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Moxifloxacin

A Review of its Clinical Potential in the Management of Community-Acquired Respiratory Tract Infections

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Data Selection

Sources: Medical literature published in any language since 1966 on Moxifloxacin, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase, Medline and EMBASE search terms were 'Moxifloxacin' or 'BAY 128039'. Searches were last updated 6 Jan 2000.

Selection: Studies in patients with respiratory tract infections who received moxifloxacin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Moxifloxacin, respiratory tract infections, pharmacodynamics, pharmacokinetics, therapeutic use, adverse events, drug interactions.

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Summary

Abstract

Moxifloxacin is an extended-spectrum fluoroquinolone which has improved coverage against Gram-positive cocci and atypical pathogens compared with older fluoroquinolone agents, while retaining good activity against Gram-negative bacteria. The antibacterial spectrum of moxifloxacin includes all major upper and lower respiratory tract pathogens; it is one of the most active fluoroquinolones against pneumococci, including penicillin- and macrolide-resistant strains. In *in vitro* studies, emergence of bacterial resistance was less common with moxifloxacin than with some other fluoroquinolones, but this requires confirmation in large-scale clinical studies.

As with other fluoroquinolones, moxifloxacin achieves good penetration into respiratory tissues and fluids. It shows a low potential for drug interactions and dosage adjustment is not required for patients of advanced age or those with renal or mild hepatic impairment.

The efficacy of oral moxifloxacin has been demonstrated in large, well-designed clinical trials in patients with community-acquired pneumonia, acute exacerbations of chronic bronchitis or acute sinusitis. Moxifloxacin 400mg once daily achieved bacteriological and clinical success rates of approximately 90% or higher. It was as effective as, or more effective than, comparators including clarithromycin, cefuroxime axetil and high dose amoxicillin in these trials.

The most commonly reported adverse events in patients receiving moxifloxacin are gastrointestinal disturbances. Moxifloxacin is also associated with QTc prolongation in some patients; there are, as yet, no data concerning the possible clinical sequelae of this effect in high-risk patients. Moxifloxacin has a low propensity for causing phototoxic reactions relative to other fluoroquinolones, and animal data suggest that it has a low potential for causing excitatory CNS and hepatotoxic effects.

Conclusions: As an extended-spectrum fluoroquinolone, moxifloxacin offers the benefits of excellent activity against pneumococci, once daily administration and a low propensity for drug interactions. Although studies are needed regarding

its tolerability in at-risk patients with QT interval prolongation, available data suggest that moxifloxacin is likely to become a first-line therapy option for the treatment of community-acquired lower respiratory tract infections, particularly in areas where drug-resistant *S. pneumoniae* or *H. influenzae* are common.

Antibacterial Activity

Moxifloxacin is an extended-spectrum fluoroquinolone which has an antibacterial spectrum that covers all of the major respiratory tract pathogens. It is one of the most active fluoroquinolones against *Streptococcus pneumoniae* (mean weighted MIC_{90} <0.3 mg/L), including penicillin- and macrolide-resistant strains. It is also active against *S. pyogenes* or group A streptococci (mean weighted MIC_{90} 0.24 mg/L) and methicillin-susceptible *Staphylococcus aureus* (mean weighted MIC_{90} 0.10 mg/L), but has more variable activity against methicillin-resistant *S. aureus* (MIC_{90} 2 to 8 mg/L) and borderline activity against ciprofloxacin-resistant strains of *S. aureus* (MIC_{90} 1 to 2 mg/L).

Moxifloxacin has good activity against Enterobacteriaceae and other Gram-negative species, including *Haemophilus influenzae*, *Moraxella catarrhalis* (β-lactamase–positive or –negative strains of both species) and *H. parainfluenzae* (MIC_{90} 0.03 to 0.125 mg/L). It is generally 2-fold less active than ciprofloxacin against Enterobacteriaceae and has poor activity (MIC_{90} 4 to >32 mg/L) against *Pseudomonas aeruginosa*.

Moxifloxacin also demonstrates good activity against the atypical respiratory tract pathogens *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* spp. (MIC_{90} ≤1 mg/L).

Minimum bactericidal concentrations of moxifloxacin were equal to, or within 1 dilution of, MIC values. Postantibiotic effects of >1 hour have been demonstrated against a range of respiratory pathogens.

Moxifloxacin was active in experimental lung infections in animals, eradicating or markedly reducing the number of *M. pneumoniae*, *S. pneumoniae*, *C. pneumoniae* or *L. pneumophila* in the lung and protecting against death or dissemination of *Legionella* infection.

Moxifloxacin has similar inhibitory activity against both of the bacterial enzymatic targets of fluoroquinolones, topoisomerase IV and DNA gyrase. The inhibitory activity of moxifloxacin appears to be little affected by characterised single genetic mutations or by the presence of the NorA efflux mechanism, and emergence of bacterial resistance among Gram-positive pathogens in *vitro* studies was less common with moxifloxacin than with other fluoroquinolones tested.

Pharmacokinetic Properties

Moxifloxacin is almost completely (≈90%) absorbed after oral administration. Thus, maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values are only slightly lower than after administration of the same dose by the intravenous route (as a 60-minute infusion). Oral absorption is not affected by food intake (including dairy products).

The pharmacokinetics of moxifloxacin are linear within the 50 to 800mg dose range. An oral dose of 400mg generally achieves a mean C_{max} of approximately 2.5 to 5 mg/L within 1 to 2 hours (t_{max}) and an AUC of approximately 27 to 45 mg/L · h.

In common with other fluoroquinolones, moxifloxacin exhibits a high volume of distribution (2 to 3.5 L/kg), relatively low binding to plasma proteins (39%) and penetrates well into respiratory tissues and fluids. Concentrations achieved in bronchial mucosa, epithelial lining fluid, sinus tissues and alveolar macrophages

exceed concurrent plasma concentrations and are ≥1 mg/L (or mg/kg) 24 hours after a 400mg dose(s). Evidence from animal studies suggests that moxifloxacin penetrates the placental and blood-brain barriers and into breast milk.

Moxifloxacin is metabolised to a sulfo- (M1) and a glucuronide (M2) derivative. The cytochrome P450 system is not involved in the metabolism of the agent. Approximately 15 to 22% of a dose is found unchanged in the urine, with a similar amount in the faeces.

The terminal elimination half-life of moxifloxacin ranges from approximately 8 to 16 (median 12.4) hours. Plasma clearance ranges from 9 to 15 L/h and renal clearance from 1.3 to 3 L/h.

The pharmacokinetics of moxifloxacin do not appear to be affected by advanced age, gender, race, renal impairment or mild hepatic impairment.

Clinical Potential

Oral moxifloxacin 400mg once daily was effective in the treatment of patients with community-acquired pneumonia, acute exacerbations of chronic bronchitis or acute sinusitis, achieving bacteriological and clinical success/resolution rates of approximately 90% or higher in clinical trials at treatment end. Clinical success/resolution was generally defined as complete resolution or considerable improvement in signs and symptoms of infection, such that no further antimicrobial treatment was required.

In patients with community-acquired pneumonia, moxifloxacin 400 mg/day was as effective as amoxicillin 1g 3 times daily and moxifloxacin 200 or 400 mg/day was as effective as clarithromycin 500mg twice daily in 3 large, well-designed trials.

In acute exacerbations of chronic bronchitis, a 5-day course of moxifloxacin 400 mg/day was more bacteriologically effective than a 7-day course of clarithromycin (91 *vs* 68% of patients), but achieved similar clinical success rates to 7- or 10-day treatment with clarithromycin in 2 large trials.

In patients with acute sinusitis, a 7-day course of moxifloxacin 400 mg/day was more effective than a 10-day course of cefuroxime axetil 250mg twice daily (clinical success: 97 *vs* 91%; bacteriological success: 95 *vs* 84% of patients) in one trial. However, in a second trial, 10-day treatment courses of moxifloxacin 400 mg/day and cefuroxime axetil 500 mg/day produced almost identical clinical response rates (90 *vs* 89%).

Tolerability

The most commonly reported adverse events in patients receiving moxifloxacin are gastrointestinal disturbances, mostly nausea (7.2% of 4926 patients in clinical trials) and diarrhoea (5.7%). Dizziness occurred in 2.8% of patients.

In comparative studies, moxifloxacin was associated with a similar overall incidence of drug-related adverse events to high dose amoxicillin and clarithromycin but a slightly higher rate of events than cefuroxime axetil in patients with respiratory tract infections.

Moxifloxacin 400 mg/day was associated with a mean prolongation of the QTc interval of 6 msec (n = 4008) versus 1 msec in recipients of comparator agents (clarithromycin, cefalexin, cefuroxime axetil, amoxicillin, doxycycline and metronidazole; n = 3689); 1 versus 4 patients experienced a cardiovascular event. At present, there are no data concerning the use of moxifloxacin in patients who have pre-existing QT prolongation or who are taking drugs which prolong the QTc interval.

Moxifloxacin appears to have a low propensity for causing phototoxic reac-

tions relative to other fluoroquinolones, as demonstrated in preclinical and clinical studies; no phototoxic events occurred in almost 5000 patients treated with the drug. Animal data suggest that the drug has a low potential for causing CNS excitatory and hepatotoxic effects.

Drug Interactions

As with other fluoroquinolones, the bioavailability of moxifloxacin is substantially reduced by coadministration with an antacid, sucralfate or an iron preparation. However, the extent of absorption of moxifloxacin is unaffected by concurrent administration of calcium-containing supplements, although the rate of absorption is slowed.

