ORIGINAL ARTICLE

Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis and COPD: a systematic review and meta-analysis

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ABSTRACT

Purpose: To evaluate the efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis (AECB) and chronic obstructive pulmonary disease (AECOPD).

Methods: We searched PubMed, EMBASE, and the Web of Science for relevant studies. Two reviewers extracted data and reviewed the quality of the studies independently. The primary outcome was clinical success at early follow-up. Study-level data were pooled using a random-effects model when I^2 was >50% or a fixed-effects model when I^2 was <50%.

Results: Eleven randomized controlled studies were considered. There was no difference between moxifloxacin and comparator agents with regard to treatment success in intention-to-treat (ITT) [odds ratio (OR) =1.18, 95% confidence interval (CI) 0.98-1.42], clinically evaluable (CE) (OR 1.13, 95% CI, 0.93-1.37) patients, or adverse effects in general (OR 1.00, 95% CI, 0.86-1.17). Moxifloxacin was associated with better microbiological success (OR 1.45; 95% CI, 1.14-1.85).

Conclusions: Moxifloxacin was as clinically equivalent and bacteriologically superior to the antibiotic regimens routinely used in patients with AECB and AECOPD. Moxifloxacin therapy may be a promising and safe alternative to empirical treatment for AECB and AECOPD.

KEYWORDS

Moxifloxacin; chronic bronchitis; chronic obstructive pulmonary disease (COPD); meta-analysis; systematic review

Introduction

Acute exacerbations of chronic bronchitis (AECB), including chronic obstructive pulmonary disease (AECOPD), represent a substantial health burden to patients, resulting in reduced lung function, increased morbidity and mortality, and long-term

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impairment in quality of life (1-3). Approximately around 40-50% of exacerbations may be attributed to bacteria while other causes include viral infections or environmental irritants (4). Current treatment guidelines recommend antibiotic therapy for patients with a more severe illness and often use acute symptom changes based on Anthonisen criteria of type I (worsening dyspnoea with increased sputum volume and purulence) or II (change in any two of these symptoms) exacerbations to define this group (5,6). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations for antibiotic therapy are based on the severity of exacerbations, the presence of risk factors, and predictors of poor outcome (e.g., comorbid conditions, frequency of AECBs, and previous antibiotic use) (7).

Moxifloxacin is a fourth-generation fluoroquinolone with a broad spectrum of activity against a wide range of the microorganisms isolated in AECB, including Gram-positive and Gram-negative bacteria, atypical pathogens, and anaerobic bacteria (8-10). Furthermore, moxifloxacin may be regarded

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as the most excellent tissue penetration ability (11). Several randomized controlled trials have been done to compare the effectiveness of moxifloxacin with various standard antimicrobials in the treatment of AECB (12-20). Most studies suggest that moxifloxacin has been approached as effective as standard antimicrobials (12-20). To date, few trials show clinical or bacteriological superiority of one antibiotic over another in AECB or AECOPD. Therefore, we performed a systematic literature review and meta-analysis to clarify whether the use of moxifloxacin could be associated with improved outcomes in comparison with standard antibiotic therapy in AECB or AECOPD.

Methods

Data sources and search strategy

To identify studies for inclusion in this review, two authors independently searched PubMed, the Cochrane Central Database of Controlled Trials, and EMBASE for relevant studies published up to July 2013. The search was limited to studies conducted with humans. No language restriction was imposed. Search terms were individualized for each database. Search terms used included: ("chronic bronchitis" OR "chronic obstructive pulmonary disease" OR "COPD") AND ("moxifloxacin"). We also searched the proceedings of major relevant conferences, trial databases, the reference lists of identified trials, and major reviews.

Study selection

Two reviewers (K.X. Liu and B. Xu) independently screened studies for inclusion, retrieved potentially relevant studies, and determined study eligibility. Any discrepancies were resolved by consensus. Analysis was restricted to randomized controlled trials. For this meta-analysis, we considered those randomized control trials (RCTs) that compared the clinical efficacy of moxifloxacin and another antibiotic in patients with AECB and AECOPD. The definition of chronic bronchitis and COPD provided by each study was used. This entity was consistently defined as the presence of productive cough for at least three months in two consecutive years. While the definitions of an exacerbation were more varied, the patients consistently considered for inclusion in these studies were those who presented combinations of the key symptoms of exacerbation: increase in dyspnea, sputum volume, and sputum purulence with or without other minor symptoms. All of the studies considered patients with type I Anthonisen exacerbations for inclusion,

and some also enrolled patients with type 2 or 3 exacerbations accompanied with increased in sputum purulence.

