolated cases have been reported with moxifloxacin,[64,65] no tendon rupture was noted in a study involving 354 COPD patients with a mean age of 63.8 ± 9.7 years and in whom concomitant usage of corticosteroids was important (57%).[66]

2.2 Toxic Cutaneous Reactions and Allergy

Severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are extremely rare with fluoroquinolones (table II), with only one report in the published literature for moxifloxacin.[69] The odds ratio is 10 for fluoroquinolones as a class versus 7 for aminopenicillins, 8 for tetracyclines, 14 for cephalosporins and up to 170 for sulfonamides (table I).[52] Acute generalized exanthematous pustulosis is a rare drug-induced event, with risk estimates (on very small samples) of 33 for fluoroquinolones versus 11 for macrolides and 23 for aminopenicillins.[70]

Table I. Odds ratios for developing adverse effect upon antibacterial exposure as determined by case/non-case studies[a]

Adverse effect	Antibacterial	No. exposed to specified antibacterial/total no. of patients		Odds ratio (CI 95%)	Reference
		Case patients	Non-case patients		
Tendon rupture	**Fluoroquinolones**	12/1 367	87/50 000	4.0 (2.1, 7.7)[b]	51
	Fluoroquinolones (age <60 y)	0/1 056	50/36 957	NA	51
	Ofloxacin (age >60 y)	5/289	5/12 653	28.4 (7.0, 115.3)[b]	51
	Ciprofloxacin	6/289	40/12 653	3.6 (1.4, 9.1)[b]	51
	Norfloxacin	1/289	5/12 653	14.2 (1.6, 128.6)[b]	51
	Amoxicillin	15/1 367	661/50 000	0.8 (0.4, 1.3)[b]	51
	Amoxicillin-clavulanic acid	5/1 367	144/50 000	1.1 (0.5, 2.9)[b]	51
	Macrolides	8/1 367	242/50 000	1.1 (0.6, 2.3)[b]	51
	Tetracycline	12/1 367	323/50 000	1.3 (0.7, 2.3)[b]	51
	Sulfonamides/trimethoprim	5/1 367	40/50 000	3.0 (1.1, 8.3)[b]	51
Stevens-Johnson syndrome or toxic epidermal necrosis	**Fluoroquinolones**	11/245	5/1 147	10 (2.6, 38)[b]	52
	Aminopenicillins	15 /245	12/1 147	6.7 (2.5, 18)[b]	52
	Cephalosporins	14/245	3/1 147	14 (3.2, 59)[b]	52
	Macrolides	6/245	5/1 147	1.6 (0.2, 13[b])	52
	Tetracyclines	5/245	4/1 147	8.1 (1.5, 43)[b]	52
	Sulfonamides	32/2 45	1/1 147	172 (75, 396)[b]	52
Hypoglycaemia	**Gatifloxacin**	61/788	77/3 791	4.3 (2.9, 6.3)[b]	53
	Moxifloxacin	24/788	162/3 791	0.8 (0.5, 1.3)[b]	53
	Levofloxacin	114/788	341/3 791	1.5 (1.2, 2.0)[b]	53
	Ciprofloxacin	209/788	1 075/3 791	0.9 (0.8, 1.1)[b]	53
	Cephalosporins	62/788	397/3 791	0.9 (0.6, 1.1)[b]	53
	Macrolides	318/788	1 739/3 791	1[b]	53
Hyperglycaemia	**Gatifloxacin**	86/470	42/2 280	16.7 (10.4, 26.8)[b]	53
	Levofloxacin	52/470	233/2 280	1.3 (0.9, 1.9)	53
	Moxifloxacin	20/470	70/2 280	1.7 (1.0, 3.0)	53
	Ciprofloxacin	113/470	576/2 280	1.1 (0.9, 1.5)[b]	53
	Cephalosporins	38/470	235/2 280	1.2 (0.8, 1.7)[b]	53
	Macrolides	161/470	1 124/2 280	1[b]	53
Hepatotoxicity	Fluoroquinolones	34/1 069	865/22 869	0.8 (0.6, 1.2)[c]	54
	Macrolides	46/1 069	587/22 869	1.7 (1.25, 23)[c]	54
	Telithromycin	20/2 219	98/20 667	1.82 (1.12, 2.96)[b]	55

a Bold characters highlight antibacterials at risk for the considered adverse effect.

b Adjusted odds ratio

c Crude odds ratio

NA = not applicable.

Table II. Case reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in the literature (updated from Salvo et al.[67] and Iannini et al.[68])

Antibacterial	SJS	TEN
Moxifloxacin	NPR	1
Ciprofloxacin	9	17
Levofloxacin	NPR	4
Amoxicillin	7	4
Ampicillin	4	6
Amoxicillin/clavulanic acid	14	2
Cephalosporins	3	2
Erythromycin	4	NPR
Azithromycin	2	NPR
Tetracyclines	2	NPR
Cotrimoxazole (sulfamethoxazole/trimethoprim)	8	7
Vancomycin	3	10
Rifampicin	1	1

NPR = no published reports.

