Selected literature related to the RELIANCE Clinical Trial

May 2019

Table of Contents

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Azithromycin during Acute COPD Exacerbations Requiring Hospitalization (BACE): a Multicentre, Randomized, Double-blind, Placebo-controlled Trial

Running title

The BACE trial

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Summary Conflict of Interest Statements

-KV is supported as a doctoral candidate by the Flemish Government Agency for Innovation by Science and Technology (Belgium).

-MG has nothing to disclose.

-JA has nothing to disclose.

-IKD has nothing to disclose.

-JLC has received speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca, Novartis, Chiesi and GlaxoSmithKline.

-EM has, within the last 5 years, received honoraria for lectures from Boehringer-Ingelheim, Chiesi and Novartis; he is a member of advisory boards for AstraZeneca, Chiesi, Boehringer-Ingelheim and Novartis.

-HS has received consultancy fees from Boehringer-Ingelheim and GlaxoSmithKline.

-CH has received speaker and consultancy fees from Boehringer-Ingelheim, Chiesi, AstraZeneca, GlaxoSmithKline and Novartis.

-MH has nothing to disclose.

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-PJ has nothing to disclose.

-RP has nothing to disclose.

-AF has nothing to disclose.

-TL has nothing to disclose.

-AD has nothing to disclose.

-BV has nothing to disclose.

-RW is supported as a senior clinical researcher by the Fund for Scientific Research Flanders (Belgium).

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-AB's institute received consultancy fees from Boehringer-Ingelheim and UCB Pharma.

-KB's institute received consultancy fees from Boehringer-Ingelheim and UCB Pharma.

-GMV has nothing to disclose.

-TT is vice president of the European Respiratory Society (2018-2019). His institute received speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca and Chiesi.

-VN has received speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca, Novartis, MSD, GlaxoSmithKline and Chiesi.

-GGB has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, Teva, UCB Pharma and Zambon; he is a member of advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron and Teva.

-WJ is supported as a senior clinical researcher by the Fund for Scientific Research Flanders (Belgium); and has received research funding, speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca, Novartis, Chiesi and GlaxoSmithKline.

Author's contributions

The protocol was initiated by WJ, designed in collaboration with GGB and modified on the basis of input from the Consortium. The data were gathered by study personnel at each participating hospital, overseen by the local investigator. The statistical analysis plan was implemented by independent biostatisticians AB and KB. The cardiac safety assessment was performed by independent cardiologists BV and RW. All authors participated in interpreting the results. The first and final draft were written by KV and revised on the basis of input from the other authors and the Steering Committee. All the authors made the decision to submit the manuscript for publication and assume responsibility for the data, the accuracy of the analyses, and vouch for the fidelity of the study to the protocol.

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Notation of prior abstract presentation

Data have been presented at the European Respiratory Society Conference (Paris, 16 September 2018).

Online data supplement

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

ABBREVIATION LIST

AECOPD	acute exacerbation of chronic obstructive pulmonary disease
BACE	Belgian trial with azithromycin for COPD exacerbations requiring hospitalization
CAT	COPD assessment test
COPD	chronic obstructive pulmonary disease
Δ	symbol used to indicate the difference
ECG	electrocardiogram
EQ5D	European Quality of Life – 5 Dimensions questionnaire
FEV1	forced expiratory volume in 1 second
GOLD	global initiative for chronic obstructive lung disease
GP	general practitioner
HR	hazard ratio
ICS	inhaled corticosteroids
ICU	intensive care unit
LABA	long-acting ß-agonist
LAMA	long-acting muscarinic antagonist
mMRC	modified Medical Research Council questionnaire
RCT	randomized controlled trial
SH	step-up in hospital care
SSQ5	Speech, Spatial and Qualities of Hearing Scale – 5 items questionnaire
STEMI	ST elevation myocardial infarction
TI	treatment intensification
TF	treatment failure
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula

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ABSTRACT

Rationale. Azithromycin prevents acute exacerbations in COPD (AECOPD); however, its value in the treatment of AECOPD requiring hospitalization is yet to be defined.

Objective. We investigated whether a 3-month intervention with low-dose azithromycin could decrease treatment failure (TF) when initiated at hospital admission and added to standard care.

Methods. In an investigator-initiated, multi-centre, randomized, double•blind, placebo-controlled trial, patients hospitalized for an AECOPD, with a smoking history of ≥10 pack-years and ≥1 exacerbation in the previous year, were randomized (1:1) within 48-hours of admission to azithromycin or placebo. The study drug (500mg/day for 3 days) was administered on top of a standardized acute treatment of systemic corticosteroids and antibiotics, and subsequently continued for 3 months (3m) (250mg/2days). Patients were followed-up for 6m thereafter. Time-to-first event analyses evaluated the TF rate within 3m as a novel primary endpoint in the intention-to-treat population, with TF defined as the composite of treatment intensification with systemic corticosteroids and/or antibiotics (TI), step-up in hospital care or readmission for respiratory reasons (SH) or all-cause mortality.

Main results. 301 patients were randomized to azithromycin (n=147) or placebo (n=154). The TF rate within 3m was 49% in the azithromycin and 60% in the placebo group (HR=0.73; 95%CI 0.53-1.01; p=0.0526). TI, SH and mortality rates within 3m were 47% *vs* 60% (p=0.0272), 13% *vs* 28% (p=0.0024) and 2% *vs* 4% (p=0.5075), respectively. Clinical benefits were lost 6m after withdrawal.

Conclusions. 3m of azithromycin for infectious AECOPD requiring hospitalization may significantly reduce TF during the highest risk period. Prolonged treatment seems needed to maintain clinical benefits.

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AT A GLANCE SUMMARY

Scientific knowledge of the subject.

Clinical trials in stable COPD and patients with increased risk of exacerbations have proven long-term (6–12 months) continuous and intermittent use of macrolide antibiotics effective in the prevention of acute exacerbations (AECOPD). Safety concerns associated with long-term use in the general COPD population, however, require new studies to define the optimal dose, treatment duration and target population.

What this study adds to the field.

The present double-blind RCT is the first to evaluate the effect of macrolide treatment by positioning the intervention in the acute setting of a severe AECOPD requiring hospitalization, in addition to a time-limited low-dose intermittent administration to prevent relapse. Though formally negative (p=0.0526), our findings show that a low-dose azithromycin intervention, initiated at the onset of a severe AECOPD requiring hospitalization (500mg/day for 3 days) and subsequently administered for 3 months (250mg/2 days), may strongly reduce the recurrence of exacerbations, especially those leading to hospital admission and transfer to intensive care, in patients at risk. Prolonged treatment, however, seems needed to maintain clinical benefits. By providing a cross-continuum between the acute treatment phase in the hospital and ambulatory therapeutic prolongation for 3 months, the proposed intervention may help to address the highest risk period for readmission and provide a new treatment strategy for severe infectious AECOPD requiring hospitalization.

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INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) requiring hospitalization are associated with a 6% risk of in-hospital mortality. Of those who survive, 35% are likely to be readmitted within 3 months after hospital discharge (80% of which is directly related to recurrent disease or relapse), during which they face a 12% risk of all-cause mortality.[1,2] The management of AECOPD requiring hospitalization has therefore been studied extensively.[3,4] However, with the exception of non-invasive ventilation administered to patients with acute respiratory acidosis,[5] no intervention has been shown to improve the prognosis over the last 40 years.[6]

Long-term treatment with 250mg azithromycin once daily has been proven effective in the prevention of AECOPD by decreasing the exacerbation rate and increasing the inter-exacerbation interval.[7,8] Despite confirmation of efficacy with an intermittent dose (500mg three times weekly) in a restricted subgroup of frequent exacerbators,[9] safety concerns associated with long-term use in the general COPD population[10] (e.g. the induction of antibiotic resistance,[11] cardiac toxicity[12] and ototoxicity[13]) require new studies to define the optimal dose, treatment duration and target population.

Published randomized controlled trials (RCT) of azithromycin therapy in COPD have focused exclusively on stable disease with increased risk of exacerbations. To date, few RCTs are evaluating new acute interventions in patients hospitalized for a severe exacerbation, facing the highest risk period for deterioration, relapse and death. We therefore performed a large investigator-initiated RCT to evaluate whether a 3-month intervention with low-dose azithromycin, initiated at the onset of a severe AECOPD requiring hospitalization, could effectively and safely decrease treatment failure (TF) in the highest risk period during and immediately after the acute event. Time-to-first event analyses evaluated TF as a novel composite primary endpoint to capture clinically relevant short-term and long-term outcomes of our intervention. Some of the results of the study have been previously reported in the form of an abstract.[14]

METHODS

STUDY DESIGN

An investigator-initiated, multi-centre, randomized, double-blind, placebo-controlled trial was performed in 6 academic and 14 non-academic hospitals within Belgium, to investigate the effectiveness of azithromycin in the acute treatment of COPD exacerbations requiring hospitalization. Between August-2014 and April-2017, patients were randomized (1:1) to receive azithromycin or placebo on top of a standardized acute treatment of systemic corticosteroids and antibiotics (Online Supplement). Within 48-hours of hospital admission, a 3-month (or 90-day) intervention with azithromycin or matching placebo was initiated at a loading dose of 500mg once daily for 3 days (hypothesis: maximizing both acute anti-microbial and anti-inflammatory effects) and subsequently administered at a lower intermittent maintenance dose of 250mg every 2 days (hypothesis: prolonging anti-inflammatory effects). Patients were followed-up for 9 months, including 6 months after study drug withdrawal to evaluate whether potential effects of the 3-month intervention could be maintained long term (Figure 1).[15] The study consisted of 3 assessments during hospitalization of the index event: randomization (day 1), start of maintenance dose (day 4) and day of discharge (day X, at the investigator's discretion). After discharge, out-patient visits occurred at one month after discharge (day X+28), end of intervention (day 90) and end of follow-up (day 270). Telephone calls were scheduled bimonthly (day 150 and day 210) between day 90 and day 270.

Written informed consent was obtained from all participants. The study was approved by the competent authorities, the central (Commissie Medische Ethiek UZ-KU Leuven, ML10232) and local ethics committees of each participating hospital.

PATIENTS

Eligible patients were 18 years or older, had an established diagnosis of COPD (based on clinical history and a pulmonary function test), had a history of ≥1 exacerbation treated with systemic corticosteroids and/or antibiotics in the previous year, had a current or past smoking history of ≥10 pack-years, had a

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normal QT interval corrected according to Bazett's formula (QTcB; ≤450msec for male or ≤470msec for female) and were hospitalized for an AECOPD deemed infectious by the local investigator within the 48-hour screening period from hospital admission, qualifying them for the standardized acute treatment of systemic corticosteroids and antibiotics. Investigators were to rely on the available evidence obtained from routine assessments (laboratory, chest X-ray and clinical presentation) in the emergency department, as the trial protocol was embedded in a real-life hospitalization setting. The main exclusion criteria were contraindications to azithromycin, respiratory insufficiency requiring mechanical or non-invasive ventilation at the time of randomization, chronic systemic corticosteroid use (>4mg methylprednisolone/day for ≥2 months) and the use of macrolide antibiotics during ≥2 weeks preceding inclusion. Presentation of lobar pneumonia was an exclusion criterion. None of the patients were taking phosphodiesterase-4 inhibitors (not commercialized in Belgium). Full list of exclusion criteria is provided in the Online Supplement.

EFFICACY OUTCOMES

The primary endpoint was the TF rate within 90 days analyzed using time-to-first event methods, with TF defined as the composite of 3 endpoints: (1) treatment intensification (TI) with systemic corticosteroids and/or antibiotics for respiratory reasons, (2) step-up in hospital care (SH) including transfer to the intensive care unit (ICU) or readmission for respiratory reasons or (3) all-cause mortality. Date of TF was defined as the time of first occurrence of one of these events. TI and SH were further specified for the hospitalization period of the index event (day 1 to day X), and the period after discharge (day X to day 90), as outlined in Table 1. All TFs and its components were adjudicated on site by a centrally blinded investigator. Three key secondary endpoints were assessed in following hierarchical order: the number of TFs, COPD assessment test (CAT) score and total days of systemic corticosteroid use at day 90. Other secondary endpoints, including the evaluation of the composite endpoint and its 3 components 6 months after study drug withdrawal, are listed in the Online Supplement.

SAFETY OUTCOMES

Standard 12-lead resting electrocardiograms (ECG), obtained at hospital admission (baseline), day 4, day X+28 and day 90 were inspected manually. The QT interval values were corrected using Bazett's formula and verified using Fridericia's (QTcF) formula, reflecting a more accurate correction in patients with tachycardia.[16] Safety outcomes also included the assessment of (serious) adverse events, the Speech, Spatial and Qualities of Hearing Scale – 5 items (SSQ5) questionnaire[17] and spontaneous sputum samples for detection of macrolide-resistant pathogens. Details are provided in the Online Supplement.

STATISTICAL ANALYSES

The required sample size was calculated at 250 patients per group, 500 in total, to show a significant difference in the primary endpoint at a two-sided significance level of 0.05 with 80% power. Calculations were based on a survival analysis using a log-rank test assuming proportional hazards, a clinical failure within 90 days of at least 45% in the placebo arm, a 35% relative improvement with azithromycin (hazard ratio [HR]=0.65) and taking into account a maximal drop-out of 25%. Due to slow recruitment and unavailability of funds, it was decided to stop enrolment early at 301 inclusions (moment of interim safety analysis, pre-specified after 300 inclusions) and the final analysis was performed once all patients reached their 270-day follow-up.

All analyses were performed in the intention-to-treat population, the primary endpoint was also assessed in the per-protocol population, excluding patients with one or more major protocol violations (which included a standardized acute treatment which was not respected, a concomitant use of macrolide antibiotics for more than 10 days and a unverifiable compliance with regards to study drug intake). Outcomes were analyzed using time-to-event methods. TF and mortality were analyzed by Kaplan-Meier survival analysis and compared between groups using a log-rank test. TI and SH were analyzed by a Cumulative Incidence Function taking mortality as a competing risk into account and compared between groups using Gray's test. Patients without an event within 90 days were censored at day 90, early terminations at their time of withdrawal. The treatment effect was estimated by the HR, obtained from a Cox regression. The treatment effect of the secondary endpoints were estimated by

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the difference in means using the Mean Cumulative Function, the difference in expected means using a weighted Generalized Estimating Equations model and the rate ratio using a Poisson Regression model, as specified in the Statistical Analysis Plan. To control the overall Type I Familywise Error Rate of the key secondary endpoints, a serial gatekeeping method was used.

ECG data were analyzed as repeated measures of differences (Δ) compared to baseline with Bonferroni post-hoc correction for multiple testing. Other safety outcomes were compared between groups using a Chi-square or Fisher's exact test. All analyses were performed using SAS software version 9.4.

RESULTS

PATIENTS

A total of 2063 patients were screened by 15 centers within the Consortium, 301 (15%) of whom were randomized to azithromycin (n=147) or placebo (n=154). The study was completed by 118 (80%) *vs* 115 (75%) patients, respectively (Figure 2). The baseline characteristics of the 301 randomized patients are summarized in Table 2. Mean study drug adherence was 95.7% *vs* 96.2%, respectively.

PRIMARY ENDPOINT AND COMPONENTS

Within 3 months after randomization, 69 patients in the azithromycin and 86 in the placebo group experienced TF. TI, SH and mortality occurred in 66 patients *vs* 85, 18 *vs* 39 and 3 *vs* 6, respectively. The unadjusted TF rate within 3 months was 49% in the azithromycin and 60% in the placebo group (HR=0.73, 95%CI 0.53;1.01, p=0.0526) (Figure 3). The unadjusted TI, SH and mortality rates were 47% *vs* 60% (HR=0.70, 95%CI 0.51;0.97, p=0.0272), 13% *vs* 28% (HR=0.43, 95%CI 0.25;0.75, p=0.0024) and 2% *vs* 4% (HR=0.62, 95%CI 0.15;2.59, p=0.5075), respectively. Differences between treatment groups were lost 6 months after study drug withdrawal (Figure 4). Results from the per-protocol analyses were almost identical to those from the intention-to-treat analyses (Online Supplement).

SECONDARY ENDPOINTS

The effect of azithromycin on the secondary endpoints is summarized in Table 3. Within 3 months after randomization, the mean cumulative number of TFs (first key hierarchical secondary endpoint) was reduced in the azithromycin group as compared to the placebo group (Δ=-0.24, 95%CI -0.48;0.00, p=0.0395). No significant differences were found in quality of life (European Quality of Life – 5 Dimensions [EQ5D] questionnaire) or symptom assessment scores (CAT, modified Medical Research Council [mMRC] and SSQ5 questionnaires). The unadjusted rate of new exacerbations (defined as the composite of a new course of systemic corticosteroids and/or antibiotics, or hospitalization for respiratory reasons, all after the index event) within 3 months was reduced in the azithromycin as compared to the placebo group (HR=0.70, 95%CI 0.49;1.00, p=0.0497). Within 3 months after randomization, the total hospital and ICU days were reduced (rate ratio=0.76, 95%CI 0.63;0.92,

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p=0.0061 and rate ratio=0.26, 95%CI 0.15;0.47, p<0.0001, respectively). Notably, the latter remained reduced 6 months after study drug withdrawal (p<0.0001). Furthermore, the total dose of systemic corticosteroid use and total days of non-study antibiotic use were respectively higher (rate ratio=1.06, 95%CI 1.04;1.08, p<0.0001) and lower (rate ratio=0.77, 95%CI 0.68;0.86, p<0.0001) in the azithromycin as compared to the placebo group. No significant group differences were found in pre-bronchodilator forced expiratory volume in 1 second (FEV1) or number of general practitioner (GP) visits.

Upon hospital discharge, the COPD inhaled maintenance therapy in both groups was adjusted compared to hospital admission with a step-up to triple therapy (combination of inhaled corticosteroids (ICS), long-acting muscarinic antagonists (LAMA), and long-acting ß-agonists (LABA)) and step-down in ICS/LABA. Three months after randomization, a slightly greater percentage of azithromycin-treated patients received triple therapy as compared to placebo (80.9% vs 71.3%), however, no significant difference in the distribution of concurrent inhaled maintenance therapy was found (Online Supplement).

SUBGROUP ANALYSES

Eight subgroups were assessed for the primary and key secondary endpoints. We found no statistically significant interaction between the intervention and any of the subgroups (Online Supplement).

SAFETY OUTCOMES

All-cause mortality at 3 months was 2% in the azithromycin and 4% in the placebo group (p=0.5023). Mortality from respiratory and cardiovascular causes at 3 months were 0% *vs* 2% (p=0.2479) and 2% *vs* 1% (p=0.6783), respectively. No significant differences were observed in the frequency of serious adverse events or adverse events leading to study drug discontinuation. Reported gastro-intestinal adverse events occurred more frequently during the treatment period as compared to the follow-up period, however, no significant group differences were found (Online Supplement).

A total of 228 patients, 114 (50%) receiving azithromycin, had all 4 ECGs available. Heart rate at baseline was significantly higher compared to the other time points (p<0.001), with no difference between treatment groups (p=0.552). The overall mean QTcB at baseline was 427.4±21.6msec, and

400.8±21.3msec for QTcF (Δ=-26.6±12.8msec, p<0.001). Overall, neither with QTcB nor with QTcF significant QTc prolongation was observed in the azithromycin group (Online Supplement). The study medication was stopped due to prolongation of the QTcB interval >500msec or ΔQTcB>60msec in 3 patients (1%): 2 in the azithromycin group at day 4 and 1 in the placebo group at day X+28. However, when using QTcF, 2 of these patients no longer had significant QTc prolongation and only for 1 patient (receiving azithromycin) the decision to discontinue the study remained valid. No patients developed clinical serious arrhythmia.

Bacterial cultures on spontaneous sputum samples were obtained in 74% in the azithromycin and 67% in the placebo group at baseline, 37% *vs* 41% at day X, 12% *vs* 17% at day 90 and 17% *vs* 13% at day 270. At baseline, the most commonly cultured bacteria were *Haemophilus influenzae* (11%), *Streptococcus pneumoniae* (9%), *Pseudomonas aeruginosa* (4%), *Morexella catarrhalis* (4%) and *Staphylococcus aureus* (2%). While no significant differences were observed in the proportion of macrolide sensitive and macrolide resistant bacteria, a significant group difference at baseline was found for *Haemophilus influenzae* (16.5% in the azithromycin *vs* 4.9% in the placebo group, p=0.006). During follow-up, no significant group differences were found for positive sputum cultures with newly acquired pathogens, neither for the acquisition of macrolide-resistant bacteria (Online Supplement).

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DISCUSSION

The Belgian trial with Azithromycin for acute COPD Exacerbations requiring hospitalization (BACE) is the first to evaluate macrolide treatment as an acute intervention for patients hospitalized for a severe AECOPD. In this trial, the 18% reduction in TF rate within 3 months after hospital admission in the azithromycin group, as compared with the placebo group, did not meet the predetermined level of statistical significance (p=0.0526), as the trial was underpowered due to early termination for slow recruitment. While formally negative, there is a strong trend in favor of the 3-month intervention with low-dose azithromycin, significantly reducing the number of TFs, as well as the rate of TI and SH for respiratory reasons with more than 20% and 50% respectively. Although methodological heterogeneity prevents direct comparison of results, the observed risk reduction in new exacerbation rate (30%) was of similar magnitude to that in other long-term macrolide studies in COPD.[7,18] We documented a 57% risk reduction for SH (comprising transfer to the ICU during the index event and readmission for new exacerbation after discharge) over a 3 month period. This effect translated in a 24% and 74% reduction in the total hospital and ICU days respectively, with the latter remaining significantly reduced 6 months after azithromycin withdrawal. Preventing COPD readmissions following an exacerbation is an international priority aimed at slowing down disease progression and limiting health care costs.[6,19] Apart from the recently published IMPACT trial showing a 34% reduction in hospital admissions with ICS,[20] and the REACT trial showing a 24% reduction with phosphodiesterase-4 inhibitors,[21] no other evidence-based chronic intervention has demonstrated such a large potential on top of maintenance therapy with long-acting bronchodilators.[22]

Moreover, acute interventions initiated for severe AECOPD are mostly restricted to the hospitalization period and are often completed before full clinical resolution. Consequently, they may leave an active inflammatory process smoldering at the time of discharge and the patient vulnerable to relapse.[23,24] By providing a cross-continuum between the acute treatment phase in the hospital and ambulatory therapeutic prolongation for 3 months, our proposed intervention may help to address the highest risk

period for readmission and provide a new treatment strategy for severe infectious AECOPD requiring hospitalization. Future post-hoc analyses are required to elucidate the underlying mechanism by assessing the added value of positioning azithromycin in the acute setting (potentially maximizing both anti-microbial and anti-inflammatory effects) in addition to a limited prolonged administration to prevent relapse. Intriguingly, the total days of antibiotic use was significantly decreased by the intervention, whereas the total dose of systemic corticosteroid use was increased. This might indicate a shift in the type of exacerbations experienced by patients under azithromycin therapy, which could also be observed in the COLUMBUS trial data.[9] While bacterial infections and exacerbations might be prevented by azithromycin therapy,[25,26] these patients remain prone to exacerbations of different etiology which may be more refractory to standard care and requiring a higher dose of systemic corticosteroids.[27,28] It may also explain why no statistically significant differences were found in quality of life or symptom assessment scores, as assessed by the EQ5D, CAT and mMRC questionnaires.

The BACE trial is also the first to explore azithromycin withdrawal after a prolonged course in high-risk patients with COPD. Time-to-event curves of TF and TI appear to diverge up to 1 month after azithromycin withdrawal and even 3 months for SH. This observation is supported by the molecule's prominent pharmacokinetic features, i.e. a long half-life and high lung tissue concentrations following repeated administration.[29] While these findings support the BACE trial rationale for dose and treatment duration to establish and maintain therapeutic benefits, they may not exclude that a maximal effect was not yet reached under the proposed 3 month duration and a reduced dosage of 250 mg of azithromycin every other day. Clear convergence of the time-to-event curves 6 months after withdrawal demonstrates that prolonged treatment appears to be needed to sustain its clinical benefits. This pleads against our hypothesis that prolonged treatment for 3 months may sufficiently interrupt the vicious circle of inflammation to alter the phenotype of 'frequent exacerbator'. Cautioned use of intermittent treatment courses of azithromycin is therefore warranted.

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The intervention was well tolerated, with no significant differences in the frequency of (serious) adverse events. Gastrointestinal symptoms were most often reported and results were comparable to those observed in long-term studies.[30] Significant QTc prolongation necessitating study drug discontinuation is rare, particularly when excluding patients with a prolonged QTc before treatment. A prolonged QTcB at admission excluded 13% of the screened population and ECG monitoring led to treatment interruption in only 2 patients treated with azithromycin, supporting earlier findings.[31] The use of QTcF could minimize false-positive cases[16] and better justify patient access to azithromycin therapy without impairing safety. The main risk of chronic use of azithromycin is the induction of bacterial resistance.[11,32] In the trial by *Albert et al.* 81% versus 41% of colonizing pathogens in the intervention group as compared to the placebo group were resistant to macrolides.[7] A related concern is the wider spread of macrolide resistance to the general population and the potential risk of losing azithromycin as part of the first-line treatment for non-tuberculous mycobacterial infections.[33,34] Macrolide resistance was monitored, however, as induced sputum was not required per protocol, the limited number of spontaneous sputum samples did not allow for thorough evaluation of antibiotic resistance induced by azithromycin on top of a standardized acute treatment of systemic corticosteroid and antibiotics in the acute setting.

In analogy with MACE (major adverse cardiovascular events) for cardiovascular research,[35] the BACE trial provides first results on a composite endpoint to evaluate interventions during an AECOPD requiring hospitalization. In addition to reducing the required sample size in a difficult setting, the use of TF allowed for the evaluation of in-hospital outcomes, as well as the relapse rate during 3 months after discharge. Although TI during hospital admission is often neglected, it may capture important differences in the resolution of the index event. As we defined TI in a continuum of 3 months, it also incorporated transfer to the ICU, readmission and new exacerbations, as these events are unavoidably associated and often preceded with new courses of systemic corticosteroids and/or antibiotics. In fact, TI was covering 96% and 99% of the total event rate of TF over 3 months in the azithromycin and placebo

group, respectively. Future studies in this setting may therefore consider TI, which includes prolongation, up-titration or new courses of medication as a major single endpoint.

By reducing the dose and treatment duration, and by restricting the intervention to subgroups with the most unmet needs, a more favorable benefit-risk ratio can be obtained for azithromycin interventions. The potential for a significant and clinically relevant reduction in total hospital and ICU days within 3 months of hospital admission, merits further investigation in large real-life pragmatic RCTs to validate the important health economic impact of prolonged low-dose treatment in such high risk groups.

The BACE trial had several limitations – First, target enrolment was not met due to a high screen failure rate (85.4%), as well as various non-scientific and funding challenges associated with investigator-initiated clinical research, which leaves the trial underpowered. Second, due to the low inclusion rate (14.6%) the obtained results are limited in their external validity and generalizability to other populations of COPD patients. In particular, the findings do not support the extrapolation to non-infectious exacerbations. Third, the 48-hour screening period to assess the infectious nature of the index AECOPD resulted in the inclusion of AECOPD of viral and bacterial aetiology. While viral AECOPD can facilitate subsequent bacterial infections,[36] procalcitonin might have provided guidance as to which events would have required antibiotics as part of the standardized acute treatment.[37,38] As most subgroup analyses were not significant when testing for interaction, these findings provide no insight into which type of infectious exacerbation, viral or bacterial, would benefit most from the intervention. Fourth, while all TFs were carefully adjudicated by the blinded study team, judgement on the necessity of TI is subjective and was left to the physician caring for the patient. This might have introduced between-site inhomogeneity. Fifth, although patients were actively asked about hearing loss and questionnaires were regularly completed, no standard audiometry was performed. Finally, spontaneous sputum samples were obtained in less than 20% at days 90 and 270 in both groups so that no conclusions can be made on shifts in bacterial resistance.

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CONCLUSIONS

A 3-month intervention with low-dose azithromycin may effectively and safely reduce TF (i.e. TI and SH) during and immediately after hospital admission for a severe exacerbation, to overcome in COPD the highest risk period for deterioration, relapse and death. Prolonged treatment, however, appears to be needed to sustain clinical benefits. A careful and individualized approach to the selection of patients, with regards to pro-arrhythmic effects and the development of antibiotic resistance, would be recommended.

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TABLES

During hospitalization of the index event	After hospital discharge
day 1 to day X	day X to day 90
Treatment intensification for respiratory reasons (TI)	
Additional dose of systemic corticosteroids	New course of systemic corticosteroids
Prolongation of systemic corticosteroids >8 days	New course of antibiotics
Upgrade of antibiotics*	
Step-up in hospital care or readmission for respiratory reasons (SH)	
Transfer to the intensive care unit	Readmission
All-cause mortality	

Table 1 – Definition of the composite primary endpoint, treatment failure (TF)

*Change or narrowing of the initial antibiotics given as part of the standardized acute treatment during the index event – *consisting of 5 days of fixed dose systemic corticosteroids and 5 to 7 days of antibiotics* – based on proven bacterial cultures was not considered as treatment failure, but as good clinical practice.

Note: day 1: randomization; day X: day of discharge, at the investigator's discretion; day 90: end of intervention.

AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201901-0094OC

	Azithromycin (N=147)	Placebo (N=154)
Demographics		
Age – years	66 ± 9	67 ± 10
Female sex – no. (%)	66 (45)	66 (43)
Weight – kg	67 ± 20	70 ± 18
Height – m	1.66 ± 9	1.66 ± 9
BMI – kg/m²	24.5 ± 5.9	25.1 ± 6.5
Comorbidity		
Charlson comorbidity index	4 [3-5]	4 [3-5]
COPD comorbidity index	1 [0-2]	1 [1-2]
Lung disease		
mMRC dyspnea score	4 [2-4]	4 [2-4]
Pre-bronchodilator FEV1 – L	0.90 [0.69-1.23]	0.95 [0.71-1.36]
Pre-bronchodilator FEV1 – % pred.	36.0 [26.3-53.8]	38.5 [29.0-52.0]
Pre-bronchodilator FVC – L	2.26 [1.77-3.19]	2.24 [1.80-2.89]
Pre-bronchodilator FVC – % pred.	73.0 [58.3-93.8]	71.5 [56.3-88.8]
Pre-bronchodilator FEV1/FVC – %	40.3 [33.6-48.0]	45.0 [37.0-52.8]
GOLD stage – no. (%)††		
A	0 (0)	1 (1)
B	26 (18)	30 (20)
C	1 (1)	2 (1)
D	120 (82)	121 (79)
Current smoker – no. (%)	63 (43)	65 (42)
Smoking history – pack-years	44 [37-50]	43 [35-50]
Number of AECOPD in previous year – no. (%)		
1	38 (26)	51 (33)
2	41 (28)	37 (24)
3	31 (21)	19 (12)
>3	37 (25)	47 (31)
Of which number of hospitalization due to AECOPD – no. (%)		
0	64 (44)	64 (42)

1	55	(37)	58	(38)
2	15	(10)	16	(10)
3	6	(4)	6	(4)
>3	7	(5)	10	(6)
Inhaled therapy for COPD – no. (%)				
LABA	136	(93)	145	(94)
LAMA	118	(80)	123	(80)
Inhaled corticosteroids	118	(80)	123	(80)
SABA	108	(73)	109	(71)
Admission presentation				
Lower respiratory symptoms – no. (%)				
Cough	115	(78)	108	(70)
Sputum production	97	(66)	86	(56)
Sputum purulence	67	(46)	57	(37)
GP intervention prior to admission				
Systemic corticosteroids	48	(33)	37	(24)
Antibiotics	50	(34)	54	(35)
Laboratory				
C-reactive protein (mg/L)	14.2	[3.5-61.4]	21.6	[4.5-59.6]
Leucocytes (x10^9/L)	10.95	[9.00-13.89]	9.90	[8.20-13.70]
Neutrophils (x10^9/L)	8.20	[6.00-11.20]	7.70	[5.60-11.20]
Eosinophils (x10^9/L)	0.06	[0.00-0.20]	0.07	[0.00-0.20]
Standardized acute treatment				
Respected – no. (%)	134	(91)	141	(92)
Received antibiotic – no. (%)	145	(99)	152	(99)
Antibiotic group – no. (%)				
ß-lactam antibiotics	91	(62)	87	(57)
Quinolone antibiotics	61	(42)	71	(46)
Clindamycin	1	(1)	1	(1)
Macrolides	2	(1)	4	(3)
Pathogen susceptible to antibiotic † – no. (%)	136	(94)	144	(95)

Table 2 – Baseline characteristics

AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201901-0094OC

Data are presented as no. (%), mean ± SD and median [Q1-Q3 interquartile range].

Note: † Susceptibility was determined based on the need for antibiotic upgrade prior to discharge. Change or narrowing of the initial antibiotic based on proven bacterial cultures was considered good clinical practice. ††GOLD stages are not taking the current hospital admission into consideration.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease, guideline 2017; GP, general practitioner; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council questionnaire; SABA, short-acting beta-agonist.

	Visit	Azithromycin (n=147)	Placebo (n=154)	Estimator	Treatment effect (95% CI)	P-value
Primary endpoint						
Treatment failure rate †	Day 90	49.5 (41.5;58.1)	60.4 (52.4;68.5)	HR	0.73 (0.53;1.01)	0.0526
Key hierarchical secondary endpoints						
Number of treatment failures ‡	Day 90	0.79 (0.62;0.95)	1.03 (0.85;1.20)	Δ in MCF	-0.24 (-0.48;0.00)	0.0395
CAT score ¥	Day 90	17.7 (16.4;19.0)	16.9 (15.5;18.3)	Δ in means	0.35 (-1.43;2.13)	0.6970
Total days of steroid use *	Day 90	15.9 (14.9;16.9)	14.8 (13.9;15.7)	Rate ratio	1.07 (0.98;1.17)	0.1217
Other secondary endpoints						
Treatment failure rate †	Day 270	82.2 (75.2;88.2)	84.8 (78.3;90.3)	HR	0.83 (0.64;1.08)	0.1570
Number of treatment failures ‡	Day 270	2.41 (2.08;2.73)	2.54 (2.21;2.87)	Δ in MCF	-0.13 (-0.60;0.34)	0.1103
CAT score ¥	Day 270	18.3 (16.8;19.8)	18.5 (17.0;20.0)	Δ in means	-0.87 (-2.85;1.12)	0.3921
Total days of steroid use *	Day 270	27.1 (26.1;28.2)	27.2 (26.2;28.3)	Rate ratio	1.00 (0.94;1.05)	0.8817
Treatment intensification rate $	Day 90	47.4 (38.8;55.4)	59.7 (51.1;67.4)	HR	0.70 (0.51;0.96)	0.0272
	Day 270	79.2 (71.2;85.3)	84.1 (76.7;89.4)	HR	0.79 (0.61;1.02)	0.0709
Step-up in hospital care rate $	Day 90	13.2 (8.2;19.5)	27.7 (20.6;35.3)	HR	0.43 (0.25;0.75)	0.0030
	Day 270	36.5 (28.3;44.7)	45.2 (36.6;53.3)	HR	0.69 (0.48;1.01)	0.0536
Mortality rate †	Day 90	2.2 (0.7;6.5)	3.6 (1.5;8.3)	HR	0.62 (0.15;2.59)	0.5075
	Day 270	5.3 (2.6;10.8)	6.7 (3.5;12.5)	HR	0.78 (0.29;2.09)	0.6170
New exacerbation rate $	Day 90	39.6 (31.3;47.7)	51.0 (42.3;59.0)	HR	0.70 (0.49;1.00)	0.0497
	Day 270	75.1 (66.6;81.7)	79.5 (71.5;85.5)	HR	0.81 (0.62;1.06)	0.1324
Number of new exacerbations ‡	Day 90	0.57 (0.44;0.70)	0.75 (0.60;0.90)	Δ in MCF	-0.18 (-0.37;0.02)	0.0770
	Day 270	2.08 (1.80;2.36)	2.18 (1.92;2.45)	Δ in MCF	-0.10 (-0.49;0.28)	0.5997
Total dose of steroid use (mg) *	Day 90	340.2 (335.4;345.1)	321.8 (317.6;326.0)	Rate ratio	1.06 (1.04;1.08)	<0.0001
	Day 270	603.4 (598.4;608.5)	603.5 (598.4;608.6)	Rate ratio	1.00 (0.99;1.01)	0.9903
Total days of non-study antibiotics *	Day 90	10.5 (9.6;11.5)	13.7 (12.8;14.7)	Rate ratio	0.77 (0.68;0.86)	<0.0001
	Day 270	21.1 (20.2;22.1)	21.6 (20.7;22.6)	Rate ratio	0.98 (0.92;1.04)	0.4592
Total hospital days *	Day 90	10.7 (9.3;12.3)	14.0 (12.3;16.1)	Rate ratio	0.76 (0.63;0.92)	0.0061
	Day 270	22.2 (18.3;27.0)	28.5 (23.8;34.2)	Rate ratio	0.78 (0.60;1.01)	0.0631

AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201901-0094OC

Total ICU days *	Day 90	3.0 (1.8;5.1)	11.4 (9.1;14.3)	Rate ratio	0.26 (0.15;0.47)	<0.0001
	Day 270	5.1 (4.0;6.5)	11.1 (9.2;13.3)	Rate ratio	0.46 (0.34;0.63)	<0.0001
Number of GP contacts *	Day 90	2.4 (2.0;2.7)	2.6 (2.3;3.0)	Rate ratio	0.90 (0.74;1.10)	0.3119
	Day 270	6.1 (5.7;6.6)	6.6 (6.1;7.1)	Rate ratio	0.92 (0.83;1.03)	0.1511
Pre-bronchodilator FEV1 (L) ¥	Day 90	1.3 (0.9;1.7)	1.2 (1.1;1.3)	Δ in means	0.13 (-0.26;0.53)	0.5008
	Day 270	1.1 (1.0;1.2)	1.2 (1.1;1.3)	Δ in means	-0.09 (-0.23;0.05)	0.1933
mMRC score ¥	Day 90	3.1 (3.0;3.3)	3.2 (3.0;3.4)	Δ in means	-0.08 (-0.33;0.17)	0.5389
	Day 270	3.3 (3.2;3.5)	3.2 (3.0;3.4)	Δ in means	0.08 (-0.20;0.35)	0.5886
EQ5D score ¥	Day 90	61.6 (58.3;65.0)	61.2 (57.7;64.6)	Δ in means	0.34 (-4.28;4.97)	0.8842
	Day 270	57.3 (53.7;60.9)	60.2 (56.3;64.1)	Δ in means	-2.73 (-7.86;2.40)	0.2967
SSQ5 score ¥	Day 90	8.1 (7.8;8.4)	7.9 (7.6;8.2)	Δ in means	0.18 (-0.13;0.49)	0.2559
	Day 270	8.2 (7.8;8.5)	8.0 (7.7;8.3)	Δ in means	0.20 (-0.12;0.52)	0.2140

Table 3 – Primary, key hierarchical and other secondary endpoints in the intention-to-treat population

Data are presented as follows: †Event rate (95% CI) obtained using Kaplan-Meier methodology. Groups were compared using a log-rank test. Treatment effect presented as hazard ratio (HR). ‡Mean Cumulative Function (MCF) (95% CI). Groups were compared using a log-rank test for MCFs. Treatment effect presented as difference in MCF. ¥Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate. Groups were compared using GEE by a Chi-squared test. Treatment effect presented as difference in expected means. *Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset. Treatment effect presented as rate ratio. $Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk. Groups were compared using Gray's test. Treatment effect presented as HR. New exacerbation is defined as the composite of TI and SH for respiratory reasons after the index event.

Abbreviations: CAT, COPD assessment test; Δ: symbol indicating difference; FEV1, forced expiratory volume in 1 second; GP, general practitioner; ICU, intensive care unit; MCF, mean cumulative function; mMRC, modified Medical Research Council questionnaire; EQ5D, European Quality of Life – 5 dimensions questionnaire; SSQ5, the Speech, Spatial and Qualities of Hearing Scale – 5 items questionnaire.

Note: day 90: end of intervention; day 270: end of follow-up.

FIGURES

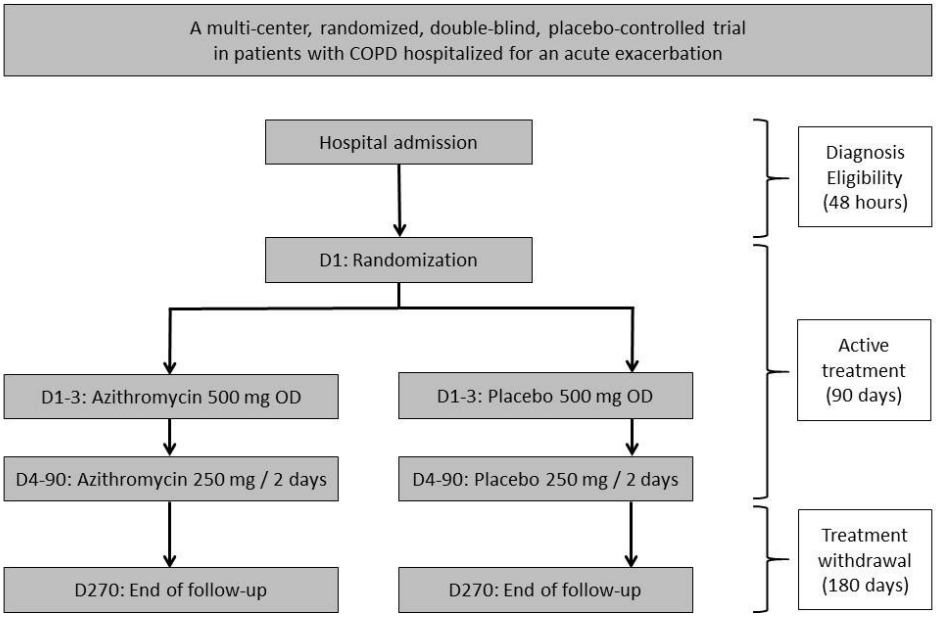

Figure 1 – The BACE trial study design.

Abbreviations: BACE, the Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization; COPD, chronic obstructive pulmonary disease; D1, day 1; D1-3, days 1-3; D4-90, days 4-90; D270, days 270; OD, once a day.

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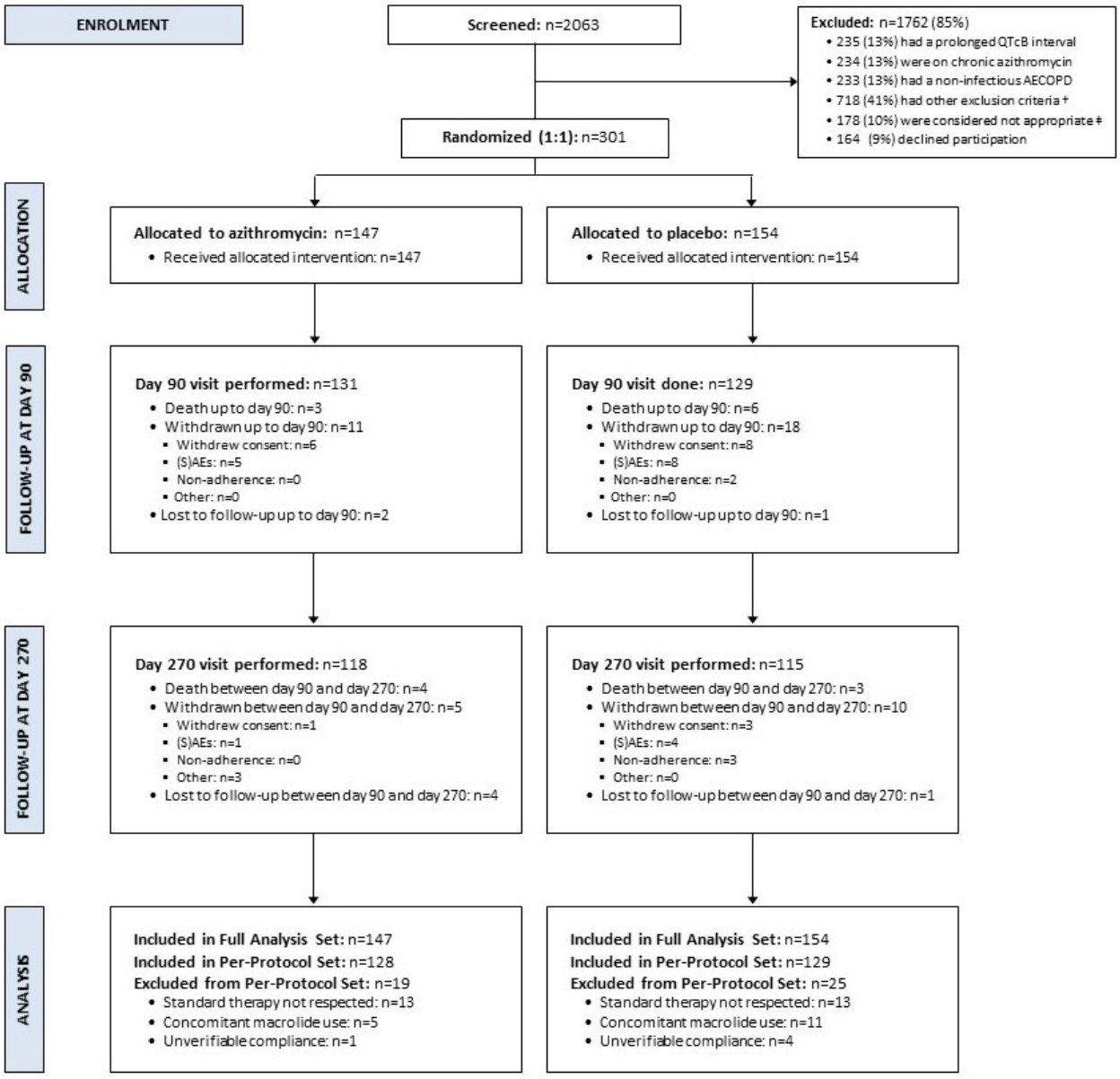

Figure 2 – Enrolment, allocation, follow-up and analysis of the trial participants.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; (S)AE, (serious) adverse event; QTcB, QT interval corrected according to Bazett's formula.

Note: † Exclusion based on ≥1 of the exclusion criteria, with the exception of a prolonged QTcB, a chronic azithromycin intake and a non-infectious AECOPD; ‡ exclusion based on criteria limiting the ability of the patient to participate in the study (e.g. comorbidities, social circumstances, etc.); day 90, end of intervention; day 270, end of follow-up.

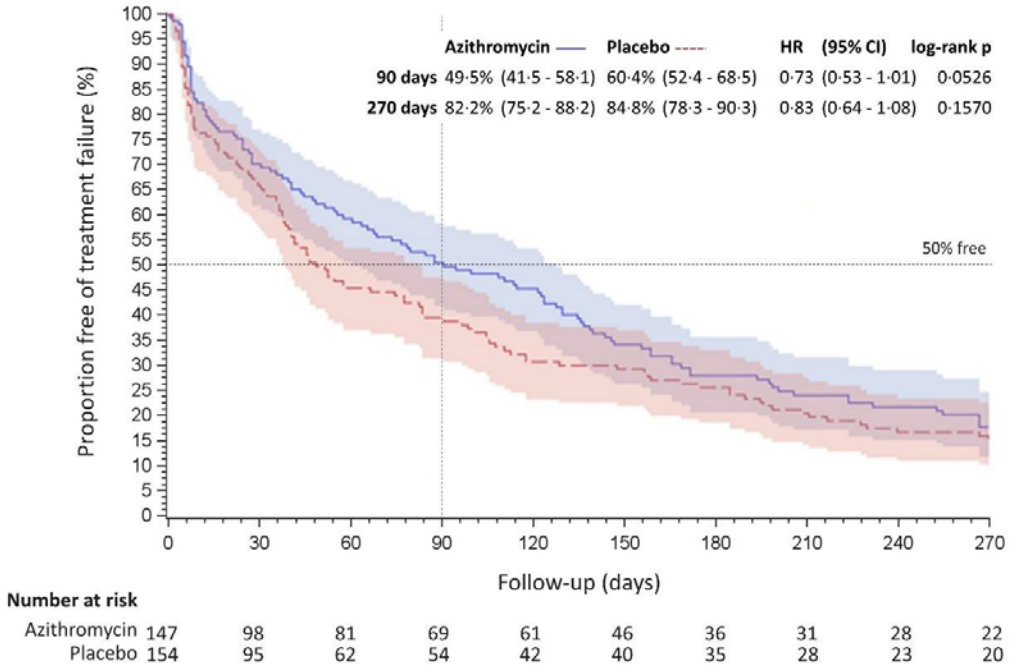

Figure 3 – Primary composite endpoint, treatment failure rate.

Percentage of patients free from treatment failure during 9 months (or 270 days) of follow-up since randomization, according to the study group. Participants who did not have an event within 270 days as well as early terminations were censored, respectively at day 270 and the time of termination.

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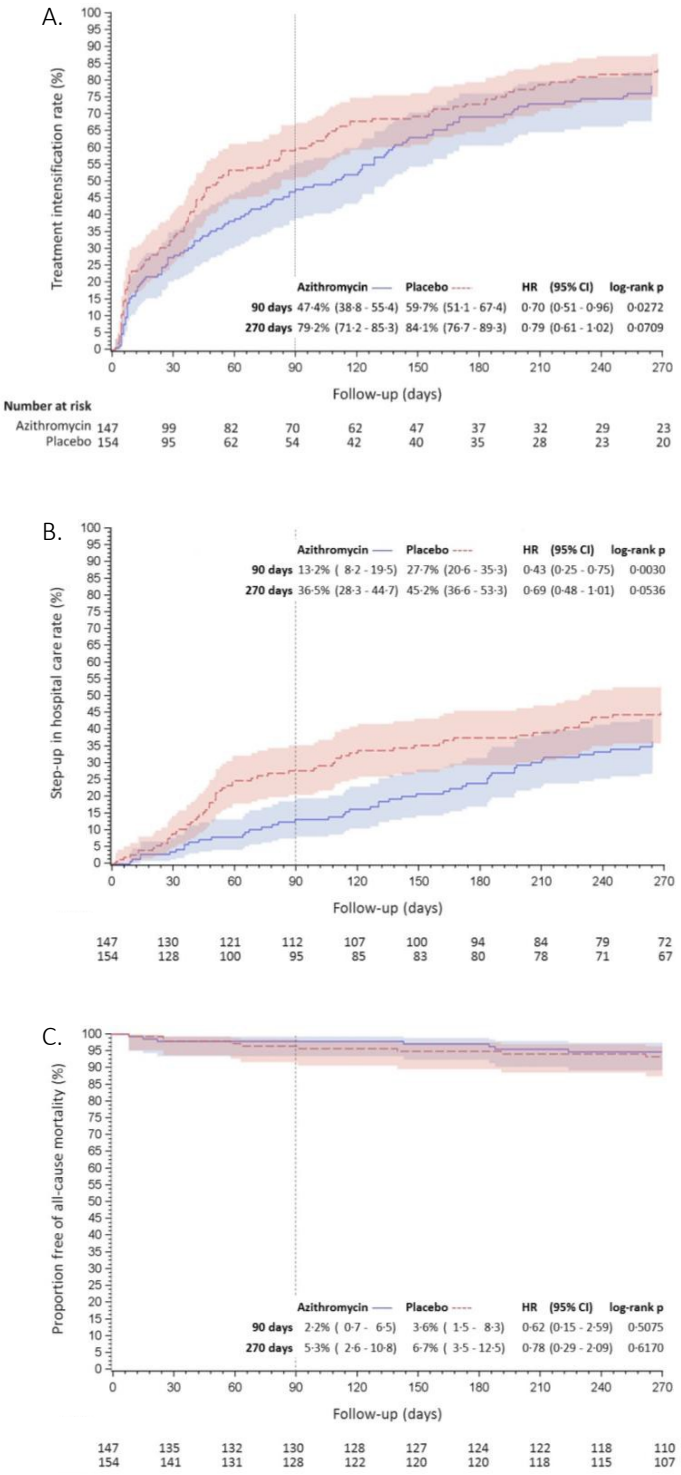

Figure 4 – The three components of treatment failure.

Percentage of patients requiring (A) treatment intensification for respiratory reasons, (B) step-up in hospital care for respiratory reasons and (C) percentage free from mortality during 9 months (or 270 days) of follow-up since randomization, according to the study group. Participants who did not have an event within 270 days as well as early terminations were censored, respectively at day 270 and the time of termination.

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ONLINE DATA SUPPLEMENT

Supplement to:
Vermeersch K, Gabrovska M, Aumann J, et al.
Azithromycin during Acute COPD Exacerbations Requiring Hospitalization (BACE): a Multicentre, Randomized, Double-blind, Placebo-controlled Trial

This supplement contains the following items:

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I. BACE TRIAL CONSORTIUM

1. AUTHOR'S CONTRIBUTIONS

The protocol was initiated by WJ, designed in collaboration with GGB and modified on the basis of input from the Consortium. The data were gathered by study personnel at each participating hospital, overseen by the local investigator. The statistical analysis plan was implemented by independent biostatisticians AB and KB. The cardiac safety assessment was performed by independent cardiologists BV and RW. All authors participated in interpreting the results. The first and final draft were written by KV and revised on the basis of input from the other authors and the Steering Committee. All the authors made the decision to submit the manuscript for publication and assume responsibility for the data, the accuracy of the analyses, and vouch for the fidelity of the study to the protocol.

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AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201901-0094OC

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II. SUPPLEMENTARY DATA

1. Methods:

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Table E1. Standardized treatment for an acute COPD exacerbation requiring hospitalization

Therapy	Specifications
Systemic corticosteroids	Methylprednisolone 40 mg IV or 32 mg PO OD for 5 days (switch IV to PO as soon as possible)
Antibiotics	
First choice:	Amoxi-Clavulanate 1 g IV QID or 2 g PO BID for 7 days (or alternative regimen of 1 g IV QID or 875/125 mg PO TID for 7 days)
Alternatives: In case of:	Moxifloxacin 400 mg IV or 400 mg PO OD for 5 days - Intolerance or allergy to Amoxi-Clavulanate - Clinical failure on GP-initiated Amoxi-Clavulanate treatment
In case of:	Anti-Pseudomonas antibiotics - Bronchiectasis - History of positive cultures for Pseudomonas - High risk of Pseudomonas - Clinical failure on GP-initiated treatment
Short-acting bronchodilators	Via inhalation
Respiratory support	Oxygen Non-invasive ventilation[a] Mechanical ventilation[a]

Note: [a]Considered as exclusion criteria if needed on moment of randomization.
Abbreviations: COPD, chronic obstructive pulmonary disease; IV, intravenous; PO, per os; OD, once a day; QID, 4 times a day; BID, 2 times a day; GP, general practitioner

Table E2. Full list of exclusion criteria

	Exclusion criteria
1	Mechanical or non-invasive ventilation at the moment of randomization
2	Prolonged QT interval on ECG: QTcB >450 msec for male or >470 msec for female
3	History of life-threatening arrhythmias
4	Myocardial infarction (NSTEMI or STEMI) less than 6 weeks before randomization
5	Unstable angina pectoris or acute myocardial infarction (NSTEMI or STEMI) at admission
6	Concomitant use of a drug with high risk for QT prolongation and *Torsade de Pointes* (amiodarone, flecainide, procainamide, sotalol, droperidol, haldol, citalopram, other macrolides)
7	Documented uncorrected severe hypokalemia (K^+ <3.0 mmol/L) or hypomagnesemia (Mg^{2+} <0.5 mmol/L)
8	Chronic systemic corticosteroid use (>4 mg methylprednisolone/day for ≥2 months)
9	Use of macrolides during at least 2 weeks preceding inclusion
10	Allergy to macrolides
11	Active cancer treatment
12	Life expectancy <3 months
13	Pregnant or breast-feeding subjects. Woman of childbearing potential must have a pregnancy test performed and a negative result must be documented before starting the treatment.

Abbreviations: ECG, electrocardiogram; NSTEMI, non-ST elevation myocardial infarction; QTcB, QT interval corrected according to Bazett's formula; STEMI, ST elevation myocardial infarction

AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201901-0094OC

Full list of secondary endpoints

Key hierarchical secondary endpoints were the number of treatment failures (TF) at day 90, the COPD assessment test (CAT) score at day 90 and total days of systemic corticosteroid use at day 90. Other secondary endpoints were the key secondary endpoints at day 270 and endpoints assessed at day 90 and day 270 including time-to-TF, time-to-first treatment intensification (TI), time-to-first step-up in hospital care (SH), time-to-death, time-to-new exacerbation (with new exacerbation defined as the composite of TI and SH after the index event), number of new exacerbations, total dose and total days of systemic corticosteroid use, total days of non-study antibiotic use, total days of hospitalization, total days of intensive care, forced expiratory volume in 1 second (FEV1), quality of life (European Quality of Life – 5 Dimensions [EQ5D] questionnaire) and symptom assessments (CAT, modified Medical Research Council [mMRC] – breathlessness questionnaire and the Speech, Spatial and Qualities of Hearing Scale – 5-items [SSQ5] questionnaire), number of general practitioner (GP) visits and average costs of hospitalization.

Table E3. Overview of study assessments

Assessment	Visit								
	Screening	**Randomization**	**Switch to maintenance dose**	**Day of discharge**	**Control visit 1: 1 month after discharge**	**Control visit 2: End of intervention**	**Telephone call 1**	**Telephone call 2**	**Control visit 3: End of follow-up**
	(48 hours)	(D1, within 48h after hospital admission)	(D4, +max 72h*)	(DX, at investigator's discretion)	(DX+28, +14 day window)	(D90, allowed from day 86 until day 150)	(D150, ±7 day window)	(D210, ±7 day window)	(D270, +14 day window)
Chest X-ray	X								
ECG[b]	X		X		X[a]	X[a]			(X[a])
Arterial blood gas	X								
Laboratory[c]	X		X						
Spontaneous sputum sample[d]	X			X[a]		X[a]			X[a]
Pre- & post-bronchodilator spirometry				X		X			X
Eligibility + informed consent	X								
Anamnesis + medical history		X							
Current respiratory medication		X		X		X			X
Vital parameters	X	X	X	X		X			X
mMRC + CAT questionnaire		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
EQ5D questionnaire		X[a]		X[a]		X[a]			X[a]
SSQ5D questionnaire		X[a]		X[a]		X[a]			X[a]
PROactive sub-study[e]				(X[a])		(X[a])			(X[a])
Study drug intake		X	X	X	X	X			
Check therapy adherence			X	X	X	X	X	X	X
Check prim./sec. endpoints			X	X	X	X	X	X	X
Record (serious) adverse events			X	X	X	X	X	X	X
Diary instruction + overview				X	X	X	X	X	X

Notes: *With exception of starting the maintenance dose; [a]Test performed in addition to clinical routine; [b]ECG only to be performed at D270 if prolonged QT interval, severe arrhythmia's or severe conductance disturbances were present on ECG of D90; [c]Screening laboratory: *hemoglobin, hematocrit, total white blood cell count and differentiation, platelets, creatinine, ureum, Na^+, K^+, Cl^-, $HCO3^-$, Mg^{2+}, AST, ALT, LDH, glucose, CRP, Ths-troponine;* D4 laboratory: *total white blood cell count and differentiation, Na^+, K^+, Cl^-, $HCO3^-$, Mg^{2+}, Ths-troponine, 25-hydroxyvitamin D, total IgE, specific Aspergillus fumigatus IgE and IgG (ImmunoCAP);* [d]If sputum sample is available, bacterial culture and antibiogram including macrolides to be performed; [e]Dynaport© to be worn for 7 days and questionnaire to be completed on day 8 only if patients consented to participation in the PROactive sub-study.

Abbreviations: ECG, electrocardiogram; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; EQ5D, European Quality of Life – 5 Dimensions; SSQ5, Speech, Spatial and Qualities of hearing scale – 5 items.

AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201901-0094OC

II. SUPPLEMENTARY DATA

2. RESULTS

Table E4. Primary, key hierarchical and other secondary endpoints in the per-protocol population

	Visit	Azithromycin (n=147)	Placebo (n=154)	Estimator	Treatment effect (95% CI)	P-value
Primary endpoint						
Treatment failure rate †	Day 90	49.0 (40.5;58.3)	59.4 (50.8;68.2)	HR	0.73 (0.52;1.03)	0.0740
Key hierarchical secondary endpoints						
Number of treatment failures ‡	Day 90	0.78 (0.60;0.96)	0.96 (0.78;1.13)	Δ in MCF	-0.17 (-0.42;0.08)	0.0950
CAT score ¥	Day 90	17.5 (16.1;18.8)	16.7 (15.2;18.2)	Δ in means	0.63 (-1.22;2.48)	0.5033
Total days of steroid use *	Day 90	14.8 (13.8;15.9)	13.9 (13.0;14.9)	Rate ratio	1.07 (0.96;1.18)	0.2124
Other secondary endpoints						
Treatment failure rate †	Day 270	81.5 (73.9;88.0)	83.3 (76.0;89.4)	HR	0.86 (0.65;1.14)	0.2880
Number of treatment failures ‡	Day 270	2.43 (2.06;2.79)	2.41 (2.07;2.75)	Δ in MCF	0.02 (-0.48;0.51)	0.4131
CAT score ¥	Day 270	18.4 (16.8;19.9)	18.7 (17.0;20.3)	Δ in means	-0.62 (-2.74;1.50)	0.5681
Total days of steroid use *	Day 270	27.1 (26.1;28.2)	27.2 (26.2;28.3)	Rate ratio	1.00 (0.94;1.05)	0.8817
Treatment intensification rate $	Day 90	46.6 (37.4;55.2)	58.6 (49.1;66.8)	HR	0.69 (0.49;0.98)	0.0377
	Day 270	79.0 (70.2;85.4)	82.5 (74.2;88.3)	HR	0.82 (0.62;1.08)	0.1601
Step-up in hospital care rate $	Day 90	12.9 (7.5;19.6)	28.4 (20.6;36.7)	HR	0.40 (0.22;0.74)	0.0033
	Day 270	36.2 (27.4;45.1)	43.3 (34.2;52.1)	HR	0.71 (0.47;1.07)	0.0979
Mortality rate †	Day 90	1.7 (0.4;6.5)	2.5 (0.8;7.4)	HR	0.68 (0.11;4.07)	0.6704
	Day 270	4.4 (1.8;10.2)	5.2 (2.4;11.3)	HR	0.82 (0.25;2.69)	0.7441
New exacerbation rate $	Day 90	40.0 (31.1;48.8)	48.8 (39.5;57.5)	HR	0.76 (0.52;1.11)	0.1528
	Day 270	75.9 (66.7;82.8)	77.8 (68.9;84.4)	HR	0.89 (0.66;1.19)	0.4130
Number of new exacerbations ‡	Day 90	0.60 (0.45;0.75)	0.68 (0.54;0.81)	Δ in MCF	-0.08 (-0.28;0.13)	0.4669
	Day 270	2.17 (1.82;2.52)	2.05 (1.72;2.37)	Δ in MCF	0.12 (-0.35;0.60)	0.6188
Total dose of steroid use (mg) *	Day 90	340.2 (335.4;345.1)	321.8 (317.6;326.0)	Rate ratio	1.06 (1.04;1.08)	<0.0001
	Day 270	603.4 (598.4;608.5)	603.5 (598.4;608.6)	Rate ratio	1.00 (0.99;1.01)	0.9903
Total days of non-study antibiotics *	Day 90	10.5 (9.6;11.5)	13.7 (12.8;14.7)	Rate ratio	0.77 (0.68;0.86)	<0.0001
	Day 270	21.1 (20.2;22.1)	21.6 (20.7;22.6)	Rate ratio	0.98 (0.92;1.04)	0.4592
Total hospital days *	Day 90	10.6 (9.1;12.3)	13.6 (11.8;15.8)	Rate ratio	0.78 (0.63;0.96)	0.0179
	Day 270	22.7 (18.5;27.9)	26.1 (21.4;31.7)	Rate ratio	0.87 (0.66;1.15)	0.3350
Total ICU days *	Day 90	3.0 (1.8;5.1)	11.9 (9.3;15.1)	Rate ratio	0.25 (0.14;0.46)	<0.0001
	Day 270	5.1 (4.0;6.5)	10.0 (8.1;12.1)	Rate ratio	0.51 (0.37;0.70)	<0.0001
Number of GP contacts *	Day 90	2.4 (2.0;2.7)	2.6 (2.3;3.0)	Rate ratio	0.90 (0.74;1.10)	0.3119
	Day 270	6.1 (5.7;6.6)	6.6 (6.1;7.1)	Rate ratio	0.92 (0.83;1.03)	0.1511
Pre-bronchodilator FEV1 (L) ¥	Day 90	1.3 (0.9;1.7)	1.2 (1.1;1.3)	Δ in means	0.11 (-0.34;0.56)	0.6262
	Day 270	1.1 (1.0;1.2)	1.2 (1.1;1.3)	Δ in means	-0.11 (-0.24;0.03)	0.1378
mMRC score ¥	Day 90	3.1 (2.9;3.3)	3.1 (2.9;3.3)	Δ in means	-0.07 (-0.35;0.20)	0.5975
	Day 270	3.4 (3.2;3.6)	3.2 (3.0;3.4)	Δ in means	0.10 (-0.19;0.40)	0.4989
EQ5D score ¥	Day 90	61.5 (57.9;65.0)	62.0 (58.3;65.7)	Δ in means	-0.65 (-5.52;4.23)	0.7951
	Day 270	56.0 (52.3;59.8)	60.9 (56.6;65.2)	Δ in means	-4.51 (-9.93;0.91)	0.1028
SSQ5 score ¥	Day 90	8.0 (7.7;8.3)	7.9 (7.6;8.2)	Δ in means	0.12 (-0.22;0.46)	0.4819
	Day 270	8.2 (7.8;8.5)	8.0 (7.7;8.3)	Δ in means	0.19 (-0.15;0.53)	0.2794

Data are presented as follows: †Event rate (95% CI) obtained using Kaplan-Meier methodology. Groups were compared using a log-rank test. Treatment effect presented as hazard ratio (HR). ‡Mean Cumulative Function (MCF) (95% CI). Groups were compared using a log-rank test for MCFs. Treatment effect presented as difference in MCF. ¥Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate. Groups were compared using GEE by a Chi-squared test. Treatment effect presented as difference in expected means. *Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset. Treatment effect presented as rate ratio. $Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk. Groups were compared using Gray's test. Treatment effect presented as HR. New exacerbation is defined as the composite of TI and SH for respiratory reasons after the index event.

Abbreviations: CAT, COPD assessment test; Δ: symbol indicating difference; FEV1, forced expiratory volume in 1 second; GP, general practitioner; ICU, intensive care unit; MCF, mean cumulative function; mMRC, modified Medical Research Council questionnaire; EQ5D, European Quality of Life – 5 dimensions questionnaire; SSQ5, the Speech, Spatial and Qualities of Hearing Scale – 5 items questionnaire.

Note: day 90: end of intervention; day 270: end of follow-up.

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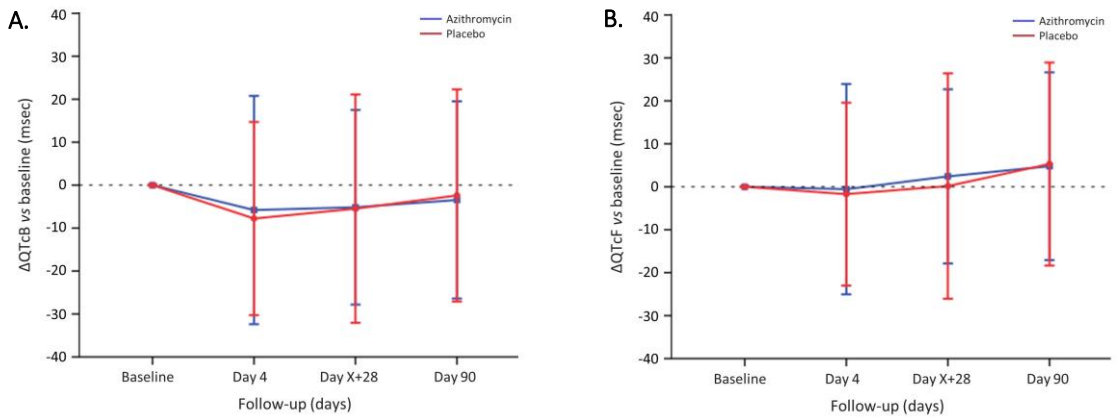

Figure E1. Effect of the 3-month intervention with low-dose azithromycin on the QT interval
Data are presented as mean QTc differences (Δ) compared to baseline with SD.
No significant QTc prolongation was observed in the azithromycin group, neither when QT correction was performed with (A) Bazett's formula (QTcB), nor with (B) Fridericia's formula (QTcF). With QTcB: Δday4= -5.8±26.6msec, ΔdayX+28= -5.2±22.7msec, Δday90= -3.5±23.0msec (p=0.154); and with QTcF: Δday4= -0.6±24.5msec, ΔdayX+28= 2.5±20.3msec, Δday90= 4.8±21.8msec (p=0.142).
Note: baseline: hospital admission; day X: day of discharge, at the investigator's discretion; day 90: end of intervention; day 270: end of follow-up.

Table E5. Overview of inhaled therapy for COPD throughout the study

		Baseline	Day X	Day 90	Day 270
	Azithromycin	n=147	n=143	n=131	n=118
	Placebo	n=154	n=150	n=129	n=115
None	Azi.	5 (3.4)	1 (0.7)	0 (0)	0 (0)
	Plac.	5 (3.2)	0 (0)	0 (0)	2 (1.7)
ICS only	Azi.	4 (2.7)	2 (1.4)	1 (0.8)	1 (0.8)
	Plac.	0 (0)	0 (0)	0 (0)	0 (0)
LAMA only	Azi.	2 (1.4)	2 (1.4)	2 (1.5)	3 (2.5)
	Plac.	3 (1.9)	5 (3.3)	6 (4.7)	3 (2.6)
LABA only	Azi.	5 (3.4)	4 (2.8)	2 (1.5)	2 (1.7)
	Plac.	5 (3.2)	4 (2.7)	3 (2.3)	4 (3.5)
ICS LABA	Azi.	15 (10.2)	7 (4.9)	3 (2.3)	7 (5.9)
	Plac.	21 (13.6)	10 (6.7)	8 (6.2)	5 (4.3)
ICS LAMA	Azi.	0 (0)	0 (0)	2 (1.5)	2 (1.7)
	Plac.	1 (0.6)	0 (0)	1 (0.8)	0 (0)
LAMA LABA	Azi.	17 (11.6)	18 (12.6)	15 (11.5)	13 (11.0)
	Plac.	18 (11.7)	23 (15.3)	19 (14.7)	15 (13.0)
ICS LAMA LABA	Azi.	99 (67.3)	109 (76.2)	106 (80.9)	90 (76.3)
	Plac.	101 (65.6)	108 (72.0)	92 (71.3)	86 (74.8)
	p-value	0.529	0.510	0.298	0.517

Data are presented as number of patients on inhaled therapy for COPD at the given time point (no. (%)).

Abbreviations: LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist

Note: baseline: hospital admission; day X: day of discharge, at the investigator's discretion; day 90: end of intervention; day 270: end of follow-up.

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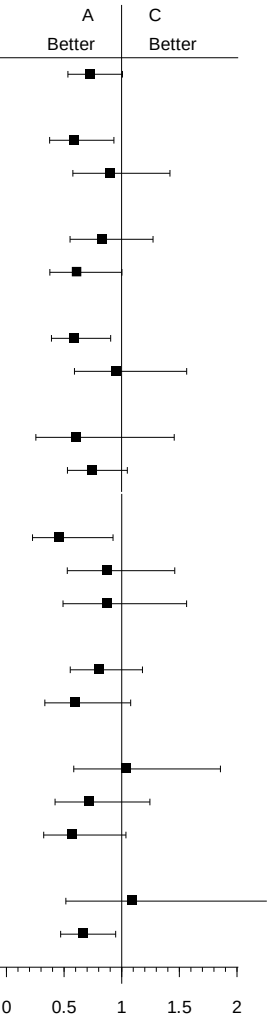
Table E6. Subgroup analyses of the primary endpoint, treatment failure rate within 90 days, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 49.5% (41.5%; 58.1%)	[154] 60.4% (52.4%; 68.5%)	0.73 (0.53; 1.01)	0.0557
Age (Interaction: p = 0.1934)				
<= 65 years	[71] 45.1% (34.1%; 57.8%)	[86] 62.3% (51.6%; 73.0%)	0.59 (0.38; 0.93)	0.0240
> 65 years	[76] 53.5% (42.5%; 65.2%)	[68] 58.2% (46.5%; 70.4%)	0.91 (0.58; 1.42)	0.6648
Gender (Interaction: p = 0.3441)				
Male	[81] 52.8% (42.2%; 64.2%)	[88] 59.0% (48.5%; 69.8%)	0.84 (0.55; 1.27)	0.4089
Female	[66] 45.4% (33.9%; 58.6%)	[66] 62.3% (50.3%; 74.4%)	0.62 (0.38; 1.00)	0.0514
Smoking (Interaction: p = 0.1434)				
Non-Smoker	[84] 47.7% (37.4%; 59.2%)	[89] 64.7% (54.2%; 75.0%)	0.60 (0.39; 0.91)	0.0153
Smoker	[63] 51.8% (39.9%; 65.0%)	[65] 54.9% (43.1%; 67.6%)	0.96 (0.59; 1.56)	0.8749
GOLD (Interaction: p = 0.6748)				
A,B	[26] 33.0% (18.0%; 55.3%)	[31] 47.8% (31.6%; 67.2%)	0.61 (0.26; 1.46)	0.2663
C,D	[121] 53.0% (44.2%; 62.3%)	[123] 63.5% (54.7%; 72.4%)	0.75 (0.53; 1.05)	0.0927
Former GOLD (Interaction: p = 0.2812)				
I, II	[36] 33.3% (20.5%; 51.2%)	[42] 55.5% (40.9%; 71.2%)	0.46 (0.23; 0.92)	0.0294
III	[55] 51.1% (38.5%; 65.1%)	[59] 57.5% (45.1%; 70.5%)	0.88 (0.53; 1.46)	0.6158
IV	[38] 58.6% (43.6%; 74.4%)	[39] 68.2% (52.7%; 82.6%)	0.88 (0.49; 1.56)	0.6532
CRP at Screening (Interaction: p = 0.4008)				
Low CRP	[103] 50.9% (41.5%; 61.1%)	[104] 59.0% (49.4%; 68.8%)	0.81 (0.55; 1.18)	0.2701
High CRP	[44] 45.9% (32.2%; 62.3%)	[49] 62.8% (48.5%; 77.1%)	0.60 (0.33; 1.08)	0.0872
Anthonisen (Interaction: p = 0.3664)				
I	[53] 52.8% (40.0%; 66.9%)	[43] 50.2% (35.9%; 66.5%)	1.04 (0.58; 1.86)	0.8914
II	[46] 53.2% (39.6%; 68.2%)	[45] 68.5% (54.4%; 81.8%)	0.72 (0.42; 1.24)	0.2428
III	[43] 43.8% (29.9%; 60.8%)	[62] 60.2% (47.6%; 73.0%)	0.58 (0.32; 1.04)	0.0659
ICS Use (Interaction: p = 0.2423)				
No	[29] 49.4% (32.9%; 68.8%)	[31] 44.6% (28.8%; 64.1%)	1.10 (0.52; 2.33)	0.8109
Yes	[118] 49.6% (40.7%; 59.2%)	[123] 64.6% (55.7%; 73.4%)	0.67 (0.47; 0.95)	0.0237

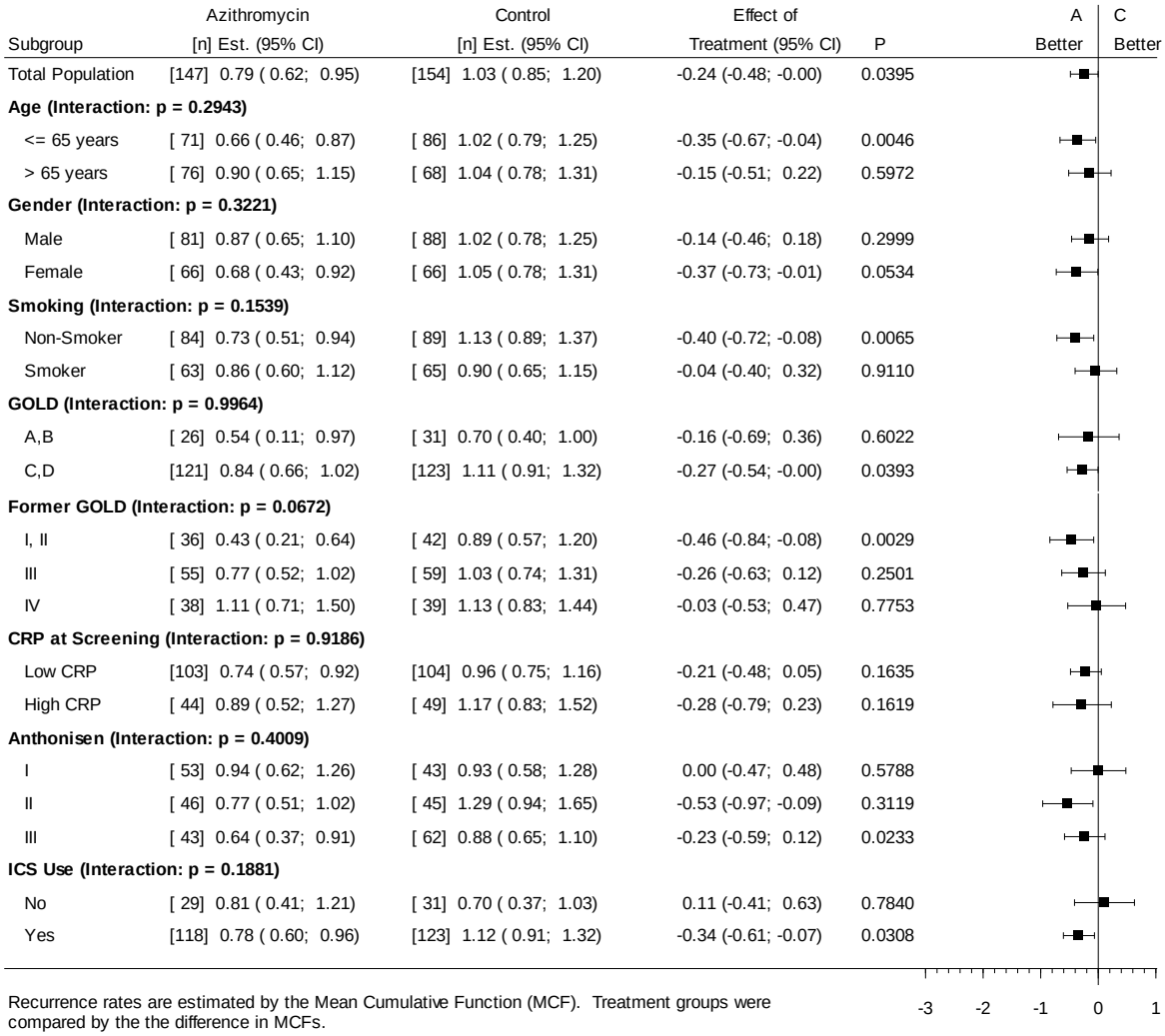


Event rates in the two groups were estimated using Kaplan-Meier methodology. Treatment Effect is a hazard ratio obtained using a Cox regression that included a factor for randomised treatment, subgroup and their interaction.

NC = Not Calculated due to an insufficient number of patients in some groups.

Table E7. Subgroup analyses of the key hierarchical secondary endpoint, number of treatment failures within 90 days, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 0.79 (0.62; 0.95)	[154] 1.03 (0.85; 1.20)	-0.24 (-0.48; -0.00)	0.0395
Age (Interaction: p = 0.2943)				
<= 65 years	[71] 0.66 (0.46; 0.87)	[86] 1.02 (0.79; 1.25)	-0.35 (-0.67; -0.04)	0.0046
> 65 years	[76] 0.90 (0.65; 1.15)	[68] 1.04 (0.78; 1.31)	-0.15 (-0.51; 0.22)	0.5972
Gender (Interaction: p = 0.3221)				
Male	[81] 0.87 (0.65; 1.10)	[88] 1.02 (0.78; 1.25)	-0.14 (-0.46; 0.18)	0.2999
Female	[66] 0.68 (0.43; 0.92)	[66] 1.05 (0.78; 1.31)	-0.37 (-0.73; -0.01)	0.0534
Smoking (Interaction: p = 0.1539)				
Non-Smoker	[84] 0.73 (0.51; 0.94)	[89] 1.13 (0.89; 1.37)	-0.40 (-0.72; -0.08)	0.0065
Smoker	[63] 0.86 (0.60; 1.12)	[65] 0.90 (0.65; 1.15)	-0.04 (-0.40; 0.32)	0.9110
GOLD (Interaction: p = 0.9964)				
A,B	[26] 0.54 (0.11; 0.97)	[31] 0.70 (0.40; 1.00)	-0.16 (-0.69; 0.36)	0.6022
C,D	[121] 0.84 (0.66; 1.02)	[123] 1.11 (0.91; 1.32)	-0.27 (-0.54; -0.00)	0.0393
Former GOLD (Interaction: p = 0.0672)				
I, II	[36] 0.43 (0.21; 0.64)	[42] 0.89 (0.57; 1.20)	-0.46 (-0.84; -0.08)	0.0029
III	[55] 0.77 (0.52; 1.02)	[59] 1.03 (0.74; 1.31)	-0.26 (-0.63; 0.12)	0.2501
IV	[38] 1.11 (0.71; 1.50)	[39] 1.13 (0.83; 1.44)	-0.03 (-0.53; 0.47)	0.7753
CRP at Screening (Interaction: p = 0.9186)				
Low CRP	[103] 0.74 (0.57; 0.92)	[104] 0.96 (0.75; 1.16)	-0.21 (-0.48; 0.05)	0.1635
High CRP	[44] 0.89 (0.52; 1.27)	[49] 1.17 (0.83; 1.52)	-0.28 (-0.79; 0.23)	0.1619
Anthonisen (Interaction: p = 0.4009)				
I	[53] 0.94 (0.62; 1.26)	[43] 0.93 (0.58; 1.28)	0.00 (-0.47; 0.48)	0.5788
II	[46] 0.77 (0.51; 1.02)	[45] 1.29 (0.94; 1.65)	-0.53 (-0.97; -0.09)	0.3119
III	[43] 0.64 (0.37; 0.91)	[62] 0.88 (0.65; 1.10)	-0.23 (-0.59; 0.12)	0.0233
ICS Use (Interaction: p = 0.1881)				
No	[29] 0.81 (0.41; 1.21)	[31] 0.70 (0.37; 1.03)	0.11 (-0.41; 0.63)	0.7840
Yes	[118] 0.78 (0.60; 0.96)	[123] 1.12 (0.91; 1.32)	-0.34 (-0.61; -0.07)	0.0308



Recurrence rates are estimated by the Mean Cumulative Function (MCF). Treatment groups were compared by the the difference in MCFs.

NC = Not Calculated due to an insufficient number of patients in some groups.