Data extraction

Two authors independently extracted data from all of the enrolled studies. Extracted data included study design (e.g., year conducted, sample size), patient characteristics, study methodology (e.g., eligibility criteria, method of randomization, and blinding), intervention (e.g., antimicrobial agents, dose, route of its administration and duration), and clinical outcomes. The primary outcome was clinical success (cure defined as resolution of all symptoms and signs of the bacterial exacerbation with a return to baseline condition, or improvement defined as subsidence of the ABECB but with an incomplete return to baseline condition) in intention-to-treat (ITT) and clinically evaluable (CE) patients. Treatment success was assessed at 6-21 days after initiation of antimicrobial treatment in order to avoid confounding due to spontaneous resolution of infection that occurs in half of the patients with AECB 21 days after the onset of infection. Treatment success in microbiologically evaluable patients (defined as the absence of pre-treatment isolated bacteria in sputum cultures) and pathogen eradication (documented or presumed) of the bacteria most frequently implicated in AECB isolates (namely *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*) were considered as secondary outcomes. When determining microbiological outcomes, we elected to assess them at the longest post-treatment time point reported in each eligible trial, in an attempt to capture possible relapses.

Quality assessment

We formally determined the methodological quality of each trial using the Jadad score (21), which incorporates randomization, blinding, and attrition to derive a score of 0 to 5; higher scores indicate higher quality. Two reviewers (K.X. Liu and B. Xu) independently appraised the quality of the included trials. Jadad score more than two was considered to denote good methodological quality of an RCT.

Statistical analysis

The meta-analysis was done using Review Manager 5.0 (Cochrane Collaboration, Oxford, UK). We computed pooled odds ratios (ORs) and 95% confidence intervals (CIs) from the adjusted ORs and 95% CIs reported in the observational studies. Potential heterogeneity should be achieved while we performing
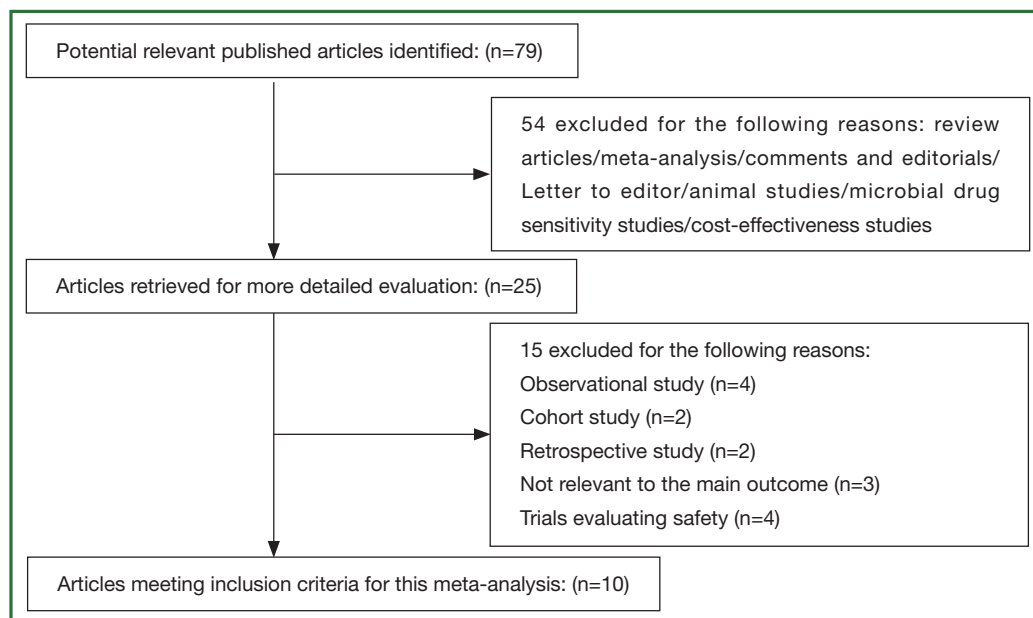
Figure 1. Flow of study selection.