The incidence of serious allergic reactions is rare and similar for moxifloxacin, ciprofloxacin and penicillins, and lower than for levofloxacin, gatifloxacin and cephalosporins. The incidence of anaphylaxis/anaphylactoid reactions is similar for fluoroquinolones, penicillins and cephalosporins.[71]

2.3 Phototoxicity

Phototoxicity is clearly associated with fluoroquinolones. The presence of the fluoro substituent in position 6 increases the risk of phototoxicity, and this is markedly enhanced in molecules with an additional halogen substituent (Cl or F) in position 8,[3] as shown for sparfloxacin (withdrawn partially for this reason) and BAY-Y-3118 (development prematurely discontinued). Phototoxicity probably results from the formation of reactive oxygen species upon light exposure,[72] and ranks as follows among clinically developed fluoroquinolones: lomefloxacin > fleroxacin (both carrying a halogen in position 8) > enoxacin > pefloxacin > ciprofloxacin > grepafloxacin > gemifloxacin > levofloxacin > norfloxacin > ofloxacin > moxifloxacin.[73] Incidences are very low for ciprofloxacin (<1%),[74] and moxifloxacin or gemifloxacin (<0.1%)[2,75] in the absence of excessive exposure to light.

2.4 CNS Toxicity

Fluoroquinolones have been commonly reported to cause dizziness, drowsiness, headache, confusion and, more rarely, seizures[73,76] (mainly in patients with predisposing factors [epilepsy, cerebral trauma], metabolic imbalance or concomitant therapies [theophylline or NSAIDs]).[76-78] These result from an interaction with GABA or glutamate receptors.[72] The global incidence with fluoroquinolones is 1–2%,[73] although higher figures (12% for fluoroquinolones vs 3.6% for other antimicrobials) have been suggested.[79] Patients with a low body mass index, such as the Asian population, could be at higher risk. Dizziness is more common in women.[80] Structure-effect relationships of drug-induced CNS toxicities are difficult to define because clinical expression results from the combination of two unrelated properties (capacity of the drug to cross the blood-brain barrier and interaction with brain targets).[3] *In vitro* models of evoked potential in rat hippocampus slices show a low toxic potential for ofloxacin, ciprofloxacin and moxifloxacin compared with other fluoroquinolones.[81] This is also globally observed in clinical studies.[73,79] According to the current labelling, moxifloxacin, as with all other fluoroquinolones, should be used with caution in patients with known or suspected CNS disorder or in the presence of risk factors that predispose to seizures or lower the seizure threshold.

2.5 Cardiotoxicity

Vital risks associated with a drug-induced prolongation of the corrected QT (QTc) interval (major cardiac rhythm perturbations and life-threatening torsade de pointes) have received much attention over the last few years, leading to withdrawal or severe restriction of many drugs. It is thought to be related to the inhibition of a specific repolarizing potassium current, I_{Kr} (mediated by the human Ether-à-go-go Related Gene [hERG] channel).[82] *In vitro* assays comparing fluoroquinolones and macrolides[83,84]

Table III. Reporting rate of torsade de pointes induced by fluoroquinolones and macrolides (based on data from 2001[89,91])

Drug	No. of US cases reported to the US FDA	No. of estimated total US prescriptions (millions)	No. of cases/10 million prescriptions (95% CI)
Moxifloxacin	0	1.4	0 (0, 26)
Ciprofloxacin	2	66	0.3 (0.0, 1.1)
Ofloxacin	2	9.5	2.1 (0.3, 7.6)
Levofloxacin	13	24	5.4 (2.9, 9.3)[a]
Gatifloxacin	8	3	27 (12, 53)[b,c]
Erythromycin	11[d] to 17[e]	151	0.7[d] to 1.1[e]
Clarithromycin	16[d] to 31[e]	90	1.8[d] to 3.4[e]
Azithromycin	7[d] to 10[e]	124	0.6[d] to 0.8[e]
Cefuroxime	1[d,e]	42	0.2[d,e]

a $p < 0.001$ for levofloxacin vs ciprofloxacin (Fisher's exact test).

b $p < 0.001$ for gatifloxacin vs ciprofloxacin (Fisher's exact test).

c $p = 0.001$ for gatifloxacin vs levofloxacin (Fisher's exact test).

d Data from the US FDA adverse event reporting system analysis.[92]

e Data from Medwatch.[93]

show a ranking (from most to least inhibitory) of sparfloxacin ≥ clarithromycin ≥ roxithromycin ≥ telithromycin > grepafloxacin > moxifloxacin ≥ erythromycin ≥ josamycin ≥ gatifloxacin > gemifloxacin > levofloxacin > ciprofloxacin.[83-86]