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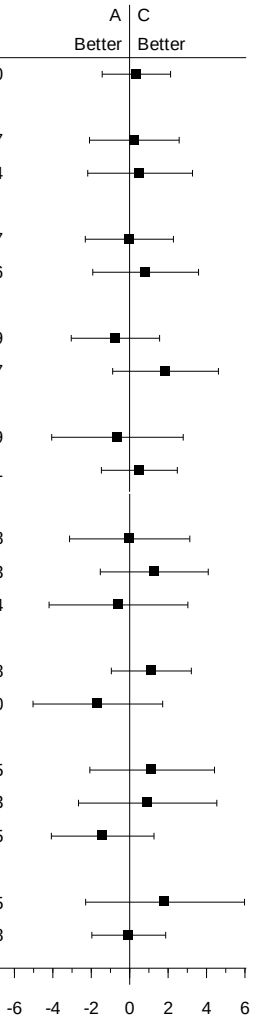
Table E8. Subgroup analyses of the key hierarchical secondary endpoint, COPD assessment test score up to day 90, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 17.70 (16.37; 19.03)	[153] 16.86 (15.46; 18.25)	0.35 (-1.43; 2.13)	0.6970
Age (Interaction: p = 0.8689)				
<= 65 years	[71] 17.29 (15.51; 19.08)	[86] 16.79 (14.97; 18.60)	0.25 (-2.09; 2.58)	0.8357
> 65 years	[76] 18.09 (16.14; 20.05)	[67] 16.95 (14.78; 19.12)	0.55 (-2.18; 3.28)	0.6934
Gender (Interaction: p = 0.6404)				
Male	[81] 16.94 (15.25; 18.63)	[87] 16.85 (15.05; 18.64)	-0.01 (-2.31; 2.28)	0.9917
Female	[66] 18.60 (16.52; 20.68)	[66] 16.87 (14.68; 19.07)	0.84 (-1.92; 3.59)	0.5516
Smoking (Interaction: p = 0.1542)				
Non-Smoker	[84] 16.96 (15.22; 18.70)	[88] 17.49 (15.71; 19.28)	-0.74 (-3.04; 1.56)	0.5299
Smoker	[63] 18.74 (16.71; 20.76)	[65] 15.98 (13.78; 18.18)	1.87 (-0.88; 4.62)	0.1827
GOLD (Interaction: p = 0.5716)				
A,B	[26] 12.75 (10.06; 15.44)	[30] 12.48 (10.45; 14.52)	-0.63 (-4.05; 2.79)	0.7179
C,D	[121] 18.85 (17.43; 20.28)	[123] 18.05 (16.44; 19.66)	0.51 (-1.47; 2.48)	0.6141
Former GOLD (Interaction: p = 0.6972)				
I, II	[36] 15.35 (12.82; 17.88)	[42] 15.19 (12.86; 17.53)	-0.00 (-3.13; 3.13)	0.9998
III	[55] 18.67 (16.71; 20.64)	[59] 16.66 (14.51; 18.81)	1.28 (-1.53; 4.09)	0.3723
IV	[38] 19.09 (16.06; 22.12)	[39] 19.13 (16.28; 21.97)	-0.58 (-4.20; 3.03)	0.7514
CRP at Screening (Interaction: p = 0.1704)				
Low CRP	[103] 18.42 (16.95; 19.89)	[104] 16.93 (15.20; 18.67)	1.13 (-0.96; 3.21)	0.2888
High CRP	[44] 15.74 (12.93; 18.54)	[48] 16.51 (14.23; 18.80)	-1.66 (-5.03; 1.72)	0.3360
Anthonisen (Interaction: p = 0.4046)				
I	[53] 18.85 (16.63; 21.07)	[42] 17.29 (14.23; 20.36)	1.17 (-2.07; 4.41)	0.4795
II	[46] 18.20 (15.64; 20.76)	[45] 17.76 (15.27; 20.24)	0.94 (-2.66; 4.54)	0.6103
III	[43] 15.92 (13.74; 18.10)	[62] 16.12 (14.07; 18.16)	-1.41 (-4.08; 1.27)	0.3025
ICS Use (Interaction: p = 0.4187)				
No	[29] 15.19 (12.32; 18.07)	[31] 13.04 (10.20; 15.87)	1.84 (-2.29; 5.98)	0.3825
Yes	[118] 18.35 (16.87; 19.82)	[122] 17.90 (16.37; 19.43)	-0.05 (-1.97; 1.87)	0.9608

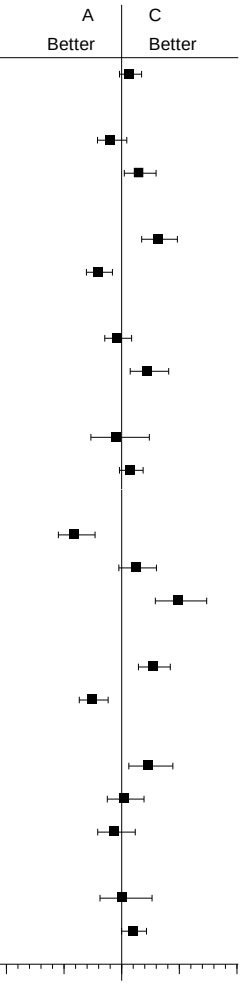


CAT scores were analysed using a GEE model for normal dadta including all visits and an independent variance-covariance matrix to account for interdepencies between the visits.

NC = Not Calculated due to an insufficient number of patients in some groups.

Table E9. Subgroup analyses of the key hierarchical secondary endpoint, total days of systemic corticosteroid use at 90 days, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 15.87 (14.86; 16.93)	[154] 14.79 (13.91; 15.72)	1.07 (0.98; 1.17)	0.1217
Age (Interaction: p < 0.0001)				
<= 65 years	[71] 12.56 (11.24; 14.03)	[86] 13.82 (12.70; 15.03)	0.91 (0.79; 1.04)	0.1785
> 65 years	[76] 18.44 (17.01; 19.99)	[68] 16.00 (14.65; 17.47)	1.15 (1.02; 1.30)	0.0195
Gender (Interaction: p < 0.0001)				
Male	[81] 18.53 (17.09; 20.09)	[88] 14.04 (12.90; 15.28)	1.32 (1.17; 1.48)	<.0001
Female	[66] 12.53 (11.23; 13.99)	[66] 15.68 (14.36; 17.12)	0.80 (0.69; 0.92)	0.0018
Smoking (Interaction: p < 0.0001)				
Non-Smoker	[84] 14.90 (13.58; 16.35)	[89] 15.47 (14.33; 16.71)	0.96 (0.85; 1.09)	0.5416
Smoker	[63] 16.93 (15.45; 18.55)	[65] 13.76 (12.46; 15.20)	1.23 (1.07; 1.41)	0.0027
GOLD (Interaction: p = 0.1417)				
A,B	[26] 11.28 (9.18; 13.85)	[31] 11.83 (10.04; 13.93)	0.95 (0.73; 1.24)	0.7230
C,D	[121] 16.62 (15.52; 17.80)	[123] 15.41 (14.43; 16.45)	1.08 (0.98; 1.19)	0.1176
Former GOLD (Interaction: p < 0.0001)				
I, II	[36] 8.57 (6.76; 10.85)	[42] 14.55 (12.85; 16.48)	0.59 (0.45; 0.77)	0.0001
III	[55] 15.75 (14.27; 17.39)	[59] 13.98 (12.59; 15.53)	1.13 (0.98; 1.30)	0.1050
IV	[38] 21.66 (19.61; 23.93)	[39] 14.46 (12.96; 16.14)	1.50 (1.29; 1.74)	<.0001
CRP at Screening (Interaction: p < 0.0001)				
Low CRP	[103] 16.08 (14.93; 17.33)	[104] 12.60 (11.66; 13.63)	1.28 (1.15; 1.42)	<.0001
High CRP	[44] 15.20 (13.30; 17.39)	[49] 20.36 (18.44; 22.48)	0.75 (0.63; 0.88)	0.0006
Anthonisen (Interaction: p < 0.0001)				
I	[53] 19.58 (17.78; 21.56)	[43] 15.81 (14.03; 17.82)	1.24 (1.06; 1.44)	0.0064
II	[46] 14.38 (12.80; 16.15)	[45] 14.07 (12.69; 15.59)	1.02 (0.88; 1.19)	0.7817
III	[43] 13.23 (11.51; 15.20)	[62] 14.06 (12.69; 15.57)	0.94 (0.79; 1.12)	0.4882
ICS Use (Interaction: p = 0.0031)				
No	[29] 13.31 (11.47; 15.44)	[31] 13.14 (11.16; 15.48)	1.01 (0.81; 1.26)	0.9101
Yes	[118] 16.63 (15.46; 17.88)	[123] 15.09 (14.13; 16.11)	1.10 (1.00; 1.22)	0.0520



All results were obtained using a Poisson regression with the total number of days as offset. Treatment, subgroup and their interaction were included as factors in the model.

NC = Not Calculated due to an insufficient number of patients in some groups.

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Table E10. Overview of most frequent adverse events

		Azithromycin		Placebo	
Gastrointestinal	**Trial phase**	(n=147)		(n=154)	
Diarrhea	Day 1 - day 90	20	(13.6)	15	(9.7)
	Day 90 - day 270	10	(6.8)	11	(7.1)
Nausea	Day 1 - day 90	12	(8.2)	11	(7.1)
	Day 90 - day 270	5	(3.4)	5	(3.3)
Anorexia	Day 1 - day 90	9	(6.1)	8	(5.2)
	Day 90 - day 270	10	(6.8)	12	(7.8)
Other					
Hearing loss	Day 1 - day 90	1	(0.7)	6	(3.9)
	Day 90 - day 270	3	(2.0)	6	(3.9)
Syncope	Day 1 - day 90	1	(0.7)	2	(1.3)
	Day 90 - day 270	2	(1.4)	1	(0.7)

Data are presented as number of patients with the specific adverse event during the given time period (no. (%)).
Note: day 1: randomization; day 90: end of intervention; day 270: end of follow-up.

Table E11. Overview of adverse events leading to study drug discontinuation

		Azithromycin	Placebo
Gastrointestinal	**Trial phase**	(n=147)	(n=154)
Diarrhea	Day 1 - day 90	2 (1.4)	0 (0)
	Day 90 - day 270	-	-
Nausea	Day 1 - day 90	1 (0.7)	0 (0)
	Day 90 - day 270	-	-
Abdominal discomfort	Day 1 - day 90	1 (0.7)	1 (0.6)
	Day 90 - day 270	-	-
Pancolitis	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Cardiovascular			
QTc prolongation	Day 1 - day 90	2 (1.4)	1 (0.6)
	Day 90 - day 270	-	-
(N)STEMI	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Takotsubo cardiomyopathy	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Other	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Respiratory			
AECOPD	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Other			
Miscellaneous	Day 1 - day 90	2 (1.4)	6 (3.9)
	Day 90 - day 270	-	-

Data are presented as number of patients with the specific adverse event during the given time period (no. (%)).
Note: day 1: randomization; day 90: end of intervention; day 270: end of follow-up.

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Table E12. Overview of serious adverse events

		Azithromycin		Placebo	
FATAL	**Trial phase**	(n=147)		(n=154)	
All-cause	Day 1 - day 90	3	(2.0)	6	(3.9)
	Day 90 - day 270	4	(2.7)	3	(1.9)
Cardiovascular	Day 1 - day 90	3	(2.0)	2	(1.3)
	Day 90 - day 270	1	(0.7)	0	(0)
Respiratory	Day 1 - day 90	0	(0)	3	(1.9)
	Day 90 - day 270	2	(1.4)	3	(1.9)
Lung cancer	Day 1 - day 90	0	(0)	1	(0.6)
	Day 90 - day 270	1	(0.7)	0	(0)
NON-FATAL					
Gastrointestinal	Day 1 - day 90	3	(2.0)	2	(1.3)
	Day 90 - day 270	1	(0.7)	3	(1.9)
Cardiovascular	Day 1 - day 90	3	(2.0)	6	(3.9)
	Day 90 - day 270	2	(1.4)	1	(0.6)
Laboratory investigations	Day 1 - day 90	1	(0.7)	0	(0)
	Day 90 - day 270	1	(0.7)	1	(0.6)
Oncology	Day 1 - day 90	0	(0)	1	(0.6)
	Day 90 - day 270	2	(1.4)	1	(0.6)
Cerebrovascular	Day 1 - day 90	0	(0)	2	(1.3)
	Day 90 - day 270	2	(1.4)	2	(1.3)
Renal	Day 1 - day 90	0	(0)	0	(0)
	Day 90 - day 270	0	(0)	2	(1.3)
Psychological	Day 1 - day 90	1	(0.7)	0	(0)
	Day 90 - day 270	1	(0.7)	1	(0.6)
Musculoskeletal	Day 1 - day 90	0	(0)	1	(0.6)
	Day 90 - day 270	2	(1.4)	3	(1.9)

Data are presented as number of patients with the specific adverse event during the given time period (no. (%)).
Note: day 1: randomization; day 90: end of intervention; day 270: end of follow-up.

Table E13. Overview of obtained spontaneous sputum samples*

	Azithromycin	Placebo
Baseline	**(n=147)**	**(n=154)**
Number of patients with sputum samples	110	109
Number of patients with bacterial culture	109	103
Number of patients with pathogens in sputum	37 (33.9)	30 (29.1)
Haemophilus influenzae	18 (16.5)	5 (4.9) †
Streptococcus pneumoniae	12 (11.0)	8 (7.8)
Pseudomonas aeruginosa	3 (2.8)	5 (4.9)
Morexella catarrhalis	2 (1.8)	6 (5.8)
Staphylococcus aureus	4 (3.7)	2 (1.9)
Other gram-negative bacteria	10 (9.2)	11 (10.7)
Number of patients with macrolide resistant bacteria	6 (5.5)	2 (1.9)
Streptococcus pneumoniae	4 (3.7)	2 (1.9)
Morexella catarrhalis	0 (0)	0 (0)
Staphylococcus aureus	2 (1.8)	0 (0)
Day X	**(n=143)**	**(n=150)**
Number of patients with sputum samples	55	62
Number of patients with bacterial culture	53	61
Number of patients with newly acquired pathogens	9	11
Number of patients with newly acquired macrolide resistant bacteria	1	3
Day 90	**(n=131)**	**(n=129)**
Number of patients with sputum samples	24	22
Number of patients with bacterial culture	23	21
Number of patients with newly acquired pathogens	4	3
Number of patients with newly acquired macrolide resistant bacteria	0	1
Day 270	**(n=118)**	**(n=115)**
Number of patients with sputum samples	20	16
Number of patients with bacterial culture	19	15
Number of patients with newly acquired pathogens	4	3
Number of patients with newly acquired macrolide resistant bacteria	0	0

Date are presented as no. (%).

*Newly acquired pathogens and macrolide resistant bacteria were counted with regards to the preceding study visit.

Note: † p=0.006. baseline: hospital admission; day X: day of discharge, at the investigator's discretion; day 90: end of intervention; day 270: end of follow-up.

Effect of daily azithromycin therapy and adherence on readmission risk in COPD

To the Editor:

Patients with chronic obstructive pulmonary disease (COPD) frequently experience unplanned hospital readmissions leading to increased morbidity [1]. The European COPD Audit found that 35% of patients admitted with acute exacerbation of COPD (AECOPD) were readmitted within 90 days [2]. In the USA, 22% of patients admitted with AECOPD experienced a 30-day readmission, motivating financial policies to incentivise readmission reduction [1]. Interventions to decrease the risk of readmissions have had mixed results [3]. In a previously published, double-blinded, placebo-controlled, randomised clinical trial (MACRO), azithromycin taken daily for 1 year reduced the risk of COPD exacerbations [4]. We hypothesised that patients taking long-term azithromycin in the MACRO study who experienced an index hospitalisation for an AECOPD would have a decreased risk of readmission when compared to the placebo arm.

Patients (n=1142) in the MACRO study had a clinical diagnosis of COPD and were randomised to receive 250 mg daily azithromycin or placebo for 1 year [4]. In this analysis, we focused on a subgroup who experienced an AECOPD hospitalisation after randomisation and survived their index hospitalisation; the outcome of interest was all-cause, unplanned readmission. Hospitalisation due to AECOPD was determined by the presence of at least two of the following symptoms: cough, shortness of breath, chest tightness, wheeze or increased sputum production and ⩾3 days of treatment with an antibiotic or steroid. To account for variable drug exposure, we calculated patient adherence to the assigned drug. This consisted of counting the number of pills taken during the study divided by the number of days within the follow up period [5]. Patient characteristics in the azithromycin *versus* placebo group were compared using Student's t-test for continuous variables and the χ^2-test for categorical variables. The association of azithromycin use and time to readmission was examined using a Cox proportional hazards regression models. The endpoint for the proportional hazards model was time to readmission after discharge from the index hospitalisation or in cases where there was no readmission, the data were censored at the end of the follow-up period.

Hospitalisations due to AECOPD occurred in 233 patients; 214 patients (116 in the placebo arm and 98 in the azithromycin arm) had time to readmission data and were included in our analysis. The average time to index hospitalisation in the placebo group was 158±105 days and 157±110 days in the azithromycin group; the p-value for the difference was 0.966. Patients in the placebo group and azithromycin group were generally well matched with regards to age, sex, post-bronchodilator forced expiratory volume in 1 s (FEV_1) % of predicted, smoking history, bronchodilator use and number of hospitalisations in the year prior to randomisation. Comorbid congestive heart failure was present in 16% (19 out of 116) patients in the placebo group *versus* 7% (seven out of 98) in the azithromycin group (p=0.04).

Readmissions occurred in 90 (42%) out of 214 patients, 35 (36%) out of 98 in the azithromycin arm and 55 (47%) out of 116 in the placebo arm. Respiratory-related readmissions occurred in 70 (77%) out of 90 patients. Our proportional hazards regression model (figure 1) demonstrates that patients receiving azithromycin did not have a significant increase in time to all-cause readmission (hazard ratio (HR) 0.70, p=0.10). Similarly, respiratory related readmission were nonsignificantly decreased in patients randomised to azithromycin (HR 0.70, p=0.14). Two patients were excluded from this analysis as respiratory-related

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Patients with COPD who were randomised to azithromycin did not experience prolonged time to hospital readmission. There was a trend toward decreased risk of readmission when adjusted for total exposure to azithromycin. http://ow.ly/NAzI30nb651

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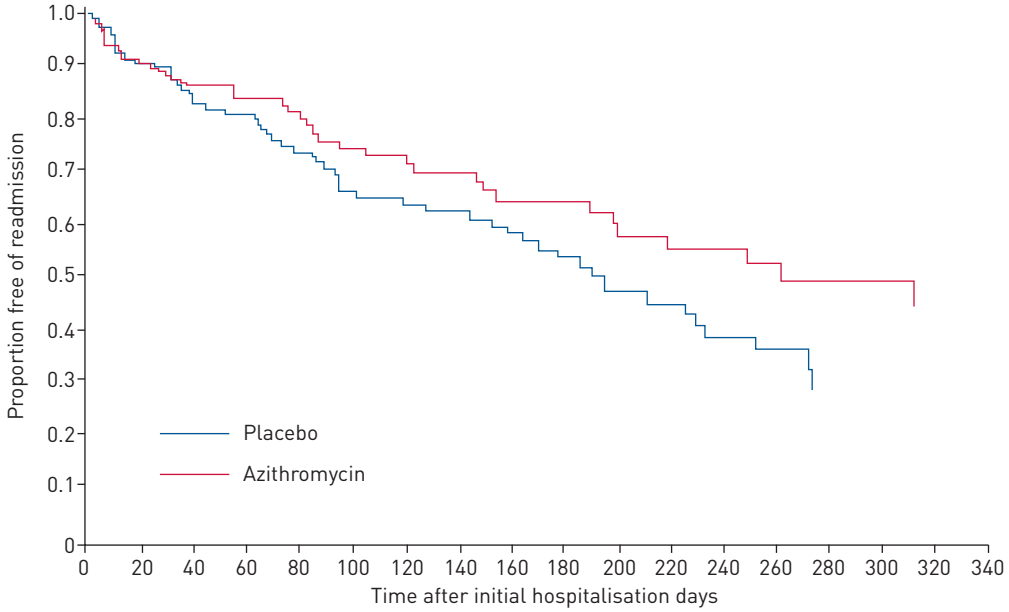

FIGURE 1 Time to readmission in the placebo arm *versus* the azithromycin arm using a Cox proportional hazards model. Patients who were randomised to azithromycin experienced a statistically nonsignificant increase in time to readmission (hazard ratio 0.70, p=0.10).

admission could not be determined from discharge summary review. We examined the association between intensity of exposure to azithromycin, with placebo patients having zero exposure intensity. Increased exposure to azithromycin was associated with a prolonged time to readmission (HR 0.82, p=0.038).

In a multivariate analysis, increased exposure to azithromycin (patients assigned to placebo had zero exposure intensity) was associated with a nonsignificant decrease in risk of readmission (HR 0.85, 95% CI 0.70–1.03; p=0.09). Female sex (HR 0.76, 95% CI 0.48–1.21; p=0.25), older age (HR 1.02, 95% CI 0.99–1.05; p=0.15), active smoking (HR 1.05, 95% CI 0.61–1.81; p=0.87), higher post bronchodilator FEV_1 % of predicted (HR 1.0, 95% CI 0.99–1.01; p=0.9) and history of congestive heart failure (HR 1.76, 95% CI 0.98–3.17; p=0.06) were not associated with risk of readmission. Previous hospitalisation in the past year, however, was associated with increased risk of readmission in our multivariate model (HR 1.81, 95% CI 1.06–3.09; p=0.03).

Two additional unadjusted Cox proportional hazards models examined whether increased adherence to the assigned drug, either azithromycin or placebo, was associated with better outcomes. In a univariate analysis restricted to the azithromycin group, time to readmission was nonsignificantly increased among patients with increased adherence (HR 0.45, p=0.16). When restricted to the placebo group, patients with increased adherence to placebo also experienced increased time to readmission (HR 0.41, p=0.039). We studied time to readmission in a single model adjusted for overall adherence as a behavioural indicator. In this model, randomisation to azithromycin demonstrated a trend to increased time to readmission (HR 0.66, p=0.05), with more adherent patients experiencing decreased readmission risk (HR 0.43, p=0.01).

To our knowledge, this is one of only a few studies designed to examine the effect of a pharmacological intervention on COPD readmissions. A systematic review examining five randomised clinical trials utilising nonpharmacological interventions demonstrated varied effects on readmission [6]. In our study, randomisation to azithromycin did not lead to a significant increase in time to readmission. However, increased exposure to azithromycin was associated with a trend to prolonged time to readmission, though this needs to be further explored in a larger sample.

We found that increased adherence to prescribed drug, either azithromycin or placebo, was also associated with increased time to readmission. This is consistent with a growing body of literature demonstrating that adherence to treatment is an important predictor of positive outcomes, regardless of whether the treatment is an active therapy or placebo. One possible explanation is the healthy adherer effect, which suggests that adherence is an indicator of overall healthy behaviour and therefore associated with improved outcomes in randomised trials [7, 8]. This has not been well explored in the COPD literature.

Limitations to our study include its *post hoc*, retrospective design and the possibility of Type II error. With only 214 patients included, there would need to be a substantial reduction in readmission rates to be able to detect an azithromycin effect in the subgroup of patients hospitalised for AECOPD. Our study may have underestimated the effect of azithromycin on readmission. Patients were already taking azithromycin when they experienced their index admission and therefore may be nonresponders to the medication for unknown reasons, resulting in a similar readmission rate as individuals taking placebo. Future studies should randomise patients to azithromycin after index hospitalisation to better estimate true effect on readmission rates.

In addition, we relied on pill pack counts to determine adherence, which do not always correlate with actual drug usage [9]. Finally, though patients in the placebo arm were not placed on long-term azithromycin therapy, some were likely prescribed infrequent short courses, which could have biased the results. The possibility of a protective effect of azithromycin in preventing COPD readmissions should be further explored in a larger sample that would decrease the possibility of Type II error. If shown to be effective in prolonging time to readmission, a targeted approach for azithromycin therapy could be developed in patients post-discharge. Future clinical trials in COPD should also consider the overall effect of adherence to medication on positive outcomes.

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Lucid, personal fees for COPD CME grand rounds from Methodist Hospital and Columbia University, personal fees for an ACO CME programme from the California Society of Allergy and Immunology, and personal fees for COPD CME presentations from Chiesi and the Puerto Rico Thoracic Society, outside the submitted work.

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Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

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Summary

Background **The phosphodiesterase-4 inhibitor roflumilast can improve lung function and prevent exacerbations in certain patients with chronic obstructive pulmonary disease (COPD). We therefore investigated whether roflumilast would reduce the frequency of exacerbations requiring corticosteroids in patients with COPD.**

Methods **In two placebo-controlled, double-blind, multicentre trials (M2-124 and M2-125) with identical design that were done in two different populations in an outpatient setting, patients with COPD older than 40 years, with severe airflow limitation, bronchitic symptoms, and a history of exacerbations were randomly assigned to oral roflumilast (500 μg once per day) or placebo for 52 weeks. Primary endpoints were change in prebronchodilator forced expiratory volume in 1 s (FEV_1) and the rate of exacerbations that were moderate (glucocorticosteroid-treated) or severe. Analysis was by intention to treat. The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.**

Findings **Patients were assigned to treatment, stratified according to smoking status and treatment with longacting β_2 agonists, and given roflumilast (n=1537) or placebo (n=1554). In both studies, the prespecified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, prebronchodilator FEV_1 increased by 48 mL with roflumilast compared with placebo (p<0·0001). The rate of exacerbations that were moderate or severe per patient per year was 1·14 with roflumilast and 1·37 with placebo (reduction 17% [95% CI 8–25], p<0·0003). Adverse events were more common with roflumilast (1040 [67%]) than with placebo (963 [62%]); 219 (14%) patients in the roflumilast group and 177 (12%) in the placebo group discontinued because of adverse events. In the pooled analysis, the difference in weight change during the study between the roflumilast and placebo groups was –2·17 kg.**

Interpretation **Since different subsets of patients exist within the broad spectrum of COPD, targeted specific therapies could improve disease management. This possibility should be explored further in prospective studies.**

Funding **Nycomed.**

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This online publication has been corrected. The corrected version first appeared at TheLancet.com on October 1, 2010

See **Editorial** page 663

See **Comment** page 665

See **Perspectives** page 679

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Introduction

Chronic obstructive pulmonary disease (COPD) is increasing in prevalence; it is associated with periodic exacerbations, resulting in patient anxiety,[1] worsening health status, lung function decline, and increase in mortality rate.[2–4] Effective management involves pharmacological and non-pharmacological treatments.[5] Longacting inhaled bronchodilator drugs (β_2 agonists and anticholinergic drugs) can improve health status and reduce the frequency of exacerbations, effects that are greater when longacting β_2 agonists are used in combination with inhaled corticosteroids.[6–9] However, there is a need for further improvement of COPD therapy.

Phosphodiesterase-4 (PDE4) inhibition provides a novel approach to the treatment of COPD. Drugs that inhibit PDE4 have a wide range of anti-inflammatory actions in vitro and in vivo.[10–12] Roflumilast, a new PDE4 inhibitor, reduces airway inflammation in COPD, as assessed with sputum neutrophil and eosinophil counts.[13] However, although roflumilast improved lung function, it did not significantly reduce the frequency of exacerbations in unselected patients with severe COPD.[14] The results of a post-hoc analysis of this study suggested that roflumilast reduced the rate of exacerbations in patients with severe airflow obstruction, frequent exacerbations, and those requiring oral steroids.[13]

To find out whether PDE4 inhibitors can have any effect on clinical outcomes in COPD, we tested the hypothesis that roflumilast reduces the rate of exacerbations requiring systemic corticosteroids in specific subsets of patients with COPD.

Methods

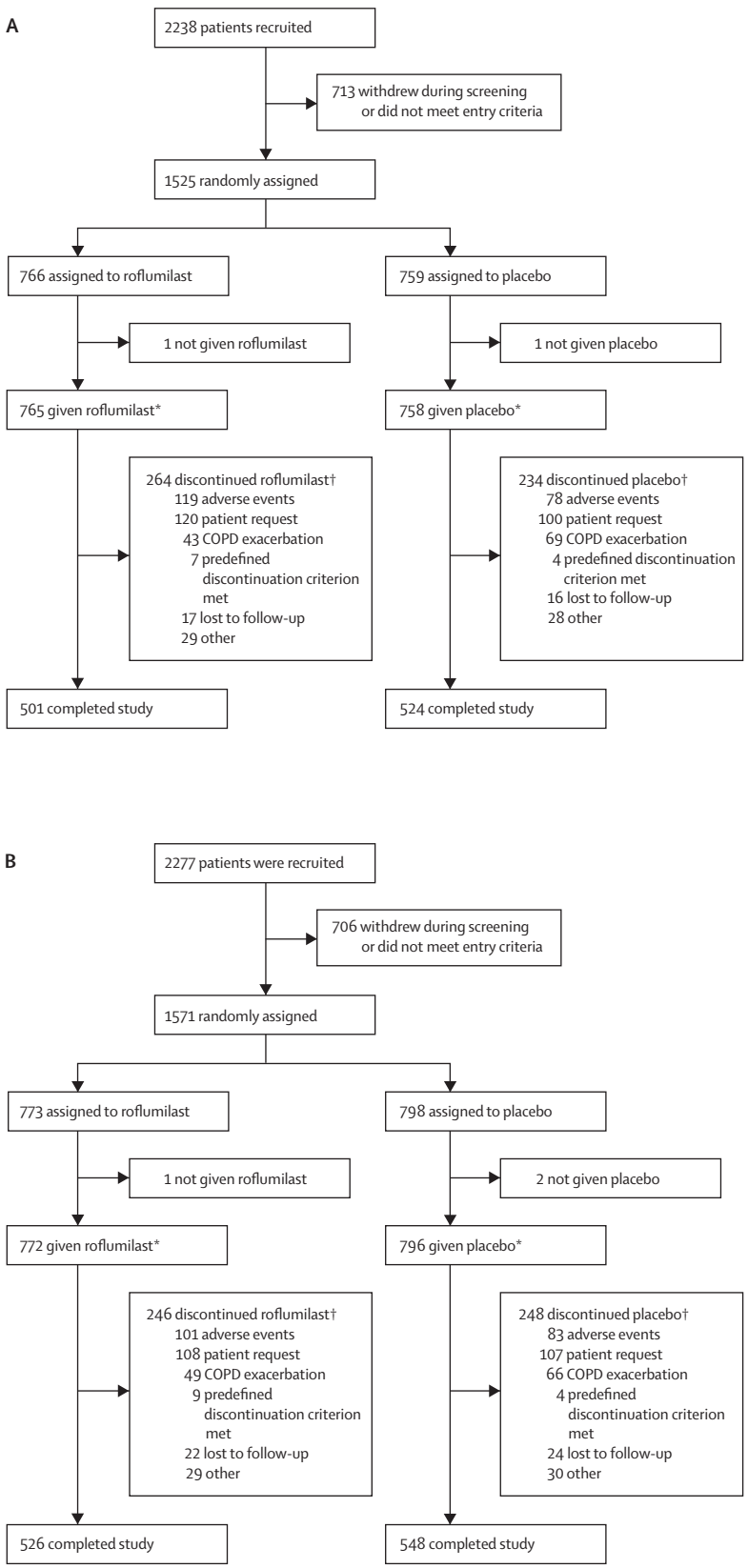
Setting

Study M2-124 was done in 246 centres in ten countries, and study M2-125 was done in 221 centres in eight countries (webappendix p 12).

Patients

For both studies, we recruited participants from an outpatient setting if they met inclusion criteria—ie, were former smokers or current smokers with at least a 20 pack-year history, older than 40 years, and had a clinical diagnosis of COPD (confirmed with a postbronchodilator [albuterol 400 μg] forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] ratio ≤70%) and chronic

See **Online** for webappendix



cough and sputum production. Their postbronchodilator FEV_1 was 50% or less than the predicted value. All patients had at least one recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital, or both, in the previous year. Exclusion criteria are shown in the webappendix (p 11); use of theophylline was not allowed from the start of the run-in period.

The studies were approved by local ethical review committees and done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Interventions

Each trial had an initial 4-week run-in, during which patients took a placebo tablet once a day in the morning, and recorded their use of shortacting bronchodilator drugs, and production of cough and sputum on their daily diary cards (webappendix p 23). In this initial study phase, patients, but not investigators, were unaware of the treatment they were assigned to. Patients were then randomly assigned to oral roflumilast 500 μg once a day or placebo, taken in the morning for the subsequent 52 weeks, provided that the total of their cough and sputum scores was greater than 14 in the week before randomisation, the haemoccult (guaiac) test during the baseline period was negative, at least 80% of prescribed placebo tablets were taken, and patients were clinically stable. Patients could use shortacting β_2 agonists as needed and could continue treatment with longacting β_2 agonists or shortacting anticholinergic drugs at stable doses. However, inhaled corticosteroids and longacting anticholinergic drugs were not allowed during the study. Eligible patients were stratified according to their use of longacting β_2 agonists and smoking status.

Randomisation and masking

The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients. In the double-blind treatment phase, all individuals involved in the studies were unaware of treatment assignment—tablets were identical in appearance. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. The sponsor and clinical research associate were notified if there was a clinical reason for an individual's treatment to be unmasked by the investigator with the interactive voice recognition system.

Figure 1: **Trial profiles of M2-124 (A) and M2-125 (B)**
COPD=chronic obstructive pulmonary disease. *In the M2-124 study, one patient was randomly assigned twice and given study medication twice. The first patient number was included in the intention-to-treat and safety analyses, whereas the second patient number was only included in the safety analysis. Four patients assigned to placebo were given roflumilast instead (at least once) and were included in the roflumilast group for safety analyses. In the M2-125 study, six patients randomly assigned to placebo were given roflumilast instead (at least once) and were included in the roflumilast group for safety analyses. †Patients might have provided more than one reason for discontinuation.

	M2-124		M2-125		M2-124 and M2-125	
	Roflumilast (n=765)	Placebo (n=758)	Roflumilast (n=772)	Placebo (n=796)	Roflumilast (n=1537)	Placebo (n=1554)
Age (years)*	64 (10)	63 (9)	64 (9)	64 (9)	64 (9)	64 (9)
Men	540 (71%)	538 (71%)	610 (79%)	648 (81%)	1150 (75%)	1186 (76%)
Cigarette pack-year*†	48 (24)	46 (23)	49 (26)	47 (24)	48 (25)	47 (23)
Smoking status*						
Current smoker	365 (48%)	361 (48%)	270 (35%)	282 (35%)	635 (41%)	643 (41%)
Former smoker	400 (52%)	397 (52%)	502 (65%)	514 (65%)	902 (59%)	911 (59%)
Prebronchodilator FEV_1 (L)‡	1·07 (0·4)	1·06 (0·4)	0·95 (0·3)	0·98 (0·4)	1·01 (0·4)	1·02 (0·4)
Postbronchodilator FEV_1 (L)‡	1·16 (0·4)	1·15 (0·4)	1·05 (0·4)	1·07 (0·4)	1·10 (0·4)	1·11 (0·4)
Prebronchodilator FEV_1 (% of predicted)‡	34·7 (10·2)	34·6 (10·3)	31·4 (10·1)	32·2 (10·8)	33·0 (10·3)	33·4 (10·6)
Postbronchodilator FEV_1 (% of predicted)‡	37·6 (10·7)	37·5 (10·4)	34·6 (10·3)	35·3 (10·9)	36·1 (10·6)	36·4 (10·7)
Postbronchodilator FEV_1/FVC (%)‡	43·3 (11·6)	42·7 (11·0)	41·2 (10·7)	41·3 (10·8)	42·3 (11·2)	42·0 (10·9)
COPD severity*§¶						
Severe	486 (64%)	510 (67%)	457 (59%)	479 (60%)	943 (61%)	989 (64%)
Very severe	199 (26%)	184 (24%)	264 (34%)	256 (32%)	463 (30%)	440 (28%)
Body-mass index (kg/m^2)‡	26·4 (5·5)	26·0 (5·5)	25·2 (6·2)	25·4 (5·9)	25·8 (5·9)	25·7 (5·7)
C-reactive protein (mg/L)*	8·1 (14·0)	7·2 (12·5)	8·3 (14·6)	9·2 (17·6)	8·2 (14·3)	8·2 (15·4)
Concomitant treatment with longacting β_2 agonists‖	378 (49%)	385 (51%)	371 (48%)	408 (51%)	749 (49%)	793 (51%)
Concomitant treatment with shortacting anticholinergics‖	240 (31%)	245 (32%)	297 (38%)	324 (41%)	537 (35%)	569 (37%)
Concomitant treatment with shortacting β_2 agonists‖	761 (99%)	753 (99%)	769 (100%)	791 (99%)	1530 (100%)	1544 (99%)
Pretreatment with inhaled corticosteroids**	338 (44%)	335 (44%)	312 (40%)	322 (40%)	650 (42%)	657 (42%)
Ethnic origin						
Asian	1 (<1%)	1 (<1%)	174 (23%)	179 (22%)	175 (11%)	180 (12%)
Native American	0	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Black	11 (1%)	15 (2%)	8 (1%)	14 (2%)	19 (1%)	29 (2%)
White	737 (96%)	732 (97%)	559 (72%)	568 (71%)	1296 (84%)	1300 (84%)
Other	16 (2%)	9 (1%)	29 (4%)	34 (4%)	45 (3%)	43 (3%)

Data are number (%) or mean (SD). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. COPD=chronic obstructive pulmonary disease. *Measurements were taken at the beginning of the run-in period. †1 pack-year=20 cigarettes per day for 1 year. ‡Measurements were taken at baseline. §Based on the criteria of the Global initiative for chronic Obstructive Lung Disease. ¶Percentages do not add up to 100% because patients with mild or moderate COPD are not shown. ‖Based on whether the patient had used medications at least once within the start and up to the end of the treatment period inclusive. **Based on whether the patient had used inhaled corticosteroids at least once within the period starting the day after the first visit until the day before randomisation, inclusive.

Table 1: **Demographics and baseline characteristics of the intention-to-treat populations in the M2-124 and M2-125 trials**

After randomisation, patients were assessed every 4 weeks up to week 12 and every 8 weeks thereafter. At each visit, spirometric measurements were recorded before and 15–45 min after administration of bronchodilator (inhaled albuterol 400 µg). Additionally, we recorded any new exacerbations or adverse events, the patient's bodyweight, adherence to tablets, completeness of the daily diary records, use of shortacting β_2 agonists, and investigator-administered transition dyspnoea index (TDI),[15] and dispensed study medication.

Study endpoints

The primary endpoints were the change in pre-bronchodilator FEV_1 during treatment and the rate of COPD exacerbations, defined as moderate if they required oral or parenteral corticosteroids, or severe if they were associated with admission or death. Key secondary outcomes included the postbronchodilator FEV_1 (change from baseline during treatment), time to death from any cause, natural log-transformed C-reactive protein concentration (a possible marker of systemic inflammation in COPD;[16] change from baseline to study end) and TDI focal score (during treatment). A change of one unit in the TDI focal score was considered clinically significant. Additionally, data for the total number of COPD exacerbations (as defined above together with episodes treated with antibiotics alone) and a range of spirometric outcomes were gathered. As part of a planned health economic analysis (data for subsequent presentation), patients completed the Euroquol 5-dimension (EQ-5D) questionnaire, a measure of health utility, at each visit.[17]

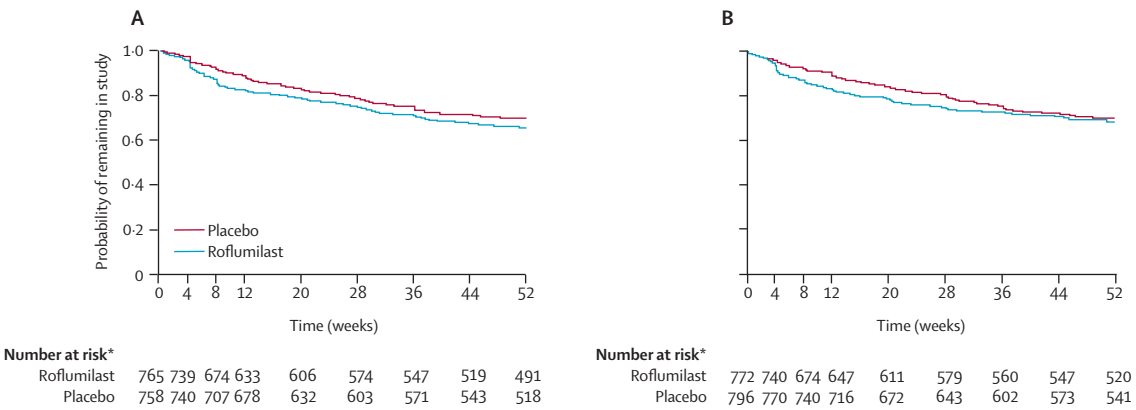


Figure 2: **Probability of treatment discontinuation in roflumilast and placebo groups in trials M2-124 (A) and M2-125 (B)**
*Number of patients still at risk at the beginning of the respective week; number at risk might be different from the number completing the study because the protocol allowed patients to finish the study up to 7 days before the end of week 52.

Bodyweight was measured with the same scales at each visit, height was measured with a stadiometer, and body-mass index (BMI) was calculated. At weeks 28 and 52 after randomisation, blood samples were taken for routine haematology and biochemistry tests, and an electrocardiogram (ECG) was done. In study M2-125, 24-h Holter monitoring was undertaken at 19 sites to identify any arrhythmias.

Statistical analysis

With the exception of the post-hoc investigation of adverse events and bodyweight, all reported efficacy analyses were prespecified in the intention-to-treat population. Data are presented as mean and SD, unless otherwise indicated. On the basis of an assumption of a mean exacerbation rate of 1·25 per patient per year in the placebo group and 1·00 in the roflumilast group, and using a Poisson regression model, with a correction for overdispersion of 2 based on previous data,[14] we estimated that 750 patients per treatment group in each trial would provide 90% power to detect a significant difference between treatments with a two-sided α level of 0·05. A negative binominal regression analysis was done to assess the robustness of the results against the distributional assumptions.

Data were analysed in the two studies separately and in a pooled analysis. We analysed changes from baseline in prebronchodilator and postbronchodilator FEV_1 using a repeated-measures analysis of covariance with all data available for patients during the 52-week treatment.[18] A Cox proportional hazard model was used to test for differences in time-to-event data. For analysis of the concentrations of C-reactive protein, an analysis of covariance model was used, with the method of the last observation carried forward for the log-transformed data for concentrations.

For the regression models (analysis of covariance, Cox, and Poisson), the covariates included treatment, age, sex, smoking status (current or former smoker), country, and treatment with longacting β_2 agonists. In the Cox analysis, country was included as a stratum. In the Poisson regression analysis, baseline post-bronchodilator FEV_1 (% of predicted value) was also included as a covariate. To address the issue of multiple comparisons, a hierarchical hypothesis-testing approach was adopted. If the primary outcomes were positive, the key secondary outcomes were tested in the order above. If a significant difference between treatments was not obtained for the primary or key secondary outcomes, all subsequent analyses were considered exploratory. No interim analyses were done in either study before unmasking. However, several statistical analyses were preplanned and done to assess the robustness of the results with respect to the effect of differential dropouts and missing data. Adverse events were analysed with descriptive statistics and 95% CIs for the differences between treatments.

The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Role of the funding source

All authors (academic investigators [PMAC, KFR, LMF, and FJM] and employees of the sponsor [U-MG and SK]) had full access to and interpreted the data, and were responsible for the decision to publish the report. The sponsor did not place any restrictions on the academic authors about the statements made in the final report.

Results

Patient recruitment began in February, 2006, and the studies ended in July, 2008. In the M2-124 study, 1523 patients were randomly assigned and treated (figure 1A). In M2-125, 1568 patients were randomly assigned and treated (figure 1B). Four patients in M2-124 and six in M2-125 were given roflumilast rather than placebo and are included in the treated group for

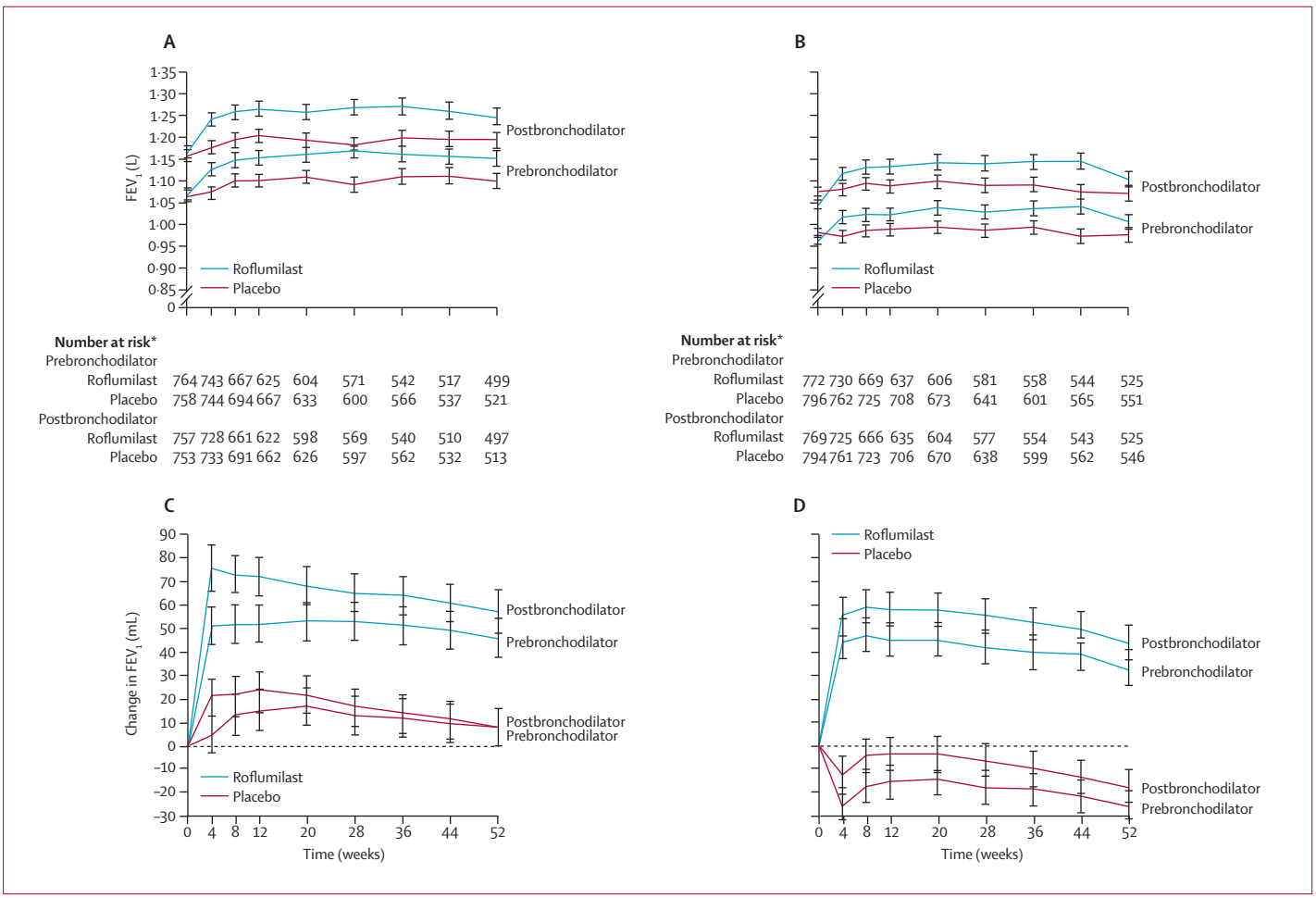


***Figure 3*: Prebronchodilator and postbronchodilator forced expiratory volumes in 1 s (FEV_1) over 52 weeks in patients in roflumilast and placebo groups in trials M2-124 (A) and M2-125 (B), and changes in prebronchodilator and postbronchodilator FEV_1 over 52 weeks in patients in roflumilast and placebo groups in trials M2-124 (C) and M2-125 (D)**

The changes from baseline that could be calculated from the crude means shown in (A) and (B) are different from the changes from baseline (based on adjusted means) shown in (C) and (D): adjusted means are based on a repeated-measures analysis of covariance, including factors and covariables that might have an effect on the crude means. Error bars are SE. Number of patients at risk for the baseline value (week 0) is not equal to the number of patients in the intention-to-treat population (table 1) because some patients did not have a baseline value according to the definition from the statistical analysis plan. Two patients in the roflumilast group left the study during the last visit but were classified as non-completers because they did not undergo all investigations; hence the number of patients with FEV_1 measurements at the last visit is greater than the number of completers in figure 1B. *Number of patients with data available; number of patients reported here differs from the number at risk in figure 2 because some patients did not have their lung function measured at the end of the study, whereas others who did not complete the study had their lung function measured at week 52.

the safety analysis. Table 1 shows the demographic and baseline characteristics of the patients who took at least one dose of study medication. The only difference between the trials was the proportion of Asian patients. The mean prebronchodilator FEV_1 was between 31% and 35% of predicted value in the different study subgroups; 40–44% had used inhaled corticosteroids previously, whereas about 50% used longacting β_2 agonists during the trials (table 1).

Patient withdrawal was similar in the roflumilast and placebo groups (35% and 31%, respectively, in M2-124, and 32% and 31%, respectively, in M2-125; figure 1). However, more patients in the roflumilast group than in the placebo group withdrew in the first 12 weeks after randomisation (figure 2A and 2B). Adherence to treatment was similar in all groups: mean compliance was 93% (SD 25) in the roflumilast group and 95% (14) in the placebo group in the M2-124 study, and 93% (16) in the roflumilast group and 96% (15) in the placebo group in the M2-125 study.

The primary endpoints were achieved in both studies. Figure 3 (A to D) shows the FEV_1 data during the studies; table 2 shows the summary results. In the pooled analysis, prebronchodilator FEV_1 increased from baseline in the roflumilast group and decreased in the placebo group (table 2). The postbronchodilator FEV_1, a secondary outcome variable, increased significantly from baseline with roflumilast compared with placebo in both studies and in the pooled analysis (table 2). Prebronchodilator FVC was significantly greater with roflumilast than with placebo in both studies (table 2). Similar significant improvements were seen in postbronchodilator FVC and

	M2-124			M2-125			M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast *vs* placebo	Roflumilast	Placebo	Roflumilast *vs* placebo	Roflumilast	Placebo	Roflumilast *vs* placebo
Lung function*									
Change in prebronchodilator FEV_1 (mL)	46 (8); n=745	8 (8); n=745	Difference 39 (18 to 60); p=0·0003	33 (7); n=730	−25 (7); n=766	Difference 58 (41 to 75); p<0·0001	40 (6); n=1475	−9 (5); n=1511	Difference 48 (35 to 62); p<0·0001
Change in postbronchodilator FEV_1 (mL)	57 (9); n=729	8 (8); n=736	Difference 49 (26 to 71); p<0·0001	44 (7); n=724	−17 (7); n=764	Difference 61 (44 to 79); p<0·0001	50 (6); n=1453	−4 (6); n=1500	Difference 55 (41 to 69); p<0·0001
Change in prebronchodilator FVC (mL)	68 (15); n=745	−21 (15); n=745	Difference 89 (51 to 127); p<0·0001	60 (14); n=730	−48 (14); n=766	Difference 108 (75 to 141); p<0·0001	64 (10); n=1475	−34 (10); n=1511	Difference 98 (73 to 123); p<0·0001
Change in postbronchodilator FVC (mL)	76 (15); n=729	−25 (15); n=736	Difference 101 (63 to 139); p<0·0001	58 (13); n=724	−45 (13); n=764	Difference 103 (72 to 134); p<0·0001	67 (10); n=1453	−35 (10); n=1500	Difference 101 (77 to 126); p<0·0001
Change in prebronchodilator FEV_1/FVC (%)	0·314 (0·223); n=745	0·001 (0·219); n=745	Difference 0·312 (−0·262 to 0·886); p=0·2858	0·200 (0·190); n=730	−0·309 (0·186); n=766	Difference 0·510 (0·061 to 0·958); p=0·0261	0·247 (0·147); n=1475	−0·146 (0·1439); n=1511	Difference 0·393 (0·028 to 0·758); p=0·0350
Change in postbronchodilator FEV_1/FVC (%)	0·488 (0·211); n=729	0·286 (0·208); n=736	Difference 0·202 (−0·343 to 0·747); p=0·4674	0·552 (0·186); n=724	−0·115 (0·182); n=764	Difference 0·668 (0·226 to 1·109); p=0·0031	0·517 (0·141); n=1453	0·090 (0·138); n=1500	Difference 0·426 (0·077 to 0·776); p=0·0169
Change in prebronchodilator FEF25–75 (mL/s)	19 (5); n=745	2 (5); n=745	Difference 17 (3 to 30); p=0·0152	15 (5); n=730	−10 (5); n=765	Difference 25 (13 to 36); p<0·0001	16 (4); n=1475	−4 (4); n=1510	Difference 20 (12 to 29); p<0·0001
Change in postbronchodilator FEF25–75 (mL/s)	22 (6); n=729	12 (6); n=736	Difference 11 (−5 to −27); p=0·1809	21 (5); n=724	−8 (5); n=763	Difference 29 (18 to 40); p<0·0001	21 (4); n=1453	2 (4); n=1499	Difference 19 (10 to 29); p<0·0001
Change in prebronchodilator PEF (L/min)	6·65 (1·45); n=745	3·58 (1·43); n=745	Difference 3·07 (−0·66 to 6·81); p=0·1063	0·75 (1·45); n=730	−3·09 (1·41); n=766	Difference 3·85 (0·46 to 7·23); p=0·0261	3·69 (1·02); n=1475	0·17 (0·99); n=1511	Difference 3·53 (1·01 to 6·04); p=0·0060
Change in postbronchodilator PEF (L/min)	8·08 (1·50); n=729	3·87 (1·48); n=736	Difference 4·21 (0·34 to 8·07); p=0·0328	1·93 (1·49); n=724	−3·14 (1·45); n=764	Difference 5·07 (1·60 to 8·53); p=0·0042	4·93 (1·05); n=1453	0·22 (1·02); n=1500	Difference 4·72 (2·13 to 7·30); p=0·0004
Exacerbations†‡									
Moderate or severe (mean rate, per patient per year [95% CI])	1·08 (0·96–1·21); n=344	1·27 (1·14–1·40); n=389	RR 0·85 (0·74 to 0·98); p=0·0278	1·21 (1·07–1·36); n=373	1·49 (1·33–1·66); n=432	RR 0·82 (0·71 to 0·94); p=0·0035	1·14 (1·05–1·24); n=717	1·37 (1·28–1·48); n=821	RR 0·83 (0·75 to 0·92); p=0·0003
Severe (mean rate, per patient per year [95% CI])	0·11 (0·07–0·15); n=69	0·12 (0·09–0·16); n=81	RR 0·89 (0·61 to 1·29); p=0·5273	0·14 (0·10–0·20); n=88	0·18 (0·13–0·25); n=117	RR 0·77 (0·53 to 1·11); p=0·1656	0·12 (0·10–0·16); n=157	0·15 (0·12–0·19); n=198	RR 0·82 (0·63 to 1·06); p=0·1334
Moderate (mean rate, per patient per year [95% CI])	0·94 (0·83–1·06); n=299	1·11 (1·00–1·25); n=343	RR 0·84 (0·72 to 0·99); p=0·0325	1·04 (0·92–1·18); n=325	1·27 (1·13–1·42); n=380	RR 0·82 (0·71 to 0·95); p=0·0075	0·99 (0·91–1·08); n=624	1·19 (1·10–1·29); n=723	RR 0·83 (0·75 to 0·92); p=0·0007
Treated with systemic corticosteroids, antibiotics, or both (mean rate, per patient per year [95% CI])	1·10 (0·98–1·23); n=336	1·30 (1·17–1·43); n=382	RR 0·85 (0·74 to 0·98); p=0·0240	1·17 (1·04–1·31); n=364	1·41 (1·27–1·57); n=416	RR 0·83 (0·72 to 0·95); p=0·0055	1·13 (1·04–1·23); n=700	1·35 (1·26–1·46); n=798	RR 0·84 (0·76 to 0·92); p=0·0003
Median time to first exacerbation (moderate or severe; days [IQR])	85·0 (29·5–185·5)	71·0 (29·0–152·0)	HR 0·88 (0·76 to 1·02); p=0·0859	73·0 (26·0–195·0)	69·5 (27·0–169·5)	HR 0·89 (0·78 to 1·03); p=0·1132	80·0 (28·0–190·0)	71·0 (28·0–160·0)	HR 0·89 (0·80 to 0·98); p=0·0185
Median time to second exacerbation (moderate or severe; days [IQR])	172·0 (102·0–253·0)	159·0 (97·0–229·0)	HR 0·79 (0·64 to 0·98); p=0·0290	188·0 (84·0–281·0)	144·0 (81·0–239·0)	HR 0·79 (0·65 to 0·97); p=0·0214	177·0 (92·0–262·0)	148·0 (85·0–236·0)	HR 0·79 (0·69 to 0·91); p=0·0014

(Continues on next page)

prebronchodilator midexpiratory flow. These changes in lung function were similar with and without treatment with longacting β_2 agonist (mean prebronchodilator FEV_1 increase with longacting β_2 agonist, 46 mL [p<0·0001] and without longacting β_2 agonist, 50 mL [p<0·0001]).

In the pooled analysis, the estimated rate of exacerbations per patient per year that were moderate or severe was 17% lower in the roflumilast group than in the placebo group (table 2). These findings were supported by the negative binomial regression analysis (data not shown). The difference in rates between treatments was independent of concomitant longacting β_2 agonist use (p=0·5382, treatment by concomitant treatment with longacting β_2 agonist interaction). The total number of exacerbations (excluding severe events) requiring treatment with systemic corticosteroids or antibiotics, or both, was also lower in the roflumilast group than in the placebo group (reduction 16%) in the pooled analysis (table 2). The times to the first and second episodes of exacerbations that were moderate or severe were significantly prolonged (table 2). When the analysis was restricted to patients who completed the

	M2-124			M2-125			M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast *vs* placebo	Roflumilast	Placebo	Roflumilast *vs* placebo	Roflumilast	Placebo	Roflumilast *vs* placebo
(Continued from previous page)									
Further prespecified secondary analyses									
TDI focal score*	0·7 (0·1); n=741	0·4 (0·1); n=745	Difference 0·2 (0·0 to 0·4); p=0·0356	0·7 (0·1); n=729	0·4 (0·1); n=769	Difference 0·3 (0·1 to 0·5); p=0·0059	0·7 (0·1); n=1470	0·4 (0·1); n=1514	Difference 0·3 (0·1 to 0·4); p=0·0009
Change in C-reactive protein from baseline to last postrandomisation visit (mg/L)*	1·0; n=691	1·1; n=694	Difference 1·0 (0·8 to 1·1); p=0·4089	1·1; n=680	1·0; n=696	Difference 1·1 (0·9 to 1·2); p=0·3627	1·1; n=1371	1·1; n=1390	Difference 1·0 (0·9 to 1·1); p=0·8670
Time to mortality (days; mean, SD)	213·8 (118·9); n=765	207·5 (108·5); n=758	HR 1·0 (0·5 to 2·0); p=0·9212	201·0 (116·9); n=772	214·6 (137·3); n=796	HR 1·2 (0·7 to 2·1); p=0·5028	206·1 (116·4); n=1537	211·7 (125·1); n=1554	HR 1·1 (0·7 to 1·8); p=0·5452
Health utility assessment									
EQ-5D total score*	0·0049 (0·0058); n=743	0·0097 (0·0057); n=740	Difference −0·0047 (−0·0196 to 0·0101); p=0·5331	0·0100 (0·0065); n=727	−0·0006 (0·0063); n=764	Difference 0·0106 (−0·0046 to 0·0257); p=0·1715	0·0072 (0·0043); n=1470	0·0049 (0·0042); n=1504	Difference 0·0023 (−0·0083 to 0·0129); p=0·6712

Data are mean (SE), mean difference (95% CI), or point estimate (95% CI), unless otherwise indicated. n=number of patients with data available (or, for exacerbations, number of patients with at least one exacerbation). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. FEF=forced expiratory flow. PEF=peak expiratory flow. RR=rate ratio. HR=hazard ratio. TDI=transition dyspnoea index. EQ-5D=Euroquol 5-dimension. *Least squares means (SE). †Estimated exacerbation rates were based on a Poisson regression model and HRs were based on a Cox proportional hazards model. ‡Since patients might have had more than one type of exacerbation, the total of moderate and severe exacerbations is different from the total of exacerbations that were moderate or severe.

Table 2: **Lung function variables, exacerbations, and other clinical outcomes**

trials, similar differences in exacerbation rates were seen between the groups, although these were not significant (webappendix p 13).

The preplanned sensitivity analyses confirmed the robustness of results for the primary endpoints with respect to the effect of dropouts and missing data (data not shown).

A total of 84 patients died during the studies. The mortality rates per year did not differ in the roflumilast and placebo groups in the M2–124 study (17 [2%] *vs* 17 [2%]), and in the roflumilast and placebo groups in the M2–125 study (25 [3%] *vs* 25 [3%]; hazard ratio for time to death from any cause was >1 in both studies; table 2). Baseline concentrations of C-reactive protein varied widely and did not change significantly during the study or with treatment. A small improvement was noted in TDI focal score from baseline with roflumilast compared with placebo but there were no differences in total EQ-5D scores (table 2).

Adverse events in the pooled study population were reported by 1040 (67%) patients in the roflumilast group and 963 (62%) in the placebo group; serious adverse events were reported by 301 (19%) and 336 (22%) patients, respectively. Discontinuations associated with adverse events were more common in the pooled roflumilast groups than in the pooled placebo groups (219 [14%] *vs* 177 [11%]). With the exception of COPD, the most frequent adverse events leading to discontinuation were diarrhoea, nausea, and headache in the pooled analysis (data not shown). The probability of withdrawal due to adverse events in the first 12 weeks was higher in roflumilast-treated patients (8% in both studies) than in placebo-treated patients (3% in both studies). The subsequent probability of withdrawal because of adverse events was similar between treatments (9% of roflumilast-treated patients in both studies, and 9% of placebo-treated patients in both studies).

Vomiting was reported by 17 (1%) patients in the roflumilast groups and 11 (<1%) in the placebo groups. More patients in the roflumilast than in the placebo groups had weight loss (table 3). The mean weight change was a reduction of 2·09 kg (SD 3·98) with roflumilast after 1 year and an increase of 0·08 kg (3·48) with placebo. The change in weight in the roflumilast group happened in the first 6 months of treatment and was attenuated thereafter. Patients in the roflumilast group reporting diarrhoea, nausea, vomiting, or headache had greater weight loss than did those not reporting these symptoms (2·60 kg [3·72] *vs* 2·02 kg [4·01]). The largest absolute weight loss with roflumilast occurred in obese patients (BMI>30; webappendix p 14). No differences were noted in the proportion of reported cardiovascular adverse events in the roflumilast and placebo groups (108 [7%] and 120 [8%], respectively). Atrial fibrillation was an infrequent complication reported by 17 (1%) patients in the roflumilast groups and 7 (<1%) of those in the placebo groups. There was no difference between roflumilast and placebo groups in the occurrence of rhythm disturbances in 33 and 22 Holter-monitored recordings, respectively (webappendix p 16). The incidence of pneumonia or other pulmonary infections did not increase during treatment with roflumilast (data not shown).

	M2-124			M2-125*		
	Roflumilast (n=769)†	Placebo (n=755)†	Roflumilast *vs* placebo (difference, 95% CI)	Roflumilast (n=778)‡	Placebo (n=790)‡	Roflumilast *vs* placebo (difference, 95% CI)
COPD	70 (9%)	82 (11%)	−1·76% (−4·90 to 1·38)	87 (11%)	122 (15%)	−4·26% (−7·74 to −0·78)
Diarrhoea	63 (8%)	26 (3%)	4·75% (2·28 to 7·21)	67 (9%)	23 (3%)	5·70% (3·28 to 8·12)
Weight loss	92 (12%)	24 (3%)	8·78% (6·04 to 11·53)	65 (8%)	20 (3%)	5·82% (3·46 to 8·18)
Nasopharyngitis	57 (7%)	50 (7%)	0·79% (−1·91 to 3·49)	35 (5%)	47 (6%)	−1·45% (−3·78 to 0·88)
Upper respiratory tract infection	16 (2%)	21 (3%)	−0·70% (−2·38 to 0·98)	33 (4%)	38 (5%)	−0·57% (−2·75 to 1·62)
Headache	26 (3%)	17 (2%)	1·13% (−0·66 to 2·92)	25 (3%)	8 (1%)	2·20% (0·65 to 3·75)
Pneumonia	17 (2%)	15 (2%)	0·22% (−1·35 to 1·79)	25 (3%)	16 (2%)	1·19% (−0·52 to 2·90)
Back pain	27 (4%)	22 (3%)	0·60% (−1·30 to 2·50)	23 (3%)	13 (2%)	1·31% (−0·30 to 2·92)
Acute bronchitis	35 (5%)	40 (5%)	−0·75% (−3·05 to 1·56)	21 (3%)	24 (3%)	−0·34% (−2·12 to 1·44)
Nausea	41 (5%)	15 (2%)	3·34% (1·34 to 5·35)	21 (3%)	15 (2%)	0·80% (−0·81 to 2·41)
Hypertension	20 (3%)	28 (4%)	−1·11% (−2·99 to 0·78)	18 (2%)	20 (3%)	−0·22% (−1·87 to 1·43)
Insomnia	19 (2%)	8 (1%)	1·41% (−0·04 to 2·86)	18 (2%)	12 (2%)	0·79% (−0·69 to 2·28)
Decreased appetite	21 (3%)	2 (<1%)	2·47% (1·13 to 3·81)	15 (2%)	5 (<1%)	1·30% (0·05 to 2·54)
Influenza	27 (4%)	18 (2%)	1·13% (−0·70 to 2·95)	12 (2%)	20 (3%)	−0·99% (−2·51 to 0·53)

Data are number (%), unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. COPD=chronic obstructive pulmonary disease. *Incidence of adverse events in roflumilast-treated patients in study M2-125 is in descending order. †One patient was randomised twice, and included twice in the safety analysis but only once in the efficacy analysis; four patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for the safety analysis; 765 patients in the roflumilast group and 758 in the placebo group were included in the efficacy analysis. ‡Six patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for safety analysis; 772 patients in the roflumilast group and 796 in the placebo group were included in the efficacy analysis.

Table 3: **Adverse events occurring in at least 2·5% of patients in one of the treatment groups**

Discussion

Roflumilast reduced exacerbation frequency and induced consistent and significant improvements in FEV_1, both before and after bronchodilator use. Similar changes occurred in FVC and midexpiratory flow, suggesting a general improvement in operating lung volume. These changes were independent of the patient's smoking status or use of concomitant medication, such as inhaled longacting β_2 agonists, and were similar to those reported in other patient populations with COPD.[14,19]

PDE4 inhibition provides a novel approach to the treatment of patients with COPD. However, results from previous studies have shown inconsistent effects of PDE4 inhibitors on clinically relevant outcomes such as acute exacerbation frequency, although results from a post-hoc analysis suggested that roflumilast might be effective in selected patients with COPD.[13] The results from the M2-124 and M2-125 studies show that carefully defined patient groups that are particularly at risk of exacerbations benefit from treatment with roflumilast.

The effects of roflumilast in our proposed subgroups, which should be easily identified clinically, were tested in these two adequately powered studies with an identical design, undertaken in two geographically different populations. Participants in both studies were preselected for specific characteristics identified from earlier trials.[7,19] They had substantial airflow limitation (stages III and IV according to the criteria of the Global initiative for chronic Obstructive Lung Disease), documented cough and sputum production as a marker for persistent airway inflammation,[20] and a history of exacerbations treated in the year before entry into the study.

Many clinical trials identify patient subgroups that seem to respond to treatment in a secondary or post-hoc analysis, which is not confirmed in studies that are better powered.[21] In an earlier study, roflumilast did not reduce overall exacerbation rate but decreased the number of exacerbations requiring oral corticosteroids.[14] Data from our two studies confirmed this finding. Treatment with inhaled corticosteroids has been shown to prevent exacerbations, including those that are subsequently managed with oral corticosteroids.[7,22] The same holds true for treatment with roflumilast. A direct comparison of the effect of inhaled steroids or roflumilast on reduction of exacerbations cannot be directly assessed with the present data, but is worth investigation in the future. The rate of exacerbations in our placebo-treated patients was higher than in previous studies, with few episodes being treated with antibiotics alone, possibly because of our study design and patient recruitment. As in other 1-year trials in patients with COPD, roflumilast did not have much effect on episodes requiring treatment in hospital,[23–25] which were infrequent. In our studies, the number of patients needed to treat with roflumilast to prevent one exacerbation per year that was moderate or severe was 5·29 in the M2-124 study and 3·64 in the M2-125 study, irrespective of concurrent treatment with an inhaled longacting β_2 agonist.

Several secondary outcomes were assessed. Mortality rate during treatment did not differ between treatments

and was similar to other events during treatment in the first year of a large COPD survival trial.[7] The concentration of C-reactive protein was unaffected by treatment. However, the use of this marker in cardiorespiratory disease has been questioned.[26] Small but significant improvements in breathlessness assessed by the investigator-administered TDI occurred in both studies, but did not reach the agreed minimum clinically important difference. Whether this result indicates that the benefit of treatment with roflumilast is predominantly on prevention of exacerbations rather than improvement of exercise performance, or is a result of the selection criteria used will require further study.

Since we allowed patients to continue using inhaled longacting β_2 agonists throughout the study, and inhaled corticosteroids were withdrawn at entry, no conclusions can be drawn about synergy or interaction between roflumilast and other drugs; further studies will be needed to test specifically the effectiveness of inhaled corticosteroids alone or in combination with roflumilast. Whether the effects of roflumilast are additive to longacting inhaled bronchodilators is addressed by Fabbri and colleagues.[27] For practical reasons, the effect of roflumilast on breathlessness was tested rather than assessment of the global health status. In general, health status improves when the exacerbation rate falls by the magnitude seen here,[28,29] but confirmation of this association by means of a disease-specific instrument is needed for roflumilast. Changes in health status were not seen in the previous 1-year roflumilast study and the general health measure EQ-5D did not seem to identify differences in the data.[14] The health-care utilisation definition of exacerbations used in this study cannot precisely define the duration of events and might miss mild episodes.[30–32] In other studies with daily diary cards, substantially more events have been identified than in our studies, including many events that were not treated with corticosteroids or antibiotics. The results of a previous study have suggested that mild events associated with increased symptoms and use of shortacting β_2 agonists could be prevented with roflumilast;[19] the reduction in use of shortacting β_2 agonists that was noted in our studies supports this finding. Since roflumilast is an anti-inflammatory drug, we focused on its ability to change corticosteroid-treated exacerbations. There were fewer antibiotic-treated episodes than expected, possibly indicating the way investigators interpreted the study protocol. Interpretation of the data has been complicated by the pattern of patient withdrawal in these trials, which differed between treatment groups in the early and late phases. In general, this pattern would tend to result in a minimum biological effect of the active therapy by reducing the statistical power of the study comparisons. In accordance with good clinical trial practice, we focused on recruiting patients likely to adhere to treatment and, thus, caution is needed when generalising these findings to the general clinical population.

No significant neurological or cardiac toxicity was noted with roflumilast. A range of predicted adverse events occurred with roflumilast that were centrally mediated (insomnia, nausea, headache, but not vomiting) or gastrointestinal (predominantly diarrhoea). These were most evident in the first 4–12 weeks of treatment when they contributed to the early difference in withdrawal in both studies. Thereafter, no difference was noted between treatment groups in the occurrence of these adverse events and the withdrawals associated with them. Patients reported weight loss more frequently in the roflumilast groups than in the placebo groups, a finding confirmed by objective measurements. The mean weight loss of 2·1 kg (SD 4·0) over the course of the study was greatest in the first 6 months of roflumilast treatment. Patients reporting gastrointestinal or neurological symptoms lost more weight, but weight loss was still seen in patients without these side-effects. The change in bodyweight was similar irrespective of initial BMI and might not be an unwelcome treatment effect in obese patients who showed the largest absolute weight loss. We did not notice the occurrence of more pneumonias among patients in the roflumilast groups than among those in the placebo groups, whereas pneumonia was reported more frequently with inhaled corticosteroids in studies with similar patient-years of treatment exposure to our studies.[33] This increased frequency suggests that pneumonia might relate to local effects of inhaled corticosteroids rather than representing a general outcome of treatment with anti-inflammatory drugs in patients with COPD.

Our results from these clinical trials with identical design that were done in two different populations have shown that roflumilast, a PDE4 inhibitor, improves lung function and reduces the frequency of exacerbations in patients with bronchitic symptoms and severe airflow limitation. It should be noted that this treatment is not suitable for all patients because of the presence of class-related adverse effects that usually arise soon after initiation of treatment. Nonetheless, these results suggest that different subsets of patients exist within the broad range of COPD, and that specific therapies might improve disease management. This possibility should be explored further in prospective studies.

Contributors

All authors were members of the steering committee that developed the design and concept of the studies, approved the statistical plans, interpreted the data, and wrote the report. PMAC wrote the first draft of the report. U-MG and SK coordinated data gathering and SK did the statistical analysis. All authors vouch for the veracity and completeness of the data and the data analysis.

Conflicts of interest

PMAC has served on advisory boards for AstraZeneca, GlaxoSmithKline, Nycomed, and Novartis; received research funding from GlaxoSmithKline, Nycomed, and Boehringer Ingelheim; and spoken at meetings supported by AstraZeneca, GlaxoSmithKline, and Nycomed. KFR has served as a consultant, participated in advisory board meetings, and received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Pfizer, Novartis, Nycomed, Merck Sharp and Dohme, and GlaxoSmithKline; and received research funding from AltanaPharma, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, and GlaxoSmithKline. LMF has served as a consultant to AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck

Sharp and Dohme, Novartis, Nycomed, Roche, Pfizer, and Sigma-Tau; received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed, Roche, and Pfizer; and received grant support from AstraZeneca, Boehringer Ingelheim, Menarini, Schering-Plough, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Nycomed, Union Chimique Belge, Pfizer, Sigma-Tau, Italian Ministry of Health, and Italian Ministry for University and Research. FJM has been a member of advisory boards for GlaxoSmithKline, Schering-Plough, Novartis, Nycomed, Genzyme, Forest/Almirall, Talecris, and Roche; on the speaker's bureau for Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca; a member of steering committees for studies supported by Gilead, Actelion, Johnson & Johnson, United BioSource, and the National Institutes of Health; and an investigator in trials supported by Boehringer Ingelheim and Actelion. U-MG and SK are employees of Nycomed.

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Chronic Obstructive Pulmonary Diseases:
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Original Research

Effects of Roflumilast on Rehospitalization and Mortality in Patients Hospitalized with a COPD Exacerbation

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Abstract

Introduction: Hospitalization for chronic obstructive pulmonary disease (COPD) exacerbation portends the greatest risk of rehospitalization and mortality. Treatments that prevent hospitalizations could significantly lessen COPD morbidity and mortality.

Methods: We performed a prospective, randomized, double-blind, placebo-controlled study of roflumilast 500 ug daily versus placebo in patients hospitalized for acute COPD exacerbation. Primary outcome was time to all-cause mortality or non-elective rehospitalization at 180 days post-randomization. Secondary outcomes were death or hospitalization from a respiratory cause, quality of life, change in health status, forced expiratory volume in 1 second (FEV_1) and roflumilast tolerance.

Results: A total of 64 patients with moderate to severe COPD (FEV1, 37.6 ± 16.4% predicted; 61% female, 61.6 ± 7.9 years old) were assigned to roflumilast or placebo. No deaths occurred in the follow-up period. There was no difference in the time to first readmission between the roflumilast and placebo groups (46.1 days versus 47.3 days respectively, p=0.93). There were 29 and 30 readmissions in the roflumilast and placebo groups, respectively (p=0.47). The St George's Respiratory Questionnaire (SGRQ) decreased 10.8 points and 7.8 points in the roflumilast and placebo groups, respectively and were not different. EuroQuality of Life Five Dimension scale (EQ5D) scores improved, but not significantly in either group. Weight loss and nausea were more common with roflumilast but not different from placebo. Change in glycosylated hemoglobin percentage (HgbA1C%) was not different between groups. Sub-analysis for the impact of chronic bronchitis did not affect outcomes.

Conclusion: In this pilot study conducted in patients hospitalized with an exacerbation of COPD, roflumilast did not affect time to all-cause rehospitalization, quality of life, FEV_1 or any other measured parameter.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; St George's Respiratory Questionnaire, **SGRQ**; EuroQuality of Life Five Dimension scale, **EQ5D**; acute exacerbation of COPD, **AECOPD**; phosphodiesterase-4, **PDE-4**; cyclic adenosinemonphosphate, **c-AMP**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; body mass index, **BMI**; forced vital capacity, **FVC**; short-acting beta-agonist, **SABA**; long-acting beta2-agonist, **LABA**; short-acting muscarinic antagonist, **SAMA**; long-acting muscarinic antagonist, **LAMA**; modified Medical Research Council, **mMRC**; white blood count, **WBC**; glycosylated hemoglobin, **HgbA1c**

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Introduction

Chronic obstructive pulmonary disease (COPD) afflicts 24 million U.S. residents and is the 4th leading cause of death .[1,2] COPD exacerbations add considerably to that burden because they cause frequent hospitalizations and readmissions, contribute directly to the death of many patients, dramatically reduce quality of life, consume the majority of resources used to manage COPD, and may hasten the progressive loss of lung function.[3,4] Acute exacerbations of COPD (AECOPD) account for 31% to 68% of the total costs of COPD care in the United States.[5,6] Treatment that prevents or ameliorates frequent or severe AECOPD could significantly lessen COPD morbidity and mortality as well as costs.

Hospitalized exacerbations are particularly important in COPD patients because they profoundly impact patient survival, function, symptoms and health status as well as account for a significant component of COPD-related costs. A review of patients from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study[7] showed that a prior history of being hospitalized for an acute exacerbation was associated with the greatest risk of readmission (47%), and that 15% of patients reported multiple readmissions. Importantly, those with repeat hospitalizations had significantly increased mortality at 1 year.

The heightened inflammation that occurs during an acute exacerbation, especially a hospitalized exacerbation, may contribute to the higher rates of morbidity and mortality. COPD exacerbations are linked to increased airway inflammation driven by neutrophils within the airway lumen, and elevated levels of pro-inflammatory cytokines and mediators of oxidative stress (e.g., higher lipid peroxidation byproducts); up-regulated CD11/CD18 neutrophil adhesion molecules; and increased cytochrome oxidase activity that are also found in the systemic circulation.[8-11] Increases in systemic inflammation may contribute to the increased incidence of major cardiac events associated with acute exacerbations of COPD.[12]

Roflumilast is a potent inhibitor of the phosphodiesterase-4 (PDE-4) pathway and is reported to have protean anti-inflammatory properties such as inhibiting hydrolysis of cyclic adenosine monophosphate (c-AMP) in inflammatory cells and decreasing neutrophilic release of inflammatory mediators and cytokines while decreasing apoptosis and expression of cell surface markers.[13,14] Studies in patients with moderate to severe COPD who were given roflumilast have reported significant improvements in forced expiratory volume in 1 second (FEV_1) measurements and a moderate reduction in exacerbation rates.[15,16] Post hoc analyses of the REACT and RE^{2}SPOND studies suggest that roflumilast is most effective in reducing the rates of moderate or severe exacerbations in a subgroup of patients who have been hospitalized with an exacerbation of COPD within the past year.[17-19] These findings highlight the potential importance that roflumilast may have on decreasing the intensity of respiratory symptoms around the time of an acute severe exacerbation that requires hospitalization, and its potential benefit on reducing mortality and the need for readmission. However, despite data suggesting that patients hospitalized with a COPD exacerbation may benefit the most from roflumilast to decrease future events, there is no data that demonstrates the safety and efficacy of administering roflumilast to patients with moderate to very severe COPD while clinically unstable during the index hospitalization, or shortly thereafter.

In this pilot study, we assessed the safety and efficacy of roflumilast initiated in patients with moderate to very severe COPD while hospitalized with an acute exacerbation, with and without a history of chronic bronchitis, on time to all cause rehospitalization or death during the 180 days post initiation of treatment.

Methods

Study Design

We conducted a parallel-group, prospective, randomized, double blind, placebo-controlled trial of roflumilast 500 ug daily versus placebo in patients following hospitalization for a COPD exacerbation at

a single center. This was done to detect a treatment effect as the initial step to complete a power analysis in preparation to conduct a larger, multicenter, prospective, randomized and controlled trial. (Figure 1). The study was approved by our Institutional Review Board for Human Research at Temple University (IRB# 21474).

Outcomes

Outcomes included: (1) Primary: Time to all-cause mortality or rehospitalization during the 180 days post-randomization to treatment; (2) Secondary: Respiratory death or respiratory rehospitalization at 180 days post-randomization; rate of death or readmission during the 30 days post-discharge; change in FEV_1, and dyspnea from baseline to 180 days post-randomization; (3) Other: tolerance of roflumilast versus placebo in patients hospitalized due to AECOPD.

Study Population

The study population consisted of 68 patients hospitalized with AECOPD at Temple University Hospital.

Inclusion Criteria

Inclusion criteria consisted of a primary diagnosis of AECOPD defined as acute increase in dyspnea, sputum volume, and/or sputum purulence without other identified cause; hospitalization; patient age greater than 40 and less than 80 years old; cigarette smoking ≥ 10 pack years; informed written consent.

Exclusion Criteria

Exclusion criteria included a prior diagnosis or high suspicion for asthma based on investigator judgment; pulmonary edema, pneumonia, interstitial lung disease or significant bronchiectasis based on admission chest x-ray; intubated and mechanically ventilated at the time of evaluation; active liver disease, or transaminase elevations (≥ 3xULN); history of alcoholism or heavy ethanol use; history of suicidal behavior ≤ 2 years or suicidal ideation ≤ 6 months prior to enrollment; pregnant or lactating females. Those taking excluded medications: P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) and CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) were also excluded from the study.

Study Design and Synopsis

Baseline

Patients were enrolled after admission to the hospital. Both groups received Global initiative for Obstructive Lung Disease (GOLD) guideline-recommended care.[20] At baseline, all patients had a medical history and physical examination with spirometry performed. Women with the potential to become pregnant were given a pregnancy test. Dyspnea scales, Deyo-Charlson index, and GOLD classification were performed. Patients completed a Columbia Suicide Severity Rating Scale to exclude patients with a history of suicidal behavior ≤ 2 years or suicidal ideation ≤ 6 months prior to enrollment.

Randomization

Patients were randomized to 1 of 2 treatment groups using a randomized block design. One group received roflumilast 500 mcg (Daliresp®) daily and the other received a matched placebo tablet. Patients were allocated to one of these treatment arms prior to hospital discharge for a total period of 180 days post enrollment.

Day of Hospital Discharge

On the day of discharge, spirometry was performed and a questionnaire assessing any adverse events during the hospitalization was completed.

Measurements

Demographics and Medical History

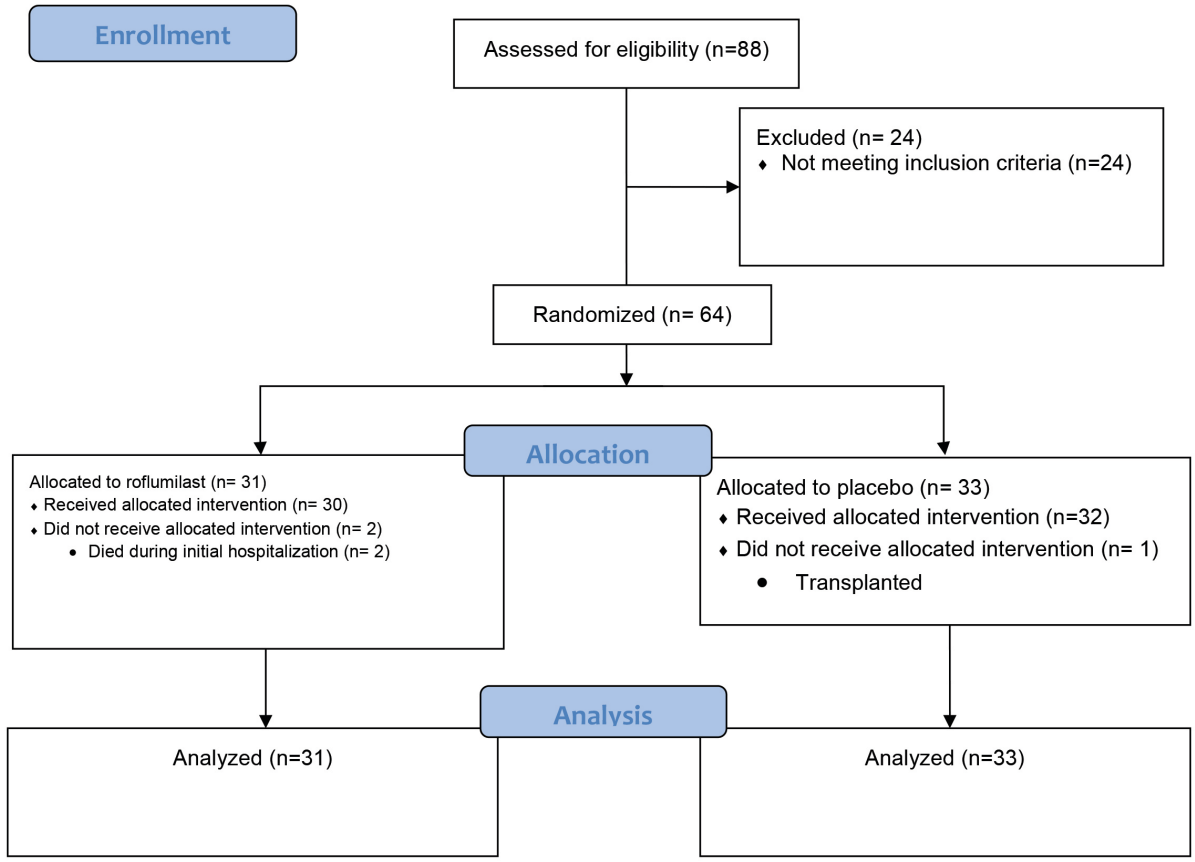
Age, gender, body mass index (BMI), presence of comorbidities, current medical therapy, history of pulmonary rehabilitation, influenza and pneumococcal vaccinations, emergency department visits and hospitalizations during the last year, number of exacerbations in prior year, history of coronary artery disease, stroke, transient ischemic attacks, and peripheral vascular disease were documented. The Deyo-Charlson index[21] was used to assess the impact of other chronic illnesses on outcome.