Cochrane Q and I^2 statistics. We predefined heterogeneity as low, moderate, and high with I^2 values of above 25%, 50%, and 75%, respectively. In the analysis of heterogeneity, we considered a P value <0.10 to be statistically significant. Study-level data were pooled using a random-effects model when I^2 was >50% or a fixed-effects model when I^2 was <50%. A funnel plot approaches of effect size *vs.* SE in the primary analysis of clinical success was employed to evaluate publication bias.

Results

Our search obtained a total of 79 references. Of these potentially eligible studies, 10 met the criteria for inclusion in the meta-analysis (11-20). A flowchart for the studies evaluated and the reasons for exclusion are shown in Figure 1.

Study characteristics

The comparator antibiotics were amoxicillin/clavulanic acid, ceftriaxone, cefuroxime-axetil, clarithromycin and azithromycin (11-20). Five RCTs had double-blind (DB) designs (11,12,17-19), while five RCTs were open-labeled (13-16,20). Most of the studies included outpatients. Characteristics of the included studies are summarized in Table 1. All studies were published from 1999 to 2013. Trials were conducted in a diverse array of countries. The eligible trials enrolled patients experiencing an AECB classified as Anthonisen type I, II, III (11,12,14); or type I, II (13,15-17); or type I (18-20). In nine RCTs, data regarding

the use of systemic corticosteroids before the occurrence of ABECB were provided. The average Jadad score of these studies was 3.5 (range: 1-5, Table 2).

Outcomes of clinical and bacteriological success rates

The primary outcome analysis was the clinical success rate at early follow-up in an ITT and CE populations. Early follow-up was before day 21 in all studies. Tests for statistical heterogeneity were performed for all analyses. Data regarding treatment success in ITT population were available for seven out the ten studies included in current meta-analysis (11,12,14,15,17,18,20). Statistically significant heterogeneity was not observed in the primary outcome of clinical success (I^2=36%, P=0.16). No difference was observed between ITT patients with AECB receive moxifloxacin versus the comparator (3,860 patients: OR 1.18; 95% CI, 0.98 to 1.42) (Figure 2). Data on treatment success in CE population were reported in nine of the trials (11-18,20). We found no evidence of statistical heterogeneity for clinical success rate in a CE population (I^2=0%, P=0.75). Treatment with moxifloxacin was not associated with statistically significant better outcome when compared with other antibiotics in CE population (3,301 patients: OR 1.13; 95% CI, 0.93-1.37) (Figure 3).

Eight RCTs reported data regarding treatment success in microbiologically evaluable patients (11-13,15-19). No statistically significant heterogeneity was found among the identified studies (I^2=0%, P=0.79) (Figure 4). Pooled analysis

Table 1. Characteristics of the study population in various studies.

Study/year	Study design	Population	Erolled patients/ITT	Regimen used	Systemic corticosteroid before ABECB
Chodosh et al. 2000 (11)	MC DB, RCT	Aged ≥18 yrs with CB or COPD with type I,II or III ABECB	936/926	Moxifloxacin 400 mg q 24 h for 5 or 10 days, Clarithromycin 500 mg q 12 h for 10 days	134/614 vs. 74/312
DeAbate et al. 2000 (12)	MC DB, RCT	Aged ≥18 yrs with CB or COPD with type I,II or III ABECB	567/567	Moxifloxacin 400 mg q 24 h for 5 days, Azithromycin 500 mg q 24 h on day 1, then 250 mg q 24 h for 4 days	NA
Grassi et al. 2000 (13)	MC RCT	Aged ≥18 yrs with CB and type I or II ABECB	476/470	Moxifloxacin 400 mg q 24 h for 5 days, Ceftriaxone 1 g q 24 h for 7 days	136/240 vs. 134/230
Kreis et al. 2000 (14)	MC RCT	Aged ≥18 yrs with CB with type I,II or III ABECB	411/399	Moxifloxacin 400 mg q 24 h for 5 days, Azithromycin 500 mg q 24 h on day 1, and 250 mg q 24 h for 4 days	NA
Schaberg et al. 2001 (15)	MC RCT	Aged ≥18 yrs with CB and type I or II ABECB	577/575	Moxifloxacin 400 mg q 24 h for 5 days	NA
Starakis et al. 2004 (16)	SC RCT	Aged ≥18 yrs with CB and type II ABECB	162/162	Moxifloxacin 400 mg q 24 h for 5 days, Amoxicillin/clavulanic acid 500/125 mg tid for 7 days	38/79 vs. 32/74
Wilson et al. 1999 (17)	MC DB, RCT	Aged ≥18 yrs with CB or COPD with type I or II ABECB	750/745	Moxifloxacin 400 mg q 24 h for 5 days, Clarithromycin 500 mg q 12 h for 7 days	160/322 vs. 128/327
Wilson et al. 2004 (18)	MC DB, RCT	Aged ≥45 yrs with CB with type I ABECB	733/730	Moxifloxacin 400 mg q 24 h for 5 days, Amoxicillin 500 mg tid for 7 days, clarithromycin 500 mg bid for 7 days, or cefuroxime-axetil 250 mg bid for 7 days	51/354 vs. 40/376
Wilson et al. 2012 (19)	MC DB, RCT	Aged ≥60 yrs with COPD with type I AECOPD, a FEV1 <60% predicted and two or more exacerbations in the last year	1,372/1,352	Moxifloxacin 400 mg q 24 h for 5 days, Amoxicillin/clavulanic acid 875/125 mg bid for 7 days	182/677 vs. 189/675
Zervos et al. 2007 (20)	MC RCT	Aged 40-75 yrs with CB and type I or II ABECB, a FEV1 >35% predicted	342/342	Moxifloxacin 400 mg q 24 h for 5 days, Azithromycin 500 mg q 24 h for 3 days	NA