In volunteers and in phase II/III trials (including intravenous [IV] administration), moxifloxacin caused a mean reproducible QTc interval prolongation of 4–7 msec,[73,87] well below the thresholds of 30 and 60 msec accepted to define borderline effect and QTc interval prolongation, respectively,[65,88] and without demonstrated significant clinical impact.[4] In a retrospective database analysis of American patients who had received fluoroquinolones between January 1996 and May 2001, the risk for developing torsade de pointes was estimated to be 0 for moxifloxacin, 0.3 for ciprofloxacin, 2.1 for ofloxacin, 5.4 for levofloxacin and 27 for gatifloxacin per 10 million prescriptions (table III); however, moxifloxacin-treated patients are under-represented because the drug was only on the market during the late data-collection period.[89] In a recently published analysis by Poluzzi et al.[90] of the public version of the FDA Adverse Event Reporting System for the 2004–7 period (containing 1 301 839 spontaneous reports for drug adverse reactions, with about half from Europe), 41 and 61 reports of torsade de pointes were noted for moxifloxacin and levofloxacin, respectively (of a total of 1665 reports for all drugs), with no statistically-significant difference in reporting odds ratios between the two drugs (calculated from cases [torsade de pointes reports] vs non-cases [all other adverse drug reactions reports for the same drug]).

A recent prospective observational and uncontrolled but monitored study conducted in 13 578 patients with respiratory tract infection and treated with moxifloxacin evidenced 1046 adverse events in 678 patients (5%; reviewed by an independent board), among which only 25 were cardiac and drug-related.[94] Nineteen patients (0.14%) were affected by palpitations (n = 13), tachycardia (4), malaise (4), vertigo (3) and/or pallor (1). There was no evidence of torsade de pointes. The current US labelling[2] states that no cardiovascular morbidity or mortality attributable to QTc interval prolongation

4 Moxifloxacin is often used in phase I trials as a 'positive' control for corrected QT (QTc) interval prolongation, which has led to the erroneous conclusion that the drug causes a potential hazard in patients. However, the reason that moxifloxacin is used is because the drug produces a measurable QTc interval increase; this allows the method used to assess QT interval prolongation to be validated while avoiding significant health risk for study subjects.

occurred with moxifloxacin treatment in the surveyed studies, including a subset of patients with hypokalaemia. In comparison, macrolides, analyzed in an FDA report published in 2001, showed incidences of 0.6–1.8 cases of torsade de pointes per 10 million prescriptions.[91] Of interest in this context is the conclusion drawn by Poluzzi et al,[90] who stated "Concerning non-cardiovascular drugs with known TdP [torsade de pointes]-liability, our data corroborate the available evidence and strengthen the notion that prescribers should be aware of this problem. This certainly applies to fluoroquinolones and macrolides".

The risk of causing torsade de pointes is always increased when drugs interacting with cytochrome P450 (CYP) enzyme or class Ia or III antiarrhythmic drugs are coadministered.[73,95,96] Among macrolides and fluoroquinolones, erythromycin is a more potent inhibitor of CYP3A4 than clarithromycin, telithromycin and azithromycin, and ciprofloxacin is a more potent inhibitor of CYP1A2 than levofloxacin or moxifloxacin.[97,98] In a recent review examining the proarrhythmic potential of antimicrobial agents, the authors observed that (i) the antimicrobials that most frequently prolong the QT interval are erythromycin, clarithromycin, fluoroquinolones, halofantrine, and pentamidine; (ii) almost every antimicrobial associated QT interval prolongation occurs in patients with multiple risk factors.[99] Thus, while moxifloxacin should not be singled out among antibiotics, its use should be made with caution in all patients with increased risk of developing arrhythmias (i.e. concomitant use of other classes of drugs that interact with the CYP system or antiarrhythmic drugs, elderly women with electrolyte disturbances, cardiac disease or history of arrhythmia).[100]

Fears have been expressed that the higher peak serum levels associated with IV administration of moxifloxacin could trigger torsade de pointes and other cardiac events if uncontrolled.[101] For this reason, IV moxifloxacin should always be administered as a 60-minute infusion, and rapid or bolus administration should be avoided.[2]