Moxifloxacin does not interact with theophylline, β-acetyldigoxin, probenecid, ranitidine, warfarin or oral contraceptives, in contrast to some other compounds of this class.

Dosage and Administration

Moxifloxacin is indicated for the treatment of acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia and acute bacterial sinusitis. The recommended oral dosage for all indications is 400mg administered once daily. Moxifloxacin should be administered for 5 days for acute exacerbations of chronic bronchitis and 10 days for acute sinusitis or community-acquired pneumonia.

No dosage adjustment is required in the elderly, patients with mild hepatic impairment or in patients with any degree of renal impairment. Currently there are no recommendations concerning the use of moxifloxacin in patients with moderate to severe liver impairment or in patients undergoing renal dialysis.

Moxifloxacin has been shown to prolong the Qtc interval in some patients. Its use should be avoided in patients with known QT interval prolongation or in those receiving concomitant drugs known to prolong the Qtc interval.

1. Introduction

Because of their excellent activity against Gram-negative organisms, older fluoroquinolones, such as the benchmark agent ciprofloxacin, are considered to be particularly suitable for the treatment of nosocomial and community-acquired respiratory tract infections which are thought to have a Gram-negative aetiology. However, older fluoroquinolones are not generally regarded as first-line agents for empirical monotherapy of community-acquired pneumonia, because of their suboptimal activity against staphylococci and, in particular, streptococci.[1,2] Such organisms are implicated in most community-acquired respiratory tract infections (table I).

Modification of the side-chain of the fluoroquinolone molecule has led to a new generation of extended-spectrum fluoroquinolones. Moxifloxacin, an 8-methoxyquinolone (fig. 1),[6] is one of several new extended-spectrum fluoroquinolones which offer improved Gram-positive and anaerobe coverage compared with the older agents.[7] This review discusses the clinical potential of oral moxifloxacin in the management of community-acquired respiratory tract infections.

2. Antibacterial Activity

2.1 *In Vitro* Activity

In this review, *in vitro* antibacterial activity refers to minimum inhibitory concentrations (MICs) determined by broth or agar dilution techniques (except in the case of intracellular bacteria such as chlamydiae, which were tested in cell culture). MIC_{50} and MIC_{90} refer to the minimum concentrations required to inhibit the growth of 50 and 90%

of strains, respectively. Proposed MIC breakpoints for moxifloxacin for Enterobacteriaceae and *Staphylococcus* spp. indicating susceptibility, intermediate susceptibility and resistance are ≤2, 4 and ≥8 mg/L, respectively. For *Streptococcus pneumoniae*, the respective breakpoints are ≤1, 2 and ≥4 mg/L and for *Haemophilus* spp. the susceptibility breakpoint is ≤1 mg/L.[8]

This section focuses on the *in vitro* activity of moxifloxacin against respiratory pathogens. Table II shows mean weighted MIC_{90} values for common respiratory pathogens for which sufficient data are available (at least 3 fully reported studies which included ≥10 clinical isolates of each organism).

2.1.1 Gram-Positive Bacteria

Moxifloxacin was the most active of several new and older fluoroquinolones (including gatifloxacin, levofloxacin and ciprofloxacin) tested against streptococci and staphylococci.[7]

Streptococci

Moxifloxacin has excellent activity against *S. pneumoniae*, with mean weighted MIC_{90} values of <0.3 mg/L regardless of penicillin susceptibility (table II).[7,13-16,18-20] It also retained activity against macrolide-resistant (erythromycin MIC ≥1 mg/L) strains (n = 40; MIC_{90} 0.12 mg/L).[23]

Table I. Pathogens implicated in community-acquired respiratory tract infections[2-5]

Lower respiratory tract infections	
Community-acquired pneumonia	*Streptococcus pneumoniae* *Haemophilus influenzae* *Staphylococcus aureus* *Klebsiella pneumoniae* *Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Legionella pneumophila*
Acute exacerbations of chronic bronchitis	*H. influenzae* *Moraxella catarrhalis* *S. pneumoniae* *H. parainfluenzae*
Upper respiratory tract infections	
Acute bacterial sinusitis	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *S. aureus*
Tonsillopharyngitis	*S. pyogenes* *S. aureus*
Epiglottitis	*H. influenzae*

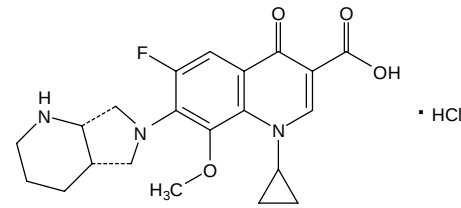

Fig. 1. Structure of moxifloxacin.

Moxifloxacin is generally 2-fold more active than sparfloxacin,[12,14,18] 2- to 4-fold more active than gatifloxacin[7] and 8- to 16-fold more active than ciprofloxacin, levofloxacin (table II) and ofloxacin[14,17-19] against pneumococci.

As expected, moxifloxacin was more active than β-lactams (amoxicillin/clavulanic acid, cefuroxime, cefpodoxime, cefaclor, cefixime) against pneumococci with intermediate or full resistance to penicillin (MIC_{90} 0.12 *vs* 0.5 to 64 mg/L). It was also more active than azithromycin, clarithromycin or erythromycin against macrolide-resistant strains of pneumococci (MIC_{90} 0.12 *vs* 16 to >64 mg/L).[23]

S. pyogenes (group A streptococci) were generally inhibited by moxifloxacin at 0.25 mg/L (mean weighted MIC_{90} 0.24 mg/L; table II);[7,9,13,20] moxifloxacin was approximately 4-fold more active than levofloxacin or ciprofloxacin against these bacteria (table II). As for other streptococci, the activity of moxifloxacin was unaffected by macrolide resistance; in a single study,[24] moxifloxacin had an MIC_{90} of 0.25 mg/L against *S. pyogenes* with various macrolide resistance phenotypes (constitutive or inducible macrolide-lincosamide-streptogramin B or M-type resistance; n = 90). Sparfloxacin was 2- to 4-fold less active against these strains.[24]

Staphylococci

Moxifloxacin has good activity against methicillin-susceptible *Staphylococcus aureus* (MSSA), with reported MIC_{90} values ranging from 0.06 to 0.125 mg/L[7,9,10,13,15,20,21] (mean weighted MIC_{90} 0.10 mg/L; table II). It is generally 8-fold more

Table II. *In vitro* activity of moxifloxacin against common community-acquired respiratory tract pathogens. All studies used broth or agar dilution techniques and an inoculum size of 10^4 to 10^6 colony-forming units and included at least 10 clinical isolates of each organism. Mean weighted MIC_{90} values are each calculated from ≥3 studies

Organism	Mean weighted MIC_{90} value (mg/L) [no. of isolates]			References
	moxifloxacin (≤2 mg/L)[a]	ciprofloxacin (≤1 mg/L)[a]	levofloxacin (≤2 mg/L)[a]	
Gram-positive bacteria				
Streptococcus pneumoniae (untyped)	0.2 [494]	2.91 [494]	–	9-12
S. pneumoniae (PEN-S)	0.22 [2451]	1.96 [2451]	1.81 [1935]	7,13-20
S. pneumoniae (PEN-I)	0.28 [430]	2.09 [430]	1.85 [246]	7,14-20
S. pneumoniae (PEN-R)	0.17 [250]	>1.76 [250]	2.10 [112]	7,14-20
S. pyogenes/group A streptococci	0.24 [191]	0.87 [191]	1.0 [137]	7,9,10,13,15,20
Staphylococcus aureus (MS)	0.10 [296]	0.88 [296]	0.35 [149]	7,9,10,13,15,20,21
S. aureus (MR)	3.73 [224]	>69.75 [224]	>15.15 [94]	7,9,10,13,15,20,21
Gram-negative bacteria				
Moraxella catarrhalis	0.07 [403]	0.04 [403]	≤0.04 [349]	7,9,13-15,20
Haemophilus influenzae (βL-)[b]	0.04 [424]	≤0.02 [424]	≤0.03 [410]	7,13-15
H. influenzae (βL+)[c]	0.04 [233]	≤0.02 [233]	≤0.03 [221]	7,13-15

a Susceptibility breakpoints for all organisms except *S. pneumoniae* and *Haemophilus spp.* for moxifloxacin which had a breakpoint of ≤1 mg/L.[8,22]

b Or ampicillin MIC <8 mg/L.

c Or ampicillin MIC ≥16 mg/L.

βL– = non-β-lactamase producing; **βL+** = β-lactamase producing; **MIC** = minimum inhibitory concentration; **MIC_{90}** = minimum concentration at which 90% of isolates were inhibited; **MR** = resistant to methicillin (MIC ≥16 mg/L); **MS** = susceptible to methicillin (MIC ≤8 mg/L); **PEN-I** = intermediately susceptible to penicillin (MIC 0.12-1 mg/L); **PEN-R** = resistant to penicillin (MIC ≥2 mg/L); **PEN-S** = susceptible to penicillin (MIC ≤0.06 mg/L).

active than ciprofloxacin and 2- to 4-fold more active than levofloxacin against these bacteria (table II).

Although moxifloxacin has more variable activity against methicillin-resistant *S. aureus* [MRSA; MIC_{90} values ranged from 2 to 8 mg/L; mean weighted MIC_{90} 3.73 mg/L (table II)], it is approximately 4-fold more active than levofloxacin and >18-fold more active than ciprofloxacin against these strains. *In vitro* data also suggest that moxifloxacin has borderline activity against ciprofloxacin-resistant (MIC_{90} 8 to 128 mg/L) strains of *S. aureus* (MIC_{90} 1 to 2 mg/L);[25-27] however, in the absence of clinical data, these results should be interpreted with caution (see also section 2.3).