Abbreviations: AECB, acute exacerbations of chronic bronchitis; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; DB, double-blind; FEV1, forced expiratory volume in 1 second; MC, multicenter; NA, not available; RCTs, randomized control trials; SC, single-center.

showed that the use of moxifloxacin was associated with better outcome in ME patients as opposed to control (1,694 patients: OR 1.45; 95% CI, 1.14-1.85). Of the RCTs included in the analysis, five reported data on pathogens isolated at baseline and eradicated. Data on the eradication rates of the three most common pathogens isolated at baseline (i.e., *H. influenzae, M. catarrhalis,* and *S. pneumoniae*) were reported in five of the eligible RCTs (11,12,17,19,20). Treatment of ABECB patients with moxifloxacin was associated with higher eradication rates of *H. influenzae* compared with treatment with comparators (329 isolates, OR 3.48, 95% CI: 1.39-8.73, I^2 51%, P=0.07), data from five RCTs (11,12,17,19,20). However, there was no difference between the compared groups on eradication rates of *M. catarrhalis* (248 isolates, OR 0.61, 95% CI: 0.29-1.27), data from five RCTs (1,12,17,19,20) or of *S. pneumoniae* (213 isolates, OR 0.80, 95% CI: 0.40-1.57).

Table 2. Quality of the 12 studies as assessed by the Jadad score.

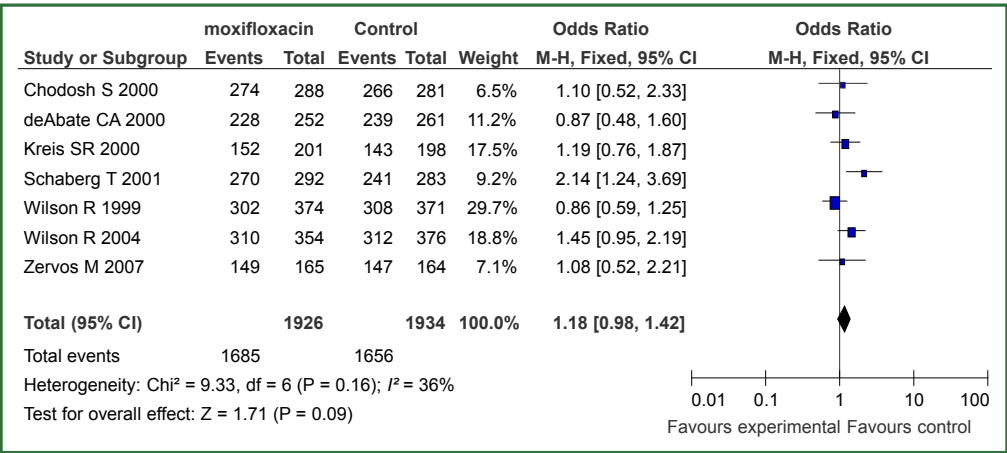| Study/year	Randomization	Blinding	Description of withdrawals and dropouts	Quality score
Chodosh et al. 2000 (11)	2	2	1	5
DeAbate et al. 2000 (12)	2	2	1	5
Grassi et al. 2000 (13)	2	0	1	2
Kreis et al. 2000 (14)	2	0	1	3
Schaberg et al. 2000 (15)	1	0	0	1
Starakis et al. 2004 (16)	1	0	1	2
Wilson et al. 1999 (17)	1	2	1	4
Wilson et al. 2004 (18)	2	2	1	5
Wilson et al. 2012 (19)	2	2	1	5
Zervos et al. 2007 (20)	1	1	1	3