The risk of cardiac toxicity of moxifloxacin (400 mg) versus levofloxacin (500 mg), both IV as initial therapy with a switch to oral administration after 3–4 days, has been specifically addressed for elderly patients with community-acquired pneumonia (≥65 years) in the CAPRIE (Community-Acquired Pneumonia Recovery in the Elderly) study.[40,41] The study involved patients hospitalized for community-acquired pneumonia, and 60% of patients had a pneumonia severity index (PSI) risk class III or higher. 12-lead ECG and 72-hour Holter monitoring was performed to capture a maximum of information even in the absence of patient complaints or clinically visible signs. There was no statistically significant difference between the treatment groups with regard to drug-related adverse events, including cardiac events; the incidence of ventricular arrhythmia events found on Holter monitoring for moxifloxacin was 8.3% versus 5.1% with levofloxacin ($p = 0.29$). Clinical events were very rare, affecting 1/195 patients treated with moxifloxacin (supraventricular tachycardia), versus 3/199 patients treated with levofloxacin (including one occurrence of torsade de pointes). The rate of all treatment-emergent adverse events was higher for moxifloxacin (84.1% vs 73.3% [$p = 0.01$]), but this was attributed to higher rates of underlying co-morbid illness, including cardiac disease, in this group. In a recent study (MOTIV [Moxifloxacin Treatment Intravenous]),[102] moxifloxacin was compared with levofloxacin plus ceftriaxone for the treatment of hospitalized community-acquired pneumonia (59% with PSI ≥4; 30.6% and 32.4% with cardiac co-morbidities; mean duration of IV therapy 6.1 vs 6.6 days). No difference was found with respect to toxicities between the two arms ($n = 368$ and 365) including for cardiac disorders (all 6.8 vs 6.8%; atrial fibrillation 1.6 vs 2.2%; QTc interval prolongation 2.2 vs 1.9%).

The reason why moxifloxacin clinical use remains free from significant cardiac adverse event remains unclear but probably stems from the three following reasons. Firstly, moxifloxacin shows a relatively large IC_{20} (concentration that produces 20% inhibition) towards the hERG channel of 31–35 μmol/L or approximately 12.6 mg/L free drug, which corresponds to a serum total moxifloxacin concentration of ~25 mg/L. This is much

higher than the maximum serum concentration of moxifloxacin seen clinically in humans. A significant risk of torsade de pointes is demonstrated in animals only at concentrations above 100 μmol/L (40 mg/L free drug).[103] In this context, it is interesting to note that even cirrhosis only marginally affects moxifloxacin pharmacokinetics.[104] A recent literature-based evaluation of 'hard endpoint' models for assessing liability for drug-induced torsade de pointes noted with respect to moxifloxacin that "because [it] has predictable pharmacokinetics, the absence of TdP [torsade de pointes] at clinically relevant dosages could provide a signal that this drug has no relevant TdP liability", and that "moxifloxacin is a problem drug, in that its human TdP liability signal is so weak as to be practically irrelevant, meaning that whether or not it is a hit in the model is debatable evidence when evaluating the validity of the model".[105] Secondly, torsade de pointes is also related to at least one additional cardiac parameter (i.e. beat-to-beat alternations in monophasic action potential duration) on which moxifloxacin has little effect.[106] Thirdly, moxifloxacin shows no CYP interactions, which is a main cause for torsade de pointes induced by many drugs.[95]

2.6 Hepatotoxicity

Many drugs are capable of inducing hepatotoxic reactions, with HMG-CoA reductase inhibitors ('statins'), antithrombotic agents and NSAIDs being the most frequently encountered.[54,107,108] In terms of the absolute number of reports of hepatotoxicity, antibacterials are also frequently incriminated, but this needs to be put into perspective with the large number of prescriptions for this class of drugs (typically about 20% of all drugs in most developed countries).

Hepatotoxic reactions need to be stratified as non-severe and severe, with the former including hepatocellular damage and cholestasis, and the latter including fulminant hepatitis and cirrhosis, leading to organ transplant or death. Hepatotoxicity is more likely to resolve when it is associated with eosinophilia,[109] and to become chronic for mixed disease,[110] whereas hepatocellular damage with jaundice is associated with a higher risk of severe reactions.[107,111]

Hepatotoxic reactions induced by antibacterials are usually non-severe and reversible,[112] decreasing the clinical importance of the effects observed.[113] If one excludes elevation of transaminase levels, which is common but benign by nature, it is often difficult to unambiguously establish the link between the administration of a given antibacterial and the development of hepatic function alterations. The clinical signs are indeed most often similar to those of acute or chronic liver diseases.[114-116] Moreover, cholestasis is typically found in patients with sepsis,[117] which may create confusion regarding the origin of this change. Therefore, diagnosis often remains subjective and based on the absence of an alternative cause, or on temporal association or improvement after cessation of drug administration.[114]

Antibacterial-induced hepatic toxicity is usually idiosyncratic and can be associated with other allergic reactions.[113] For macrolides, it has been suggested that reactive metabolites such as nitrosoalkanes covalently bind to the SH-groups of proteins, forming modified antigens that can be released in the circulation as a result of minor hepatocellular toxicity and cause immunoallergic hepatitis.[118] For tetracyclines, hepatotoxicity could result from an inhibition of the mitochondrial β-oxidation of fatty acids.[119] For currently marketed fluoroquinolones, hepatotoxicity remains anecdotal and unpredictable,[113] but with a higher incidence for molecules with substituents generating reactive intermediates, such as a difluoroaniline (in temafloxacin and trovafloxacin)[3,120-122] or the cyclopropylamine of trovafloxacin[123] (for which a recent animal study also suggests the role of co-exposure to lipopolysaccharide[124]).