Spirometry

Spirometry was performed (post bronchodilator administration) at the time of enrollment (baseline) or as soon as the participant was able to perform spirometry while hospitalized, at the day of discharge and then 180 days post randomization.[22] Airflow obstruction was defined by postbronchodilator

Figure 1. Effects of Roflumilast in Hospitalized COPD on Mortality and Rehospitalization

CONSORT Flow Diagram



measured FEV_1 to forced vital capacity (FVC) ratio < 70% and FEV_1 < 70% predicted at time of inclusion and was used to define GOLD Stages.

Quality of Life and Functional Status

Patients completed general and disease-specific, self-administered quality of life and functional questionnaires: EuroQol Five Dimension scale (EQ5D)[23] and the St George's Respiratory Questionnaire (SGRQ).[24] The Columbia-Suicide Severity Rating Scale (C-SSRS)[25] was used to prospectively assess suicidal ideation and behavior using a structured interview face to face for patient responses.

Measurements of Dyspnea

Dyspnea was measured by the modified Medical Research Council (mMRC) Dyspnea score.

Description of Optimized Standard Care for COPD Exacerbations

All patients received standardized, optimized care for AECOPD. Noninvasive positive pressure ventilation was utilized at the discretion of the treating physicians but followed accepted guidelines.[26]

Drug/Placebo Supply

Roflumilast and matching placebo were provided by Forest Laboratories and subsequently Astra Zeneca and stored by the Investigational Pharmacy Unit at Temple University Hospital.

Statistical Methods

This was a pilot study and the intent was to determine if there is a signal that would justify a larger clinical trial. Therefore, the significance level was set to 0.1

and the power was set at 0.7. A total of 100 patients is required in a 2 treatment parallel-design study. There is a 70% probability that the study will detect a treatment difference at a 2-sided 10% significance level, if the true hazard ratio is 1.654. This is based on the assumption that the accrual period will be 36 months and the follow up period will be 6 months and the median time to event is 8 months. The total number of events will be 73.

Vital status was determined for all randomized patients for the intention to treat analysis. Data are presented as the mean (standard deviation) for continuous variables. Statistical comparisons were performed using the Student's t-test for continuous data and x^2 test for categorical data. Categorical and continuous data were analyzed using JMP® Pro 13.0.0© 2016 SAS Institute. Event-free survival curves were determined by Kaplan-Meier analysis, and differences between survival curves were compared using the log-rank test. Event was defined as the first readmission or death. Univariate and multivariable Cox regression was done using Stata® release 15. *P* values less than 0.05 are considered statistically significant.

Results

Patient Population

Over 500 patients were prescreened to determine eligibility for the trial. Most were initially excluded because they were identified outside of a 12-hour time enrollment window post hospitalization; because of this, the enrollment window was increased to begin the investigational drug while hospitalized. Ultimately, 88 patients were screened for study enrollment and 64 were enrolled. The consort diagram for the study is provided in Figure 1.

Patient Demographics

Baseline characteristics are provided in Table 1 . The roflumilast and placebo groups were well matched on most clinical characteristics including sex, smoking history, number of COPD exacerbations in the year prior to enrollment, level of airflow obstruction, fibrinogen levels and total white blood count (WBC), SGRQ and EQ5D scores, distribution of mMRC scores and baseline respiratory medication use. The group assigned to roflumilast were slightly older than the placebo group and had eosinophil levels that were statistically significantly higher at the time of

Table 1. Demographic and Baseline Data

Characteristic	Roflumilast N = 31	Placebo N = 33	*P*
Age – years (SD)	64.2 (7)	59.3 (8.1)	0.012
Female Sex – no. (%)	20 (61)	19 (59)	0.56
Smoking (pack years) (SD)	42.7 (27.2)	32.3 (20.2)	0.085
Number of Prior AECOPD Hospitalizations (SD)	2.3 (1.64)	2.3 (1.99)	0.91
Chronic Bronchitis Phenotype %	36%	64%	0.08
Initial Hospitalization			
Required intubation (N)	2	0	
Total care days median (IQR)	4 (2 – 6.25)	3.8 (2 – 4)	0.17
Spirometry	N = 31	N = 30	
FEV_1 % (SD)	38.9 (2.9)	36.5 (3.0)	0.56
Health-related Quality of Life	N = 29	N = 32	
Age Adjusted Deyo-Charlson Index (SD)	3.7 (1.3)	3.8 (1.6)	0.75
SGRQ Total Score (SD)	67.2 (16.6)	68.3 (11.2)	0.58
EQ5D (SD)	0.65 (0.2)	0.63 (0.2)	0.55
mMRC no.			
1	3	2	
2	3	4	
3	9	6	0.74
4	12	12	
5	1	3	
Laboratory Parameters			
Fibrinogen mg/dl (SD)	375 (109)	356 (72)	0.75
HgbA1c %	6.5 (1.6)	6.3 (1.3)	0.62
Complete Blood Count			
Hgb g/dl (SD)	12.7 (1.7)	13.2 (1.5)	0.25
Hct % (SD)	39 (4.4)	40 (4.4)	0.33
WBC (SD)	10.6 (4.5)	9.8 (2.8)	0.49
Eosinophils % (SD)	4.3 (4.0)	2.0 (3.3)	0.02
Eosinophils absolute cells/μL (SD)	39.1 (36.6)	17.4 (26.8)	0.011
Medication Use % of patients			
SABA	87%	82%	0.73
LABA	71%	79%	0.57
SAMA	32%	31%	0.87
LAMA	71%	79%	0.57
ICS	71%	79%	0.57
Theophylline	9.7%	12.5%	0.71

SD=standard deviation; AECOPD=acute exacerbation of COPD; IQR=interquartile range; FEV_1=forced expiratory volume in 1 second; SGRQ=St George's Respiratory Questionnaire; EQ5D= EuroQuality of Life Five Dimension scale; mMRC=modified Medical Research Council Dyspnea scale; HgbA1c%=glycosylated hemoglobin percentage; WBC=white blood count; SABA=short-acting beta agonist; LABA=long-acting beta2-agonist; SAMA=short-acting muscarinic antagonist; LAMA=long-acting muscarinic antagonist; ICS=inhaled corticosteroid steriod

enrollment.

Chronic Bronchitic Phenotype

Chronic bronchitis was identified using the first 2 responses on SGRQ. Individuals were classified as having SGRQ chronic bronchitic phenotype if they answered "almost every day" or "most days a week" to the following questions: "Over the last 4 weeks, I have coughed:" and "Over the last 4 weeks, I have brought up phlegm (sputum).[27] Twenty-seven patients were found to have a chronic bronchitic phenotype based on this methodology. The distribution between the 2 groups was uneven (33% roflumilast versus 67% placebo) although this did not quite reach statistical significance.

Primary Outcome Parameter:Time to COPD Readmission or Death

The primary outcome for the study was the difference between placebo and roflumilast on the time to first all cause rehospitalization or death. Although 2 patients died (both assigned to the active treatment group during the initial hospitalization) there were no deaths that occurred in the follow-up period. There was no difference in the time to first readmission between the roflumilast and placebo groups (54 days versus 55 days respectively [p=0.93]). (Figure 2)

Secondary Outcome Parameters

There was a total of 31 and 35 all-cause readmissions in the roflumilast and placebo groups respectively (p=0.93). (Table 2)

Change in Quality of Life Scores

SGRQ scores for both the roflumilast and placebo groups improved from the point of hospital discharge to the 180-day study visit. SGRQ decreased an average of 10.8 points and 7.8 points in the roflumilast and placebo groups, respectively. No significant differences were detected between groups. (Table 2)

The EQ5D scores improved slightly, but not significantly in both the roflumilast and placebo groups. No difference between groups was detected.

Change in Glycosylated Hemoglobin Percentage

The gylcosylated hemoglobin percentage (HgbA1c%) dropped slightly in both groups. No significant difference between groups. (Table 2)

Figure 2. Kaplan-Meier Survival Curve for Time to First Rehospitalization or Death

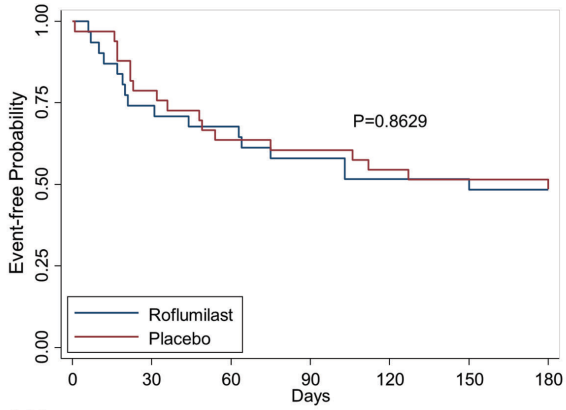


Table 2. Study Outcomes

Parameter	Roflumilast N = 31	Placebo N = 33	*P*
Total Rehospitalizations and Deaths	31	35	0.47
AECOPD rehospitalizations	21	29	
Percentage of Patients with a Rehospitalization	41%	47%	0.79
Average Number of Rehospitalizations (SD)	0.67 (1.04)	0.88 (1.43)	0.52
Time to First Rehospitalization Days (SD)	54 (52.7)	55 (49.7)	0.93
Length of Stay for Readmissions Days (SD)	4.2 (2.4)	5.1 (5.1)	0.46
SGRQ Total Score Change (SD)	-10.8 (21.2)	-7.8 (18.8)	0.68
EQ5D Score Change (SD)	0.09 (0.22)	0.08 (0.21)	0.88
mMRC Dyspnea Score Change (SD)	-0.44 (1.2)	-0.63 (1)	0.64
HgbA1C % Change (SD)	-0.04 (0.41)	-0.025 (0.23)	0.87

AECOPD=acute exacerbation of COPD; SD=standard deviation; SGRQ=St George's Respiratory Questionnaire; EQ5D=EuroQuality of Life Five Dimension scale; mMRC=modified Medical Research Council Dyspnea scale; HgbA1c%=glycosylated hemoglobin percentage

Univariate and Multivariable Analyses

Two characteristics were found to be significantly different between the roflumilast and placebo groups at baseline, age and eosinophil levels whether reported as a percentage or as an absolute number. To determine the effect of underlying clinical characteristics on the time to first exacerbation, a standard least squares regression model was developed that included the patient's age and percentage of eosinophils as these

were statistically significantly different between groups at baseline. Also included in the model were the number of prior exacerbations, which is known to affect the rate of future exacerbations and the number of pack years of smoking. The results of the univariate analysis are found in Table 3. As shown, the time to admission was related to the number of prior acute exacerbations and a higher percentage of eosinophils in the peripheral blood. Pack years, age, and treatment group assignment did not influence time to readmission. Percentage of eosinophils and number of prior exacerbations remained significant in the multivariable analysis (Table 4).

Discussion

In this single center, prospective, randomized and placebo-controlled pilot study conducted in patients hospitalized with an exacerbation of COPD, roflumilast had no effect time on all-cause mortality or rehospitalization during the 180 days post-randomization to treatment, on the number of respiratory deaths or respiratory rehospitalizations during the 180 days post-randomization; on rates of death or readmission during the 30 days post-discharge; and changes in dyspnea during the 180 days post-randomization. We found no effect of roflumilast on any of these parameters in the subgroup of patients with the chronic bronchitic phenotype. Tolerance of roflumilast in patients during the period surrounding the hospitalized COPD exacerbation was limited due to nausea and loose stools, fatigue, weight loss and headache with a frequency and severity that was similar to prior reports (Table 5). Two large, multicentered trials have shown that roflumilast, as an add-on therapy to inhaled bronchodilators in patients with moderate to severe COPD and a history of chronic bronchitis and prior exacerbations, had a 48 ml increase in FEV_1 and 17% reduction in the rate of moderate and severe exacerbations of COPD compared to placebo at 52 weeks.[28]

Another post hoc analysis of the same dataset pooling patients from the 2 studies and classifying them as frequent (≥ 2 events in prior year) or infrequent exacerbators (<2 events) showed that treatment with roflumilast shifted patients from the frequent to the more stable infrequent exacerbator state.[29] The REACT study enrolled patients with moderate to severe COPD with a history of chronic bronchitis and at least 2 exacerbations in the previous year to receive roflumilast 500 µg or placebo orally once daily together with a fixed inhaled corticosteroid and long-acting beta2-agonist combination. The rate of moderate-to-severe exacerbations was 13.2% lower in the roflumilast group than in the placebo group.[17] Another recent study (RE^2SPOND) was conducted in patients with moderate and very severe COPD, chronic bronchitis and 2 or more moderate exacerbations or hospitalizations in the previous year who were receiving inhaled beta-agonists and corticosteroids either with, or without, a long- acting anticholinergic agent to once daily roflumilast or placebo for 1 year.[18] Roflumilast failed to reduce moderate or severe exacerbations in the overall population, but was reported to improve lung function and reduce

Table 3. Univariate Analysis of Time to First Readmission or Death

Term	Hazard Ratio	*p*
Number of Prior AECOPD	1.125	0.002
Percentage Eosinophils	1.125	0.004
Pack Years	0.99	0.22
Age	1.03	0.24
Treatment group	1.06	0.86

AECOPD=acute exacerbation of COPD

Table 4. Multivariable Analysis Time to First Readmission or Death

Term	Hazard Ratio	*p*
Number of Prior AECOPDs	1.19	0.012
Eosinophil Percentage	1.11	0.013

AECOPD=acute exacerbation of COPD

Table 5. Adverse Events

	Number of Patients Reporting	
	Roflumilast	Placebo
Diarrhea	8	10
Weight Loss	7	3
Nausea	11	4
Headache	12	15
Back Pain	13	16
Insomnia	16	15
Decreased Appetite	10	8
Dizziness	9	8
Depression	8	8

AECOPD=acute exacerbation of COPD

exacerbations in the subgroup of patients with a history of more frequent exacerbations or hospitalization.

Another post hoc pooled analysis of the REACT and RE^{2}SPOND trials suggests that patients with prior hospitalization for COPD exacerbations had the greatest benefit with roflumilast in terms of reduction of future exacerbations or rehospitalizations.[19] In REACT, patients with prior hospitalization had a significant reduction in the combination of moderate and severe exacerbations and prolongation in the time to rehospitalization. Post hoc analysis of RE^{2}SPOND showed similar benefits with roflumilast, those with prior history of hospitalization had a 25% greater reduction in rehospitalization. An analysis of summary data released by the U.S. Food and Drug Administration found benefit with roflumilast reducing future exacerbations if the risk of 1 severe exacerbation per year exceeded 22%.[30] Together these results suggest that roflumilast is potentially most effective in reducing moderate to severe exacerbations in the subgroup of patients who required hospitalization in the prior year.

Why would a history of prior hospitalizations for COPD exacerbations indicate a subgroup that may have an enhanced beneficial response to roflumilast? Prior hospitalization may be an epimarker of a sicker patient group– one with more airflow obstruction, poorer health status, older age, more radiologic evidence of emphysema and leukocytosis, factors that also increase the risk for repeated hospitalization.[31] Prior hospitalizations may also indicate a patient group that is more unstable and have more active disease that is not maximally controlled by background anti-inflammatory therapy. Besides the previously described anti-inflammatory effects of roflumilast mediated by an increase in intracellular c-AMP in inflammatory cells, bronchial and smooth muscle cells and reduction in leukotrienes, reactive oxygen species and tumor necrosis factor, roflumilast may also attenuate inflammation by interrupting the proline-glycine-proline and its actelyated form breakdown of extracellular matrix generated proteins that act as neutrophilic chemoattractants.[32] These anti-inflammatory effects may be most important at the small airway level where roflumilast treatment has been reported to improve lobar ventilation in patients also treated with triple inhaled therapy assessed by functional respiratory imaging.[33] Thus, prior hospitalization may indicate a patient group that predominately suffers from small airway dysfunction that benefits from roflumilast decreasing airway resistance and enhancing the delivery of inhaled bronchodilators and steroids at the lobar level.

We did not enroll patients based on the presence of a chronic bronchitis phenotype but sought to evaluate the effects of roflumilast based on a history of 1 or more prior hospitalizations in the previous year. Although the publication was not available to us at the start of our study, this approach is partially supported by the retrospective analysis of Rabe and colleagues who found that a history of COPD hospitalization was also a predictor of a benefit to roflumilast use.[19]

Despite these potential benefits of roflumilast, we found no benefit of using roflumilast compared to matched placebo in our patient group that began roflumilast during a hospitalization for a COPD exacerbation and was followed for 180 days. The reasons for our failure to detect a treatment effect are not known but could be due to several factors. It is possible that our patient population was more impaired by airflow obstruction, hyperinflation, a greater degree of emphysema compared to prior studies or that the treatment effects of roflumilast take longer to manifest their benefits than 6 months in patients with an active ongoing exacerbation.

Other studies have also failed to detect a significant clinically meaningful short term benefit with roflumilast therapy. A prospective controlled trial showed that 12 weeks of roflumilast therapy was associated with small increases in FEV_1 and FVC and small decreases in specific airways resistance and no change in any measurement of lung hyperinflation.[34] Another prospective, randomized controlled trial in 81 patients (TREAT) who were treated at outpatient exacerbation presentation (those who required hospitalization were not included) were randomized to roflumilast or placebo for 4 weeks with a change in sputum neutrophil count being the primary endpoint.[35] Although patients treated with roflumilast had a significant reduction in percentage of sputum neutrophils and sputum myeloperoxidase, the primary endpoint, a reduction in sputum neutrophils at 2 weeks, was not different, nor was a change in lung function at 4 weeks. Additionally, adverse events and drug withdrawal were more common in the roflumilast than placebo group with a 2 kg weight loss being observed in the roflumilast group. These data suggest that the acute effects of roflumilast on attenuating airway inflammation may not be immediate, or of the

magnitude of the effect that is needed to induce a meaningful improvement in clinical outcome and may account in part for some of our trial's negative results.

Safety is always a concern when a drug that has been reported to be efficacious in a restricted patient population during a stable state in a controlled outpatient trial is utilized in a more severely ill and potentially less stable inpatient population. Most random controlled trials have shown rates of adverse effects to be about 9.5% when compared to placebo, but real-life use analyses have reported much higher adverse events rates of 69% - 72%.[36] Our rates and types of adverse events reassuringly are in line with prior random controlled trial data and suggest that the acutely hospitalized group of patients tolerated roflumilast as well as the more stable outpatient group of patients with moderate to severe COPD.

The influence of eosinophils on time to first readmission was unexpected since the absolute eosinophil number (median 15.8 cells per μL; interquartile range [IQR] 0.69 – 42.5) was well below that reported as a COPD eosinophilic phenotype of > 150 or > 300 cells per μL.[37] Kim et al, in an analysis of the AERIS cohort, found that blood eosinophil levels ≥ 2% placed individuals at risk of eosinophilic inflammation and exacerbation.[38] In our study the median eosinophil percentage for the overall study population was 1.4% (IQR 0.1% - 4.5%). As reported by Pavord et al, eosinophil numbers less than 150 cells per μL may be predictive of response to mepolizumab (and therefore related to eosinophilic inflammation) in those patients who have a historical eosinophil count ≥ 300 cells per μL.[37] Unfortunately, we do not have historical eosinophil counts collected for the patients in this study.

Our study had several important limitations that may affect our results, notably its small sample size, shorter duration of exposure (6 months), single center nature, absence of chronic bronchitic symptoms in all participants and lack of mortality events as a measurable endpoint. The trial was to be conducted at 3 sites, however 2 of these were never activated. Treatments administered prior to hospitalization were not collected as the purpose of the study was to determine the effect of roflumilast on subsequent hospitalizations. The differences we found in baseline characteristics between the intervention and control groups were unexpected. The randomization scheme was prepared by the sponsor prior to enrolling any patient into the study. We recognize that differences in prehospitalization treatments may have influenced the disparities we found in baseline eosinophil counts. The limitations of a single center design, small numbers and short duration of drug exposure were preplanned as this was a pilot study to determine the feasibility and safety and potential effect size of the intervention to design a prospective larger and longer multicenter trial in this population. The low mortality in our trial is a reflection of the small numbers and short duration of our study. We found no significant treatment effect of roflumilast in patients with chronic symptoms of chronic bronchitis (as defined by the first 2 questions of the SGRQ) in the propensity matched sub-analyses. We acknowledge the limitations of this approach in identifying chronic bronchitis in all enrolled participants, which may have influenced our negative results.

In summary, in this small single center prospective and controlled pilot efficacy study, we found no effect of roflumilast initiated during hospitalization on prolonging the time to readmission, or treatment effect on any other measured outcome in patients with, and without chronic bronchitis and severe COPD. Hopefully, a soon to be initiated comparative effectiveness trial that compares roflumilast to azithromycin on time to next readmission (RELIANCE) will provide important knowledge on the utility of roflumilast to decrease rehospitalization in patients with moderate to severe COPD.

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Author contributions: Huaqing Zhao performed the data analysis. Michael R. Jacobs and Gerard J. Criner interpreted the data. Gerard J. Criner drafted the manuscript. Gerard J. Criner, Nathaniel Marchetti and Michael R. Jacobs revised the final draft. All authors approved the final version to be published.

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Declaration of Interest

Dr. Gerard J. Criner received grants from the National Institutes of Health and the Department of Defense. He consults for AstraZeneca, Boehringer Ingelheim, Holaira, Mereo BioPharma, Third Pole, PneumRx, Pulmonx, Pearl Therapeutics, Almirall, CSA Medical, Broncus, AVISA, Lungpacer, and GlaxoSmithKline. He has also contracted clinical trials from AstraZeneca, Avisa, Mereo BioPharma, Boehringer Ingelheim,

Broncus Medical, GlaxoSmithKline, Lungpacer Medical, Pulmonx, PneumRx/BTG and Yungjin. All other authors have nothing to declare.

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ORIGINAL RESEARCH

Use of a 4-week up-titration regimen of roflumilast in patients with severe COPD

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Background: The oral selective phosphodiesterase-4 inhibitor roflumilast (ROF) reduces exacerbations in patients with severe COPD. Adverse events (AEs) can cause early ROF discontinuation. Alternative dosing strategies may help patients continue their therapy.

Methods: In this multicenter, double-blind trial, 1,321 patients with severe COPD were randomized 1:1:1 to 4 weeks' treatment with ROF 250 µg once daily (OD), 500 µg every other day (EOD), or 500 µg OD, each followed by ROF 500 µg OD for 8 weeks, plus standard therapy. The primary end point was the percentage of patients prematurely discontinuing study treatment.

Results: Patients in the 250 µg OD/500 µg OD group had significantly fewer treatment discontinuations (odds ratio [OR] 0.66 [95% CI 0.47–0.93], p=0.017) and lower rates of AEs of interest such as diarrhea, nausea, headache, decreased appetite, insomnia and abdominal pain (OR 0.63 [95% CI 0.47–0.83], p=0.001) compared with those in the 500 µg OD group. Although rates of discontinuation and AEs of interest were numerically lower with ROF 500 µg EOD/500 µg OD, the difference was not significant (OR 0.76, p=0.114, and OR 0.78, p=0.091, respectively) compared with ROF 500 µg OD.

Conclusion: A dose of ROF 250 µg OD for 4 weeks before escalation to the approved maintenance dose of 500 µg OD resulted in reduced treatment discontinuation and improved tolerability.

Keywords: roflumilast, COPD, discontinuation, adverse event

Introduction

Severe exacerbations of COPD are associated with a poor prognosis.[1–3] Roflumilast (ROF) is a selective, oral phosphodiesterase-4 (PDE4) inhibitor used for the treatment of patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[4] Previous studies have shown that ROF as an add-on to inhaled COPD therapy reduces exacerbations in this patient population.[5,6] More recently, this has been shown in the ROF and Exacerbations in patients receiving Appropriate Combination Therapy (REACT) study – in patients using ROF therapy in addition to an inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) ± long-acting muscarinic antagonist (LAMA) combination[7] – a finding most evident in those with a history of hospitalization.[8]

Patients initiating treatment with the approved 500 µg dose of ROF may report side effects in the first few weeks, including diarrhea, nausea, headache, insomnia, abdominal pain, loss of appetite and a reduction in body weight.[4,6,9] These are predominantly mild to moderate in severity and, with the exception of body weight reduction, typically transient – often resolving within the first few weeks of treatment.[10] However, they are a common cause of early treatment discontinuation. Overall rates of discontinuations for patients taking 500 µg of ROF in recent 52-week clinical trials have been in the region of 30%,[7,11] although the rates of discontinuation are thought to be higher

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in clinical practice.[12] Therefore, alternative dosing strategies to improve tolerability over the first few weeks of treatment may help patients continue their therapy.

The present study, referred to as OPTIMIZE (ClinicalTrials.gov: NCT02165826), investigated whether treatment discontinuation rates could be reduced and tolerability could be improved by using a reduced dose of ROF for a short initial treatment period. Phase I dose-ranging and modeling studies[13] have previously suggested that a daily dose of 250 µg is associated with an improved side effect profile compared with the approved 500 µg dose. However, the 250 µg dose is less efficacious, associated with less forced expiratory volume in 1 second (FEV_1) improvement, than the 500 µg dose[14,15] and is not appropriate for long-term maintenance therapy.

The 12-week OPTIMIZE study evaluated the tolerability and discontinuation rate associated with a daily dose of 250 µg ROF for the first 4 weeks, before escalation to 500 µg for 8 weeks. In a parallel treatment arm, 500 µg was given on alternate days for the first 4 weeks of treatment, before increasing to 500 µg daily. The results of both up-titration strategies were compared with 500 µg dose daily, taken continuously for 12 weeks. Pharmacokinetic analyses were undertaken to evaluate drug exposure in patients receiving the three treatment strategies to assess any correlation between drug exposure and ability to tolerate ROF.

Methods

Patients

Patients aged ≥40 years with a history of COPD associated with chronic productive cough, ≥1 moderate or severe exacerbation in the previous 12 months, and who were former/current smokers (history of ≥10 pack-years) were eligible for enrollment. A post-bronchodilator FEV_1 ≤50% of predicted and an FEV_1/forced vital capacity (FVC) ratio <70% were required. Patients had to be receiving standard of care COPD treatment (LABA or LAMA or a combination of the two for at least 12 weeks). Patients were excluded if they had a COPD exacerbation ongoing at screening, a lower respiratory tract infection unresolved within 4 weeks prior to screening, asthma/other relevant lung disease, or known α1-antitrypsin deficiency (refer Supplementary materials for the full list of inclusion/exclusion criteria). ICS and theophylline were permitted if taken at a constant daily dose for 12 weeks prior. All patients involved in the OPTMIZE trial provided their written informed consent.

Study design and interventions

OPTIMIZE was a multicenter, double-blind, Phase III randomized trial conducted over 12 weeks, which included an initial 4-week up-titration period. All patients discontinuing the trial were offered the opportunity to enter an 8-week open-label down-titration phase, during which they received ROF 250 µg OD (Figure S1).

Patients were randomized (by a computerized interactive voice response system/interactive web response system) to one of three treatment regimens (1:1:1) (Figure S1): ROF 250 µg once daily (OD) for 4 weeks and then 500 µg OD thereafter (250 µg OD/500 µg OD), ROF 500 µg every other day (EOD) for 4 weeks and then 500 µg OD thereafter (500 µg EOD/500 µg OD) or ROF 500 µg OD for 12 weeks (500 µg OD). Patients continued receiving their usual maintenance therapy.

The first 4 weeks (up-titration) of the trial were double blinded, and the remaining 8 weeks (maintenance period) were single blinded, with only the sponsor and investigators aware that the patient was receiving ROF 500 µg OD. The original randomized treatment regimen remained blinded to all parties involved in the study for the duration of the study. ROF 250 and 500 µg and placebo were supplied as identical white, round, biplane tablets in wallet cards containing 20 tablets, with identical labeling and packaging.

Patients attended clinics at screening, randomization and Weeks 2, 4, 8 and 12. Those discontinuing and entering the down-titration phase also attended clinic on Weeks 2, 4 and 8 of the down-titration. Study medication was accounted for at each visit to assess compliance.

The study protocol was approved by each respective institutional review board and followed established good clinical practice guidelines. A list of all approving institutional review boards is available in Table S1. All patients gave written informed consent for this study.

Outcomes and end points

The primary end point was the percentage of patients prematurely discontinuing study treatment for any reason during the 12-week study period. Secondary end points included the percentage of patients with adverse events (AEs) of interest (diarrhea, nausea, headache, decreased appetite, insomnia and abdominal pain) during the trial, percentage of patients prematurely discontinuing study treatment for any reason during the down-titration phase, and change in pre-bronchodilator FEV_1 during both the trial and the down-titration phase. The six types of AEs of interest used to evaluate tolerability were selected as they are the most common AEs associated with ROF treatment, the main reason for treatment discontinuation, and assumed to be related to PDE4 inhibition.

Safety assessments included monitoring AEs and assessment of Columbia-Suicide Severity Rating Scale (C-SSRS),

body weight, and body mass index (BMI). AEs of interest (occurrence and intensity) were assessed on a daily basis using diary cards. Intensity (mild/moderate/severe) was evaluated using a 7-point Likert scale.

Pharmacokinetic evaluations

Pharmacokinetics (PK) of ROF and ROF *N*-oxide were measured using 6 mL blood samples by Pharmaceutical Product Development (Middleton, WI, USA) using a high-performance liquid chromatography tandem mass spectrometer, as described previously.[16]

An integrated population PK (popPK) model was developed to predict individual ROF/ROF *N*-oxide exposure levels and total PDE4 inhibitory activity (tPDE4i) levels and assess whether patients unable to tolerate ROF 500 µg OD have drug exposure with 250 µg OD, similar to patients on a 500 µg OD dose. The integrated popPK model was developed from an earlier base model in which the structural parameters were fixed to estimates from a dataset of 21 Phase I and two Phase II/III studies.[16] This base model used combined REACT/OPTIMIZE datasets.[7,17]

Statistical analyses

A hierarchical testing approach was followed; if significance (5%) was not reached, subsequent tests were exploratory. The hierarchy of testing for the null hypothesis was first: if the percentage of patient discontinuations on ROF 250 µg OD/500 µg were not lower than or equal to that on ROF 500 µg OD by Week 12, then the percentage of patient discontinuations on ROF 500 µg EOD/500 µg OD were not lower than or equal to that on ROF 500 µg OD by Week 12 (refer Supplementary materials for full list).

The primary end point and secondary safety end points were based on the safety analysis set (SAS) and performed using a logistic regression model. For the primary end point and AEs of interest, the treatment odds ratio (OR) and relative risk (RR) between groups[18] were calculated. The secondary efficacy end point, change in pre-bronchodilator FEV_1, was based on the full analysis set (FAS) and analyzed using an analysis of covariance model.

Additional post hoc exploratory analyses were undertaken to further assess whether weight loss on ROF was related to, 1) baseline BMI, and 2) gastrointestinal AEs and/or decreased appetite (no formal statistical testing performed).

For calculation of sample size, rates of discontinuation for any reason were estimated based on pooled data from the ROF COPD pivotal studies,[6,9] which included a similar patient population to the OPTIMIZE study. Assuming a discontinuation rate of 20% with ROF 500 µg OD and 13% with either up-titration regimen, a total of 441 patients per treatment arm, 1,323 overall, would provide 80% power to declare superiority of each of ROF 250 µg OD/500 µg OD and ROF 500 µg EOD/500 µg OD versus ROF 500 µg OD for 12 weeks.

Results

Patients

The study was conducted at 161 sites across 15 countries (refer Supplementary materials for full list) between April 2014 and October 2015. In total, 1,323 patients were randomized, of whom 1,321 received treatment. A total of 104 patients entered the down-titration phase (Figure 1). Data presented hereafter are for the 12-week trial population; data on the down-titration phase are included in the Supplementary materials.

Baseline characteristics were generally balanced across the treatment arms (Table 1). Patients had a mean age of 64.6 years and were predominantly male (74.4%). Compliance with study medication ranged from 101% to 104% across treatment arms. Demographic and baseline characteristics of patients who entered the down-titration phase are presented in Table S2.

Study discontinuations

The greatest between-group difference in discontinuations occurred in the first few weeks of treatment (Figure 2A). Significantly fewer patients discontinued treatment (for any reason) in the ROF 250 µg OD/500 µg OD group compared with the ROF 500 µg OD group (18.4% versus 24.6%; RR 0.72 [95% CI 0.54–0.95], OR 0.66 [95% CI 0.47–0.93], p=0.017; Figure 2B). There were fewer treatment discontinuations in the ROF 500 µg EOD/500 µg OD group compared with the ROF 500 µg OD group, but this difference did not reach statistical significance (20.1% versus 24.6%; RR 0.81 [95% CI 0.62–1.05], OR 0.76 [95% CI 0.55–1.07], p=0.114; Figure 2). Based on the hierarchical testing approach, all interpretations of p-values after the second hierarchical test are exploratory.

Tolerability

Significantly fewer patients experienced AEs of interest in the ROF 250 µg OD/500 µg OD arm compared with the ROF 500 µg OD arm (45.4% versus 54.2%; RR 0.79 [95% CI 0.66–0.91], OR 0.63 [95% CI 0.47–0.83], p=0.001; Figure 3). The frequency of all AEs of interest was lower, and the median time to onset was longer in the ROF 250 µg OD/500 µg OD arm compared with the ROF 500 µg OD arm (Table S3). The proportion of patients reporting AEs of interest was numerically lower in the ROF 500 µg EOD/500 µg OD arm compared with the 500 µg OD arm, but

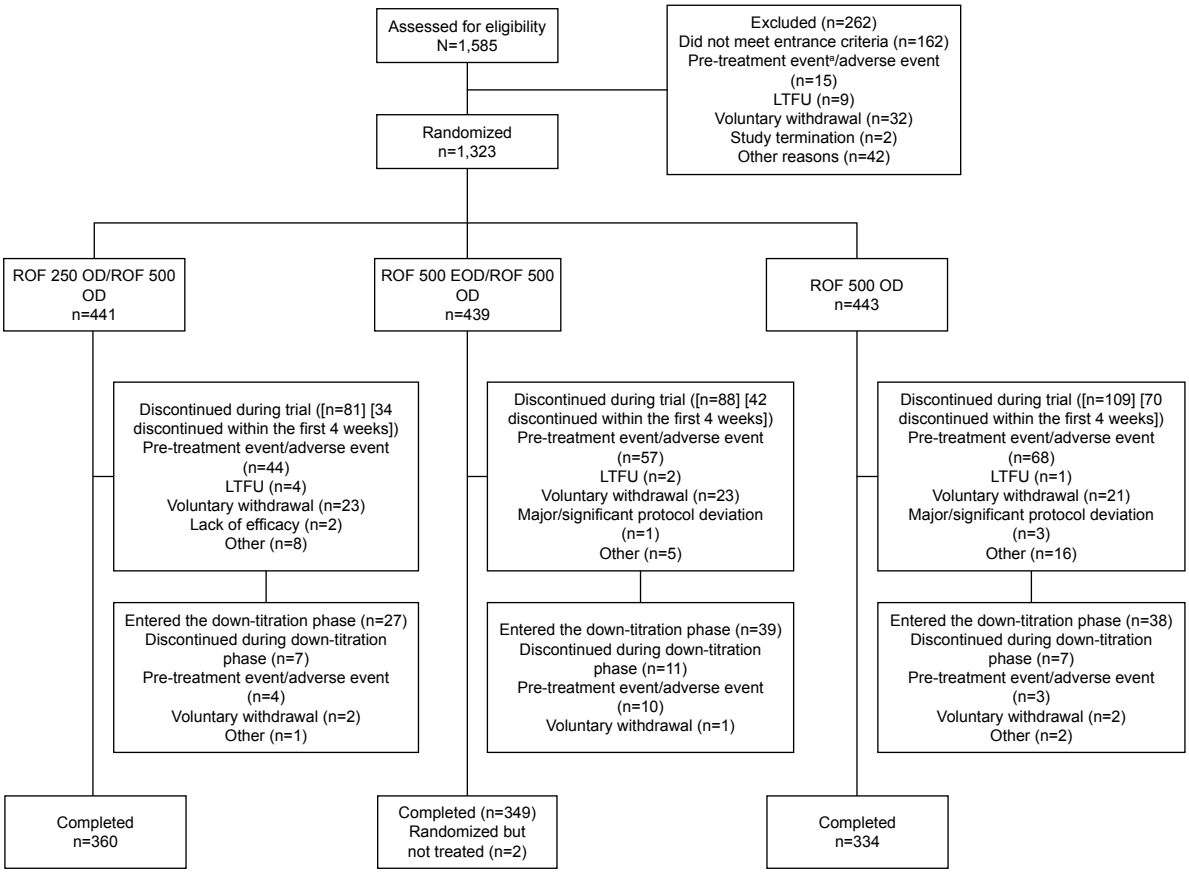

Figure 1 Patient disposition.
Notes: [a]A pre-treatment event is defined as any untoward medical occurrence in a patient who had signed written informed consent to participate in a study, but prior to administration of any study medication; it did not necessarily have to have a causal relationship with study participation.
Abbreviations: EOD, every other day; LTFU, lost to follow-up; OD, once daily; ROF, roflumilast; 250, 250 μg; 500, 500 μg.

Table 1 Baseline patient characteristics

Characteristics	ROF 250 OD/ROF 500 OD (n=441)	ROF 500 EOD/ROF 500 OD (n=437)	ROF 500 OD (n=443)
Age, years	64.2 (7.8)	65.0 (8.2)	64.6 (8.4)
Male, n (%)	320 (72.6)	325 (74.4)	338 (76.3)
White, n (%)	405 (91.8)	399 (91.3)	405 (91.4)
BMI, kg/m^2	26.4 (6.0)	26.01 (5.6)	26.46 (5.9)
Cigarette pack years	38.1 (17.5)	40.2 (19.2)	37.6 (17.7)
Current smoker, n (%)	213 (48.3)	198 (45.3)	196 (44.2)
Pre-bronchodilator FEV_1, L	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)
Pre-bronchodilator FVC, L	2.3 (0.7)	2.3 (0.7)	2.3 (0.7)
% predicted FEV_1	36.0 (8.8)	36.7 (8.8)	36.0 (9.5)
Post-bronchodilator FEV_1/FVC	0.46 (0.1)	0.47 (0.1)	0.46 (0.1)
% FEV_1 reversibility	7.1 (12.0)	6.45 (14.4)	7.4 (11.4)
≤2 exacerbations, n (%)	435 (98.6)	427 (97.7)	432 (97.5)
>2 exacerbations, n (%)	6 (1.4)	9 (2.1)	9 (2.0)
Most commonly reported concomitant medication, n (%)[a]	440 (99.8)	437 (100.0)	443 (100.0)
LAMA (tiotropium bromide)	245 (55.6)	235 (53.8)	225 (50.8)
ICS/LABA (seretide, budesonide)	202 (45.8)	197 (45.0)	217 (48.9)
Theophylline	80 (18.1)	85 (19.5)	80 (18.1)

Notes: Data are taken from the SAS and expressed as mean (SD) unless otherwise stated. [a]Taken in ≥10% of all patients.
Abbreviations: BMI, body mass index; EOD, every other day; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; OD, once daily; ROF, roflumilast; SAS, safety analysis set; SD, standard deviation; 250, 250 μg; 500, 500 μg.

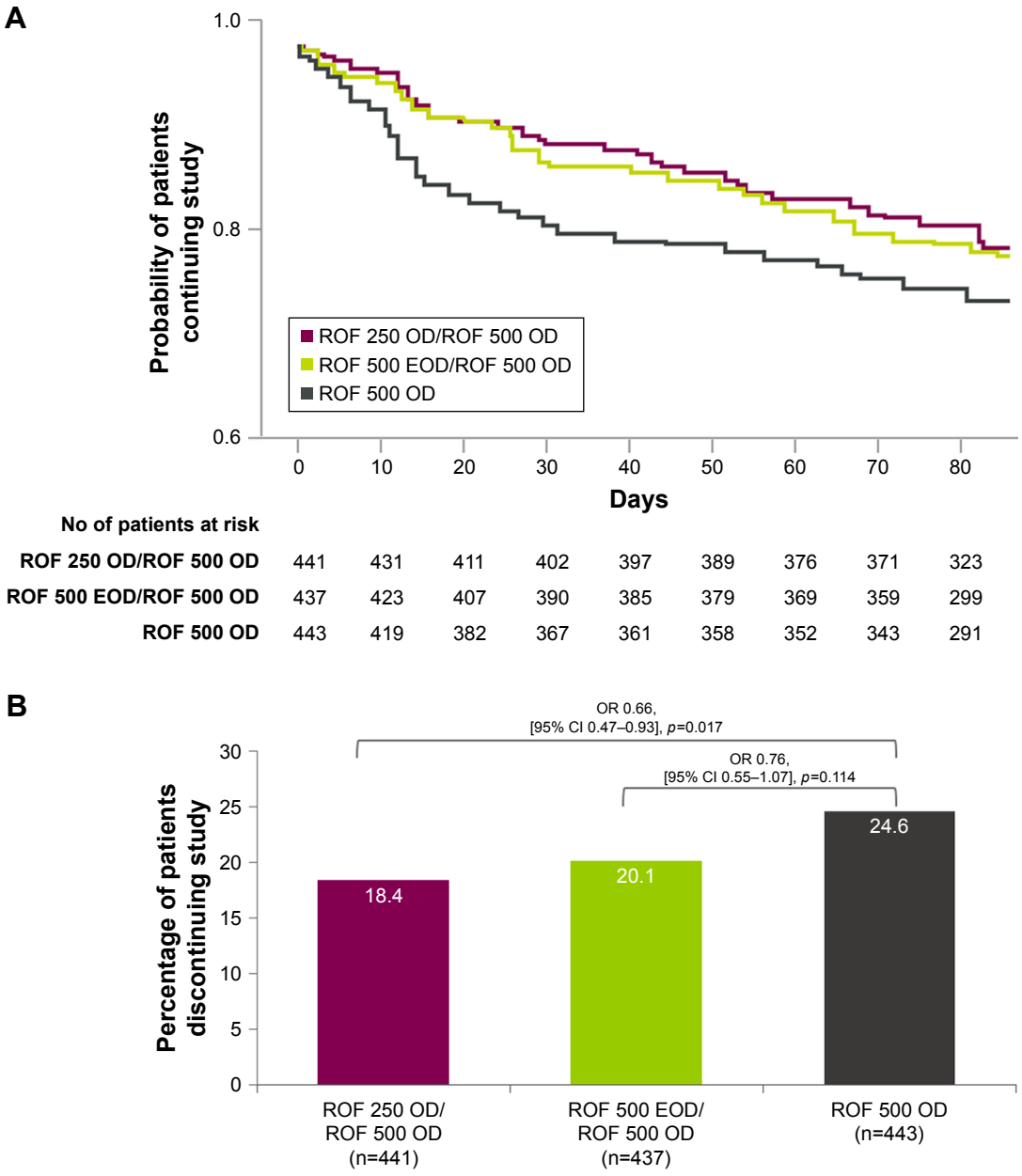

Figure 2 (**A**) Probability of patients continuing the 12-week trial for any reason (SAS). (**B**) Percentage of patients discontinuing for any reason.
Abbreviations: CI, confidence interval; EOD, every other day; OD, once daily; OR, odds ratio; ROF, roflumilast; SAS, safety analysis set; 250, 250 µg; 500, 500 µg.

the difference was not significant (48.3% versus 54.2%; OR 0.78 [95% CI 0.59–1.04, p=0.091]); (Figure 3 and Table S3). The AEs of interest were predominantly mild or moderate (Table S4) and of short duration (2–4 days; data include discontinued patients; Table S3). For each treatment arm, among patients who discontinued, the most commonly reported AE of interest was diarrhea (19.8%, 31.8%, and 33%, in the ROF 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD and the 500 µg OD arms respectively; Table S5).

The percentage of patients who withdrew from treatment due to AEs was 13.2%, 15.3%, and 17.4% with ROF 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD, respectively. AEs that most commonly led to discontinuation in the ROF 250 µg OD/500 µg OD arm, 500 µg EOD/500 µg OD arm, and 500 µg OD arm, were diarrhea (3.6%, 6.4%, and 8.1% of patients, respectively), decreased appetite (3.6%, 4.6%, and 7.4% of patients, respectively), and nausea (3.9%, 3.7%, 6.1% of patients, respectively).

Overall, 63.7% of patients experienced any AE: 61.2%, 64.3%, and 65.7% with ROF 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD, respectively. The most frequently reported AEs were those assessed as AEs

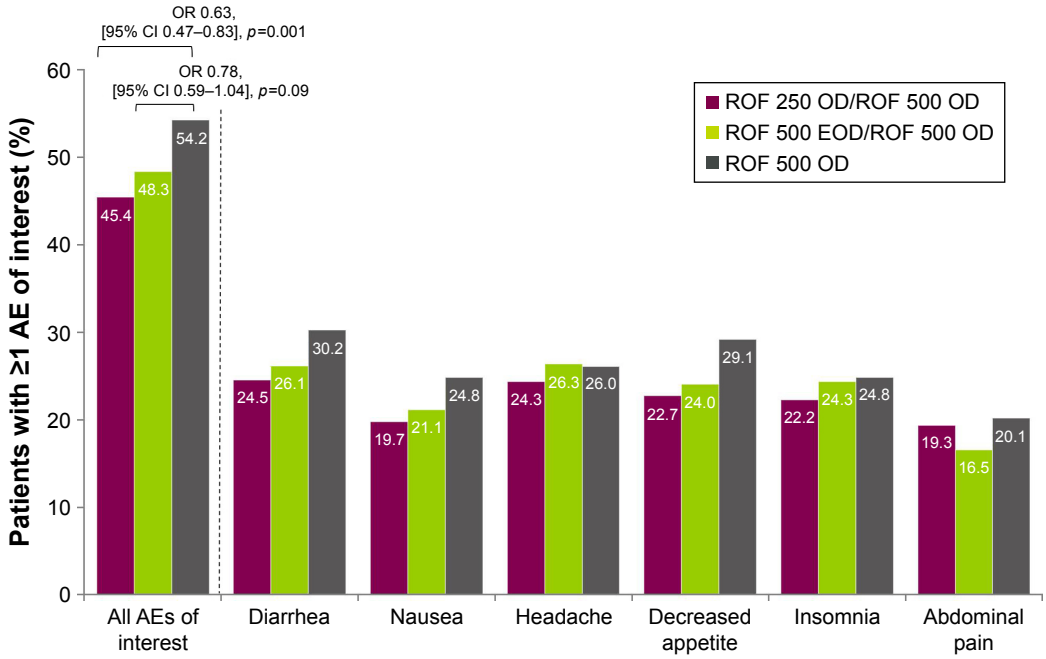

Figure 3 Summary of AEs of interest.
Note: Percentage of patients with ≥1 AE to evaluate tolerability.
Abbreviations: AE, adverse event; CI, confidence interval; EOD, every other day; OD, once daily; OR, odds ratio; ROF, roflumilast; 250, 250 μg; 500, 500 μg.

of interest. During the trial, 4.6% of patients experienced a serious AE and six deaths were reported (three in the 250 μg OD/500 μg OD arm [COPD, cardiac failure, and cardiopulmonary failure], one in the 500 μg EOD/500 μg OD arm [pneumothorax spontaneous], and two in the 500 μg OD arm [lung adenocarcinoma and myocardial infarction]). Suicidal ideation was reported in one patient in the ROF 500 μg OD group during the trial, and this patient discontinued treatment as a result.

Weight decrease was self-reported by 2.3%, 2.1%, and 3.8% of patients who received 250 μg OD/500 μg OD, 500 μg EOD/500 μg OD, and 500 μg OD, respectively. Reduction in body weight was evident from Week 2 and was of a similar magnitude across treatment groups (mean decrease 1.02, 0.82, and 0.98 kg, respectively; Figure 4). In post hoc analyses, weight loss tended to be greater in patients with a BMI >25 kg/m^2 compared with those with a BMI ≤25 kg/m^2 in all treatment groups (Table S6).

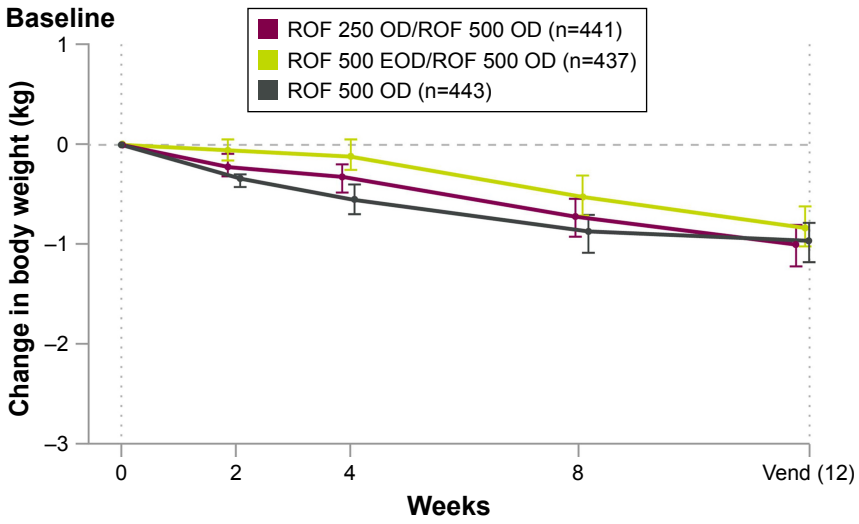

Figure 4 Mean change in body weight.
Notes: Measurements are mean, with bars showing SD. Vend was the last measurement obtained before dropout/study completion.
Abbreviations: EOD, every other day; OD, once daily; ROF, roflumilast; SD, standard deviation; 250, 250 μg; 500, 500 μg.

Lung function

Improvements from baseline in pre-bronchodilator FEV_1 over the trial were minimally different between ROF 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups (least squares [LS] mean change 90, 130, and 110 mL, respectively).

Pharmacokinetics

Individual PK parameters and tPDE4i values were derived for 1,238 patients with at least one quantifiable PK sample,[17] including 101 patients who discontinued the 12-week trial and entered the down-titration phase, of whom 76 entered after not tolerating at least one dose of ROF 500 µg. Patients who discontinued ROF 500 µg OD in the trial because of AEs of interest had a slightly higher median tPDE4i (>10%) than those able to tolerate this dose (median tPDE4i level: 1.28 and 1.16, respectively; Figure 5). However, as expected with linear PK, reducing the dose to 250 µg OD in these patients reduced tPDE4i to below that typically observed in patients able to tolerate the 500 µg OD (median tPDE4i level: 0.65).

Discussion

Although the side effects that may occur soon after initiation of ROF are often transient in nature and predominantly mild to moderate in severity, they are a common reason for discontinuing treatment. Using an alternative reduced dosing regimen for a short initial treatment period (as used successfully with other systemic therapies)[19–22] is one strategy to help increase the acceptability of ROF treatment and help patients stay on therapy. The OPTIMIZE study supports this concept. While use of a reduced dose of ROF as long-term maintenance therapy may not induce sufficient PDE4 inhibition to exert the clinical efficacy of the 500 µg dose,[14,15] it can be used as part of an up-titration regimen to overcome tolerability issues in the first weeks of treatment and hence reduce discontinuation rates.

Initiating ROF at a 250 µg daily dose for 4 weeks, before escalating to 500 µg daily dose for 8 weeks, was associated with a statistically significant decrease in the percentage of patients discontinuing treatment for any reason and reporting side effects of interest. The overall discontinuation rate for

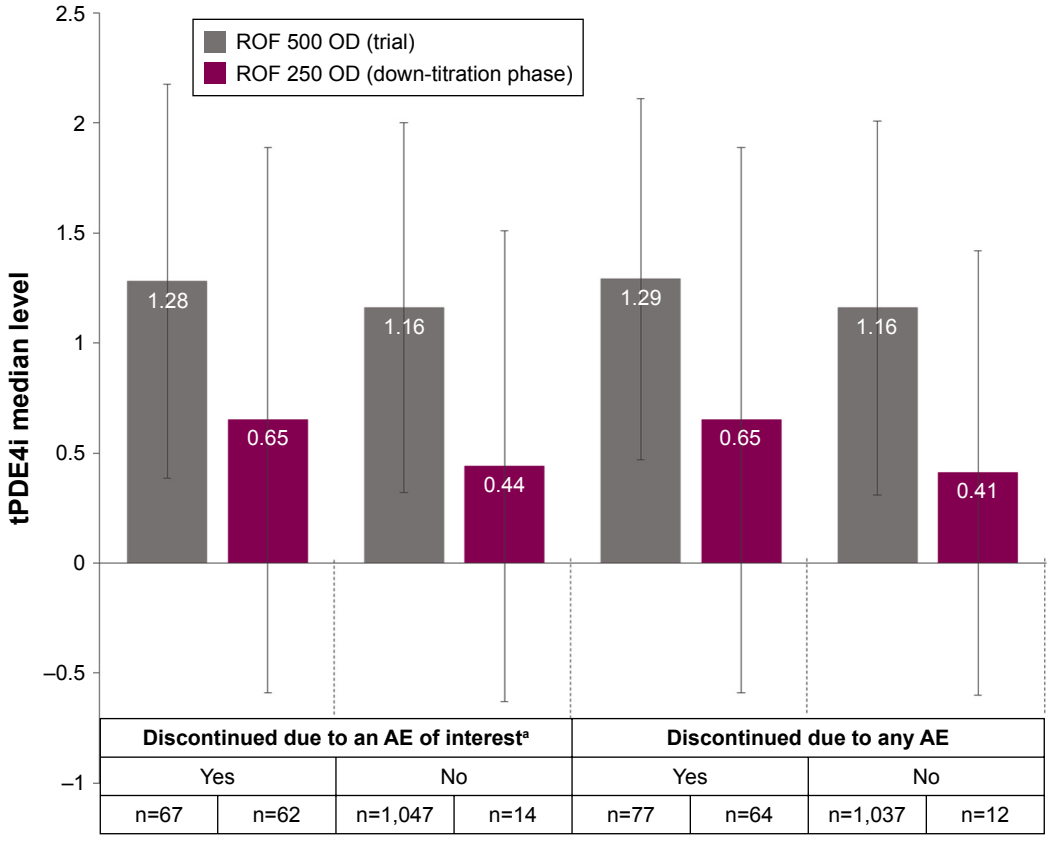

Figure 5 Comparison of tPDE4i levels achieved with ROF 500 µg or 250 µg according to whether patients were able to tolerate the dose.
Notes: Medians in trial and down-titration phase. [a]For consistency with previous popPK models, the list of preferred terms included in the AEs of interest for the popPK model is larger than that used to investigate safety in this study (Table S7). Error bars are 95% CI.
Abbreviations: AE, adverse event; CI, confidence interval; OD, once daily; popPK, population pharmacokinetics; ROF, roflumilast; tPDE4i, total phosphodiesterase-4 inhibitory activity; 250, 250 µg; 500, 500 µg.

patients taking ROF 500 µg daily in the current study was in line with that observed in recent ROF clinical trials,[7,11] and for patients starting at the reduced dosing of 250 µg daily, the odds of early discontinuation and experiencing side effects of interest were 34% and 37% lower (RR reduction 28% and 21%). Patients starting ROF at 500 µg on alternate days also reported fewer side effects and lower treatment discontinuation rates, but this was not significantly different compared with the 500 µg daily regimen.

The AEs of interest selected as a focus for OPTIMIZE study have previously been identified as limiting tolerability to ROF.[4,6,9] Diarrhea and other gastrointestinal side effects particularly, have been perceived as a barrier to ROF treatment. Diarrhea accounted for approximately one-third of discontinuations with the 500 µg dose, and this was lowered to approximately 20% with reduced dosing.

The mechanisms by which ROF causes nausea and diarrhea are believed to be distinct. Nausea is mediated by PDE4-D; located outside the blood–brain barrier, this subtype is accessible to ROF.[23] The mechanism behind diarrhea is less clear; activators of the cystic fibrosis transmembrane conductance regulator (CFTR) are known to be potent inducers of diarrhea, and it is thought that PDE4 inhibition could activate this mechanism.[24,25]

Weight loss is a known systemic side effect of ROF[6,9] and has been reported with both selective and nonselective PDE inhibitors.[26] However, it did not appear to be a significant reason for discontinuation in OPTIMIZE, accounting for <1% of discontinuations overall. Reductions in body weight were similar between all three dosing regimens and comparable with previous studies when treatment length is taken into account.[6,9] Absolute weight loss tended to be more pronounced in patients with a higher baseline BMI and in those who also experienced gastrointestinal side effects or loss of appetite with ROF (as seen previously).[6] While the mechanism by which ROF causes weight decrease remains to be fully elucidated, it is thought to be related to the effects of increased cAMP on signaling pathways regulating lipolysis.[15]

Frequency of individual side effects of interest was always lowest in the 250 µg/500 µg OD group followed by the 500 µg EOD/500 µg OD group and then the 500 µg OD group. One exception was abdominal pain; the reason for this was unclear. Frequencies of some side effects of interest were higher in this study than those reported in previous studies;[7,11] one explanation for this finding may be that OPTIMIZE, in contrast to previous studies, used a daily patient-assessed diary method to record side effects of interest. As OPTIMIZE did not include a placebo arm, the impact of the use of daily diary cards on side effect rates cannot be assessed. Additionally, levels of theophylline were not known in the 80 patients who were taking it, but may have contributed to increased reporting of side effects in these patients.

The 250 µg daily dose was selected as the appropriate reduced dose following modeling studies, suggesting an improved side effect profile, compared with the 500 µg maintenance dose.[13] Lung function measurements in OPTIMIZE revealed that the initial 4-week up-titration regimens did not appear to reduce the effect of the drug on lung function. FEV_1 improvements of ~100 mL in all treatment arms were observed; this improvement is at the upper range of changes compared with previous studies.[6,7,9,11]

Following oral dosing, ROF is rapidly converted by cytochrome P450 enzymes to its active metabolite ROF *N*-oxide, which contributes to ~90% of the tPDE4i activity.[27,28] ROF *N*-oxide is primarily cleared by the enzyme CYP3A4, and a number of covariates can affect the activity.[29,30] PK analyses found that patients who discontinued ROF 500 µg daily in the main 12-week trial of OPTIMIZE because of side effects of interest had a slightly higher median tPDE4i than those able to tolerate this dose. It is plausible that higher tPDE4i levels lead to more potential off-target effects of ROF such as nausea and diarrhea. However, as expected with linear PK, reducing the dose to 250 µg daily in these patients reduced tPDE4i to well below that typically observed in patients able to tolerate 500 µg daily. However, a daily dose of 250 µg should not be considered suitable as a therapeutic maintenance dose, as efficacy in exacerbation reduction has not been adequately demonstrated in clinical studies.

A recent Korean study retrospectively analyzed data from 85 patients with severe/very severe COPD taking either 500 µg or 250 µg ROF daily, up-titrated to 500 µg daily up to 3 months after. There was a trend toward fewer AEs and discontinuations with the reduced initial dose.[31] Similarly, a recent PK modeling analysis[13] predicted that ROF 250 µg daily and 500 µg on alternate days were associated with lower plasma drug concentrations, lower tPDE4i, and lower incidence of diarrhea, nausea, and headache compared with ROF 500 µg daily. These data support the findings of the OPTIMIZE study.

Limitations of the current study include the lack of a placebo arm, the low sample size in the down-titration phase, and a short study duration of 12 weeks compared with a long-term maintenance treatment. Nonetheless, the study population is one of the largest to investigate side effects in a targeted COPD population, and gives us confidence in the validity of our conclusions.

Conclusion

Starting ROF treatment at 250 µg daily for 4 weeks before increasing to the therapeutic maintenance dose of 500 µg daily reduced treatment discontinuations and improved the tolerability profile compared with initiating treatment at 500 µg daily. In practice, this should help patients with COPD to stay longer on treatment with the therapeutic dose. However, use of 250 µg OD as long-term maintenance therapy may not induce sufficient PDE4 inhibition to exert clinical efficacy.

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Disclosure

NB was employed by Takeda Development Centre Europe Ltd, London, UK. The authors report no other conflicts of interest in this work.

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Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD) (Review)

Herath SC, Normansell R, Maisey S, Poole P

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TABLE OF CONTENTS

[Intervention Review]

Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

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ABSTRACT

Background

There has been renewal of interest in the use of prophylactic antibiotics to reduce the frequency of exacerbations and improve quality of life in chronic obstructive pulmonary disease (COPD).

Objectives

To determine whether or not regular (continuous, intermittent or pulsed) treatment of COPD patients with prophylactic antibiotics reduces exacerbations or affects quality of life.

Search methods

We searched the Cochrane Airways Group Trials Register and bibliographies of relevant studies. The latest literature search was performed on 27 July 2018.

Selection criteria

Randomised controlled trials (RCTs) that compared prophylactic antibiotics with placebo in patients with COPD.

Data collection and analysis

We used the standard Cochrane methods. Two independent review authors selected studies for inclusion, extracted data, and assessed risk of bias. We resolved discrepancies by involving a third review author.

Main results

We included 14 studies involving 3932 participants in this review. We identified two further studies meeting inclusion criteria but both were terminated early without providing results. All studies were published between 2001 and 2015. Nine studies were of continuous macrolide antibiotics, two studies were of intermittent antibiotic prophylaxis (three times per week) and two were of pulsed antibiotic regimens (e.g. five days every eight weeks). The final study included one continuous, one intermittent and one pulsed arm. The antibiotics investigated were azithromycin, erythromycin, clarithromycin, doxycyline, roxithromycin and moxifloxacin. The study duration varied from three months to 36 months and all used intention-to-treat analysis. Most of the pooled results were of moderate quality. The risk of bias of the included studies was generally low.

The studies recruited participants with a mean age between 65 and 72 years and mostly at least moderate-severity COPD. Five studies only included participants with frequent exacerbations and two studies recruited participants requiring systemic steroids or antibiotics or both, or who were at the end stage of their disease and required oxygen. One study recruited participants with pulmonary hypertension secondary to COPD and a further study was specifically designed to asses whether eradication of *Chlamydia pneumoniae* reduced exacerbation rates.

The co-primary outcomes for this review were the number of exacerbations and quality of life.

With use of prophylactic antibiotics, the number of participants experiencing one or more exacerbations was reduced (odds ratio (OR) 0.57, 95% CI 0.42 to 0.78; participants = 2716; studies = 8; moderate-quality evidence). This represented a reduction from 61% of participants in the control group compared to 47% in the treatment group (95% CI 39% to 55%). The number needed to treat for an additional beneficial outcome with prophylactic antibiotics given for three to 12 months to prevent one person from experiencing an exacerbation (NNTB) was 8 (95% CI 5 to 17). The test for subgroup difference suggested that continuous and intermittent antibiotics may be more effective than pulsed antibiotics ($P = 0.02$, $I^2 = 73.3\%$).

The frequency of exacerbations per patient per year was also reduced with prophylactic antibiotic treatment (rate ratio 0.67; 95% CI 0.54 to 0.83; participants = 1384; studies = 5; moderate-quality evidence). Although we were unable to pool the result, six of the seven studies reporting time to first exacerbation identified an increase (i.e. benefit) with antibiotics, which was reported as statistically significant in four studies.

There was a statistically significant improvement in quality of life as measured by the St George's Respiratory Questionnaire (SGRQ) with prophylactic antibiotic treatment, but this was smaller than the four unit improvement that is regarded as being clinically significant (mean difference (MD) -1.94, 95% CI -3.13 to -0.75; participants = 2237; studies = 7, high-quality evidence).

Prophylactic antibiotics showed no significant effect on the secondary outcomes of frequency of hospital admissions, change in forced expiratory volume in one second (FEV1), serious adverse events or all-cause mortality (moderate-quality evidence). There was some evidence of benefit in exercise tolerance, but this was driven by a single study of lower methodological quality.

The adverse events that were recorded varied among the studies depending on the antibiotics used. Azithromycin was associated with significant hearing loss in the treatment group, which was in many cases reversible or partially reversible. The moxifloxacin pulsed study reported a significantly higher number of adverse events in the treatment arm due to the marked increase in gastrointestinal adverse events ($P < 0.001$). Some adverse events that led to drug discontinuation, such as development of long QTc or tinnitus, were not significantly more frequent in the treatment group than the placebo group but pose important considerations in clinical practice.

The development of antibiotic resistance in the community is of major concern. Six studies reported on this, but we were unable to combine results. One study found newly colonised participants to have higher rates of antibiotic resistance. Participants colonised with moxifloxacin-sensitive pseudomonas at initiation of therapy rapidly became resistant with the quinolone treatment. A further study with three active treatment arms found an increase in the degree of antibiotic resistance of isolates in all three arms after 13 weeks treatment.

Authors' conclusions

Use of continuous and intermittent prophylactic antibiotics results in a clinically significant benefit in reducing exacerbations in COPD patients. All studies of continuous and intermittent antibiotics used macrolides, hence the noted benefit applies only to the use of macrolide antibiotics prescribed at least three times per week. The impact of pulsed antibiotics remains uncertain and requires further research.

The studies in this review included mostly participants who were frequent exacerbators with at least moderate-severity COPD. There were also older individuals with a mean age over 65 years. The results of these studies apply only to the group of participants who were studied in these studies and may not be generalisable to other groups.

Because of concerns about antibiotic resistance and specific adverse effects, consideration of prophylactic antibiotic use should be mindful of the balance between benefits to individual patients and the potential harms to society created by antibiotic overuse. Monitoring of significant side effects including hearing loss, tinnitus, and long QTc in the community in this elderly patient group may require extra health resources.

PLAIN LANGUAGE SUMMARY

Preventative antibiotic therapy for people with COPD

What is COPD?

COPD is a common chronic respiratory disease mainly affecting people who smoke now or have done so previously. It could become the third leading cause of death worldwide by 2020. People with COPD experience gradually worsening shortness of breath and cough with sputum (phlegm) because of permanent damage to their airways and lungs. Those with COPD may have flare-ups (or exacerbations) most commonly with respiratory infections. Exacerbations may lead to further irreversible loss of lung function, as well as days off work, hospital admission, reduction in quality of life, or even death.

Why did we do this review?

We wanted to find out if giving antibiotics to prevent a flare-up ('prophylactic' antibiotics) would reduce the frequency of flare-ups and improve quality of life. Studies that were taken into consideration used either continuous prophylactic antibiotics (every day), or antibiotics that were used intermittently (three times per week) or pulsed (e.g. for five days every eight weeks)

What evidence did we find?

We carried out the latest search for studies in July 2018. We found 14 randomised controlled trials (RCTs) involving 3932 participants. All studies were published between 2001 and 2015. Nine studies were of continuous antibiotics, two studies were of intermittent antibiotic prophylaxis and two were of pulsed antibiotics. The final study included one continuous, one intermittent, one pulsed and one placebo arm. The antibiotics investigated were azithromycin, erythromycin, clarithromycin, roxithromycin, doxycycline and moxifloxacin. On average, the people involved in the studies were 65 to 72 years old and had moderate or severe COPD. Three studies included participants with frequent exacerbations and two of the studies recruited participants requiring steroid tablets or antibiotics or both, or who were at the end stage of their disease and required oxygen. One study only included people with a particular complication of COPD, involving the heart and blood vessels in the lungs (known as pulmonary hypertension).

Results and conclusions

We found that, with the use of antibiotics, the number of participants who developed an exacerbation reduced markedly. For every eight participants treated, one person would be prevented from suffering an exacerbation. However, not all the antibiotic regimens had the same impact on exacerbations. The results suggested that antibiotics given at least three times per week may be more effective than antibiotics given daily for a few days followed by a break of several weeks. We also found there may have been a benefit on patient-reported quality of life with the antibiotics. On the other hand, use of antibiotics did not significantly affect the number of deaths due to any cause, the frequency of hospitalisation, or the loss of lung function during the study period.

Even though there may be fewer exacerbations with antibiotics, there are considerable drawbacks of taking antibiotics. First, there were specific adverse events associated with the antibiotics, which differed according to the antibiotic used; second, patients have to take antibiotics regularly for months or years; finally, the resulting increase in antibiotic resistance will have implications for both individual patients and the wider community through reducing the effectiveness of currently available antibiotics.

Because of concerns about antibiotic resistance and specific adverse effects, consideration of prophylactic antibiotic use should be mindful of the balance between benefits to individual patients and the potential harms to society created by antibiotic overuse.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotics versus placebo for COPD (data from pulsed and continuous courses of antibiotics presented in the same table)

Patient or population: Adults (aged 40 or over) with COPD presenting with 1 or more exacerbations in the previous year. The two larger studies (Albert 2011; Sethi 2010) recruited participants who required systemic steroids or antibiotics for exacerbations or participants on supplemental oxygen
Settings: Outpatients presenting to hospital clinics
Intervention: Administration of an oral prophylactic antibiotic continuously or intermittently
Comparison: Administration of a placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotics versus placebo				
Number of people with one or more exacerbations WMD of follow-up of 49 weeks	**606 per 1,000**	**468 per 1,000** (393 to 546)	**OR 0.57** (0.42 to 0.78)	2716 (8 RCTs)	⊕⊕⊕◯ **Moderate**[1]	Subgroup analysis of continuous versus intermittent versus pulsed antibiotics suggested that pulsed antibiotics were less effective at reducing exacerbations (P = 0.01 for subgroup difference; I^2 = 77.3%)
Rate of exacerbation per patient/year WMD of follow-up 54 weeks			**Rate ratio 0.67** (0.54 to 0.83)	1384 (5 RCTs)	⊕⊕⊕◯ **Moderate**[2]	Test for subgroup difference between continuous and intermittent antibiotics not significant (P = 0.38; I^2 = 0%)

HRQoL, SGRQ (total score) Scale from: 0 to 100. SGRQ comprises responses to 50 items, 0 being the best possible score and 100 the worst. WMD of follow-up 48 weeks	The mean change in SGRQ ranged across control groups from a **0.9 unit increase to a 5.7 unit decrease**	The mean HRQoL (SGRQ total score) in the intervention group was **1.94 lower** (3.13 lower to 0.75 lower)		2237 (7 RCTs)	⊕⊕⊕⊕ **High**	The minimally clinically important response to treatment is described as 4 points Test for subgroup differences between continuous, intermittent and pulsed antibiotics not significant (P = 0.35; I^2 = 5.2%)
All-cause mortality WMD of follow-up 70 weeks	**78 per 1000**	**68 per 1,000** (53 to 88)	**OR 0.87** (0.66 to 1.15)	3309 (6 RCTs)	⊕⊕⊕◯ **Moderate**[3]	Test for subgroup differences between continuous, intermittent and pulsed antibiotics not significant (P = 0.60; I^2 = 0%)
Serious adverse events WMD of follow-up 51 weeks	**253 per 1000**	**229 per 1,000** (200 to 262)	**OR 0.88** (0.74 to 1.05)	2978 (9 RCTs)	⊕⊕⊕◯ **Moderate**[3]	See Effects of interventions for specific adverse events related to the individual antibiotics Test for subgroup differences between continuous, intermittent and pulsed antibiotics not significant (P = 0.60; I^2 = 0%)
Any adverse event WMD of follow-up 47 weeks	640 per 1,000	**655 per 1,000** (551 to 748)	**OR 1.07** (0.69 to 1.67)	512 (4 RCTs)	⊕⊕⊕◯ **Moderate**[3]	Test for subgroup differences between continuous, intermittent and pulsed antibiotics not significant (P = 0.28), I^2 = 21.9%)

FEV1 (mL) WMD of follow-up 26 weeks	The mean FEV1 in the control group ranged from **1,000 to 2,320 mL**	The mean FEV1 in the intervention group was **20.21 mL higher** (26.19 lower to 66.61 higher)	-	658 (6 RCTs)	⊕⊕⊕○ **Moderate**[4]	MCID for this outcomes was approximately 100 mLs. Mean difference and confidence interval lied within this MCID Test for subgroup differences between continuous, intermittent and pulsed antibiotics not significant (P = 0. 37; I^2 = 0.6%)

*The basis for the **assumed risk** was the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; $FEV1: forced expiratory volume in 1 second; HRQoL: health-related quality of life; MCID: minimum clinically important difference; SGRQ: St George's respiratory questionnaire$ **OR:** Odds ratio; **WMD**: weight mean duration

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Clinical and statistical heterogeneity between studies (I^2 = 58%), partly explained by antibiotic regimen. Downgraded once for inconsistency
[2] Clinical and statistical heterogeneity between trials (I^2 = 52%). Downgraded once for inconsistency
[3] Confidence intervals included the possibility that prophylactic antibiotics may increase or decrease mortality or adverse events. Downgraded once for imprecision
[4]Confidence interval included both a decrease or increase in FEV1 associated with the intervention. However, the mean difference and confidence interval lay within the MCID. No downgrade
[5]Studies contributing majority of weight in analysis reported outcome at approximately 3 months. Duration may be too short to detect a difference in lung function between groups. Downgraded once for indirectness

BACKGROUND

Description of the condition

The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) defines chronic obstructive pulmonary disease (COPD) as "a common, preventable and treatable disease, that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar *(small air sacs within the lungs where gas exchange takes place)* abnormalities usually caused by significant exposure to noxious particles or gases" (GOLD 2018). It has become a leading cause of morbidity and mortality worldwide, with latest figures suggesting it was responsible for approximately 3.2 million deaths globally in 2015, making it the fourth leading cause of death that year (WHO). Projections estimate it will become the third leading cause of death worldwide by 2020, due to an aging global population with prolonged exposure to COPD risk factors (GOLD 2018). COPD in high-income countries is almost exclusively a disease of tobacco smoking, although a small proportion of nonsmokers have COPD secondary to passive smoking or genetic diseases, including alpha$_1$ antitrypsin deficiency (nonsmokers with COPD are usually excluded from clinical trials). In lower-income countries the major risk factor is indoor pollution (burning wood for heating or biomass fuels for cooking) which contributes more than smoking to the disease burden (WHO). Most reported deaths due to COPD are from high- and middle-income countries; however, it is estimated that 90% of COPD-related deaths occur in low-middle-income countries, where population-based prevention strategies are either inaccessible or not implemented (WHO).

COPD is diagnosed by spirometry (a type of breathing assessment) and clinical symptoms of dyspnoea (difficulty breathing), chronic cough, or sputum production and a history of exposure to known risk factors, e.g. smoking. To make the diagnosis, a post-bronchodilator cut-off of a ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) less than 0.7 is used as an objective measure of airflow limitation. To individualise the management of COPD for each patient, GOLD has developed staging systems to classify severity. Patients are graded from stage one to stage four according to spirometric criteria, with stage one representing mild airflow obstruction (FEV1 $\geq$ 80% predicted), stage two moderate (FEV1 < 80% but $\geq$ 50% predicted), stage three severe (FEV1 < 50% but $\geq$ 30% predicted) and stage four very severe (FEV1 < 30%) (GOLD 2018). However, the most recent report de-emphasises FEV1 as a useful prognostic tool at an individual level and instead focuses on functional limitation and symptoms to guide therapy for stable COPD (Group A: 0 to 1 exacerbations not leading to hospital admission and COPD assessment test (CAT) score < 10 or Modified Medical Research Council Dyspnea Scale (MMRC) 0 to 1; group B: 0 to 1 exacerbations not leading to hospital admission and CAT $\geq$ 10 or MMRC $\geq$ 2; group C: $\geq$ 2 exacerbations or $\geq$ 1 exacerbation leading to hospital admission and CAT < 10 or MMRC 0 to 1; group D: $\geq$ 2 exacerbations or $\geq$ 1 exacerbation leading to hospital admission and CAT $\geq$ 10 or MMRC $\geq$ 2)).

Many people with COPD experience acute exacerbations, which are defined as "an acute worsening of respiratory symptoms that result in additional therapy" (GOLD 2018). Exacerbations of COPD range in severity between individuals, have a substantial impact on quality of life and contribute to overall disease progression (GOLD 2018). Therefore, preventing and treating exacerbations is an important part of COPD management in order to improve quality of life and prognostic outcomes. Exacerbations of COPD are a common cause of days off work and hospital admissions (TSANZ 2004), and so have a significant socioeconomic impact globally. Furthermore the long-term prognosis following hospitalisation for an exacerbation of COPD is poor, with a five-year mortality rate of approximately 50% (GOLD 2018).

Respiratory infections are known triggers for COPD exacerbations, with current evidence suggesting that viral infections account for the majority of exacerbations (GOLD 2018; Woodhead 2011). However, bacterial respiratory infections and changes in the local environment, such as an increase in air pollution, are also recognised as exacerbation triggers (Papi 2006). The role of bacteria in exacerbations is an area that has been greatly studied, yet remains controversial. It has been demonstrated that respiratory bacterial loads are greater in patients with stable COPD compared to healthy individuals, and that the bacterial loads increase with disease severity (Beasley 2012). However, the high bacterial isolation rates in stable COPD makes it difficult to identify a causative role of bacteria in exacerbations. Despite this, studies do suggest an increase in bacterial infection rates amongst participants with acute COPD exacerbations (Beasley 2012). Wilkinson 2006 found that the prevalence of potentially pathogenic microorganisms rose from 48.2% at baseline in stable COPD participants to 69.6% in the same group of participants at the time of an exacerbation. The most commonly isolated bacterial organisms in COPD exacerbations include "*Haemophilus influenzae* (11% of all exacerbating participants), *Streptococcus pneumoniae* (10%), *Moraxella catarrhalis* (10%) and *Pseudomonas aeruginosa* (4%), with Gram-negative bacteria occurring more rarely" (Sapey 2006).

There are numerous evidence-based approaches that aim to reduce the number of COPD exacerbations. An essential first step is the avoidance of cigarette smoke and air pollution, wherever possible. Furthermore, vaccination against influenza is a universally accepted measure to prevent COPD exacerbations. Vaccination for pneumococcal disease may also reduce pneumonia and COPD exacerbations (Lee 2007). Inhaled medications shown to reduce exacerbation frequency include tiotropium, a long-acting muscarinic antagonist (LAMA, UPLIFT 2008), long-acting beta agonists (LABA, Wang 2012) and corticosteroids (ICS, TORCH 2007). Oral medications shown to reduce exacerbations include phosphodiesterase 4 (PDE_4) inhibitors (Chong 2017) and mucolytic agents (drugs that help break down sputum making it eas-

ier to cough up) (Poole 2012).

Description of the intervention

One approach to reduce exacerbation frequency has been to use prophylactic antibiotics. The word prophylactic comes from the Greek for 'an advance guard', an apt term for a measure taken to fend off a disease or another unwanted consequence. A prophylactic intervention is a medication or treatment designed and used to prevent a disease from occurring. Thirty years ago, the use of prophylactic antibiotics was common for chronic bronchitis in both the United Kingdom and elsewhere, but concerns over effectiveness and antibiotic resistance led to a decline in this approach.

How the intervention might work

COPD is characterised by persistent airways inflammation due to chronic bacterial colonisation of the damaged respiratory epithelium (the layer of cells lining the airways) leading to the continuing release of bacterial and host-mediated pro-inflammatory factors and additional epithelial damage (Matkovic 2013; Sethi 2008). In an exacerbation, there is superimposed acute inflammation (Hurst 2006). By reducing bacterial colonisation, chronic antibiotic therapy could help in reducing progression of the disease by breaking the above vicious cycle. In addition, some antibiotics have intrinsic anti-inflammatory properties (Martinez 2008).

Why it is important to do this review

This review incorporates and builds upon earlier Cochrane reviews.The most recent review concluded that the "use of continuous prophylactic macrolide antibiotics for a period of up to 12 months is likely to reduce the number of patients with exacerbations and exacerbation frequency, increase the median time to first exacerbation and possibly health-related quality of life" (Herath 2013). However, adverse effects and the potential for the development of antibiotic resistance remain a concern. Since the 2013 review, a number of new studies into prophylactic antibiotic use in COPD have been published. Given the fine balance between the need to reduce exacerbation frequency in COPD, with the threat of widespread antibiotic resistance, it is important that the most up-to-date research is incorporated into this review, so that physicians and patients can make well informed decisions before embarking on long-term treatment. This updated review also expands on the analysis of specific prophylactic antibiotic regimens including continuous, intermittent, and pulsed regimens to determine their relative efficacy and safety. Furthermore, many of the new studies have included more comprehensive assessments of quality of life indicators, which were not previously explored in great detail.

OBJECTIVES

To determine whether or not regular (continuous, intermittent or pulsed) treatment of COPD patients with prophylactic antibiotics reduces exacerbations or affects quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of antibiotic versus placebo. Trials comparing different antibiotics head-to-head will form the basis of another review. We planned to include cluster-randomised trials and crossover trials, if found.

Types of participants

We included studies of adults (older than 18 years of age) with a diagnosis of COPD, as defined by the American Thoracic Society, European Respiratory Society or GOLD, with airflow obstruction evident by spirometry (post-bronchodilator FEV1 of less than 80% of the predicted value and an FEV1/FVC of 0.7 or less). The review included studies only if they confirmed diagnosis with lung function testing (spirometry).

We excluded studies of participants with bronchiectasis, asthma, or genetic diseases, such as cystic fibrosis or primary ciliary dyskinesia (which may also lead to chronic airflow limitation as part of a secondary process). Where we encountered trials that included participants with these diseases in addition to participants with COPD, we only extracted the data for the participants with COPD, where the data were presented separately. However, although the studies excluded participants with clinical presentation of bronchiectasis, computed tomography (CT) screening to confirm radiological evidence of bronchiectasis was performed only in two studies (Albert 2011 and Uzun 2014) prior to study entry.

Types of interventions

We included studies of oral antibiotics, including penicillin (amoxycillin, amoxicillin, clavulanic acid), tetracycline (doxycycline, tetracycline), quinolones (ciprofloxacin, moxifloxacin), macrolides (clarithromycin, erythromycin, roxithromycin, azithromycin) and sulphonamides (co-trimoxazole), administered in appropriate doses for a period of at least three months.

Types of outcome measures

Primary outcomes

1. Number of exacerbations, using an accepted definition. This included total numbers of participants with one or more exacerbation as well as the frequency of exacerbations in the study period and time to first exacerbation.
2. Health-related quality of life, using an accepted measure such as the St George's Respiratory Questionnaire (SGRQ) (Jones 2009) or Chronic Respiratory Diseases Questionnaire (CRQ) (Guyatt 1987).

Secondary outcomes

1. Duration and severity (using an accepted definition) of exacerbations;
2. Days of disability (defined as days where the participant was unable to undertake normal activities);
3. Frequency and duration of hospital admissions;
4. Reduction in lung function from baseline, as measured by FEV1 and FVC;
5. Drug resistance as measured by microbial sensitivity;
6. Death due to all-cause mortality, as well as due to respiratory causes;
7. Adverse effects.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Trials Register up to 27 July 2018 with no restrictions on language or type of publication. The Cochrane Airways Trials Register is maintained by the information specialist for Cochrane Airways and contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS);
2. Weekly searches of MEDLINE Ovid SP;
3. Weekly searches of Embase Ovid SP;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We conducted a search of ClinicalTrials.gov with the search strategy in Appendix 3 up to 27 July 2018. For the 2018 update, we managed references using Rayyan (Ouzzani 2016).

Searching other resources

We checked the reference lists of all eligible primary studies and review articles for additional references. For the original review, we contacted authors of Mygind 2010 and asked them to supply the data from their unpublished study. For the 2018 update, we contacted the authors of all newly included studies and we are grateful for the responses received from the authors of Berkhof 2013; Shafuddin 2015; Simpson 2014 and Uzun 2014. We have checked the references of the included and excluded studies from the previous review on chronic bronchitis for possible studies (Staykova 2003).