Figure 2. Clinical success in the ITT patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.
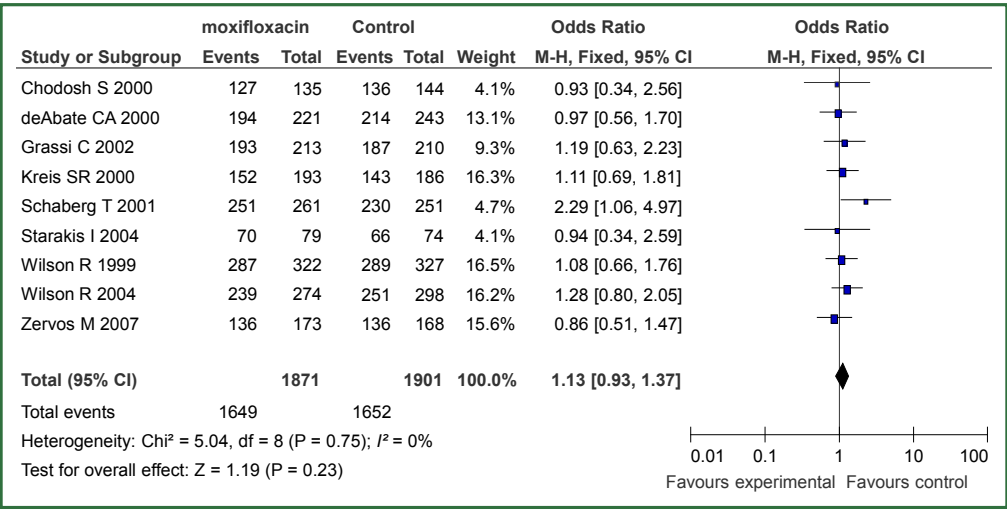
Figure 3. Clinical success in the CE patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.
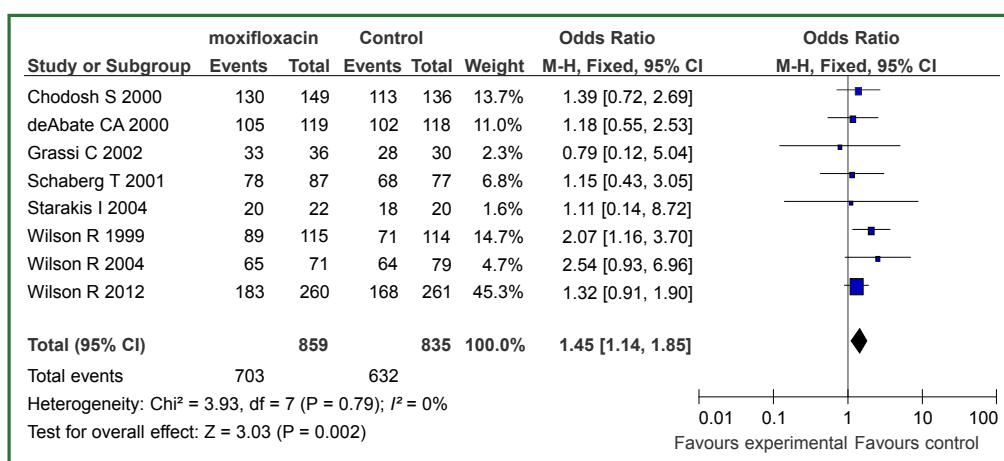
Study or Subgroup	moxifloxacin Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Chodosh S 2000	130	149	113	136	13.7%	1.39 [0.72, 2.69]	
deAbate CA 2000	105	119	102	118	11.0%	1.18 [0.55, 2.53]	
Grassi C 2002	33	36	28	30	2.3%	0.79 [0.12, 5.04]	
Schaberg T 2001	78	87	68	77	6.8%	1.15 [0.43, 3.05]	
Starakis I 2004	20	22	18	20	1.6%	1.11 [0.14, 8.72]	
Wilson R 1999	89	115	71	114	14.7%	2.07 [1.16, 3.70]	
Wilson R 2004	65	71	64	79	4.7%	2.54 [0.93, 6.96]	
Wilson R 2012	183	260	168	261	45.3%	1.32 [0.91, 1.90]	
Total (95% CI)		859		835	100.0%	1.45 [1.14, 1.85]	
Total events	703		632				