Table IV compares the risk of antibacterials with that of other drugs in a series of studies based either on report analysis or on case/non-case approaches. Globally, these studies show that amoxicillin-clavulanic acid is the most frequently incriminated antibacterial, causing, according to the authors, 10–13.5% of total drug-induced hepatotoxic reactions. It is also the most common cause of hospitalization for hepatic adverse

Table IV. Drug-induced hepatic injury with antibacterials compared with other drug classes: data from report analyses and case/non-case studies

Antibacterial	Type of study		Drug-induced hepatic adverse effects			Type of effect (where specified)[a] [no.]				
	report analysis	case/non-case	Total no.	No. related to specified antibacterial	% related to specified antibacterial	H	C	M	C or M	Other
Fluoroquinolones		√[b]	1069	34	3.2					
Moxifloxacin	√[c]		77	1	1.1		1			
Ciprofloxacin	√[c]		77	4	5.2	2	1	1		
	√[d]		784	7	0.9	3	0	0	4	Fatal in two cases
		√[e]	126	1	0.8	0	1	0		
Norfloxacin		√[e]	126	1	0.8	0	1	0		
Trovafloxacin	√[f]		446	5	1.1	4	0	1		Including eosinophilia in two and hospitalization in three cases
	√[g]		32	1	3.1			1		
	√[h]		4690	57	1.2	0	0	0		Fatal in all 57 cases
		√[e]	126	1	0.8	0	0	1		
β-Lactams: amoxicillin-clavulanic acid (5), cloxacillin (1)	√[i]		34	4	11.8	2	0	2		
Amoxicillin-clavulanic acid	√[c]		77	1	1.1		1			
	√[f]		446	59	12.8	22	16	21		Including eosinophilia in 19 cases. 40 cases hospitalized, fatal in one case
	√[g]		32	4	12.5					
		√[e]	126	17	13.5	3	9	5		
		√[j]	128	13	10.3	4	3	5		Unknown in one case
Amoxicillin	√[i]		34	1	2.9	0	1	0		
		√[e]	126	3	2.3	1	0	2		
Cloxacillin	√[i]		34	1	2.9	0	0	1		
(di)Cloxacillin	√[d]		784	3	0.4	0	0	0	3	Fatal in one case
Flucloxacillin	√[d]		784	129	16.5	25	0	0	104	Fatal in seven cases
	√[c]		77	8	10.4	0	7	1		

Continued next page

Table IV. Contd

Antibacterial	Type of study		Drug-induced hepatic adverse effects			Type of effect (where specified)[a] [no.]				
	report analysis	case/non-case	Total no.	No. related to specified antibacterial	% related to specified antibacterial	H	C	M	C or M	Other
		√[j]	128	4	3.2	0	1	2		Unknown in one case
Cephalosporins		√[e]	126	5	4.0	2	2	1		
Macrolides (erythromycin, clarithromycin)		√[b]	1069	46	4.3					
Macrolides	√[c]		77	3	3.8	2	0	1		
		√[j]	128	6	4.8	1	3	0		Unknown in two cases
Erythromycin	√[f]		446	6	1.3	0	4	2		Hospitalization in three cases
	√[d]		784	42	5.6	32	0	0	10	
		√[e]	126	3	2.4	1	0	2		
Clarithromycin	√[h]		4690	51	1.1					Fatal in all cases
Telithromycin	√[g]		32	1	3.1			1		
Tetracycline		√[j]	128	6	4.8	2	1	3		
Doxycycline	√[c]		77	1	1.1	0	1	0		
Cotrimoxazole (sulfamethoxazole/trimethoprim)	√[d]		784	21	2.7	6	0	0	14	Fatal in two cases
	√[h]		4690	~60	1.3					Fatal in all cases
		√[e]	126	1	0.8	0	1	0		

a Where specified, the effect is defined by elevation of ALT/alkaline phosphatase levels as follows: cholestatic (C) ≤2-fold; hepatocellular (H) ≥5-fold; mixed (M) 2 <ratio <5-fold.[125]

b Case/non-case analysis based on spontaneous reports in Italy (1990–2005).[54]

c Analysis of outpatient clinics database in Sweden referred to a hepatology service (1995–2005).[108]

d Reports of suspected hepatic adverse drug reactions received by the Swedish Adverse Drug Reactions Advisory Committee (1970–2004).[111]

e Case/non-case analysis from a population survey study of acute liver injury in 12 hospitals in Spain (1993–1999).[126]

f Spontaneous reports to Spanish national registry of drug-induced liver injury (1994–2004).[107]

g Analysis of records of patients diagnosed with acute drug-induced hepatitis and referred to a hepatology service in the US (1993–2002).[127]

h Reports of drug-induced injury with fatal outcome from the WHO database (1968–2003).[128]

i Collection of drug-induced liver injury data from 135 practitioners in France (1997–2000).[129]

j Case/non-case analysis from a search of the UK-based General Practice Research Database for patients referred to a hospital or consultant for drug-induced hepatic injury (1994–1999).[130]

effects.[107] The reporting rate of hepatitis is, on average, 9-fold higher for the amoxicillin-clavulanic acid combination than for amoxicillin alone,[67] suggesting the predominant role of the β-lactamase inhibitor in this adverse effect. Values for macrolides and fluoroquinolones range between 1% and 5% of total drug-induced hepatotoxic reactions.