Data collection and analysis

Selection of studies

For this update, two review authors (SH and RN) independently screened the abstracts of studies identified by the search as to whether or not they met our inclusion criteria. We obtained the full texts of publications for those that were considered definite or possible for inclusion. These were then reviewed independently by two review authors (SH and RN) to assess eligibility. We resolved any disagreement by discussion and consensus followed by an independent opinion from the third investigator (PP).

Data extraction and management

Both review authors independently extracted the data from the eligible studies.

We extracted the following data.

- Methods: study design, duration of follow-up.
- Participants: age, gender, smoking status, study setting, inclusion and exclusion criteria.
- Intervention: drug name, dose, duration of treatment, control or standard therapy.
- Information on outcome measures.

Where appropriate, we have combined the data from studies using RevMan 5 2008.

Assessment of risk of bias in included studies

Two investigators independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic*

Reviews of Interventions (Higgins 2011). Any disagreement was resolved by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear risk.

Measures of treatment effect

Results for continuous variables were expressed using a random-effects model mean difference (MD) with 95% confidence interval (CI). Results for pooled outcomes with dichotomous variables were expressed using a random-effects model odds ratio (OR) with 95% CI. We regarded a P value of less than 0.05 as statistically significant. We combined rate data (e.g. number of exacerbations per participant per year) using generic inverse variance (GIV) and expressed the outcome as a rate ratio.

For ease of communication and clarity, the number needed to treat for an additional beneficial outcome (NNTB) was derived from the OR and mean control group event rate using Visual Rx.

Unit of analysis issues

We did not find any crossover trials or cluster-randomised trials that met our inclusion criteria. However, if we had encountered them, we planned to evaluate the cluster-randomised trials for trial quality and, if the design and analysis were of poor quality, exclude them. We planned to analyse any eligible cluster-randomised trials with the help of a statistician.

Dealing with missing data

We contacted the investigators from Mygind 2010 in writing in order to verify key study characteristics and to obtain missing numerical outcome data. We were unable to get more details.

Assessment of heterogeneity

From the forest plot, we tested for heterogeneity where the CIs did not overlap with each other. We used the I^2 statistic to measure heterogeneity among the studies in each analysis. Where we identified heterogeneity ($I^2 \geq 40\%$), we explored this using a prespecified subgroup analysis. We used the following overlapping cut-off to define heterogeneity (Higgins 2011).

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity

Assessment of reporting biases

Where we suspected reporting bias, we attempted to contact the study authors to ask them to provide the missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, the impact of including such studies in the overall assessment of results was explored by a sensitivity analysis**.**

Data synthesis

For the 2018 update, we subgrouped all meta-analyses by regimen, grouping interventions into continuous (i.e. daily) antibiotic use, intermittent (e.g. two or three times per week) antibiotic use and pulsed (e.g. daily for five days every four weeks) antibiotic use. We performed meta-analysis only where the study populations were sufficiently similar for pooling to make sense.

We created a 'Summary of findings' table using the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and GRADEpro software for the following outcomes.

1. Number of exacerbations, using an accepted definition.
2. Days of disability (defined as days where the participant was unable to undertake normal activities).
3. Frequency and duration of hospital admissions.
4. Health-related quality of life, using an accepted measure such as SGRQ or CRQ.
5. Death.
6. Drug resistance.
7. Other adverse effects of treatment.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses for the primary outcome (number of exacerbations).

1. Severity of COPD according to FEV1 and the GOLD criteria.
2. Type of antibiotic.
3. Duration of antibiotic use ($\geq$ 3 months to < 6 months, $\geq$ 6 months to < 12 months and $\geq$ 12 months).
4. Year of conduct of study (2005 to 2009, 2010 to 2014 and 2014 to 2019)
5. Whether the antibiotic was used primarily as an antimicrobial or as an anti-inflammatory agent.
6. Treatment regimen including dose, frequency, route of administration.
7. History of exacerbations (studies in which participants were only included in they had experienced at least one exacerbation in the preceding year versus those in which exacerbation history was not an inclusion criteria).

Sensitivity analysis

We conducted a sensitivity analysis on our primary outcome (people with one or more exacerbations) by removing studies judged

to be at high or unclear risk of bias for the domains of sequence generation, allocation concealment, or blinding.

RESULTS

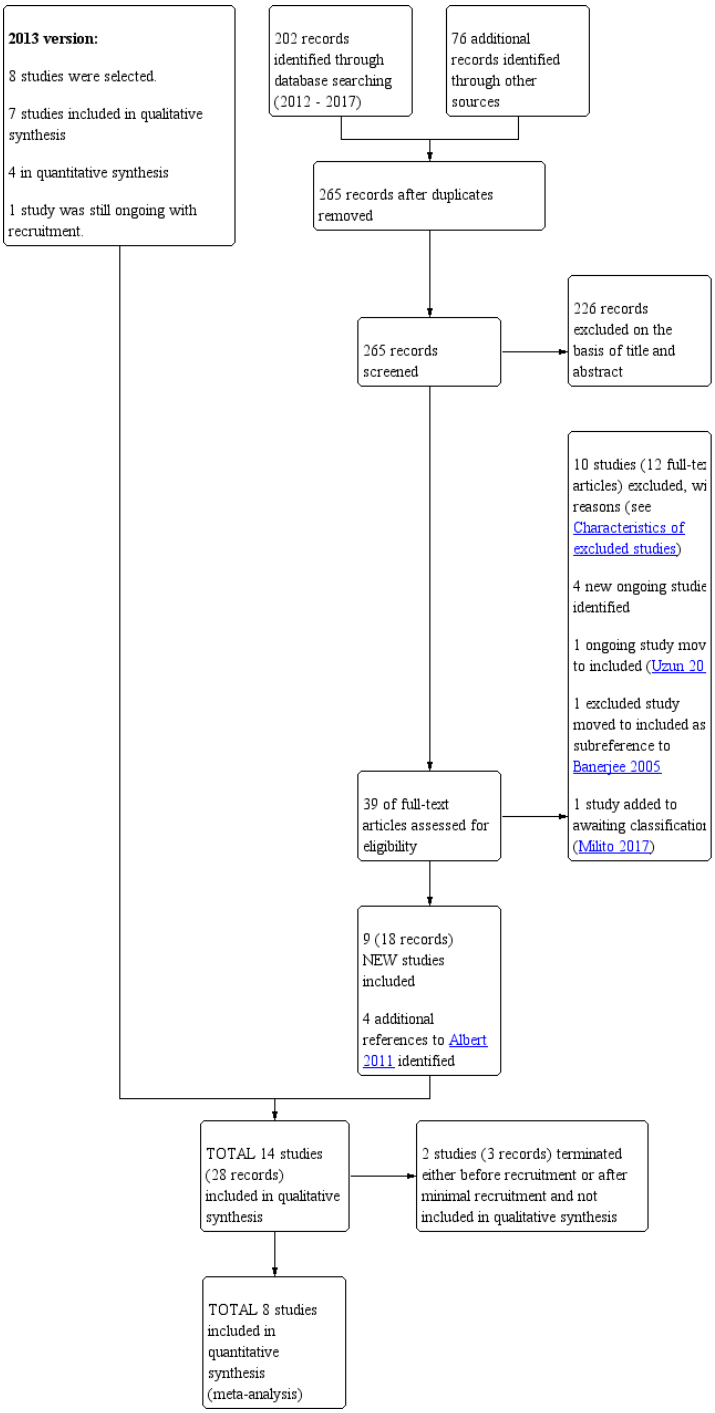
Description of studies

Results of the search

We included seven studies in the 2013 version of this review. For the 2018 update, we identified 202 records through database searching and a further 76 additional records through other sources. We screened 265 records after removing duplicates. We excluded 226 records on the basis of the title and abstracts, leaving 39 full-text articles which we assessed for eligibility. Of these, we excluded 10 studies (12 full-text articles) and identified one as awaiting classification (Characteristics of studies awaiting classification). We identified four new ongoing studies, four new references to an included study (Albert 2011) and one ongoing study was moved to the included studies section (Uzun 2014). We moved one study from the excluded studies section to be a subreference of an included study (Banerjee 2005).

We identified nine new studies that were eligible for inclusion in this systematic review, taking the total number of eligible studies to 16 (Figure 1).

Figure 1. Study flow diagram: review update



Included studies

We identified 16 studies as eligible for the systematic review (Albert 2011; Banerjee 2005; Berkhof 2013; Brill 2015; He 2010; Mygind 2010; NCT00524095; NCT02628769; Seemungal 2008; Sethi 2010; Shafuddin 2015; Simpson 2014; Suzuki 2001; Tan 2016; Uzun 2014; Wang 2017). The study durations varied from three to 36 months. For reasons not given, one study was terminated before the treatment phase (NCT00524095) and another was terminated after enrolment of five participants due to hepatotoxicity of the study drug, solithromycin (NCT02628769). See Characteristics of included studies and Table 1 for further details.

From this point forward, we will describe only the 14 completed studies, involving 3932 participants.

Nine studies involving 1925 participants investigated continuous macrolide antibiotics administered on at least a daily basis. These included azithromycin (Albert 2011; Simpson 2014; Wang 2017), erythromycin (He 2010; Seemungal 2008; Suzuki 2001; Tan 2016), roxithromycin (Shafuddin 2015), and clarithromycin (Banerjee 2005). Shafuddin 2015 compared the combination of a macrolide and tetracycline (roxithromycin and doxycycline) with roxithromycin alone, and included a placebo arm.

Two studies involving 176 participants investigated intermittent antibiotics which were administered three times a week for 12 weeks and 12 months respectively (Berkhof 2013; Uzun 2014).

Two studies involving 1732 participants investigated pulsed antibiotic prophylaxis (Mygind 2010; Sethi 2010). In Mygind 2010, azithromycin was given for three days every month for 36 months and in Sethi 2010, moxifloxacin was given for five days every eight weeks for a total of six antibiotic courses.

One study that involved 99 participants compared three treatment arms with placebo for a duration of 13 weeks. One arm involved a continuous regimen (doxycycline 100 mg daily), one arm involved an intermittent regimen (azithromycin 250 mg for 3 times a week) and one arm involved a pulsed regimen (moxifloxacin daily for five days every four weeks) (Brill 2015). As such, Brill 2015 was included in the subgroup analyses for all three regimen groups, with the control group split three ways.

All except one study (Wang 2017) were randomised, placebo-controlled, parallel group trials. Ten studies were double-blinded. One was single-blinded (Brill 2015), one was not blinded (Suzuki 2001), and there were no comments regarding blinding methods in two of the studies (Tan 2016; Wang 2017). All studies were published in journals except Mygind 2010, which was an oral presentation at the European Respiratory Society Conference in 2010. The studies were published or presented between 2001 and 2017.

All studies, except Tan 2016 and Wang 2017, listed exacerbation frequency and/or health-related quality of life as primary, co-primary or secondary outcomes. Twelve studies were analysed using intention-to-treat analysis. For two studies, it was unclear if intention-to-treat analysis was used (Tan 2016; Wang 2017). Sethi 2010 reported both a per protocol analysis as well as an intention-to-treat analysis, but, for the review, we have included only the intention-to-treat analysis results.

Of note, the Shafuddin 2015 study was originally designed "to test the hypothesis that *Chlamydia pneumoniae* (now *Chlamydophilia pneumoniae*) was a pathogenic factor in the aetiology of COPD and that eradication of *C. pneumoniae* infections could reduce exacerbation rates". In view of this original hypothesis, the study design was such that all included participants tested positive for *C. pneumoniae*, and the antibiotic regimens were chosen with the aim of eradicating *C. pneumoniae* infection specifically. This included a combined treatment arm of roxithromycin and doxycycline, which was thought to be more successful at eradicating *C. pneumoniae* compared to roxithromycin alone. In their background text, the authors explained that "this hypothesis is now considered unsubstantiated and is no longer believed to be clinically relevant". However, they have used their collected data to examine the effect of prophylactic antibiotic therapy on COPD exacerbations, reporting that their data may reasonably be applied to the general COPD population with frequent exacerbations, as differences between their included participants with *C. pneumoniae* are unlikely to have an effect on efficacy endpoints or the interpretation of results (Shafuddin 2015).

Study funding

Albert 2011 was supported by grants from the National Institutes of Health, Banerjee 2005 received a grant from Abbott, Berkhof 2013 received financial support from Stichting Astma Bestrijding, Brill 2015 was funded by the National Institute for Health Research, He 2010 was supported by grants from the National Nature Science Foundation of China, Seemungal 2008 was supported by the British Lung foundation, Sethi 2010 was supported by a research grant from Bayer HealthCare AB, Shafuddin 2015 was supported by Sanofi-Aventis Australia Pty Ltd, Simpson 2014 was funded by the National Health and Medical Research Council of Australia, Tan 2016 was funded by the National Nature Science Foundation of China and the Guangxi Natural Science Foundation, and Uzun 2014 was funded by a trust called SoLong, which is associated with the department of Respiratory Medicine of the Amphia Hospital in the Netherlands. From the material available to us, the funding for Mygind 2010 and Suzuki 2001 was unclear. Wang 2017 reported that they had no grant support or financial disclosures.

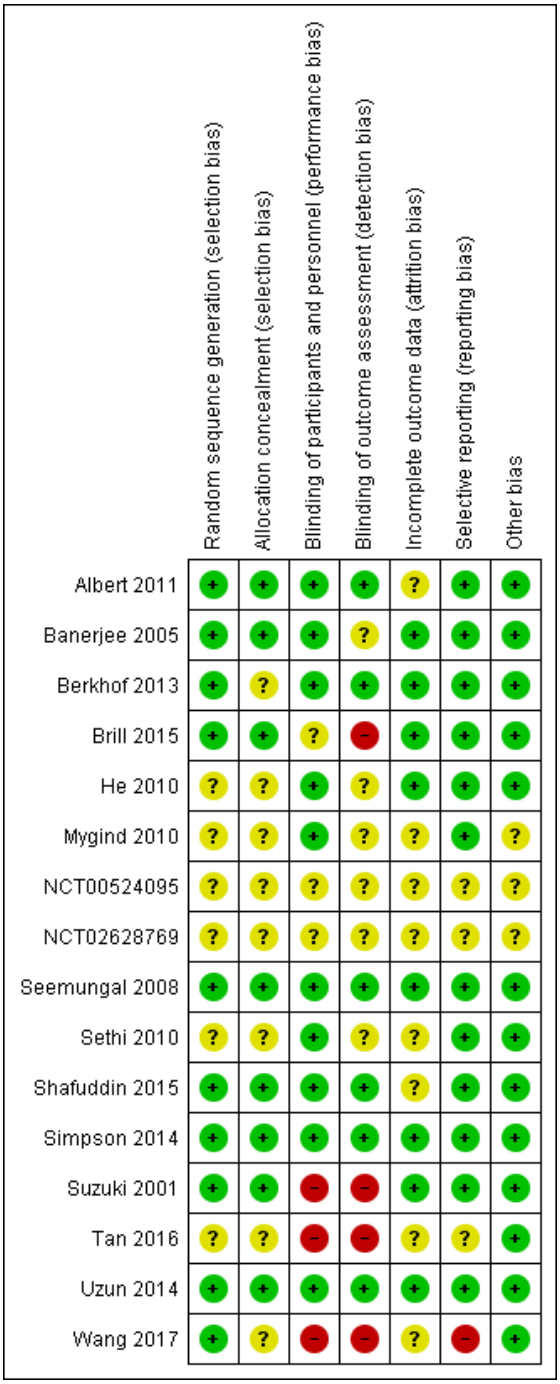
Excluded studies

Excluded studies are listed in the Characteristics of excluded studies table, along with the reasons for exclusion.

Risk of bias in included studies

Judgements and reasons for the judgements can be found in Characteristics of included studies and an overview of our judgements can be found in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation was well described in ten of the studies, which we judged to be at low risk of bias in this domain (Albert 2011; Banerjee 2005; Berkhof 2013; Brill 2015; Seemungal 2008; Shafuddin 2015; Simpson 2014; Suzuki 2001; Uzun 2014; Wang 2017). Four studies did not describe random sequence generation clearly and we judged them to be at unclear risk (He 2010; Mygind 2010; Sethi 2010; Tan 2016).

Allocation concealment was well described in eight studies, which we judged to be at low risk of bias in this domain (Albert 2011; Banerjee 2005; Brill 2015; Seemungal 2008; Shafuddin 2015; Simpson 2014; Suzuki 2001; Uzun 2014). Six studies did not describe allocation concealment clearly and we judged them to be at unclear risk in this domain (Berkhof 2013; He 2010; Mygind 2010; Sethi 2010; Tan 2016; Wang 2017).

Mygind 2010 is a conference presentation, and, as such, we had access to limited data. We were not successful in obtaining further information from authors despite multiple attempts by email and post.

Blinding

Blinding of the participants and personnel (performance bias) was described in ten of the included studies (Albert 2011; Banerjee 2005; Berkhof 2013; He 2010; Mygind 2010; Seemungal 2008; Sethi 2010; Shafuddin 2015; Simpson 2014; Uzun 2014), which we rated as low risk. Suzuki 2001 was not blinded and therefore judged to be at high risk of bias. Brill 2015 was a single-blinded study with only the participants being blinded to treatment allocation, so we judged this to be at unclear risk of bias. Blinding of participants and personnel was not described in Tan 2016 or Wang 2017 and despite multiple attempts by email to obtain further information from the corresponding authors, no responses have been received. We therefore judged these studies to be at high risk of bias.

Blinding of the outcome assessment (detection bias) was well described in six of the included studies (Albert 2011; Berkhof 2013; Seemungal 2008; Shafuddin 2015; Simpson 2014; Uzun 2014), while four were judged to be at a high risk of bias (Brill 2015; Suzuki 2001; Tan 2016; Wang 2017), and the remaining four were unclear.

Incomplete outcome data

Outcomes of the study participants were well described using either a CONSORT diagram (Albert 2011; Berkhof 2013; Brill 2015; He 2010; Seemungal 2008; Sethi 2010; Shafuddin 2015; Simpson 2014; Uzun 2014) or by a dedicated paragraph or table (Banerjee 2005; Suzuki 2001; Tan 2016). Overall, withdrawal rates were similar between both studies and treatments and we judged these studies to be at low risk of attrition bias, with the exception of four studies (Albert 2011; Sethi 2010; Shafuddin 2015; Tan 2016).

In both Albert 2011 and Sethi 2010, we noted the reason for missing health-related quality of life (HRQoL) data was not given, and we therefore rated the studies at unclear risk. We also judged Shafuddin 2015 to be at unclear risk because more participants dropped out of the combined antibiotic treatment arm compared to the single antibiotic and placebo arms (21 versus 13 versus 10), although all randomised participants were included in the intention-to-treat analysis. We judged Tan 2016 to be at unclear risk because the authors did not describe how many participants were analysed at each time point.

Mygind 2010 was a conference presentation of unpublished data and thus we had limited information on which to judge the attrition bias and we therefore rated the study to be at unclear risk. Wang 2017 also did not include any information on the outcomes of study participants and we judged it to be at unclear risk.

Selective reporting

Twelve of the included studies reported all prespecified primary and secondary outcomes and these were judged to be at low risk of bias. For Tan 2016, we were unable to identify a prospective trial registration or protocol so it was not clear if outcomes of interest for this review may have been collected but not reported (e.g. serious adverse events, exacerbations, and quality of life). We identified one study as being at high risk for selective reporting bias (Wang 2017). See Characteristics of included studies to view bias tables for more details.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotics versus placebo for COPD

An overview of the results together with a summary of the our confidence in the evidence per outcome is presented in Summary of findings for the main comparison.

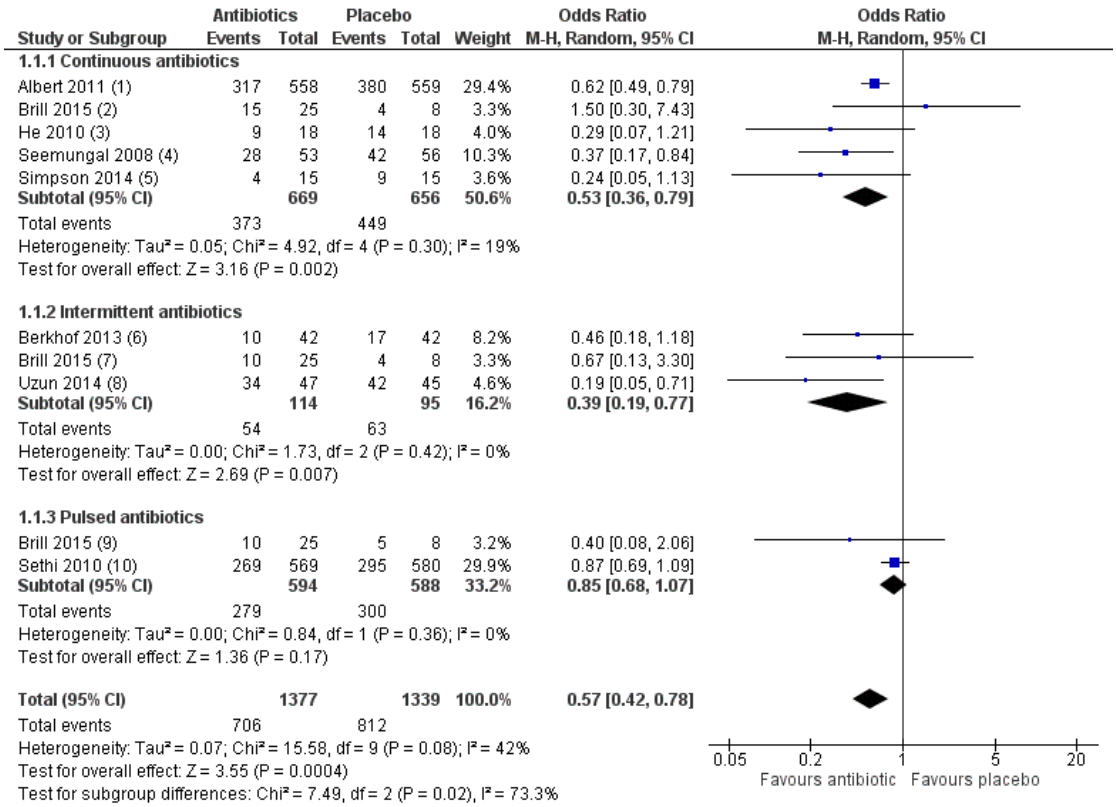
Primary outcome: number of participants with one or more exacerbations

We included eight studies in the meta-analysis of the number of participants experiencing one or more exacerbations of COPD (Albert 2011; Berkhof 2013; Brill 2015; He 2010; Seemungal

2008; Sethi 2010; Simpson 2014; Uzun 2014). Suzuki 2001 was not included in the meta-analysis as this study was not blinded.

We found that prophylactic antibiotics reduce the overall odds of having one or more exacerbations over the treatment period compared to placebo (OR 0.57, 95% CI 0.42 to 0.78; participants = 2716; studies = 8; I^2 = 42%; moderate-quality evidence, Analysis 1.1; Figure 3). This equates to a 13.9 percentage-point reduction in absolute risk. In the control group, 61 people out of 100 had one or more exacerbations compared to 47 (95% CI 39 to 55) out of 100 in the antibiotic group (Figure 4). The number needed to treat for an additional beneficial outcome (NNTB) was 8 (95% CI 5 to 17).

Figure 3. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.1 Number of people with one or more exacerbations.



Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(3) Erythromycin 125mg three times/day for six months.
(4) Erythromycin 250mg twice/day for 12 months.
(5) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(6) Azithromycin 250mg three times/week for 12 weeks.
(7) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(8) Azithromycin 500mg three times/week for 12 months.
(9) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.
(10) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Figure 4. In the control group, 61 people out of 100 had one or more exacerbations over 12 weeks to 12 months, compared to 47 (95% CI 39 to 55) out of 100 for the antibiotic treatment group (Analysis 1.1)

The heterogeneity of the eight studies analysed for this outcome was moderate (I^2 = 42%), which has been explored using pre-planned subgroup analyses.

Of these studies, five (including one arm of Brill 2015), were of continuous antibiotic prophylaxis. Compared to placebo, continuous antibiotics reduced the number of participants experiencing one or more exacerbations (OR 0.53, 95% CI 0.36 to 0.79; participants = 1325; studies = 5; I^2 = 19%; Analysis 1.1). This equated to a number needed to treat for an additional beneficial outcome of 7 (95% CI 5 to 19).

Similarly, the analysis of three studies investigating intermittent antibiotic regimens (including one arm of Brill 2015) suggested a benefit in favour of antibiotics compared to placebo in reducing the number of participants experiencing one or more exacerbations (OR 0.39, 95% CI 0.19 to 0.77; participants = 209; studies = 3; I^2 = 0%; Analysis 1.1).The number needed to treat to for an additional beneficial outcome was 5 (95% CI 3 to 17).

Pulsed antibiotic regimens did not significantly reduce the number of people with at least one exacerbation (OR 0.85, 95% CI 0.68 to 1.07; participants = 1182; studies = 2; I^2 = 0% Analysis 1.1).

The test for subgroup differences between continuous, intermit-

tent, and pulsed regimens suggested a statistically significant difference between the groups (Chi² = 7.49, df = 2 (P = 0.02), I² = 73.3%). However, this was largely driven by the pulsed antibiotic subgroup, as when this subgroup was removed, the test for subgroup differences between the continuous and intermittent antibiotic groups was not significant (Chi² = 0.62, df = 1 (P = 0.43), I² = 0%).

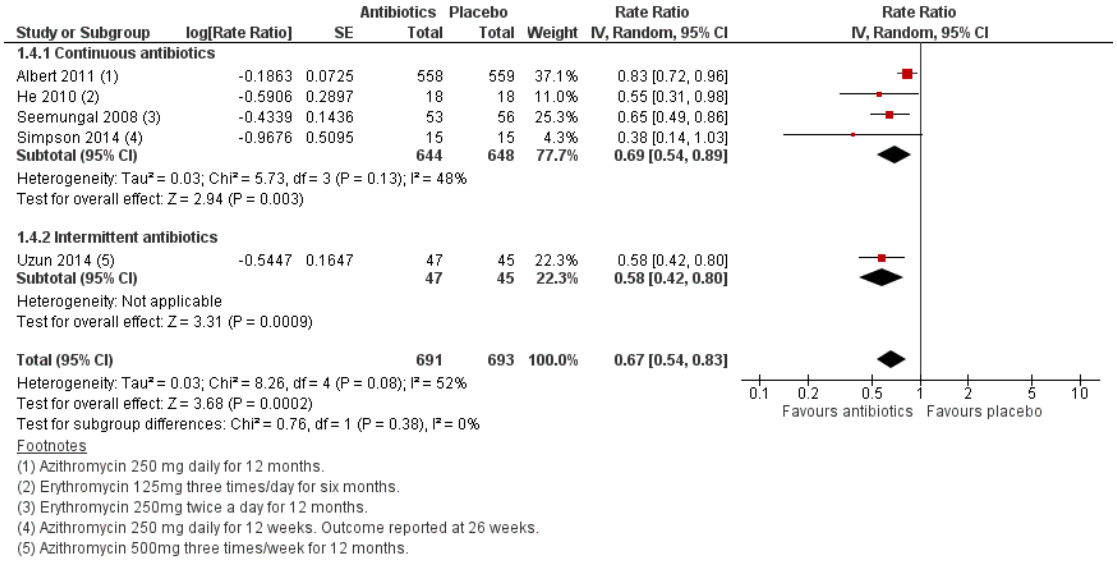
One study of 84 participants, that investigated continuous azithromycin versus placebo, reported the number of exacerbations of COPD that required hospitalisation (Berkhof 2013). The number of events were too infrequent to draw any conclusion on the impact of prophylactic antibiotics in this situation.

Primary outcome: rate of exacerbations per patient per year

The exacerbation rate was expressed as a rate ratio, which was calculated using the generic inverse variance (GIV) method in RevMan software.

Five studies contributed data to this analysis, four investigating continuous regimens (Albert 2011; He 2010; Seemungal 2008; Simpson 2014) and one investigating an intermittent regimen (Uzun 2014). Compared to placebo, prophylactic antibiotics reduced the rate of exacerbations per patient per year (rate ratio 0.67, 95% CI 0.54 to 0.83; participants = 1384; studies = 5; moderate-quality evidence; Analysis 1.4; Figure 5). Considering the different regimens separately, use of continuous prophylactic antibiotics was also associated with a reduction (rate ratio 0.69, 95% CI 0.54 to 0.89; participants = 1292; studies = 4) as was use of intermittent antibiotics (rate ratio 0.58, 95% CI 0.42 to 0.80; participants = 92; studies = 1). There was a moderate level of heterogeneity among the included studies (I^2 = 52%).

Figure 5. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.4 Rate of exacerbation per patient per year.



A subgroup analysis performed in two studies (Albert 2011; Sethi 2010), according to the severity of COPD as defined by the GOLD criteria which were current at that time (2011), did not show a difference between the subgroups in the effect of antibiotics on exacerbation frequency (Analysis 1.8).

Time to first exacerbation

The median time to first exacerbation was analysed using a Kaplan-Meier survival curve and log-rank test. We did not perform a meta-analysis for this outcome and findings from individual studies are tabulated in Analysis 1.5. Data were available for six studies involving 2620 participants (Albert 2011; Berkhof 2013; He 2010; Seemungal 2008; Sethi 2010; Uzun 2014).

Three studies used continuous prophylactic antibiotics, involving 1287 participants. Use of a continuous prophylactic antibiotic lengthened the time to first exacerbation in all three studies

compared with placebo, and this was a statistically significant difference in all three. In Albert 2011, this was 266 days (antibiotic) versus 174 days (placebo) (P < 0.001); in He 2010,155 days versus 86 days (P = 0.032) and in Seemungal 2008, 271 days versus 89 days (P = 0.02).

Two studies, involving a total of 176 participants, investigated intermittent antibiotics and similarly found the time to first exacerbation was lengthened in both studies. In Uzun 2014, this was 130 days versus 59 days (P = 0.001). In Berkhof 2013, the 20th percentile time to first exacerbation was 105 days (antibiotic) versus 66 days (placebo), but this was not statistically significantly different (P = 0.13).

The median time to the first exacerbation in Sethi 2010 was increased by the use of pulsed antibiotics, but the difference was not statistically significant: 364 days versus 336 days (P = 0.062).

One study, Shafuddin 2015, that involved 292 participants allocated to receive either continuous roxithromycin and doxycyline, continuous roxithromycin alone or placebo, reported the mean time (in days) to first exacerbation of COPD. Their results were inconclusive for this outcome and there was no significant difference between the treatment arms (MD -17 days, 95% CI -46 to 13; participants = 266; I^2 = 0%)

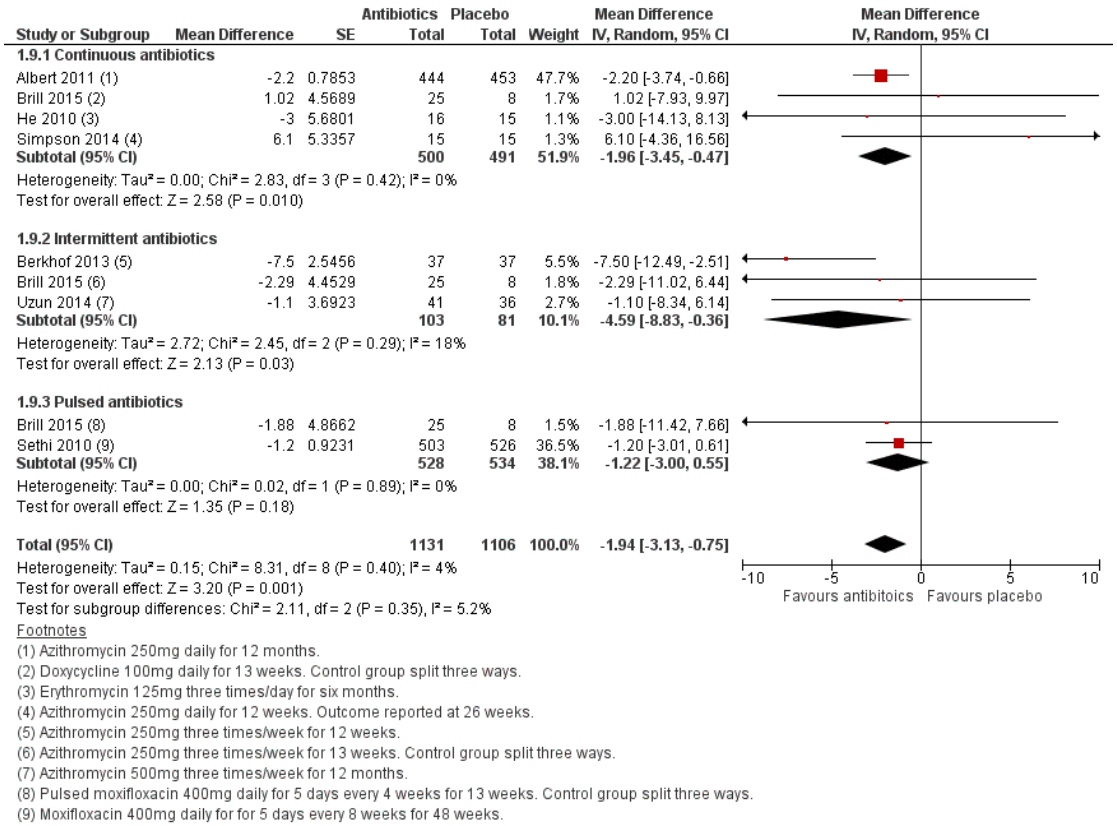
In Albert 2011, which used continuous azithromycin, a predefined subgroup analysis in 22 subgroups found that prophylactic antibiotics were associated with greater treatment effects in terms of lengthening time to first exacerbation in participants who had given up smoking (test for interaction P = 0.012), were not on steroid inhaler treatment at enrolment (P = 0.032), or older than 65 years (P = 0.012).

Primary outcome: health-related quality of life

Health-related quality of life was explored in nine studies (Albert 2011; Banerjee 2005; Berkhof 2013; Brill 2015; He 2010; Mygind 2010; Sethi 2010; Simpson 2014; Uzun 2014). The quality of life assessment tools used in these studies included the St George's Respiratory Questionnaire (SGRQ) (Jones 2009), the Leicester Cough Questionnaire (LCQ) (Birring 2003), the Short Form Health Survey-36 (SF-36), the Short Form Health Survey-12 (SF-12), the Chronic Respiratory Disease Questionnaire (CRQ) and the Clinical COPD Questionnaire (CCQ). We were not able to include data from Banerjee 2005 and Mygind 2010 in the meta-analyses.

Seven studies assessed quality of life using the SGRQ. The meta-analysis demonstrated a benefit of prophylactic antibiotics compared to placebo (MD -1.94, 95% CI -3.13 to -0.75; participants = 2237; studies = 7; high-quality evidence; Analysis 1.9; Figure 6). However, the mean difference did not reach the level of clinical significance according to the conventional cut-off of at least a four-unit reduction (Jones 2009).

Figure 6. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.9 HRQoL, SGRQ (total score).



When we grouped the studies by antibiotic regimen, we noted a similar improvement with continuous prophylactic antibiotic use (MD -1.96, 95% CI -3.45 to -0.47; participants = 991; studies = 4). While the pooled mean difference did not exceed the MCID of four units, it should be noted that Albert 2011 (1142 participants) reported a responder analysis, which demonstrated that more participants in the continuous azithromycin group (43%) than the placebo group (36%) had at least a four-unit reduction in the SGRQ (P = 0.03). We found a larger benefit with intermittent antibiotic use (MD -4.59, 95% CI -8.83 to -0.36; participants = 184; studies = 3). There was no statistically or clinically significant improvement in SGRQ total scores with pulsed antibiotics (MD -1.22, 95% CI -3.00 to 0.55; participants = 1062; studies = 2; Analysis 1.9). However, the formal test for subgroup difference did not identify a significant difference between continuous, intermittent, and pulsed antibiotics.

The SGRQ comprises three subcomponents; symptom score, impact score, and activity score. Four studies presented data for these subcomponents which were analysed separately (Albert 2011; Berkhof 2013: Sethi 2010; Uzun 2014). All three domains improved with antibiotics compared to placebo, although the improvement in the activity score was more uncertain (symptom score: MD -4.07, 95% CI -5.72 to -2.41; impact score: MD -2.56, 95% CI -5.02 to -0.10; activity score: MD -0.99, 95% CI -2.62 to 0.65; Analysis 1.10). In terms of clinically significant improvements with antibiotic use versus placebo in the subgroup analysis, the symptom score showed the greatest difference, with three studies having greater than a four-unit mean difference (Berkhof 2013 9.3 units, Uzun 2014 5.7 units and Sethi 2010 4.4 units).

The authors of Banerjee 2005, Mygind 2010 and Simpson 2014 reported no statistically significant difference in the total SGRQ scores. However, Banerjee 2005 did report a significant improvement only in the symptom domain score in the participants treated with continuous prophylactic clarithromycin over a three-month period (MD -10.2; 95% CI -18.7 to -1.6).

In addition to the SGRQ, Berkhof 2013 used the LCQ and SF-36 as quality of life assessment tools. The LCQ is a 19-point questionnaire designed to assess cough-related quality of life that is divided into three domains (physical, psychological, and social). The domain scores range from one to seven and therefore the total score range is three to 21; higher scores are indicative of a

better quality of life. The authors of Berkhof 2013 reported an improvement in total LCQ score with intermittent azithromycin use (MD 1.30, 95% CI 0.32 to 2.28; Analysis 1.11). The only domain that did not show a clear improvement with the antibiotics was the social domain (MD 0.40, 95% CI -0.15 to 0.95; Analysis 1.14).

Four studies used the SF-36 (Albert 2011; Banerjee 2005; Berkhof 2013; He 2010). The SF-36 is a 36-item nonspecific health-related quality of life questionnaire. It is divided into eight domains that are each scored on a 100-point scale where 100 is equivalent to no disability. The domains include general health, physical functioning, bodily pain, vitality, role emotional, social functioning, mental health, and role physical. Three of the four studies (Albert 2011; Berkhof 2013; He 2010) that used SF-36 to assess quality of life, involving 1262 participants, presented data that we were able to extract for meta-analysis. Albert 2011 used continuous azithromycin for 12 months, Berkhof 2013 used intermittent azithromycin for three months and He 2010 used continuous erythromycin for six months. Given the spread of treatment duration and the different time points of data available for us to extract, we chose to extract data as close to six months as possible, which involved outcomes at six months for Albert 2011 and He 2010, and three months for Berkhof 2013. Only the general health domain showed a clear benefit of antibiotics over placebo (MD 4.06, 95% CI 0.70 to 7.42; participants = 1071; studies = 3; I^2 = 18%; Analysis 1.13) but the confidence intervals for each domain effect estimate were highly overlapping. Banerjee 2005 also used the SF-36 but the raw data were not available for extraction for inclusion in the meta-analysis; however, in their text; they reported a significant improvement in the physical functioning score in the group that used prophylactic clarithromycin for three months (MD 12.9; 95% CI 3.1 to 22.6).

One study used SF-12 in addition to the SGRQ, and found no difference in the mental (MD 0.90, 95% CI -4.68 to 6.48) nor the physical (MD -0.40, 95% CI -5.10 to 4.30) health domains after 12 months of treatment with prophylactic antibiotics (intermittent azithromycin) (overall; MD 0.14, 95% CI -3.45 to 3.73; Analysis 1.12) (Uzun 2014) . They did, however, report "a significant difference in mean change in the mental component score at three months in favour of azithromycin (MD 6.6; CI 1.4 to 11.8; P = 0.013)" (Uzun 2014).

Simpson 2014 similarly found no significant improvement in quality of life as assessed by the CCQ with continuous antibiotic (azithromycin) use at the end of their treatment period (MD 1.80, 95% CI -5.11 to 8.71; Analysis 1.15). Finally, Shafuddin 2015 used the CRQ (which assesses four domains: dyspnoea, fatigue, emotional function, and mastery) and found no significant improvement in any of these domains with continuous antibiotic use (roxithromycin/doxycycline or doxycycline alone) (Analysis 1.16).

Secondary outcome: frequency of hospitalisation

The frequency of hospitalisation was assessed using data from four studies involving 2958 participants (Albert 2011; Mygind 2010; Sethi 2010; Suzuki 2001). In this update, none of the new studies presented data on the frequency of hospitalisation and as such, our data remained unchanged from the previous update (Herath 2013).

The study by Sethi 2010, involving pulsed moxifloxacin in 1157 participants, did not show any improvement in the hospitalisation frequency (131/569 treatment arm versus 136/580 placebo arm; P = 0.46; Analysis 1.18).

The study by Albert 2011, involving continuous azithromycin in 1142 participants, calculated the rate of exacerbations requiring hospitalisation per patient per year according to the severity of COPD by the GOLD criteria (Analysis 1.18). The rate ratio was 0.77 (GOLD stage 2), 0.89 (GOLD stage 3) and 0.72 (GOLD stage 4). There were not adequate data to calculate the statistical significance of this outcome but there did not appear to be a trend. The other two studies had inadequate data to calculate the mean event rate per year. Of these, one study involving 109 participants found a statistically significant reduction (P < 0.001) in hospitalisation while using erythromycin 200 to 400 mg daily for a 12-month period (Suzuki 2001). The other study (Mygind 2010) did not show a statistically significant difference in the frequency of hospitalisations.

Secondary outcome: duration of exacerbations

The duration of exacerbations was addressed by only two studies involving 684 participants (Mygind 2010; Seemungal 2008), again already included in the previous version of this review (Herath 2013). None of the new studies in this update presented data on the impact of prophylactic antibiotics on the duration of exacerbations. Seemungal 2008 showed that antibiotic use was associated with a lower median number of exacerbation days: 9 days (interquartile range (IQR) 6 to 13 days) compared to 13 days on placebo (IQR 6 to 24 days) (P = 0.036). Similar findings were reported by Mygind 2010. This study had 575 participants and used pulsed azithromycin over a 36-month period. The median number of exacerbation days (at home or in hospital) was 93 in the azithromycin group compared to 111 in the placebo group (P = 0.04). Prophylactic pulsed antibiotic use (Mygind 2010) reduced the number of days with severe exacerbations managed at home: a median of 31 days versus 42.5 days for the placebo group (P = 0.01). A meta-analysis was not carried out for this comparison due to paucity of data.

Furthermore, Mygind 2010 reported data on hospitalisation due to COPD exacerbations. The study showed no difference in the number of hospitalisations between the treatment and placebo arms; however, there was a median reduction in hospital stay from 18 days in the placebo group to 15.5 days in the treatment group. No P value was stated for this comparison.

Secondary outcome: days of disability

Only one study reported on the number of days the participant was unable to undertake normal activity (Mygind 2010). The median number of days spent at home due to a mild exacerbation was no different between the treatment and placebo arms (42 days in each arm). However, there was a reduction in the median number of days spent at home due to a moderate to severe exacerbation from 42.5 days in the placebo group to 31 days in the azithromycin group (P = 0.01).

Secondary outcome: change in lung function

Change in lung function was addressed in nine studies (Berkhof 2013; Brill 2015; Mygind 2010; Seemungal 2008; Sethi 2010; Shafuddin 2015; Simpson 2014; Tan 2016; Uzun 2014). Six analysed changes in FEV1 in a total of 658 participants. The meta-analysis showed no significant difference in FEV1 (MD 20 mL, 95% CI -26 to 67; participants = 658; studies = 9; moderate-quality evidence; Analysis 1.20) with prophylactic antibiotics (continuous, intermittent, or pulsed) compared to placebo. Similarly, there was no significant difference in FEV1 % predicted values (MD 0.33, 95% CI -1.56 to 2.22; participants = 1737; studies = 6; Analysis 1.22). However, there appeared to be an improvement in FVC with antibiotic use (combining available data for continuous and intermittent regimens) (MD 0.12 L, 95% CI 0.01 to 0.23; participants = 514; studies = 4; Analysis 1.21). We did not detect any statistically significant differences between the antibiotic regimen subgroups.

Secondary outcome: functional capacity

Two studies (Tan 2016 and Uzun 2014) assessed functional exercise capacity. Both studies measured the six-minute walk test (6MWT) at baseline, three, six, nine, and 12 months. The meta-analysis demonstrated a significant difference in favour of antibiotics in improving performance at 12 months, but with a high level of heterogeneity (MD 68 m, 95% CI 16 to 119; participants = 126; studies = 2; I^2 = 64%; Analysis 1.23). Tan 2016, an unblinded study considered to be at high risk of bias, investigated continuous antibiotics and had two treatment arms (group A: erythromycin 125 mg three times a day for 12 months and group B: erythromycin 125 mg three times a day for six months) and a placebo arm. Their data suggested an improvement in exercise capacity at six months with erythromycin use compared to placebo, with similar results seen for both treatment groups, as would be expected (group A: mean distance 388 m ± 62 , n = 17; group B: mean distance 389 m ± 61, n = 17; placebo mean distance 326 m ± 79, n = 15). Uzun 2014 investigated the use of intermittent azithromycin and, when isolated from Tan 2016, this study did not show an improvement in 6MWT results with antibiotic use (MD 36, 95% CI -16 to 88; participants = 77).

Secondary outcome: death (all-cause and respiratory aetiology)

Mortality data were reported in six studies involving 3309 participants and were combined in a meta-analysis (Albert 2011; Berkhof 2013; Mygind 2010; Sethi 2010; Shafuddin 2015; Uzun 2014). There was no significant difference between the treatment and placebo arms in all-cause mortality (OR 0.87, 95% CI 0.66 to 1.15; participants = 3309; studies = 6; I^2 = 0%; moderate-quality evidence; Analysis 1.24), but confidence intervals were not sufficiently narrow to exclude a clinically important difference. Data on mortality secondary to a respiratory cause were available in the two larger studies (Albert 2011; Sethi 2010), which again showed no significant difference between groups (OR 1.17, 95% CI 0.63 to 2.19; Analysis 1.25), but the estimate was imprecise.

Secondary outcome: serious adverse events

Adverse events were well explained in ten studies (Albert 2011; Berkhof 2013; Brill 2015; He 2010; Seemungal 2008; Sethi 2010; Simpson 2014; Shafuddin 2015; Tan 2016; Uzun 2014), but there was no uniform system for reporting them.

There was a reduction in serious adverse events as defined by the trialists, with prophylactic antibiotics, but the confidence interval included no difference (OR 0.88, 95% CI 0.74 to 1.05; participants = 2978; studies = 9; I^2 = 0%; moderate-quality evidence; Analysis 1.26). Similarly, there was no significant difference in the total number of any adverse event, as defined by the trialists, between antibiotic prophylaxis and placebo arms (OR 1.07, 95% CI 0.69 to 1.67; participants = 512; studies = 4; I^2 = 0%; moderate-quality evidence; Analysis 1.27), but the confidence interval was wide.

Looking at specific adverse events, there were no significant differences in the number of adverse events between the treatment and placebo arms related to the respiratory system (Analysis 1.28.1), gastrointestinal system (Analysis 1.28.2), QTc prolongation (Analysis 1.28.3), musculoskeletal system (Analysis 1.28.5), hypersensitivity (Analysis 1.28.6), nervous system (Analysis 1.28.7) or the cardiovascular system (Analysis 1.28.8), but all estimates lacked precision.

The adverse event most frequently recorded across the studies (Albert 2011; Berkhof 2013; He 2010; Seemungal 2008; Sethi 2010; Simpson 2014) was gastrointestinal in origin (OR 1.16, 95% CI 0.43 to 3.11; participants = 2522; studies = 6; I^2 = 72%, Analysis 1.28). There was significant heterogeneity among these studies which suggested differences among the antibiotics and their adverse events for each study.

Individual studies did show some differences which may have clinical relevance.

Sethi 2010 reported significantly higher numbers of adverse events in the treatment arm with moxifloxacin (P < 0.001) secondary to increased gastrointestinal adverse events including diarrhoea, nausea, and vomiting (OR 7.17; 95% CI 2.49 to 20.63; Analysis

1.28), representing a number needed to treat for an additional harmful outcome (NNTH) of 25 (95% CI 98 to 9). The intervention group in this study received moxifloxacin 400 mg daily for 5 days, every 8 weeks for 48 weeks. A single case of diarrhoea was reported secondary to *Clostridium difficile* in the placebo group. Sethi 2010 stated that the adverse events were drug-related.

Albert 2011 reported that azithromycin 250 mg daily for a 12-month period was associated with a significant increase in hearing impairment (OR 1.39; 95% CI 1.05 to 1.85) representing a NNTH of 18 (95% CI 128 to 9). The authors reported that the majority of the drug discontinuations due to a drug-related adverse events were due to hearing impairment (treatment group, N = 142 (25%) versus placebo group, N = 110 (20%) by three months). It should be noted that all participants in this study had baseline audiometry, with participants with hearing impairment below the 95% percentile excluded from the study. Since there were a large number of participants in both the treatment and placebo arms that had drug discontinuation secondary to hearing loss, the authors commented that this could be due to a measurement error.

In Albert 2011, while there were no statistically significant differences observed in cardiovascular disease or QTc prolongation, six participants in the treatment group had to discontinue the medication due to development of prolonged QTc compared to four participants in the placebo group (P = 0.55). This study excluded participants with tachycardia, long QTc, and participants taking medications that could prolong the QTc.

In the non-blinded study of Suzuki 2001, it was reported that participants in the treatment group did not have any apparent adverse effects from erythromycin therapy during the study period.

Shafuddin 2015 reported one case of an abnormal electrocardiogram (ECG) deemed to be related to the combined roxithromycin/doxycyline medication.

Brill 2015 found that 40% of adverse events, although reported as minor, were in the moxifloxacin group, with half of those being gastrointestinal. In four cases, therapy was withdrawn in this group.

Secondary outcome: antibiotic resistance

The development of antibiotic resistance was assessed in six studies involving 2610 participants (Albert 2011; Banerjee 2005; Brill 2015; He 2010; Seemungal 2008; Sethi 2010). Because of the variety of ways in which resistance was evaluated and reported, it has proved impossible to combine these results in a meta-analysis.

In Brill 2015, both sputum bacterial load and antibiotic resistance was assessed pre- and post- 13 weeks antibiotic treatment. Bacterial load was reduced by all three antibiotic treatments, and most substantially (by 62%) in the pulsed moxifloxacin arm, but there was not a statistically significant difference when compared to placebo in any of the three treatment arms. The most common isolate both pre and post-treatment was non-*Pneumoniae streptococcus* species. There were increases in the degree of antibiotic resistance of isolates in all three antibiotic arms after 13 weeks treatment. Compared to placebo, moxifloxacin was associated with a factor increase in mean inhibitory concentration (MIC) of 4.82 (95% CI 1.44 to 16.19, P = 0.01), doxycycline 3.74 (95% CI 1.46 to 9.58, P = 0.01) and azithromycin 6.23 (95% CI 1.66 to 23.35, P = 0.01). Furthermore, isolates from participants in the doxycycline group were more likely to be resistant to doxycycline than in the placebo group (OR 5.77, 95% CI 1.40 to 23.74, P = 0.02). ORs for the moxifloxacin and azithromycin were also greater than 2, but not statistically significant.

Albert 2011 used sputum from participants who could expectorate as well as nasopharyngeal swabs. They found only 15% of participants were able to expectorate at the end of the three-month treatment period. The commonest organisms identified in the treatment versus placebo groups were: *Staphylococcus aureus* (N = 60 (10.7%) versus N = 71 (12.7%)); *Moraxella spp* (N=13 (2.3%) versus N = 6 (1%)); and *S. pneumoniae* (N = 6 (1.1%) versus N = 6 (1.1%)). The predominance of *S. aureus* in this COPD population was out of keeping with the usual pathogens anticipated and was thought to be due to the nasopharyngeal sampling. During the study period, the participants in the placebo group without bacterial colonisation (N = 172) became colonised at a significantly higher rate than those treated with 250 mg of daily azithromycin (N = 66) (P < 0.001). However, in the group that became newly colonised throughout the study period, the resistance to macrolide was higher in the treatment group: 81% compared to 41% in the placebo group (P < 0.001).

In Sethi 2010, which used pulsed moxifloxacin over a 48-week period, the sampling for organisms was carried out using sputum sampling and rectal sampling. Only 24% of all participants could produce sputum. The commonest organisms isolated were: *H. influenzae* (8.3%), *Haemophilus parainfluenzae* (6.6%) and *S. pneumoniae* (4.3%); *S. aureus* was isolated in 2.6%. The MIC for moxifloxacin for *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, *M. catarrhalis* and *S. aureus* did not change during the study period. A single moxifloxacin-resistant *S. pneumoniae* isolate was identified at the end of the study period (MIC 4 mg/L). There were one to three moxifloxacin-resistant isolates at different points of the study that were not persistent. Participants who had produced cultures of moxifloxacin-resistant pseudomonas were excluded from the study. However, participants with moxifloxacin-sensitive pseudomonas were included. During the 24th week of the study, the median MIC of moxifloxacin had increased to 4 mg/L, which returned to baseline at the end of the treatment period. The median MIC of the placebo group with pseudomonas-sensitive moxifloxacin increased from 0.5 mg/L to 2 mg/L at the end of the treatment period. The study authors recommended not using moxifloxacin in patients with known pseudomonas colonisation owing to the possibility of developing rapid resistance.

Seemungal 2008 investigated 109 participants with twice daily erythromycin 250 mg over a 12-month period. They encountered only one participant who developed resistance to *S. pneumoniae* at

the end of the treatment period. All *H. influenzae* isolated (22/109) were found to be resistant to erythromycin. The microorganism milieu was as expected for the COPD population: *H. influenzae* (N = 22/36), *S. pneumoniae* (N = 6/36) and *M. catarrhalis* (N = 3/36).

The other two studies, (Banerjee 2005 using long-acting clarithromycin 500 mg daily (Klaricid XL 500 mg) and He 2010 using erythromycin 125 mg every eight hours), found a similar milieu of respiratory pathogens. They did not observe significant differences in the colonisation rate of the organisms or emergence of resistance. However, these two studies were of a shorter duration than those mentioned above, six months and three months, respectively.

Subgroup and sensitivity analyses

Subgroup analyses

We performed subgroup analysis on our primary outcome only: number of people with one or more exacerbations. We subgrouped studies according to mean baseline FEV1 % predicted but only one study was included in the > 50% predicted subgroup and thus we cannot draw any conclusions from this analysis (Analysis 2.1). We did not find any statistically significant impact of study duration (three to six months, six to 12 months and over 12 months) on this outcome (Analysis 2.2). We subgrouped studies according to their date of publication in five-year groups from 2005 to 2009, 2010 to 2014 and 2015 onwards (Analysis 2.3). Six out of the eight studies appearing in this analysis were published between 2010 and 2014, so again, this analysis was inconclusive. When subgrouped according to frequency of antibiotic administration (once daily, 2 to 3 times daily, 2 to 3 times per week and pulsed), there was some evidence that pulsed antibiotics were less effective than regimens that require more frequent dosing, in keeping with our other findings (Analysis 2.4; test for subgroup differences: Chi^2 = 9.51, df = 3 (P = 0.02), I^2 = 68.4%). Finally, we did not find a statistically significant subgroup difference when we grouped studies according to exacerbation history as an inclusion criterion (studies in which participants were required to have had at least one exacerbation in the preceding year versus those in which exacerbation history was not an inclusion criterion) (Analysis 2.5). However, it should be noted that many of the studies included in the second subgroup recruited participants who had a positive exacerbation history, despite it not being a requirement for study entry.

Sensitivity analyses

We applied our sensitivity analysis to our primary outcome only: number of people with one or more exacerbations. This resulted in the removal of all three arms of the single-blind study Brill 2015. This had a minimal impact on the effect estimate (0.54, 95% CI 0.38 to 0.77 versus OR 0.57, 95% CI 0.42 to 0.78).

DISCUSSION

Summary of main results

In this review, we analysed a total of 14 completed studies, involving 3932 participants, that investigated the use of prophylactic antibiotics for the prevention of COPD exacerbations. All participants were adult (over the age of 40 years), with the mean age between 65 and 72 years. Most participants had at least moderate-severity COPD and we only included studies if they confirmed this diagnosis with spirometry. The antibiotics investigated were azithromycin, erythromycin, clarithromycin, doxycyline, roxithromycin, and moxifloxacin. Nine studies involving 1925 participants investigated continuous macrolide antibiotic regimens, two studies involving 176 participants investigated intermittent azithromycin antibiotic regimens (administered three times a week), two studies involving 1732 participants investigated different pulsed antibiotic regimens (one macrolide and one quinolone) and one study involving 99 participants compared three treatment arms with placebo; one continuous doxycycline regimen, one intermittent azithromycin regimen and one pulsed moxifloxacin regimen. The study duration varied from three months to 36 months and all used intention-to-treat analysis. Most of the pooled results were of moderate quality. The risk of bias of the included studies was generally low, and we did not downgrade the quality of evidence for risk of bias.

Primary outcomes

Eight studies including 2716 participants were included in the meta-analysis of the number of people with one or more exacerbations (Figure 3). The results of this analysis indicated that the number of participants experiencing one or more exacerbations was significantly reduced with the use of prophylactic antibiotics (OR 0.57, 95% CI 0.42 to 0.78; participants = 2716; studies = 10; I^2 = 42%) .The subgroup analysis for this outcome suggested that there was a statistically significant difference between continuous and intermittent regimens and pulsed regimens for the number of people with one or more exacerbations, with pulsed antibiotic regimens having a smaller treatment effect. Similarly, the rate of exacerbations per patient per year with continuous and intermittent antibiotic use were significantly reduced (Analysis 1.4; moderate-quality evidence). The median time to first exacerbation was lengthened with continuous and intermittent antibiotic prophylaxis (Analysis 1.5), however, only the continuous antibiotic regimens and one intermittent antibiotic regimen were associated with statistically significant delays. Pulsed antibiotic prophylaxis did not appear to be associated with the same benefits.

Health-related quality of life was explored in nine studies using different assessment tools, as detailed in the above results. The results were mixed, with some studies finding no or uncertain improvement in quality of life indicators with antibiotic prophylaxis whilst others found improvement in some quality of life domains. The most commonly used quality of life scale was the SGRQ. It was used in seven studies involving 2237 participants and our meta-analysis suggested a statistically significant benefit in quality of life total score with antibiotic prophylaxis compared to placebo (MD -1.94, 95% CI -3.13 to -0.75; participants = 2237; high-quality evidence) (Analysis 1.9). While this mean difference did not reach the accepted level of clinical significance (Jones 2009), a responder analysis carried out in Albert 2011 demonstrated that more participants in the continuous azithromycin group (43%) than the placebo group (36%) had at least a four-unit reduction in the SGRQ (P = 0.03). Again, with subgroup analysis, where an improvement in quality of life was identified, it appeared to be with continuous and intermittent antibiotic prophylaxis. No clear improvement was found with pulsed antibiotic regimens.

Secondary outcomes

One study, Suzuki 2001, found a statistically significant reduction in hospital admissions with prophylactic erythromycin use, whilst three other studies found no significant reduction in hospital admissions (Albert 2011; Mygind 2010; Sethi 2010). There was no statistically significant difference between antibiotic prophylaxis and placebo in FEV1, all-cause mortality, or adverse events (moderate-quality evidence) but, for both mortality and adverse events, confidence intervals were too wide to rule out an effect. However, specific adverse events reported in some of the studies may have clinical relevance, given their severity.

The 6MWT was used to measure the functional capacity in two studies in the meta-analysis involving 126 participants (Analysis 1.23). One study, considered to be at high risk of bias (Tan 2016) investigated continuous antibiotics and demonstrated a statistically significant benefit in the 6MWT (MD 84.5 m (45.7 to 123.29) with use of antibiotics whilst the result was uncertain in a study using intermittent antibiotics (Uzun 2014).

The development of antibiotic resistance was addressed in six studies involving 2486 participants. Due to the multitude of methodologies used to detect and report resistance, the data were not able to be pooled in a meta-analysis. Of concern, four of these six studies identified evidence of antibiotic resistance. However, there was not sufficient evidence for us to predict how the use of prophylactic antibiotics would affect the resistance patterns in the community and studies with a longer duration of follow-up will be required to assess this further.

Overall completeness and applicability of evidence

The participants in the studies in this review were aged 40 years or over (mean age, 67 years) and had at least moderate-severity COPD (mean FEV1 1.2 L). Three studies (Albert 2011; Mygind 2010; Sethi 2010) included participants who experienced one to two exacerbations during the previous year. Uzun 2014 included participants who had experienced three exacerbations within the last year. Albert 2011 and Sethi 2010 included participants who were on long-term supplemental oxygen or systemic steroids, or both (see Characteristics of included studies, Summary of findings for the main comparison). Hence, the results can be generalised only to this group of participants who are at the more severe end of the COPD spectrum. Such participants may also be more likely to be receiving high-dose ICS, which have been associated with an increased risk of pneumonia (Kew 2014). This may further decrease generalisability to broader COPD populations.

Data from Albert 2011 suggested that prophylactic antibiotics may be most useful in patients who have given up smoking, who are not on any inhaler treatment (long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), or inhaled corticosteroid (ICS) in any combination), on oxygen therapy, or older than 65 years.

Although these results were obtained from prespecified subgroup analyses, the sample sizes were much smaller than the randomised sample size. There were 22 analyses carried out giving a 62% chance of one analysis yielding a statistically significant result. For this reason, the authors are aware that there may be false positives in these results and recommend additional studies that are adequately powered to explore these subgroups.

It is also important to note that the study participants had undergone strict exclusion criteria. Participants with tachycardia, arrhythmia, long QTc, as well as being on medication that could potentially increase the QTc (a long list), or baseline hearing deficit based on audiometry were excluded. Participants will likely have been excluded from the trial if they were currently prescribed an interacting medication that could not be stopped or substituted and this may have further limited the applicability of the evidence to the wider COPD population. There was regular monitoring throughout the study period and drugs were discontinued in the event of a significant adverse event. Furthermore, only two studies (Albert 2011 and Uzun 2014) performed CT chest to screen for participants with underlying bronchiectasis. This is a drawback as, although this review had a strict criteria for COPD diagnosis, many people with COPD (estimates range from 4% to 72%), especially those with recurrent infections, have a degree of underlying bronchiectasis (Martinez-Garcia 2017). Therefore, identifying the group with bronchiectasis and analysing this group as a subgroup would have given us valuable information on whether the group would benefit more from prophylactic antibiotics. Furthermore, it is not clear from the studies the extent to which participants had other treatments for their COPD optimised (for example, smoking cessation programmes, pulmonary rehabilitation, vaccination).

In current clinical practice, prophylactic antibiotics tend to be used as a last resort because of concerns about antibiotic resistance in the community. If an informed decision is made to start prophylactic antibiotics in a particular patient, there needs to be baseline checks to confirm the identity of the infection (for example, sputum cultures), ECG, and consideration of audiometry, depending on the planned antibiotic, as well as ongoing monitoring of the same.

Although all the included studies were conducted in the last 20 years, even over this time period, the care of people with COPD has changed markedly, as evidenced by regular guideline updates (GOLD 2018). The threshold for both admission and duration of hospital stay once admitted has changed and more care is carried out at home in many settings. For example, a retrospective analysis of data in the UK suggested that the mean duration of hospital stay for an emergency admission with COPD fell by approximately one day between 2006 and 2010, in keeping with international trends (Harries 2015).

A further limitation of the evidence presented is that most of the included studies measured outcomes at or soon after discontinuation of antibiotics. We therefore cannot comment on any possible prolonged benefits or harms which might extend beyond the treatment period. Furthermore, drug interactions may also require consideration, particularly as macrolide antibiotics may interact with other commonly prescribed drugs in the COPD population, such as statins and theophylline (BNF 2018).

Finally, the analyses of continuous and intermittent antibiotics were dominated by macrolide antibiotics (e.g. azithromycin and erythromycin). The majority of the evidence for pulsed antibiotics was contributed by studies of moxifloxacin, a quinolone. Therefore, care should be taken when drawing conclusions about the relative efficacy of continuous, intermittent and pulsed regimens as this comparison is confounded by the different classes of antibiotic used in the studies.

Quality of the evidence

Overall, we graded the quality of the evidence to be moderate, meaning "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate". We presented our grade ratings in Summary of findings for the main comparison.

We downgraded three outcomes (mortality, serious adverse events, and all adverse events) for imprecision; the confidence intervals were not sufficiently narrow enough to rule out a potentially important effect. We downgraded two outcomes (number of participants with one or more exacerbations and exacerbation rate) for inconsistency; the I^2 was greater than 50% in both analyses. We downgraded FEV1 (mL) for indirectness as the studies contributing the majority of the weight in this analysis were of short duration. We were not able to create a funnel plot as no analyses contained 10 unique studies, so publication bias could not be formally assessed. Finally, while we rated four studies to be at high risk of bias in at least one domain, the overall methodological quality of the studies contributing data to the meta-analyses was good, and therefore we did not downgrade any outcome for risk of bias.

Potential biases in the review process

We attempted to minimise bias during the review process by completing a comprehensive electronic search of all published and unpublished data, as well as handsearching the bibliographies from selected studies. The data were extracted and full-text articles reviewed by three authors with disagreement being resolved by discussion.

However, not all included studies clearly described the criteria used to diagnose an acute exacerbation of COPD. This may have led to us combining results from studies in which different criteria were used, which may impact the interpretability of these analyses. Furthermore, exacerbation rates in COPD vary markedly between seasons; shorter studies may therefore fail to accurately reflect the true year-round exacerbation burden. In addition, our categorisation of continuous, intermittent, and pulsed regimens was a post hoc decision for the 2018 update, although taken before data analysis. We recognise that, due to sustained tissue concentrations of azithromycin, a three times a week regimen could be considered essentially continuous (Matzneller 2013). Despite this, we suggest that intermittent regimens have different implications for patient adherence and costs and therefore maintained these subgroups for analysis.

Agreements and disagreements with other studies or reviews

Our findings are consistent with an earlier Cochrane review of prophylactic antibiotics in chronic bronchitis (Staykova 2003), even though the definitions of cases are tighter in the present review. The study findings further strengthen and are in line with the findings of the previous version of this Cochrane review, published in 2013 (Herath 2013).

A case-based review article in the New England Journal of Medicine (NEJM) on antibiotic prevention of acute exacerbations of COPD recommends the use of azithromycin 250 mg three times a week to reduce exacerbation frequency in patients on maximal COPD treatment who were still having two or more exacerbations per year (Wenzel 2012). Careful selection, prior investigations, and proper follow-up were emphasised, which is concordant with our findings and recommendations.

AUTHORS' CONCLUSIONS

Implications for practice

Use of prophylactic macrolide antibiotics for a period of up to 12 months is likely to reduce the number of patients with one or more exacerbations, exacerbation frequency, increase the median time to first exacerbation and improve health-related quality of life. Benefits appear to be driven by continuous and intermittent macrolide regimens, with pulsed regimens being less effective. However, the benefits need to be balanced against the risk of harm, notably antibiotic resistance, and the cost and adherence implications for the patient and the health care system, as well as potential costs of monitoring for adverse effects.

Reducing the frequency of exacerbations would reduce healthcare costs and might be expected to preserve lung function and quality of life, as well as lower the risk of mortality, although we did not find evidence of any of the latter in this review. In part, this is due to the dearth of studies that have addressed the frequency and duration of hospital admissions and the relatively small numbers of participants in most of the studies; that is, the studies were underpowered to measure these outcomes. The more recent studies did not address the days of disability or hospital admissions and therefore there was no additional contribution in this area since the 2013 review.

The benefit in prevention of exacerbations was seen in the type of participants that were included in the studies. These participants had at least moderately severe COPD and were mostly frequent exacerbators. Evidence available from a single study suggests that individuals over 65 years benefited more than younger individuals. Hence, carefully identifying the patient group that would benefit most from the use of prophylactic antibiotics is of paramount importance.

Although the selection of patients for prophylactic antibiotics is critical, the evidence base for making statements about patient selection is poor since not all studies have used the same selection criteria, only three studies used frequent exacerbations as an inclusion criterion, and only two studies screened for bronchiectasis with CT imaging.

There are some potentially serious adverse effects with prophylactic antibiotics. Furthermore, development of antibiotic resistance remains of major concern. This is particularly so for those patients colonised with pseudomonas. More broadly, there are calls worldwide to reduce the total amount of antibiotics prescribed. Hence, even though the NNTs to prevent one person having an exacerbation were relatively small, this has to be balanced with the risks of harm either to that individual or indirectly to others via antibiotic resistance. So far, the evidence suggests that, with the use of prophylactic antibiotics, the sputum bacterial load reduces. However, included studies reported that, in participants with ongoing bacterial isolation, the isolates had increased resistance to the given antibiotic, sometimes demonstrating a MIC with a fourfold rise at the end of the study period. One study that had follow-up to 36 months had demonstrated that the rise in MIC may be transient and may return to baseline with cessation of antibiotics during the follow-up period. Therefore, there remains uncertainty about the long-term effects of the use of prophylactic antibiotics in the bacterial milieu in the community in terms of developing persistent resistance in this era of constant fear of developing 'super-bugs'.

Implications for research

While there is a growing body of evidence to support the use of prophylactic antibiotics in people with COPD, better identification of the subsets of patients who would benefit most would be of great value in future research, so as to deliver targeted treatment to the right patient. Future trialists should ensure that the study population is well characterised, with a particular focus on the potential effect modifiers of prophylactic antibiotic therapy, including underlying bronchiectasis, exacerbation frequency, bacterial colonisation, and baseline FEV1. Future studies that incorporate potential biomarkers might be useful for patient selection. Importantly, participants in all arms of clinical studies of prophylactic antibiotics should receive the full package of evidence-based interventions in COPD, as well as the study interventions.

At present, there is a larger body of data available for the use of continuous antibiotic use and their benefit in comparison to intermittent or pulsed antibiotics. It would be worthwhile exploring the benefit of intermittent or pulsed antibiotics further as administering them less frequently may improve patient adherence, reduce adverse effects, and costs to both the patient and healthcare systems. Head-to-head comparisons of pulsed versus intermittent versus continuous antibiotics would be useful in this context. Furthermore, shorter placebo-controlled studies through winter months, when exacerbations are more common, might be useful to determine if this is a pragmatic strategy. Regimens which focus on winter months only might also improve adherence and reduce costs, but this needs to be tested in a trial setting.

Duration of hospital admissions and days of disability due to an exacerbation were not well addressed in the studies. Future studies should document these outcomes. Additionally, a cost-effectiveness analysis would be useful. Most of the costs in severe COPD are related to hospitalisation. On the face of it, antibiotics may be cheaper than some inhalers, but there are hidden costs, such as the cost of screening for adverse effects and the direct and indirect costs of antimicrobial resistance.

A challenge is how to balance the benefits of antibiotic therapy to the individual over the potential harms to the community through antibiotic resistance. The maximal duration of continuous prophylactic antibiotics was 12 months, and for pulsed antibiotics it was 36 months. Hence, there are no data on the impact of very long-term antibiotic use on antibiotic resistance patterns in the community. The latter will require local surveillance and the cor-

relation of resistance and prescribing patterns. This will help us understand if the higher MIC noted during the use of prophylactic antibiotics would return to baseline when antibiotics were discontinued and after how long, which would enable us to determine the need for 'breaks' from treatment, as well as determine the duration of these 'breaks'. If persistent resistance patterns are identified despite these measures, this would increase the need for caution in the use of prophylactic antibiotics. Furthermore, modelling of resistance detected in trials at a population level might be a useful approach.

Yet to be determined is whether prophylactic antibiotics are able to alter the rate of deterioration of lung function in COPD and, if they do, whether this is due to antibiotic or anti-inflammatory effects. This would be a helpful advance in the understanding of the pathophysiology of this common and debilitating disease. Long-term follow-up studies of participants who have been in prophylactic antibiotic studies may help to answer these questions. Identifing biomarkers of inflammation in these patients would also help if antibiotics with anti-inflammatory effects work better in this group.

Future studies directed at the use of inhaled antibiotics, which may result in fewer systemic effects and higher local concentrations, would be useful in reducing potential side effects of oral prophylactic antibiotic therapy. Such studies were excluded from this review.

Studies looking into continuous or intermittent antibiotic therapy in clear relation to other interventions that are useful for frequent exacerbators would help determine the advantages and disadvantages of antibiotic therapy over the already established measures used to reduce exacerbations. The subgroup analysis conducted of one of the included studies (Albert 2011) suggests that further exploration of the modifying effect of baseline treatments such as LAMA, LABA, and ICS is warranted.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Albert 2011

Methods	Prospective, randomised, double-blind, placebo-controlled clinical trial with 12-month treatment duration Intention-to-treat analysis
Participants	N = 1142. Aged 40 years or over. Mean age (years): 65 (azithromycin) and 66 (placebo) 41% female Severity of COPD: moderate or worse as defined by GOLD criteria Mean FEV1 (L): 1.10 (SD 0.50) (azithromycin) and 1.12 (SD 0.52) (placebo) Presence of either a) using continuous supplemental oxygen, or b) received systemic glucocorticoids within the previous year/had gone to an emergency room/hospitalisation for an acute exacerbation No acute exacerbation of COPD for at least 4 weeks Exclusions: asthma, resting heart rate > 100/min, prolonged QT interval > 450 ms, using medications that prolong QTc, hearing impairment documented by audiometry
Interventions	Prophylaxis: 1. Azithromycin 250 mg daily 2. Placebo
Outcomes	Primary: 1. Time to the first acute exacerbation of COPD Secondary: 1. Quality of life 2. Nasopharyngeal colonisation of selected respiratory pathogens 3. Compliance to the treatment 4. Adverse events
Notes	Funding: Grants listed from National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The stratified random sequence generation was well described in the journal article under "protocol": "Randomization will be carried out by linking to the Data Coordinating Center through a website, (http://www.copdcrn.org)"
Allocation concealment (selection bias)	Low risk	Well explained. Central allocation was pharmacy controlled: "Only the pharmacist and the staff of the Data Coordinating Center knew this schedule and the phar-

Albert 2011 (*Continued*)

		macists could not know the actual assignment until after the DCC specified an accession number. Treatment assignment was only disclosed in cases of emergency."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active drug and placebo will be identical in appearance. Both participants and treating medical staff were blinded: "The actual assignment will only be revealed in cases of emergencies where caregivers need to know what drugs the person was taking to provide treatment, or to avoid prescribing other medications that might adversely interact with the study drug. Active-drug and placebo capsules will be identical in appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial staff were unaware of the randomisation: "Clinic staff (who undertook outcome assessment) will make no attempt to determine the content of any capsules except in cases of emergency"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All outcome data accounted for in a consort diagram for the entire study However, data on the secondary outcome (HRQoL) had reported loss to follow-up of 20% in the prophylactic antibiotic arm and 18% on the placebo arm. The reasons for the missing data pertaining to HRQoL were not given
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been reported
Other bias	Low risk	No other bias identified

Banerjee 2005

Methods	Prospective, randomised, double-blind, placebo-controlled clinical trial. Treatment duration of 3 months. Intention-to-treat analysis
Participants	N = 67 Mean age (years): 65.1 (clarithromycin) and 68.1 (placebo) Mean FEV1 (L): 1.12 (clarithromycin) and 1.13 (placebo) Severity of COPD: moderate or worse according to BTS guidelines. All participants were taking ICS Patients enrolled from hospital clinics

Banerjee 2005 (*Continued*)

	No acute exacerbations of COPD over the last 6 weeks Exclusions: Previous documented allergies to macrolides; a clinical history of lung cancer, asthma or bronchiectasis
Interventions	Prophylaxis: 1. Clarithromycin (long-acting Klaricid XL 500 mg/daily) 2. Placebo
Outcomes	Primary: 1. Health-related quality of life Secondary: 1. Infective exacerbation rate 2. Shuttle walk test 3. Serum CRP level 4. Sputum bacterial quantities load
Notes	Funding: Received grant support from Abbott Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation was carried out: "Subjects were then block randomised into a prospective, double-blind controlled study. .. Patients were randomised by the Birmingham Heartlands Hospital pharmacy department, independent of trial staff"
Allocation concealment (selection bias)	Low risk	Participant randomisation was not known to the trial staff. Randomisation carried out by the Birmingham Hospital pharmacy department: "Patients were randomised by the Birmingham Heartlands Hospital pharmacy department, independent of trial staff"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial staff were unaware of the allocation, but blinding of outcome assessors not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data described
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported

Banerjee 2005 (*Continued*)

Other bias	Low risk	No other bias identified

Berkhof 2013

Methods	Prospective, randomised, double-blind, placebo-controlled clinical trial. Treatment duration of 12 weeks; 6-week post-treatment follow-up Intention-to-treat analysis
Participants	N = 84. Aged 40 years or over. Mean age (years): 67 (azithromycin) and 68 (placebo) Female: 26% (azithromycin) and 24% (placebo) Mean FEV1 % predicted: 49.8 (SD 16.4) (azithromycin) and 47.4 (SD 12.9) (placebo) Clinical diagnosis of COPD: GOLD stage ≥ 2 (defined as a post bronchodilator of FEV1 < 80% and a ratio of FEV1/FVC < 70%), and were suffering from chronic productive cough, defined as cough for at least the last 12 weeks, in two subsequent years Exclusions: prior history of asthma; use of intravenous or OCS and/or antibiotics for an exacerbation three weeks before inclusion; other relevant lung or liver diseases at the discretion of the treating physician; pregnancy or lactation; use of macrolides in the last six weeks prior to inclusion; allergy or intolerance to macrolides; or use of other investigational medication started two months prior to inclusion
Interventions	Prophylaxis: 1. Azithromycin 250 mg 3 times a week 2. Placebo
Outcomes	Primary: 1. mean LCQ total and domain scores Seondary: 1. SGRQ total score 2. SF-36 score 3. Post-bronchodilator spirometry 4. Blood values 5. Microbiology 6. Time to first exacerbation of COPD 7. Exacerbations 8. Hospitalizations for COPD 9. Adverse events
Notes	Funding: "We want to thank Stichting Astma Bestrijding (SAB) for financial support."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation codes were generated using a computer allocation program, with a 1:1 ratio and a permutated block size of 4. "

Berkhof 2013 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not specifically described, but probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Investigators, research nurses, and participants were masked to treatment allocation until final analyses of the data were performed"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators, research nurses, and participants were masked to treatment allocation until final analyses of the data were performed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout low and balanced. All participants accounted for in flow diagram
Selective reporting (reporting bias)	Low risk	FEV1 measured but not reported in a way allowing inclusion in meta-analysis in the published paper, but authors supplied additional data on request
Other bias	Low risk	No other bias identified

Brill 2015

Methods	Prospective, randomised, single-blind, placebo-controlled clinical trial. Treatment duration of 13 weeks Intention-to-treat analysis
Participants	N = 99. Aged 45 to 80 years. Mean age (years) 70.0 (moxifloxacin), 70.4 (doxycyline), 67.9 (azithromycin) and 68.7 (placebo) Female: 32% (moxifloxacin), 28% (doxycyline), 36% (azithromycin), and 25% (placebo) Mean FEV1 % predicted: 52 (SD 13) (moxifloxacin), 53 (SD 14) (doxycyline), 44 (SD 17), (azithromycin), and 53 (SD 13) (placebo) Stable patients with chronic bronchitis (self-reported sputum expectoration on most days when clinically stable) and spirometrically-confirmed COPD (defined by FEV1 < 80% predicted, FEV1 to FVC ratio < 0.7, and a history of smoking) Exclusions: patients who reported either treatment for an exacerbation, an episode of symptoms worsening in the 4 weeks prior to screening, or were unable to enrol for safety reasons (significant hepatic/renal impairment, QT prolongation, pre-existing long-term antibiotic use, and hypersensitivity to the treatments under investigation)
Interventions	Prophylaxis: 1. Moxifloxacin 400 mg daily for 5 days every 4 weeks 2. Doxycyline 100 mg daily 3. Azithromycin 250 mg 3 times a week 4. Placebo

Brill 2015 (*Continued*)

Outcomes	Primary: 1. Change in sputum bacterial load, as assessed by quantitative culture Secondary: 1. Changes in resistance to the three tested antibiotics 2. Changes in FEV1 3. Adherence to therapy 4, Health status as measured by total SGRQ scores 5. Adverse events Exploratory: 1. Changes in sputum bacterial load as assessed by 16S rRNA gene-targeted qPCR 2. Changes in sputum inflammation
Notes	Funding: funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research programme (RP-PG-0109-10056) and the NIHR Royal Brompton Respiratory Biomedical Research Unit. The moxifloxacin for the study was provided by Bayer Pharma AG, Berlin, Germany and the study sponsor was University College, London, UK. Neither Bayer, the funder, nor the Sponsor had any influence in the study design, collection, analysis and interpretation of the data, the writing of the report, or the decision to submit for publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Internet randomisation into groups of 1:1:1:1 was performed using a computer-generated permuted block system of variable sizes (Sealed Envelope, UK)"
Allocation concealment (selection bias)	Low risk	"Internet randomisation into groups of 1:1:1:1 was performed using a computer-generated permuted block system of variable sizes (Sealed Envelope, UK). Participants remained blinded to treatment allocation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Patients remained blinded to treatment allocation". However, not clear if study personnel were blinded. Described as single-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	No description of outcome assessor blinding, although blinded participants assessed outcomes such as quality of life
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout low and balanced. All participants accounted for in flow diagram

Brill 2015 (*Continued*)

Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported
Other bias	Low risk	No other bias identified

He 2010

Methods	Prospective, randomised, double-blind, placebo-controlled clinical trial. Treatment duration was 6 months. Intention-to-treat analysis
Participants	N = 36. Participants were 40 years or older. Mean age (years): 68.8 (erythromycin) and 69.3 (placebo) Females: 17% (erythromycin) versus 10% (placebo) FEV1 between 30% to 70% predicted. Mean FEV1 (L): 1.12 (erythromycin) versus 1.02 (placebo) At least 10 pack/year smoking history No acute exacerbations during the previous 1 month Exclusions: patients with significant other respiratory disorders other than COPD; history of unstable cardiovascular disease; hypersensitivity to macrolides
Interventions	Prophylaxis: 1. Erythromycin 125 mg 3 times a day 2. Placebo
Outcomes	Primary: 1. Number of acute COPD exacerbations 2. Neutrophil count in sputum Secondary: 1. Quality of life 2. Spirometry
Notes	Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation done but not clearly explained: "Eligible participants were randomly assigned to receive oral erythromycin....or placebo for 6 months."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as a double-blind trial: "Eligible participants were randomly assigned to receive oral erythromycin....or placebo for 6 months."