2.1.2 Gram-Negative Bacteria

Haemophilus influenzae and *Moraxella (Branhamella) catarrhalis* are highly susceptible to moxifloxacin with MIC_{90} values ranging from 0.03 to 0.125 mg/L (mean weighted MIC_{90} 0.04 and 0.07 mg/L, respectively; table II). β-Lactamase production had no effect on MIC values (table II).[7,13-15] *H. parainfluenzae* (MIC_{90} 0.03 mg/L; 109 strains),[28] *Bordetella pertussis* (MIC_{90} 0.03 mg/L; 34 strains)[29] and *B. parapertussis* (MIC_{90} 0.06 mg/L; 34 strains)[29] are also highly susceptible to moxifloxacin.

MIC_{90} values for moxifloxacin against *Klebsiella* spp. and *K. pneumoniae* generally range from 0.5 to 1.0 mg/L.[9,15,20] However, MIC_{90} values were higher in ceftazidime-resistant strains (8 mg/L; n = 25 *vs* 0.13 mg/L in ceftazidime-susceptible strains; n = 61)[7] and/or strains producing extended-spectrum β-lactamases (MIC_{90} 2 mg/L; n = 35).[30] Reported MIC_{90} values for moxifloxacin against *Escherichia coli* range from 0.06 to 1 mg/L.[9,15,20]

Moxifloxacin has poor activity against *Pseudomonas aeruginosa* (MIC_{90} 4 to >32 mg/L),[7,9,15,20] although this is an unusual pathogen in community-acquired respiratory tract infections. Moxifloxacin is 2- to 8-fold less active than ciprofloxacin against *P. aeruginosa*.[7,9,20]

2.1.3 Atypical Pathogens

Moxifloxacin has good activity against atypical respiratory tract pathogens, with MIC_{90} values against *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* spp. of ≤1 mg/L (table III). Against *C. pneumoniae* (in cell culture), moxifloxacin (MIC_{90} 0.06 to 1 mg/L) was as active as levofloxacin[33] but less active than doxycycline,[31] erythromycin[31] or clarithromycin.[33] Against *M. pneumoniae*, moxifloxacin had similar activity to sparfloxacin and doxycycline (MIC_{90} 0.12 mg/L for all 3 drugs)[34] and was less active than clarithromycin (table III) and markedly more active than levofloxacin (MIC_{90} 0.063 *vs* 0.5 mg/L)[35] (table III).

Moxifloxacin (MIC_{90} 0.06 mg/L) was slightly less active than levofloxacin, and markedly less active than clarithromycin or rifampicin against *Legionella* spp. when tested in buffered starch-yeast extract agar medium (table III).[36] When tested against 52 *Legionella* spp. on supplemented buffered charcoal yeast extract agar, moxifloxacin was as active as ciprofloxacin, with a mean MIC of 0.004 mg/L with an inoculum of 10^3 colony-forming units (cfu) and 0.018 mg/L with an inoculum of 10^5 cfu (corrected for binding to charcoal).[37]

2.1.4 Factors Affecting Antibacterial Activity

Increasing the inoculum size from 10^4 to 10^6 or 10^3 to 10^5 cfu had little effect on moxifloxacin MIC values for most bacteria.[9] However, 2- to 4-fold increases in MIC were seen with some Gram-negative strains, including *K. pneumoniae*[9] and *Legionella* spp.[37]

Human serum, albumin, globulin and dead bacteria had little effect on the activity of moxifloxacin,[9,38] although in one time-kill study, the presence of serum markedly increased the killing rate of moxifloxacin against *K. pneumoniae*.[39] The presence of pus delayed bacterial killing by moxifloxacin.[38]

2.1.5 Bactericidal Activity

As with other fluoroquinolones, minimum bactericidal concentrations (MBCs) of moxifloxacin were equal to, or within 1 dilution of, MIC values for most species tested.[9] Against mycoplasmal species, MBCs were 2- to 8-fold higher than MICs.[34] In time-kill assays, moxifloxacin showed bactericidal effects (generally defined as a 2 to 3 log_{10} decrease in cfu/ml) against Gram-positive and Gram-negative organisms.[23,27,40-42]

Bactericidal effects were time- and concentration-dependent. With pneumococci, these were seen at 16 × MIC after 4 hours, 8 × MIC after 6 hours and at 2 × MIC after 24 hours' incubation.[23] Bactericidal effects were achieved at the MIC in <2 hours with *E. coli* and at 4 × MIC in approximately 2 to 8 hours with *S. aureus*.[27,41] At 10 × MIC, moxifloxacin was bactericidal against both intracellular and extracellular *S. aureus*, including

Table III. *In vitro* activity of moxifloxacin against atypical respiratory tract pathogens. MIC_{90} values obtained by agar or broth dilution, except in the case of *Chlamydia pneumoniae*, which was tested in cell culture

Organism	MIC or MIC_{90} values (mg/L) [no. of isolates]							References
	moxifloxacin	sparfloxacin	levofloxacin	clarithromycin	erythromycin	doxycycline	rifampicin	
C. pneumoniae	0.06-1 [27]	–	1 [14]	0.06 [14]	0.125 [10]	0.25 [10]	–	31-33
Mycoplasma pneumoniae	0.063-0.12 [93]	0.12 [32]	0.5 [61]	≤0.008-0.06 [93]	–	0.12 [32]	–	34,35
Legionella pneumophila	0.06 [30]	–	0.03 [30]	≤0.004 [30]	–	–	0.008 [30]	36

MIC = minimum concentration which inhibited growth; **MIC_{90}** = minimum concentration at which 90% of isolates were inhibited (or no inclusions were seen in the case of chlamydiae).

MRSA, killing >95% of extracellular and 50% of intracellular *S. aureus* after 4 hours.[43]

In *in vitro* pharmacodynamic models simulating the fluctuating concentrations of moxifloxacin found in human serum after therapeutic administration, concentrations corresponding to those produced after a 400mg dose eliminated *S. pneumoniae* or *S. aureus* within 8 to 12 hours.[44] In contrast, sparfloxacin did not eliminate all organisms: at 200 and 400mg, it reduced counts of *S. aureus* by 1 to 4 $\log_{10}$ and of *S. pneumoniae* by 1.5 to 2.0 $\log_{10}$ within the same time frame.[44]

More rapid bactericidal effects were seen against Gram-negative bacteria,[40,44,45] even at a 100mg dose level.[44] At the 400mg dose level, *E. coli* numbers were reduced to below the level of detectability in <1 hour[40] and a 5.5 $\log_{10}$ reduction was seen in *M. catarrhalis* within 4 hours.[45]

2.1.6 Postantibiotic Effect

Moxifloxacin showed postantibiotic effects (PAEs) at concentrations equal to or above the MIC against various Gram-positive and Gram-negative bacteria (*E. coli*, *S. aureus*, *H. influenzae*, *S. pyogenes* and *S. pneumoniae*).[41,46] PAEs tended to increase with moxifloxacin concentration and were generally >1 hour at 4 × MIC.[41,46] For instance, PAEs at 4 × MIC were 2.3 hours against *S. pneumoniae* and 2.8 hours against *H. influenzae*. At 10 × MIC, PAEs were extended to 3.3 and 3.5 hours, respectively. PAE duration did not differ significantly between penicillin-susceptible and -resistant pneumococci.[46]

2.2 *In Vivo* Activity

In experimental lung infections in guinea-pigs[47,48] or mice,[49,50] moxifloxacin (1 to 100 mg/kg) eradicated or markedly reduced the number of *M. pneumoniae*,[47] *S. pneumoniae*,[49,50] *C. pneumoniae*[50] or *L. pneumophila*[48] in the lung. Moxifloxacin also protected against death or dissemination of *Legionella* infection to the spleen (no further details given).[48]

2.3 Mechanism of Action and Resistance Issues

Fluoroquinolones inhibit growth of bacteria by inhibiting bacterial DNA gyrase (GyrA and GyrB) and/or DNA topoisomerase IV (ParC and ParE), which are essential for replication. Proposed mechanisms of fluoroquinolone resistance include mutations in various genes: *gyrA* and *gyrB* (which encode DNA gyrase) and *parC* (*grlA*) and *parE* (*grlB*) [which encode topoisomerase IV] and *norA* (which encodes a membrane-associated active efflux pump and reduces accumulation of these drugs within bacteria). High level resistance results from multiple resistance mechanisms.[51-53]

The primary enzymatic target of fluoroquinolones may vary according to the type of bacteria: topoisomerase IV appears to be the primary target of fluoroquinolones in Gram-positive bacteria,[51-53] whereas DNA gyrase appears to be the main target in Gram-negative species. Topoisomerase IV and DNA gyrase can both act as secondary targets. However, the primary target may also depend on the fluoroquinolone and the newer fluoroquinolones can differ from older compounds in this regard.[54]

2.3.1 Activity Against Strains with Characterised Mutations

The inhibitory activity of moxifloxacin was less affected by genetic mutations than those of the other fluoroquinolones. A double mutation in *gyrA* increased the IC_{50} for ciprofloxacin, sparfloxacin and norfloxacin by ≥500-fold compared with the wild-type gyrase, whereas that of moxifloxacin was increased by only 12-fold. A *parC* mutation did not affect the IC_{50} of moxifloxacin against topoisomerase IV but markedly increased the IC_{50} for ciprofloxacin (approximately 5-fold). Single mutations in *gyrA* had little effect on IC_{50} values for any of the fluoroquinolones (increases were <3-fold).[55]