Heterogeneity: Chi² = 3.93, df = 7 (P = 0.79); I² = 0%
Test for overall effect: Z = 3.03 (P = 0.002)

0.01 0.1 1 10 100
Favours experimental Favours control

Figure 4. Bacteriological success in patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.

Study or Subgroup	moxifloxacin Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Chodosh S 2000	70	312	99	312	24.2%	0.62 [0.44, 0.89]	
deAbate CA 2000	58	283	48	283	12.0%	1.26 [0.83, 1.93]	
Grassi C 2002	22	240	11	230	3.2%	2.01 [0.95, 4.24]	
Kreis SR 2000	25	201	18	198	5.0%	1.42 [0.75, 2.70]	
Schaberg T 2001	37	292	41	283	11.4%	0.86 [0.53, 1.38]	
Starakis I 2004	8	83	9	79	2.6%	0.83 [0.30, 2.27]	
Wilson R 1999	58	374	65	371	17.4%	0.86 [0.59, 1.27]	
Wilson R 2004	25	354	18	376	5.1%	1.51 [0.81, 2.82]	
Wilson R 2012	53	677	41	675	11.9%	1.31 [0.86, 2.00]	
Zervos M 2007	23	173	26	169	7.2%	0.84 [0.46, 1.55]	
Total (95% CI)		2989		2976	100.0%	1.00 [0.86, 1.17]	
Total events	379		376				

Heterogeneity: Chi² = 17.10, df = 9 (P = 0.05); I² = 47%
Test for overall effect: Z = 0.02 (P = 0.99)

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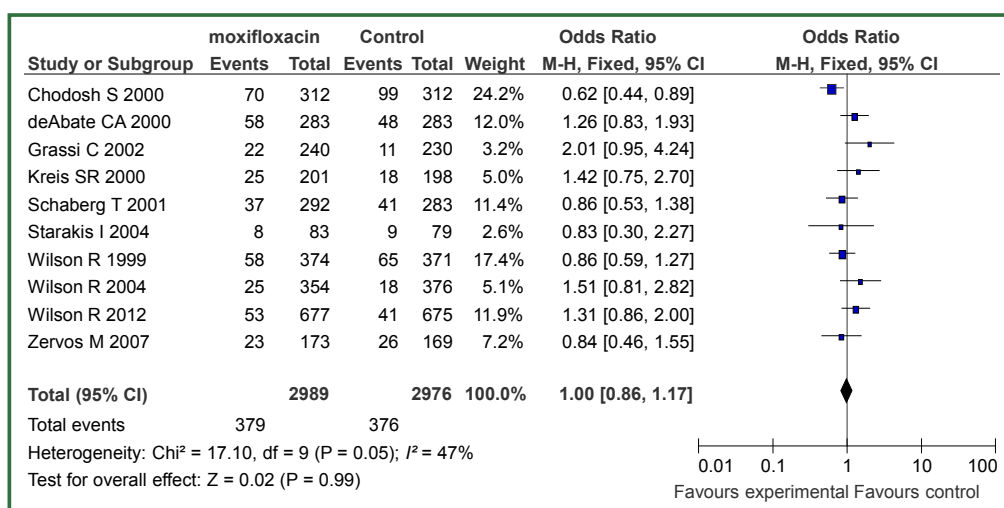Favours experimental Favours control

Figure 5. Drug-related adverse events in patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.

Adverse events

Data on adverse events possibly or probably related to the study medications were reported for all included trials. The most common adverse events included nausea, vomiting, diarrhoea, hypersensitivity, dyspnoea, urticaria and upper abdominal pain. The frequencies of any adverse event were similar for moxifloxacin versus comparator drugs (OR 1.00, 95% CI: 0.86-1.17) (Figure 5).