He 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcomes assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data described using a CONSORT diagram
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other bias identified

Mygind 2010

Methods	Prospective, randomised, placebo-controlled double-blind study. Treatment duration was 36 months. Intention-to-treat analysis
Participants	N = 575. Aged > 50 years Severity of COPD was moderate or severe with FEV1 < 60% predicted. Mean FEV1 (L) was 0.9 (both treatment and placebo arms) At least one admission to hospital with exacerbation of COPD Ex or current smokers Exclusions: end stage COPD patients (if not expected to survive over 3 years), or bedridden patients; patients with a history of asthma, bronchiectasis, or other significant respiratory disease; history of azithromycin allergy; patients with heart, liver or renal insufficiency; already receiving prophylactic antibiotic
Interventions	Intermittent prophylaxis: 1. Azithromycin 500 mg/daily for 3 days every months, for 36 months 2. Placebo daily for 3 days every month, for 36 months
Outcomes	Primary: 1. Rate of decline in lung function (FEV1) Secondary: 1. Frequency of exacerbation 2. Health-related quality of life (SGRQ) 3. Adverse events 4. Mortality 5. Duration of exacerbations 6. Number of days of hospitalisation 7. Frequency of hospitalisation
Notes	Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mygind 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as "randomised" but method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as a "double-blind study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcomes assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All outcome data were presented. Only 55% completed 3 years
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	This was a conference presentation and not a full publication. Attempts to contact the authors were not successful. Only limited data are available for evaluation of the risk of bias

NCT00524095

Methods	Prospective, randomised, controlled cross-over trial. Open-label. Planned 52 weeks treatment duration
Participants	Planned recruitment of 210 participants aged 45 to 85 years Smokers or former smokers of at least 10 pack-years, COPD demonstrated by forced spirometry with FEV1 > 0.7 L, FEV1 post-bronchodilator < 60% and FEV1/FVC < 70%, bronchodilator test performed at inclusion or no more than 6 months before inclusion should have been negative (increase in FEV1 < 200 mL and 12%, 10 minutes after administration of 2 puffs of salbutamol). Stable phase defined by clinical criteria of the attending investigator, but at least 6 weeks from the last exacerbation Exclusions: receiving OCS at any dose or another immunosuppressor, formal contraindication for sputum collection, or impossibility to obtain a sample of sputum valid for analysis, allergy to steroids or macrolides
Interventions	Prophylaxis: 1. Azithromycin 500 mg 3 times a week for 6 months and then inhaled steroids (fluticasone 500 μg twice a day) for 6 months 2. Inhaled steroids (fluticasone 500 μg twice a day) for 6 months and then azithromycin 500 mg 3 times a week for 6 months 3. Usual care

NCT00524095 (*Continued*)

Outcomes	Primary 1. Effects of treatments on bronchial inflammation parameters Secondary: 2. Effects of treatments on exacerbations frequency (time frame: six months) 3. Effects of treatments on pulmonary function (time frame: six months)
Notes	NB: study terminated before treatment phase. Reason not given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not assessed as study terminated before treatment phase
Allocation concealment (selection bias)	Unclear risk	Not assessed as study terminated before treatment phase
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not assessed as study terminated before treatment phase
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not assessed as study terminated before treatment phase
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not assessed as study terminated before treatment phase
Selective reporting (reporting bias)	Unclear risk	Not assessed as study terminated before treatment phase
Other bias	Unclear risk	Not assessed as study terminated before treatment phase

NCT02628769

Methods	Prospective, randomised, controlled double-blind cross-over trial. Planned 12 weeks treatment duration
Participants	N = 5. Aged 45 years and older History of cigarette smoking > 10 pack-years, post-bronchodilator FEV1/FVC of < 0. 70 and FEV1 of 30% to 79% of predicted normal value, nonpregnant females, willing and able to comply with all study visits and procedures, a suitable candidate for oral therapy and be able to swallow capsules intact, no evidence of active bacterial infection in sputum by qPCR evaluation Exclusions: acute exacerbation of COPD within the previous 60 days or during the washout period of the study, any condition that could possibly affect oral drug absorption,

	currently taking medication for HIV, chronic hepatitis B, or hepatitis C virus infection, currently taking theophylline or other xanthine medication, currently taking warfarin, known concomitant infection, QTc greater than 450 msec for males or females as corrected by the Fridericia formula, current use of drugs known to prolong the QT interval, concomitant use of drugs, foods, or herbal products known to be moderate to potent inhibitors of CYP3A4 isozymes, any use within the prior 7 days of drugs or herbal products known to be moderate to potent inducers of CYP3A4 isozymes, required current use of drugs with narrow therapeutic indices that are principally metabolised by CYP3A4 or transported by P-glycoprotein, for which a drug interaction with solithromycin could result in higher and possibly unsafe exposures to these drugs, history of organ transplant, cytotoxic chemotherapy or radiation therapy within the previous 3 months, known neuromuscular disorder from clinical history, known significant renal, hepatic, or haematologic impairment, any investigational drugs taken or investigational devices used within 4 weeks before administration of the first dose of the study drug, history of intolerance or hypersensitivity to macrolide antibiotics, any concomitant condition that, in the opinion of the Investigator, would preclude an evaluation of a response or make it unlikely that the contemplated course of therapy and follow-up could be completed (e.g. life expectancy < 30 days)
Interventions	Prophylaxis: 1. Solithromycin 400 mg daily 2. Placebo
Outcomes	Primary: 1. Number of sputum neutrophils per mL Secondary: 1. Sputum chemokines 2. Concentrations of CXCL8 in nasal lining fluid 3. FEV1 4. R5 to R20 (assessed by impulse oscillometry) 5. CAT scores 6. Adverse events Exploratory: 1. Activity of HDAC2 in sputum macrophages from participants 2. Activity of PI3K in sputum macrophages from participants 3. Activity of NF-κB in sputum macrophages from participants 4. Levels of the serum CRP 5. Levels of serum biomarkers fibrinogen
Notes	NB: study terminated after enrolment of 5 participants due to hepatotoxicity of the study drug

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not assessed as study terminated after enrolment of 5 participants

NCT02628769 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not assessed as study terminated after enrolment of 5 participants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not assessed as study terminated after enrolment of 5 participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not assessed as study terminated after enrolment of 5 participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not assessed as study terminated after enrolment of 5 participants
Selective reporting (reporting bias)	Unclear risk	Not assessed as study terminated after enrolment of 5 participants
Other bias	Unclear risk	Not assessed as study terminated after enrolment of 5 participants

Seemungal 2008

Methods	Prospective, randomised, double-blind, placebo-controlled clinical trial with 12 month follow-up
Participants	N = 109. Participants recruited from outpatient chest clinic from a single centre Mean age (years): 66 (erythromycin) and 68 (placebo) Females: 38% (erythromycin) and 36% (placebo) Severity of COPD was moderate to severe. FEV1 between 30% to 70% predicted. Mean FEV1 (L): 1.27 (erythromycin) and 1.36 (placebo) Exclusions: history of asthma, bronchiectasis, neoplasia, unstable cardiac status (including prolonged QTc and arrhythmias), macrolide allergy, or history of abnormal liver functions
Interventions	Prophylaxis: 1. Erythromycin 250 mg twice daily 2. Placebo
Outcomes	Primary: 1. Exacerbation frequency 2. Airway inflammation
Notes	Calculated sample size was 115 for 90% power and P value 0.05. However only 109 participants were recruited Funding: British Lung Foundation
Risk of bias	

Seemungal 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block random sequence generation carried out: "Computer-generated randomization. ..Randomization was taken in blocks of 10 (5 placebo, 5 erythromycin)"
Allocation concealment (selection bias)	Low risk	"Computer-generated randomization numbers were stored in sealed envelopes. Medication was randomized before commencement of the study by the hospital pharmacy, independently of trial staff, and patients were automatically dispensed the next allocated treatment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo and erythromycin (250 mg) were concealed in identical capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Unblinding occurred after data entry"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes/dropouts explained in a CONSORT diagram
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other bias identified

Sethi 2010

Methods	Prospective double-blind randomised placebo-controlled clinical trial. Total treatment period was 48 weeks 1. Analysis was done using intention-to-treat and per protocol. For this review, only the results of the intention-to-treat analysis were taken 2. Exacerbation of COPD was defined by two definitions. A primary definition (any confirmed acute exacerbation of COPD, unconfirmed pneumonia, or any other lower respiratory tract infections) and a secondary definition (only confirmed exacerbations of COPD, excluding confirmed/unconfirmed pneumonia and any other lower respiratory tract infection) For this review, only the primary definition was used as it was an extended definition and hence was the more conservative definition
Participants	N = 1157. Aged 45 years or over. Severity of COPD was GOLD stage 2 or worse. Had at least 2 exacerbations requiring treatment with antibiotics and/or oral steroids in the 12 months prior to enrolment

Sethi 2010 (*Continued*)

	Total follow-up period was 72 weeks. Total treatment period was 48 weeks
Interventions	Pulsed prophylaxis: 1. Moxifloxacin 400 mg/daily for 5 days. Treatment repeated every 8 weeks for a total of 6 courses 2. Placebo daily for 5 days. Treatment repeated every 8 weeks for a total of 6 courses
Outcomes	Primary: 1. Frequency of exacerbations Secondary: 1. HRQoL (assessed using SGRQ) 2. Hospitalisations 3. Mortality 4. Changes in lung function 5. Adverse events
Notes	Funding: received grant support from Bayer HealthCare AG

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomised" but method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blind, placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcomes assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All outcome data were described using a CONSORT diagram for the entire study However, data on the secondary outcome, HRQoL, had reported loss to follow-up of 12% in the prophylactic antibiotic arm and 10% in the placebo arm. The reasons for the missing data pertaining to HRQoL outcome were not given
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were well described

Sethi 2010 (*Continued*)

Other bias	Low risk	Data were analysed as intention-to-treat as well as per protocol analysis. Both analyses were published

Shafuddin 2015

Methods	Prospective, randomised, double-blind, placebo-controlled trial. Duration of treatment 13 weeks with 48 week post-treatment follow up Intention-to-treat analysis Originally designed to investigate the role antibiotics in eradicating *C. pneumoniae* in patients with COPD
Participants	N = 292. Aged 45 years and above. Mean age (years): 68.5 (roxithromycin/doxycyline), 67.6 (roxithromycin), and 66.7 (placebo) Female: 36.6% (roxithromycin/doxycyline), 14.4% (doxycyline), 28.7% (placebo) Mean FEV1 % predicted, mean: 32.53 (SD 13.55) (roxithromycin/doxycyline), 33.93 (SD 15.3) (doxycyline), 35.8 (SD 15.2) (placebo) Meeting spirometric criteria for COPD (FEV1 $\leq$ 70 % predicted, FEV1/FVC $\leq$ 60 %, reversibility of $\leq$ 10 % of predicted FEV1 or $\leq$ 200 mL if predicted FEV1 $\leq$ 2 L); smoking history $\geq$ 20 pack years; and at least three confirmed moderate or severe COPD exacerbations in the past two years (i.e. requiring treatment with antibiotics and/or OCS and/or hospitalisation), positive serology for *C. pneumoniae* (IgG antibody titre $\geq$ 1:64). Exclusions: pulmonary disease other than COPD; treatment with antibiotics, exacerbation or an investigational drug in the four weeks before randomisation; pregnancy (serum pregnancy test) or breast feeding; history of hypersensitivity to macrolides, tetracyclines, beta-lactams or sulfamethoxazole:trimethoprim; serious cardiovascular, hepatic, renal or other systemic diseases; known long QT syndrome or corrected QT interval (QTc) > 450 ms, sick sinus syndrome, bradycardia (< 50 beats per minute) or severe hypokalaemia; epilepsy; treatment with medicine known to have important interaction with macrolides or tetracyclines; impaired hepatic function (aspartate aminotransferase or alanine aminotransferase $\geq$ 2 times of the upper limit of normal (ULN), alkaline phosphatase $\geq$ 1.25 times the ULN, bilirubin > 2 times the ULN and albumin < 30 g/L); or unlikely to comply
Interventions	Prophylaxis: 1. Roxithromycin 300 mg daily plus doxycycline 100 mg daily 2. Roxithromycin 100 mg daily 3. Placebo
Outcomes	Primary: 1. COPD exacerbations over 48-week post-treatment period Secondary 1. COPD exacerbations over the 12-week treatment period and the first and last 24-week post-treatment periods 2. FEV1 and FVC over 60-week period 3. CRQ scores over 60-week period 4. Adverse events

Shafuddin 2015 (*Continued*)

Notes	Funding: supported by Sanofi-Aventis Australia Pty Ltd (formally Hoechst Marion Roussel Pty Ltd). Sanofi-Aventis had no role in the preparation of this manuscript for publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Each eligible patient was assigned a sequential subject number followed by randomisation number provided by Hoechst Marion Roussel, Australia. Subjects were supplied with one of the three treatments according to their randomisation number". Clinical trials registry clarified: "computer sequence generation used for randomisation of subjects into treatment arms with 1:1:1 ratio"
Allocation concealment (selection bias)	Low risk	"Each eligible patient was assigned a sequential subject number followed by randomisation number provided by Hoechst Marion Roussel, Australia. Subjects were supplied with one of the three treatments according to their randomisation number. "
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study medication was packed by Hoechst Marion Roussel in bottles labelled with the randomisation and batch numbers. The investigators, pharmacists and subjects were blinded to the study medication in these bottles."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Correspondence with trialists confirmed that all participants, personnel, and outcome assessors remained blinded until data had been analysed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More participants dropped out of combined antibiotics treatment arm (21 versus 13 in single antibiotic arm and 10 in placebo arm), although, according to trialists, reasons were not related to study medication. All participants included in ITT analysis
Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported

Shafuddin 2015 (*Continued*)

Other bias	Low risk	No other bias identified

Simpson 2014

Methods	Prospective, randomised, double-blind, placebo-controlled trial. Duration of treatment 12 weeks with 12 week post-treatment follow up Intention-to-treat analysis
Participants	N = 30. Aged 55 years and above. Mean age (years): 71.7 (azithromycin) and 69.9 (placebo) Female: 40% (azithromycin) and 33.3% (placebo) FEV1% predicted, mean: 56.5 (SD 13.7) (azithromycin) and 51.1 (SD 13.7) (placebo) Adults (males and nonpregnant females) with a doctor's diagnosis of symptomatic COPD, post-bronchodilator FEV1/FVC < 70% and FEV1 < 80% and persistent neutrophilic bronchitis defined as sputum neutrophil proportion of more than 61% or more than 162 x 10^4/mL sputum neutrophils demonstrated on two occasions Exclusions: no reported exacerbations or alterations in respiratory medications in the previous 4 weeks, inability to produce an adequate sputum sample, a FEV1 < 0.5 L, current smoking or having ceased smoking in the past 6 months, a known hypersensitivity to macrolides, an ECG assessment showing a prolonged QTc interval or an impairment of liver function
Interventions	Prophylaxis: 1. Azithromycin 250 mg daily 2. Placebo
Outcomes	Primary: 1. Reduction in sputum CXCL8 Secondary: 1. Change in sputum neutrophil proportion 2. Total bacterial load in sputum 3. Health care utilisation 4. Quality of life (SGRQ) 5. Severe exacerbations 6. Pulmonary function tests 7. Chest computed tomography to measure airway thickness 8. Adverse events
Notes	Funding: funded by the National Health and Medical Research Council of Australia through a project grant, ID 455508 2007-2009. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Simpson 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Concealed random allocation was undertaken by a blinded staff member who took no further part in the study...A random numbers table was computer generated (www.randomization.com) for treatment allocation using permuted blocks of six and participants were stratified according to smoking history (never or previous smokers)."
Allocation concealment (selection bias)	Low risk	"Concealed random allocation was undertaken by a blinded staff member who took no further part in the study..The active medication and placebo were prepared and packaged identically by a compounding chemist and dispensed by the John Hunter Hospital pharmacy according to the random number table."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both participants and study staff were blinded to the assignment of intervention. "
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The people assessing the outcomes are described as blinded in the trial registration
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and balanced dropout. Reasons for discontinuation unrelated to study medication
Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported
Other bias	Low risk	No other bias identified

Suzuki 2001

Methods	Prospective, randomised, placebo-controlled clinical trial. Not blinded
Participants	N = 109 Mean age (years): 69 (erythromycin) and 72 (placebo) Mean FEV1 (L): 1.47 (erythromycin) and 1.30 (placebo) Females: 13% in erythromycin group versus 18% in placebo group All study participants were treated with sustained-release theophylline and inhaled anticholinergic agents Exclusions: patients diagnosed with bronchiectasis or diffuse pan bronchiolitis

Suzuki 2001 (*Continued*)

Interventions	Prophylaxis: 1. Erythromycin 200 mg to 400 mg/daily 2. Placebo
Outcomes	1. Acute exacerbations of COPD 2. Adverse events
Notes	Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed by a random-number table, and the list was held independently of the investigators"
Allocation concealment (selection bias)	Low risk	"Randomization was performed by a random-number table, and the list was held independently of the investigators"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"This study was not blinded".
Blinding of outcome assessment (detection bias) All outcomes	High risk	"This study was not blinded".
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant excluded due to adverse events of erythromycin, all participants clearly accounted for
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other bias identified

Tan 2016

Methods	Prospective, randomised controlled trial. Blinding not stated in main trial report. Treatment duration 52 weeks
Participants	N = 54. Age range: 49 to 70 years. Mean age (years): 68.8 (erythromycin, 12 months), 67.3 (erythromycin, 6 months) and 69.3 (control) Female: 16.7% (erythromycin, 12 months), 5.6% (erythromycin, 6 months) and 11.1% (control) Mean FEV1 % predicted: 44.8 (SD 13.9) (erythromycin, 12 months), 46.5 (SD 8.9) (erythromycin, 6 months), and 42.1 (SD 18.6) (control)

Tan 2016 (*Continued*)

	Stable COPD outpatients (GOLD stages II-IV of 2006 guidelines: FEV 1 < 80% predicted and FEV1/FVC < 70% after bronchial relaxation); no acute exacerbation; no change in therapeutic schedule; and no treatment with any antibiotics or glucocorticoids in the previous 4 weeks Exclusions: patients with bronchial asthma, primary bronchiectasis, diffuse panbronchiolitis, active tuberculosis, lung cancer, pneumoconiosis, or other lung diseases with restrictive ventilatory impairment; patients with other serious systemic illnesses such as cardiovascular, nervous, or endocrine system illnesses, blood, hepatic, or kidney diseases, and malignant tumours; patients who were not cooperative or were completely unable to communicate; and patients who experienced serious adverse reactions to erythromycin
Interventions	Prophylaxis: 1. Erythromycin 125 mg 3 times a day for 12 months 2. Erythromycin 125 mg 3 times a day for 6 months 3. Control group (no antibiotic treatment)
Outcomes	1. Concentrations of IL-17 and IL-23 in peripheral blood and induced sputum 2. Six-minute walk distance (Primary and secondary outcomes not specified)
Notes	Funding: funded by the National Nature Science Foundation of China (81460009) and the Guangxi Natural Science Foundation (2015GXNSFAA139189, Z2012077, and Z2012081)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants "randomly divided" but method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Assumed open-label (although abstract stated double-blind). Authors contacted but no response received to date
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Assumed open-label (although abstract stated double-blind). Authors contacted but no response received to date
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low and balanced dropout but details not given of how many people were analysed at each time point

Tan 2016 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No prospective trial registration or protocol identified so not clear if outcomes of interest for this review may have been collected but not reported (e.g. serious adverse events, exacerbations, quality of life)
Other bias	Low risk	No additional bias identified

Uzun 2014

Methods	Prospective, randomised double-blind placebo-controlled trial. Treatment duration 52 weeks Intention-to-treat analysis
Participants	N = 92. Aged 18 years and above. Mean age (years): 64.7 (azithromycin) and 64.9 (placebo) Female: 53% (azithromycin) and 60% (placebo) Mean FEV1 % predicted: 44.2 (SD 19.3) (azithromycin) and 45.0 (SD 19.5) (placebo) Diagnosis of COPD according to the GOLD guidelines, had received treatment for three or more exacerbations of COPD in the previous year for which they received steroids or antibiotic treatment, clinically stable, and could not have had a COPD exacerbation or respiratory-tract infection in the month before involvement in the study Exclusions: history of other clinically significant respiratory diseases (e.g. asthma, cystic fibrosis); presence of bronchiectasis, as assessed by CT scan; maintenance antibiotic treatment; use of more than 10 mg prednisolone a day; allergy to macrolides; pregnancy or lactation in women; liver disease (alanine transaminase or aspartate transaminase concentrations that were two or more times the upper limit of normal); malignant disease of any kind for which the patient received treatment or was being monitored as part of follow-up after treatment; heart failure; and the use of drugs that could adversely interact with macrolides and for which therapeutic monitoring could not be undertaken
Interventions	Prophylaxis: 1. Azithromycin 500 mg 3 times per week 2. Placebo
Outcomes	Primary: 1. Rate of exacerbations of COPD Secondary: 1. Time to first exacerbation 2. Hospital admission for acute exacerbations 3. Change in proportion of exacerbations needing admission to hospital versus treatment in an outpatient department compared with the previous year 4. Treatment for an acute exacerbation of COPD 5. FEV1 after bronchodilation 6. FVC after bronchodilation 7. Six-minute walk test 8. Quality of life, as assessed by the SF-12 and the SGRQ 9. Acquisition of macrolide resistant microorganisms in sputum

	10. Adverse events	
Notes	Funding: SoLong Trust. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An independent pharmacy randomly assigned patients (1:1), via a computer-generated randomisation sequence with permuted blocks of ten."
Allocation concealment (selection bias)	Low risk	"Patients were automatically given the next allocated treatment by clinical trials staff at the hospital pharmacy. Participants and investigators were masked to treatment allocation throughout the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants and investigators were masked to treatment allocation throughout the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"After data collection and data cleaning were completed, and after final database lock, investigators were unmasked and could assess outcomes and complete the data analysis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Higher drop out in placebo arm, but results from the unadjusted and adjusted per-protocol analyses were almost identical to those from the intention-to-treat analysis and all participants included in safety analysis
Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported
Other bias	Low risk	No additional bias identified

Wang 2017

Methods	Prospective, parallel, randomised controlled trial. Blinding not reported. Duration of treatment 26 weeks
Participants	N = 86. Age range: 61 to 83 years. Mean age (years): 70.5 (azithromycin) and 72.4 (placebo) Female: 44.2% (azithromycin) and 37.2 (placebo) 10 cases of cardiac functional grade II, 27 cases of grade III and 6 cases of grade IV (azithromycin) and 11 cases of cardiac functional grade II, 23 cases of grade III and 9 cases of grade IV (placebo) Patients with pulmonary hypertension secondary to COPD. Patients whose mean arterial pressure was detected as not less than 25 mmHg by right cardiac catheterisation in a quiescent condition or as no less than 30 mmHg in a motion state, and patients who had not suffered from acute attack of COPD or acute lung infection Exclusions: severe cardiac, hepatic, and liver function abnormality, pulmonary thromboembolism, allergic rhinitis, asthma or primary pulmonary hypertension, or were allergic to the drugs used in the study
Interventions	Prophylaxis: 1. Azithromycin 250 mg daily 2. Control group (no antibiotic treatment)
Outcomes	1. PaO_2 2. $PaCO_2$ 3. Blood pH 4. FEV1 5. FVC 6. Six minutes walking distance 7. Pulmonary arterial pressure
Notes	Funding: "Grant Support & Financial Disclosures: None".

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly divided into an observation group and a control group using random number table, 43 in each group"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Assumed open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Assumed open-label

Wang 2017 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	No prospective trial registration or protocol identified. Dyspnea grade reported as measured in the abstract and not reported. Not clear currently if FEV1 and FVC variance were SDs or SEs
Other bias	Low risk	No additional bias identified

BTS: British Thoracic Society; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CRQ: chronic respiratory disease questionnaire; CYP: cytochrome P450; CXCL8: C-X-C motif ligand 8 (interleukin 8); ECG: electrocardiogram; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HDAC2: histone deacetylase 2; HIV: human immunodeficiency virus; HRQoL: health related quality of life; ICS: inhaled corticosteroid; IgG: immunoglobulin G; IL: interleukin; ITT: intention-to-treat; L: litres; LCQ: Leicester Cough Questionnaire; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; OCS: oral corticosteroids; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; pH: potential of hydrogen; PI3K: phosphoinositide 3-kinase; qPCR: quantitative polymerase chain reaction; QTc: Q-T Corrected (corrected Q-T interval); QT: Q-T interval; rRNA: ribosomal ribonucleic acid; R5-R20: total respiratory system resistance, measured at 5 to 20 Hz; SD: standard deviation; SF-12/36: Short-Form 12/36; SGRQ: St George's Respiratory Questionnaire; ULN: upper limit of normal

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beeh 2016	Comparison: ELOM-080 (a distillate of essential oils) versus placebo Problem: drug under investigation not a conventional antibiotic
Bier 1971	Comparison: doxycyclin versus placebo Problem: spirometric criteria were not used in diagnosing COPD
Blasi 2010	Comparison: azithromycin 500 mg three day a week for 6 months versus placebo Problem: pilot study, uncontrolled Study done on tracheostomy patients
Bruninx 1973	Comparison: bactrim versus ledermycin over 1070 months Problem: 1) heterogeneous participant population including bronchiectasis, anthracosilicosis, and bronchitis; 2) no placebo arm
Buchanan 1958	Comparison: tetracycline 250 mg twice daily versus placebo for 12 months duration Problems: single-blinded (only participants were blinded); spirometric criteria were not used to diagnose COPD

(*Continued*)

Bussi 1980	Comparison: intermittent tetracyclines 200 mg weekly for 3 years versus placebo Problem: spirometry criteria not used for diagnosis of COPD. Heterogenic group of participants
Davies 1961	Comparison: tetracycline for 2 days each week versus placebo Problem: spirometric criteria were not used in diagnosing COPD; blinding not known
Douglas 1957	Not a randomised controlled trial Heterogeneous group of participants including large proportion with bronchiectasis Intial treatment with intramuscular penicillin Participants who failed penicillin were allocated to either chloramphenicol 0.5 g 6-hourly or oxytetracycline 0.5 g 6-hourly
Edwards 1958	Comparison: oxytetracycline or sulfonamide versus placebo Problems: *H. influenzae* vaccination co-administered; no suitable outcome measures
Elmes 1957	Comparison: oxytetracycline versus placebo Problem: not prophylactic, antibiotic versus placebo at the onset of symptoms
Fletcher 1966	Comparison: treatment for 7 months/year over 5-year period. 1) oxytetracycline 0.5 g daily for 7 months over years 1 to 3; 2) oxytetracycline 0.5 g twice daily over 7 months in year 4; 3) oxytetacyline 1 g twice daily over 7 months in year 5; versus placebo Problem: spirometric criteria not used to diagnose COPD
Frances 1964	Problem: spirometric criteria were not used to diagnose COPD
Francis 1960	Comparison: 3 groups: 1) tetracycline 250 mg twice daily for 3 months; 2) penicillin V 312 mg twice daily for 3 months; 3) placebo for 3 months Problems: spirometric criteria were not used in diagnosing COPD
Goslings 1967	Comparison: 1) sulfaphenazole 500 mg twice daily; 2) tetracycline 500 mg twice daily; 3) saccharum 500 mg twice daily (placebo) over 5-month period Problem: spirometric criteria were not used to diagnose COPD
Grossman 1998	Comparison: ciprofloxacin 500 mg twice daily versus placebo for acute exacerbations of chronic bronchitis, treatment given during acute exacerbations during 12-month period versus usual care during an acute exacerbation Problem: ciprofloxacin was given during an exacerbation of chronic bronchitis. Not prophylaxis
Hahn 1972	Comparison: tetracycline or ampicillin versus placebo Problems: not a true long-term prophylaxis. Prophylaxis is defined as antibiotics instituted by the participants at the first sign of a cold and were continued only for 5 days
Haidl 2013	Comparison: inhaled tobramycin versus placebo Problem: antibiotic given via inhalation, not orally
Hallett 1959	Comparison: erythromycin 250 mg 4 times a day versus placebo for 12 week duration Problem: not a randomised controlled trial; participants were matched in pairs (treatment and placebo groups) on the basis of similar clinical characteristics

(*Continued*)

Helm 1956	Not a randomised controlled trial
Johnston 1961	Comparison: Four treatment arms 1.Tetracycline 500 mg twice daily for 6 months treatment per year for 5 years 2. Placebo for 6 months treatment per year for 5 years 3. Tetracycline for the first 2 winters and placebo for the next three 4. Placebo for 2 winters and tetracycline for the next three Problem: Partial crossover due to re-randomisation after two years Spirometric criteria were not used to diagnose COPD
Johnston 1961	Comparison: phenethicillin versus placebo Problems: spirometric criteria were not used to diagnose COPD
Kilpatrick 1954	Comparison: sulphadimidine 0.5 g three times daily versus placebo for 3 to 6 months Problem: spirometric criteria were not used when diagnosing COPD
Legler 1977	Problem: not randomised Spirometric criteria were not used for diagnosing COPD
Liippo 1987	Comparison: trimethoprim 300 mg per day versus placebo. Treatment for 6 months duration Problem: heterogeneous group of participants. Participants with bronchiectasis and asthma included. Spirometry criteria for COPD not used
Maraffi 2010	Review article on 13 previous randomised controlled trials from 1957 to 2010
Matthys 2015	Wrong intervention: drug being trialled is not an antibiotic
May 1956	Comparison: oxytetracycline or tetracycline versus 'controlled group' who were observed and antibiotic prophylaxis was not given Problem: not a true randomised controlled trial. The 'controlled group' consisted of 14 participants who were observed without any prophylactic therapy. They were not randomly selected
Miravitlles 2009	Comparison: moxifloxacin 400 mg daily versus placebo Problem: short duration of study with only 5 days of treatment
Moyes 1959	Comparison: four groups: 1) erythromycin 1g daily for 7 days ,then a course of 1 g daily for five days taken at the sign of first infection; 2) erythromycin 1 g daily for 7 days, then a regular course of 1 g daily for five days every 4 weeks; 3) tetracycline 1 g daily for 7 days , then a course of 1 g daily for five days taken at the sign of first infection 4) tetracycline 1 g daily for 7 days , then 750 mg/daily for 4 months Problems: no placebo group
Murdoch 1959	Comparison: sigamycin (167 mg of tetracycline and 83 mg of oleandomycin) versus placebo for 3 months Problem: spirometric criteria not used in diagnosing COPD

(*Continued*)

Murray 1964	Comparison: ampicillin 250 mg 4 times daily versus placebo over 17 months Problem: spirometric criteria were not used to diagnose COPD. Unclear whether randomisation took place
Nicholson 2016	Problem: not a randomised controlled trial
Norman 1962	Comparison: tetracycline 1 g daily or placebo for 3 months and then the groups were crossed over with continuation of treatment for further 3 months Problem: randomised cross-over trial. Spirometry criteria not used when diagnosing COPD
Pines 1967	Comparison: sulphormethoxine 2 g weekly for 10 weeks versus placebo Problems: spirometric criteria were not used in diagnosing COPD patients
Pridie 1960	Comparison: penicillin-sulphonamide, oxytetracycline versus placebo Problem: spirometric criteria were not taken into account when diagnosing COPD
Prins 2016	Duration of intervention too short: 3 weeks of doxycycline
Ras 1984	Comparison: 1) erythromycin 1500 mg/day for 2 weeks followed by 100 mg/day for 12 weeks; 2) amoxycillin 1500 mg/day for 2 weeks followed by 100 mg/day for 12 weeks; 3) placebo Problem: randomisation not well explained. Spirometric criteria not used when diagnosing COPD
Segal 2017	Comparison: azithromycin versus placebo Problem: study of effect on microbiome; duration too short (8 weeks)
Siva 2014	Duration of intervention too short: 7 days of levofloxacin
Stass 2013	Problem: trial of one-off dose of inhaled ciprofloxacin to assess lung deposition patterns
Vandenbergh 1970	Comparison: sulfonamide 2 g once a week versus placebo for 6 months Problem: none of the primary outcomes were measured (frequency of exacerbations or quality of life) Spirometric criteria were not used in diagnosing COPD
Velzen 2016	Comparison: long-term effects of antibiotics given for acute exacerbations of COPD Problem: antibiotics given for acute COPD, not as prophylaxis
Vermeersch 2016	Comparison: azithromycin versus placebo for acute exacerbations of COPD Problem: antibiotics given for acute COPD, not as prophylaxis
Watanabe 1991	Comparison; 1) ofloxacin 200 mg daily for 6 months; 2) ofloxacin 200 mg three times daily for 2 weeks followed by 2 weeks without treatment for 6 months Problem: prophylaxis was given to participants with any chronic respiratory tract infection, including bronchiectasis and pulmonary tuberculosis. No placebo arm
Watanabe 1994	Comparison: ciprofloxacin 200 mg/daily versus erythromycin 200 mg/daily versus combined ciprofloxacin 200 mg/d + erythromycin 200 mg/d Problem: no placebo. Participants with bronchiectasis included

(*Continued*)

Watanabe 1995	Duplicate study of Watanabe 1991 with addition of 7 participants
Webster 1971	Comparison: trimethoprim-sulfamethoxazole versus sulfamethoxazole Problem: no placebo group. Treatment duration was only 10 days

COPD: chronic obstructive pulmonary disease

Characteristics of studies awaiting assessment *[ordered by study ID]*

Milito 2017

Methods	Multicentre randomised placebo-controlled double-blind trial
Participants	89 participants with primary antibody deficiency and chronic obstructive pulmonary disease with exacerbations
Interventions	Azithomycin 250 mg three times per week on consecutive days for 24 months versus placebo
Outcomes	Exacerbations, no use of additional antibiotics, an increase of respiratory volumes, an improvement of the Health-Related Quality of Life measures
Notes	Conference abstract describing study protocol and participant dropouts only. Study was due to complete in December 2016, but we have been unable to identify a full-text publication to confirm eligibility and extract outcomes

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IOR-16008820

Trial name or title	Effect of low-dose erythromycin on the treatment of COPD
Methods	Randomised parallel group controlled trial. Planned recruitment 160 participants
Participants	1. Participants meeting the GOLD 2015 diagnostic criteria for COPD (a ratio of post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity of < 70%,and a post-bronchodilator FEV1 of < 80% of the predicted value); 2. Participants aged 40 years and more; 3. Participants were past or present cigarette smokers with at least a 10 pack-year smoking history; 4. Participants were studied when clinically stable for at least 4 weeks following an exacerbation; no change in any therapy; no received systemic glucocorticoids
Interventions	Intervention: erythromycin Control: placebo
Outcomes	Exacerbations of COPD, lung function

ChiCTR-IOR-16008820 (*Continued*)

Starting date	July 2016
Contact information	Zhong Xiaoning (xiaoningzhong@sina.com) Department of Respiratory Medicine, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China
Notes	Study due to complete July 2019

NCT02205242

Trial name or title	BACE trial - Physical activity as a crucial patient-reported outcome in COPD
Methods	Randomised parallel group controlled trial. Planned recruitment 500 participants (planned to measure physical activity outcomes for a subset of 60 participants)
Participants	1. Established diagnosis of COPD by medical doctor (based on clinical history OR pulmonary function test) 2. Smoking history of at least 10 pack-years (10 pack-years were defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years, etc.) 3. Current hospitalisation for potential infectious AECOPD treated with standard therapy 4. History of at least one exacerbation during the last year (prior to the current hospital admission) for which systemic steroids and/or antibiotics were taken 5. ECG at admission
Interventions	Intervention: from day 1 up to and including day 3: 500 mg azithromycin PO once a day, from day 4 up to and including day 90: 250 mg azithromycin PO once every 2 days Control: from day 1 up to and including day 3: 500 mg placebo PO once a day, from day 4 up to and including day 90: 250 mg placebo PO once every 2 days
Outcomes	Objective physical activity levels measured by an activity monitor
Starting date	September 2014
Contact information	Wim Janssens (wim.janssens@kuleuven.be) Katholieke Universiteit Leuven, O&N I Herestraat 49 - box 706, 3000 Leuven, Belgium
Notes	Study due to complete April 2018

NCT02205255

Trial name or title	BACE trial - the pharmaco-economic impact of the azithromycin intervention
Methods	Randomised parallel group controlled trial. Planned recruitment 350 participants (a second subanalysis of the BACE trial including a detailed cost-effectiveness study)
Participants	1. Established diagnosis of COPD by medical doctor (based on clinical history OR pulmonary function test) 2. Smoking history of at least 10 pack-years (10 pack-years were defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years, etc.)

NCT02205255 (*Continued*)

	3. Current hospitalisation for potential infectious AECOPD treated with standard therapy 4. History of at least one exacerbation during the last year (prior to the current hospital admission) for which systemic steroids and/or antibiotics were taken 5. ECG at admission
Interventions	Intervention: from day 1 up to and including day 3: 500 mg azithromycin PO once a day, from day 4 up to and including day 90: 250 mg azithromycin PO once every 2 days Control: from day 1 up to and including day 3: 500 mg placebo PO once a day, from day 4 up to and including day 90: 250 mg placebo PO once every 2 days
Outcomes	Total costs, direct costs, indirect costs
Starting date	August 2014
Contact information	Wim Janssens (wim.janssens@kuleuven.be) Katholieke Universiteit Leuven, O&N I Herestraat 49 - box 706, 3000 Leuven, Belgium
Notes	April 2018

NCT02305940

Trial name or title	A phase III double-blind, randomised, placebo controlled trial of long term therapy on exacerbation rate in patients with stable COPD using doxycycline
Methods	Randomised parallel group controlled trial
Participants	Aged 45 years and over Confirmed COPD diagnosis Severity of disease: participants with a measured FEV1 < 80% of predicted normal values At least one treated exacerbation (participant recalled an episode of symptomatic worsening which was treated and was consistent with a COPD exacerbation) in the previous year
Interventions	Intervention: doxycycline 100 mg once daily, for a total duration of 52 weeks Control: placebo
Outcomes	Primary: rate of exacerbations (per person/year) Secondary: lung function (FEV1, FVC, FEV1/FVC ratio, FEV1 as % predicted), SGRQ (total and individual components) respiratory health status (using diary cards), airway bacteria numbers from sputum samples, changes in C-reactive protein (CRP) levels from baseline, hospital admissions, time to 1st exacerbation, rate of exacerbations treated with steroids and antibiotics, adherence, antibiotic resistance
Starting date	July 2014
Contact information	Wisia Wedzicha (j.wedzicha@imperial.ac.uk) Emmanuel Kaye Building, Royal Brompton Campus, Imperial College, London, UK
Notes	July 2017

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ECG: electrocardiogram; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; PO: *per os* (orally)

DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of people with one or more exacerbations	8	2716	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
1.1 Continuous antibiotics	5	1325	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.36, 0.79]
1.2 Intermittent antibiotics	3	209	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.19, 0.77]
1.3 Pulsed antibiotics	2	1182	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.68, 1.07]
2 Number of people with one or more exacerbations requiring hospitalisation	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Intermittent antibiotics	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Annualised exacerbation rate per patient per year during 12-week active treatment			Other data	No numeric data
3.1 Continuous antibiotics			Other data	No numeric data
4 Rate of exacerbation per patient per year	5	1384	Rate Ratio (Random, 95% CI)	0.67 [0.54, 0.83]
4.1 Continuous antibiotics	4	1292	Rate Ratio (Random, 95% CI)	0.69 [0.54, 0.89]
4.2 Intermittent antibiotics	1	92	Rate Ratio (Random, 95% CI)	0.58 [0.42, 0.80]
5 Time to the first exacerbation			Other data	No numeric data
5.1 Continuous antibiotic			Other data	No numeric data
5.2 Intermittent antibiotics			Other data	No numeric data
5.3 Pulsed antibiotics			Other data	No numeric data
6 Mean time to first exacerbation (days)	1	266	Mean Difference (IV, Random, 95% CI)	-16.59 [-46.05, 12.86]
6.1 Continuous antibiotics	1	266	Mean Difference (IV, Random, 95% CI)	-16.59 [-46.05, 12.86]
7 COPD exacerbations according to severity of COPD - continuous antibiotics			Other data	No numeric data
8 COPD exacerbations according to severity of COPD - pulsed antibiotics			Other data	No numeric data
9 HRQoL, SGRQ (total score)	7	2237	Mean Difference (Random, 95% CI)	-1.94 [-3.13, -0.75]
9.1 Continuous antibiotics	4	991	Mean Difference (Random, 95% CI)	-1.96 [-3.45, -0.47]
9.2 Intermittent antibiotics	3	184	Mean Difference (Random, 95% CI)	-4.59 [-8.83, -0.36]
9.3 Pulsed antibiotics	2	1062	Mean Difference (Random, 95% CI)	-1.22 [-3.00, 0.55]
10 HRQoL, SGRQ (domains)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 SGRQ activity	4	2077	Mean Difference (IV, Random, 95% CI)	-0.99 [-2.62, 0.65]
10.2 SGRQ symptoms	4	2077	Mean Difference (IV, Random, 95% CI)	-4.07 [-5.72, -2.41]
10.3 SGRQ impact	4	2077	Mean Difference (IV, Random, 95% CI)	-2.56 [-5.02, -0.10]
11 HRQoL, LCQ (total)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Intermittent antibiotics	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 HRQoL, SF-12 (domains)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.1 SF-12 physical	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

12.2 SF-12 mental	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 HRQoL SF-36 (domains)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 SF-36 general health	3	1071	Mean Difference (IV, Random, 95% CI)	4.06 [0.70, 7.42]
13.2 SF-36 physical functioning	3	1071	Mean Difference (IV, Random, 95% CI)	1.88 [-1.01, 4.77]
13.3 SF-36 bodily pain	3	1072	Mean Difference (IV, Random, 95% CI)	0.53 [-2.47, 3.53]
13.4 SF-36 vitality	3	1070	Mean Difference (IV, Random, 95% CI)	2.03 [-0.38, 4.43]
13.5 SF-36 role emotional	3	1072	Mean Difference (IV, Random, 95% CI)	-0.75 [-5.55, 4.04]
13.6 SF-36 social functioning	3	1072	Mean Difference (IV, Random, 95% CI)	7.19 [-2.40, 16.78]
13.7 SF-36 mental health	3	1070	Mean Difference (IV, Random, 95% CI)	2.37 [-1.13, 5.86]
13.8 SF-36 role physical	3	1072	Mean Difference (IV, Random, 95% CI)	4.63 [-9.82, 19.09]
14 HRQoL, LCQ (domains)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 LCQ physical	1	79	Mean Difference (IV, Random, 95% CI)	0.40 [0.12, 0.68]
14.2 LCQ psychological	1	79	Mean Difference (IV, Random, 95% CI)	0.5 [0.22, 0.78]
14.3 LCQ social	1	79	Mean Difference (IV, Random, 95% CI)	0.4 [-0.15, 0.95]
15 HRQoL, CCQ (total)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15.1 Continuous antibiotics	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16 HRQoL, CRQ (domains)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 CRQ dyspnoea	1	275	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.79, 0.94]
16.2 CRQ fatigue	1	275	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.74, 0.62]
16.3 CRQ emotional function	1	275	Mean Difference (IV, Random, 95% CI)	-0.66 [-1.94, 0.62]
16.4 CRQ mastery	1	275	Mean Difference (IV, Random, 95% CI)	-0.21 [-1.29, 0.87]
17 Frequency of hospital admissions - continuous antibiotics			Other data	No numeric data
18 Frequency of hospital admissions - pulsed antibiotics			Other data	No numeric data
19 Duration of exacerbation			Other data	No numeric data
19.1 Continuous antibiotics			Other data	No numeric data
19.2 Pulsed antibiotics			Other data	No numeric data
20 FEV1 (mL)	6	658	Mean Difference (Random, 95% CI)	20.21 [-26.19, 66.61]
20.1 Continuous antibiotics	4	441	Mean Difference (Random, 95% CI)	-12.69 [-77.66, 52.28]
20.2 Intermittent antibiotics	3	184	Mean Difference (Random, 95% CI)	53.95 [-16.90, 124.81]
20.3 Pulsed antibiotics	1	33	Mean Difference (Random, 95% CI)	58.0 [-129.63, 245.63]
21 FVC (L)	4	514	Mean Difference (IV, Random, 95% CI)	0.12 [0.01, 0.23]
21.1 Continuous antibiotics	2	363	Mean Difference (IV, Random, 95% CI)	0.13 [-0.04, 0.30]
21.2 Intermittent antibiotics	2	151	Mean Difference (IV, Random, 95% CI)	0.17 [-0.01, 0.36]
22 FEV1 % predicted	6	1737	Mean Difference (IV, Random, 95% CI)	0.33 [-1.56, 2.22]
22.1 Continuous antibiotics	3	437	Mean Difference (IV, Random, 95% CI)	1.43 [-1.97, 4.83]
22.2 Intermittent antibiotics	2	151	Mean Difference (IV, Random, 95% CI)	1.67 [-1.33, 4.68]
22.3 Pulsed antibiotics	1	1149	Mean Difference (IV, Random, 95% CI)	-1.35 [-3.28, 0.58]
23 Exercise capacity (6MWT)	2	126	Mean Difference (IV, Random, 95% CI)	67.67 [16.20, 119.14]
23.1 Continuous antibiotics	1	49	Mean Difference (IV, Random, 95% CI)	84.20 [13.38, 155.03]
23.2 Intermittent antibiotics	1	77	Mean Difference (IV, Random, 95% CI)	36.0 [-15.53, 87.53]
24 All-cause mortality	6	3309	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.66, 1.15]
24.1 Continuous antibiotics	2	1409	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.49, 1.51]

24.2 Intermittent antibiotics	2	176	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.92]
24.3 Pulsed antibiotics	2	1724	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.23]
25 Respiratory-related mortality	2	2266	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.63, 2.19]
25.1 Continuous antibiotics	1	1117	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.54, 3.81]
25.2 Pulsed antibiotics	1	1149	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.45, 2.29]
26 Serious adverse events	9	2978	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.05]
26.1 Continuous antibiotics	7	1671	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.68, 1.05]
26.2 Intermittent antibiotics	2	125	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.12, 2.43]
26.3 Pulsed antibiotics	2	1182	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.34]
27 Any adverse event	4	512	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.69, 1.67]
27.1 Continuous antibiotics	3	355	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.73]
27.2 Intermittent antibiotics	2	124	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.37, 2.41]
27.3 Pulsed antibiotics	1	33	Odds Ratio (M-H, Random, 95% CI)	11.52 [0.60, 221.75]
28 Adverse events (specific)	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 Respiratory disorders	3	2350	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.33, 3.41]
28.2 Gastrointestinal disorders	6	2522	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.43, 3.11]
28.3 QTc prolongation	1	1117	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.39, 3.51]
28.4 Hearing impairment	1	1117	Odds Ratio (M-H, Random, 95% CI)	1.39 [1.05, 1.85]
28.5 Musculoskeletal disorders	1	1149	Odds Ratio (M-H, Random, 95% CI)	3.07 [0.32, 29.59]
28.6 Hypersensitivity/skin rash	2	1258	Odds Ratio (M-H, Random, 95% CI)	1.63 [0.63, 4.26]
28.7 Nervous system disorders	2	1179	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.38, 4.08]
28.8 Cardiovascular	1	84	Odds Ratio (M-H, Random, 95% CI)	2.05 [0.18, 23.51]

Comparison 2. Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Subgroup analysis: number of people with one or more exacerbations by mean % predicted FEV1	8	2716	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
1.1 Mean FEV1 % ≥ 50	1	30	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.05, 1.13]
1.2 Mean FEV1 % < 50	7	2686	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.44, 0.81]
2 Subgroup analysis: number of people with one or more exacerbations by treatment duration	8	2716	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
2.1 ≥ 3 months to < 6 months	3	213	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.28, 0.94]
2.2 ≥ 6 months to < 12 months	2	1185	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.24, 1.69]
2.3 ≥ 12 months	3	1318	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.25, 0.81]
3 Subgroup analysis: number of people with one or more exacerbations by year carried out	8	2716	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
3.1 2005 to 2009	1	109	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.17, 0.84]

3.2 2010 to 2014	6	2508	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.39, 0.83]
3.3 2015 to 2019	1	99	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.29, 1.89]
4 Subgroup analysis: number of people with one or more exacerbations by regimen	8	2716	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
4.1 Once daily antibiotic	3	1180	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.34, 1.09]
4.2 Twice or three times daily antibiotic	2	145	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.17, 0.71]
4.3 Three times a week antibiotic	3	209	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.19, 0.77]
4.4 Pulsed antibiotic	2	1182	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.68, 1.07]
5 Subgroup analysis: number of people with one or more exacerbations by exacerbation history	8	2716	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
5.1 Inclusion criteria of ≥ 1 exacerbation in preceding year	3	2358	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.43, 0.99]
5.2 Exacerbation history not an inclusion criteria	5	358	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.27, 0.69]

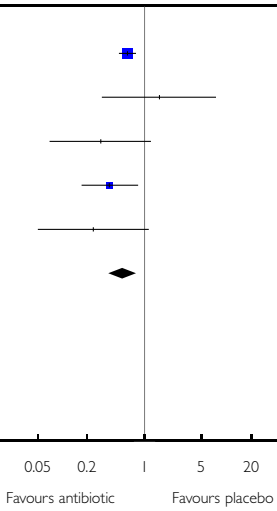
Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Number of people with one or more exacerbations.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 1 Number of people with one or more exacerbations

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Continuous antibiotics					
Albert 2011 (1)	317/558	380/559		29.4 %	0.62 [0.49, 0.79]
Brill 2015 (2)	15/25	4/8		3.3 %	1.50 [0.30, 7.43]
He 2010 (3)	9/18	14/18		4.0 %	0.29 [0.07, 1.21]
Seemungal 2008 (4)	28/53	42/56		10.3 %	0.37 [0.17, 0.84]
Simpson 2014 (5)	4/15	9/15		3.6 %	0.24 [0.05, 1.13]
Subtotal (95% CI)	**669**	**656**		**50.6 %**	**0.53 [0.36, 0.79]**
Total events: 373 (Antibiotics), 449 (Placebo)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 4.92, df = 4 (P = 0.30); I^2 =19%					
Test for overall effect: Z = 3.16 (P = 0.0016)					
2 Intermittent antibiotics					



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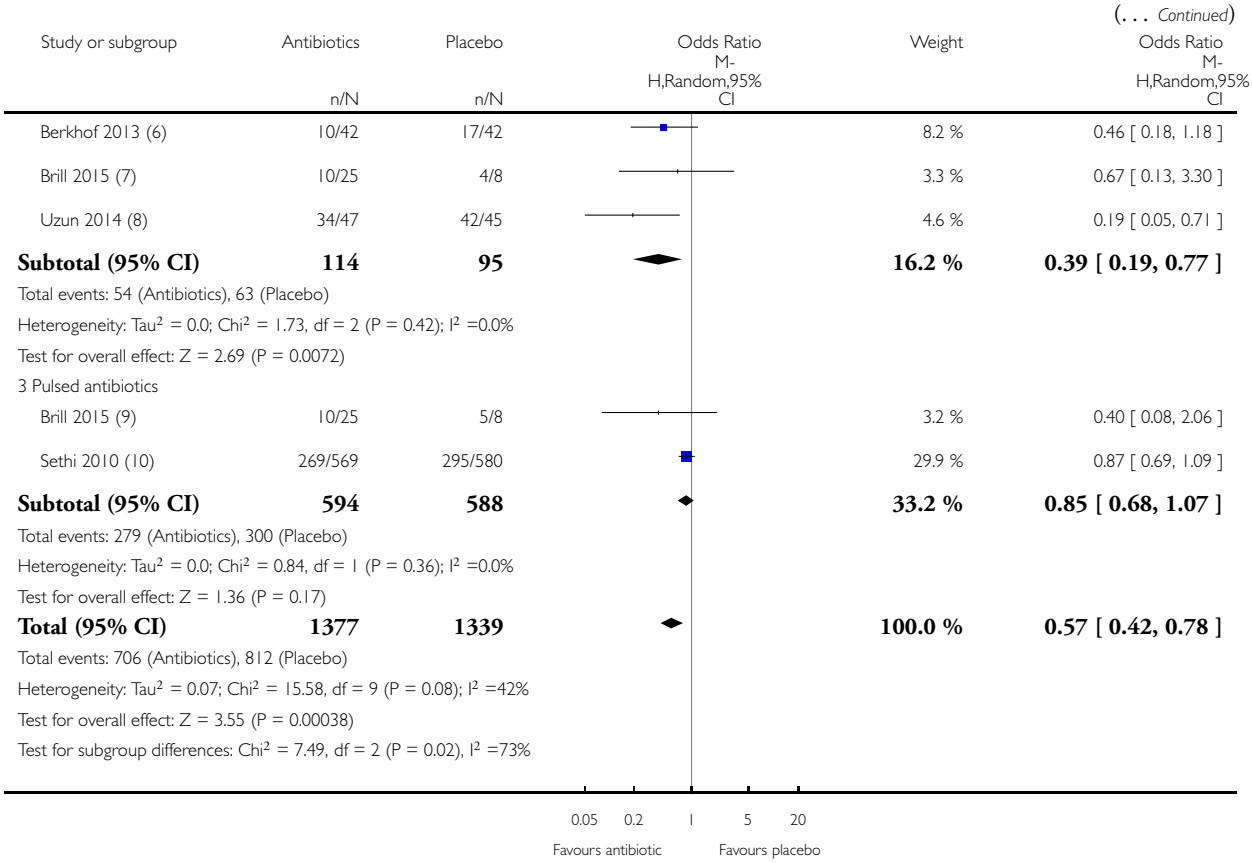


(1) Azithromycin 250mg daily for 12 months.

(2) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

(3) Erythromycin 125mg three times/day for six months.

(4) Erythromycin 250mg twice/day for 12 months.

(5) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.

(6) Azithromycin 250mg three times/week for 12 weeks.

(7) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.

(8) Azithromycin 500mg three times/week for 12 months.

(9) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

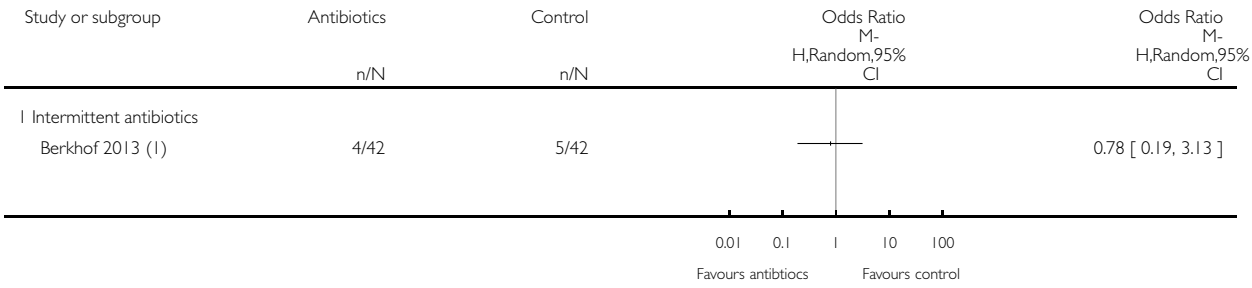
(10) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Number of people with one or more exacerbations requiring hospitalisation.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 2 Number of people with one or more exacerbations requiring hospitalisation



(1) Azithromycin 250 mg three times/week for 12 weeks.

Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Annualised exacerbation rate per patient per year during 12-week active treatment.

Annualised exacerbation rate per patient per year during 12-week active treatment

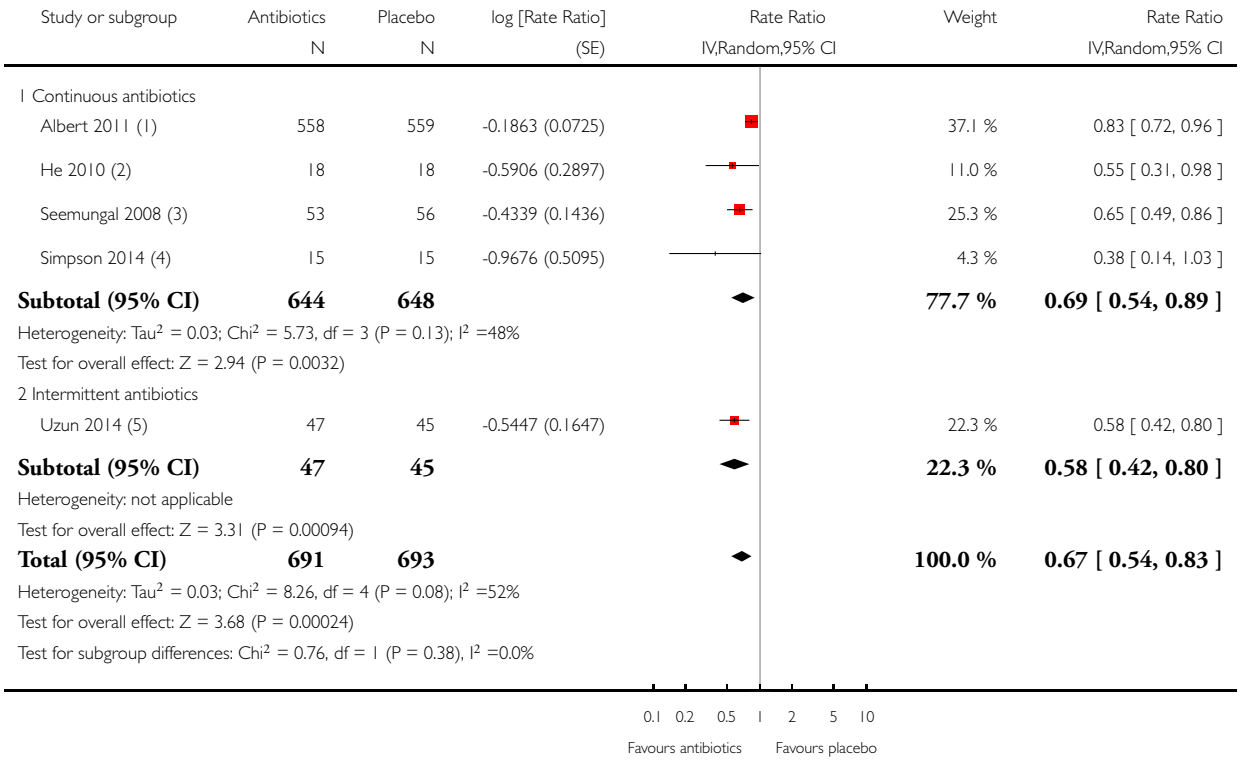
Study	Intervention arm	Rate per patient per year	P value compared to control
Continuous antibiotics			
Shafuddin 2015	Roxithromycin	1.74	0.2545
Shafuddin 2015	Roxithromycin+doxycyline	1.64	0.1709
Shafuddin 2015	Placebo	2.25	N/A

Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 Rate of exacerbation per patient per year.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 4 Rate of exacerbation per patient per year



(1) Azithromycin 250 mg daily for 12 months.

(2) Erythromycin 125mg three times/day for six months.

(3) Erythromycin 250mg twice a day for 12 months.

(4) Azithromycin 250 mg daily for 12 weeks. Outcome reported at 26 weeks.

(5) Azithromycin 500mg three times/week for 12 months.

Analysis 1.5. Comparison 1 Antibiotics versus placebo, Outcome 5 Time to the first exacerbation.

Time to the first exacerbation

Study	MEDIAN Time to 1st exacerbation (days) treatment	MEDIAN Time to 1st exacerbation (days) placebo	P value	Test used	Hazard ratio
Continuous antibiotic					
Albert 2011	266 (227 to 313)	174 (143 to 215)	P < 0.001	log-rank test	0.73 (0.63, 0.84)

Time to the first exacerbation (*Continued*)

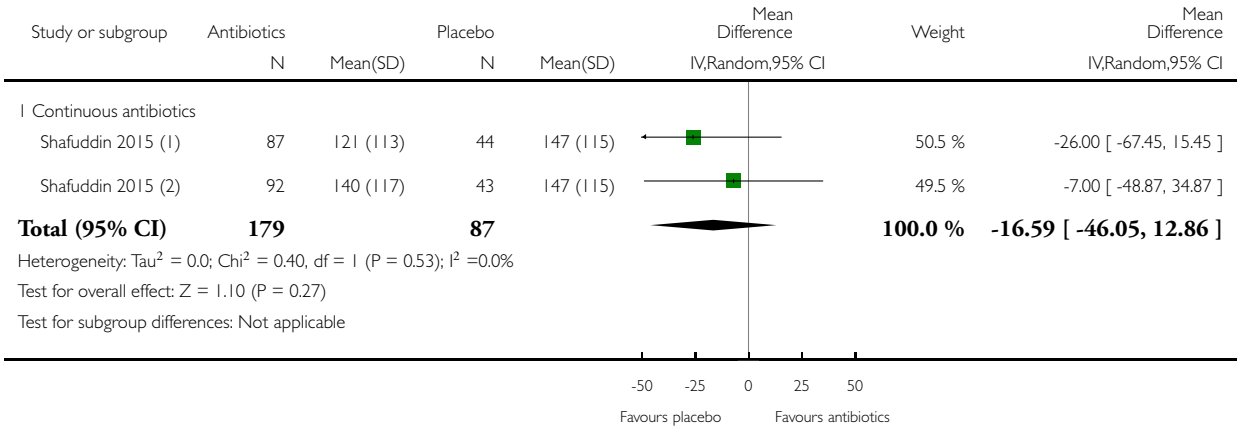
He 2010	155	86	P = 0.032	Kaplan-Meier survival analysis	not given
Seemungal 2008	271	89	P = 0.02	log-rank test	not given
Intermittent antibiotics					
Berkhof 2013	20th percentile time to the first exacerbation 105 (30)	20th percentile time to the first exacerbation 66 (21)	P = 0.13	log-rank test	not given
Uzun 2014	130 (95% CI 28 to 232)	59 (95% CI 31 to 87)	P = 0.001	log-rank test	not given
Pulsed antibiotics					
Sethi 2010	364	336	P = 0.062	Kaplan-Meier survival analysis	not given

Analysis 1.6. Comparison 1 Antibiotics versus placebo, Outcome 6 Mean time to first exacerbation (days).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 6 Mean time to first exacerbation (days)



(1) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 60 weeks. Control group halved.

(2) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group halved.

Analysis 1.7. Comparison 1 Antibiotics versus placebo, Outcome 7 COPD exacerbations according to severity of COPD - continuous antibiotics.

COPD exacerbations according to severity of COPD - continuous antibiotics

Study	Gold stage	Rate of exacerbations per patient year on azithromycin (Mean +/- SD)	Rate of exacerbations per patient year on placebo (Mean +/- SD)
Albert 2011	2 : FEV1 (80% - 50%)	1.02 (+/- 0.15)	1.68 (+/- 0.16)
Albert 2011	3 : FEV1 (50% - 30%)	1.53 (+/- 0.13)	1.75 (+/- 0.13)
Albert 2011	4 : FEV1 < 30%	1.75 (+/- 0.12)	2.05 (+/- 0.28)

Analysis 1.8. Comparison 1 Antibiotics versus placebo, Outcome 8 COPD exacerbations according to severity of COPD - pulsed antibiotics.

COPD exacerbations according to severity of COPD - pulsed antibiotics

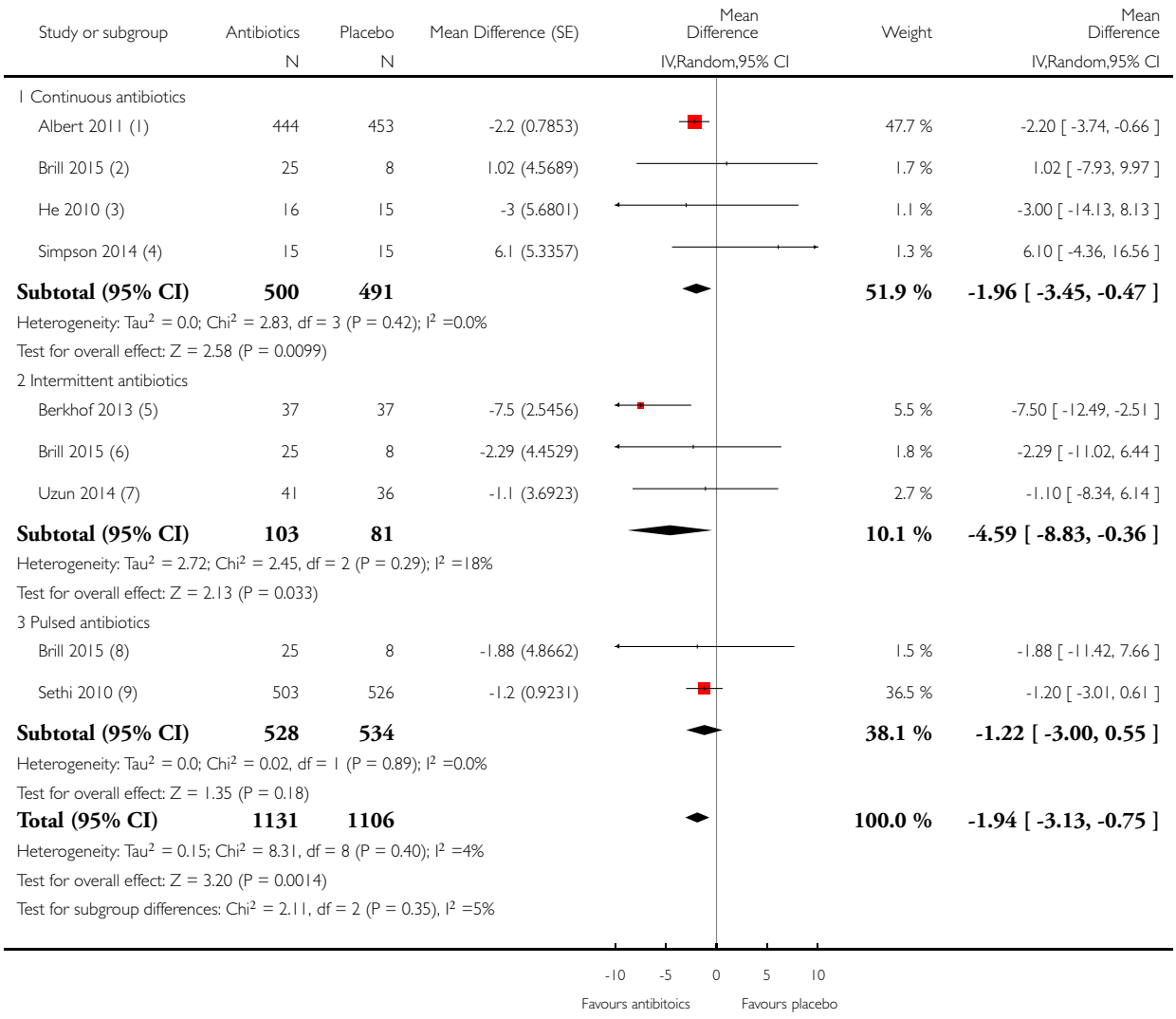
Study	Gold stage	Odds ratio for exacerbations, moxifloxacin vs placebo (95% CI)	P value
Sethi 2010	2 : FEV1 (80% - 50%)	0.65 (0.39 to 1.06)	0.091
Sethi 2010	3 : FEV1 (50% - 30%)	0.81 (0.58 to 1.10)	0.192
Sethi 2010	4 : FEV1 (< 30%)	0.83 (0.54 to 1.28)	0.459

Analysis 1.9. Comparison 1 Antibiotics versus placebo, Outcome 9 HRQoL, SGRQ (total score).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 9 HRQoL, SGRQ (total score)



(1) Azithromycin 250mg daily for 12 months.

(2) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

(3) Erythromycin 125mg three times/day for six months.

(4) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.

(5) Azithromycin 250mg three times/week for 12 weeks.

(6) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.

(7) Azithromycin 500mg three times/week for 12 months.

(8) Pulsed moxifloxacin 400mg daily for 5 days every 4 weeks for 13 weeks. Control group split three ways.

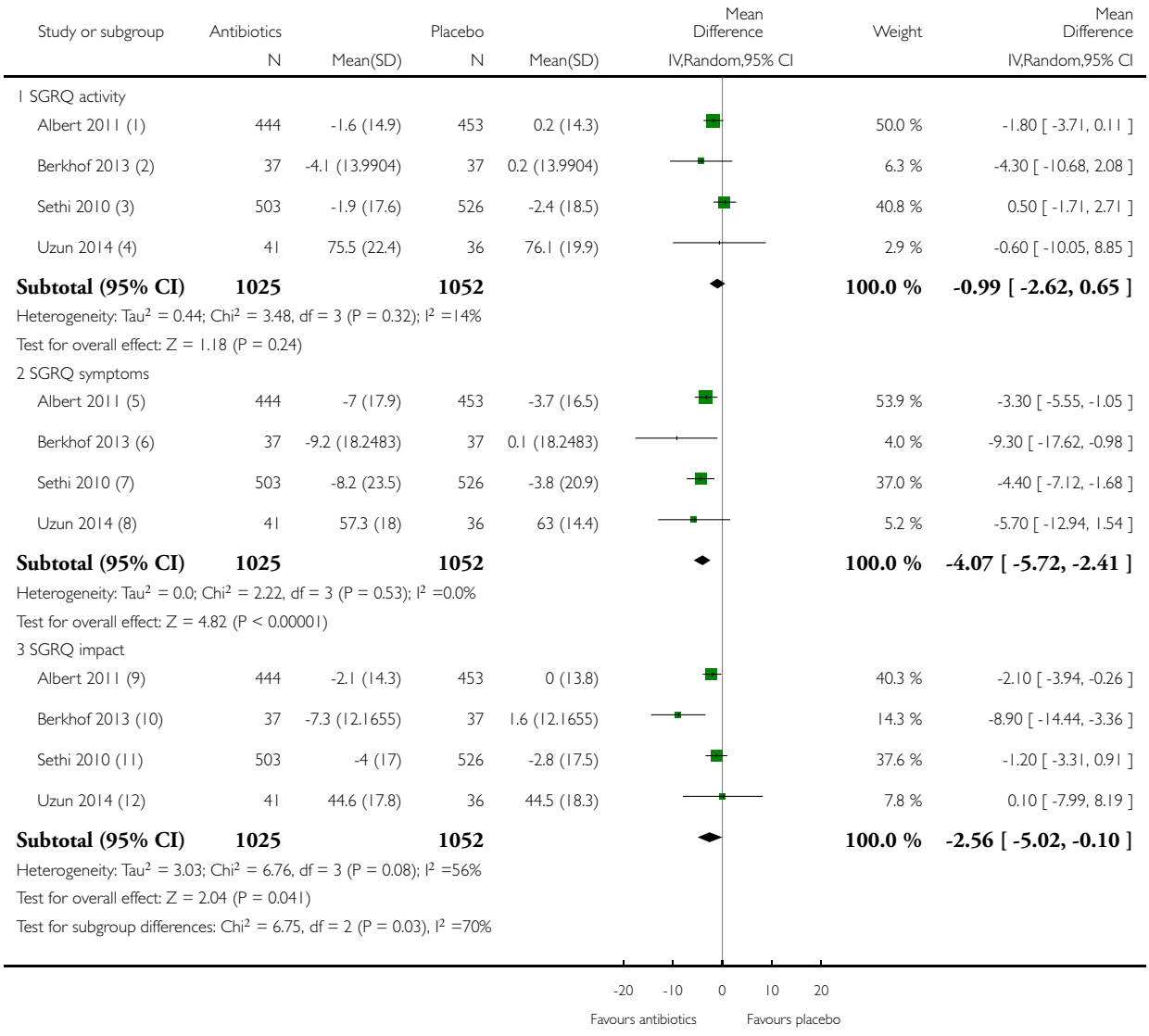
(9) Moxifloxacin 400mg daily for for 5 days every 8 weeks for 48 weeks.

Analysis 1.10. Comparison 1 Antibiotics versus placebo, Outcome 10 HRQoL, SGRQ (domains).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 10 HRQoL, SGRQ (domains)



(1) Azithromycin 250mg daily for 12 months.
(2) Azithromycin 250mg three times/week for 12 weeks.
(3) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.
(4) Azithromycin 500mg three times/week for 12 months.
(5) Azithromycin 250mg daily for 12 months.
(6) Azithromycin 250mg three times/week for 12 weeks.
(7) Moxifloxacin 400mg daily for five days every eight weeks for 48 weeks.
(8) Azithromycin 500mg three times/week for 12 months.
(9) Azithromycin 250mg daily for 12 months.
(10) Azithromycin 250mg three times/week for 12 weeks.
(11) Moxifloxacin 400mg daily for five days every eight weeks for 48 weeks.
(12) Azithromycin 500mg three times/week for 12 months.

Analysis 1.11. Comparison 1 Antibiotics versus placebo, Outcome 11 HRQoL, LCQ (total).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)
Comparison: 1 Antibiotics versus placebo
Outcome: 11 HRQoL, LCQ (total)

Study or subgroup	Antibiotics		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
1 Intermittent antibiotics						
Berkhof 2013 (1)	38	2.2 (2.4658)	41	0.9 (1.9209)		1.30 [0.32, 2.28]

(1) Azithromycin 250mg three times/week for 12 weeks.

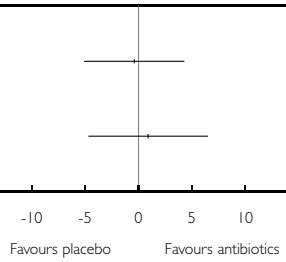
Analysis 1.12. Comparison 1 Antibiotics versus placebo, Outcome 12 HRQoL, SF-12 (domains).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 12 HRQoL, SF-12 (domains)

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 SF-12 physical						
Uzun 2014 (1)	41	32.3 (10.7)	36	32.7 (10.3)		-0.40 [-5.10, 4.30]
2 SF-12 mental						
Uzun 2014 (2)	41	36.8 (11.7)	36	35.9 (13.1)		0.90 [-4.68, 6.48]



(1) Azithromycin 500mg three times/week for 12 months.

(2) Azithromycin 500mg three times/week for 12 months.

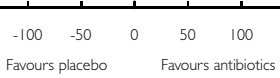
Analysis 1.13. Comparison 1 Antibiotics versus placebo, Outcome 13 HRQoL SF-36 (domains).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 13 HRQoL SF-36 (domains)

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 SF-36 general health							
Albert 2011 (1)	484	41.8 (20.9)	483	39.1 (20.3)		72.2 %	2.70 [0.10, 5.30]
Berkhof 2013 (2)	36	4.5 (14.4)	36	-3.8 (14.4)		21.2 %	8.30 [1.65, 14.95]
He 2010 (3)	16	45.1 (19.5172)	16	39.8 (17.2652)		6.6 %	5.30 [-7.47, 18.07]
Subtotal (95% CI)	**536**		**535**			**100.0 %**	**4.06 [0.70, 7.42]**
Heterogeneity: Tau^2 = 2.31; Chi^2 = 2.44, df = 2 (P = 0.30); I^2 =18%							
Test for overall effect: Z = 2.37 (P = 0.018)							
2 SF-36 physical functioning							
Albert 2011 (4)	484	39.3 (25.8)	483	38.6 (24.1)		74.4 %	0.70 [-2.45, 3.85]
Berkhof 2013 (5)	37	5.5 (13.3821)	36	0.7 (13.8)		20.8 %	4.80 [-1.44, 11.04]



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Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
He 2010 (6)	16	65 (18.3912)	15	57.6 (18.5994)		4.9 %	7.40 [-5.63, 20.43]
Subtotal (95% CI)	**537**		**534**			**100.0 %**	**1.88 [-1.01, 4.77]**
Heterogeneity: Tau^2 = 0.35; Chi^2 = 2.07, df = 2 (P = 0.36); I^2 =3%							
Test for overall effect: Z = 1.27 (P = 0.20)							
3 SF-36 bodily pain							
Albert 2011 (7)	484	68.9 (26.2)	483	69.1 (26)		83.0 %	-0.20 [-3.49, 3.09]
Berkhof 2013 (8)	37	5.6 (20.0731)	37	-0.9 (20.0731)		10.7 %	6.50 [-2.65, 15.65]
He 2010 (9)	16	80.4 (17.4529)	15	80.4 (16.613)		6.2 %	0.0 [-11.99, 11.99]
Subtotal (95% CI)	**537**		**535**			**100.0 %**	**0.53 [-2.47, 3.53]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.83, df = 2 (P = 0.40); I^2 =0.0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
4 SF-36 vitality							
Albert 2011 (10)	484	48.3 (21.1)	483	46.9 (20.8)		82.6 %	1.40 [-1.24, 4.04]
Berkhof 2013 (11)	36	4 (14.4)	36	-2 (14.4)		13.0 %	6.00 [-0.65, 12.65]
He 2010 (12)	16	66.1 (18.9542)	15	64.1 (13.5432)		4.3 %	2.00 [-9.54, 13.54]
Subtotal (95% CI)	**536**		**534**			**100.0 %**	**2.03 [-0.38, 4.43]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.59, df = 2 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 1.65 (P = 0.098)							
5 SF-36 role emotional							
Albert 2011 (13)	484	66.5 (41.3)	483	68.3 (41.5)		84.4 %	-1.80 [-7.02, 3.42]
Berkhof 2013 (14)	37	-0.4 (34.0635)	37	-6.3 (34.0635)		9.5 %	5.90 [-9.62, 21.42]
He 2010 (15)	16	63.4 (33.7798)	15	60 (20.5857)		6.0 %	3.40 [-16.16, 22.96]
Subtotal (95% CI)	**537**		**535**			**100.0 %**	**-0.75 [-5.55, 4.04]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.03, df = 2 (P = 0.60); I^2 =0.0%							
Test for overall effect: Z = 0.31 (P = 0.76)							
6 SF-36 social functioning							
Albert 2011 (16)	484	71.7 (25.4)	483	70.8 (26.9)		45.7 %	0.90 [-2.40, 4.20]
Berkhof 2013 (17)	37	4.4 (18.8566)	37	-8.5 (18.8566)		34.8 %	12.90 [4.31, 21.49]
He 2010 (18)	16	70.5 (24.2089)	15	58.8 (23.2944)		19.6 %	11.70 [-5.02, 28.42]
Subtotal (95% CI)	**537**		**535**			**100.0 %**	**7.19 [-2.40, 16.78]**
Heterogeneity: Tau^2 = 49.60; Chi^2 = 7.67, df = 2 (P = 0.02); I^2 =74%							
Test for overall effect: Z = 1.47 (P = 0.14)							
7 SF-36 mental health							
Albert 2011 (19)	484	75.9 (17.7)	483	75.2 (18)		63.3 %	0.70 [-1.55, 2.95]
Berkhof 2013 (20)	36	2.2 (11.4)	36	-3.5 (11.4)		29.1 %	5.70 [0.43, 10.97]
He 2010 (21)	16	80 (17.4529)	15	76.5 (16.7936)		7.7 %	3.50 [-8.56, 15.56]
Subtotal (95% CI)	**536**		**534**			**100.0 %**	**2.37 [-1.13, 5.86]**

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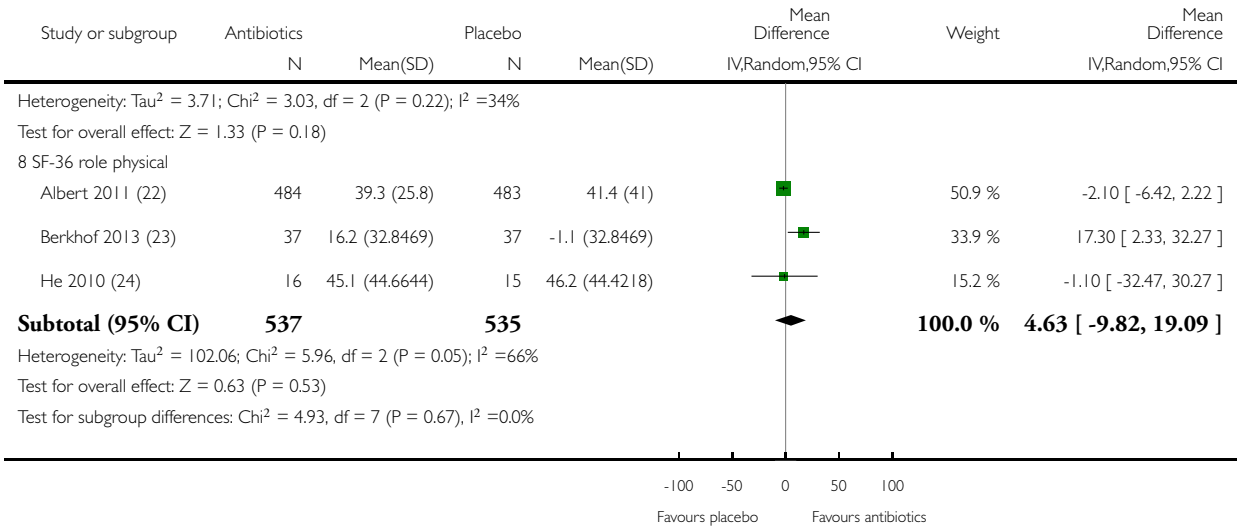


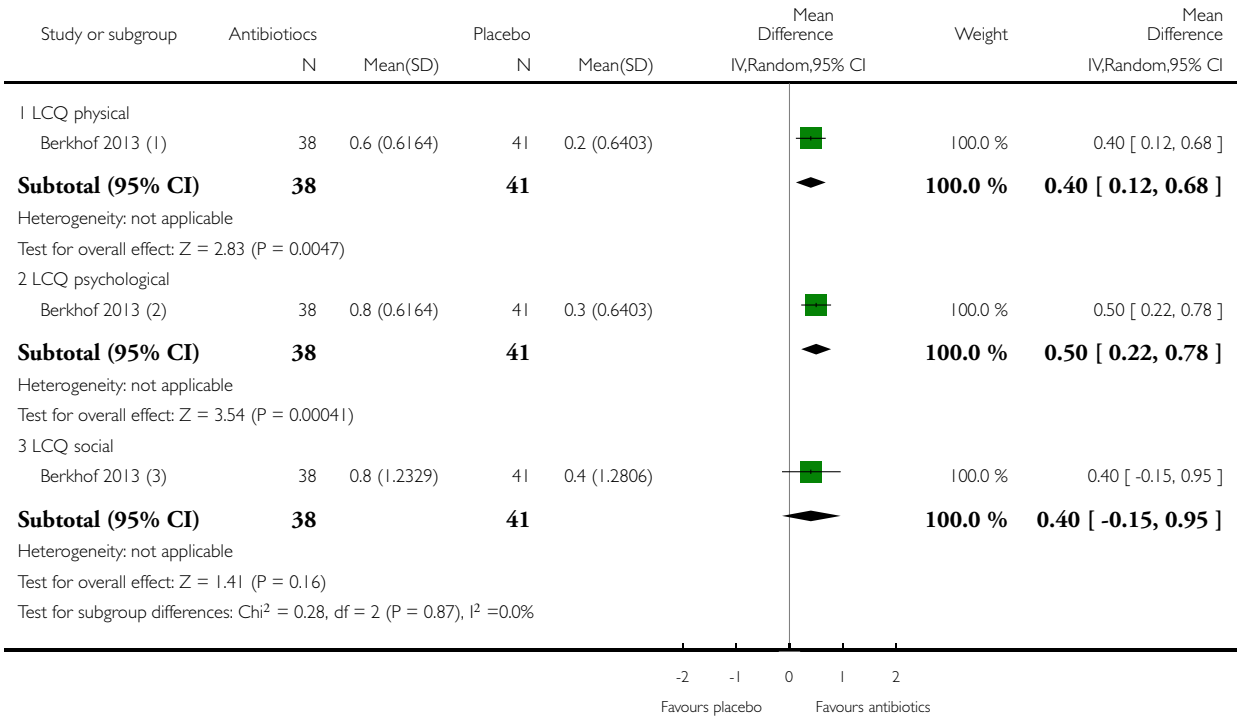
(1) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(2) Azithromycin 250mg three times/week for 12 weeks.
(3) Erythromycin 125mg three times/day for 6 months.
(4) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(5) Azithromycin 250mg three times/week for 12 weeks.
(6) Erythromycin 125mg three times/day for 6 months.
(7) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(8) Azithromycin 250mg three times/week for 12 weeks.
(9) Erythromycin 125mg three times/day for 6 months.
(10) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(11) Azithromycin 250mg three times/week for 12 weeks.
(12) Erythromycin 125mg three times/day for 6 months.
(13) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(14) Azithromycin 250mg three times/week for 12 weeks.
(15) Erythromycin 125mg three times/day for 6 months.
(16) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(17) Azithromycin 250mg three times/week for 12 weeks.
(18) Erythromycin 125mg three times/day for 6 months.
(19) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(20) Azithromycin 250mg three times/week for 12 weeks.
(21) Erythromycin 125mg three times/day for 6 months.
(22) Azithromycin 250mg daily for 12 months. Outcome extracted at 6 months.
(23) Azithromycin 250mg three times/week for 12 weeks.
(24) Erythromycin 125mg three times/day for 6 months.

Analysis 1.14. Comparison 1 Antibiotics versus placebo, Outcome 14 HRQoL, LCQ (domains).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 14 HRQoL, LCQ (domains)



(1) Azithromycin 250mg three times/week for 12 weeks.

(2) Azithromycin 250mg three times/week for 12 weeks.

(3) Azithromycin 250mg three times/week for 12 weeks.

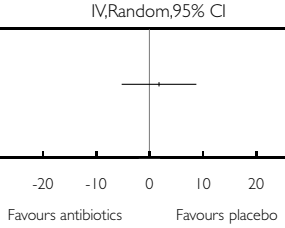
Analysis 1.15. Comparison 1 Antibiotics versus placebo, Outcome 15 HRQoL, CCQ (total).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 15 HRQoL, CCQ (total)

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Continuous antibiotics						
Simpson 2014 (1)	15	16.9 (10.1)	15	15.1 (9.2)		1.80 [-5.11, 8.71]



(1) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.