Some of the newer fluoroquinolones (e.g. moxifloxacin, sparfloxacin, gatifloxacin) retain activity against pneumococci that have a single *parC* mutation.[56-58] MICs for moxifloxacin against these mutants ranged from 0.25 to 0.5 mg/L.[57,58] In-

deed, mutations in both *gyrA* and *parC* were required to produce clinically significant resistance to moxifloxacin in pneumococci (MIC not stated)[58] or *S. aureus* (MIC 8 mg/L).[55]

Of 5 fluoroquinolones tested, moxifloxacin was the least affected by mutations in *gyrA*, *gyrB*, *parC* or *parE* in *S. aureus* (n = 70 strains), inhibiting ciprofloxacin-resistant strains at 0.5 to 2 mg/L (MIC_{90} 1 mg/L). Rank order of MICs was ciprofloxacin > ofloxacin > levofloxacin > sparfloxacin > moxifloxacin.[26] Moxifloxacin (MICs 8 to 32 mg/L) was more active than levofloxacin and sparfloxacin (MICs 16 to 128 mg/L) against *S. aureus* mutants with multiple mechanisms resulting in high level ciprofloxacin resistance (MIC ≥256 mg/L).[55]

The contribution of multidrug efflux pumps, such as NorA, to fluoroquinolone resistance is thought to be less important for hydrophobic drugs such as moxifloxacin and sparfloxacin. Indeed, studies in *S. aureus* and *S. pneumoniae* suggest that the activity of moxifloxacin is little affected by NorA efflux mechanisms.[59-61] In contrast, ciprofloxacin (which is hydrophilic) has shown decreases in MIC of ≤8-fold in the presence of efflux pump inhibition with reserpine.[59,61]

2.3.2 Selection of Resistant Strains

Compared with other fluoroquinolones (particularly older compounds), moxifloxacin may have a reduced potential to select for bacterial resistance, at least in Gram-positive species. This may reflect its high intrinsic affinity for both topoisomerase IV and DNA gyrase.[55]

In Vitro

In Gram-positive bacteria, spontaneous resistance to moxifloxacin developed less frequently *in vitro* than with other fluoroquinolones. At 4 × MIC, the frequency of spontaneous mutation in *S. pneumoniae* was $<1.45 \times 10^{-9}$ compared with $<10^{-8}$ for ofloxacin and grepafloxacin. Corresponding values for *S. aureus* were 7.06×10^{-8} versus 1.5×10^{-6} and 1.2×10^{-5}. Differences between moxifloxacin and the other fluoroquinolones were less marked when Gram-negative bacteria were tested.[62]

At 8 × MIC, the frequency of spontaneous resistance to moxifloxacin among typical Gram-positive and Gram-negative respiratory tract pathogens was $<4 \times 10^{-8}$. Repeat testing showed that MICs of these clones were identical to those of the parent strains, suggesting that any mutations were not stable.[13]

Multistep resistance to moxifloxacin also emerged less frequently than to sparfloxacin, levofloxacin or ofloxacin on serial passage of Gram-positive bacteria (*S. pneumoniae* and/or ciprofloxacin-susceptible or -resistant *S. aureus*) through subinhibitory concentrations. No numerical data were presented in this abstract report.[62]

In Vivo

In the rat granuloma pouch model, resistance to moxifloxacin did not emerge in infecting *S. aureus* or *S. pneumoniae* strains when either suboptimal doses, or oral doses that simulated human serum kinetics following a 400mg dose, were administered.[63,64] Both wild-type and first-step mutants of *S. aureus* or *S. pneumoniae* were used in the model.[64]

3. Pharmacokinetic Properties

Table IV summarises pharmacokinetic data from healthy volunteers given single or repeated doses of moxifloxacin by the oral or intravenous route. Concentrations of moxifloxacin in body tissues and fluids were measured by high performance liquid chromatography (HPLC) and/or bioassay; methods of measuring concentrations of moxifloxacin are reviewed by Möller et al.[65]

3.1 Absorption and Plasma Concentrations

Moxifloxacin is almost completely absorbed after oral administration (absolute bioavailability 86 to 92%).[71,72] Thus, administration of moxifloxacin by the intravenous route (as a 60-minute infusion) produces peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values only slightly higher than the oral route.[68,72]

Table IV. Pharmacokinetics of moxifloxacin. Summary of mean pharmacokinetic parameters after oral or intravenous administration of moxifloxacin to healthy volunteers

Reference	No. of volunteers	Dose (mg) and route	t_{max} (h)	C_{max} (mg/L)	AUC (mg/L • h)	Vd (L/kg)	CL (L/h)	CL_R (L/h)	$t_{1/2\beta}$ (h)	f_e (%)
Single dose studies										
Stass & Kubitza[66]	12 (co)	400 IV	1.0	3.6	34.6	2.1	11.6	2.6	15.4	22
		400 PO	2.0	2.5	29.8	3.1	11.6	2.6	15.6	19
Stass et al.[67]	6	50 PO	1.8	0.3	3.9	2.5	12.9	2.8	11.4	20
	6	100 PO	2.0	0.6	8.5	2.9	11.8	2.4	12.2	19
	6	200 PO	2.5	1.2	15.4	3.3	13.0	2.6	14.0	20
	7	400 PO	1.5	2.5	26.9	3.6	14.9	3.0	13.1	20
	7	600 PO	2.5	3.2	39.9	3.3	15.0	2.7	12.5	18
	7	800 PO	3.0	4.7	59.9	2.8	13.4	2.5	12.3	19
Wise et al.[68]	7 (co)	400 IV		5.1	45.3		9.1	1.3	8.2	15
		400 PO	1.0	5.0	45.5		8.9	1.4	8.3	15
Multiple dose[a] studies										
Hiemer-Bau et al.[69]	12	400 × 1 PO	1.5	3.1	35.1	2.1	11.4			22
		400 × 7 PO	1.4	3.9	38.9	2.9	10.3			33
Kubitza et al.[70]	23	400 × 1 PO	0.92	3.1	30.8				9.6	15
		400 × 5 PO	1.2	3.2	33.9				15.2	21

a Multiple doses were given once daily.

AUC = area under the plasma concentration-time curve (values for time zero to infinity are shown if reported); **CL** = total body clearance; **CL_R** = renal clearance; **C_{max}** = maximum plasma drug concentrations; **co** = crossover study; **f_e** = fraction of the dose recovered in urine; **IV** = intravenously (60-minute infusion); **t_{max}** = time to C_{max}; **$t_{1/2\beta}$** = plasma elimination half-life; **PO** = orally; **Vd** = volume of distribution.

Oral absorption is not affected by concomitant food intake (including dairy products)[73,74] or by pretreatment with ranitidine (section 6). However, as with other fluoroquinolones, absorption of moxifloxacin is impaired by concomitant administration of antacid, sucralfate or iron supplements (see section 6).

C_{max} and AUC are dose-proportional within the 50 to 800mg dose range.[67] An oral dose of 400mg produces a mean C_{max} of approximately 2.5 to 5 mg/L within 1 to 2 hours (t_{max}) and AUC of approximately 27 to 45 mg/L • h (table IV).

Repeated administration of 400mg once daily led to AUC values which were approximately 10% higher than after single dose administration in 2 studies.[69,70] C_{max} values were 4.5 and 27% higher.[69,70]

3.2 Distribution

As with other fluoroquinolones, moxifloxacin has a high volume of distribution (approximately 2 to 3.5 L/kg; table IV) and achieves good penetration into body tissues and fluids.[75]

Peak moxifloxacin concentrations achieved in bronchial mucosa, epithelial lining fluid and alveolar macrophages after a dosage of 400mg once daily or in sinus tissue after five 400mg doses (fig. 2) greatly exceed MIC_{90} values for the common respiratory pathogens *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (section 2.1). These concentrations exceeded concurrent plasma concentrations at all timepoints (by approximately 1.5- to 2-fold in bronchial mucosa, 7-fold in epithelial lining fluid, 19- to 89-fold in alveolar macrophages and 2- to 3-fold in sinus tissue) and were ≥1 mg/L (or mg/kg) 24 hours postdose.[76,77]

In skin blister fluid, AUCs of moxifloxacin were similar to those in plasma; drug concentrations were approximately 2-fold higher than concurrent plasma concentrations 24 hours postdose in healthy volunteers given a single 400mg oral or intravenous dose.[68,75] Moxifloxacin also concentrated almost 90-fold in alveolar macrophages of

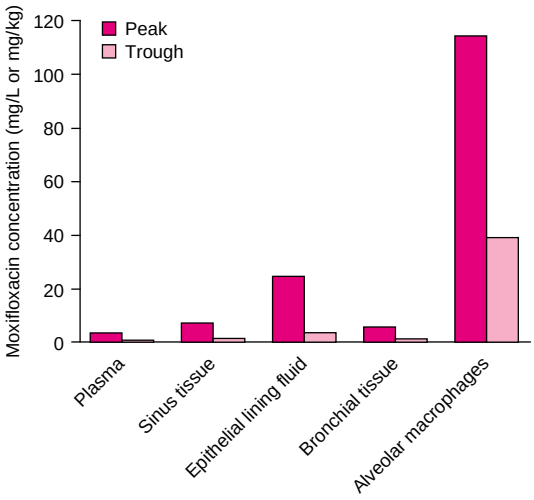

Fig. 2. Penetration of moxifloxacin into respiratory tissues and fluids. Peak and trough (24 hours postdose) concentrations of moxifloxacin in sinus tissues[77] and epithelial lining fluid, bronchial tissue and alveolar macrophages[78] in patients undergoing sinus surgery (after 5 oral 400mg doses; n = 34)[77] or diagnostic bronchoscopy (after a single oral 400mg dose; n = 18).[78] Moxifloxacin plasma concentrations reported by Gehanno et al.[77] are also included.