The crude incidence of acute liver injury in antibacterial users based on data available in the literature is shown in table V. Again, amoxicillin-clavulanic acid appears as the most frequently incriminated antibacterial, with an incidence rate of about 20/100 000 users versus 2 for erythromycin and less than 1 for fluoroquinolones as a whole and 0.1 for moxifloxacin.

Severe, but rare reactions have been the focus of additional analyses. Table VI shows the reporting rate to the FDA for acute liver failure and critical hepatic events for a series of fluoroquinolones and macrolides compared with amoxicillin-clavulanic acid. Trovafloxacin, and to a lesser extent telithromycin, emerge as being associated with the highest rates of reports of both acute liver failures and critical events; indications for both drugs are now severely restricted in the US (life-threatening infections for trovafloxacin; community-acquired pneumonia for telithromycin). There are only rare cases reported for other fluoroquinolones such as levofloxacin[136-138] and moxifloxacin,[139] and because most occurred in patients with many co-morbidities and in which drug association could not be unambiguously established, the only measure taken has consisted of updating their labelling to mention the risk of fulminant hepatitis with the potential for liver failure and in some cases death.[1,2] An analysis of the hepatic toxicity of moxifloxacin has been conducted recently by the *ad hoc* committee of the European Medicines Agency (EMEA), based on what was considered as a potential signal from the Periodic Safety Update Reports presented to the German authorities by the drug manufacturer. In view

Table V. Crude incidence rates of acute liver injury in users of anti-infective agents (literature data)

Antibacterial	Population	Incidence rate (95% CI)			Reference
		per 100 000 users	per 100 000 prescriptions	endpoint	
Fluoroquinolones (except moxifloxacin)	Outpatient clinic, Sweden (1995–2005)	0.7 (0.5, 1.1)		International consensus	108
Moxifloxacin	Outpatient clinic, Sweden (1995–2005)	0.08 (0.0, 0.5)		International consensus	108
Amoxicillin-clavulanic acid	General practice research database, UK (1991–2)	22.5 (14.7, 34.4)	17.4 (11.4, 26.5)	International consensus	131
Amoxicillin	General practice research database, UK (1991–2)	3.9 (2.3, 6.5)	2.7 (1.6, 4.6)	International consensus	131
	Saskatchewan Health Plan, Canada (1982–6)	0.4 (0.1, 1.2)	2.0 (0.7, 5.8)	International consensus, hospitalization	132
Ampicillin	Saskatchewan Health Plan, Canada (1982–6)	0.2 (0.0, 1.1)	1.0 (0.2, 5.5)	International consensus, hospitalization	132
Cephalexin	Saskatchewan Health Plan, Canada (1982–6)	0.6 (0.2, 1.6)	2.9 (1.0, 8.6)	International consensus, hospitalization	132
Erythromycin	Saskatchewan Health Plan, Canada (1982–6)	2.0 (0.7, 5.9)	14.0 (4.8, 41.2)	International consensus, hospitalization	132
Cotrimoxazole (sulfamethoxazole/trimethoprim)	Saskatchewan Health Plan, Canada (1982–6)	1.0 (0.2, 5.7)	4.9 (0.9, 27.6)	International consensus, hospitalization	132

Table VI. US FDA reporting rate[a] of liver adverse effects induced by antibacterials (based on data from Rullo,[133] Brinker[134] and the US augmentin package[135])

Antibacterial	Reporting rate per 10 million prescriptions	
	Acute liver failure[b]	critical event[c]
Moxifloxacin	6.6	1.6
Levofloxacin	2.1	2.2
Gatifloxacin	6.0	
Trovafloxacin	58	42.9
Amoxicillin-clavulanic acid	10	
Clarithromycin		1.0
Azithromycin		1.0
Telithromycin	23	5.8

a Reporting rates are not incidence rates and different figures between drugs may not mean different risks because the differences may be explained by other factors.

b Acute or severe liver injury with encephalopathy, liver transplant following acute illness, death in the setting of acute liver injury (hospitalization with elevation of transaminase levels, hyperbilirubinaemia or clinical jaundice).

c No definition given for this criterion.

of the safety data available, the Committee concluded that the very rare cases of fatal hepatotoxicity should be reflected in the product information by adding the statement ''including fatal cases'' to the corresponding part of the drug label (see the new UK label as an example).[140]