Analysis 1.16. Comparison 1 Antibiotics versus placebo, Outcome 16 HRQoL, CRQ (domains).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 16 HRQoL, CRQ (domains)

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 CRQ dyspnoea							
Shafuddin 2015 (1)	93	2.21 (5.35)	44	2.33 (5.58)		47.7 %	-0.12 [-2.10, 1.86]
Shafuddin 2015 (2)	94	1.63 (4.53)	44	2.33 (5.58)		52.3 %	-0.70 [-2.59, 1.19]
Subtotal (95% CI)	**187**		**88**			**100.0 %**	**-0.42 [-1.79, 0.94]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%							
Test for overall effect: Z = 0.61 (P = 0.54)							
2 CRQ fatigue							
Shafuddin 2015 (3)	93	0.68 (3.79)	44	1.23 (4.99)		50.2 %	-0.55 [-2.21, 1.11]
Shafuddin 2015 (4)	94	0.663 (3.87)	44	1.23 (4.99)		49.8 %	-0.57 [-2.24, 1.10]
Subtotal (95% CI)	**187**		**88**			**100.0 %**	**-0.56 [-1.74, 0.62]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%							
Test for overall effect: Z = 0.93 (P = 0.35)							
3 CRQ emotional function							

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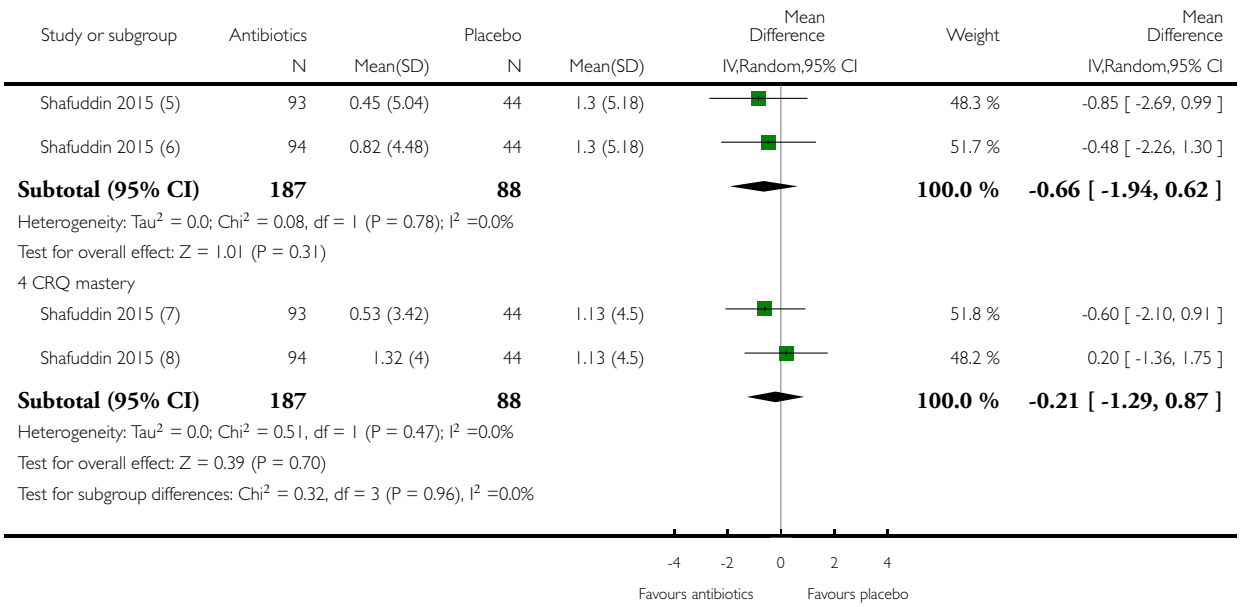


(1) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 12 weeks. Control group halved.
(2) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.
(3) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 12 weeks. Control group halved.
(4) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.
(5) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 12 weeks. Control group halved.
(6) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.
(7) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 12 weeks. Control group halved.
(8) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.

Analysis 1.17. Comparison 1 Antibiotics versus placebo, Outcome 17 Frequency of hospital admissions - continuous antibiotics.

Frequency of hospital admissions - continuous antibiotics

Study	GOLD stage	Rate of hospitalisations per patient year on moxifloxacin (Mean +/-SD)	Rate of hospitalisations per patient year on placebo (Mean +/-SD)
Albert 2011	2 : FEV1 (80% - 50%)	0.50 +/-0.12	0.65 +/- 0.11
Albert 2011	3 : FEV1 (50% - 30%)	0.85 +/- 0.12	0.96 +/- 0.12
Albert 2011	4 : FEV1 < 30%	0.74 +/- 0.12	1.03 +/- 0.27

Analysis 1.18. Comparison 1 Antibiotics versus placebo, Outcome 18 Frequency of hospital admissions - pulsed antibiotics.

Frequency of hospital admissions - pulsed antibiotics

Study	Frequency of hospitalisation (%) on moxifloxacin	Frequency of hospitalisation (%) on placebo	P value
Sethi 2010	131 (23.02%)	136 (23.45%)	0.46

Analysis 1.19. Comparison 1 Antibiotics versus placebo, Outcome 19 Duration of exacerbation.

Duration of exacerbation

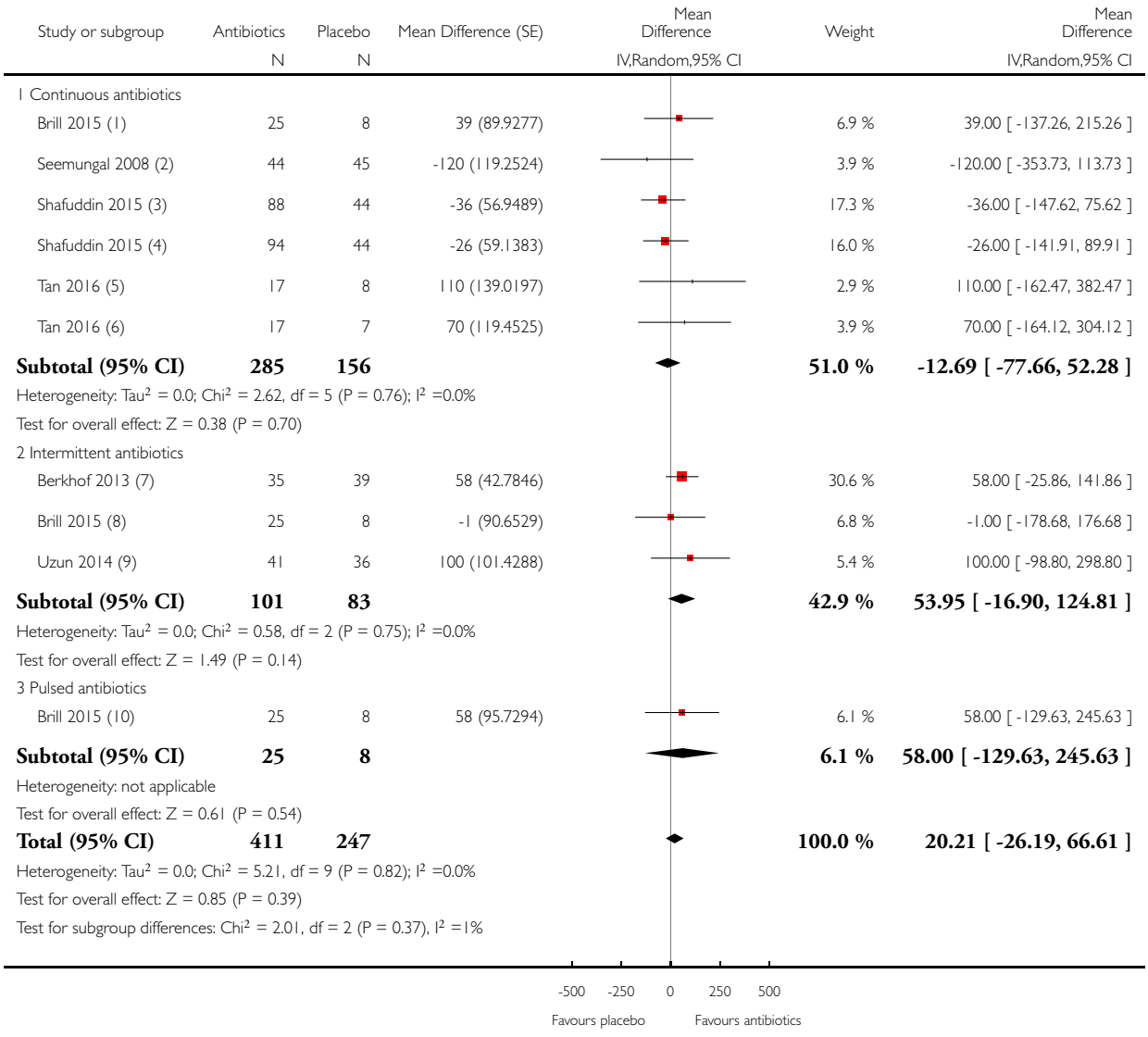
Study	Median days of exacerbation, treatment arm	Median days of exacerbation, placebo arm	P value
Continuous antibiotics			
Seemungal 2008	9 (6 to14)	13 (6 to 24)	0.036 Mann-Whitney test
Pulsed antibiotics			
Mygind 2010	93 (total exacerbation days at home or hospitalised)	111 (total exacerbations days at home or hospitalised)	0.04

Analysis 1.20. Comparison 1 Antibiotics versus placebo, Outcome 20 FEV1 (mL).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 20 FEV1 (mL)



(1) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

(2) Erythromycin 250mg twice/day for 12 months.

(3) Roxithromycin 300mg daily + doxycyline 100mg for 12 weeks. Outcome reported at 12 weeks. Control group halved.

(4) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.

(5) Erythromycin 125mg three times/day for 12 months. Control group halved.

(6) Erythromycin 125mg three times/day for six months. Control group halved.

(7) Azithromycin 250mg three times/week for 12 weeks. Extracted from database supplied by author.

(8) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.

(9) Azithromycin 500mg three times/week for 12 months.

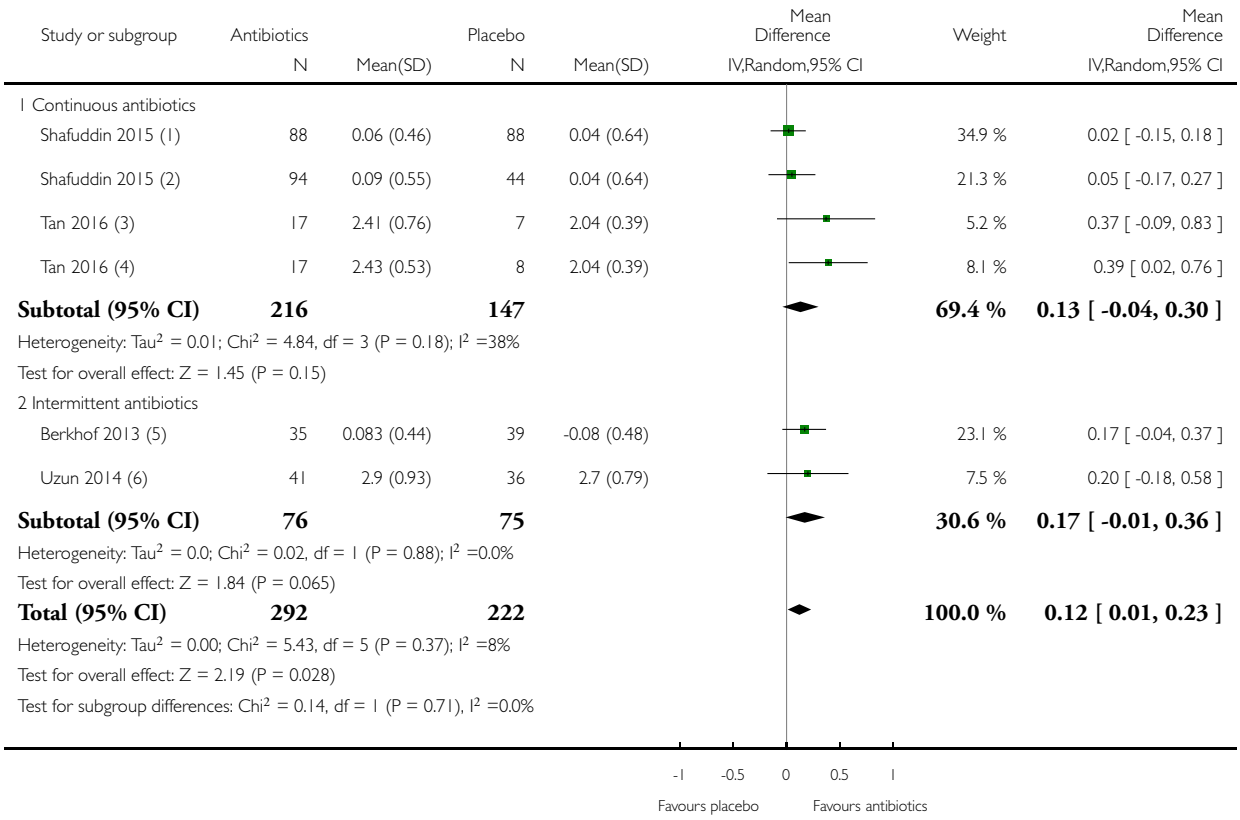
(10) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

Analysis 1.21. Comparison 1 Antibiotics versus placebo, Outcome 21 FVC (L).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 21 FVC (L)



(1) Roxithromycin 300mg daily + doxycyline 100mg for 12 weeks. Outcome reported at 12 weeks. Control group halved.

(2) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.

(3) Erythromycin 125mg three times/day for 12 months. Control group halved.

(4) Erythromycin 125mg three times/day for six months. Control group halved.

(5) Azithromycin 250mg three times/week for 12 weeks. Extracted from database supplied by author.

(6) Azithromycin 500mg three times/week for 12 months.

Analysis 1.22. Comparison 1 Antibiotics versus placebo, Outcome 22 FEV1 % predicted.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 22 FEV1 % predicted

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Continuous antibiotics							
Shafuddin 2015 (1)	88	1.7 (9)	88	3.03 (11)		19.5 %	-1.33 [-4.30, 1.64]
Shafuddin 2015 (2)	94	1.87 (11)	88	3.03 (11)		18.1 %	-1.16 [-4.36, 2.04]
Simpson 2014 (3)	15	57.79 (13.9)	15	52.17 (14.3)		3.2 %	5.62 [-4.47, 15.71]
Tan 2016 (4)	17	45.49 (9.09)	8	40.03 (8.5)		5.7 %	5.46 [-1.85, 12.77]
Tan 2016 (5)	17	48.58 (13.24)	7	40.03 (8.5)		4.0 %	8.55 [-0.35, 17.45]
Subtotal (95% CI)	**231**		**206**			**50.6 %**	**1.43 [-1.97, 4.83]**
Heterogeneity: Tau^2 = 6.72; Chi^2 = 8.16, df = 4 (P = 0.09); I^2 =51%							
Test for overall effect: Z = 0.82 (P = 0.41)							
2 Intermittent antibiotics							
Berkhof 2013 (6)	35	1.4 (6.5)	39	-0.62 (7.59)		18.1 %	2.02 [-1.19, 5.23]
Uzun 2014 (7)	41	43.4 (17.9)	36	44.2 (20.1)		4.3 %	-0.80 [-9.35, 7.75]
Subtotal (95% CI)	**76**		**75**			**22.4 %**	**1.67 [-1.33, 4.68]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.37, df = 1 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 1.09 (P = 0.28)							
3 Pulsed antibiotics							
Sethi 2010 (8)	569	39.79 (16.793)	580	41.14 (16.6174)		27.1 %	-1.35 [-3.28, 0.58]
Subtotal (95% CI)	**569**		**580**			**27.1 %**	**-1.35 [-3.28, 0.58]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.37 (P = 0.17)							
Total (95% CI)	**876**		**861**			**100.0 %**	**0.33 [-1.56, 2.22]**
Heterogeneity: Tau^2 = 2.46; Chi^2 = 11.40, df = 7 (P = 0.12); I^2 =39%							
Test for overall effect: Z = 0.34 (P = 0.73)							
Test for subgroup differences: Chi^2 = 3.72, df = 2 (P = 0.16), I^2 =46%							

(1) Roxithromycin 300mg daily + doxycyline 100mg for 12 weeks. Change from baseline. Outcome reported at ?12 weeks. Control group halved.

(2) Roxithromycin 300mg daily for 12 weeks. Change from baseline. Outcome reported at ?12 weeks. Control group halved.

(3) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks. ?Endpoint

(4) Erythromycin 125mg three times/day for six months. Control group halved.

(5) Erythromycin 125mg three times/day for 12 months. Control group halved.

(6) Azithromycin 250mg three times/week for 12 weeks. Extracted from database supplied by author.

(7) Azithromycin 500mg three times/week for 12 months.

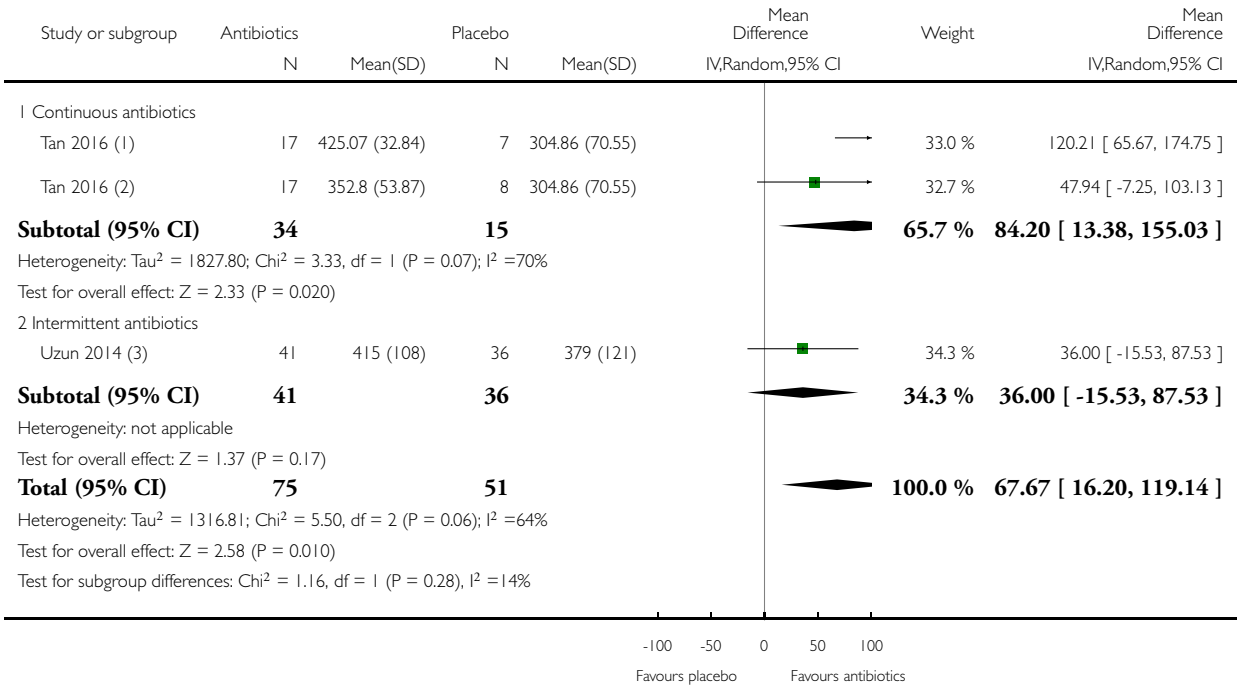
(8) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Analysis 1.23. Comparison 1 Antibiotics versus placebo, Outcome 23 Exercise capacity (6MWT).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 23 Exercise capacity (6MWT)



(1) Erythromycin 125mg three times/day for 12 months. Control group halved.

(2) Erythromycin 125mg three times/day for six months. Control group halved.

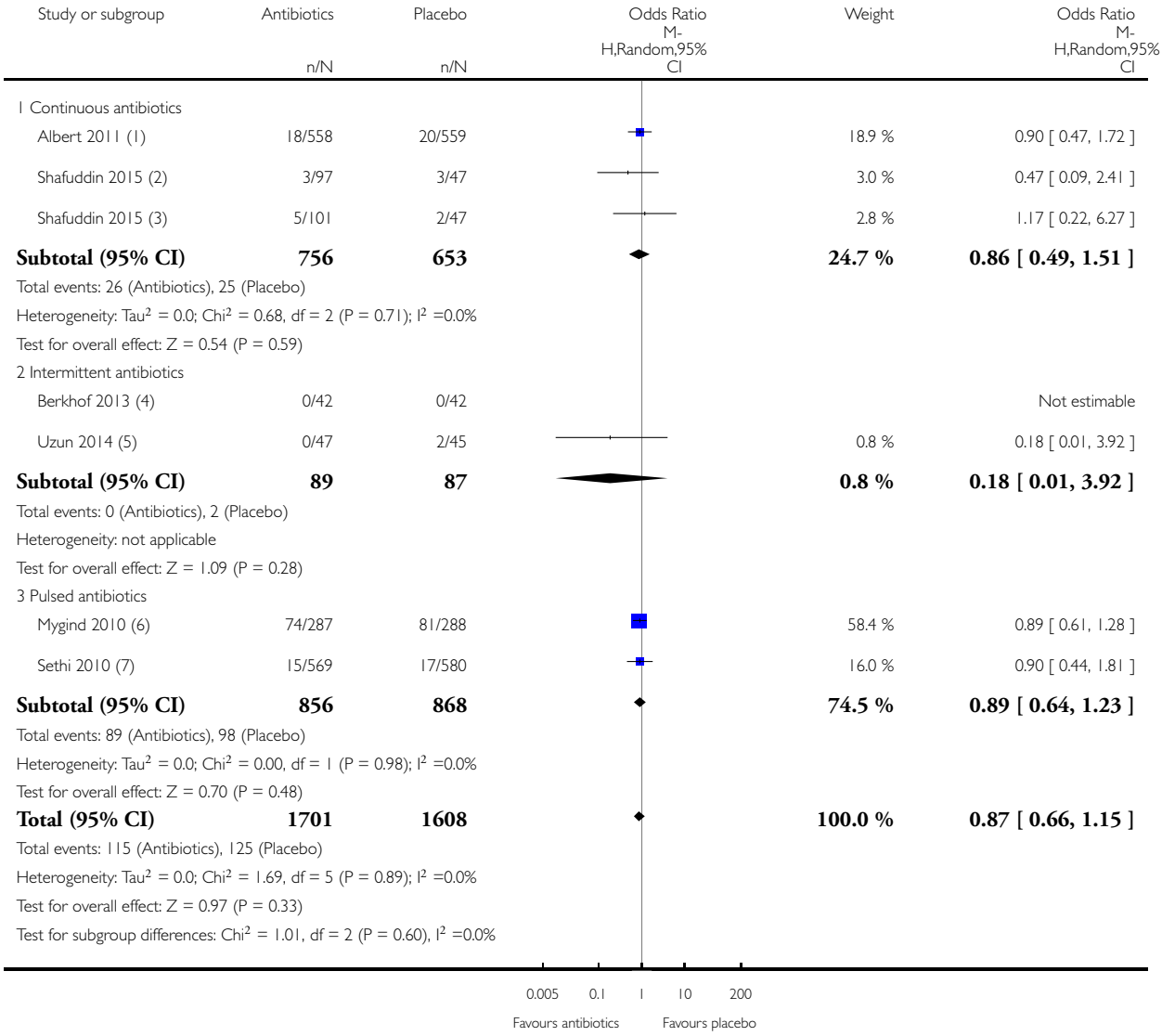
(3) Azithromycin 500mg three times/week for 12 months.

Analysis 1.24. Comparison 1 Antibiotics versus placebo, Outcome 24 All-cause mortality.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 24 All-cause mortality



(1) Azithromycin 250mg daily for 12 months.

(2) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group (5 deaths total) halved.

(3) Roxithromycin 300mg daily + doxycyline 100mg for 12 weeks. Outcome reported at 60 weeks. Control group (5 deaths total) halved.

(4) Azithromycin 250mg three times/week for 12 weeks.

(5) Azithromycin 500mg three times/week for 12 months.

(6) Azithromycin 500mg daily for 3 days every month for 36 months.

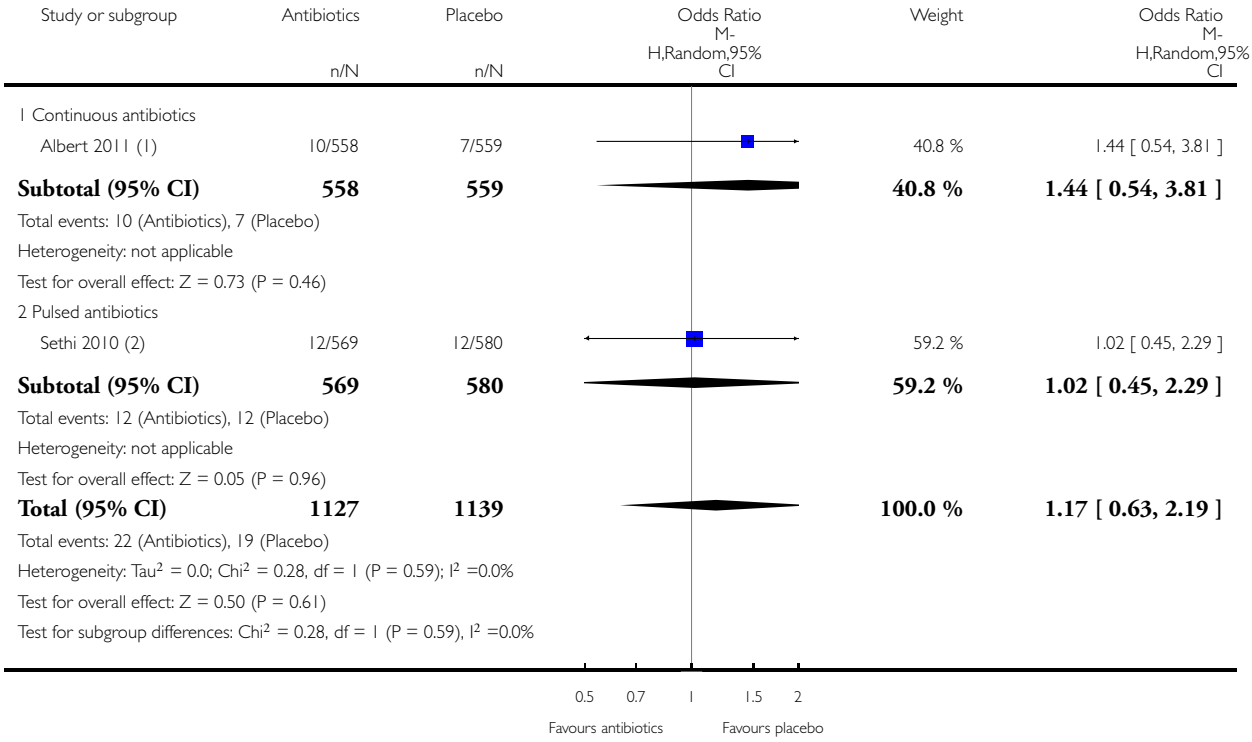
(7) Moxifloxacin 400mg daily for five days every eight weeks for 48 weeks.

Analysis 1.25. Comparison 1 Antibiotics versus placebo, Outcome 25 Respiratory-related mortality.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 25 Respiratory-related mortality



(1) Azithromycin 250mg daily for 12 months.

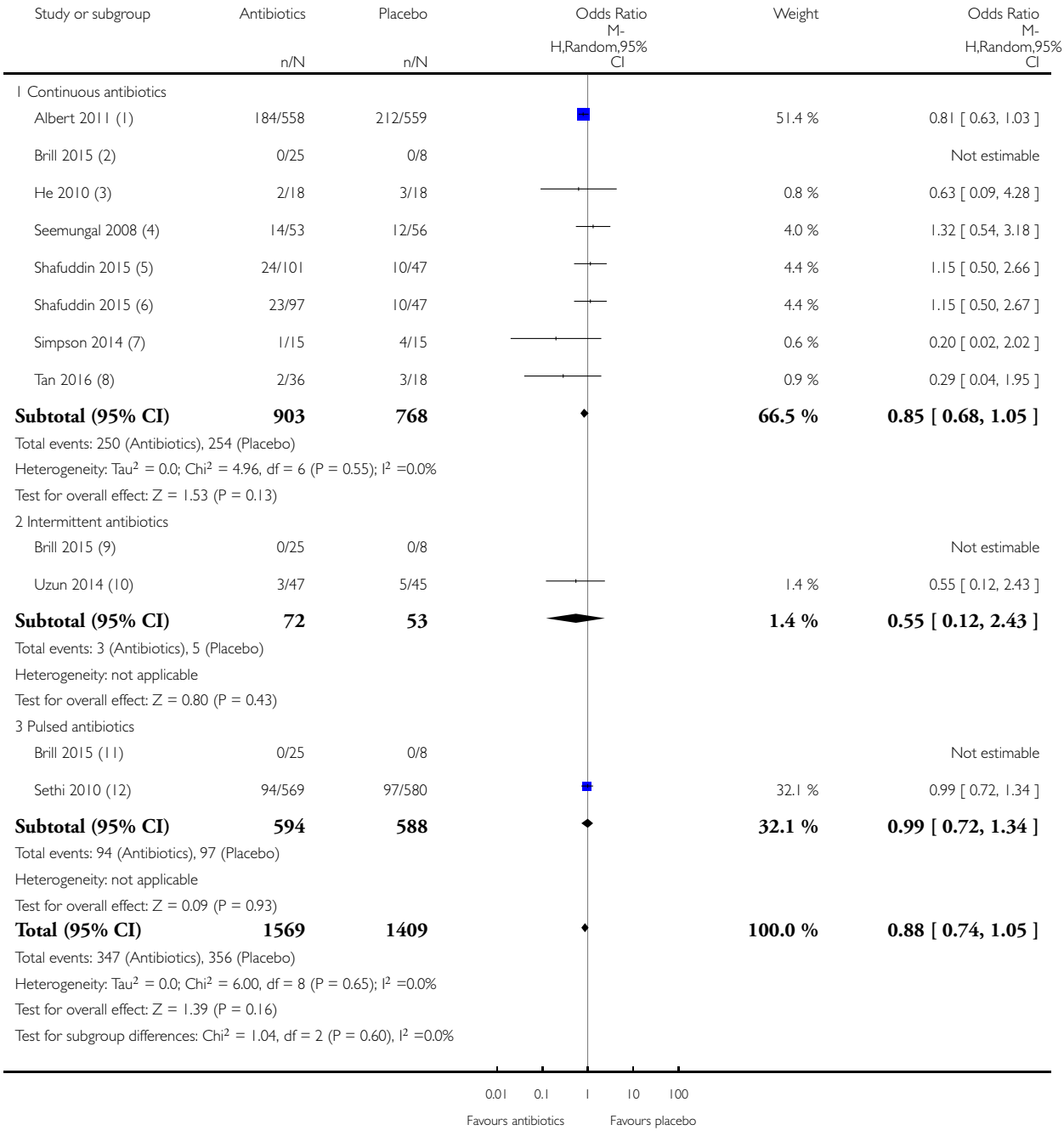
(2) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Analysis 1.26. Comparison 1 Antibiotics versus placebo, Outcome 26 Serious adverse events.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 26 Serious adverse events



(1) Azithromycin 250mg daily for 12 months.

(2) Doxycycline 100mg daily. Control group split (No events reported)

(3) Erythromycin 125mg three times/day for six months.

(4) Erythromycin 250mg twice a day for 12 months.

(5) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 60 weeks. Control group halved.

(6) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group halved.

(7) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.

(8) Adverse event leading to discontinuation. Two erythromycin arms combined (erythromycin 125mg three times/day for 6 months and 12 months; 1 discontinuation in each arm).

(9) Azithromycin 250mg three times/week. Control group split (No events reported)

(10) Azithromycin 500mg three times/week for 12 months.

(11) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split (No events reported).

(12) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

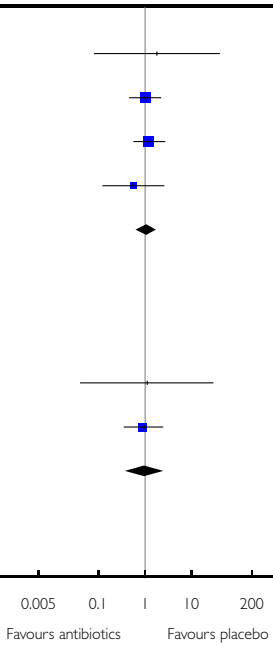
Analysis 1.27. Comparison 1 Antibiotics versus placebo, Outcome 27 Any adverse event.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 27 Any adverse event

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Continuous antibiotics					
Brill 2015 (1)	2/25	0/8		2.0 %	1.81 [0.08, 41.62]
Shafuddin 2015 (2)	73/101	34/47		33.1 %	1.00 [0.46, 2.16]
Shafuddin 2015 (3)	74/97	34/47		31.6 %	1.23 [0.56, 2.72]
Simpson 2014 (4)	9/15	11/15		8.3 %	0.55 [0.12, 2.55]
Subtotal (95% CI)	**238**	**117**		**75.0 %**	**1.03 [0.62, 1.73]**
Total events: 158 (Antibiotics), 79 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.98, df = 3 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 0.13 (P = 0.90)					
2 Intermittent antibiotics					
Brill 2015 (5)	1/24	0/8		1.8 %	1.09 [0.04, 29.28]
Uzun 2014 (6)	36/47	35/45		20.9 %	0.94 [0.35, 2.48]
Subtotal (95% CI)	**71**	**53**		**22.7 %**	**0.95 [0.37, 2.41]**
Total events: 37 (Antibiotics), 35 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					



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Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.12 (P = 0.91)					
3 Pulsed antibiotics					
Brill 2015 (7)	10/25	0/8		2.3 %	11.52 [0.60, 221.75]
Subtotal (95% CI)	**25**	**8**		**2.3 %**	**11.52 [0.60, 221.75]**
Total events: 10 (Antibiotics), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.62 (P = 0.11)					
Total (95% CI)	**334**	**178**		**100.0 %**	**1.07 [0.69, 1.67]**
Total events: 205 (Antibiotics), 114 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.61, df = 6 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 0.30 (P = 0.76)					
Test for subgroup differences: Chi^2 = 2.56, df = 2 (P = 0.28), I^2 =22%					

(1) Doxycycline 100mg daily for 13 weeks. Treatment related AEs. Control group split three ways.

(2) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 60 weeks. Control group halved.

(3) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group halved.

(4) Azithromycin 250mg daily for 12 weeks. "Other" adverse event. Outcome reported at 26 weeks.

(5) Azithromycin 250mg three times/week for 13 weeks. Treatment related AEs. Control group split three ways

(6) Azithromycin 500mg three times/week for 12 months.

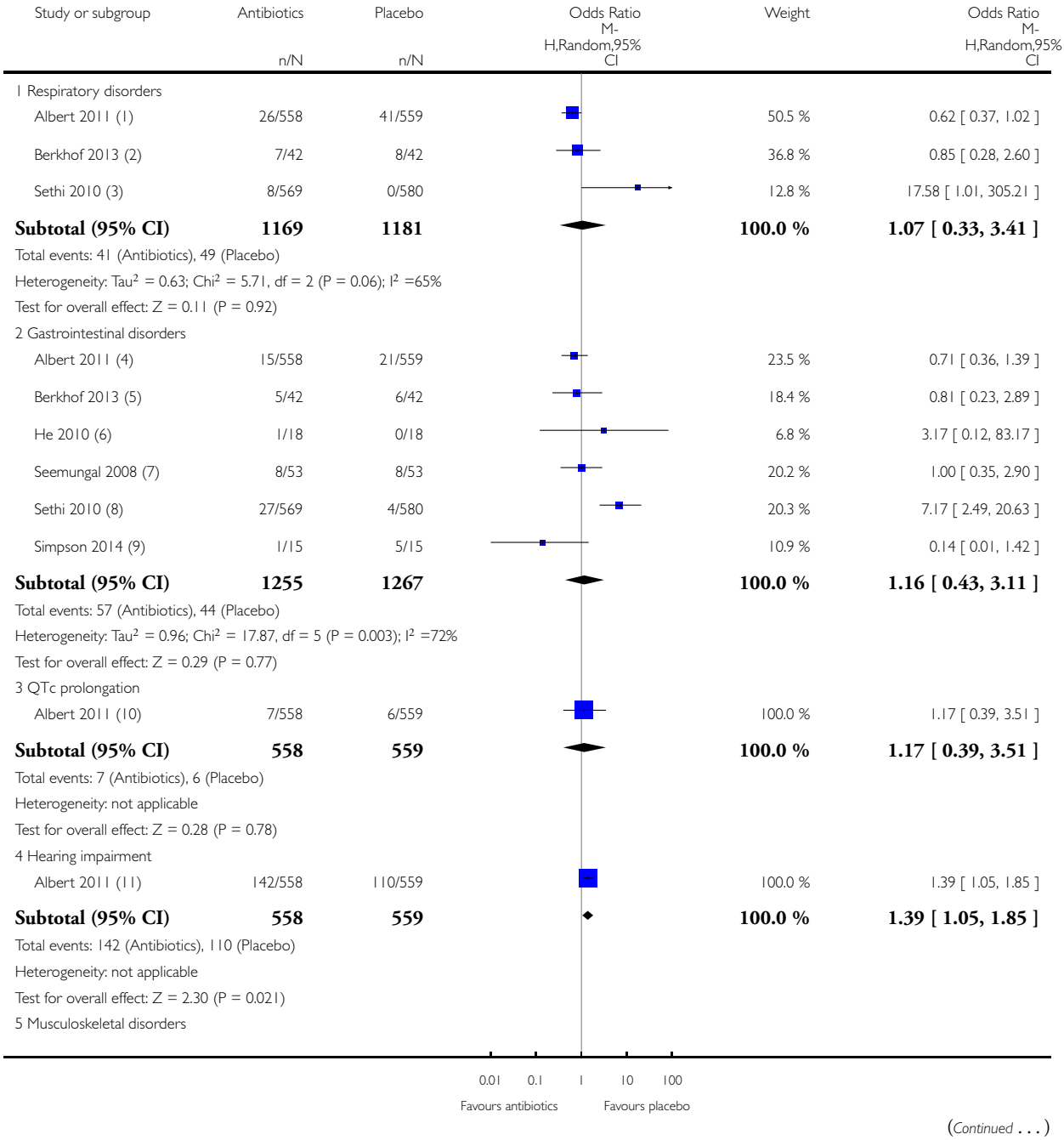
(7) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Treatment related AEs. Control group split three ways.

Analysis 1.28. Comparison 1 Antibiotics versus placebo, Outcome 28 Adverse events (specific).

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Antibiotics versus placebo

Outcome: 28 Adverse events (specific)



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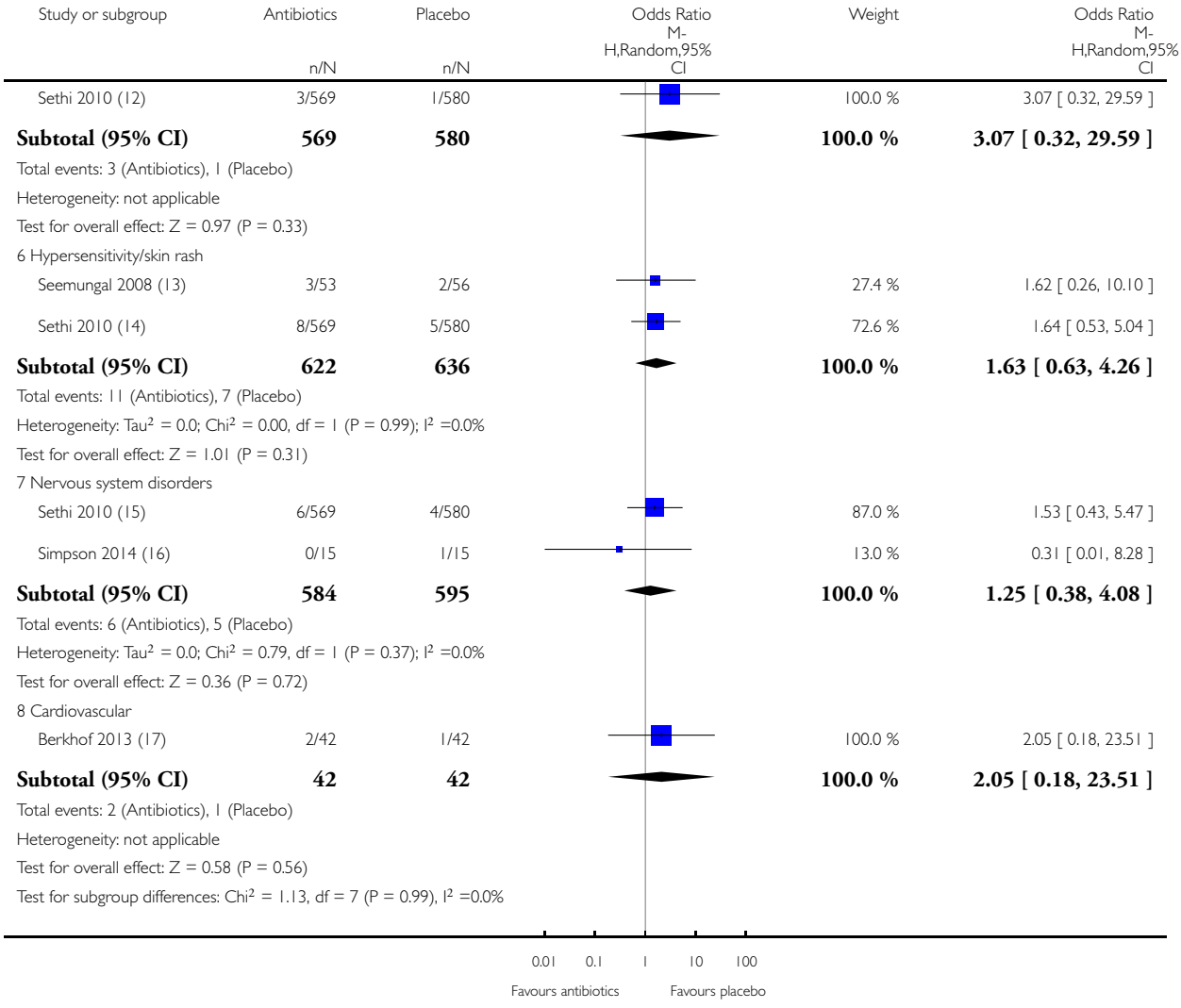

(1) Azithromycin 250mg daily for 12 months.
(2) Azithromycin 250mg three times/week for 12 weeks.
(3) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(4) Azithromycin 250mg daily for 12 months.
(5) Azithromycin 250mg three times/week for 12 weeks.
(6) Erythromycin 125mg three times/day for six months.
(7) Erythromycin 250mg twice/day for 12 months.
(8) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(9) Azithromycin 250mg daily for 12 weeks. "Diarrhoea". Outcome reported at 26 weeks.
(10) Azithromycin 250mg daily for 12 months.
(11) Azithromycin 250mg daily for 12 months.
(12) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(13) Erythromycin 250mg twice/day for 12 months.
(14) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(15) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(16) Azithromycin 250mg daily for 12 weeks. "Headache". Outcome reported at 26 weeks.
(17) Azithromycin 250mg three times/week for 12 weeks.

Analysis 2.1. Comparison 2 Subgroup analyses, Outcome 1 Subgroup analysis: number of people with one or more exacerbations by mean % predicted FEV1.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Subgroup analyses

Outcome: 1 Subgroup analysis: number of people with one or more exacerbations by mean % predicted FEV1

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Mean FEV1 % ≥ 50					
Simpson 2014 (1)	4/15	9/15		3.6 %	0.24 [0.05, 1.13]
Subtotal (95% CI)	**15**	**15**		**3.6 %**	**0.24 [0.05, 1.13]**
Total events: 4 (Antibiotics), 9 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.80 (P = 0.072)					
2 Mean FEV1 % < 50					
Albert 2011 (2)	317/558	380/559		29.4 %	0.62 [0.49, 0.79]
Berkhof 2013 (3)	10/42	17/42		8.2 %	0.46 [0.18, 1.18]
Brill 2015 (4)	15/25	4/8		3.3 %	1.50 [0.30, 7.43]
Brill 2015 (5)	10/25	4/8		3.3 %	0.67 [0.13, 3.30]

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Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Brill 2015 (6)	10/25	5/8		3.2 %	0.40 [0.08, 2.06]
He 2010 (7)	9/18	14/18		4.0 %	0.29 [0.07, 1.21]
Seemungal 2008 (8)	28/53	42/56		10.3 %	0.37 [0.17, 0.84]
Sethi 2010 (9)	269/569	295/580		29.9 %	0.87 [0.69, 1.09]
Uzun 2014 (10)	34/47	42/45		4.6 %	0.19 [0.05, 0.71]
Subtotal (95% CI)	**1362**	**1324**		**96.4 %**	**0.60 [0.44, 0.81]**
Total events: 702 (Antibiotics), 803 (Placebo)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 13.83, df = 8 (P = 0.09); I^2 =42%					
Test for overall effect: Z = 3.33 (P = 0.00087)					
Total (95% CI)	**1377**	**1339**		**100.0 %**	**0.57 [0.42, 0.78]**
Total events: 706 (Antibiotics), 812 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 15.58, df = 9 (P = 0.08); I^2 =42%					
Test for overall effect: Z = 3.55 (P = 0.00038)					
Test for subgroup differences: Chi^2 = 1.26, df = 1 (P = 0.26), I^2 =21%					

(1) Azithromycin 250mg daily for 12 weeks. Severe exacerbations (requiring unscheduled visit, antibiotics and/or steroids). Outcome reported at 26 weeks.

(2) Azithromycin 250mg daily for 12 months.

(3) Azithromycin 250mg three times/week for 12 weeks. Outcome reported at 18 weeks.

(4) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

(5) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.

(6) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

(7) Erythromycin 125mg three times/day for six months.

(8) Erythromycin 250mg twice/day for 12 months.

(9) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

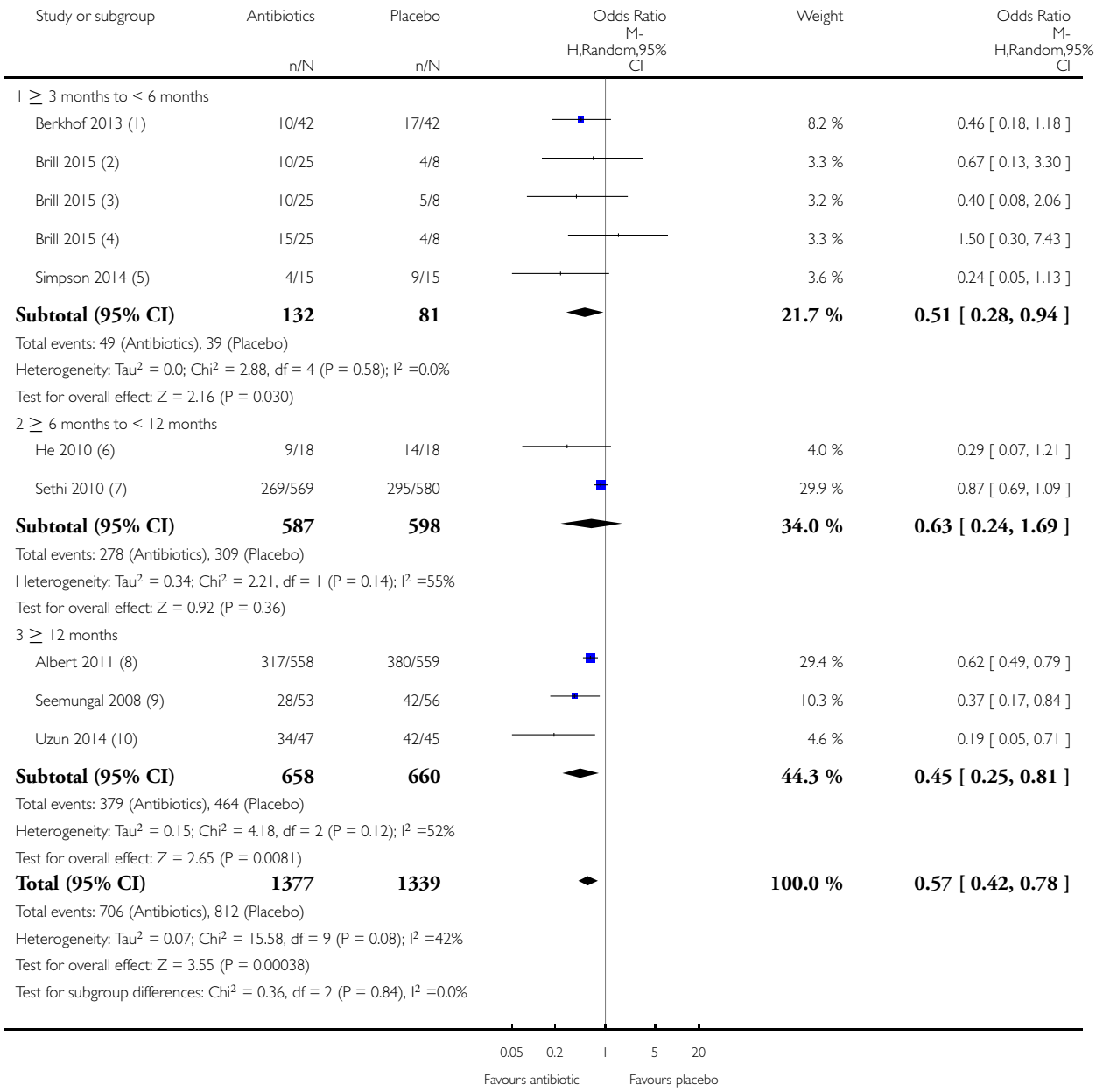
(10) Azithromycin 500mg three times/week for 12 months.

Analysis 2.2. Comparison 2 Subgroup analyses, Outcome 2 Subgroup analysis: number of people with one or more exacerbations by treatment duration.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Subgroup analyses

Outcome: 2 Subgroup analysis: number of people with one or more exacerbations by treatment duration



(1) Azithromycin 250mg three times/week for 12 weeks. Outcome reported at 18 weeks.

(2) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.

(3) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

(4) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

(5) Azithromycin 250mg daily for 12 weeks. Severe exacerbations (requiring unscheduled visit, antibiotics and/or steroids). Outcome reported at 26 weeks.

(6) Erythromycin 125mg three times/day for six months.

(7) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

(8) Azithromycin 250mg daily for 12 months.

(9) Erythromycin 250mg twice/day for 12 months.

(10) Azithromycin 500mg three times/week for 12 months.

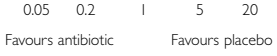
Analysis 2.3. Comparison 2 Subgroup analyses, Outcome 3 Subgroup analysis: number of people with one or more exacerbations by year carried out.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Subgroup analyses

Outcome: 3 Subgroup analysis: number of people with one or more exacerbations by year carried out

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 2005 to 2009					
Seemungal 2008 (1)	28/53	42/56		10.3 %	0.37 [0.17, 0.84]
Subtotal (95% CI)	**53**	**56**		**10.3 %**	**0.37 [0.17, 0.84]**
Total events: 28 (Antibiotics), 42 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.38 (P = 0.017)					
2 2010 to 2014					
Albert 2011 (2)	317/558	380/559		29.4 %	0.62 [0.49, 0.79]
Berkhof 2013 (3)	10/42	17/42		8.2 %	0.46 [0.18, 1.18]
He 2010 (4)	9/18	14/18		4.0 %	0.29 [0.07, 1.21]
Sethi 2010 (5)	269/569	295/580		29.9 %	0.87 [0.69, 1.09]
Simpson 2014 (6)	4/15	9/15		3.6 %	0.24 [0.05, 1.13]
Uzun 2014 (7)	34/47	42/45		4.6 %	0.19 [0.05, 0.71]
Subtotal (95% CI)	**1249**	**1259**		**79.8 %**	**0.57 [0.39, 0.83]**
Total events: 643 (Antibiotics), 757 (Placebo)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 12.05, df = 5 (P = 0.03); I^2 =58%					
Test for overall effect: Z = 2.97 (P = 0.0030)					



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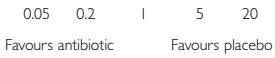
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
3 2015 to 2019					
Brill 2015 (8)	10/25	4/8		3.3 %	0.67 [0.13, 3.30]
Brill 2015 (9)	10/25	5/8		3.2 %	0.40 [0.08, 2.06]
Brill 2015 (10)	15/25	4/8		3.3 %	1.50 [0.30, 7.43]
Subtotal (95% CI)	**75**	**24**		**9.9 %**	**0.74 [0.29, 1.89]**
Total events: 35 (Antibiotics), 13 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.31$, df = 2 (P = 0.52); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.62 (P = 0.53)					
Total (95% CI)	**1377**	**1339**		**100.0 %**	**0.57 [0.42, 0.78]**
Total events: 706 (Antibiotics), 812 (Placebo)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 15.58$, df = 9 (P = 0.08); $I^2 = 42\%$					
Test for overall effect: Z = 3.55 (P = 0.00038)					
Test for subgroup differences: $Chi^2 = 1.32$, df = 2 (P = 0.52), $I^2 = 0.0\%$					



(1) Erythromycin 250mg twice/day for 12 months.

(2) Azithromycin 250mg daily for 12 months.

(3) Azithromycin 250mg three times/week for 12 weeks.

(4) Erythromycin 125mg three times/day for six months.

(5) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

(6) Azithromycin 250mg daily for 12 weeks. Severe exacerbations (requiring unscheduled visit, antibiotics and/or steroids). Outcome reported at 26 weeks.

(7) Azithromycin 500mg three times/week for 12 months.

(8) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.

(9) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

(10) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

Analysis 2.4. Comparison 2 Subgroup analyses, Outcome 4 Subgroup analysis: number of people with one or more exacerbations by regimen.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Subgroup analyses

Outcome: 4 Subgroup analysis: number of people with one or more exacerbations by regimen

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Once daily antibiotic					
Albert 2011 (1)	317/558	380/559		29.4 %	0.62 [0.49, 0.79]
Brill 2015 (2)	15/25	4/8		3.3 %	1.50 [0.30, 7.43]
Simpson 2014 (3)	4/15	9/15		3.6 %	0.24 [0.05, 1.13]
Subtotal (95% CI)	**598**	**582**		**36.3 %**	**0.61 [0.34, 1.09]**
Total events: 336 (Antibiotics), 393 (Placebo)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 2.60, df = 2 (P = 0.27); I^2 =23%					
Test for overall effect: Z = 1.66 (P = 0.096)					
2 Twice or three times daily antibiotic					
He 2010 (4)	9/18	14/18		4.0 %	0.29 [0.07, 1.21]
Seemungal 2008 (5)	28/53	42/56		10.3 %	0.37 [0.17, 0.84]
Subtotal (95% CI)	**71**	**74**		**14.3 %**	**0.35 [0.17, 0.71]**
Total events: 37 (Antibiotics), 56 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 2.91 (P = 0.0036)					
3 Three times a week antibiotic					
Berkhof 2013 (6)	10/42	17/42		8.2 %	0.46 [0.18, 1.18]
Brill 2015 (7)	10/25	4/8		3.3 %	0.67 [0.13, 3.30]
Uzun 2014 (8)	34/47	42/45		4.6 %	0.19 [0.05, 0.71]
Subtotal (95% CI)	**114**	**95**		**16.2 %**	**0.39 [0.19, 0.77]**
Total events: 54 (Antibiotics), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.73, df = 2 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 2.69 (P = 0.0072)					
4 Pulsed antibiotic					
Brill 2015 (9)	10/25	5/8		3.2 %	0.40 [0.08, 2.06]
Sethi 2010 (10)	269/569	295/580		29.9 %	0.87 [0.69, 1.09]
Subtotal (95% CI)	**594**	**588**		**33.2 %**	**0.85 [0.68, 1.07]**
Total events: 279 (Antibiotics), 300 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.84, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 1.36 (P = 0.17)					
Total (95% CI)	**1377**	**1339**		**100.0 %**	**0.57 [0.42, 0.78]**

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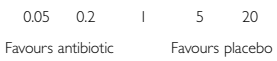
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Total events: 706 (Antibiotics), 812 (Placebo)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 15.58$, df = 9 (P = 0.08); $I^2 = 42\%$					
Test for overall effect: Z = 3.55 (P = 0.00038)					
Test for subgroup differences: $Chi^2 = 9.51$, df = 3 (P = 0.02), $I^2 = 68\%$					



(1) Azithromycin 250mg daily for 12 months.

(2) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

(3) Azithromycin 250mg daily for 12 weeks. Severe exacerbations (requiring unscheduled visit, antibiotics and/or steroids). Outcome reported at 26 weeks.

(4) Erythromycin 125mg three times/day for six months.

(5) Erythromycin 250mg twice/day for 12 months.

(6) Azithromycin 250mg three times/week for 12 weeks.

(7) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.

(8) Azithromycin 500mg three times/week for 12 months.

(9) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

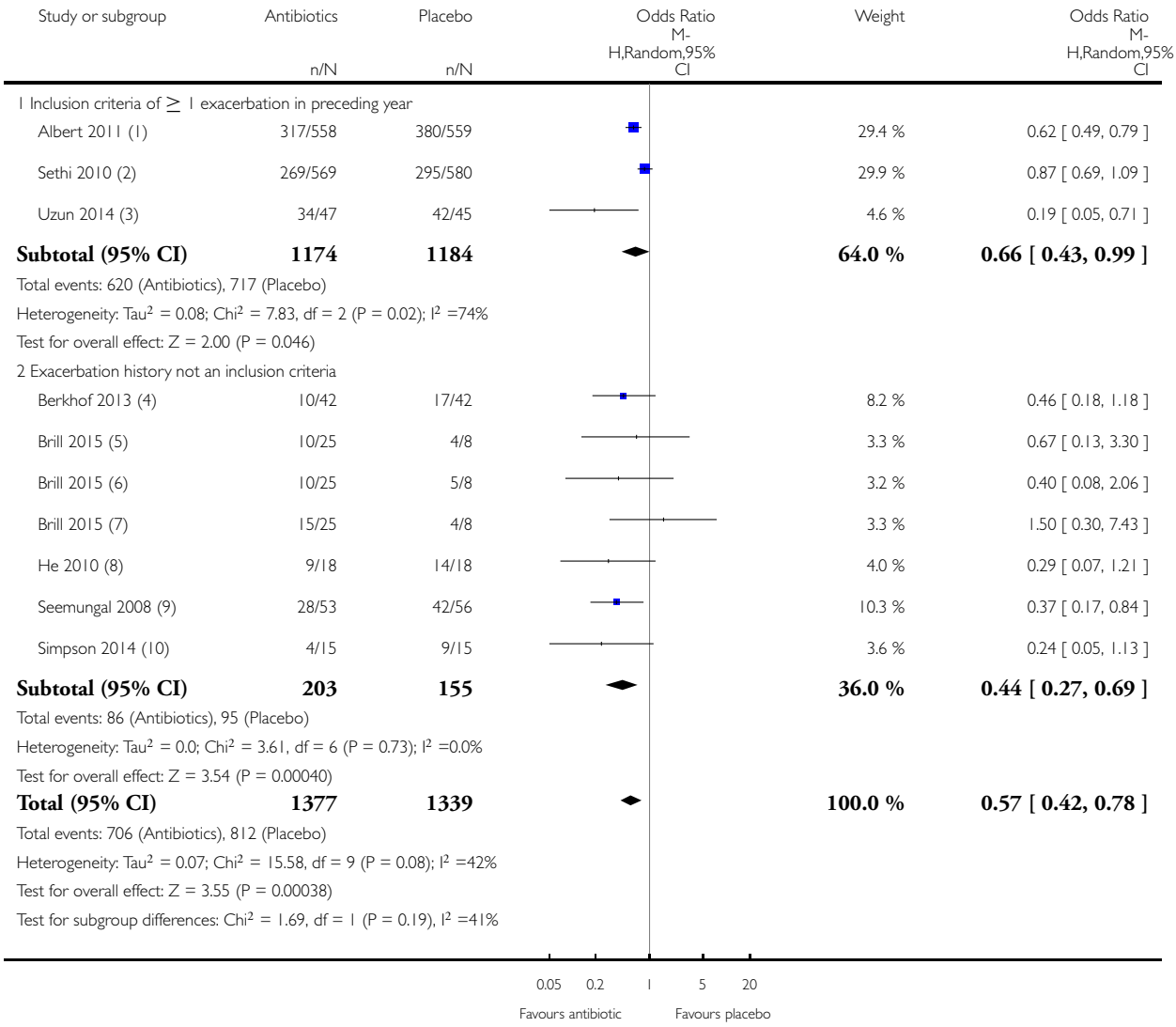
(10) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Analysis 2.5. Comparison 2 Subgroup analyses, Outcome 5 Subgroup analysis: number of people with one or more exacerbations by exacerbation history.

Review: Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Subgroup analyses

Outcome: 5 Subgroup analysis: number of people with one or more exacerbations by exacerbation history



(1) Azithromycin 250mg daily for 12 months.
(2) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.
(3) Azithromycin 500mg three times/week for 12 months.
(4) Azithromycin 250mg three times/week for 12 weeks.
(5) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(6) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.
(7) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(8) Erythromycin 125mg three times/day for six months.
(9) Erythromycin 250mg twice/day for 12 months.
(10) Azithromycin 250mg daily for 12 weeks. Severe exacerbations (requiring unscheduled visit, antibiotics and/or steroids). Outcome reported at 26 weeks.

ADDITIONAL TABLES

Table 1. Summary of study characteristics

Study	Country	No. of patients	Age (range unless otherwise stated)	% predicted FEV1 (range) unless otherwise stated	Intervention	Comparator	Duration of treatment
Albert 2011	United States of America	1142	65 - 66	39 - 40	Azithromycin 250 mg daily	Placebo	12 months
Banerjee 2005	United Kingdom	67	65.1 - 68.1	42.5 - 43.9	Clarithromycin - long-acting Klaricid XL 500 mg daily	Placebo	3 months
Berkhof 2013	Netherlands	84	67 - 68	47.4 - 49.8	Azithromycin 250 mg 3 times a week	Placebo	12 weeks
Brill 2015	United Kingdom	99	67.9 - 70.4	44 - 53	Moxifloxacin 400 mg/day for 5 days every 4 weeks Doxycycline 100 mg daily Azithromycin 250 mg 3 times a week	Placebo	13 weeks

Table 1. Summary of study characteristics (*Continued*)

He 2010	China	36	68.8 - 69.3	42.1 - 44.3	Erythromycin 125 mg 3 times a day	Placebo	6 months
Mygind 2010	Denmark	575	71 (median)	38.4 (median)	Azithromycin 500 mg 3 days a month	Placebo	36 months
NCT00524095 (terminated; details given represent proposal)	Italy	210	45 - 85	N/A	Azithromycin 500 mg 3 times a week for 6 months, then fluticasone 500 μg twice a day for 6 months	Usual care	1 year
					Fluticasone 500 μg twice a day for 6 months, then azithromycin 500 mg 3 times a week for 6 months		
NCT02628769 (terminated; details given represent proposal)	United Kingdom	5	N/A	N/A	Solithromycin 400 mg daily	Placebo	28 days
Seemungal 2008	United Kingdom	109	66 - 68	49.25 - 50.55	Erythromycin 250 mg twice a day	Placebo	12 months
Sethi 2010	International	1157	66.1 - 66.6	40.6 - 42.2	Moxifloxacin 400 mg daily for 5 days every 8 weeks	Placebo	48 weeks
Shafuddin 2015	Australia & New Zealand	292	65.8 - 67.6	32.53 - 35.8	Roxithromycin 300 mg daily and Doxycycline 100 mg daily	Placebo	12 weeks

Table 1. Summary of study characteristics (*Continued*)

					Rox-ithromycin 300 mg daily		
Simpson 2014	Australia	30	69.9 - 71.1	51.1 - 56.5	Azithromycin 250 mg daily	Placebo	12 weeks
Suzuki 2001	Japan	109	69.1 - 71.7	1.3 - 1.47 L	Erythromycin 200 - 400 mg daily	Riboflavin 10 mg daily	Unclear
Tan 2016	China	54	67.3 - 69.3	42.1 - 46.5	Erythromycin 125 mg 3 times a day for 12 months	Placebo	12 months
					Erythrom-cyin 125 mg 3 times a day for 6 months		
Uzun 2014	Netherlands	92	64.7 - 64.9	44.2 - 45	Azithromycin 500 mg three times a week	Placebo	12 months
Wang 2017	China	86	70.54 - 72.43	Unclear	Azithromycin 250 mg daily	Simvastatin 20 mg daily	6 months

FEV1: forced expiratory volume in one second.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD/chronic bronchitis search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

[The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases]

Appendix 2. Search strategy to identify relevant records from the Cochrane Airways Trials Register

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Anti-Bacterial Agents Explode 1
#8 chemoprophylaxis
#9 antibiotic* NEAR prophyla*
#10 continuous NEAR antibiotic*
#11 antibiotic*
#12 penicillin
#13 phenoxymethylpenicillin
#14 phenethicillin
#15 amoxicillin
#16 amoxycillin
#17 clavulanic acid
#18 tetracycline
#19 oxytetracycline
#20 doxycycline
#21 quinolone
#22 ciprofloxacin
#23 moxifloxacin
#24 macrolide
#25 erythromycin
#26 roxithromycin

#27 azithromycin
#28 sulphonamide
#29 co-trimoxazole
#30 sulphaphenazole
#31 trimethoprim
#32 sigmamycin
#33 tetracycline AND oleandomycin
#34 sulfamethoxazole
#35 sulfaphenazole
#36 sulfonamide
#37 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
#38 #6 and #37

Appendix 3. Search strategy for ClinicalTrials.gov

Intervention	antibiotic OR *cillin OR *mycin OR *cycline OR *floxacin OR *azole OR macrolide OR clavulanic OR sulfonamide OR quinolone OR trimethoprim
Condition	COPD
Study type	Interventional

FEEDBACK

Feedback, 30 June 2014

Summary

1) One of the conclusions in the review was that there was no significant difference in total serious adverse events (SAE) between treatment and placebo. The definition of a serious adverse event includes any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or results in persistent or significant disability (1).
According to this definition, a moderate to severe COPD exacerbation would be considered a SAE. It is unclear whether the four analysed studies (Albert, He, Seemungal, Sethi) included COPD exacerbation in their SAE data. The following concerns only exist if trial authors included moderate to severe COPD exacerbations as SAEs. If the total numbers of SAEs are approximately equal between the treatment arms and COPD exacerbations were decreased in the antibiotic group, one can expect another type of SAE to have increased in the antibiotic group. Our fear is that there may be an unidentified SAE occurring in the antibiotic arm that is not present in the placebo arm.
We noted your documentation of attempting to contact the Mygind authors for more information and were curious as to whether Banerjee or Suzuki could be reached to determine more about SAE reporting in their trials. We also emailed the authors of Albert 2011 to inquire about how SAEs were classified and documented in that trial.
Furthermore, the three studies for which SAE data were not available (Banerjee, Suzuki, Mygind) have 751 participants, which equates to 23.5% of the total review participants. The missing SAE data from these three studies could potentially change the conclusion of this review on SAEs. Based on the two concerns we expressed above, additional information will be needed to confirm any difference in SAEs between treatment and placebo.
In addition, these further conclusions about the possible SAEs associated with prophylactic antibiotics are required before patients can make an informed decision about whether the benefits of therapy justify the risks.

2) In the review, the authors discussed that a cost-effectiveness analysis would be useful in deciding the value of antibiotics in prophylaxis of COPD exacerbation. Upon reviewing the Albert 2011 trial, we noted that cost-effectiveness was a secondary outcome that was included in the study protocol but not reported in the final data. The protocol suggested that this would have been calculated as the ratio of incremental costs to the ratio of incremental quality-adjusted life years. If this missing data can be obtained from the authors and included into the review, it will be an added piece of valuable information for the readers when considering practice changes.
3) In the analysis on frequency of hospitalisation, the authors report the rate ratios of exacerbation requiring hospitalisation (/patient/year), but stated it as the rate ratios of exacerbation (/patient/year). Since the Albert 2011 trial reported both the rates of exacerbation (/patient/year) and the rates of exacerbation requiring hospitalisation (/patient/year), we feel it would be in the interest of clarity to state "rate of exacerbations requiring hospitalisation per patient per year according to the severity of COPD by the GOLD criteria."

References

1. Therapeutics Initiative. Serious adverse event analysis: lipid-lowering therapy revisited. Therapeutics Letter. 2001 Aug-Oct; Issue 42. Available from: www.ti.ubc.ca/pages/letter42.htm [cited 2014 Jun 22]

Reply

Question 1

We agree that elucidating all antibiotic-related SAEs is of paramount importance for patients and physicians prescribing these prophylactic antibiotics in order to make informed choices.

1. Albert and colleagues included COPD as a cause of fatal SAE causing death in 10 patients in the antibiotic group and 7 patients in the placebo group. However, given that there were 317 exacerbations in 558 patients in the antibiotic group and 380 exacerbations in 559 patients in the placebo group, it does not seem possible that COPD exacerbations were looked at and included as SAEs. However, we agree that this needs to be clarified with the authors and we have written to Albert and colleagues requesting clarification as to whether they included moderate to severe COPD exacerbations as a SAE.
2. In the Seemungal and colleagues study, the only listed adverse events are upper GI, lower GI, rash, and "other". Relooking at the raw data, 28 out of the 53 patients in the treatment group and 42 out of the 56 patients in the placebo group had experienced COPD exacerbations; hence they did not include COPD exacerbations as SAEs.
3. In the He study, listed adverse events were abdominal pain and heart failure in two patients in the antibiotic group and respiratory insuffiencey in two patients in the placebo group. Again, the COPD exacerbations were not included as SAEs.
4. In the Sethi and colleagues study, COPD exacerbations were not reported as SAEs. Looking closely at the adverse event table from the paper, only four patients reported dyspnoea in the treatment group and no patients reported dyspnoea in the placebo group. Given the much larger number of COPD exacerbations that had occurred in both groups, it seems that exacerbations were not included as SAEs.
5. The Mygind study did not report SAEs in detail. However, they categorised adverse events as upper GI, lower GI, infection and "other" and did not include COPD exacerbations as adverse events. However, these data were from an oral presentation slide and, as mentioned in the paper, we did not receive a response from the authors.
6. The Banerjee study had indicated in the paper that one participant withdrew in the treatment arm due to GI disturbance.
7. The Suzuki study had listed that one patient was excluded from the treatment group due to diarrhoea, with no other antibiotic-related adverse event listed.

In summary, all four papers with detailed data on adverse events (Albert, He, Seemungal, Sethi) did not include COPD exacerbations as SAEs according to the raw data we have. Albert had included COPD as a cause of death and we have written to the authors to clarify this point. The three studies with limited data (Banerjee, Suzuki, and Mygind) had not listed COPD exacerbations as SAEs.
While moderate to severe COPD exacerbations, by definition, qualify as SAEs, the most likely rationale for reporting these as separate entities was that exacerbations were the primary outcomes assessed by these studies. Separating exacerbations from adverse events will give a better idea of whether there are other SAEs that would occur in the treatment group (other than the assessed primary outcome of exacerbations).

Question 2

We agree with this point. Assessing cost-effectiveness of this intervention is of fundamental importance and we have written to the Albert group requesting that the group supply these data. This certainly is a factor that we will explore during the future updates.

Question 3

We agree that the sentence you have suggested clarifies the meaning better and have made the suggested change.
At the time of publication of this feedback, we await a response from Albert and colleagues.

Contributors

Debbie Au and Caitlin Lang, Lower Mainland Pharmacy Services, Pharmacy Residents, UBC
Dr. Aaron Tejani, Lower Mainland Pharmacy Services, Medication Use Evaluation Coordinator

WHAT'S NEW

Date	Event	Description
27 July 2018	New citation required and conclusions have changed	Conclusions strengthened and evidence now suggests that continuous and intermittent regimens may be more effective than pulsed regimens. Additonal information about antibiotic resistance added. Text updated throughout review Two new authors added to author team for 2018 update. Seven new studies added to qualitative synthesis (Berkhof 2013; Brill 2015; Shafuddin 2015; Simpson 2014; Tan 2016; Uzun 2014; Wang 2017). Fourteen studies now included in qualitative synthesis and eight studies in quantitative synthesis. Outcomes subgrouped by antibiotic regimen (continuous, intermittent, and pulsed)
27 July 2018	New search has been performed	Literature search updated.

HISTORY

Protocol first published: Issue 4, 2012

Review first published: Issue 11, 2013

Date	Event	Description
26 August 2014	Feedback has been incorporated	Feedback and author response added to the review.

CONTRIBUTIONS OF AUTHORS

For the 2013 version of the review, equal contributions were made from both authors (SH and PP) to the protocol, data extraction, analysis, write-up, and response to reviewers comments.

For the 2018 update, SH and RN screened included studies, with input from PP. SH, SM, and RN performed data extraction and entry and carried out the analysis, with advice and input from PP. SM updated the background text, methods, and results. All four authors contributed to interpreting the analyses, writing up results, and discussion and all approved the final version of the review.

DECLARATIONS OF INTEREST

RN is joint Coordinating Editor of Cochrane Airways and supported by an National Institute of Health Research grant.

SOURCES OF SUPPORT

Internal sources

- Rebecca Normansell, UK.

St George's, University of London

External sources

- National Institute for Health Research, UK.

Cochrane Programme Grant 16/114/21: NHS priorities in the management of chronic respiratory disease.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol stated that studies using antibiotics at least three times a week for a minimum period of three months would be included. We have amended this to include a regular schedule of pulsed antibiotics for a period of at least three months in order to include more studies using pulsed antibiotics. Furthermore, in the 2018 update, we chose to group analyses into continuous antibiotic regimens (at least daily), intermittent (i.e. two to three times per week) and pulsed (e.g. five days of antibiotics every eight weeks).

In 2018, we also extracted and included data on functional capacity (i.e. six-minute walk test). Before seeing the results, it was agreed amongst the author team that this was a patient-important outcome and if data were available, they should be extracted and presented.

For the 2018 update we used a random-effects rather than fixed-effect model in the meta-analyses because we judged a random-effects model to more accurately reflect the underlying clinical heterogeneity of the included studies. Furthermore, we added cut-offs for identifying statistical heterogeneity according to Higgins 2011.

Some additional text has been added to the background and discussion for the 2018 update.

In a post-hoc decision, we excluded data from Suzuki 2001 from the primary analysis as the study was not blinded.

INDEX TERMS

Medical Subject Headings (MeSH)

*Disease Progression; *Quality of Life; Anti-Bacterial Agents [*therapeutic use]; Antibiotic Prophylaxis [*methods]; Aza Compounds [therapeutic use]; Azithromycin [therapeutic use]; Clarithromycin [therapeutic use]; Erythromycin [therapeutic use]; Fluoroquinolones; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Quinolines [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Humans

Cochrane Library

Cochrane Database of Systematic Reviews

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

Chong J, Leung B, Poole P

Chong J, Leung B, Poole P.
Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD002309.
DOI: 10.1002/14651858.CD002309.pub5.

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TABLE OF CONTENTS

[Intervention Review]

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

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Contact address: Phillippa Poole, Department of Medicine, University of Auckland, Auckland, New Zealand. p.poole@auckland.ac.nz.

Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2017.

Citation: Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD002309. DOI: 10.1002/14651858.CD002309.pub5.

ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is associated with cough, sputum production or dyspnoea and a reduction in lung function, quality of life and life expectancy. Apart from smoking cessation, there are no other treatments that slow lung function decline. Roflumilast and cilomilast are oral phosphodiesterase 4 (PDE_4) inhibitors proposed to reduce the airway inflammation and bronchoconstriction seen in COPD. This is an update of a Cochrane review first published in 2011 and updated in 2013.

Objectives

To evaluate the efficacy and safety of oral PDE_4 inhibitors in the management of stable COPD.

Search methods

We identified randomised controlled trials (RCTs) from the Cochrane Airways Trials Register (date of last search October 2016). We found other trials from web-based clinical trials registers.

Selection criteria

We included RCTs if they compared oral PDE_4 inhibitors with placebo in people with COPD. We allowed co-administration of standard COPD therapy.

Data collection and analysis

One review author extracted data and a second review author checked the data. We reported pooled data in Review Manager as mean differences (MD), standardised mean differences (SMD) or odds ratios (OR). We converted the odds ratios into absolute treatment effects in a 'Summary of findings' table.

Main results

Thirty-four separate RCTs studying roflumilast (20 trials with 17,627 participants) or cilomilast (14 trials with 6457 participants) met the inclusion criteria, with a duration of between six weeks and one year. These included people across international study centres with moderate to very severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II-IV), with a mean age of 64 years.

We considered that the methodological quality of the 34 published and unpublished trials was acceptable overall. Treatment with a PDE_4 inhibitor was associated with a significant improvement in forced expiratory volume in one second (FEV_1) over the trial period

compared with placebo (MD 51.53 mL, 95% confidence interval (CI) 43.17 to 59.90, 27 trials with 20,585 participants, moderate-quality evidence due to moderate levels of heterogeneity and risk of reporting bias). There were small improvements in quality of life (St George's Respiratory Questionnaire (SGRQ), MD -1.06 units, 95% CI -1.68 to -0.43, 11 trials with 7645 participants, moderate-quality evidence due to moderate levels of heterogeneity and risk of reporting bias) and COPD-related symptoms, but no significant change in exercise tolerance. Treatment with a PDE_4 inhibitor was associated with a reduced likelihood of COPD exacerbation (OR 0.78, 95% CI 0.73 to 0.83; 23 trials with 19,948 participants, high-quality evidence). For every 100 people treated with PDE_4 inhibitors, five more remained exacerbation-free during the study period compared with placebo (number needed to treat for an additional beneficial outcome (NNTB) 20, 95% CI 16 to 26). More participants in the treatment groups experienced non-serious adverse events compared with controls, particularly a range of gastrointestinal symptoms such as diarrhoea, nausea, vomiting or dyspepsia. For every 100 people treated with PDE_4 inhibitors, seven more suffered from diarrhoea during the study period compared with placebo (number needed to treat for an additional harmful outcome (NNTH) 15, 95% CI 13 to 17). Roflumilast in particular was associated with weight loss during the trial period and an increase in insomnia and depressive mood symptoms. There was no significant effect of treatment on non-fatal serious adverse events (OR 0.99, 95% CI 0.91 to 1.07) or mortality (OR 0.97, 95% CI 0.76 to 1.23), although mortality was a rare event during the trials. Participants treated with PDE_4 inhibitors were more likely to withdraw from the trials because of adverse effects; on average 14% in the treatment groups withdrew compared with 8% in the control groups.

Authors' conclusions

In people with COPD, PDE_4 inhibitors offered benefit over placebo in improving lung function and reducing the likelihood of exacerbations; however, they had little impact on quality of life or symptoms. Gastrointestinal adverse effects and weight loss were common, and safety data submitted to the US Food and Drug Administration (FDA) have raised concerns over psychiatric adverse events with roflumilast. The findings of this review give cautious support to the use of PDE_4 inhibitors in COPD. They may be best used as add-on therapy in a subgroup of people with persistent symptoms or exacerbations despite optimal COPD management. This is in accordance with the GOLD 2017 guidelines. Longer-term trials are needed to determine whether or not PDE_4 inhibitors modify FEV_1 decline, hospitalisation or mortality in COPD.

PLAIN LANGUAGE SUMMARY

In people with chronic obstructive pulmonary disease (COPD), what are the benefits and risks of phosphodiesterase 4 inhibitors?

Background of the review

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition caused by damage from harmful chemicals that are breathed in and is predominantly seen in people who smoke tobacco. These chemicals set up a cascade of inflammatory reactions, which damage structures in the lung but also increase mucus production in the airways. These processes lead to intermittent symptoms of breathlessness and decreased capacity to perform day-to-day tasks. In addition, people with COPD are at greater risk of developing exacerbations ('flare ups'), which become more frequent and severe over time. People vary in terms of how they are affected by COPD. This is in part related to the severity of the disease but also to differences in response to medicines, an individual's fitness and coexistent conditions. The only way to prevent further lung damage in most people is to stop smoking.

Medicines prescribed to manage COPD generally aim to improve symptoms, reduce exacerbations or both. In the early stages, bronchodilator medicines are helpful because these relax the small muscles in the airway allowing more air to move freely in and out of the lungs. Some long-acting agents may reduce exacerbations. Steroid-containing inhalers may be added specifically to target inflammation in the lungs and thus modestly reduce the number of exacerbations.

Phosphodiesterase 4 (PDE_4) inhibitors are a relatively new class of medicines that have been marketed to improve COPD. They have both bronchodilator and anti-inflammatory effects. Moreover, the two currently available medicines, roflumilast and cilomilast, are taken as a tablet. Our review collated and analysed existing trials to define the benefits and risks of PDE_4 inhibitors in COPD.

What did we look at?

We found 34 completed trials involving 24,084 adults, with results reported up to October 2016. These consisted mainly of trials in people with moderate to very severe disease who discontinued other regular COPD medications. However, there were seven trials that allowed continuation of usual COPD medicines. The trials ranged from 6 to 52 weeks' duration and the average age of participants was 64 years. The trials were all sponsored by the manufacturers of PDE_4 inhibitors.

What did we find out?

Compared with placebo, these medicines provide a small improvement in lung function measurements and reduce the likelihood of an exacerbation of COPD. Based on these results, we would expect that out of 100 people who took PDE_4 inhibitors every day for a year, 28 would experience at least one exacerbation which is five fewer than for others who did not receive these medicines.

However, people reported that these medicines only provided a small effect on levels of breathlessness and quality of life. Furthermore, around 5% to 10% of people in trials who received roflumilast or cilomilast reported side effects such as diarrhoea, nausea and vomiting. We would expect that out of 100 people who took PDE_4 inhibitors every day for a year, 11 would experience diarrhoea, which is seven more than for others who did not receive these medicines. There was also a two- to three-fold increase in the risk of sleep or mood disturbance for the roflumilast 500 μg dose, although overall the total number of reported incidents was still small. There was no effect on rates of hospitalisation and deaths. The effects were the same regardless of the severity of COPD, or whether other medicines for COPD were being taken.

Quality of the evidence

The studies were generally well designed, as people did not know if they were receiving this new treatment or a placebo medicine. Overall we rated the evidence as being of moderate to high quality.

It is of concern that results seen in trials published in journals by pharmaceutical companies showed a greater benefit of these medicines than those which were unpublished. Therefore, this relies on unpublished trial data being made accessible and up to date. The psychiatric adverse effects data remain unpublished. Longer-term trials are necessary to get a more accurate estimate of the benefits and safety of these medicines over time, including whether they slow COPD disease progression.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Phosphodiesterase 4 inhibitors compared to placebo for chronic obstructive pulmonary disease

Patient or population: people with stable chronic obstructive pulmonary disease
Settings: community-based, randomised, parallel, double-blind, placebo-controlled trials
Intervention: phosphodiesterase 4 inhibitors
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)[1]	Comments
	Assumed risk	Corresponding risk				
	Placebo	Phosphodiesterase IV inhibitors				
Change in FEV_1 lung function (mL) Follow-up: mean 28.0 weeks	The mean change in FEV_1 lung function in the control groups was a fall of **20.67 mL**	The mean change in FEV_1 lung function in the intervention groups was **49.27 mL better** (44.11 to 54.44 higher)		20,585 (27 studies)	⊕⊕⊕◯ **moderate**[2,3]	
Change in quality of life St George's Respiratory Questionnaire Follow-up: mean 24.2 weeks	The mean change in quality of life in the control groups was an improvement of 2.21 **SGRQ units**	The mean change in quality of life in the intervention groups was **1.06 units better** (0.43 to 1.68)		7645 (11 studies)	⊕⊕⊕◯ **moderate**[2,3]	Lower scores on SGRQ represent improved quality of life. This result does not reach the minimum clinically important difference for this scale
COPD exacerbations No. of participants with exacerbations Follow-up: 12 to 52 weeks	**33 per 100**	**28 per 100** (26 to 29)	**OR 0.78** (0.73 to 0.83)	19,948 (23 studies)	⊕⊕⊕⊕ **high**	See Figure 1

Adverse events No. of participants experiencing any adverse event Follow-up: 6 to 52 weeks	**64 per 100**	**69 per 100** (70 to 73)	**OR 1.29** (1.22 to 1.37)	20,988 (27 studies)	⊕⊕⊕◯ **moderate**[4]	This outcome includes participants who reported COPD exacerbations as an adverse event
Gastrointestinal side effects No. of participants experiencing diarrhoea Follow-up: 6 to 52 weeks	**4 per 100**	**11 per 100** (10 to 12)	**OR 3.13** (2.76 to 3.54)	20,181 (25 studies)	⊕⊕⊕⊕ **high**	Diarrhoea was the most commonly reported gastrointestinal side effect. See Figure 2 Weight loss was more common, and may be a result of diarrhoea
Psychiatric adverse events (roflumilast 500 µg) No. of participants Follow-up: 12 to 52 weeks	**35 per 1000**	**71 per 1000** (60 to 83)	**OR 2.13** (1.79 to 2.54)	11,168 (14 studies)	⊕⊕⊕◯ **moderate**[5]	Pooled data from FDA website, not individual trial reports
Mortality (all-cause) No. of participants Follow-up: 6 to 52 weeks	**1 per 100**	**1 per 100** (1 to 2)	**OR 0.97** (0.76 to 1.23)	19,344 (23 studies)	⊕⊕⊕◯ **moderate**[6]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **COPD:** chronic obstructive pulmonary disease; **FDA:** Food and Drug Administration (USA); **FEV_1:** forced expiratory volume in one second; **OR:** odds ratio; **SGRQ:** St George's Respiratory Questionnaire

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]There was a greater proportion of participant withdrawals in the treatment (24%) compared with the control group (19%), but not sufficient to warrant downgrading the quality of evidence.