patients who received a single 400mg dose before undergoing bronchoscopy (fig. 2)[76] and approximately 11-fold in human neutrophils exposed to a concentration of 5 mg/L *in vitro*.[78]

Moxifloxacin and its glucuronide metabolite showed relatively low binding to plasma proteins (39 and 5%, respectively), whereas the sulfo-metabolite was highly bound (90%).[66]

Evidence from animal studies suggests that moxifloxacin penetrates the placental barrier, into breast milk[79] and into normal and purulent CSF.[80,81]

3.3 Metabolism and Elimination

The cytochrome P450 system is not involved in the metabolism of moxifloxacin.[8] Moxifloxacin is metabolised via conjugation to a sulfo- (M1) and a glucuronide (M2) derivative.[66] As there is good correlation between the results of bioassay and HPLC,[67] this suggests that the metabolites do not contribute significantly to the antimicrobial activity of moxifloxacin. Moxifloxacin and M1 and M2 metabolites recovered from the faeces and urine account for nearly all of an administered dose (>96%) according to mass balance data.[66]

In healthy volunteers, 19 and 22% of an orally or intravenously administered dose is eliminated unchanged in the urine (table IV), with a similar (unchanged) amount eliminated in the faeces.[66] An estimated 4.5% of a moxifloxacin dose was eliminated by transepithelial intestinal elimination over a 120-minute study period in rabbits.[82]

The reported mean plasma elimination half-life ($t_{½\beta}$) of oral moxifloxacin 50 to 800mg ranges from 8 to 16 hours (median 12.4 hours; table IV). Plasma clearance ranges from 9 to 15 L/h and occurs primarily by nonrenal mechanisms, with renal clearance being approximately 1.3 to 3 L/h (table IV).

3.4 Influence of Age, Race and Disease

The pharmacokinetics of moxifloxacin do not appear to be significantly affected by advanced age or gender, if correction is made for bodyweight. In a study involving 3 groups of 12 volunteers who received a single 200mg oral dose, C_{max} and AUC values were higher in elderly women (1.9 mg/L and 25.2 mg/L · h) than in elderly men (1.6 mg/L and 19.9 mg/L · h) [mean age of both 74 years] and young men (1.4 mg/L and 19.1 mg/L · h). However, between-group differences were insignificant after normalisation of these parameters for bodyweight.[83]

Similarly, no clinically significant differences were found with regard to pharmacokinetic parameters between Japanese, German or American volunteers given moxifloxacin (dosage not clearly stated).[84]

Renal impairment did not affect the clearance of oral moxifloxacin, although renal clearance of the drug decreased as a function of creatinine clearance (CL_{CR}), in 32 volunteers with CL_{CR} values of <1.8 to >5.4 L/h/1.73m^2 who received a single oral 400mg dose.[85] However, multiple doses of oral moxifloxacin do not appear to have been studied in patients with renal dysfunction.

Patients with mild to moderate hepatic dysfunction [Child-Pugh class A (n = 6) or B (n = 2)] tended to have lower C_{max} and AUC values (13 and 23% lower, respectively) than healthy individuals (n = 10), but t_{max}, $t_{½\beta}$ and renal clearance values were similar in the 2 groups.[86]

4. Clinical Potential

Moxifloxacin has been evaluated in the treatment of patients with upper and lower respiratory tract infections, including community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute sinusitis. Moxifloxacin was given at a dosage of 400mg once daily in all studies, except for one which also investigated the efficacy of a 200mg once daily dosage.[87] All comparative trials were randomised and double-blind in design.

In these studies, bacteriological success was defined as elimination of the pretreatment pathogen (this was presumed in patients in whom sampling was not possible because of clinical improvement). Clinical success (or resolution) generally encompassed complete resolution, or reduction in the severity, of signs and symptoms of infection.[87,88] In several studies,[89-93] it was specified that only patients who did not require further antibacterial therapy could be included in the clinical response/resolution category. Some inconsistencies were noted within study reports. For instance, in one study clinical response was graded as resolution (no signs and symptoms of infection remaining), improvement (only mild intensity of signs and symptoms remaining), failure or indeterminate. However, results were only given in terms of resolution, indeterminate or missing data.[94]

Response rates stated in this section refer to the efficacy-evaluable patient population. Patients were generally assessed for response at the end of treatment (0 to 6 days post-treatment) and at follow up (usually 2 to 5 weeks after completing treatment).

In comparative studies, 2-sided 95% confidence intervals were calculated for the difference between response rates for comparators, in order to detect any significant differences in efficacy between treatments.

4.1 Community-Acquired Pneumonia

Moxifloxacin (administered 400mg once daily in all but one study) has been evaluated in a non-comparative study[88] and in 3 comparative multicentre studies (n > 400 patients each) in the management of patients with mild to moderate community-acquired pneumonia confirmed by chest x-ray (table V). Patients in most trials were ambulatory, with the exception of one study[89] in which approximately 80% of patients were hospitalised. Comparator agents were high dose oral amoxicillin (1g 3 times daily)[89] or oral clarithromycin (500mg twice daily).[87,92] Antibacterial therapy was given for 10 days in all studies.

One study enrolled patients with suspected pneumococcal pneumonia, but one-third of microbiologically evaluable patients were found to be infected with other pathogens.[89] Another study performed in the US found a very high incidence of atypical pretherapy pathogens, with *C. pneumoniae* representing almost one-half and *M. pneumoniae* almost one-quarter of pathogens identified.[92]

Moxifloxacin achieved bacteriological and clinical success/resolution rates of ≥90% in all studies and was at least as effective as comparators (table V). Moxifloxacin 400 mg/day produced slightly higher bacteriological response rates than comparator agents in 2 studies (90 *vs* 85% with clarithromycin[87] and 90 *vs* 82% with high dose amoxicillin[89]). Clinical success rates at follow up were similar to those at end of treatment, indicating a low incidence of relapse (table V).

In studies which reported bacteriological results for individual pathogens,[88,89,92] eradication rates for moxifloxacin were 90 to 100% for *S. pneumoniae*, 85 to 100% for *H. influenzae*, 100% for *M. catarrhalis* and *K. pneumoniae*, 89 to 92% for *C. pneumoniae* and 93 to 96% for *M. pneumoniae*. Of bacteriological failures reported at follow up in one comparative study, persistent organisms were *C. pneumoniae* (4 moxifloxacin *vs* 1 clarithromycin

Table V. Efficacy of moxifloxacin (MOX) in patients with mild to moderate community-acquired pneumonia: summary of multicentre randomised double-blind comparative trials and a noncomparative trial. All drugs were administered orally for 10 days

Reference	No. of patients enrolled	Treatment and dosage (mg)	Bacteriological success [no. of patients (%)][a,b]	Clinical success [no. of patients (%)][b]		Follow up [clinical success (%)][d]	Comparative efficacy
				success/resolution	failure		
Noncomparative study							
Patel et al.[88]	254	MOX 400 od	106/116 (91)[e]	184/190 (97)		94	
Comparative studies							
Fogarty et al.[92]	474	MOX 400 od	99/102 (97)	177/194 (91)	6 (3)	95	MOX ≡ CLR
		CLR 500 bid	95/99 (96)	173/188 (92)	9 (5)	95	
Höffken et al.[87][f]	678	MOX 200 od	29/32 (91)	169/180 (94)		91	MOX 200 ≡ MOX 400 ≡ CLR; MOX 200 ≡ MOX 400 ≥ CLR[g]
		MOX 400 od	37/41 (90)	167/177 (94)		93	
		CLR 500 bid	29/34 (85)	164/174 (94)		92	
Petitpretz et al.[89][f]	411	MOX 400 od	61/68 (90)	162/177 (92)	15 (9)	89	MOX ≡ AMX; MOX ≥ AMX[g]
		AMX 1000 tid	56/68 (82)	166/185 (90)	19 (10)	89	

a Documented or presumed eradication of the pretreatment pathogen.

b Refers to evaluable patient population only, assessed at the end of treatment (0 to 6 days post-therapy).

c Clinical success or resolution was defined as complete resolution of signs and symptoms of infection or sufficient improvement that no further antibacterial therapy was required.

d Follow-up evaluation was performed 14-35d[88,92] or 3-4wk[87,89] after therapy.

e Combined result for end of therapy and follow-up responses.

f Abstract report.

g On the basis of clinical response; bacteriological response.

AMX = amoxicillin; **bid** = twice daily; CLR = clarithromycin; **od** = once daily; **tid** = 3 times daily; ≡ indicates that treatments were equivalent; ≥ indicates that MOX tended to be more effective than comparator, but this did not reach statistical significance according to 95% confidence intervals.

recipient), *H. influenzae* (1 *vs* 2), *M. pneumoniae* (1 *vs* 0) and *S. pneumoniae* (0 *vs* 1).[92] When penicillin susceptibility was taken into account in patients with pneumococcal pneumonia, moxifloxacin achieved a similar clinical success rate to amoxicillin in patients with strains with intermediate or full resistance to penicillin (94 *vs* 87%); results were not given for resistant and intermediate strains separately.[89]

4.2 Acute Exacerbations of Chronic Bronchitis

Moxifloxacin has been evaluated in 2 large comparative trials in patients with mild to moderate acute exacerbations of chronic bronchitis[90,93] (table VI). In both trials, moxifloxacin 400mg administered once daily for 5 or 10 days demonstrated equivalent clinical efficacy to clarithromycin 500mg administered twice daily for 7 or 10 days. At the end of treatment, clinical success was achieved in 94% of all moxifloxacin recipients and 94 to 95% of clarithromycin recipients (table VI).