Publication bias

Upon visual inspection of the funnel plot for the primary outcome, we found evidence of publication bias (absence of small studies in the right lower corner in Figure 6).

Discussion

This systematic review with meta-analysis compared the efficacy and safety of moxifloxacin with that of comparator agents for AECB patients. This meta-analysis indicates that moxifloxacin was associated with similar rates of treatment success and with higher bacteriological success rates compared with comparators (Figures 2,3). The safety analysis regarding the incidence of adverse events proved no difference between the compared treatment arms.

Despite the present evidence suggests that moxifloxacin has a similar efficacy as comparator agents, several unique characteristics make it a superior choice to existing regimens in specific occasions. The results of this study are in agreement with a recent study that was not designed as an RCT. The response to
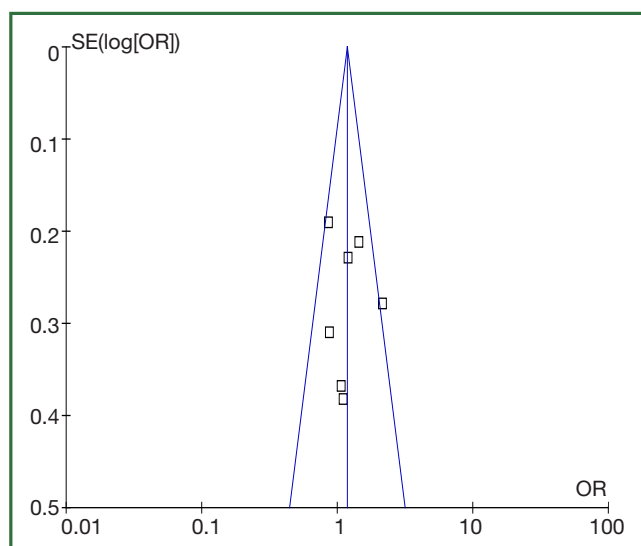
Figure 6. Funnel plot showing the possibility of a small publication bias.

moxifloxacin treatment was broadly independent of the patients' demographic and disease background. First, moxifloxacin has a broad spectrum of antimicrobial activity, ranging from aerobic to anaerobic, Gram-positive, and Gram-negative bacteria. Moreover, it has an excellent effect against drug-resistant *S. pneumoniae*, and respiratory Gramnegative pathogens, such as *H. influenzae*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, and atypical organisms (i.e., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*). Second, moxifloxacin may mitigate the emergence of resistant strains (22). Studies demonstrated a low spontaneous mutation rate for resistance to moxifloxacin, particularly for *Staphylococcus aureus* and *H. influenzae* (23,24). According to the mutant selection window hypothesis, resistant mutants are always selected at antibiotic concentrations above the minimum inhibitory concentration (MIC) but below the mutant prevention concentration (25). Studies determined that the therapeutic concentrations of moxifloxacin lay well above the MPC for *S. pneumoniae* (26). Third, the once-daily dosing of moxifloxacin may offer benefits compared with regimens that require multiple dosing or combination therapy, including patient convenience and comfort and a lower risk of medication errors. Decreasing the duration of antibiotic courses in respiratory tract infections might contribute to a decrease in these resistance rates. Similarly, the meta-analysis by El Moussaoui *et al.* demonstrated that a short course of antibiotic treatment is as effective as the traditional longer treatment in patients with mild to moderate AECB and AECOPD (27).

Pathogen eradication has been shown to correlate with improved clinical outcomes and decreased relapse rate. It also contributes to the prevention of emergence and dissemination of resistant pathogens (28,29). Although moxifloxacin provided superior bacterial eradication rates than comparator agents, few studies have demonstrated that treatment with moxifloxacin was associated with a prolonged time to recurrence (30). In the included studies, bacterial load was not determined, so it is possible that, although patients were infected with bacteria, a proportion of them would have an alternative cause of their exacerbation. If the bacterial infection is not the major driver of the clinical manifestations of AECB in all cases then it could be one explanation for the dissociation between clinical and bacteriological outcome would be expected. The present meta-analysis showed no difference between moxifloxacin and the comparator antibiotics for the eradication of *M. catarrhalis*, and *S. pneumoniae*. The number of microbiologically evaluable patients was too small to detect differences between them. For patients with AECB due to *H. influenzae*, moxifloxacin provided superior bacterial eradication rates than s other antimicrobial treatment. Moxifloxacin has excellent role in vitro activity against *H. influenzae*, that is independent of macrolide resistance mechanisms (31). The predominant bacterial pathogen implicated in AECB and AECOPD is *Haemophilus influenzae,* which is present in 50% of all bacterial exacerbations, with approximately a further one-third of isolates being either *Streptococcus pneumoniae* or *Moraxella catarrhalis*. It should be noted that the causative pathogens of AECB could not be identified in the majority of patients. Thus, correlation of clinical outcomes with bacteriologic outcomes was not possible for most patients.