[2]There was moderate heterogeneity between the studies (I^2 = 30% to 50%).

[3]There was a statistically significant difference between published and unpublished studies.

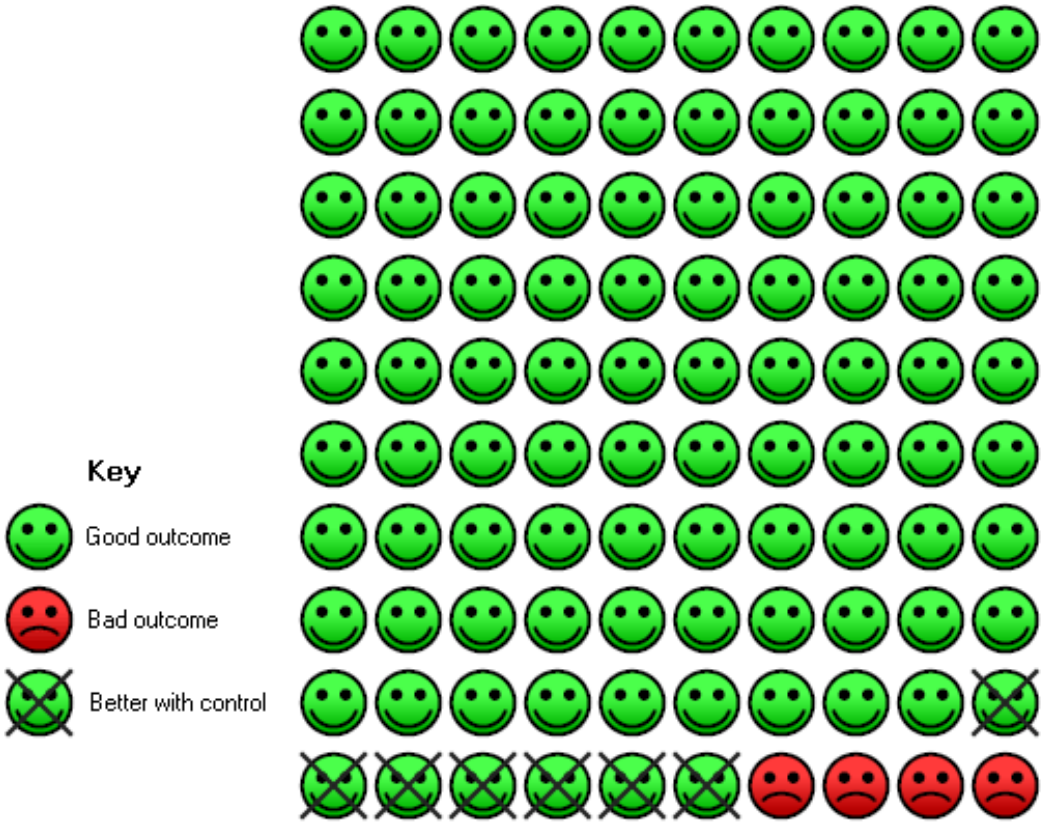
[4]There was high level of heterogeneity between study results (I^2 > 50%).

[5]Based on data from the combined COPD safety pool. Individual study data not obtained.

[6]There were very few events, leading to wide confidence intervals.

Figure 1. In the control group 33 people out of 100 had an exacerbation of COPD over 6-52 weeks, compared to 28 (95% CI 27 to 29) out of 100 for the active treatment group.

Figure 2. In the control group 4 people out of 100 had diarrhoea over 6-52 weeks, compared to 11 (95% CI 10 to 12) out of 100 for the active treatment group.



BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of global morbidity and mortality, resulting in a growing social and economic burden (GOLD 2017). In 2002, it was estimated to be the fifth leading cause of death, responsible for approximately 4.8% of total deaths worldwide and it is projected to rise to fourth position by the year 2030 (Mathers 2005).

This diagnosis of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2017) says that it is a "common, preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by exposure to noxious particles or gases." COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations. Besides exposures, host factors predispose individuals to develop COPD. Co-morbidities contribute to the overall severity and mortality in individual people. (GOLD 2017). Diagnosis is based on a history of exposure to risk factors for this disease and symptoms of cough, sputum production or dyspnoea (shortness of breath). Spirometry is required for diagnosis, with airflow obstruction being confirmed by a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) of 0.7 or lower (Celli 2004). Life expectancy is reduced in people diagnosed with COPD and, although prognosis is variable, age and FEV_1 are the strongest predictors of mortality.

The predominant risk factor for COPD is tobacco smoking, with other environmental pollutants also known to contribute. Cigarette smoke leads to the activation of macrophages and CD8 T lymphocytes that release inflammatory mediators and cytokines. The process also involves neutrophil attraction and cell apoptosis (Barnes 2000). To date, smoking cessation is the only interven-

tion known to slow the decline in lung function associated with COPD (GOLD 2017).

Pharmacotherapy is commonly used to treat people with COPD, with effects on symptoms, quality of life, or frequency and severity of exacerbations (Celli 2004; GOLD 2017). Mainstays of treatment include short- and long-acting inhaled beta-2 agonists and anticholinergics, corticosteroids and methylxanthines. New approaches to treatment are needed, as no individual agent slows the decline in lung function or survival. In the TORCH study (Calverley 2007) a combination of salmeterol 50 μg and fluticasone 500 μg twice daily reduced the risk of death by 17% compared with placebo over the three-year trial period; however, this did not reach the pre-defined level of statistical significance for the study.

An exacerbation of COPD is an acute and sustained increase in symptoms that result in additional therapy (GOLD 2017). The risk of exacerbation significantly increases in more severe COPD. Exacerbations have a negative impact on quality of life and lead to more rapid COPD progression, as well as higher health care utilisation and associated costs. Common triggers are respiratory viral infections, bacterial infections or air pollution (Wedzicha 2007; White 2003), which may lead to an increase in airway inflammation, production of mucus, acute deterioration in lung function, hyperinflation from gas trapping, or a combination of these symptoms (Van Geffen 2015). These processes contribute to the symptoms of increased dyspnoea and cough, as well as to changes in the character or volume of sputum.

Description of the intervention

The intervention is an oral medicine that is a selective inhibitor of the isoenzyme phosphodiesterase 4 (PDE_4). This isoenzyme has a role in airway inflammation and bronchoconstriction, both of which are pathological features of COPD (Boswell-Smith 2006). Two medicines in this class that have been studied are roflumilast and cilomilast.

How the intervention might work

Cyclic adenosine monophosphate (cAMP) is a secondary messenger that suppresses the activity of inflammatory cells and mediates the process of smooth muscle relaxation in the airways. Phosphodiesterases, in turn, hydrolyse and turn off the biological activity of cAMP (Boswell-Smith 2006). Therefore, inhibitors of phosphodiesterase action should theoretically provide improvements in the extent of airway narrowing and damage from inflammation.

Non-selective phosphodiesterase (PDE) inhibitors such as theophylline, a methylxanthine, have been used in the management of people with COPD for years. These are recommended by current international guidelines as part of adjunctive therapy to long-acting bronchodilators (GOLD 2017). Limitations to their use include a narrow therapeutic margin, and the frequency of adverse effects, which may occur even when the plasma level is within the therapeutic range (Boswell-Smith 2006). Common adverse effects associated with theophylline include headache, nausea, vomiting, diarrhoea, restlessness, nervousness, insomnia and gastrointestinal effects (Barnes 2003). Less common, but more serious, are the increased risks of cardiac arrhythmias and seizures (Barnes 2003). Some of the adverse effects associated with theophylline have been attributed to its non-selective PDE inhibition and concurrent adenosine receptor antagonism (Barnes 2005).

The isoenzyme PDE_4 is the predominant isoenzyme involved with metabolising cAMP in immune and inflammatory immune cells, such as neutrophils, macrophages, T cells and endothelial cells in COPD, in airway smooth muscle and pulmonary nerves (Agusti 2005; Boswell-Smith 2006; Torphy 1998; Vignola 2004). Inhibition of PDE_4 leads to elevation of cAMP in inflammatory and immunomodulatory cells, resulting in suppression of inflammatory cell function, relaxation of airways smooth muscle and modulation of pulmonary nerves (Boswell-Smith 2006; Essayan 2001; Torphy 1999). Thus, PDE_4 is an attractive target for inhibition in COPD. Furthermore, the central nervous system (CNS) and cardiovascular adverse effects experienced in patients treated with the non-selective PDE inhibitor, theophylline, are a result of adenosine receptor antagonism. This feature is not present with PDE_4 specific inhibitors (Vignola 2004).

Why it is important to do this review

The development of selective PDE_4 inhibitors offers new hope for therapy offering both anti-inflammatory and bronchodilatory effects in COPD, with fewer of the adverse effects encountered with non-selective inhibitors. Additionally, PDE_4 inhibitors may be easier to use because there is less pharmacokinetic variability and lower potential for drug interactions compared with theophylline (Barnes 2005). Several PDE_4 inhibitors have been developed, with some progressing to phase III clinical trials. These include the second-generation PDE_4 inhibitors roflumilast (Nycomed, formerly Altana) and cilomilast (GlaxoSmithKline).

The 2017 GOLD guidelines (GOLD 2017) state that roflumilast may be considered in patients on triple inhaled therapy who still have exacerbations, an FEV_1 of less than 50% predicted and chronic bronchitis, especially if they have had a hospitalisation in the last year.

This review focuses on the effect of PDE_4 inhibitors in the management of people with stable COPD, using clinically important outcomes. Collating this evidence into a systematic review allows an assessment as to whether or not the theoretical benefits of PDE_4 inhibitors translate into useful clinical effects, and may suggest the potential place of PDE_4 inhibitors within the increasing pharmacopoeia of COPD treatments.

OBJECTIVES

To evaluate the efficacy and safety of oral PDE_4 inhibitors in the management of stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that compared orally administered PDE_4 inhibitors with placebo. We included any chronic treatment trials, but excluded single-dose trials, as well as trials in acute exacerbations of COPD. We also excluded cross-over trials.

Types of participants

Adults (over 18 years of age) with COPD, as defined by the American Thoracic Society, European Respiratory Society or GOLD, with airflow obstruction evident by spirometry with post-bronchodilator FEV_1/FVC of 0.7 or less (GOLD 2017). We considered trials that included participants with both COPD and asthma only if data from participants with COPD could be extracted separately from the study report, or through correspondence with the study authors. We excluded ex-vivo experiments and trials with participants requiring mechanical ventilation on presentation.

Types of interventions

We included trials if they compared outcomes for participants who received an orally administered PDE_4 inhibitor with those of control participants who received placebo.
In this latest update of the review, although not mentioned in the initial protocol, we have excluded cross-over design studies as a way to minimise non-random sources of bias between studies.

Types of outcome measures

Primary outcomes

- Changes in lung function from baseline including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) or peak expiratory flow rate (PEF)
- Quality of life (e.g. total score on St George's Respiratory Questionnaire (SGRQ))

Secondary outcomes

- Incidence of COPD exacerbations
- Symptoms (breathlessness on Borg and other scales and Shortness of Breath Questionnaire; composite measures (summary symptom score))
- Exercise tolerance (six-minute walk test)
- Adverse effects (number of participants experiencing one or more adverse event, e.g. gastrointestinal, central nervous system (CNS) and cardiovascular adverse events, change in weight, withdrawal rates)
- Serious adverse events and mortality

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Specialised Register contains studies identified from several sources:

- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
- weekly searches of MEDLINE Ovid SP 1946 to date;
- weekly searches of Embase Ovid SP 1974 to date;
- Monthly searches of PsycINFO Ovid SP;
- Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
- Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
- handsearches of the proceedings of major respiratory conferences.

Studies contained in the Specialised Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.
We conducted the most recent search in October 2016, with no restriction on language of publication. The original strategy for this review, which was more sensitive but less specific, is in Appendix 3.

Searching other resources

We reviewed the reference lists of all primary trials and review articles for additional references. We contacted investigators in this area and pharmaceutical companies manufacturing PDE_4 inhibitors to ascertain if they could provide any potentially relevant trial data. We also searched the US Food & Drug Administration

(FDA) website and US National Institutes of Health (NIH) clinical trials registry, ClinicalTrials.gov (last accessed 31 May 2017).

Data collection and analysis

Selection of studies

Two review authors (JC, PP) independently screened the search results to select citations to retrieve in full text. The same two review authors then screened the full-text articles to identify studies for inclusion.

Data extraction and management

One review author (JC) extracted data from the eligible studies and a second review author (BL or PP) checked the data. We entered data into Review Manager 5 (RevMan 5) RevMan 2014. In some cases, we estimated information regarding outcomes from graphs. Where standard errors (SE) were reported, we converted them to standard deviations (SD).

We extracted the following data.

- Methods: trial design, duration of follow-up
- Participants: age, gender, smoking status, study setting, inclusion and exclusion criteria
- Intervention: drug name, dose, duration of treatment, control and/or standard therapy
- Outcome measures

We categorised references according to the trial name (by drug name and number, or by author and year). We obtained data on additional outcomes from other references to the same trial, and more detailed descriptions of study populations from information submitted by the drug manufacturer to the FDA website.

Where there were data from more than one report of the same trial, we considered the data from the primary published reference with the most complete data on the primary outcome(s) to take priority. For primary outcomes, we used intention-to-treat analysis in preference to per-protocol analysis. On the other hand, the trial data on the company website for Cilomilast 076 provided more complete details of adverse events than Gamble 2003, and we used this preferentially.

Our initial plan had been to perform meta-analysis on the change from baseline in post-bronchodilator FEV_1. Only pre-bronchodilator values were reported for the majority of cilomilast trials, with pre- and post-bronchodilator values available for most trials of roflumilast, with the exception of Roflumilast DAL-MD-01, Roflumilast FK1 101, Roflumilast FK1 103, Roflumilast FLUI-2011-77 and Roflumilast IN-108 for which only post-bronchodilator measures were available and only predose measurements available for Roflumilast ROF-MD-07(RE2SPOND).

In order to increase the number of trials in the meta-analysis, we decided to use the change in the pre-bronchodilator FEV_1 for all trials, except for the five just mentioned, where it was not available. Between them, these three trials contributed only 3.4% to the mean difference (MD), with the mean change seen from baseline in FEV_1 similar to other trials.

Lung function is reported in millilitres (mL). Exercise tolerance is reported in metres (m).

The outcome 'total adverse events' included the participants in each group experiencing one or more adverse events, including an acute exacerbation of COPD. Similarly, serious adverse events included conditions requiring hospital-level treatment and encompassed more serious COPD exacerbations.

Assessment of risk of bias in included studies

We assessed trials using the 'Risk of bias' methods outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) as low, unclear or high.

Measures of treatment effect

Where appropriate, we combined data from trials using RevMan 2014. We expressed results for continuous variables using a fixed-effect MD, or standardised mean difference (SMD), with 95% confidence intervals (CI). We expressed results for pooled outcomes with dichotomous variables using a fixed-effect odds ratio (OR) with 95% CI. We considered a P value of less than 0.05 statistically significant. We combined rate ratios on a natural logarithm scale and weighted them by the inverse of the variance of the log rate ratio.

Unit of analysis issues

The unit of analysis was the participant, with the exception of analysis of exacerbation rates

Dealing with missing data

We contacted the respective pharmaceutical companies for missing trial data. In particular, Nycomed and Forest Laboratories provided us with some study details and results extracted from published articles and abstracts that were not identified in our initial search.

Assessment of heterogeneity

We used Chi^2 and I^2 statistics, along with P values (Higgins 2003) to measure heterogeneity among the trials in each analysis. Where we identified substantial heterogeneity we planned to report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We compared available published outcomes with prescribed methods and, where available, original study protocols.

Data synthesis

We presented the findings of our primary outcomes in a 'Summary of findings' table generated using GRADEpro GDT 2015 software and based on the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses a priori.

- Severity of airflow obstruction at baseline (FEV_1 % predicted GOLD Grade II 50% to 80%, Grade III 30% to 50%, Grade IV less than 30%) (GOLD 2017)
- Drug (e.g. roflumilast, cilomilast)
- Dose (e.g. roflumilast 250 μg or 500 μg)
- Duration of therapy (12 weeks or less; 24 to 26 weeks; 52 weeks)
- Concomitant therapy (inhaled or oral corticosteroids, inhaled long-acting beta-2 agonists, or anticholinergics, or both)

Sensitivity analysis

We planned the following sensitivity analyses a priori.

- Fixed-effect versus random-effects models for studies with unexplained heterogeneity
- Methodological quality

We did not anticipate the large number of unpublished trials at the protocol stage. Consequently, we undertook a sensitivity analysis of the effect sizes of the primary outcomes seen in published and unpublished trials.

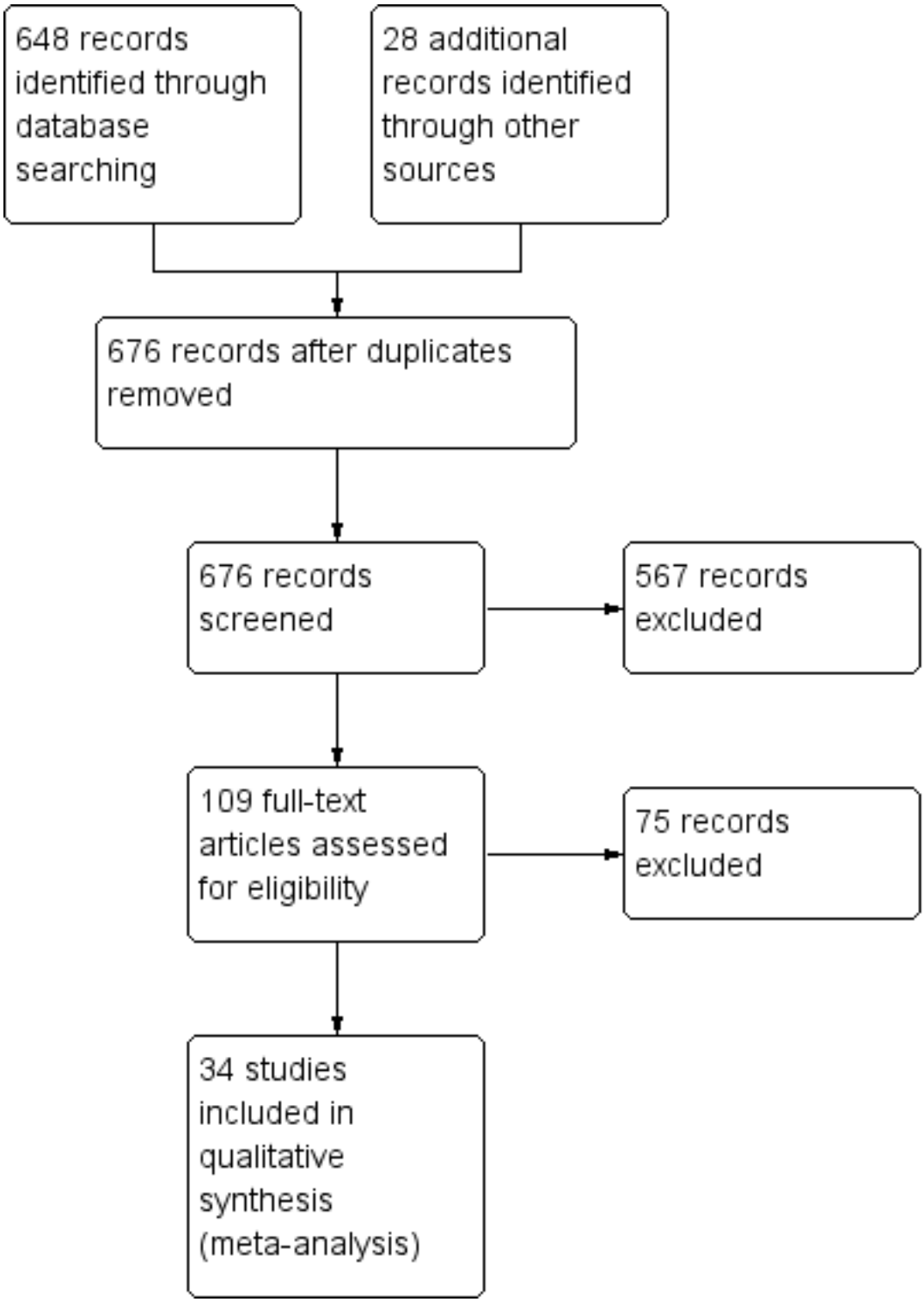
RESULTS

Description of studies

Results of the search

See Figure 3 for study flow diagram (Moher 2009).

Figure 3. Study flow diagram



For the initial search in October 2006, we identified 477 abstracts of potentially relevant trials, which was narrowed to 71 abstracts using a less sensitive search of the Cochrane Airways Specialised Register. We searched again in 2008 and located 79 abstracts; in 2010 finding 17 abstracts; and in 2013, locating 20 abstracts. For the present update, the search found 55 abstracts (48 excluding duplicates). In total 648 records were identified from database screening. Many abstracts were reports of earlier trials. We decided whether or not to seek the full text based on a review of the abstract text, title and MeSH headings of all identified citations, with the numbers of full papers sought outlined in Table 1.

For this update we sought full papers for 28 abstracts. For each update, two review authors (JC and PP) assessed the full-text versions of the trials to determine whether or not they met the inclusion criteria. We resolved any differences by discussion. We then assessed trials that met the inclusion criteria for methodological quality.

In addition, in the course of earlier updates we found 15 completed trials for roflumilast and one for cilomilast in participants with COPD in a search of the online clinical trials registry of the US National Institutes of Health (NIH). After attempting to correlate each unique NIH study number with trials already identified in the above searches of the Airways registry, there were seven studies of roflumilast on the NIH clinical trials registry that had not been published elsewhere in any form. For the 2016 update, no new completed trials were located on the NIH websites that had not already been published.

For cilomilast, we identified one trial (Compton 2001) from the literature search and obtained the full text. Further, we found a summary of the study design, along with a report of results, for 12 individual phase II or III trials on the GlaxoSmithKline (GSK) website.

We identified another two trials, both through the literature search and from the GSK website (Cilomilast 039; Cilomilast 076). Gamble 2003 is the primary published reference for the latter study.

During the 2016 update we identified 5 new studies of roflumilast but none of cilomilast. All the roflumilast studies used a study dose of 500 μg (RO-2455-301-RD (ACROSS); RO-2455-404-RD (REACT); Roflumilast DAL-MD-01; Roflumilast FLUI-2011-77; Roflumilast ROF-MD-07(RE2SPOND)).

Included studies

Thirty-four separate RCTs studying roflumilast (20 trials with 17,627 participants) or cilomilast (14 trials with 6457 participants) met the inclusion criteria. Twenty-one of these 34 studies have been published in full in a peer-reviewed journal. Further details may be found in the Characteristics of included studies table. Those for roflumilast included the following.

- An early-dose selection study comparing participants given roflumilast 250 μg and 500 μg (Roflumilast M2-107) for 24 weeks. Subsequent studies all used 500 µg of roflumilast in the intervention group and this is the dose that appears in the analyses except where otherwise stipulated.
- The first published one-year study of PDE_4 inhibitor treatment in COPD (Roflumilast M2-112). This was the only trial included in this review that allowed concomitant corticosteroid use during the treatment period. Since then, the results of a replicate study have been published (Roflumilast M2-111).
- This was followed by two, year-long studies (Roflumilast M2-124; Roflumilast M2-125) investigating the effect in a specific subgroup - severe to very severe COPD associated with chronic bronchitis in participants at risk of exacerbations.
- Two studies (Roflumilast M2-127; Roflumilast M2-128) that evaluated the add-on use of roflumilast with long-acting bronchodilator agents, the first with salmeterol and the second with tiotropium. Both studies ran for 24 weeks. A further two RO-2455-404-RD (REACT) and Roflumilast ROF-MD-07(RE2SPOND) added roflumilast or placebo to a fixed-dose inhaled corticosteroid-long-acting beta-2 agonist combination.
- Roflumilast M2-118 was a 12-week study that focused on airway physiology during rest and exercise in participants with moderate to severe disease. In addition, Roflumilast M2-119 investigated pulmonary function and safety in a group of participants recruited in centres across the Asia-Pacific regions. Roflumilast DAL-MD-01 was mainly interested in effect on sputum and other biomarkers, and Roflumilast FLUI-2011-77, airway architecture by imaging techniques.
- More recent large RCTs were RO-2455-301-RD (ACROSS), a 24 week trial across three centres in mainland China, Hong Kong and Singapore, and RO-2455-404-RD (REACT) and Roflumilast ROF-MD-07(RE2SPOND) year-long multi-centre trials.

There were two trials reported only as conference posters: Roflumilast FK1 101 and Roflumilast FK1 103. The first compared roflumilast 500 µg, roflumilast 250 µg and placebo for 26 weeks; the second compared roflumilast 500 µg once daily for 24 weeks with roflumilast 500 µg once daily for 12 weeks, then placebo once daily for the following 12 weeks.

Unpublished results were identified for two further studies: Roflumilast IN-108 compared the safety and efficacy of roflumilast 250 μg and 500 μg in participants recruited from five centres across India; however, no inclusion criteria were stated, concomitant medications were poorly described and only 15 participants in the placebo group completed the protocol; Roflumilast JP-706 was a 24-week study sponsored by a different collaborator that, in

addition to treatment effects, monitored pharmacokinetic levels of roflumilast and its metabolite roflumilast-N-oxide.
All of these were designed as randomised, double-blind, placebo-controlled studies and, apart from Roflumilast JP-706, all studies prior to 2013 were included in combined safety figures for roflumilast that have been made available through publications on the FDA website (https://www.accessdata.fda.gov/drugsatfda˙docs/nda/2011/022522Orig1s000MedR.pdf). This also includes participants in two other 24-week studies (Roflumilast M2-110; Roflumilast M2-121), which have results that have not been published (roflumilast 500 µg: 5970, roflumilast 250 µg: 1002 and placebo: 5682).
For cilomilast, data were mainly from phase III clinical trials with one phase II/III trial. These included unpublished studies. All used a 15 mg dose twice daily except for Compton 2001.
The trials fell into four groups:

- Compton 2001 was a parallel, six-week, dose-ranging study comparing placebo with 5 mg, 10 mg and 15 mg doses of cilomilast, with FEV_1 as the primary outcome.
- Pivotal efficacy studies (Cilomilast 039; Cilomilast 042; Cilomilast 091; Cilomilast 156), all of which were 24 weeks in duration. The studies Cilomilast 039 and Cilomilast 156 were conducted in North America, while Cilomilast 042 and Cilomilast 091 were conducted in the European Union. Here the primary study outcomes were change in FEV_1, lung function and SGRQ quality-of-life score.
- Supporting studies (Cilomilast 076; Cilomilast 110; Cilomilast 111; Cilomilast 168), all of which lasted for less than 24 weeks, with an average trial duration of 10.8 weeks, where neither FEV_1 lung function nor SGRQ were the primary outcomes.
- Other studies were Cilomilast 121 (phase II/III 24 weeks), Cilomilast 157 (52 weeks) and Cilomilast 103657 (24 weeks), which followed the pivotal efficacy studies and were smaller in sample size. Cilomilast 180 (18 weeks) had a primary lung function endpoint, functional residual capacity, and Cilomilast 181 (13 weeks) assessed the number of inflammatory cells in a bronchial biopsy.

Almost all studies used inclusion criteria of spirometry and a history of smoking. Only four of the 29 studies mandated a history of exacerbation in the previous year (Cilomilast 103657; Cilomilast 121; Roflumilast M2-124; Roflumilast M2-125).
The mean age of participants in the trials ranged from 60 to 70 years with the proportion of male participants between 49% and 96%. Mean FEV_1 (% predicted) in the trials that reported it ranged from 33% to 51%. The majority of trials included participants at all stages of COPD, however limitation to those with severe and very severe COPD occurred in Roflumilast M2-124; Roflumilast M2-125; RO-2455-301-RD (ACROSS); RO-2455-404-RD (REACT); Roflumilast DAL-MD-01; Roflumilast M2-111; Roflumilast M2-112; Roflumilast ROF-MD-07(RE2SPOND).

Excluded studies

We excluded 75 records after studying the full text. We provided reasons for the exclusion of 26 studies, which can be found in Characteristics of excluded studies. For some of these the reason was that data were unusable (e.g. Borker 2003; Knobil 2003).

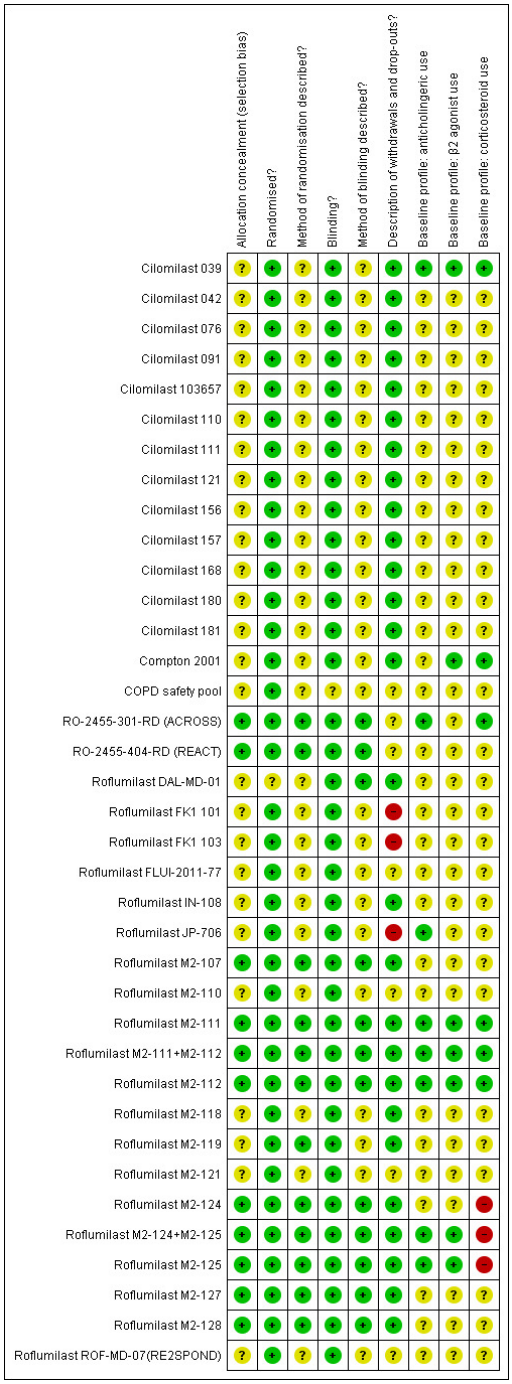
Risk of bias in included studies

We considered that the methodological quality of the 34 published and unpublished trials was acceptable overall.

Allocation

In the roflumilast trials, there were adequate descriptions of allocation concealment and method of blinding in nine out of 20 trials. Information about allocation concealment and blinding was only provided for one of the 14 cilomilast trials, while further details for the remaining trials were unclear. The risk of bias for each parameter in the 34 studies is shown in Figure 4.

Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Blinding

All studies included in this review were double-blind, RCTs.

Incomplete outcome data

The percentage of participant withdrawals varied among the 34 trials that reported this outcome. Withdrawals were significantly higher in the PDE_4 inhibitor-treated groups compared with control groups. The mean withdrawal rate for roflumilast studies, because of adverse events, was 13% in the treatment group (range 3% to 37%) and 8% in the control group (range 3% to 27%). In the cilomilast studies a mean of 25% of the participants withdrew due to adverse events in the treatment group (range 13% to 34%) and 21% (range 9% to 40%) in the control group.

Since the participants who withdraw tended to have poorer outcome measures than those remaining, the higher withdrawal rates for the PDE_4 inhibitor-treated groups may have inflated the apparent benefits of treatment.

Selective reporting

There were 23 published and 11 unpublished trials. We performed analyses of differences in treatment effect between published and unpublished treatment groups for primary outcomes and this is reported in the subgroup and sensitivity analysis below.

Other potential sources of bias

In some trials there were minor differences in baseline characteristics such as age, gender, FEV_1 and smoking history.

Effects of interventions

See: **Summary of findings for the main comparison** Phosphodiesterase 4 inhibitors compared to placebo for chronic obstructive pulmonary disease

Change in lung function from baseline

Based on the 27 trials that reported this outcome, there was a statistically significant improvement in FEV_1 from baseline in the PDE_4 inhibitor-treated participants compared with controls (MD 51.53 mL, 95% CI 43.17 to 59.90, 20,585 participants), over the study period (Analysis 1.1).

The effect on FEV_1 was seen for roflumilast 500 µg (MD 56.45 mL, 95% CI 48.01 to 64.89), roflumilast 250 µg (MD 56.88 mL, 95% CI 24.38 to 89.38) and for cilomilast 15 mg twice daily (MD 41.03 mL ,95% CI 23.93 to 58.13). A moderate level of heterogeneity existed for this outcome (Chi^2 = 56, df = 29, P = 0.002; I^2 = 48%), which is only partially explained by investigating differences between roflumilast and cilomilast. This is discussed further in the sensitivity analysis below. Analysis of a dose effect was possible in three trials: Roflumilast FK1 101; Roflumilast M2-107 and Roflumilast IN-108. Roflumilast 500 μg was associated with a greater change in FEV_1 than roflumilast 250 μg, but this was not statistically significant (MD 22.61, 95% CI -5.95 to 51.16).

With respect to PDE_4 inhibitor use with concomitant therapies (Analysis 1.5), the largest increases in FEV_1 were seen in the two trials where participants were taking regular, long-acting bronchodilators: in one, salmeterol (Roflumilast M2-127) and in the other, tiotropium (Roflumilast M2-128) (overall MD 60.52 mL, 95% CI 40.57 to 80.46). The next largest improvements were seen in trials where all concomitant medications (including long-acting bronchodilators if previously received) were continued (RO-2455-301-RD (ACROSS); RO-2455-404-RD (REACT); Roflumilast ROF-MD-07(RE2SPOND) (MD 56.58 mL, 95% CI 46.91 to 66.25).

Similar improvements were seen in trials where all medications apart from short-acting beta 2 agonists were stopped (MD 44.78 mL, 95% CI 37.67 to 51.90) and in the three trials (Roflumilast M2-111; Roflumilast M2-112; Roflumilast M2-118) where both treatment and control groups continued on an inhaled corticosteroid (MD 42.26 mL, 95% CI 25.46 to 59.05).

Treatment with a PDE_4 inhibitor was associated with a statistically greater change in FVC from baseline than placebo (MD 87.28 mL, 95% CI 74.87 to 99.70) with minimal heterogeneity among the 16 trials (Analysis 1.9). Change in PEF was measured in only five of the 34 trials, but was significantly higher with treatment than in controls (MD 6.54 L/min, 95% CI 3.95 to 9.13) (Analysis 1.10).

Quality of life

Note that with the SGRQ, a decrease in the total score represents an improvement in the quality of life. We noted a small but statistically significant decrease in total score on the SGRQ from baseline in participants treated with PDE_4 inhibitors compared with those in the control groups (MD -1.06, 95% CI -1.68 to -0.43, P = 0.0009) (Analysis 1.11). There was heterogeneity in this observation (Chi^2 = 21, df = 11, P = 0.03, I^2 = 47%).

It was notable that in the two trials with a duration of one year that reported total SGRQ, there was no significant change in quality of life seen with treatment compared with control (MD 0.26, 95% CI -1.18 to 1.69). We did not include outcome data for Roflumilast M2-111 as data were provided in the form of a 'repeated measures analysis' and pooled data did not equal the sum of numbers in each of the individual studies.

Exacerbations

Use of PDE_4 inhibitors was associated with a statistically significant reduction in the numbers of participants experiencing one or more COPD exacerbations. This is a relative reduction of more than 20% (OR 0.78, 95% CI 0.73 to 0.83) (Analysis 1.16), from a representative risk of 33 per 100 on placebo to 28 per hundred on PDE_4 inhibitors over 12 to 52 weeks (Figure 1 and Summary of findings for the main comparison). There was little heterogeneity among trials (Chi^2 = 23, df = 22, P = 0.38, I^2 = 6%). Similar efficacy was seen for both roflumilast and cilomilast and where use of concomitant long-acting bronchodilators was permitted (Analysis 1.17).

In terms of exacerbation rate and the number of exacerbations experienced on average per participant per year (Analysis 1.18), we observed a small significant benefit with treatment, representing a 12% reduction in the rate ratio (rate ratio 0.88, 95% CI 0.83 to 0.93).

The Roflumilast FK1 101 trial reported that the probability of experiencing an exacerbation was reduced by 8% with 250 μg of roflumilast and 48% with 500 μg, although the absolute value was not reported, nor whether this was statistically significant.

Symptoms and exercise tolerance

Overall, the mean difference in change from baseline with PDE_4 inhibitor treatment compared with controls on COPD-related symptoms was small, regardless of the scale used to measure it. The only statistically significant effect was seen in one trial of cilomilast, for breathlessness scored using a Borg scale (MD -0.19, 95% CI -0.33 to -0.05) (Analysis 1.19). This is a small absolute difference so is of doubtful clinical relevance.

Exercise tolerance using the six-minute walk test was measured in four cilomilast trials. There was no significant difference in walk test distance between treatment and controls (MD 2.09 m, 95% CI -7.39 to 11.57) (Analysis 1.22).

Adverse events

The likelihood of a participant experiencing an adverse event was higher with PDE_4 inhibitor treatment than with placebo (OR 1.29, 95% CI 1.22 to 1.37) (Analysis 1.23). This effect was seen for both roflumilast and cilomilast.

We noted a range of adverse effects that occurred more frequently in PDE_4 inhibitor-treated participants. Diarrhoea was more common in PDE_4 inhibitor-treated groups than in controls (OR 3.13, 95% CI 2.76 to 3.54) (Analysis 1.25 and Figure 2), as was nausea (OR 3.78, 95% CI 3.23 to 4.43) (Analysis 1.26), headache (OR 1.69, 95% CI 1.47 to 1.95) (Analysis 1.27), vomiting (OR 4.01, 95% CI 2.80 to 5.74) (Analysis 1.28), dyspepsia (OR 3.17, 95% CI 2.33 to 4.30) (Analysis 1.29) and abdominal pain (OR 2.04, (95% CI 1.63 to 2.55) (Analysis 1.30). More than 10% of participants in the treatment group experienced gastrointestinal-related side effects, with the most frequently reported symptom being diarrhoea Figure 2 (number needed to treat for an additional harmful outcome (NNTH): 15, 95% CI 13 to 17). Weight loss was more likely in the treatment groups in the 10 roflumilast trials (OR 3.76, 95% CI 3.11 to 4.54) (Analysis 1.31), but was not reported in the cilomilast trials. There were no significant differences in the incidence of either influenza-like symptoms (Analysis 1.32) or upper respiratory tract infections (Analysis 1.33) between treatment and control groups.

The higher dose of roflumilast (500 μg) was associated with more adverse effects than the 250 μg dose; however, this was based on only four trials and confidence intervals were wide (OR 1.21, 95% CI 1.01 to 1.46) (Analysis 1.24). In the trial of Compton 2001 that studied the effects of varying doses of cilomilast, adverse effects were seen in 52% of the placebo group, 48% of the cilomilast 5 mg group, 47% of the 10 mg group and 61% of the 15 mg group, with rates of serious adverse events similar across the groups.

An increase in withdrawals attributed to adverse effects was recorded for both roflumilast and cilomilast treatment groups (OR 1.90, 95% CI 1.74 to 2.09) (Analysis 1.34). There was, however, no significant effect of treatment on non-fatal serious adverse events (OR 0.99, 95% CI 0.91 to 1.07) (Analysis 1.35) or mortality (OR 0.97, 95% CI 0.76 to 1.23) (Analysis 1.36), although mortality was a relatively rare event during the trials.

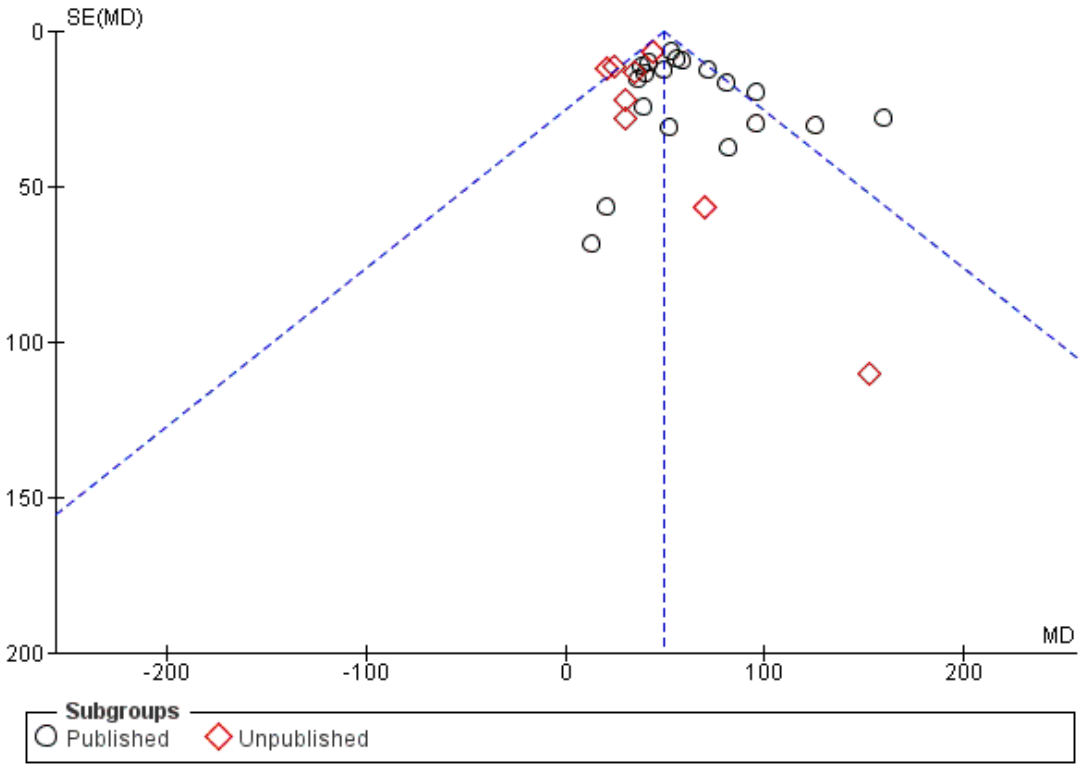
We recorded the number of psychiatric adverse events from pooled data from all parallel-design, double-blind studies investigating roflumilast collated and presented to the FDA. This included data from the 15 fully published trials, but excluded Roflumilast JP-706, which was conducted by a different study collaborator. These results reported symptoms of depression separately from depressed mood, depressive symptoms or major depression. There was a higher risk in the roflumilast 500 μg treatment group, compared with placebo, of experiencing a psychiatric-related adverse event (OR 2.13, 95% CI 1.79 to 2.54) (Analysis 1.37). This was reported in three people out of 100 in the placebo group, compared to seven (95% CI 6 to 8) out of 100 for the PDE_4 inhibitor-treated group (NNTH 28, 95% CI 21 to 39). Based on outcomes reported in more recent roflumilast trials the numbers of participants experiencing insomnia or sleep disorders (OR 1.48, 95% CI 0.81 to 2.70) (Analysis 1.38), symptoms of anxiety (OR 1.81, 95% CI 1.26 to 2.62) (Analysis 1.39) or depression (OR 1.59, 95% CI 1.11 to 2.27) (Analysis 1.40) were higher in the roflumilast group compared with the placebo. There was no statistically significant difference in the rate of psychiatric adverse events in the roflumilast 250 μg treatment group compared with placebo as in each of the analyses, the 95% confidence intervals crossed the midline.

In the roflumilast COPD safety database (n = 12,054 participants), there were three reports of completed suicides and two suicide attempts in roflumilast-treated participants compared to none in participants treated with placebo.

Subgroup and sensitivity analyses

A moderate but significant level of heterogeneity existed for the change in FEV_1 outcome when all trials were pooled (I^2 = 48%). Using a random-effects model made no difference to the levels of statistical significance or degree of heterogeneity for the change in FEV_1 (Analysis 1.7). There were too many 'Risk of bias' domains judged to be at 'unclear' risk of bias to do subgroup analysis according to study quality. Of note, some effect sizes were greater in the published trials; for example, the treatment effect on FEV_1 was MD 55.75 mL (95% CI 49.44 to 62.06) in the 19 published trials, and MD 34.82 (95% CI 25.44 to 44.19) in the eight unpublished trials (Analysis 1.6), which was a statistically significant difference (test for subgroup differences: Chi^2 = 13.18, df = 1 (P = 0.0003)). This is illustrated in the funnel plot with more unpublished studies showing a smaller treatment effect (Figure 5).

Figure 5. Funnel plot of comparison: 1 PDE4 inhibitor versus placebo, outcome: 1.6 FEV1 (published versus unpublished).



By visual analysis of the forest plot and sequential elimination, the six-week Compton 2001 cilomilast trial was identified as a major contributor towards the heterogeneity of pooled FEV_1 results. When it was removed, the overall I^2 statistic decreased from 48% to 31% and in the cilomilast subgroup from 62% to 0%. It is

notable that this study had the shortest treatment duration of six weeks and showed the largest improvement in FEV_1 lung function from baseline in the treatment group across all studies.

To see whether the size of the treatment effect varied with COPD severity, we conducted subgroup analyses of trials where the mean per cent predicted FEV_1 at baseline was available (Analysis 1.2). The effects seen in both old GOLD grades I or II (FEV_1 50% or more) predicted and old GOLD grades III or IV (FEV_1 less than 50%) were both statistically significant, and of similar magnitude, test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.86).

Similarly, there was a difference in the effect size of the total SGRQ score between published and unpublished trials (MD -1.98, 95% CI -3.07 to -0.89 versus MD -0.43, 95% CI -1.26 to 0.40, test for subgroup differences: $Chi^2 = 4.94$, df = 1 (P = 0.03)) (Analysis 1.12). Subgroup analysis showed COPD severity had no bearing on the size of the change in quality-of-life score test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.89) (Analysis 1.14).

For both primary outcomes, that is, FEV_1 and SGRQ score, the size of the treatment effect, that is, the mean difference between PDE_4 and placebo groups, was significantly greater in short studies of 6 to 12 weeks, compared with 24- and 52-week studies (Analysis 1.4; Analysis 1.13).

DISCUSSION

Summary of main results

This systematic review evaluated randomised controlled trials (RCTs) that assessed the efficacy and safety of oral phosphodiesterase 4 (PDE_4) inhibitors in people with chronic obstructive pulmonary disease (COPD). The first major finding, based on data from 34 trials, was that both roflumilast and cilomilast led to significantly greater improvements in lung function from baseline, as measured by forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) or peak expiratory flow rate (PEF), than placebo. Furthermore, the improvement in lung function was seen regardless of the severity of the disease. This improvement in FEV_1 lung function occurred whether or not treatment was given in addition to other COPD treatments, such as long-acting beta-2 agonists or anticholinergics, compared to treatment alone or with inhaled corticosteroids (ICS).

The mean change in FEV_1 was, however, below what is usually considered a minimum clinically important difference (100 mL, Donohue 2005), but comparable to those seen with other COPD treatments in recent large RCTs. For example, the mean improvement in FEV_1 of 49 mL with treatment seen in moderate to severe COPD in this review is of similar magnitude to that seen with fluticasone (47 mL), salmeterol (42 mL), and fluticasone and salmeterol combined (92 mL) in the TORCH 2007 study in people with severe COPD.

A second major finding, based on data from 23 trials, was that participants were more likely to be exacerbation-free while being treated with PDE_4 inhibitors compared with controls. Overall, participants were 22% less likely to have an exacerbation, translating to a number needed to treat for an additional beneficial outcome (NNTB) of around 20 (95% CI 16 to 26), for one person to be exacerbation-free in the study period Figure 1. While the likelihood of an individual experiencing an exacerbation was lowered with PDE_4 inhibitor treatment, the decrease in the overall rate of exacerbations was less marked, with a relative reduction of 13%.

Taken together, these two major findings suggest that PDE_4 inhibitors in people with COPD are acting independently of other treatments, particularly bronchodilators. This is an encouraging finding that could be consistent with a broad anti-inflammatory effect (Fabbri 2009). On the other hand, short-duration studies showed more favourable results than the longer studies, but the reasons for this are unclear. Significant heterogeneity was noted among the trials, suggesting that unmeasured differences between the trials may be having an impact.

A third major finding of the review was that, despite significant improvements in lung function and a reduction in exacerbations in participants treated with PDE_4 inhibitors, there was only a small improvement in quality of life as assessed by the St George's Respiratory Questionnaire (SGRQ) total score. Quality of life had been chosen as a primary outcome because of concerns as to whether or not the adverse effects of PDE_4 inhibitors might outweigh any beneficial COPD-related effects. The average change in SGRQ total score was 1.06 units (over a duration of between six and 12 months), and was of similar magnitude among trials of participants with milder or more severe COPD. Although this improvement was statistically significant, a change of greater than four units is usually regarded as the minimum clinically important difference (Jones 2005). While symptom scores were marginally better in the treatment groups, there was no change seen in exercise tolerance, suggesting that improvements in respiratory symptoms may not necessarily translate into enhancement of physical functioning. There were, though, fewer trials assessable for these outcomes, raising the possibility of type 1 or type 2 errors.

This review found that adverse effects were greater in the roflumilast and cilomilast-treated participants than in those receiving placebo, particularly gastrointestinal-related effects such as diarrhoea, nausea, vomiting and dyspepsia. More recently, there has been greater awareness of the risk of psychiatric adverse events associated with roflumilast treatment, in particular the increased likelihood of experiencing sleep disturbances, anxiety and depressed mood. Participants in the treatment groups were also more likely to withdraw from the trials because of adverse effects; on average 14% in the treatment groups withdrew compared with 8% in the control groups. Similarly, there is a slight excess in the total number of participants in the treatment groups experiencing any adverse effect, compared with controls (Analysis 1.23). As this analysis included symptoms as well as exacerbations, which were

reduced in the treatment groups, this analysis will tend to underestimate the excess of non COPD-related adverse effects occurring with PDE_4 inhibitor treatment.

It was notable that treatment with roflumilast was associated with a significant chance of weight loss. Whether this was due to anorexia from gastrointestinal adverse effects, or another effect, is not yet clear. Also not clear is whether cilomilast has the same effect, as it has not been studied. Weight loss may be a beneficial effect in people with COPD who are obese. In contrast, low body mass in the later stages of COPD is associated with a worse prognosis and is notoriously difficult to reverse (GOLD 2017). This adverse effect warrants further investigation. Reassuringly, there was no increase in serious adverse effects or mortality, although trials were of relatively short duration, and analyses were underpowered to report on the latter outcome.

While a lower dose (250 μg) of roflumilast produced similar improvements in FEV_1 (Analysis 1.8) and was associated with slightly fewer adverse effects (Analysis 1.24) than the larger dose, this was associated with a smaller reduction in rate of exacerbations than the 500 μg dose, in the one trial that reported this (Roflumilast FK1 101). Moreover, data on the lower dose were only available in a limited number of studies and it has not been studied as add-on therapy to other bronchodilators.

Overall completeness and applicability of evidence

We have reviewed all known published and unpublished trials identified from standard Cochrane searches, as well as from the trials register for the NIH and from pharmaceutical websites.

We have not been able to verify the pooled endpoint data for psychiatric- (treatment possibly harmful) and cardiovascular-related adverse events (treatment possibly beneficial) as they were obtained from reports on the US Food and Drug Administration (FDA) website and from White 2013, respectively.

To ensure our Cochrane systematic review accurately reflects all known outcomes of roflumilast therapy, for the previous update we approached the manufacturer of roflumilast for study-level data on each of the cardiovascular outcomes (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) as well as the composite outcome, major adverse cardiovascular events (MACE). This would have allowed us to perform comparisons both within (i.e. between roflumilast and placebo groups) and among the studies. Unfortunately, our request for individual trial data was refused with the following reasons being cited:

- it is inappropriate from a statistical perspective to look into individual trials with too small a sample size for this kind of relatively rare endpoint;
- it was part of the retrospective analyses to evaluate the whole data set with a sufficiently broad database and not to go into subcuts per study that would comprise studies with numbers in each treatment arm that were too low for conclusive interpretation;
- in none of the studies was the blinded adjudication of the events implemented as a prospective analysis, which would have required a data release in terms of transparency in each individual study (which is the reason why it was not mentioned in the original publications of the individual trials).

In response to the statement by representatives of Takeda Pharmaceuticals Limited, we have urged that these issues be reconsidered for future studies and that study data be made more widely available. Finally, caution must be used when interpreting associations between COPD exacerbations and MACE, because although the treatment groups were matched at baseline, it cannot be assumed that these groups are equivalent when looking only at the group of participants who experienced exacerbations. These concerns could not be assessed in this review as further study data were not provided.

Quality of the evidence

For the key outcomes of changes in lung function and quality of life, there were greater beneficial effects of PDE_4 inhibitors reported in the published studies than in the unpublished studies, raising concerns about publication bias. There was a moderate level of heterogeneity identified in both of the primary outcomes for this review, which is not fully explained by subgroup or sensitivity analyses according to study duration or concomitant medication use. This suggests unknown factors that may impact on the effect size, and has led us to downgrade the quality of the evidence and certainty of our findings (Summary of findings for the main comparison). In contrast, the blinded design of the studies comparing roflumilast or cilomilast with placebo protected against detection bias in our view. The quality of evidence for a reduction in exacerbation was therefore higher for this comparison. On balance, we believe the true beneficial effect of PDE_4 inhibitors is likely to be no greater than we have reported, and probably less; equally the harms may have been understated (partly due to higher withdrawal rates in active treatment arms). On the other hand, as subgroup analyses for COPD severity are based on the mean predicted lung function for the study group and not individual participants, we cannot rule out that there is a benefit for individuals of a specific COPD phenotype.

Potential biases in the review process

Potential biases in the review process were minimised by double-checking of data extraction and input. The authors have no conflicts of interest to declare and have not been involved in prescribing these medicines as neither roflumilast nor cilomilast are available on the New Zealand pharmaceutical schedule.

Agreements and disagreements with other studies or reviews

There have been several other meta analyses conducted, such as Oba 2013; Yan 2014 and Luo 2016. Each of these had fewer studies than the present review, but had findings and conclusions that were similar.

In a post hoc pooled analysis (n =5595) of four trials in this review (Rennard 2014), roflumilast significantly improved transition dyspnoea index (TDI) focal scores of breathlessness versus placebo at week 52 (treatment difference, 0.327; P < 0.0001). Roflumilast was associated with significantly greater TDI responders and significantly fewer TDI deteriorators (≥ 1-unit increase or decrease from baseline, respectively) versus placebo at week 52 (P < 0.01, both). Rates of MACE in COPD participants treated with PDE_4 inhibitors have been meta-analysed and reported in a paper published by White 2013. This found that the risk of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, when combined into a composite outcome (MACE), was reduced in the roflumilast group compared with placebo (hazard ratio 0.65, 95% CI 0.45 to 0.93; P = 0.019). On the other hand, hazard ratios for treatment effects for each of these types of event individually were statistically different. Cardiovascular events were higher in participants with baseline cardiovascular risk factors than in those without baseline cardiovascular risk (defined as the presence of hypertension, diabetes mellitus, hyperlipidaemia and/or a history of heart disease). In addition, it was found that the difference between treatment and placebo was only statistically significant in the group of participants without baseline risk factors. Event rates in a subgroup of trials that were one year in duration found no significant difference between treatment and placebo groups in the proportion of participants who reported a MACE, even when divided into those who did, or did not experience a COPD exacerbation. Similarly, between participants with and without MACE events, the proportions of participants experiencing exacerbations was similar (43.2% and 42.1%, respectively).

AUTHORS' CONCLUSIONS

Implications for practice

Phosphodiesterase 4 inhibitors (PDE_4) are oral medicines that may be taken in combination with other standard chronic obstructive pulmonary disease (COPD) treatments. Most evidence exists for roflumilast at a dose of 500 μg daily and cilomilast at 15 mg twice daily.

Phosphodiesterase 4 inhibitors join an increasing list of treatments for COPD that improve short-term lung function and reduce exacerbations, but have not been shown to increase life expectancy. Trials to date have been one year or less in duration. In contrast to long-acting bronchodilators, PDE_4 inhibitors have minimal benefits on symptoms on a day-to-day basis, or quality of life, and are often associated with adverse effects, especially of the gastrointestinal system, and headaches. Roflumilast is associated with significant weight loss and more psychiatric symptoms than placebo treatment. Thus, the findings of this review support the use of PDE_4 inhibitors: however, their use may best be limited to add-on therapy in a subgroup of people with persistent symptoms or exacerbations despite optimal COPD management, providing they are well-tolerated.

Implications for research

This review has highlighted several possible areas for further study:

- longer-duration studies to look at the effect of PDE_4 inhibitors on forced expiratory volume in one second ($FEV_{1)}$ decline and mortality;
- subgroup analysis in participants with/without chronic bronchitis and with/without history of exacerbations;
- effect of PDE_4 inhibitors in participants with frequent exacerbations;
- effect of PDE_4 inhibitors on healthcare utilisation, including hospitalisation (incidence and bed days);
- a direct comparison of PDE_4 inhibitors and inhaled corticosteroids (ICS), when used as add-on therapies to either tiotropium or long-acting beta-2 agonists, or both;
- a direct comparison of either tiotropium or long-acting beta-2 agonists, or both, as add-on therapies to PDE_4 inhibitors (+/- ICS);
- effect of roflumilast on quality of life;
- better characterisation of the weight loss seen with PDE_4 inhibitors in COPD;
- better description of the nature of the effect on the exacerbations that do occur;
- use of PDE_4 inhibitors in acute exacerbations;
- cost-effectiveness of PDE_4 inhibitors;
- ascertaining more exercise-tolerance data for roflumilast;
- determining if there is any benefit on cardiovascular outcomes with PDE_4 inhibitors in COPD;
- using the effects of PDE_4 inhibitors to better understand the pathophysiology of COPD.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cilomilast 039

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 102 centres in Canada, Mexico and the USA Participants: 647 (15 mg cilomilast: 431, placebo: 216) Baseline characteristics: mean age: 65 years, 62% male, mean FEV_1% predicted of 49.7%, mean smoking history of 59.9 pack-years for cilomilast and 56.1 pack-years for placebo, or current smokers (44% and 47%, respectively) Inclusion criteria: $FEV_1/FVC \leq 0.7$, FEV_1 30% -70% with smoking history > 10 pack-years or current smokers Exclusion criteria: active tuberculosis, lung cancer and bronchiectasis Total number of participant withdrawals: 137 (32%) and 52 (24%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks, single-blind. Placebo tablets to assess suitability Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: "The only other permitted medications for the treatment of airways disease were stable doses of Ipratropium, via a metered-dose inhaler, and mucolytic agents." • Short-acting $\beta 2$ agonist: "...the short-acting ß$_2$-agonist Albuterol, which was administered via a metered- dose inhaler, was supplied for the relief of acute respiratory symptoms." • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: none
Outcomes	**Primary outcomes**: lung function; change in FEV_1, SGRQ averaged over 24 weeks **Secondary outcomes**: incidence rate of COPD exacerbations, adverse events, FVC at the trough, 6-MWT, post-exercise dyspnoea
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available

Cilomilast 039 (*Continued*)

Randomised?	Low risk	"Eligible subjects were randomised in a 2:1 ratio to receive oral cilomilast, 15 mg bid, or placebo for 24 weeks."
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	"The primary reasons for the withdrawal of subjects from the study prior to randomisation were the failure to meet inclusion/exclusion criteria (15.4%) and the presence of adverse effects, including COPD exacerbations (8.5%). More subjects receiving cilomilast than placebo withdrew from the double-blind phase of study (31.8% (n = 137) versus 24.1% (n = 52)."
Baseline profile: anticholingeric use	Low risk	54% in cilomilast; 58% placebo used ipratropium
Baseline profile: $\beta 2$ agonist use	Low risk	99% in cilomilast; 100% placebo used albuterol. 9% in cilomilast; 12% placebo used salmeterol
Baseline profile: corticosteroid use	Low risk	7% in cilomilast; 8% placebo used triamcinolone. 6% in cilomilast; 7% placebo used beclomethasone

Cilomilast 042

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 98 centres in Australia and New Zealand, Germany, Spain, South Africa and the UK Participants: 700 (15 mg cilomilast: 474, placebo: 226) Baseline characteristics: mean age: 64.6 years, 80% male, mean FEV_1% predicted of 49% with 5.1% reversibility, DLCO was 71% predicted, also with higher rates of chronic bronchitis 80.1%. 45% active smokers Inclusion criteria: aged 40-80 years, $FEV_1/FVC \leq 0.7$, FEV_1 30%-70% with smoking history > 10 pack-years Exclusion criteria: active tuberculosis, lung cancer and bronchiectasis Total number of participant withdrawals: 122 (26%) and 51 (23%) from treatment and

Cilomilast 042 (*Continued*)

	control groups, respectively
Interventions	Run-in: 4 weeks, single-blind with placebo Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: 2% in cilomilast; 3% placebo used salbutamol. 3% in cilomilast; 1% placebo used ipratropium • Short-acting β2 agonist: "Albuterol MDI was used as rescue medication" • Corticosteroid: none • Long-acting β2 bronchodilator: none
Outcomes	**Primary outcomes**: lung function; change in FEV_1, SGRQ averaged over 24 weeks **Secondary outcomes**: incidence rate of COPD exacerbations, summary symptom score, FVC at the trough, 6-MWT, post-exercise dyspnoea
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised in a 2:1 ratio to receive oral cilomilast, 15 mg twice daily, or placebo for 24 weeks
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 51 (23%) placebo, 122 (26%) cilomilast, primarily due to adverse events, of which most were not from COPD exacerbations
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 076

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Analysis was done per-protocol population
Participants	Setting: not stated Participants: 59 (15 mg cilomilast: 29, placebo: 30) Baseline characteristics: mean age: 61-62 years, 81% male, 53% active smokers, mean 46 pack-years, 53%-58% FEV_1 predicted Inclusion criteria: aged 40-80 years, fixed airflow obstruction, smoking history > 10 pack-years Exclusion criteria: not stated Total number of participant withdrawals: 4 (14%) and 2 (7%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks, single-blind with placebo Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: "14 of 59 used ipratropium bromide at a constant dosage (eight in the placebo group, six in the cilomilast group)." • Short-acting $\beta 2$ agonist: "All patients were given albuterol for use as required" • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: none Used alongside short-acting ß2 agonists (available to all) and anticholingeric drugs (offered to 24%)
Outcomes	**Primary outcomes**: change in neutrophil percentage in induced sputum **Secondary outcomes**: FEV_1, numbers of subepithelial CD8+ cells, CD 68+ cells, epithelial and subepithelial neutrophils
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Randomised to a ratio of 1:1
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated

Cilomilast 076 (*Continued*)

Description of withdrawals and drop-outs?	Low risk	"One patient was lost to follow-up 3 days after randomisation and another withdrawn for non-compliance 32 days after randomisation. Four patients were withdrawn after adverse events."
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 091

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 110 centres in Belgium, Finland, France, Italy, the Netherlands, Norway, Portugal, Spain and the UK Participants: 711 (15 mg cilomilast: 469, placebo: 242) Baseline characteristics: mean age: 64.6 years, 86% male, mean FEV_1 % predicted of 53% with 5.0% reversibility. 38% active smokers Inclusion criteria: $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years Exclusion criteria: active tuberculosis, lung cancer and bronchiectasis Total number of participant withdrawals: 121 (26%) and 63 (26%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks, single-blind with placebo Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: 0.9% in cilomilast; 4% placebo used salbutamol. 1% in cilomilast; 3% placebo used ipratropium • Short-acting β2 agonist: "Albuterol MDI was used as rescue medication" • Corticosteroid: none • Long-acting β2 bronchodilator: none
Outcomes	**Primary outcomes**: lung function; change in FEV_1, SGRQ averaged over 24 weeks **Secondary outcomes**: incidence rate of COPD exacerbations, summary symptom score, FVC at the trough, 6-MWT, post-exercise dyspnoea
Notes	

Risk of bias

Cilomilast 091 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	"Eligible patients were randomised to receive either SB 207499 or matching placebo ina ratio of 2:1 for 24 weeks."
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 63 (26%) placebo, 121 (26%) cilomilast, primarily due to adverse events, of which most were not from COPD exacerbations
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: $\beta 2$ agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 103657

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 103 centres in the USA Participants: 613 (15 mg cilomilast: 296, placebo: 317) Baseline characteristics: mean age: 63.2 years: placebo and 63.1 years; cilomilast. 47% male: placebo and 46% male: cilomilast. Mean FEV_1 % predicted not available Inclusion criteria: aged $\geq$ 40 years of age. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. $\leq$ 70%, post-albuterol reversibility $\leq$ 15% or $\leq$ 200 mL (or both), post-albuterol $FEV_1 \leq 70\%$ of predicted normal and at least 1 COPD exacerbation within the 12 months prior to screening Exclusion criteria: not stated Total number of participant withdrawals: 105 (35%) and 76 (24%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily

Cilomilast 103657 (*Continued*)

	Concomitant medication • Short-acting anticholingeric: no information available • Short-acting $\beta 2$ agonist: no information available • Corticosteroid: no information available • Long-acting $\beta 2$ bronchodilator: no information available
Outcomes	**Primary outcomes**: change from baseline to endpoint in trough pre-bronchodilator FEV_1. Change in total score of SGRQ averaged over 24 weeks **Secondary outcomes**: changes from baseline in clinic trough FVC, time to first level 2 or level 3 COPD exacerbation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomised. No other information given
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 76 (24%) placebo, 105 (35%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: $\beta 2$ agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 110

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Analysis was done per-protocol population
Participants	Setting: 10 centres in the USA Participants: 65 (15 mg cilomilast: 31, placebo: 34) Baseline characteristics: mean age: 64.4 years: placebo and 66.1 years: cilomilast. 67%

Cilomilast 110 (*Continued*)

	male: placebo and 84% male: cilomilast. Mean FEV_1 % predicted not available Inclusion criteria: aged 40-80 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Post-salbutamol reversibility $\leq$ 15% or 200 mL and a post-salbutamol FEV_1 at least 1.0 L and between 30% and 70% of predicted Exclusion criteria: not stated Total number of participant withdrawals: 1 (3%) and 1 (3%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • Short-acting $\beta 2$ agonist: no information available • Corticosteroid: no information available • Long-acting $\beta 2$ bronchodilator: no information available
Outcomes	**Primary outcomes**: change from baseline at endpoint in neutrophils as a percentage of total cells in induced sputum **Secondary outcomes**: FVC at the trough, sputum macrophages, eosinophils and lymphocytes as a percentage of total cells in induced sputum. Total cell counts in induced sputum
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	All participants were randomised to receive either cilomilast 15 mg or matching placebo
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 1 (3%) placebo, 1 (3%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: $\beta 2$ agonist use	Unclear risk	No information available

Cilomilast 110 (*Continued*)

Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 111

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: stated
Participants	Setting: 32 centres in the USA, Canada and Australia Participants: 156 (15 mg cilomilast: 79, placebo: 77) Baseline characteristics: mean age: 64.2 years: placebo and 65 years; cilomilast. 66% male: placebo and 65% male: cilomilast. Mean FEV_1 % predicted not available Inclusion criteria: aged 40-80 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Post-salbutamol reversibility $\leq$ 15% or 200 mL and a post-salbutamol FEV_1 at least 1.0 L and between 30% and 70% of predicted. Baseline RV (from plethysmography) $\geq$ 120% of predicted RV Exclusion criteria: not stated Total number of participant withdrawals: 15 (19%) and 14 (18%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • Short-acting $\beta 2$ agonist: no information available • Corticosteroid: no information available • Long-acting $\beta 2$ bronchodilator: no information available
Outcomes	**Primary outcomes**: change from baseline to endpoint in volume of trapped gas (D) **Secondary outcomes**: lung volume measurements, including SVC and RV, 6-MWT and exertional dyspnoea
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo
Method of randomisation described?	Unclear risk	Not stated

Cilomilast 111 (*Continued*)

Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 14 (18%) placebo, 15 (19%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 121

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 22 centres in China Participants: 1018 (15 mg cilomilast: 678, placebo: 340) Baseline characteristics: mean age: 63.9 years: placebo and 64.6 years; cilomilast. 91% male: placebo and 93% male: cilomilast. Mean FEV_1 % predicted not available Inclusion criteria: aged 40-75 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Documented history of COPD exacerbations each year for 3 years prior to screening. At least 1 exacerbation in the last year that required oral corticosteroids or antibiotics. Post-salbutamol reversibility $\leq$ 15% or 200 mL and a post-salbutamol FEV_1 at least 1.0 L and between 25% and 70% of predicted. % predicted FRC of $\geq$ 120% from plethysmography Exclusion criteria: not stated Total number of participant withdrawals: 124 (18%) and 35 (10%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • Short-acting β2 agonist: no information available • Corticosteroid: no information available • Long-acting β2 bronchodilator: no information available
Outcomes	**Primary outcomes**: change from baseline to endpoint in trough pre-bronchodilator FEV_1 **Secondary outcomes**: time to first level 2 or level 3 COPD exacerbation. Level 2 is defined as acute worsening of COPD that requires additional treatment or hospital

Cilomilast 121 (*Continued*)

	outpatient visit. Level 3 is hospital admission for treatment. Change from baseline to endpoint RV and FRC. Change from baseline total score of SGRQ
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to a 2:1 ratio for cilomilast 15 mg to placebo
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 35 (10%) placebo, 124 (18%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: $\beta 2$ agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 156

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 132 centres in USA and Canada Participants: 825 (15 mg cilomilast: 418, placebo: 407) Baseline characteristics: mean age: 64.4 years: placebo and 64.5 years; cilomilast. 62% male: placebo and 56% male: cilomilast > 50% predicted FEV_1 for both groups Inclusion criteria: aged 40-80 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Post-salbutamol reversibility $\leq$ 15% or 200 mL and a post-salbutamol FEV_1 at least 1.0 L and between 30% and 70% of predicted Exclusion criteria: not stated Total number of participant withdrawals: 143 (34%) and 96 (24%) from treatment and control groups, respectively

Cilomilast 156 (*Continued*)

Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: 8.1% in cilomilast; 8.6% placebo used salbutamol. 1.7% in cilomilast; 2% placebo used ipratropium bromide • Short-acting β2 agonist: "Albuterol MDI was used as rescue medication" • Corticosteroid: none • Long-acting β2 bronchodilator: none
Outcomes	**Primary outcomes**: change from baseline to endpoint in trough pre-bronchodilator FEV_1. Change in total score of SGRQ averaged over 24 weeks **Secondary outcomes**: post-exercise breathlessness, clinic trough FVC, time to first level 2 or level 3 COPD exacerbation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 96 (24%) placebo, 143 (34%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 157

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: 137 centres from 18 countries Participants: 907 (15 mg cilomilast: 455, placebo: 452) Baseline characteristics: mean age: 63.3 years: placebo and 64.6 years; cilomilast. 73% male: placebo and 78% male: cilomilast. 42% current smokers Inclusion criteria: aged 40-80 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Poor reversibility of airway obstruction, defined by $\leq$ 10% of predicted normal or $\leq$ 200 mL (or both) increase in FEV_1 after administration of salbutamol 400 µg via MDI at screening; post-salbutamol FEV_1 of between 30%-70% predicted normal at screening Exclusion criteria: not stated Total number of participant withdrawals: 167 (37%) and 121 (27%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • Short-acting $\beta 2$ agonist: no information available • Corticosteroid: no information available • Long-acting $\beta 2$ bronchodilator: no information available
Outcomes	**Primary outcomes**: mean change from baseline in trough pre-bronchodilator FEV_1 averaged over 52 weeks. Incidence rate of level 2 (moderate) and level 3 (severe) COPD exacerbations during the treatment period **Secondary outcomes**: time to first level 2 or level 3 COPD exacerbation. Quality of life determined by SGRQ
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	A randomisation criteria was used. No other information available

Cilomilast 157 (*Continued*)

Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 121 (27%) placebo, 167 (37%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 168

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: not stated
Participants	Setting: 42 centres in the USA Participants: 306 (15 mg cilomilast: 203, placebo: 103) Baseline characteristics: mean age: 64.3 years: placebo and 65.0 years; cilomilast. 64% male: placebo and 70% male: cilomilast Inclusion criteria: pre-albuterol $FEV_1/FVC \leq 0.7$. Post-albuterol FEV_1 between 30% and 70% of predicted Exclusion criteria: not stated Total number of participant withdrawals: 61 (30%) and 14 (14%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • Short-acting β2 agonist: no information available • Corticosteroid: no information available • Long-acting β2 bronchodilator: no information available
Outcomes	**Primary outcomes**: no primary efficacy or safety analyses were defined. Descriptive statistics of change from baseline in minimum and maximum heart rate via 24-h Holter monitoring reported **Secondary outcomes**: no secondary efficacy or safety analyses were defined
Notes	

Risk of bias

Cilomilast 168 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised at 2:1 ratio of cilomilast to placebo
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 14 (14%) placebo, 61 (30%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No other information available
Baseline profile: $\beta 2$ agonist use	Unclear risk	No other information available
Baseline profile: corticosteroid use	Unclear risk	No other information available

Cilomilast 180

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 18 weeks Intention-to-treat analysis: stated
Participants	Setting: 34 centres in the USA, Canada and South America 2) Participants: 199 (15 mg cilomilast: 97, placebo: 102) Baseline characteristics: mean age: 64.7 years: placebo and 63.7 years; cilomilast. 76% male: placebo and 69% male: cilomilast Inclusion criteria: age at least 40 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Baseline FEV_1 < 70% predicted normal. Moderate to severe chronic dyspnoea defined by baseline Dyspnoea Index focal score ≤ 7, evidence of hyperinflation defined by RFRC at least 140% of predicted. Exercise limitation, defined as peak symptom limited VO_2 < 75% Exclusion criteria: not stated Total number of participant withdrawals: 24 (25%) and 13 (13%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available

Cilomilast 180 (*Continued*)

	• Short-acting β2 agonist: no information available • Corticosteroid: no information available • Long-acting β2 bronchodilator: no information available
Outcomes	**Primary outcomes**: change from baseline at endpoint in RFRC **Secondary outcomes**: change from baseline at endpoint in IC during exercise, exertional dyspnoea as measured by the modified Borg scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 13 (13%) placebo, 24 (25%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 181

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 13 weeks Analysis was done per-protocol population
Participants	Setting: 27 centres in Australia, Canada, Finland, Ireland, Lithuania, Norway, Romania, Slovakia, Slovenia, South Africa, Sweden and the UK Participants: 127 (15 mg cilomilast: 65, placebo: 62) Baseline characteristics: mean age: 63.4 years: placebo and 61.4 years; cilomilast. 76% male: placebo and 72% male: cilomilast

Cilomilast 181 (*Continued*)

	Inclusion criteria: aged 40-80 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Post-bronchodilator FEV_1 between 40% and 80% predicted normal. Poor reversibility of ≤ 10% or 200 mL increase in FEV_1 Exclusion criteria: not stated Total number of participant withdrawals: 8 (12%) and 6 (10%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • Short-acting $\beta 2$ agonist: no information available • Corticosteroid: no information available • Long-acting $\beta 2$ bronchodilator: no information available
Outcomes	**Primary outcome**: change from baseline at endpoint in CD68+ (macrophages) and CD8+ (cytotoxic T-lymphocytes) per unit area of tissue **Secondary outcome**: change from baseline in numbers of sub-epithelial cells per unit area in biopsy for neutrophil elastase positive (ne+) cells, CD4+, IL-8 mRNA positive cells, TNF-alpha mRNA positive cells
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinding
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 6 (10%) placebo, 8 (12%) cilomilast
Baseline profile: anticholingeric use	Unclear risk	No other information available
Baseline profile: $\beta 2$ agonist use	Unclear risk	No other information available

Cilomilast 181 (*Continued*)

Baseline profile: corticosteroid use	Unclear risk	No other information available

Compton 2001

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 6 weeks Intention-to-treat analysis: stated
Participants	Setting: 60 centres in Austria, France, Germany, the Netherlands and the UK Participants: 424 (5 mg cilomilast: 109, 10 mg cilomilast: 102, 15 mg cilomilast: 107, placebo: 106) Baseline characteristics: mean age: 62-63 years, 75%-78% male, mean FEV_1% predicted of 46.8%, mean smoking history of 36-43 (SD 22.4) pack-years Inclusion criteria: $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years Exclusion criteria: asthma, poorly controlled COPD needing hospital visit 6 weeks before study, recent COPD exacerbations or recent corticosteroid use Total number of participant withdrawals: 18 (17%) and 17 (16%) from treatment and control groups, respectively
Interventions	Run-in: 2 weeks, single-blind. Placebo tablets to assess compliance Cilomilast 5 mg, 10 mg, 15 mg twice daily Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: 382 (90%) participants were given concomitant treatment for COPD during the study; 267 (70%) salbutamol and 115 (30%) ipratropium bromide • Short-acting $\beta 2$ agonist: salbutamol used in 70% • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: none
Outcomes	**Primary outcomes**: lung function: change in FEV1, SGRQ **Secondary outcomes**: peak expiratory flow and FVC, the first dose effect of active treatment on FEV_1
Notes	Post-bronchodilator results not given so pre-bronchodilator values used in analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	"Eligible patients were randomly assigned to receive a 5, 10, or 15 mg tablet of cilomilast twice daily (morning and evening) or

Compton 2001 (*Continued*)

		matching placebo for 6 weeks."
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	"14 patients (13%) taking cilomilast 15 mg had adverse events leading to patient withdrawal, as did 12 each in the 5 and 10 mg groups (11 and 12%, respectively) and eight (8%) in the placebo group."
Baseline profile: anticholingeric use	Unclear risk	Information not available
Baseline profile: $\beta 2$ agonist use	Low risk	102 (24%) participants had been taking long-acting ß$_2$- agonists; e.g. salmeterol, formoterol
Baseline profile: corticosteroid use	Low risk	331 (78%) individuals had taken other medications for their COPD, the most common being inhaled steroids. 229 (54%) took beclomethasone, budesonide or fluticasone

COPD safety pool

Methods	14 double-blind and placebo-controlled studies (Roflumilast FK1 101; Roflumilast FK1 103; Roflumilast IN-108; Roflumilast M2-107; Roflumilast M2-110; Roflumilast M2-111; Roflumilast M2-112; Roflumilast M2-118; Roflumilast M2-119; Roflumilast M2-121; Roflumilast M2-124; Roflumilast M2-125; Roflumilast M2-127; Roflumilast M2-128)	
Participants	See individual studies	
Interventions	Roflumilast 500 µg once daily Roflumilast 250 µg once daily Placebo once daily	
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

COPD safety pool (*Continued*)

Allocation concealment (selection bias)	Unclear risk	See individual studies
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	See individual studies
Blinding?	Unclear risk	Double-blind
Method of blinding described?	Unclear risk	See individual studies
Description of withdrawals and drop-outs?	Unclear risk	See individuals studies
Baseline profile: anticholingeric use	Unclear risk	See individuals studies
Baseline profile: β2 agonist use	Unclear risk	See individuals studies
Baseline profile: corticosteroid use	Unclear risk	See individuals studies

RO-2455-301-RD (ACROSS)

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 43 centres in mainland China, Hong Kong and Singapore Participants: 626 (500 µg roflumilast: 313, placebo: 313) Baseline characteristics: mean age: 64 years, 91% male, mean FEV_1% predicted of 36%, mean smoking history of 37.2 pack-years for roflumilast and 37.5 pack-years for placebo) or current smokers (24% and 29%, respectively) Inclusion criteria: Chinese, Malay or Indian ethnicity, age 40-80 years with severe-very severe COPD $FEV_1/FVC \leq 0.7$, and post-bronchodilator $FEV_1 \leq 50\%$. Current smokers or ex-smokers with smoking history > 10 pack-years or current smokers. 12-month history of COPD and $\geq$ 14 puffs of rescue medication during the week prior to randomisation Exclusion criteria: primary bronchiectasis, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease, or active TB, lower respiratory tract infection, diagnosis of asthma at < 40 years of age, or a_1-antitrypsin deficiency Total number of participant withdrawals: 67 (21.4%) and 50 (16%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks, single-blind. Placebo tablets to assess suitability Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** Participants were allowed to continue taking fixed combinations of ICS plus LABA or LAMA monotherapy (e.g. tiotropium) if taken at a stable dose for at least 6 months prior to the run-in period. SAMAs (e.g., ipratropium) were allowed at a constant daily

	dose as concomitant medication if taken on a regular basis for at least 4 weeks prior to study inclusion. All other COPD treatments were not allowed
Outcomes	**Primary outcomes**: lung function; change in pre-bronchodilator FEV_1 **Secondary outcomes**: change in post-bronchodilator FEV_1, FVC, incidence rate of COPD exacerbations, time to first COPD exacerbation, transition dyspnoea index, proportional of participants experiencing a COPD exacerbation, adverse events, changes in body weight, laboratory values, vital signs and physical examination findings
Notes	NCT number: NCT01313494 Funded by Takeda

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling
Randomised?	Low risk	The investigators used an automated, interactive voice-response system to randomly assign participants
Method of randomisation described?	Low risk	The sponsor generated a list of participant numbers using a pseudorandom number generator
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	Tablets were identical in appearance.
Description of withdrawals and drop-outs?	Unclear risk	Total number of participants that discontinued 50 (16%) placebo, 67 (21.4%) roflumilast
Baseline profile: anticholingeric use	Low risk	LAMA: 17.9% for placebo; 20.4% for roflumilast SAMA: 18.2% for placebo; 17.3% for roflumilast
Baseline profile: $\beta 2$ agonist use	Unclear risk	No information available. SABA allowed
Baseline profile: corticosteroid use	Low risk	ICS/LABA: 55.9% for placebo; 59.7% for roflumilast

RO-2455-404-RD (REACT)

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: 203 centres in 21 countries (see online appendix) Participants: 1945 (500 µg roflumilast: 969; placebo: 966) Baseline characteristics: mean age: 65 years, 75% male, mean FEV_1% predicted of 35%, mean smoking history of 48 pack-years for roflumilast and 48 pack-years for placebo) or current smokers (42% and 45%, respectively) Inclusion criteria: ≥ 40 years with a smoking history of at least 20 pack-years and a diagnosis of chronic obstructive pulmonary disease with severe airflow limitation (confirmed by a post-bronchodilator FEV_1/FVC ratio < 0·70 and a post-bronchodilator FEV_1 of ≤ 50% predicted), symptoms of chronic bronchitis, and a history of at least two exacerbations in the previous year Participants must have been taking an ICS-LABA combination for 12 months before the study and a constant dose of an ICS-LABA fixed combination for at least 3 months before enrolment, with placebo tablet compliance of 80%-125% during the 4-week baseline observation period and with a total cough and sputum score of ≥ 14 (in which the score was a sum of daily scores on 4-point scales for cough and sputum) recorded in a daily diary during the week preceding the randomisation visit Exclusion criteria: chronic obstructive pulmonary disease exacerbation that was ongoing during the baseline period, or had a diagnosis of asthma or other major lung disease Total number of participant withdrawals: 269 (28%) and 192 (20%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks, single-blind. Placebo tablets to assess suitability Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** All participants used a fixed-dose ICS-LABA combination during the baseline and treatment period. If a participant had an exacerbation that needed additional treatment during the study, the investigator could give them up to 40 mg prednisolone, administered systemically, per day for 7-14 days. In the case of purulent sputum or suspected bacterial infection, additional antibiotic therapy was allowed The use of the following treatments was not allowed: oral and parenteral glucocorticosteroids (except to treat acute exacerbations), LABA or ICS mono therapy, SAMA, and any short-acting β2 agonists (with the exception of salbutamol) or oral β2 agonists Participants already taking inhaled tiotropium bromide (a LAMA) were allowed to continue this treatment
Outcomes	**Primary outcomes**: rate of moderate-to-severe chronic obstructive pulmonary disease exacerbations per patient per year. This was assessed in several ways: rate of exacerbations; % with exacerbation; time to first, second or third exacerbation; NNTB to avoid 1 moderate to severe exacerbation **Secondary outcomes**: change in post-bronchodilator FEV_1, rate of severe chronic obstructive pulmonary disease exacerbations per patient per year, laboratory values, vital signs, physical examination findings, changes in bodyweight and body-mass index, and reported adverse events, including mortality