With regard to bacteriological results, moxifloxacin demonstrated superior efficacy to clarithromycin in one trial [91 *vs* 68% at treatment end (95% confidence intervals 8.5%, 27.7%)][90] but similar efficacy in the other[93] (table VI). When analysed by pathogen, moxifloxacin eradicated *H. influenzae* more effectively than clarithromycin in both trials (91 *vs* 54%[90] and 89 or 97% *vs* 76%;[93] no statistical analysis provided) at 7 to 17 days' follow-up. Eradication rates against other common pathogens (*M. catarrhalis*, *S. pneumoniae*, *S. aureus*, *K. pneumoniae* and *H. parainfluenzae*) were generally similar between treatment groups (84 to 100% with 5-day moxifloxacin, 93 to 100% with 10-day moxifloxacin and 88 to 100% with clarithromycin).[90,93] No strains resistant to moxifloxacin

were detected, but 49 isolates were resistant to clarithromycin in one trial.[90]

Meta-analysis of data from 4 multinational studies in patients with acute exacerbations of chronic bronchitis showed that 96 to 98% of *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae* and *M. catarrhalis* were eradicated after treatment with moxifloxacin 400 mg/day; clinical success was documented in 92 to 100% of patients.[96]

4.3 Acute Sinusitis

Seven- and 10-day courses of moxifloxacin once daily have been compared with 10-day courses of oral cefuroxime axetil 250mg twice daily or oral trovafloxacin 200mg once daily in 3 randomised, double-blind multicentre studies in patients with acute bacterial sinusitis (table VII). Patients had nasal congestion, postnasal drainage, frequent coughing or throat clearing, frontal headache, malar pain/tenderness and/or purulent nasal discharge. Sinusitis was graded as moderate to severe in over 90% of patients.[91,94,97] Bacteriological assessment was performed by swab or cannulation of the middle meatus or by sinus puncture/aspiration in one study.[94]

A 10-day course of moxifloxacin produced an almost identical clinical response rate (cure or improvement) to a 10-day course of cefuroxime axetil [90 *vs* 89% of patients; 95% confidence intervals (–5.1%, 6.2%)] in one study.[91] However, in another study, a 7-day course of moxifloxacin was more clinically and bacteriologically effective than a 10-day course of cefuroxime axetil.[94] Complete resolution of clinical symptoms was achieved in 97% of moxifloxacin versus 91% of cefuroxime axetil recipients [95% confidence intervals (1.5%; 10.6%)]. Similar results were seen in the intent-to-treat population: clinical resolution was documented in 216 of 242 moxifloxacin recipients (89%) and 219 of 251 cefuroxime recipients (87%) at the end of treatment [95% confidence intervals (–3.7%; 7.8%)].[94]

Bacteriological success was achieved in 95% of patients in the moxifloxacin group versus 84% in the cefuroxime axetil group [95% confidence intervals (3.6%; 19.7%); table VII]. Over 97% of *S. pneumoniae* (n = 39), *H. influenzae* (n = 29) and *M. catarrhalis* (n = 14) and 89% of *S. aureus* (n = 9) were eradicated in the moxifloxacin group. Persisting pathogens were *S. pneumoniae* (1 moxi-

Table VI. Comparative efficacy of moxifloxacin (MOX) in patients with mild to moderate[a] acute exacerbations of chronic bronchitis. All drugs were administered orally

Reference (study design)	No. of patients enrolled	Treatment and dosage (mg) x duration (d)	Bacteriological success [no. of patients (%)][bc]		Clinical success [no. of patients (%)][cd]		Comparative efficacy
			end of treatment[e]	follow-up[f]	end of treatment[e]	follow-up[f]	
Chodosh et al.[93] (r, db)	936	MOX 400 od × 5	127/135 (94)	127/143 (89)	127/135 (94)	127/135 (94)	MOX 5d ≡ MOX 10d ≡ CLR
		MOX 400 od × 10	138/145 (95)	135/148 (91)	136/144 (94)	134/140 (96)	
		CLR 500 bid × 10	115/127 (91)	110/129 (85)	121/127 (95)	118/123 (96)	
Wilson et al.[90] (r, db, mc)	750	MOX 400 od × 5	105/115 (91)	89/115 (77)	304/322 (94)	287/322 (89)	MOX ≡ CLR; MOX > CLR[g]
		CLR 500 bid × 7	78/114 (68)	71/114 (62)	307/327 (94)	289/327 (88)	

a All but 16 patients in 1 trial[93] had type I or II acute exacerbations as described by Anthonisen et al.[95] Most patients (68 to 79% per treatment group) had type I exacerbations.

b Documented or presumed eradication of the pretreatment infecting pathogen.

c Refers to evaluable patient population. In one trial,[93] all evaluable patients had a baseline causative pathogen.

d Defined as complete resolution of signs and symptoms of infection or sufficient improvement that no further antibacterial therapy was required.

e End of treatment evaluation was performed 0-2[90] or 0-6 days post-therapy.[93]

f Follow-up evaluation was performed 7-9[90] or 7-17 days post-therapy.[93]

g On the basis of clinical response; bacteriological response.

CLR = clarithromycin; **bid** = twice daily; **db** = double-blind; **mc** = multicentre; **od** = once daily; **r** = randomised; ≡ indicates that treatments were equivalent; **>** indicates that MOX was more effective than comparator, according to 95% confidence intervals (8.5%, 27.7%).

floxacin *vs* 3 cefuroxime axetil recipients), *H. influenzae* (1 *vs* 5), *P. aeruginosa* (2 *vs* 0), *P. mirabilis* (1 *vs* 0), *S. epidermidis* (0 *vs* 1) and *Streptococcus* spp. (0 *vs* 2). All persisting organisms remained susceptible to the administered drug, with the exception of 1 *S. aureus* strain (cefuroxime MIC increased from 0.5 to 4 mg/L after treatment).[94]

5. Tolerability

5.1 General Tolerability

Meta-analysis of data from 20 phase II and III studies involving 4926 patients treated with moxifloxacin (400 mg/day in most patients) indicated that adverse events were mostly mild and transient and led to discontinuation of treatment in 3.8% of patients. The most frequent events were nausea (7.2%) and diarrhoea (5.7%). Dizziness occurred in 2.8% of patients; however, this report was presented as an abstract and few details are available.[98]

In large comparative studies in patients with lower respiratory tract infections (n > 400), moxifloxacin was associated with a similar incidence of adverse events compared with clarithromycin (21 to 35% *vs* 22 to 34%).[90,92,93] Gastrointestinal events (usually nausea, diarrhoea) were the most commonly reported events with both agents,[90,93] although dizziness seemed to be more common with moxifloxacin (3 to 5 *vs* 1%) and taste perversion with clarithromycin (0 to 2 *vs* 3.5 to 8%).[90,93] Data from 2 comparative trials are presented in figure 3.

Compared with β-lactam agents, moxifloxacin was associated with a similar overall incidence of drug-related adverse events to high dose oral amoxicillin,[89] but a higher rate of events than in cefuroxime axetil recipients (31 *vs* 23%; n = 493 and 37 *vs* 26%; n = 537).[91,94] Nausea was more significantly common with moxifloxacin than with cefuroxime axetil in one trial (11 *vs* 4%; p = 0.003; fig. 3)[91] but not another (4 *vs* 2%).[94]

Compared with trovafloxacin, moxifloxacin was associated with a similar overall incidence of adverse events (33 *vs* 37%), a slightly higher incidence of gastrointestinal events (22 *vs* 16%) but a lower incidence of CNS events (8 *vs* 24%).[97]

5.2 Cardiac Effects

Some quinolones are associated with QTc prolongation, notably sparfloxacin[99] and, more re-

Table VII. Comparative efficacy of moxifloxacin (MOX) in patients with acute suspected bacterial sinusitis. All studies were multicentre, randomised, double-blind in design and all drugs were administered orally. Use of oral of nasal decongestants or antihistamines was permitted

Reference	No. of patients enrolled	Treatment and dosage (mg) × duration (d)	Bacteriological success [no. of patients (%)][ab]	Clinical success [no. of patients (%)][ac]		Comparative efficacy
			end of treatment[d]	end of treatment[d]	follow-up[e]	
Baz et al.[97]	594	MOX 400 od × 10	–	223/253 (88)	–	MOX ≡ TRO
		TRO 200 od × 10	–	232/260 (89)	–	
Burke et al.[91]	542	MOX 400 od × 10	–	200/223 (90)	181/184 (98)	MOX ≡ CXM
		CXM 250 bid × 10	–	209/234 (89)	197/202 (98)	
Siegert et al.[94]	498	MOX 400 od × 7	103/109 (95)	204/211 (97)	185/204 (91)	MOX > CXM
		CXM 250 bid × 10	96/115 (84)	204/225 (91)	182/204 (89)	

a Refers to evaluable patient population.

b Documented or presumed eradication of the pretreatment infecting pathogen.

c Defined as complete resolution of signs and symptoms of infection or sufficient improvement that no further antibacterial therapy was required.

d End of treatment evaluation was performed 4 to 7[94] or 7 to 21d post-treatment.[91,97]

e Follow-up evaluation was performed 27-31d post-treatment.

bid = twice daily; **CXM** = cefuroxime axetil; **od** = once daily; **TRO** = trovafloxacin; ≡ indicates that treatments were equivalent, according to 95% confidence intervals; **>** indicates that MOX was significantly better than comparator, according to 95% confidence intervals (1.5%;10.6% for clinical and 3.6%;19.7% for bacteriological results).