In terms of safety, no difference was found between compared treatments. Adverse events are usually mild to moderate, in line with the known safety profile of moxifloxacin. A meta-analysis of clinical trial and postmarketing surveillance data for moxifloxacin identified nausea, dizziness, and diarrhea as the most frequent adverse events, which occurred at a rate similar to comparator medications (32,33).

The results of this meta-analysis should be interpreted carefully based on other considerations. First, analysis of any study should critically examine if its endpoints were adequate to demonstrate the potential benefits of the intervention being tested and were clinically relevant. Unfortunately, in the vast majority of antibiotic comparison trials in exacerbations of COPD, end-points used favor the demonstration of equivalence rather than differences among the arms. Clinical studies of antimicrobials in exacerbations of CB such as those performed in the original clinical program have been limited by factors such as inadequate information on patient condition prior to

the exacerbation and lack of long-term follow-up, as well as a lack of prospective control for steroid use, which can positively affect the outcome. Second, the ITT principle overlooks the fact that patients may not always receive all their allotted treatment. ITT analysis of noninferiority trials is not conservative, because the inclusion of patients who violate the protocol will tend to minimize differences between study arms, thereby increasing the possibility of results showing noninferiority. Thirdly, a significant proportion of the RCTs included in the meta-analysis allowed the enrolment of patients with an Anthonisen type III ABECB (mild ABECB) (11,12,14) as well as the enrollment of patients without impaired lung function (i.e., without a decrease in FEV1). It may be expected that less significant differences in the effectiveness would be found between different antibiotics. Finally, most of the studies included in the meta-analysis were conducted in the community, even though at least four studies also included hospital inpatients. However, almost all exacerbations were classified as Anthonisen type I or II, we feel some caution is necessary when applying our findings to patients with severe exacerbations who are admitted to hospital with respiratory failure.

Our analysis has several limitations. First, the majority of the RCTs included in current meta-analysis were not designed to focus on long-term outcome, such as exacerbation-free interval or frequency of exacerbations (recurrences) after the resolution of an initial episode of AECB (34). Second, COPD is a heterogenous disease, and acute exacerbations can be of varying severity, partly dependent upon the type of patients in which they occur (35). Most of the studies lack an objective definition of AECB or AECPD. The small number of studies so far does not allow for stratified analysis according to severity of COPD exacerbation. Superiority outcome clinical studies would require considerably larger sample sizes than non-inferiority studies. We should take the heterogeneity of COPD into account, particularly differences in COPD severity, exacerbation frequency and bacterial colonization. In addition, there is heterogeneity in some of the relevant aspects (the patients and comparative drugs included). The clinical effectiveness was assessed at different days in the various RCTs included in the analysis. Trials usually had a primary end point hence after end of treatment we may have missed early relapse due to inadequate treatment. Third, although we extensively searched for relevant studies using multiple databases and multiple search items, and no language restriction was placed on the search, some degree of funnel plot asymmetry suggested the possibility of publication bias. Forth, some patients concomitantly received corticosteroids therapy that could probably have had an impact on the examined outcomes. Finally, the quality of the included

studies was not consistent. Some RCTs included in our analysis had major methodological flaws (15,16). Only eight of the included trials were double-blinded. The quality of trials can affect the direction and magnitude of treatment effects when doing a meta-analysis.

Conclusions

In conclusion, despite the limitations of our meta-analysis, we conclude that moxifloxacin has clinical efficacy and microbiological treatment success rates similar to those of comparator drugs in patients with AECB. Moxifloxacin therapy may be a useful alternative to empirical treatment for AECB. Large, well-designed, randomized, multi-center trials warranted to clarify the clinical outcomes (especially long-term outcomes) of patients with AECB receiving moxifloxacin treatment.

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