2.7 Dysglycaemia

Interaction of fluoroquinolones with potassium channels at the surface of β-cells that alter insulin release[141,142] can result in hypo- or hyperglycaemia. Risks factors for hypoglycaemia include age, increased serum creatinine levels, decreased albumin levels, liver disease, chronic heart failure, malignancy, sepsis, female sex and treatment with insulin and sulfonylureas.[143-145] Risk factors for hyperglycaemia include age, diabetes, high carbohydrate intake, stress and the use of corticosteroids.[146] Dysglycaemia has been mainly seen with gatifloxacin (see table I), which can cause either hypo- or hyperglycaemia, with no difference between diabetic and non-diabetic patients.[53] Levofloxacin was also able to cause hypoglycaemia, but to a much lesser extent than gatifloxacin.[53,146,147] No dysglycaemic effect has been reported for moxifloxacin.

2.8 *Clostridium Difficile*-Associated Disease

In contrast to the other adverse effects examined in this review, which rely on collateral effects of moxifloxacin (and other antibacterials) that are unrelated to the antibacterial's primary pharmacological properties, *Clostridium difficile* colitis is a potential consequence of the drug's broad spectrum antibacterial activity. Risk factors that have been evidenced for *C. difficile* colitis include previous antibacterial exposure and number of antibacterials received, previous hospitalization and co-morbidies, capacity to develop an immune response to toxin A and lower intestinal condition.[148,149] Based on case/non-case retrospective studies with large cohorts, third-generation cephalosporins, fluoroquinolones, clindamycin and penicillins are most frequently incriminated.[149,150]

It has been suggested that fluoroquinolones with higher anti-anaerobic activity such as gatifloxacin and moxifloxacin may be associated with a higher risk.[151] However, rates reported in phase II/III clinical trials are very similar to those reported for levofloxacin (4–6%).[19] A case/non-case study conducted to evaluate the risk of developing colitis in patients exposed to fluoroquinolones over a 3-year period failed to reveal any statistically significant difference between levofloxacin, gatifloxacin or moxifloxacin.[152] Of note, switches from gatifloxacin or moxifloxacin to levofloxacin in hospital formularies produced contradictory results with regards to the incidence of colitis.[151,153]

As recently reviewed,[154] prevention of *C. difficile*-associated diarrhoea usually involves infection-control interventions, although the usefulness of antimicrobial restriction policies may not be fully substantiated by currently available data. However, restricting antimicrobial use seems a prudent approach in outbreak situations.

3. Clinical Implications

Toxicities of fluoroquinolones are well known today and are increasingly taken into account.

Table VII. Safety warnings as defined in the US prescribing information (package insert) of moxifloxacin, other fluoroquinolones and main comparators

Class	Drugs within the class	Warnings in the package insert	Black-box warning[155] (date)	Populations at higher risk of adverse effects
β-Lactams	Amoxicillin-clavulanic acid[135]	• Anaphylactic reactions • *Clostridium difficile*-associated colitis • Hepatic toxicity		• Erythematous skin rash: patients with mononucleosis • Nephrotoxicity: elderly patients
	Cefuroxime axetil[156]	• Anaphylactic reactions • *C. difficile*-associated colitis		• Seizures: renal impairment • Alteration of renal function: co-administration of diuretics
Macrolides	Clarithromycin[157]	• Pregnancy • *C. difficile*-associated colitis • Drug interaction (colchicine)		• Cardiac effects: patients taking other drugs with effects on QTc interval or class 1A or III antiarrythmics
	Azithromycin[158]	• Anaphylactic reactions • *C. difficile*-associated colitis		• Hepatotoxicity: patients with liver failure
	Telithromycin[159]	• Hepatotoxicity • Visual disturbance • Loss of consciousness • QTc interval prolongation • *C. difficile*-associated colitis	Respiratory failure in patients with myasthenia gravis (12 February 2007)	• Cardiac effects: elderly patients taking other drugs with effects on QTc interval or class 1A or III antiarrythmics, or with known QT interval prolongation or hypokalaemia • Myopathies: co-administration of HMG-CoA reductase inhibitors ('statins')
Fluoroquinolones	Trovafloxacin		Hepatotoxicity, risk increased by treatment duration >14 days (9 June 1999)	
	Ciprofloxacin[74]	• Pregnancy, lactation, infants • Anaphylactic reactions and allergic skin reactions • CNS effects • Drug interactions (theophylline) • Peripheral neuropathy • *C. difficile*-associated colitis	Tendinitis and tendon rupture (8 July 2008)	• Tendon disorders: elderly patients taking corticosteroids • Cardiac effects: elderly patients taking other drugs with effects on QTc interval or class 1A or III antiarrythmics, or with known QT interval prolongation or hypokalaemia • CNS effects: patients at risk of epilepsy
	Levofloxacin,[1] ofloxacin	• Anaphylactic reactions and allergic skin reactions • Haematological toxicity • Hepatotoxicity • CNS effects • Peripheral neuropathy • Prolongation of the QT interval and isolated cases of torsade de pointes • *C. difficile*-associated colitis	Tendinitis and tendon rupture (8 July 2008)	• Tendon disorders: elderly, patients taking corticosteroids, or with kidney, heart or lung transplants • Cardiac effects: elderly patients taking other drugs with effects on QTc interval or class 1A or III antiarrythmics or with known QT interval prolongation or hypokalaemia • CNS effects: patients at risk of epilepsy • Dysglycaemia: patients with diabetes mellitus
	Moxifloxacin[2]	• Pregnancy, lactation, infants • Anaphylactic reactions and allergic skin reactions • Peripheral neuropathy	Tendinitis and tendon rupture (8 July 2008)	• Tendon disorders: elderly, patients taking corticoids, or with kidney, heart or lung transplants • Cardiac effects: elderly patients taking other drugs with effects on QTc interval or class 1A or III antiarrythmics