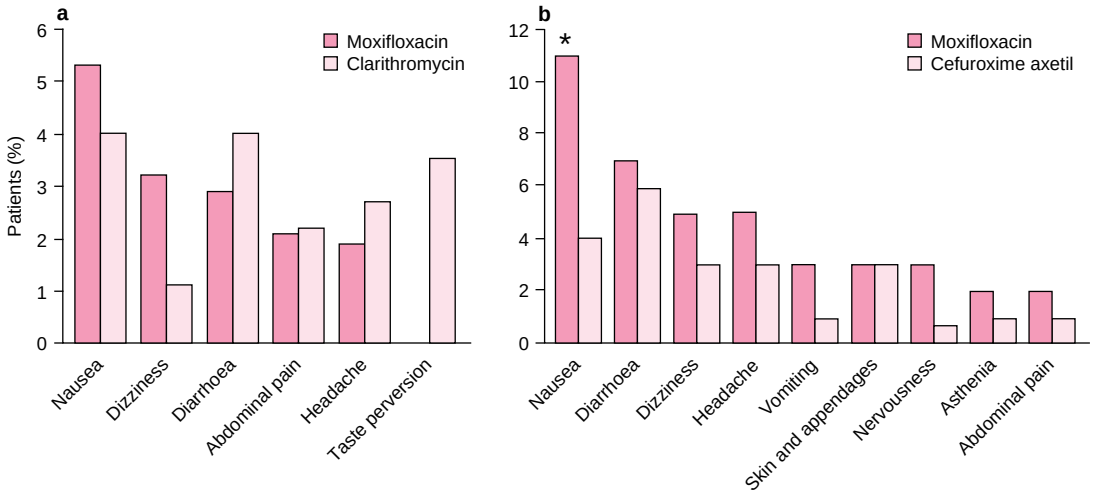

Fig. 3. Comparative tolerability of moxifloxacin versus clarithromycin (**a**) and cefuroxime axetil (**b**). Drug-related adverse events (reported at a frequency of ≥2% with moxifloxacin) in patients treated with (**a**) moxifloxacin 400mg once daily for 5 days (n = 374) or clarithromycin 500mg twice daily for 7 days (n = 371) for acute exacerbations of chronic bronchitis[90] or (**b**) moxifloxacin 400mg once daily (n = 263) or cefuroxime axetil 250mg twice daily (n = 274) for 10 days for acute sinusitis.[91] All drugs were administered orally; * p = 0.003 *vs* cefuroxime axetil.

cently, grepafloxacin which has been withdrawn from clinical use for this reason.[100]

Moxifloxacin did not affect the QTc interval, blood pressure or heart rate and was not associated with arrhythmias in beagle dogs given doses of <90 mg/kg/day. However, QT interval prolongation was observed 2 hours after drug administration (25 msec increase from baseline) at a dose of 90 mg/kg.[101]

In clinical trials, the QTc interval was prolonged in moxifloxacin 400 mg/day recipients (n = 4008) by a mean 6 msec versus 1 msec in recipients of comparator agents (clarithromycin, cefalexin, cefuroxime axetil, amoxicillin, doxycycline and metronidazole; n = 3689). 38 versus 28 patients were classified as outliers (QT interval of >450 msec in men and >470 msec in women), of whom 1 versus 4 experienced a cardiovascular event.[102]

At present, there are no data on the use of moxifloxacin in patients who have pre-existing QTc prolongation or who are taking drugs which prolong the QTc interval; these were a stated exclusion criterion in most clinical trials of moxifloxacin.[87-89,91-93] For this reason, the use of moxifloxacin should be avoided in patients with congenital or acquired syndromes of QTc prolongation or in those receiving concomitant drugs known to prolong the QTc interval (section 7).

5.3 Phototoxic Potential

As a class, the fluoroquinolones are known to have photosensitising potential which varies considerably between different agents and can produce reactions ranging from mild erythema to severe bullous eruptions on sun-exposed skin. Agents with a fluorine substituent at position 8, such as lomefloxacin, sparfloxacin and fleroxacin, are associated with relatively high incidences of phototoxic reactions.[103]

Data from human,[104] animal[105] and *in vitro*[105] studies suggest that moxifloxacin has a low propensity for inducing phototoxic effects relative to other fluoroquinolones. It is thought that the methoxy group or lack of halogen at position 8 of the fluoroquinolone molecule confers low phototoxic potential.[106] Drug-related phototoxicity did not occur in almost 5000 patients treated with moxifloxacin in clinical trials.[98]

Moxifloxacin (200 or 400 mg/day for 7 days) did not produce any measurable phototoxicity (as measured by the minimum dose of ultraviolet irradiation to cause visible erythema) in a double-blind, placebo-controlled study in 32 Caucasian volunteers. In contrast, lomefloxacin (400 mg/day) increased sensitivity to ultraviolet light by almost 4-fold.[104]

No increase of skin reddening in response to ultraviolet exposure was seen in guinea-pigs and rats given moxifloxacin (30 to 100 mg/kg), whereas sparfloxacin (30 to 100 mg/kg) produced a pronounced and long-lasting skin reaction after irradiation. *In vitro*, moxifloxacin did not induce any cytotoxicity with or without ultraviolet irradiation in murine fibroblasts; in comparison sparfloxacin produced a marked phototoxic effect in this assay.[107]

5.4 CNS Excitatory Potential

Adverse CNS effects of the fluoroquinolones can include headache, dizziness, tiredness, insomnia, disturbed vision, nightmares and, more rarely, psychotic reactions, hallucinations, depression and seizures.[103]

In vitro electrophysiological testing in rat hippocampal slices indicated that moxifloxacin had a potential similar to that of ciprofloxacin for producing CNS adverse effects. At a concentration of 2 μmol/L, moxifloxacin increased the population spike amplitude to 170% of control compared with an increase of 155% for ciprofloxacin and 192% for enoxacin.[108]

Although moxifloxacin doses of ≥150 mg/kg induced convulsions in monkeys, administration of fenbufen, ibuprofen or diclofenac (at dosages equivalent to 30 times the therapeutic dosages) with moxifloxacin (300 mg/kg) did not increase its CNS toxicity in mice.[101] The epileptogenic potential of fluoroquinolones can be enhanced by coadministration of the nonsteroidal anti-inflammatory drug fenbufen. This is achieved possibly via enhancement of inhibition of γ-aminobutyric acid (GABA) receptor binding by the fluoroquinolones (reviewed by Sörgel & Kinzig[109] and Depperman & Lode[110]).

5.5 Other Effects

In volunteer studies (n = 103), moxifloxacin (single doses of 50 to 800mg or multiple doses up to 600mg once daily for 10 days) did not cause any clinically relevant changes in vital signs, haematology, blood chemistry or ECG.[111]

Other characteristic adverse events associated with fluoroquinolones include chondrotoxicity and tendon disorders.[103] Chondropathy was seen in young beagle dogs at moxifloxacin dosages of 30 and 90 mg/kg/day.[101] However, the potential of moxifloxacin to induce such events during therapeutic use awaits clarification in large-scale clinical studies.

No degenerative changes in liver histopathology were observed in monkeys administered oral moxifloxacin 150 mg/kg (18 times the recommended therapeutic dose in humans) for 4 weeks. Transient elevations in liver enzyme levels were observed after administration of moxifloxacin 45 or 135 mg/kg for 3 to 6 months.[112]

6. Drug Interactions

The fluoroquinolones interact with a wide range of drugs, although there is considerable variation between individual agents with regard to their propensity for drug interactions. Unlike moxifloxacin, some agents inhibit the cytochrome P450-dependent metabolism of methylxanthines (theophylline and caffeine) and coumarin anticoagulants, resulting in increased serum concentrations and increased toxicity of these drugs if coadministered with them. The fluoroquinolones also chelate alkaline earth and transition metal cations and their absorption may be reduced by coadministration with antacids containing magnesium, aluminium or calcium, sucralfate, preparations containing iron and multivitamin preparations containing zinc.[109,110]

The bioavailability of moxifloxacin (400mg) was substantially reduced when it was coadministered with an antacid (Maalox®; 3 times daily)[113] or sucralfate (1g).[114] AUC and C_{max} values were

decreased by >50%.[113,114] Similarly, absorption of moxifloxacin 400mg was significantly decreased by concomitant administration of an iron preparation (Erifer®; dosage not stated). AUC and C_{max} values were reduced by 39 and 59%, respectively.[115] The extent of absorption of moxifloxacin 400mg was, however, unaffected by concomitant administration of calcium-containing supplements; C_{max} of moxifloxacin was decreased by approximately 16%, although t_{max} increased from 0.9 to 2.5 hours with the addition of calcium.[116]

However, moxifloxacin did not show any clinically relevant interaction with theophylline (400mg twice daily),[117] β-acetyldigoxin (0.6mg),[118] probenecid (500mg twice daily),[119] ranitidine (150mg twice daily),[120] warfarin (25mg)[121] or oral contraceptives (ethinylestradiol 0.03mg/levonorgestrel 0.15mg).[122] Thus, dosage adjustments do not appear to be warranted if moxifloxacin is coadministered with these agents.