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Table VII. Contd

Class	Drugs within the class	Warnings in the package insert	Black-box warning[155] (date)	Populations at higher risk of adverse effects
		• Prolongation of the QT interval • *C. difficile*-associated colitis		or with known QT interval prolongation or hypokalaemia • CNS effects: patients at risk of epilepsy
	Gemifloxacin[75]	• Pregnancy, lactation, infants • Anaphylactic reactions and allergic skin reactions • CNS effects • Peripheral neuropathy • Prolongation of the QT interval • *C. difficile*-associated colitis	Tendinitis and tendon rupture (8 July 2008)	• Tendon disorders: elderly, patients taking corticosteroids or with kidney, heart or lung transplants • Cardiac effects: elderly patients taking other drugs with effects on QTc interval or class 1A or III antiarrythmics, or with known QT interval prolongation or hypokalaemia • CNS effects: patients at risk of epilepsy

Table VII indeed illustrates how pharmacovigilance has led to modifications in the labelling of fluoroquinolones and their main comparators (β-lactams, macrolides) over the last few years to avoid excessive risk in particular populations. The risk/benefit balance can therefore be assessed before prescribing a fluoroquinolone and compared with that of other antibacterials with similar indications.[56]

Considering moxifloxacin safety, current data (reflected in the labelling) point to a series of adverse effects, but these are not more frequent than with any comparator in clinical trials, and calculation of risk incidence does not evidence higher risk than with other fluoroquinolones for class-specific effects. For adverse effects that are also observed with other antibacterials, such as hepatotoxicity or toxic cutaneous reactions, the risk is even lower than for other commonly prescribed antibacterials such as amoxicillin-clavulanic acid. As for all fluoroquinolones, the elderly or patients experiencing hepatic or cardiovascular disorders, or taking medications susceptible to enhancing fluoroquinolone toxicity, should be treated with caution.[160] Yet, it is interesting to note that in a large COPD study, it was patients ≥65 years of age who significantly benefited most from moxifloxacin treatment.[161]

The considerable clinical experience acquired with moxifloxacin over the last few years has evidenced an efficacy similar to or, in some occasions, superior (mainly in eradication rate or prevention of relapses)[30,31,37,46,48,66] than comparators in key respiratory indications. This can be ascribed to the favourable pharmacokinetic/pharmacodynamic properties of moxifloxacin that include a high bactericidal effect, an appropriate penetration in body fluids and tissues, and an easy scheme of administration that favours compliance.[3,6] Pharmacoeconomic studies also point to a lower overall cost of moxifloxacin treatment as compared with β-lactams, macrolides, or other respiratory fluoroquinolones in acute sinusitis,[162] acute exacerbations of chronic bronchitis[35,163,164] and community-acquired pneumonia,[165-169] which arises from a lower number of failures (especially in the setting of high resistance to other drugs), less recurrences, shorter treatment durations and reduced hospitalization costs or length of stay.[170]

An amendment of the labelling for oral moxifloxacin has been introduced in Europe[5] where it now states that moxifloxacin should only be prescribed for adults with acute bacterial sinusitis and acute exacerbations of chronic bronchitis when other commonly recommended antibacterials

5 Moxifloxacin was registered in Europe through a decentralized procedure. The amended labelling will be put into effect and made available in each Member country starting in 2009.

cannot be used or have failed, and should only be prescribed for community acquired pneumonia when treatment with other commonly recommended antibacterials cannot be used. Thus, in a world where there is increasing resistance to macrolides and reduced susceptibility towards β-lactams and levofloxacin,[6] moxifloxacin, given its safety profile presented in this review, stands as a reasonable therapeutic option once patients at risk have been clearly identified. As stated earlier,[3] it will, however, be important not to lose this valuable addition to our anti-infective armamentarium through indiscriminate overconsumption.

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