7. Dosage and Administration

Moxifloxacin is indicated for the treatment of adult (≥18 years) patients with acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia or acute bacterial sinusitis. The recommended oral dosage for all indications is 400mg administered once daily. Moxifloxacin should be administered for 5 days for acute exacerbations of chronic bronchitis and 10 days for acute sinusitis and for community-acquired pneumonia.[8]

No dosage adjustment is required in the elderly, patients with mild hepatic impairment (Child-Pugh class A) or in patients with any degree of renal impairment. Currently there are no or insufficient data available concerning the use of moxifloxacin in patients with moderate to severe liver impairment or in patients undergoing renal dialysis.[8]

Antacids (containing aluminium, magnesium or calcium), metal cations, multivitamins (containing iron or zinc), sucralfate or formulations containing divalent or trivalent cations (e.g. didanosine chewable/buffered tablets) should be administered at least 4 hours before or 8 hours after oral moxifloxacin, as these agents can impair absorption of the quinolone. Moxifloxacin does not interact with theophylline, warfarin, digoxin, glibenclamide, probenecid or ranitidine, although monitoring of the prothrombin time or other coagulation test is recommended in patients receiving concomitant warfarin or its derivatives.[8]

Moxifloxacin has been shown to prolong the QTc interval in some patients. Therefore its use should be avoided in patients with known QT interval prolongation or in those receiving concomitant drugs known to prolong the QTc interval.[8]

As with other quinolones, moxifloxacin should be used with caution in those with a history of convulsions. Pain, inflammation or rupture of a tendon can occur with quinolones; treatment should be discontinued if symptoms are observed. Exposure to excessive sunlight or artificial ultraviolet light should be avoided during quinolone therapy. The use of moxifloxacin in children, adolescents <18 years of age, nursing mothers and during pregnancy is not recommended.[8]

8. Potential Place of Moxifloxacin in the Management of Community-Acquired Respiratory Tract Infections

In the management of community-acquired pneumonia[2] an empirical approach, based on antimicrobial therapy which is effective against the major pathogens implicated (see table I), is usually taken. This is because of the recognised inaccuracies of sputum culture and the time required to obtain the results of culture. Indeed, no pathogen is identified in ≥50% of microbiologically evaluated patients.[123]

The past few decades have seen an evolution in the spectrum of pathogens responsible for community-acquired pneumonia, with the role of the atypical pathogens, *M. pneumoniae*, *C. pneumoniae* and *Legionella* spp., increasing.[4] *S. pneumoniae* remains the most common pathogen implicated in community-acquired pneumonia and must be covered by any empirical regimen. Notably, there has

been a dramatic worldwide increase in the resistance of pneumococci to penicillins and macrolides.[3,123]

The agents commonly recommended to treat community-acquired pneumonia are β-lactams, such as amoxicillin, amoxicillin/clavulanic acid or cefuroxime axetil, and macrolides.[123] As already mentioned, older fluoroquinolones such as ciprofloxacin are not generally recommended because of inadequate activity against Gram-positive pathogens. However, several quinolones with improved activity against pneumococci have been developed. These include sparfloxacin[99] and, to some extent, levofloxacin[124] which offer some improvements over ciprofloxacin with regard to Gram-positive coverage. There are also the newer extended-spectrum agents, such as gatifloxacin[125] and moxifloxacin, which have recently become available or are under development and have improved activity against Gram-positive and anaerobic pathogens. These agents have markedly better antipneumococcal activity than older compounds (section 2.1.1). Because of this, sparfloxacin and levofloxacin are recommended for the empirical treatment of patients with community-acquired pneumonia in the US, particularly if penicillin-resistant pneumococcal disease is suspected.[2] They are also recommended for treatment of confirmed infections caused by penicillin-intermediate or -resistant *S. pneumoniae*, *H. influenzae*, *C. pneumoniae*, *M. pneumoniae* or *Legionella* spp.[2] However, recommendations vary between countries, according to local epidemiological factors and preferred practices. For instance, in the UK, penicillins (amoxicillin, ampicillin or benzylpenicillin) are recommended as first-line treatment, as pathogen resistance to these agents is less common than in most countries[126] and atypical pathogens are also perceived to be less of a concern.

Although the role of antimicrobial therapy in patients with acute bacterial exacerbations of chronic bronchitis has been controversial, it has recently been shown to be of benefit in the treatment of such patients (reviewed by Meyer[127] and Balter & Grossman[128]). As with community-acquired pneumonia, antibacterial therapy is usually empirical and directed at the most likely pathogens (see table I). Fluoroquinolones are recommended for all severities of illness.[129]

Moxifloxacin has good activity against community-acquired respiratory pathogens, including the common pathogens (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*), the less common (e.g. *S. aureus*, *K. pneumoniae*) and the atypical pathogens (*M. pneumoniae*, *C. pneumoniae*, *Legionella* spp.) offering the potential for single-agent treatment of community-acquired respiratory tract infections. Importantly, it is one of the most active fluoroquinolones against pneumococci, including those resistant to penicillin and macrolides. However, it has poor activity against *P. aeruginosa*, although this pathogen is of limited importance for community-acquired infections (section 2.1.2).

Extensive use and misuse of the fluoroquinolones has led to the emergence and spread of resistant strains. Fluoroquinolone resistance has become common in MRSA.[130] High level fluoroquinolone resistance results from multiple mutations in bacterial enzyme targets (topoisomerase IV and DNA gyrase); thus use of fluoroquinolones with activity against both enzymes (e.g. moxifloxacin) may limit the development of resistance during therapy. Indeed, moxifloxacin appears to be less affected by bacterial resistance mechanisms than some other fluoroquinolones and has shown a low propensity for inducing bacterial resistance in *in vitro* and animal studies (section 2.3); however, these observations require confirmation in clinical trials.

As with other fluoroquinolones, moxifloxacin achieves good penetration into respiratory tissues and fluids. In common with sparfloxacin[99] and gatifloxacin,[125] it offers the advantages of once daily administration and a low potential for drug interactions. Moreover, dosage adjustment is not required for advanced age or renal or mild hepatic impairment (section 7).

In clinical trials in patients with community-acquired pneumonia or acute exacerbations of chronic bronchitis, oral moxifloxacin 400mg once

daily achieved bacteriological and clinical success rates of approximately 90% or higher. These response rates are equivalent to or better than those obtained with standard treatments including clarithromycin and high dose amoxicillin. In patients with acute exacerbations of chronic bronchitis, a 5-day course of moxifloxacin was more effective bacteriologically than a 7-day course of clarithromycin 500mg twice daily. Shorter treatment courses are likely to improve patient compliance, especially if only one daily dose is required, but these promising findings require further confirmation. An intravenous formulation of moxifloxacin, which is under development (section 3), is likely to provide an alternative to oral therapy in more seriously ill patients.

The spectrum of activity of moxifloxacin also supports its use as an alternative therapy in upper respiratory tract infections. A 7-day course of moxifloxacin was significantly more effective than a 10-day course of cefuroxime axetil in patients with acute bacterial sinusitis in one trial, although 10-day courses of the 2 agents were equivalent in another trial. Moxifloxacin has been compared with trovafloxacin in patients with sinusitis,[97] but this is of limited clinical relevance as use of the latter agent is restricted in many markets.

With the exception of trovafloxacin, there have been no other studies, as yet, comparing moxifloxacin with other fluoroquinolones with enhanced Gram-positive coverage, such as gatifloxacin, sparfloxacin and levofloxacin. Although, on the basis of *in vitro* data, moxifloxacin appears to be one of the most promising of the newer agents, studies are needed to determine whether any differences in *in vitro* activity between moxifloxacin and these agents translate into clinical benefits.

Tolerability has been an issue with some fluoroquinolone agents. Sparfloxacin is associated with some tolerability problems (a relatively high incidence of phototoxicity and QTc prolongation),[99] and trovafloxacin[131] and grepafloxacin,[132] two promising extended-spectrum agents, have been withdrawn from several or all major markets as a result of hepatotoxicity and cardiovascular events, respectively.[100,133] Moxifloxacin is generally well tolerated, with the most common adverse events being gastrointestinal disturbances. Moxifloxacin has, however, been associated with a small degree of QTc prolongation (mean increase of 6 *vs* 1 msec with comparator agents) in clinical trials. Until data are available in high-risk patients, the use of moxifloxacin should be avoided in patients with congenital or acquired syndromes of QT prolongation or in those receiving concomitant drugs known to prolong the QTc interval.

In comparative studies, moxifloxacin was associated with a similar overall incidence of drug-related adverse events to high dose amoxicillin and clarithromycin and a slightly higher rate of events than cefuroxime axetil in patients with respiratory tract infections. Available data suggest that moxifloxacin has a low propensity for inducing phototoxic effects relative to other fluoroquinolones, and preliminary data also suggest that it has a low potential for inducing CNS and hepatotoxic events.

Development of the newer fluoroquinolones with improved activity against Gram-positive cocci represents an important advance in the management of community-acquired lower respiratory tract infections. As a representative of this group of agents, moxifloxacin offers the benefits of excellent activity against pneumococci, once daily administration and a low propensity for drug interactions. Although studies are needed regarding its tolerability in at-risk patients with QT interval prolongation, available data suggest that moxifloxacin is likely to become a first-line therapy option for the treatment of community-acquired lower respiratory tract infections, particularly in areas where drug-resistant *S. pneumoniae* or *H. influenzae* are common.

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