RO-2455-404-RD (REACT) (*Continued*)

Notes	NCT number: NCT01329029 Sponsored by Takeda

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	All parties involved in the study were masked to treatment assignment
Randomised?	Low risk	Randomised
Method of randomisation described?	Low risk	Enrolled participants were randomly assigned in a 1:1 ratio, with a block size of 4, by a computerised central randomisation system, the Interactive Voice Response System-Interactive Web Response System (PPD Global Limited, Cambridge, UK)
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	Roflumilast and placebo were supplied as identical yellow triangular tablets in wallet cards containing 40 tablets
Description of withdrawals and drop-outs?	Unclear risk	269 participants (28%) discontinued from study in the roflumilast group and 192 (20%) discontinued from the placebo group
Baseline profile: anticholingeric use	Unclear risk	LAMA: 69% for placebo; 70% for roflumilast
Baseline profile: β2 agonist use	Unclear risk	No group differences stated; however 1900 (98%) of 1935 participants were using a combination of ICS-LABA according to the protocol
Baseline profile: corticosteroid use	Unclear risk	As above

Roflumilast DAL-MD-01

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: stated
Participants	Setting: single centre in USA Participants: 27 (500 µg roflumilast: 11, placebo: 16) Baseline characteristics: mean age: 62 years, 64% male, mean FEV_1% predicted of 45%, mean smoking history of 44 pack-years for roflumilast and 47 pack-years for placebo) or current smokers (63% and 55%, respectively) Inclusion criteria: > 40 years old with a diagnosis of moderate-to-severe COPD as defined by Global Initiative for Chronic Obstructive Lung Disease criteria, current or former cigarette smokers with more than 10 pack-years of total consumption, chronic bronchitis defined by chronic cough and sputum production lasting at least 3 months for 2 consecutive years Exclusion criteria: asthma as defined by the American Thoracic Society/European Respiratory Society guidelines, clinically significant bronchiectasis, known sensitivity to roflumilast, the use of other methylxanthines (specifically theophylline) within 1 month of screening, changes to maintenance COPD therapy within 1 month of screening Total number of participant withdrawals: 1 (9%) and 1 (6%) from treatment and control groups, respectively
Interventions	Run-in: no run in Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** Allowed, except for theophylline. For roflumilast and placebo groups respectively: LAMA was used by 8 (50%) and 6 (55%); ICS or LABA/ICS was used by 10 (63%) 6 (55%)
Outcomes	**Primary outcomes**: change in induced sputum AcPGP at 12 weeks post-randomisation in an intention-to-treat analysis **Secondary outcomes**: changes in plasma AcPGP, sputum neutrophil counts, additional sputum biomarkers, 6MWT, the Breathlessness Cough and Sputum Scale, SGRQ scores, and changes in post-bronchodilator FEV_1 at the 12-week visit
Notes	NCT number: NCT01572948

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Unclear risk	Randomised
Method of randomisation described?	Unclear risk	Sealed envelope. Block randomisation schema using a block size of four and an allocation ratio of 1:1. Block randomization was stratified by current smoking sta-

Roflumilast DAL-MD-01 (*Continued*)

		tus and ICS use
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	Identical white tablets containing a 30-day supply of either roflumilast, 500 mg or placebo
Description of withdrawals and drop-outs?	Low risk	No withdrawals described
Baseline profile: anticholingeric use	Unclear risk	Not stated
Baseline profile: $\beta 2$ agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast FK1 101

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 26 weeks Intention-to-treat analysis: stated
Participants	Setting: not stated Participants: 516 (roflumilast 250 µg: 175, roflumilast 500 µg: 169, placebo: 172) Baseline characteristics: median age: 61-62 years. 72% male. Mean 38 to 63 pack-years. 53% current smokers Inclusion criteria: aged 40-75 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Reversibility < 12% or 200 mL post-bronchodilator FEV_1 35%-75% predicted Exclusion criteria: not stated Participant withdrawals: not stated
Interventions	Run-in: 2 weeks with placebo Roflumilast 500 µg once daily Roflumilast 250 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: allowed at a constant daily dose for those treated before with anticholinergics on a constant dosage • Short-acting $\beta 2$ agonist: salbutamol was allowed as rescue medication • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: none
Outcomes	**Primary outcomes**: post-bronchodilator FEV_1 and FEF between 25%-75% of vital capacity **Secondary outcomes**: number of moderate or severe COPD exacerbations which required treatment with oral steroids

Roflumilast FK1 101 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomised. No other information available
Randomised?	Low risk	Participants randomised in either roflumilast 250 µg, roflumilast 500 µg or placebo groups
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	High risk	Not stated
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast FK1 103

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: not stated Participants: 518 (roflumilast 500 µg: 200, placebo: 186) Baseline characteristics: mean age: 60 years. 75% male. 62% current smokers. Average of 35 pack-years Inclusion criteria: aged 40-75 years. $FEV_1/FVC \leq 0.7$. Post-bronchodilator FEV_1 35%-75% of predicted. FEV_1 reversibility $\leq$ 12% and $\leq$ 200 mL. Pre-bronchodilator $FEV_1/FVC \leq 70\%$ Exclusion criteria: not stated Participant withdrawals not stated
Interventions	Run-in: 2 weeks with placebo Roflumilast 500 µg once daily for 24 weeks Roflumilast 500 µg once daily for 12 weeks. Placebo once daily for following 12 weeks

Roflumilast FK1 103 (*Continued*)

	Concomitant medication • Short-acting anticholingeric: all medications were withdrawn except constant dose short-acting anticholinergics • Short-acting β2 agonist: as rescue medication • Corticosteroid: none • Long-acting β2 bronchodilator: none Used alongside short-acting ß$_2$ agonists (available to all)
Outcomes	**Primary outcomes**: results for 12/24 week post-bronchodilator FEV_1
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information available
Randomised?	Low risk	"After randomisation, patients received placebo or roflumilast 500 µg once daily for 24 weeks or roflumilast 500 µg for 12 weeks followed by placebo for 12 weeks"
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	High risk	Not stated
Baseline profile: anticholingeric use	Unclear risk	No further information available
Baseline profile: β2 agonist use	Unclear risk	No further information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast FLUI-2011-77

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 6 months Intention-to-treat analysis: stated Responder analysis for the most part
Participants	Setting: 2 centres Participants: 41 (500 µg roflumilast: 30, placebo: 11) Baseline characteristics: not stated

Roflumilast FLUI-2011-77 (*Continued*)

	Inclusion criteria: not stated Exclusion criteria: not stated Total number of participant withdrawals: not stated
Interventions	Run-in: not stated **Concomitant medication**: not stated
Outcomes	**Primary outcomes**: postbronchodilation: spirometry, body plethysmography, 6MWT, Patient reported outcomes **Secondary outcomes**: not stated
Notes	NCT number: NCT01480661 Funded by Takeda

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Unclear risk	Not stated
Baseline profile: anticholingeric use	Unclear risk	Not stated
Baseline profile: β2 agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast IN-108

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: not stated
Participants	Setting: 5 centres in India Participants: 118 recruited (roflumilast 500 µg: 47; roflumilast 200 µg: 46, placebo: 25) Baseline characteristics: mean age: 60 years. 98% male. 41% current smokers. Post-bronchodilator FEV_1 of 57%-61%. Average of 25 pack-years Inclusion criteria: not stated

Roflumilast IN-108 (*Continued*)

	Exclusion criteria: not stated Participant withdrawals: roflumilast 500 µg: 13 (28%); roflumilast 200 µg: 7 (15%) and 10 (40%) from control group
Interventions	Roflumilast 250 µg once daily Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: not stated • Short-acting β2 agonist: not stated • Corticosteroid: none • Long-acting β2 bronchodilator: not stated
Outcomes	To study the safety and tolerability of roflumilast 250 μg versus roflumilast 500 μg versus placebo To investigate the effect of roflumilast 250 μg versus roflumilast 500 μg versus placebo on pulmonary function, efficacy rating and exacerbation rate To evaluate plasma levels of roflumilast and its major metabolite roflumilast N-oxide Note: only the third objective is discussed here
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Data as above
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast JP-706

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: not stated
Participants	Setting: Japan Participants: 600 (roflumilast 250 µg: 205, roflumilast 500 µg: 204, placebo: 191) Baseline characteristics: mean age: 70 years. 96% male. Post-bronchodilator FEV_1 not stated. Average of 56 pack-years. 37% current smokers Inclusion criteria: not stated Exclusion criteria: not stated Total number of participant withdrawals: not stated
Interventions	Run-in: single-blind 4 weeks with placebo Roflumilast 500 µg once daily Roflumilast 250 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: used at a constant daily dose • Short-acting β2 agonist: not stated • Corticosteroid: not stated • Long-acting β2 bronchodilator: not stated
Outcomes	To investigate the efficacy and safety after 24-week treatment of APTA-2217 (roflumilast) at doses of 500 µg and 250 µg in people with COPD using placebo as a control To investigate the pharmacokinetics of roflumilast and roflumilast N-oxide after repeated administration of APTA-2217 at doses of 500 µg and 250 µg
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	High risk	Not described
Baseline profile: anticholingeric use	Low risk	Constant dose of short anticholinergics used in 35% (roflumilast 500 µg), 33% (roflumilast 200 µg) and 33% (placebo),

Roflumilast JP-706 (*Continued*)

		respectively
Baseline profile: β2 agonist use	Unclear risk	Not described
Baseline profile: corticosteroid use	Unclear risk	Not described

Roflumilast M2-107

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 159 centres in Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, South Africa, Spain and the UK Participants: 1411 (roflumilast 250 µg: 576, roflumilast 500 µg: 555, placebo: 280) Baseline characteristics: median age: 64 years. 74% male. Post-bronchodilator FEV_1 is 51% for both groups. Average of 42 pack-years. 45% current smokers Inclusion criteria: aged $\geq$ 40 with history of COPD > 12 months. FEV_1 < 50% predicted, $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Reversibility < 12% or 200 mL. Mean post-bronchodilator FEV_1 30%-80% predicted Exclusion criteria: asthma, lung cancer or bronchiectasis, long-term oxygen treatment, recent exacerbation that required a course of systemic corticosteroids, emergency room treatment or hospital admission within 4 weeks before the run-in period Total number of participant withdrawals: 124 (22%) and 32 (11%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo Roflumilast 500 µg once daily Roflumilast 250 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: used at a constant daily dose • Short-acting β2 agonist: salbutamol as rescue medication • Corticosteroid: none • Long-acting β2 bronchodilator: none
Outcomes	**Primary outcomes**: post-bronchodilator FEV_1 and SGRQ total score **Secondary outcomes**: change from baseline in pre-bronchodilator FEV_1, post-bronchodilator FVC, post-bronchodilator FEV in 6 seconds and FVC, FEF rate between 25%-75% of vital capacity and number of moderate or severe COPD exacerbations
Notes	There is inconsistency in the quoting of statistical errors. Within the text and Table 2, data are quoted as "least squares means and SD", however in Figures 2 and 3, SE bars are shown. It is more likely that the results represent SE and not SD

Risk of bias

Roflumilast M2-107 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	"No person involved in data analysis had knowledge of the randomisation sequence"
Randomised?	Low risk	"Treatment was assigned by the investigators with sequential study numbers according to a block randomisation list in ratios of 2:2:1 (Roflumilast 250 µg, Roflumilast 500 µg, Placebo)."
Method of randomisation described?	Low risk	"The randomisation sequence was generated by ALTANA Pharma AG in a blinded manner"
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"Medication boxes were labelled with the study protocol number, randomisation number, and visit code; coding prevented the investigator and people at the study centre from knowing which medication was given."
Description of withdrawals and drop-outs?	Low risk	100 participants discontinued from study from the roflumilast 250 µg group, 124 from the roflumilast 500 µg group and 32 from the placebo group
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast M2-110

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: not stated
Participants	Setting: 36 centres in Argentina, Canada, Columbia, Mexico, Peru and the USA Participants: estimated enrolment of 1000 participants Baseline characteristics: not stated Inclusion criteria: • Clinical diagnosis of COPD

Roflumilast M2-110 (*Continued*)

	• Currently stable COPD with no change in COPD treatment in the prior 4 weeks Exclusion criteria: • Clinical diagnosis of asthma • Poorly controlled COPD • Regular need for daily oxygen therapy Total number of participant withdrawals: not stated
Interventions	Roflumilast 500 µg daily versus placebo
Outcomes	**Primary outcomes**: pulmonary function **Secondary outcomes**: exacerbation rate, quality of life, symptoms, use of rescue medication, safety and tolerability
Notes	ClinicalTrials.gov Identifier: nCT00062582

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Unclear risk	Not stated
Baseline profile: anticholingeric use	Unclear risk	Not stated
Baseline profile: β2 agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-111

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: M2-111 was conducted in 188 centres in 6 countries, and M2-112 in 159 centres in 14 countries Participants: data combined with M2-112 showing 2686 (roflumilast 500 µg: 1327, placebo: 1359), suggesting total n for this study was 1173.

Roflumilast M2-111 (*Continued*)

	Baseline characteristics: severe COPD according to GOLD criteria grades III and IV. Mean age: 64-65 years. 72% male Inclusion criteria: aged ≥ 40 years. Post-bronchodilator FEV_1 < 50% predicted. Reversibility < 15%. Mean post-bronchodilator FEV_1 42%. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. 40% current smokers, 60% ex-smokers; average 46-48 pack-years Exclusion criteria: history of asthma, lung cancer or bronchiectasis, need for long-term oxygen therapy, known $\alpha_1$antitrypsin deficiency or clinically significant cardiopulmonary co-morbidity Total number of participant withdrawals: data combined with M2-112 showing 433 (33%) and 348 (26%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: 891 patients on short-acting anticholinergics • Short-acting $\beta 2$ agonist: salbutamol as rescue medication • Corticosteroid: 943 patients continued corticosteroid use • Long-acting $\beta 2$ bronchodilator: none Used alongside corticosteroids, anticholinergics and rescue short-acting ß$_2$ agonists 54% overall (available to all)
Outcomes	**Primary outcomes**: change from baseline to endpoint in post-bronchodilator FEV_1 and the number of moderate or severe exacerbations per patient per year **Secondary outcomes**: change from baseline in SGRQ total score, change from baseline in prebronchial FEV_1, post-bronchodilator FEV in 6 seconds and FVC, FEF rate between 25%-75% of vital capacity and number of moderate or severe COPD exacerbations requiring systemic corticosteroid treatment per patient per year
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	"Each study participant who qualified was assigned a number in sequential order. Code labelling prevented the investigator and the patient from knowing which drug was administered."
Randomised?	Low risk	"randomised (1:1)"
Method of randomisation described?	Low risk	"The randomisation list was generated using a multiplicative congruential pseudo-random number generator (program RANDOM, based on Fishman and Moore)."

Roflumilast M2-111 (*Continued*)

Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"There was a stratification of patients according to smoking status (current smokers/ex-smokers) and treatment with inhaled corticosteroids (yes/no)."
Description of withdrawals and drop-outs?	Low risk	Data combined with M2-112
Baseline profile: anticholingeric use	Low risk	Data combined with M2-112 showing 1604 (60%) participants used anticholinergics
Baseline profile: β2 agonist use	Low risk	1463 (55%) participants on short-acting β_2-agonists
Baseline profile: corticosteroid use	Low risk	1622 (61%) on concomitant ICS

Roflumilast M2-111+M2-112

Methods	As described in separate studies above and below	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	See individual trials
Randomised?	Low risk	See individual trials
Method of randomisation described?	Low risk	See individual trials
Blinding?	Low risk	See individual trials
Method of blinding described?	Low risk	See individual trials
Description of withdrawals and drop-outs?	Low risk	See individual trials
Baseline profile: anticholingeric use	Low risk	See individual trials

Roflumilast M2-111+M2-112 (*Continued*)

Baseline profile: β2 agonist use	Low risk	See individual trials
Baseline profile: corticosteroid use	Low risk	See individual trials

Roflumilast M2-112

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: 159 centres in 14 countries Participants: 1513 (roflumilast 500 µg: 760, placebo: 753) Baseline characteristics: severe COPD according to GOLD criteria grades III and IV. Mean age: 65 years. 75% male Inclusion criteria: aged $\geq$ 40 years. Post-bronchodilator FEV_1 < 50% predicted. Reversibility < 15%. Mean post-bronchodilator FEV_1 41%. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. 37% current smokers, 63% ex-smokers; average 44 pack-years Exclusion criteria: history of asthma, lung cancer or bronchiectasis, need for long-term oxygen therapy, known $\alpha_1$antitrypsin deficiency or clinically significant cardiopulmonary co-morbidity Total number of participant withdrawals: 217 (29%) and 163 (22%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: 891 participants on short-acting anticholinergics • Short-acting β2 agonist: salbutamol as rescue medication • Corticosteroid: 943 participants continued corticosteroid use • Long-acting β2 bronchodilator: none Used alongside corticosteroids, anticholinergics and rescue short-acting ß$_2$ agonists 54% overall (available to all)
Outcomes	**Primary outcomes**: change from baseline to endpoint in post-bronchodilator FEV_1 and the number of moderate or severe exacerbations per patient per year **Secondary outcomes**: change from baseline in SGRQ total score, change from baseline in prebronchial FEV_1, post-bronchodilator FEV in 6 seconds and FVC, FEF rate between 25%-75% of vital capacity and number of moderate or severe COPD exacerbations requiring systemic corticosteroid treatment per patient per year
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Roflumilast M2-112 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Each study participant who qualified was assigned a number in sequential order. Code labelling prevented the investigator and the patient from knowing which drug was administered."
Randomised?	Low risk	"randomised (1:1)"
Method of randomisation described?	Low risk	"The randomisation list was generated using a multiplicative congruential pseudo-random number generator (program RANDOM, based on Fishman and Moore)."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"There was a stratification of patients according to smoking status (current smokers/ex-smokers) and treatment with inhaled corticosteroids (yes/no)."
Description of withdrawals and drop-outs?	Low risk	"Over 70% of patients completed the study. The reasons for withdrawal were similar between groups except for adverse events, which occurred more frequently with roflumilast." "Withdrawal due to COPD exacerbations was reported in 3.5 and 3.2% of patients in roflumilast and placebo groups, respectively."
Baseline profile: anticholingeric use	Low risk	739 participants used anticholinergics
Baseline profile: β2 agonist use	Low risk	820 participants on short-acting β_2-agonists
Baseline profile: corticosteroid use	Low risk	727 participants on beclomethasone dipropionate 2000 µg or less

Roflumilast M2-118

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: stated
Participants	Setting: 22 centres in 4 countries Participants: 250 (roflumilast 500 µg: 127, placebo: 123) Baseline characteristics: mean age: 60 years. 73% (roflumilast) versus 84% (placebo)

Roflumilast M2-118 (*Continued*)

	male. Post-bronchodilator FEV_1 55% predicted. Average of 41 pack-years. 53% current smokers Inclusion criteria: participants were clinically stable patients ≥ 40 years with a smoking history of > 10 pack-years and a 12-month history of COPD. Other inclusion criteria included: post-bronchodilator FEV_1 30%-80% predicted, FEV_1/forced vital capacity (FVC) < 0.7 and set plethysmographic FRC and peak oxygen uptake requirements Exclusion criteria: asthma or a lung disease other than COPD; a1-antitrypsin deficiency; participation in a pulmonary rehabilitation programme within 2 months; supplemental oxygen therapy; a significant medical comorbidity that may influence exercise tolerance Total number of participant withdrawals: 16 (13%) and 12 (10%) from treatment and control groups, respectively
Interventions	Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: participants could use ipratropium bromide in regular stable doses as needed • Short-acting β2 agonist: participants could use short-acting β_2-agonists as needed • Corticosteroid: ICS were permitted throughout the study if taken at a constant dosage for > 3 months prior to the study • Long-acting β2 bronchodilator: none
Outcomes	Activity-related dyspnoea (TDI). Spirometry and body plethysmography. Symptom-limited exercise tests
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	A 1:1 randomisation ratio was used
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Of the 250 randomised participants, 16 from the roflumilast group and 12 from the placebo group discontinued prematurely
Baseline profile: anticholingeric use	Unclear risk	Not stated
Baseline profile: β2 agonist use	Unclear risk	Not stated

Roflumilast M2-118 (*Continued*)

Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-119

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: stated
Participants	Setting: 32 centres in 5 countries Participants: 410 (roflumilast 500 µg: 203, placebo: 207) Baseline characteristics: mean age: 68 years. 93% male. Post-bronchodilator FEV_1 50. 5% predicted. Average of 44 pack-years. 69% current smokers Inclusion criteria: former or current smokers with at least a 10 pack-year history. Aged $\geq$ 40 years. Post-bronchodilator $FEV_1/FVC \leq 0.7$ and FEV_1 of 30%-80%. Clinically stable COPD within 4 weeks prior to baseline Exclusion criteria: history of asthma or other relevant lung disease, COPD exacerbation with the 4 weeks prior to baseline, need for long-term oxygen therapy, known $\alpha_1$antitrypsin deficiency or clinically significant cardiopulmonary co-morbidity Total number of participant withdrawals: 40 (20%) and 18 (9%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: "Short-acting anticholinergics at a constant daily dosage as concomitant medication if already taken on a regular basis at a constant dosage for at least 4 weeks prior to the study." • Short-acting $\beta 2$ agonist: patients could use short-acting β_2 agonists as needed • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: none
Outcomes	**Primary outcome**: mean change in post-bronchodilator FEV_1 from baseline **Secondary outcomes**: mean change in pre-bronchodilator FEV_1 from baseline, change in other lung function measures, time to COPD exacerbation, proportion of participants experiencing exacerbations, time to study withdrawal and adverse effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised

Roflumilast M2-119 (*Continued*)

Method of randomisation described?	Low risk	Computer-generated randomisation list used
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Participant numbers at different stages of the study described in figure
Baseline profile: anticholingeric use	Unclear risk	Not stated
Baseline profile: $\beta 2$ agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-121

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: stated
Participants	Setting: 16 centres in 6 countries Participants: estimated enrolment 550 participants Baseline characteristics: not stated Inclusion criteria: people with a history of COPD for at least 12 months as defined by the GOLD criteria, age $\geq$ 40 years, FEV1/FVC ratio (post-bronchodilator) $\leq$ 70%, FEV_1 (post-bronchodilator) $\leq$ 65% of predicted, FRC (post-bronchodilator) $\leq$ 120% of predicted Exclusion criteria: COPD exacerbation indicated by a treatment with systemic glucocorticosteroids not stopped at least 4 weeks prior to the baseline visit, non-smoker, current smoker or ex-smoker (smoking cessation at least 1 year ago) with a smoking history of < 10 pack-years, or suffering from any concomitant disease that might interfere with study procedures or evaluation Total number of participant withdrawals: not stated
Interventions	500 µg roflumilast tablets once daily versus placebo
Outcomes	**Primary outcome**: lung function parameters indicative of hyperinflation in people with COPD **Secondary outcomes**: • Mean change from randomisation to endpoint in additional pre- and post-bronchodilator spirometric and lung volume parameters • Measurement of quality of life parameters and dyspnoea
Notes	ClinicalTrials.gov Identifier: NCT00108823

Roflumilast M2-121 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Unclear risk	Not stated
Baseline profile: anticholingeric use	Unclear risk	Not stated
Baseline profile: $\beta 2$ agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-124

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: 246 centres in 10 countries Participants: 1513 (roflumilast 500 µg: 760, placebo: 753) Baseline characteristics: mean age: 64 years. 71% male. Post-bronchodilator FEV_1 37. 6% predicted. Average of 47 pack-years. 48% current smokers Inclusion criteria: former or current smokers with at least a 20 pack-year history. Aged $\geq$ 40 years. Post-bronchodilator $FEV_1/FVC \leq 0.7$. Chronic cough and sputum production. Post-bronchodilator FEV_1 < 50% predicted. At least 1 recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital in previous year Exclusion criteria: available in the online web appendix (pg 11) Total number of participant withdrawals: 264 (34%) and 234 (31%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: 31% of those in the roflumilast group and 32% on placebo

Roflumilast M2-124 (*Continued*)

	• Short-acting $\beta 2$ agonist: "Patients could use short acting β_2 agonists as needed" • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: "Eligible patients were stratified according to their use of long acting $\beta 2$ agonists and smoking status." Roflumilast 49%, placebo 51%
Outcomes	**Primary outcomes**: mean change in pre-bronchodilator FEV_1 from baseline to each post-randomisation visit during the treatment period. Mean rate of COPD exacerbations requiring oral or parenteral glucocorticosteroids or requiring hospitalisation or leading to death, per patient per year **Secondary outcomes**: mean change in post-bronchodilator FEV_1 from baseline to each post-randomisation visit during the treatment period. Time to mortality due to any reason. Natural log-transformed C Reactive Protein (mg/L), Mean TDI focal score during the treatment period
Notes	Adverse event data are pooled with numbers from study M2-125 that followed an identical study design

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 µg once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. Tablets were identical in appearance. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling."
Description of withdrawals and drop-outs?	Low risk	264 participants discontinued from study in the roflumilast group and 234 discontinued from the placebo group

Roflumilast M2-124 (*Continued*)

Baseline profile: anticholingeric use	Unclear risk	No other information available
Baseline profile: β2 agonist use	Unclear risk	No other information available
Baseline profile: corticosteroid use	High risk	Pretreatment of 44% in both roflumilast and placebo groups

Roflumilast M2-124+M2-125

Methods	As described in separate studies above and below	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	See individual studies
Randomised?	Low risk	See individual studies
Method of randomisation described?	Low risk	See individual studies
Blinding?	Low risk	See individual studies
Method of blinding described?	Low risk	See individual studies
Description of withdrawals and drop-outs?	Low risk	See individual studies
Baseline profile: anticholingeric use	Low risk	See individual studies
Baseline profile: β2 agonist use	Low risk	See individual studies
Baseline profile: corticosteroid use	High risk	See individual studies

Roflumilast M2-125

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: 221 centres in 8 countries Participants: 1571 (roflumilast 500 µg: 773, placebo: 798) Baseline characteristics: mean age: 64 years. 80% male. Average of 48 pack-years. 35% current smokers Inclusion criteria: former or current smokers with at least a 20 pack-year history. Aged ≥ 40 years. Post-bronchodilator $FEV_1/FVC \leq 0.7$. Chronic cough and sputum production. Post-bronchodilator FEV_1 < 50% predicted. At least 1 recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital in previous year Exclusion criteria: available in the online web appendix (pg 11) Total number of participant withdrawals: 246 (32%) and 248 (31%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: 38% of those in the roflumilast group and 41% on placebo • Short-acting $\beta 2$ agonist: "Patients could use short acting β_2 agonists as needed" • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: "Eligible patients were stratified according to their use of long acting $\beta 2$ agonists and smoking status." Roflumilast 48%, placebo 51%
Outcomes	**Primary outcomes**: mean change in pre-bronchodilator FEV_1 from baseline to each post-randomisation visit during the treatment period. Mean rate of COPD exacerbations requiring oral or parenteral glucocorticosteroids or requiring hospitalisation or leading to death, per patient per year **Secondary outcomes**: mean change in post-bronchodilator FEV_1 from baseline to each post-randomisation visit during the treatment period. Time to mortality due to any reason. Natural log-transformed CRP (mg/L), Mean TDI focal score during the treatment period
Notes	Adverse event data are pooled with numbers from study M2-124 that followed an identical study design

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment

Roflumilast M2-125 (*Continued*)

Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 µg once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. Tablets were identical in appearance. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling."
Description of withdrawals and drop-outs?	Low risk	246 patients discontinued from study in the roflumilast group and 248 discontinued from the placebo group
Baseline profile: anticholingeric use	Low risk	No other information available
Baseline profile: $\beta 2$ agonist use	Low risk	No other information available
Baseline profile: corticosteroid use	High risk	Pretreatment of 40% in both roflumilast and placebo groups

Roflumilast M2-127

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 135 centres in 10 countries Participants: 1221 (roflumilast 500 µg: 467, placebo: 468) Baseline characteristics: mean age: 65 years. 71% male. Post-bronchodilator FEV_1 54. 7% and 55.3% predicted (roflumilast and placebo). Average of 43 pack-years. 39% current smokers Inclusion criteria: former or current smokers with ($\geq$ 1 year smoking cessation) and at least a 10 pack-year history. Aged $\geq$ 40 years. Post-bronchodilator $FEV_1/FVC \leq 0.7$. Post-bronchodilator FEV_1 40% to 70% predicted. Partial reversibility to albuterol with increase from baseline FEV_1 of $\leq$ 12% or 200 mL Exclusion criteria: available in the online web appendix (pg 10)

Roflumilast M2-127 (*Continued*)

	Total number of participant withdrawals: 107 (23%) and 82 (18%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo once a day Roflumilast 500 µg and salmeterol once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: none • Short-acting $\beta 2$ agonist: participants used short-acting β_2 as rescue medication • Corticosteroid: none • Long-acting $\beta 2$ bronchodilator: none
Outcomes	**Primary outcomes**: change in mean pre-bronchodilator FEV_1 from baseline to each post-randomisation visit **Secondary outcomes**: post-bronchodilator FEV_1 and FVC, TDI score, SOBQ, rate of COPD exacerbations, and use of rescue medication
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 µg once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. Tablets were identical in appearance."
Description of withdrawals and drop-outs?	Low risk	107 participants discontinued from study in the roflumilast group and 82 discontinued from the placebo group

Roflumilast M2-127 (*Continued*)

Baseline profile: anticholingeric use	Unclear risk	No other information available
Baseline profile: β2 agonist use	Unclear risk	No other information available
Baseline profile: corticosteroid use	Unclear risk	No other information available

Roflumilast M2-128

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 85 centres in 7 countries Participants: 910 (roflumilast 500 µg: 372, placebo: 372) Baseline characteristics: mean age: 64 years. 71% male. Post-bronchodilator FEV_1 56. 0% and 56.2% predicted (roflumilast and placebo). Average of 44 pack-years. 40% current smokers Inclusion criteria: former or current smokers with ($\geq$ 1 year smoking cessation) and at least a 10 pack-year history. Aged $\geq$ 40 years. Post-bronchodilator FEV_1/FVC $\leq$ 0.7. Post-bronchodilator FEV_1 40% to 70% predicted. Partial reversibility to albuterol with increase from baseline FEV_1 of $\leq$ 12% or 200 mL Exclusion criteria: available in the online web appendix (pg 10) Total number of participant withdrawals: 62 (17%) and 39 (11%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo once a day Roflumilast 500 µg and tiotropium once daily Placebo once daily **Concomitant medication** • Short-acting anticholingeric: none • Short-acting β2 agonist: participants used short-acting β_2 as rescue medication • Corticosteroid: none • Long-acting β2 bronchodilator: none
Outcomes	**Primary outcomes**: change in mean pre-bronchodilator FEV_1 from baseline to each post-randomisation visit **Secondary outcomes**: post-bronchodilator FEV_1 and FVC, TDI score, SOBQ, rate of COPD exacerbations and use of rescue medication
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Roflumilast M2-128 (*Continued*)

Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 µg once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. Tablets were identical in appearance."
Description of withdrawals and drop-outs?	Low risk	62 participants discontinued from study in the roflumilast group and 39 discontinued from the placebo group
Baseline profile: anticholingeric use	Unclear risk	No information available
Baseline profile: $\beta 2$ agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast ROF-MD-07(RE2SPOND)

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: 338 locations across Australia, Argentina, Canada, Chile, Columbia, Italy, Malaysia, Peru, Phillippines, Romania, Russia, Serbia, Spain, Taiwan, Ukraine Participants: 2354 (500 µg roflumilast: 1178; placebo: 1176) Baseline characteristics: mean age: 64 years, 68% male, mean FEV_1% predicted of 33%, mean smoking history of 52.2 pack-years for roflumilast and 53.1 pack-years for placebo) or current smokers (39% and 40%, respectively) Inclusion criteria: $\geq$ 40 years with severe-very severe COPD, chronic bronchitis, $\geq$ 2 exacerbations and/or hospitalisations in the previous year, and were receiving ICS/LABA

Roflumilast ROF-MD-07(RE2SPOND) (*Continued*)

	with or without LAMA daily for ≥ 3 months Exclusion criteria: participants were excluded if, within the 4 weeks prior to enrolment, they had a moderate or severe COPD exacerbation and/or COPD exacerbation treated with antibiotics or systemic corticosteroids or a lower respiratory tract infection. Other exclusionary criteria included diagnoses of other lung diseases, moderate-to-severe liver impairment (Child-Pugh B or C), HIV or hepatitis infection, current diagnosis of asthma, cancer in the past 5 years, α1-antitrypsin deficiency, a clinically significant cardiovascular condition, a resting QTc interval > 470 ms, or a body mass index ≥ 45 kg/m Total number of participant withdrawals: 337 (29%) and 254 (21%) from treatment and control groups, respectively
Interventions	Run-in: 2 weeks, single-blind. Placebo tablets to assess suitability Roflumilast 500 µg once daily Placebo once daily **Concomitant medication** ICS/LABA FDC (fluticasone propionate/salmeterol, 250/50 mg (1 inhalation twice a day), or budesonide/formoterol, 160/4.5 mg (2 inhalations twice a day) Participants taking fluticasone propionate/salmeterol, 500/50 mg, at study entry were required to switch to the lower dosage (250/50 mg) before entry. Up to 60% of participants were allowed concomitant LAMA (e.g. tiotropium) if administered for ≥3 months before screening, with no dose change. Those not on LAMA were allowed a SAMA
Outcomes	**Primary outcomes**: rate of moderate or severe COPD exacerbations per patient per year **Secondary outcomes**: rate of severe exacerbations, rate of moderate or severe antibiotic-treated COPD exacerbations, and mean change from baseline in predose FEV_1 over 52 weeks, frequency of moderate or severe COPD exacerbations, median time to first moderate or severe exacerbation, mean changes from baseline in predose FVC, mean changes from baseline over time in the COPD Assessment Test (CAT), and daily symptoms measured via EXAcerbation of Chronic Pulmonary Disease Tool-Patient Reported Outcomes (EXACT-PRO), adverse events, Columbia-Suicide Severity Rating Scale, laboratory parameters and vital signs
Notes	NCT01443845 Sponsored by Activas and Astra Zeneca

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double blind
Method of blinding described?	Unclear risk	Not stated

Roflumilast ROF-MD-07(RE2SPOND) (*Continued*)

Description of withdrawals and drop-outs?	Unclear risk	337 participants (29%) discontinued from study in the roflumilast group and 254 (22%) discontinued from the placebo group
Baseline profile: anticholingeric use	Unclear risk	LAMA: 47% for placebo; 47% for roflumilast
Baseline profile: β2 agonist use	Unclear risk	Combined LABA/ICS Fluticasone propionate/salmeterol FDC 65% for placebo; 65% for roflumilast Budesonide/formoterol FDC 35% for placebo; 35% for roflumilast
Baseline profile: corticosteroid use	Unclear risk	As above

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity of the lung for carbon monoxide; FDC: fixed dose combination; FEF: forced expiratory flow; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IC: inspiratory capacity; ICS: inhaled corticosteroid; L: litre; LABA: Long-acting beta-2 agonist; LAMA: Long acting muscarinic antagonist; MDI: metered dose inhaler; mL: millilitre; RFRC: resting functional residue capacity; RV: residual volume; SAMA: Short acting muscarinic antagonist; SD: standard deviation; SE: standard error; SGRQ: St George's Respiratory Questionnaire
SOBQ: Shortness of Breath Questionnaire; SVC: slow vital capacity; TDI: transition dyspnoea index; 6MWT: 6-minute walk test

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Borker 2003	Insufficient data. Only RR of QOL improvement provided
Ferguson 2003	Integrated results from four 24-week cilomilast trials
Fischer 2003	Analysis focused on participants with a baseline SGRQ score of $\geq$ the median SGRQ score only
Grootendorst 2001	Endpoint: first dose-bronchodilator effects only
Grootendorst 2002	Treatment Bayer BAY 19-8004; 11 participants only 1 week in duration
Grootendorst 2003	Endpoint: first-dose bronchodilator effects only
Grootendorst 2007	Cross-over design
GSK256066	Phase II trial. No primary outcome measure investigating lung function. Only 1 trial to date

(*Continued*)

Kelsen 2002	No study ID or group numbers identified
Knobil 2003	No SD or SE given
Lim 2004	Combining results from 2 pivotal European phase III cilomilast trials
Nieman 1999	Study 038. Insufficient data available for changes in lung function and exacerbation rates
Pascoe 2007	Treatment QAK423 (Novartis), discontinued. Only 1 trial available
Reisner 2003	Combined results. Individual studies already included in review
Roflumilast JP708	JP108 is an extension study of APTA-2217-06 study. After the key-open of APTA-2217-06 study, administration to placebo group would be terminated. Not all participants enrolled in JP106 continued onto the JP108 study
Sadigov 2014	No placebo group
Sadigov 2015	Open label. No placebo group
SB207499/040	Open-label study. Men or women with COPD who successfully completed study 042 or 091 where participants received cilomilast 15 mg twice daily or placebo for 24 weeks in study 042 and 26 weeks in study 091 without tolerability problems. Concomitant COPD medication use allowed, given placebo or placebo/Ariflo during study period
SB207499/041	Open-label study. Men or women with COPD who successfully completed study 039 where participants received cilomilast 15 mg twice daily or placebo for 24 weeks without tolerability problems. Concomitant COPD medication use allowed, given placebo or placebo/Ariflo during study period
Song 2005	Abstract only. Unable to contact study author
Spencer 2002	No study ID or group numbers identified
Vestbo 2007	Treatment UK-500,001 (Pfizer). Discontinued
Vestbo 2009	Treatment UK-500,001 (Pfizer). Discontinued
Wang 2005	Although quoted as significant, mean and SD figures not provided
Watz 2013	Inhaled therapy

COPD: chronic obstructive pulmonary disease
RR: risk ratio
QOL: quality of life
SD: standard deviation
SE: standard error

Characteristics of studies awaiting assessment *[ordered by study ID]*

Barnes 2014

Methods	An international, 16-week, randomised, double-blind, placebo-controlled, parallel-group study investigating the effects of roflumilast 500 µg once-daily versus placebo on inflammatory parameters in bronchial biopsy tissue specimens, sputum and blood serum
Participants	150 participants with COPD and chronic bronchitis for at least 12 months will be recruited into the study and randomized in a 1:1 ratio to receive either roflumilast or placebo
Interventions	Roflumilast and placebo
Outcomes	The primary endpoint will be the number of CD8+ cells in bronchial biopsy tissue specimens (sub-mucosa) and the key secondary endpoint will be the number of CD68+ cells assessed by indirect immunohistochemistry
Notes	Completed awaiting results

Mahmud 2013

Methods	Single-blind, randomised, placebo-controlled study was carried out in the Department of Respiratory Medicine at National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh
Participants	130 participants were recruited initially and randomly distributed into Group-A where they got conventional therapy (inhaled salmeterol + fluticasone and tiotropium) and roflumilast (0.5 mg once daily) and Group- B where participants got placebo with conventional therapy Study duration was 3 months
Interventions	As above
Outcomes	The primary outcome variable was change in mean FEV_1 and secondary outcome variable was change in mean CAT score from baseline
Notes	No data provided. Study authors contacted

CAT: COPD Assessment Test
COPD: chronic obstructive pulmonary disease

Characteristics of ongoing studies *[ordered by study ID]*

NCT02451540 2015

Trial name or title	Evaluation of the effect of roflumilast in hyperinflated COPD patients using functional respiratory imaging
Methods	Parallel RCT
Participants	40 people who are stable on LABA/LAMA therapy and who are prone to dynamics hyperinflation
Interventions	Roflumilast and placebo
Outcomes	Radiological (CT) changes in airway measures Changes in spirometry and body plethysmography
Starting date	September 2015
Contact information	University Hospital of Antwerp
Notes	Other Study ID Numbers: FLUI-2014-134, EudraCT Estimated study completion date: January 2017

NCT02671942 2016

Trial name or title	A multicenter randomized double-blind clinical study evaluated the safety, pharmacokinetic and pharmacodynamic characteristics of roflumilast in COPD patients
Methods	Parallel RCT
Participants	People with COPD in China
Interventions	Roflumilast and placebo
Outcomes	Area under the plasma concentration after versus drug dose Percentage of participants with adverse events of interest Change in pre-bronchodilator FEV_1 during the down titration period
Starting date	March 2016
Contact information	Contact: Zheng Jinping
Notes	Estimated enrolment: 120 Estimated study completion date: August 2017

COPD: chronic obstructive pulmonary disease
FEV_1: forced expiratory volume in first second
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. PDE_4 inhibitor versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 (by drug)	27	20585	Mean Difference (IV, Random, 95% CI)	51.53 [43.17, 59.90]
1.1 Roflumilast 500 μg	17	14230	Mean Difference (IV, Random, 95% CI)	56.45 [48.01, 64.89]
1.2 Roflumilast 250 μg	3	1033	Mean Difference (IV, Random, 95% CI)	56.88 [24.38, 89.38]
1.3 Cilomilast 15 mg	10	5322	Mean Difference (IV, Random, 95% CI)	41.03 [23.93, 58.13]
2 FEV_1 (by mean COPD severity)	21	16659	Mean Difference (IV, Fixed, 95% CI)	52.77 [46.73, 58.82]
2.1 GOLD grade I + II (FEV1 $\geq$ 50% predicted)	9	4647	Mean Difference (IV, Fixed, 95% CI)	51.79 [38.99, 64.59]
2.2 GOLD grade III + IV (FEV1 < 50% predicted)	12	12012	Mean Difference (IV, Fixed, 95% CI)	53.06 [46.19, 59.92]
3 FEV_1 (Roflumilast 500 μg by mean COPD severity)	15	13742	Mean Difference (IV, Fixed, 95% CI)	55.51 [48.88, 62.14]
3.1 GOLD grade I + II (FEV_1 $\geq$ 50% predicted)	6	3187	Mean Difference (IV, Fixed, 95% CI)	69.86 [53.34, 86.38]
3.2 GOLD grade III + IV (FEV_1 < 50% predicted)	9	10555	Mean Difference (IV, Fixed, 95% CI)	52.75 [45.52, 59.99]
4 FEV_1 (by study duration)	27	19785	Mean Difference (IV, Fixed, 95% CI)	49.08 [43.85, 54.32]
4.1 Duration $\leq$ 12 weeks	7	1037	Mean Difference (IV, Fixed, 95% CI)	102.21 [71.26, 133.16]
4.2 Duration 24 to 26 weeks	13	8086	Mean Difference (IV, Fixed, 95% CI)	46.14 [38.44, 53.84]
4.3 Duration 52 weeks	7	10662	Mean Difference (IV, Fixed, 95% CI)	48.77 [41.44, 56.10]
5 FEV_1 (additional medication)	27	19565	Mean Difference (IV, Fixed, 95% CI)	49.08 [43.84, 54.31]
5.1 Long-acting bronchodilator	2	1645	Mean Difference (IV, Fixed, 95% CI)	60.52 [40.57, 80.46]
5.2 Corticosteroids	3	2904	Mean Difference (IV, Fixed, 95% CI)	42.26 [25.46, 59.05]
5.3 PDE_4i treatment only	19	10169	Mean Difference (IV, Fixed, 95% CI)	44.78 [37.67, 51.90]
5.4 Various concomitant treatments	3	4847	Mean Difference (IV, Fixed, 95% CI)	56.58 [46.91, 66.25]
6 FEV_1 (published versus unpublished)	27	19785	Mean Difference (IV, Fixed, 95% CI)	49.23 [43.99, 54.46]
6.1 Published	19	15244	Mean Difference (IV, Fixed, 95% CI)	55.75 [49.44, 62.06]
6.2 Unpublished	8	4541	Mean Difference (IV, Fixed, 95% CI)	34.82 [25.44, 44.19]
7 FEV_1 (random-effects model)	27	19785	Mean Difference (IV, Random, 95% CI)	51.47 [42.68, 60.26]
8 FEV_1 (roflumilast 500 μg versus 250 μg)	3	1560	Mean Difference (IV, Fixed, 95% CI)	22.61 [-5.95, 51.16]
9 FVC	16	21954	Mean Difference (IV, Fixed, 95% CI)	87.28 [74.87, 99.70]
10 PEF	5	4245	Mean Difference (IV, Fixed, 95% CI)	6.54 [3.95, 9.13]
10.1 Roflumilast 500 μg	4	3685	Mean Difference (IV, Fixed, 95% CI)	5.46 [2.74, 8.17]
10.2 Roflumilast 250 μg	1	347	Mean Difference (IV, Fixed, 95% CI)	7.0 [-4.05, 18.05]
10.3 Cilomilast 15 mg	1	213	Mean Difference (IV, Fixed, 95% CI)	34.0 [20.14, 47.86]
11 SGRQ total score	11	7645	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.68, -0.43]
11.1 Roflumilast 500 μg	3	2235	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-2.16, 0.58]
11.2 Roflumilast 250 μg	1	716	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-3.56, 0.36]
11.3 Cilomilast 15 mg	8	4694	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.81, -0.31]

12 SGRQ total score (by published versus unpublished)	11	7069	Mean Difference (IV, Fixed, 95% CI)	1.00 [-1.65, -0.34]
12.1 Published	5	3079	Mean Difference (IV, Fixed, 95% CI)	-1.98 [-3.07, -0.89]
12.2 Unpublished	6	3990	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-1.26, 0.40]
13 SGRQ total score (by duration)	11	7069	Mean Difference (IV, Fixed, 95% CI)	-0.99 [-1.65, -0.33]
13.1 Duration < 12 weeks	2	240	Mean Difference (IV, Fixed, 95% CI)	-4.19 [-7.60, -0.78]
13.2 Duration 24 to 26 weeks	7	4600	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-1.94, -0.42]
13.3 Duration 52 weeks	2	2229	Mean Difference (IV, Fixed, 95% CI)	0.26 [-1.18, 1.69]
14 SGRQ total score (by mean COPD severity)	8	4851	Mean Difference (IV, Fixed, 95% CI)	-1.56 [-2.39, -0.74]
14.1 GOLD grade I and II	3	2042	Mean Difference (IV, Fixed, 95% CI)	-1.62 [-2.80, -0.44]
14.2 GOLD grade III and IV	5	2809	Mean Difference (IV, Fixed, 95% CI)	-1.51 [-2.67, -0.34]
15 SGRQ symptom score	2	1048	Mean Difference (IV, Fixed, 95% CI)	-1.53 [-4.11, 1.06]
15.1 Roflumilast	1	835	Mean Difference (IV, Fixed, 95% CI)	1.00 [-3.78, 1.78]
15.2 Cilomilast	1	213	Mean Difference (IV, Fixed, 95% CI)	-4.80 [-11.73, 2.13]
16 Number of participants with one or more exacerbations (by drug)	23	19948	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.73, 0.83]
16.1 Roflumilast 500 μg	13	14420	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.73, 0.86]
16.2 Cilomilast	10	5528	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.67, 0.85]
17 Number of participants on roflumilast with one or more exacerbations (additional medication)	13	14420	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.73, 0.86]
17.1 Long-acting bronchodilators	2	1676	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.54, 0.88]
17.2 Corticosteroids	1	2686	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.70, 0.95]
17.3 Treatment only	7	5145	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.67, 0.93]
17.4 Various concomitant treatments	3	4913	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
18 Exacerbation rate (inverse variance)	9		Rate Ratio (Fixed, 95% CI)	0.88 [0.83, 0.93]
18.1 Roflumilast	8		Rate Ratio (Fixed, 95% CI)	0.87 [0.82, 0.92]
18.2 Cilomilast	1		Rate Ratio (Fixed, 95% CI)	0.95 [0.78, 1.17]
19 Borg Scale	6	2860	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.33, -0.05]
19.1 Cilomilast	6	2860	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.33, -0.05]
20 Summary symptom score	5	6186	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.07, 0.03]
20.1 Roflumilast	2	4287	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.08, 0.04]
20.2 Cilomilast	3	1899	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.13, 0.06]
21 Shortness of breath questionnaire	2	1633	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-2.47, 0.28]
22 6-minute walk test	5	1975	Mean Difference (IV, Fixed, 95% CI)	2.09 [-7.39, 11.57]
22.1 Roflumilast	1	27	Mean Difference (IV, Fixed, 95% CI)	55.0 [-111.29, 221.29]
22.2 Cilomilast	4	1948	Mean Difference (IV, Fixed, 95% CI)	1.92 [-7.58, 11.41]
23 Number of participants experiencing an adverse effect	27	20988	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [1.22, 1.37]
23.1 Roflumilast 500 μg	13	14446	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [1.24, 1.42]
23.2 Cilomilast 15 mg	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [1.08, 1.36]

24 Number of participants experiencing an adverse event (Roflumilast 500 μg versus 250 μg)	4	1977	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [1.01, 1.46]
25 Diarrhoea	25	20181	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [2.76, 3.54]
25.1 Roflumilast	11	13639	Odds Ratio (M-H, Fixed, 95% CI)	3.72 [3.15, 4.38]
25.2 Cilomilast	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	2.47 [2.05, 2.98]
26 Nausea	24	20627	Odds Ratio (M-H, Fixed, 95% CI)	3.78 [3.23, 4.43]
26.1 Roflumilast 500 μg	10	13229	Odds Ratio (M-H, Fixed, 95% CI)	3.21 [2.57, 4.03]
26.2 Roflumilast 250 μg	1	856	Odds Ratio (M-H, Fixed, 95% CI)	3.97 [0.91, 17.39]
26.3 Cilomilast 15 mg	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	4.37 [3.49, 5.47]
27 Headache	21	18977	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.47, 1.95]
27.1 Roflumilast 500 μg	10	13327	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [1.76, 2.63]
27.2 Roflumilast 250 μg	1	347	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.24, 3.99]
27.3 Cilomilast 15 mg	11	5303	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [1.08, 1.62]
28 Vomiting	11	5828	Odds Ratio (M-H, Fixed, 95% CI)	4.01 [2.80, 5.74]
28.1 Roflumilast	1	835	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.06, 37.37]
28.2 Cilomilast	10	4993	Odds Ratio (M-H, Fixed, 95% CI)	4.06 [2.83, 5.82]
29 Dyspepsia	13	6247	Odds Ratio (M-H, Fixed, 95% CI)	3.17 [2.33, 4.30]
29.1 Roflumilast	1	626	Odds Ratio (M-H, Fixed, 95% CI)	7.07 [0.36, 137.40]
29.2 Cilomilast	12	5621	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [2.30, 4.27]
30 Abdominal pain	13	8165	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [1.63, 2.55]
30.1 Roflumilast	2	2561	Odds Ratio (M-H, Fixed, 95% CI)	2.76 [1.35, 5.62]
30.2 Cilomilast	11	5604	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [1.55, 2.49]
31 Weight loss	9	12178	Odds Ratio (M-H, Fixed, 95% CI)	3.76 [3.11, 4.54]
31.1 Roflumilast	9	12178	Odds Ratio (M-H, Fixed, 95% CI)	3.76 [3.11, 4.54]
32 Influenza-like symptoms	9	11460	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.87, 1.36]
32.1 Roflumilast 500 μg	7	10147	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.87, 1.41]
32.2 Roflumilast 250 μg	1	347	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [0.18, 22.00]
32.3 Cilomilast 15 mg	2	966	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.75]
33 Upper respiratory tract infection	20	16902	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.02]
33.1 Roflumilast 500 μg	10	11419	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.07]
33.2 Roflumilast 250 μg	2	1203	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
33.3 Cilomilast 15 mg	10	4280	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.13]
34 Withdrawals due to adverse events	28	20996	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.74, 2.09]
34.1 Roflumilast 500 μg	14	14451	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [1.71, 2.13]
34.2 Cilomilast 15 mg	14	6545	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.61, 2.24]
35 Non-fatal serious adverse events	24	18689	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.07]
35.1 Roflumilast 500 μg	10	12144	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.11]
35.2 Cilomilast 15 mg	14	6545	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
36 Mortality	23	19344	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.76, 1.23]
36.1 Roflumilast	10	13012	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.29]
36.2 Cilomilast	13	6332	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.34, 1.45]
37 All psychiatric disorders (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 Roflumilast 500 μg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	2.13 [1.79, 2.54]
37.2 Roflumilast 250 μg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.56, 1.33]
38 Insomnia and sleep disorders (roflumilast)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 Roflumilast 500 μg	4	15482	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [2.11, 3.38]

38.2 Roflumilast 250 μg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.81, 2.70]
39 Anxiety or anxiety disorder (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
39.1 Roflumilast 500 μg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.26, 2.62]
39.2 Roflumilast 250 μg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.40, 2.21]
40 Depression (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.1 Roflumilast 500 μg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [1.11, 2.27]
40.2 Roflumilast 250 μg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.56]

Analysis 1.1. Comparison 1 PDE4 inhibitor versus placebo, Outcome 1 FEV1 (by drug).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 1 FEV_1 (by drug)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Roflumilast 500 μ g							
RO-2455-301-RD (ACROSS)	313	49 (159.5692)	313	-22 (159.5692)		5.0 %	71.00 [46.00, 96.00]
RO-2455-404-RD (REACT)	928	52 (194.9638)	941	-4 (196.3246)		6.4 %	56.00 [38.26, 73.74]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.4 %	13.00 [-120.78, 146.78]
Roflumilast FK1 101	169	109 (273)	86	57 (213)		1.6 %	52.00 [-9.00, 113.00]
Roflumilast FK1 103	200	78 (240)	186	39 (245)		2.2 %	39.00 [-9.44, 87.44]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		1.6 %	125.00 [64.96, 185.04]
Roflumilast IN-108	42	28 (486)	12	-124 (281)		0.1 %	152.00 [-64.52, 368.52]
Roflumilast M2-107	555	49 (283)	140	-39 (189)		3.0 %	88.00 [48.83, 127.17]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		5.8 %	42.00 [21.08, 62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		4.1 %	36.00 [5.52, 66.48]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		1.1 %	82.00 [8.34, 155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		1.7 %	96.00 [37.74, 154.26]
Roflumilast M2-124	745	46 (218)	745	8 (218)		5.5 %	38.00 [15.86, 60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		6.1 %	58.00 [38.59, 77.41]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		5.0 %	49.00 [24.07, 73.93]
Roflumilast M2-128	365	65 (229)	364	-16 (229)		3.7 %	81.00 [47.75, 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.836)	1174	0 (160.836)		7.4 %	53.00 [40.00, 66.00]

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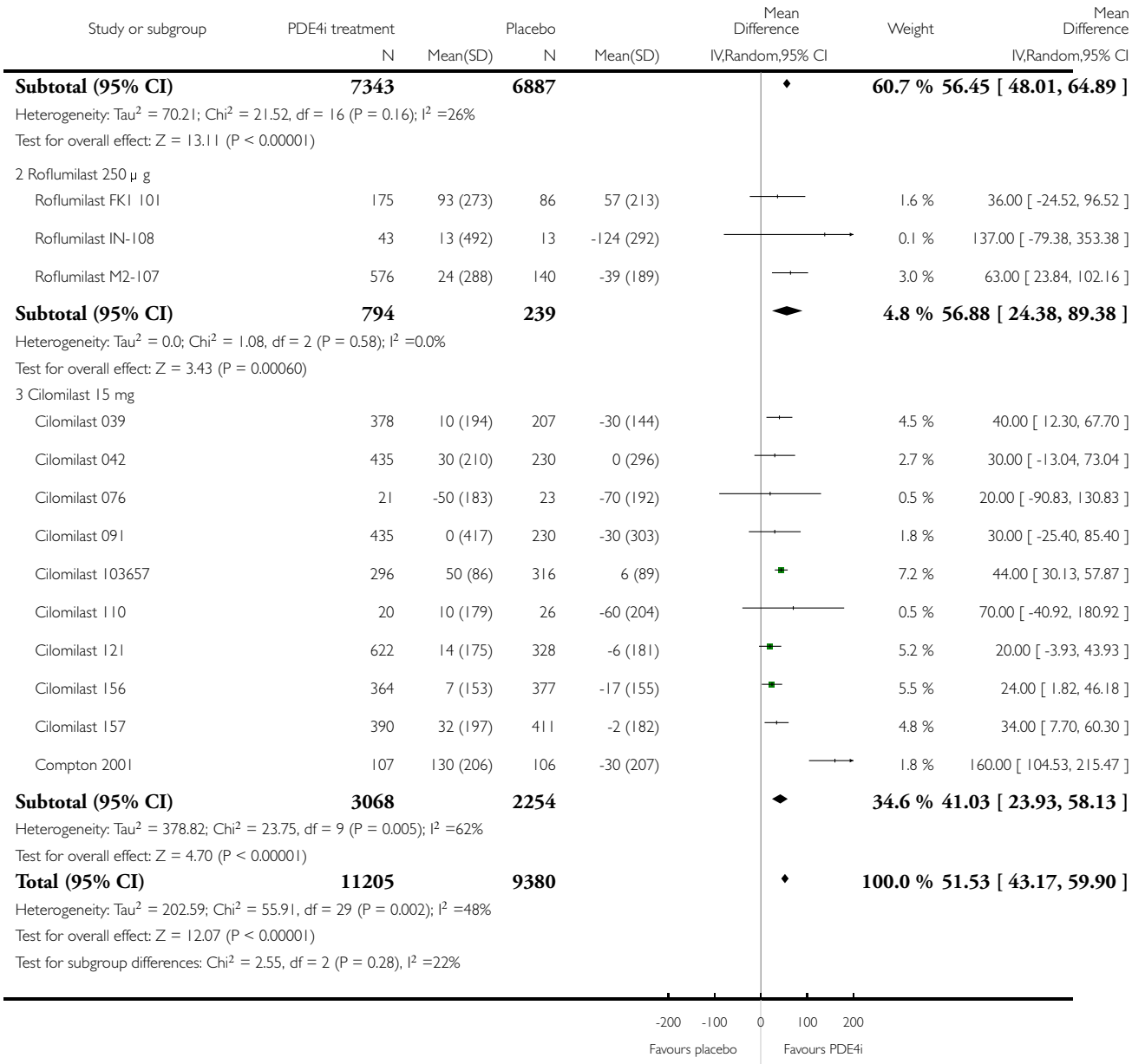

Analysis 1.2. Comparison 1 PDE4 inhibitor versus placebo, Outcome 2 FEV1 (by mean COPD severity).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 2 FEV_1 (by mean COPD severity)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 GOLD grade I + II (FEV1 ≥ 50% predicted)							
Cilomilast 076	21	-50 (183)	23	-70 (192)		0.3 %	20.00 [-90.83, 130.83]
Cilomilast 091	443	-30 (421)	232	-60 (305)		1.2 %	30.00 [-25.47, 85.47]
Cilomilast 156	364	7 (153)	377	-17 (155)		7.4 %	24.00 [1.82, 46.18]
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.1 %	152.00 [-64.35, 368.35]
Roflumilast M2-107	555	49 (283)	280	-39 (268)		2.4 %	88.00 [48.76, 127.24]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		0.7 %	82.00 [8.34, 155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		1.1 %	96.00 [37.74, 154.26]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		5.9 %	49.00 [24.07, 73.93]
Roflumilast M2-128	365	65 (229)	364	-16 (229)		3.3 %	81.00 [47.75, 114.25]
Subtotal (95% CI)	**2562**		**2085**		◆	**22.3 %**	**51.79 [38.99, 64.59]**
Heterogeneity: Chi^2 = 16.91, df = 8 (P = 0.03); I^2 =53%							
Test for overall effect: Z = 7.93 (P < 0.00001)							
2 GOLD grade III + IV (FEV1 < 50% predicted)							
Cilomilast 039	378	10 (194)	207	-30 (144)		4.8 %	40.00 [12.30, 67.70]
Cilomilast 042	440	30 (210)	219	0 (296)		1.9 %	30.00 [-13.84, 73.84]
Compton 2001	107	130 (206)	106	-30 (207)		1.2 %	160.00 [104.53, 215.47]
RO-2455-301-RD (ACROSS)	313	49 (159.5692)	313	-22 (159.5692)		5.9 %	71.00 [46.00, 96.00]
RO-2455-404-RD (REACT)	928	52 (194.9638)	941	-4 (196.3246)		11.6 %	56.00 [38.26, 73.74]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.2 %	13.00 [-120.78, 146.78]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		1.0 %	125.00 [64.96, 185.04]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		8.4 %	42.00 [21.08, 62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		3.9 %	36.00 [5.52, 66.48]
Roflumilast M2-124	745	46 (218)	745	8 (218)		7.5 %	38.00 [15.86, 60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		9.7 %	58.00 [38.59, 77.41]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.836)	1174	0 (160.836)		21.6 %	53.00 [40.00, 66.00]

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Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**6165**		**5847**		♦	**77.7 %**	**53.06 [46.19, 59.92]**
Heterogeneity: Chi^2 = 28.44, df = 11 (P = 0.003); I^2 =61%							
Test for overall effect: Z = 15.15 (P < 0.00001)							
Total (95% CI)	**8727**		**7932**		♦	**100.0 %**	**52.77 [46.73, 58.82]**
Heterogeneity: Chi^2 = 45.38, df = 20 (P = 0.00098); I^2 =56%							
Test for overall effect: Z = 17.10 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.86), I^2 =0.0%							

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Favours placebo Favours PDE4i

Analysis 1.3. Comparison 1 PDE4 inhibitor versus placebo, Outcome 3 FEV1 (Roflumilast 500 μg by mean COPD severity).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 3 FEV_1 (Roflumilast 500 μ g by mean COPD severity)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 GOLD grade I + II ($FEV_1 \geq$ 50% predicted)							
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.1 %	152.00 [-64.35, 368.35]
Roflumilast M2-107	555	49 (283)	280	-39 (268)		2.9 %	88.00 [48.76, 127.24]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		0.8 %	82.00 [8.34, 155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		1.3 %	96.00 [37.74, 154.26]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		7.1 %	49.00 [24.07, 73.93]
Roflumilast M2-128	365	65 (229)	364	-16 (229)		4.0 %	81.00 [47.75, 114.25]
Subtotal (95% CI)	**1734**		**1453**		◆	**16.1 %**	**69.86 [53.34, 86.38]**
Heterogeneity: Chi^2 = 5.37, df = 5 (P = 0.37); I^2 =7%							
Test for overall effect: Z = 8.29 (P < 0.00001)							

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Favours placebo Favours PDE4i

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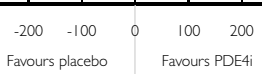
Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
2 GOLD grade III + IV (FEV_1 < 50% predicted)							
RO-2455-301-RD (ACROSS)	313	49 (159.5692)	313	-22 (159.5692)		7.0 %	71.00 [46.00, 96.00]
RO-2455-404-RD (REACT)	928	52 (194.9638)	941	-4 (196.3246)		14.0 %	56.00 [38.26, 73.74]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.2 %	13.00 [-120.78, 146.78]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		1.2 %	125.00 [64.96, 185.04]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		10.0 %	42.00 [21.08, 62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		4.7 %	36.00 [5.52, 66.48]
Roflumilast M2-124	745	46 (218)	745	8 (218)		9.0 %	38.00 [15.86, 60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		11.7 %	58.00 [38.59, 77.41]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.836)	1174	0 (160.836)		26.0 %	53.00 [40.00, 66.00]
Subtotal (95% CI)	**5240**		**5315**			**83.9 %**	**52.75 [45.52, 59.99]**
Heterogeneity: Chi^2 = 12.24, df = 8 (P = 0.14); I^2 =35%							
Test for overall effect: Z = 14.28 (P < 0.00001)							
Total (95% CI)	**6974**		**6768**			**100.0 %**	**55.51 [48.88, 62.14]**
Heterogeneity: Chi^2 = 21.07, df = 14 (P = 0.10); I^2 =34%							
Test for overall effect: Z = 16.41 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.45, df = 1 (P = 0.06), I^2 =71%							



Analysis 1.4. Comparison 1 PDE4 inhibitor versus placebo, Outcome 4 FEV1 (by study duration).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 4 FEV_1 (by study duration)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Duration ≤ 12 weeks							
Cilomilast 076	21	-50 (183)	23	-70 (192)		0.2 %	20.00 [-90.83, 130.83]
Cilomilast 110	20	10 (179)	26	-60 (204)		0.2 %	70.00 [-40.92, 180.92]
Compton 2001	107	130 (206)	106	-30 (207)		0.9 %	160.00 [104.53, 215.47]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.2 %	13.00 [-120.78, 146.78]
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.1 %	152.00 [-64.35, 368.35]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		0.5 %	82.00 [8.34, 155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		0.8 %	96.00 [37.74, 154.26]
Subtotal (95% CI)	**517**		**520**			**2.9 %**	**102.21 [71.26, 133.16]**
Heterogeneity: Chi^2 = 8.85, df = 6 (P = 0.18); I^2 =32%							
Test for overall effect: Z = 6.47 (P < 0.00001)							
2 Duration 24 to 26 weeks							
Cilomilast 039	378	10 (194)	207	-30 (144)		3.6 %	40.00 [12.30, 67.70]
Cilomilast 042	440	30 (210)	219	0 (296)		1.4 %	30.00 [-13.84, 73.84]
Cilomilast 091	435	0 (417)	230	-30 (303)		0.9 %	30.00 [-25.40, 85.40]
Cilomilast 103657	296	50 (86)	316	6 (89)		14.2 %	44.00 [30.13, 57.87]
Cilomilast 121	622	14 (175)	328	-6 (181)		4.8 %	20.00 [-3.93, 43.93]
Cilomilast 156	364	7 (153)	377	-17 (155)		5.6 %	24.00 [1.82, 46.18]
RO-2455-301-RD (ACROSS)	313	49 (159.5692)	313	-22 (159.5692)		4.4 %	71.00 [46.00, 96.00]
Roflumilast FK1 101	169	109 (273)	172	57 (302)		0.7 %	52.00 [-9.08, 113.08]
Roflumilast FK1 103	200	78 (240)	186	39 (245)		1.2 %	39.00 [-9.44, 87.44]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		0.8 %	125.00 [64.96, 185.04]
Roflumilast M2-107	555	49 (283)	280	-39 (268)		1.8 %	88.00 [48.76, 127.24]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		4.4 %	49.00 [24.07, 73.93]
Roflumilast M2-128	365	65 (229)	364	-16 (229)		2.5 %	81.00 [47.75, 114.25]
Subtotal (95% CI)	**4623**		**3463**			**46.2 %**	**46.14 [38.44, 53.84]**
Heterogeneity: Chi^2 = 28.73, df = 12 (P = 0.004); I^2 =58%							

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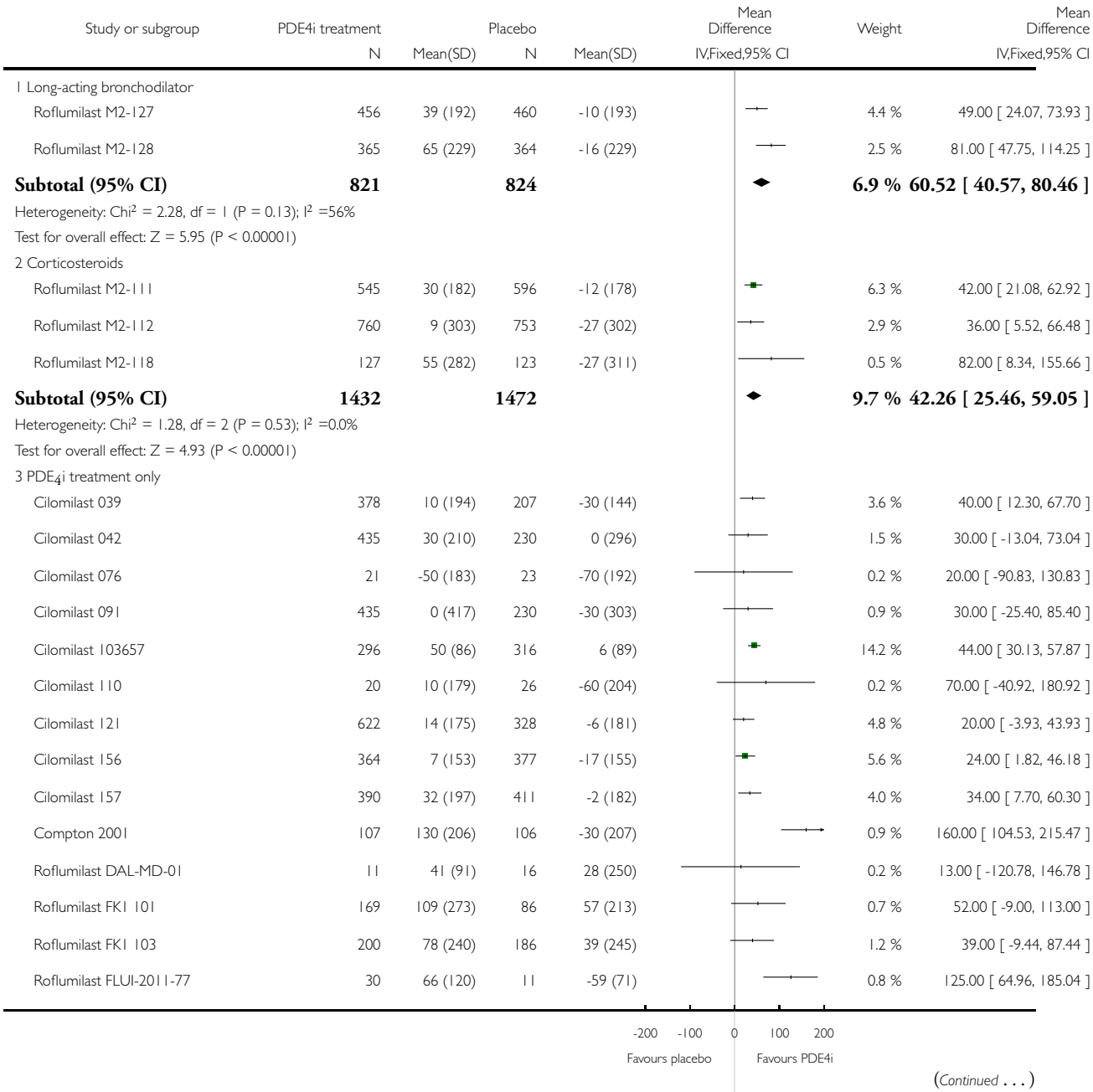
Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Test for overall effect: Z = 11.74 (P < 0.00001)							
3 Duration 52 weeks							
Cilomilast 157	390	32 (197)	411	-2 (182)		4.0 %	34.00 [7.70, 60.30]
RO-2455-404-RD (REACT)	928	52 (194.9638)	941	-4 (196.3246)		8.7 %	56.00 [38.26, 73.74]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		6.3 %	42.00 [21.08, 62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		2.9 %	36.00 [5.52, 66.48]
Roflumilast M2-124	745	46 (218)	745	8 (218)		5.6 %	38.00 [15.86, 60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		7.3 %	58.00 [38.59, 77.41]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.836)	1174	0 (160.836)		16.2 %	53.00 [40.00, 66.00]
Subtotal (95% CI)	**5276**		**5386**			**50.9 %**	**48.77 [41.44, 56.10]**
Heterogeneity: Chi^2 = 5.11, df = 6 (P = 0.53); I^2 =0.0%							
Test for overall effect: Z = 13.03 (P < 0.00001)							
Total (95% CI)	**10416**		**9369**			**100.0 %**	**49.08 [43.85, 54.32]**
Heterogeneity: Chi^2 = 54.58, df = 26 (P = 0.00086); I^2 =52%							
Test for overall effect: Z = 18.38 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 11.88, df = 2 (P = 0.00), I^2 =83%							

Analysis 1.5. Comparison 1 PDE4 inhibitor versus placebo, Outcome 5 FEV1 (additional medication).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 5 FEV_1 (additional medication)



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Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.1 %	152.00 [-64.35, 368.35]
Roflumilast M2-107	555	49 (283)	140	-39 (189)		1.8 %	88.00 [48.83, 127.17]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		0.8 %	96.00 [37.74, 154.26]
Roflumilast M2-124	745	46 (218)	745	8 (218)		5.6 %	38.00 [15.86, 60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		7.3 %	58.00 [38.59, 77.41]
Subtotal (95% CI)	**5739**		**4430**			**54.1 %**	**44.78 [37.67, 51.90]**
Heterogeneity: Chi^2 = 43.87, df = 18 (P = 0.00060); I^2 =59%							
Test for overall effect: Z = 12.34 (P < 0.00001)							
4 Various concomitant treatments							
RO-2455-301-RD (ACROSS)	313	49 (159.5692)	313	-22 (159.5692)		4.4 %	71.00 [46.00, 96.00]
RO-2455-404-RD (REACT)	928	52 (194.9638)	941	-4 (196.3246)		8.7 %	56.00 [38.26, 73.74]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.836)	1174	0 (160.836)		16.2 %	53.00 [40.00, 66.00]
Subtotal (95% CI)	**2419**		**2428**			**29.3 %**	**56.58 [46.91, 66.25]**
Heterogeneity: Chi^2 = 1.57, df = 2 (P = 0.46); I^2 =0.0%							
Test for overall effect: Z = 11.47 (P < 0.00001)							
Total (95% CI)	**10411**		**9154**			**100.0 %**	**49.08 [43.84, 54.31]**
Heterogeneity: Chi^2 = 54.62, df = 26 (P = 0.00085); I^2 =52%							
Test for overall effect: Z = 18.38 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 5.61, df = 3 (P = 0.13), I^2 =47%							

Analysis 1.6. Comparison 1 PDE4 inhibitor versus placebo, Outcome 6 FEV1 (published versus unpublished).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 6 FEV_1 (published versus unpublished)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Published							
Cilomilast 039	378	10 (194)	207	-30 (144)		3.6 %	40.00 [12.30, 67.70]
Cilomilast 076	21	-50 (183)	23	-70 (192)		0.2 %	20.00 [-90.83, 130.83]
Compton 2001	107	130 (206)	106	-30 (207)		0.9 %	160.00 [104.53, 215.47]
RO-2455-301-RD (ACROSS)	313	49 (159.5692)	313	-22 (159.5692)		4.4 %	71.00 [46.00, 96.00]
RO-2455-404-RD (REACT)	928	52 (194.9638)	941	-4 (196.3246)		8.7 %	56.00 [38.26, 73.74]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.2 %	13.00 [-120.78, 146.78]
Roflumilast FKI 101	169	109 (273)	172	57 (302)		0.7 %	52.00 [-9.08, 113.08]
Roflumilast FKI 103	200	78 (240)	186	39 (245)		1.2 %	39.00 [-9.44, 87.44]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		0.8 %	125.00 [64.96, 185.04]
Roflumilast M2-107	555	51 (283)	280	-45 (268)		1.8 %	96.00 [56.76, 135.24]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		6.3 %	42.00 [21.08, 62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		2.9 %	36.00 [5.52, 66.48]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		0.5 %	82.00 [8.34, 155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		0.8 %	96.00 [37.74, 154.26]
Roflumilast M2-124	745	46 (218)	745	8 (218)		5.6 %	38.00 [15.86, 60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		7.3 %	58.00 [38.59, 77.41]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		4.4 %	49.00 [24.07, 73.93]
Roflumilast M2-128	365	65 (229)	364	-16 (229)		2.5 %	81.00 [47.75, 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.836)	1174	0 (160.836)		16.2 %	53.00 [40.00, 66.00]
Subtotal (95% CI)	**7807**		**7437**			**68.8 %**	**55.75 [49.44, 62.06]**
Heterogeneity: Chi^2 = 37.44, df = 18 (P = 0.005); I^2 =52%							
Test for overall effect: Z = 17.32 (P < 0.00001)							
2 Unpublished							
Cilomilast 042	440	30 (210)	219	0 (296)		1.4 %	30.00 [-13.84, 73.84]
Cilomilast 091	435	0 (417)	230	-30 (303)		0.9 %	30.00 [-25.40, 85.40]

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Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Cilomilast 103657	296	50 (86)	316	6 (89)		14.2 %	44.00 [30.13, 57.87]
Cilomilast 110	20	10 (179)	26	-60 (204)		0.2 %	70.00 [-40.92, 180.92]
Cilomilast 121	622	14 (175)	328	-6 (181)		4.8 %	20.00 [-3.93, 43.93]
Cilomilast 156	364	7 (153)	377	-17 (155)		5.6 %	24.00 [1.82, 46.18]
Cilomilast 157	390	32 (197)	411	-2 (182)		4.0 %	34.00 [7.70, 60.30]
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.1 %	152.00 [-64.35, 368.35]
Subtotal (95% CI)	**2609**		**1932**			**31.2 %**	**34.82 [25.44, 44.19]**
Heterogeneity: Chi^2 = 5.66, df = 7 (P = 0.58); I^2 =0.0%							
Test for overall effect: Z = 7.28 (P < 0.00001)							
Total (95% CI)	**10416**		**9369**			**100.0 %**	**49.23 [43.99, 54.46]**
Heterogeneity: Chi^2 = 56.29, df = 26 (P = 0.00052); I^2 =54%							
Test for overall effect: Z = 18.43 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 13.18, df = 1 (P = 0.00), I^2 =92%							

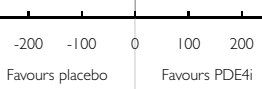
Analysis 1.7. Comparison 1 PDE4 inhibitor versus placebo, Outcome 7 FEV1 (random-effects model).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 7 FEV_1 (random-effects model)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Cilomilast 039	378	10 (194)	207	-30 (144)		4.8 %	40.00 [12.30, 67.70]
Cilomilast 042	440	30 (210)	219	0 (296)		2.8 %	30.00 [-13.84, 73.84]
Cilomilast 076	21	-50 (183)	23	-70 (192)		0.6 %	20.00 [-90.83, 130.83]
Cilomilast 091	435	0 (417)	230	-30 (303)		2.0 %	30.00 [-25.40, 85.40]
Cilomilast 103657	296	50 (86)	316	6 (89)		7.4 %	44.00 [30.13, 57.87]
Cilomilast 110	20	10 (179)	26	-60 (204)		0.6 %	70.00 [-40.92, 180.92]
Cilomilast 121	622	14 (175)	328	-6 (181)		5.4 %	20.00 [-3.93, 43.93]
Cilomilast 156	364	7 (153)	377	-17 (155)		5.8 %	24.00 [1.82, 46.18]
Cilomilast 157	390	32 (197)	411	-2 (182)		5.0 %	34.00 [7.70, 60.30]
Compton 2001	107	130 (206)	106	-30 (207)		2.0 %	160.00 [104.53, 215.47]
RO-2455-301-RD (ACROSS)	313	49 (159.5692)	313	-22 (159.5692)		5.2 %	71.00 [46.00, 96.00]
RO-2455-404-RD (REACT)	928	52 (194.9638)	941	-4 (196.3246)		6.6 %	56.00 [38.26, 73.74]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.4 %	13.00 [-120.78, 146.78]
Roflumilast FK1 101	169	109 (273)	172	57 (302)		1.7 %	52.00 [-9.08, 113.08]
Roflumilast FK1 103	200	78 (240)	186	39 (245)		2.4 %	39.00 [-9.44, 87.44]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		1.7 %	125.00 [64.96, 185.04]
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.2 %	152.00 [-64.35, 368.35]
Roflumilast M2-107	555	49 (283)	280	-39 (268)		3.2 %	88.00 [48.76, 127.24]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		6.0 %	42.00 [21.08, 62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		4.3 %	36.00 [5.52, 66.48]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		1.2 %	82.00 [8.34, 155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		1.8 %	96.00 [37.74, 154.26]
Roflumilast M2-124	745	46 (218)	745	8 (218)		5.8 %	38.00 [15.86, 60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		6.3 %	58.00 [38.59, 77.41]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		5.2 %	49.00 [24.07, 73.93]



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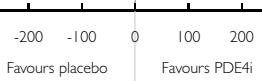
Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Roflumilast M2-128	365	65 (229)	364	-16 (229)		4.0 %	81.00 [47.75, 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.836)	1174	0 (160.836)		7.6 %	53.00 [40.00, 66.00]
Total (95% CI)	**10416**		**9369**			**100.0 %**	**51.47 [42.68, 60.26]**

Heterogeneity: Tau^2 = 221.76; Chi^2 = 54.58, df = 26 (P = 0.00086); I^2 =52%

Test for overall effect: Z = 11.47 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 PDE4 inhibitor versus placebo, Outcome 8 FEV1 (roflumilast 500 μg versus 250 μg).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 8 FEV_1 (roflumilast 500 μ g versus 250 μ g)

Study or subgroup	Roflumilast 500 μ g N	Mean(SD)	Roflumilast 250 μ g N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Roflumilast FK1 101	169	109 (273)	175	93 (273)		24.5 %	16.00 [-41.71, 73.71]
Roflumilast IN-108	42	28 (486)	43	13 (492)		1.9 %	15.00 [-192.91, 222.91]
Roflumilast M2-107	555	49 (283)	576	24 (288)		73.6 %	25.00 [-8.28, 58.28]
Total (95% CI)	**766**		**794**			**100.0 %**	**22.61 [-5.95, 51.16]**

Heterogeneity: Chi^2 = 0.08, df = 2 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 1.55 (P = 0.12)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 PDE4 inhibitor versus placebo, Outcome 9 FVC.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 9 FVC

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Cilomilast 039	394	-10 (397)	208	-120 (433)		3.1 %	110.00 [39.29, 180.71]
Cilomilast 042	448	30 (635)	220	-20 (445)		2.2 %	50.00 [-33.16, 133.16]
Cilomilast 091	443	-20 (631)	232	-70 (609)		1.6 %	50.00 [-47.95, 147.95]
Cilomilast 103657	296	25 (447)	316	-2 (409)		3.3 %	27.00 [-41.02, 95.02]
Cilomilast 156	377	20 (388)	383	-40 (391)		5.0 %	60.00 [4.62, 115.38]
Compton 2001	107	180 (517)	106	-15 (515)		0.8 %	195.00 [56.41, 333.59]
RO-2455-301-RD (ACROSS)	313	100 (306.3729)	313	-9 (306.3729)		6.7 %	109.00 [61.00, 157.00]
RO-2455-404-RD (REACT)	928	36 (347.2793)	7187	-57 (941)		15.8 %	93.00 [61.81, 124.19]
Roflumilast M2-107	555	39 (495)	280	-75 (452)		3.4 %	114.00 [46.93, 181.07]
Roflumilast M2-112	760	-33 (716)	753	-80 (713)		3.0 %	47.00 [-25.00, 119.00]
Roflumilast M2-119	189	51 (481)	202	-100 (483)		1.7 %	151.00 [55.40, 246.60]
Roflumilast M2-124	729	76 (405)	736	-25 (407)		8.9 %	101.00 [59.42, 142.58]
Roflumilast M2-125	724	58 (350)	764	-45 (359)		11.9 %	103.00 [66.97, 139.03]
Roflumilast M2-127	452	67 (319)	460	10 (322)		8.9 %	57.00 [15.40, 98.60]
Roflumilast M2-128	364	27 (439)	363	-74 (419)		4.0 %	101.00 [38.62, 163.38]
Roflumilast ROF-MD-07(RE2SPOND)	1178	83 (346.416)	1174	0 (346.416)		19.7 %	83.00 [55.00, 111.00]
Total (95% CI)	**8257**		**13697**			**100.0 %**	**87.28 [74.87, 99.70]**

Heterogeneity: Chi^2 = 15.89, df = 15 (P = 0.39); I^2 =6%

Test for overall effect: Z = 13.78 (P < 0.00001)

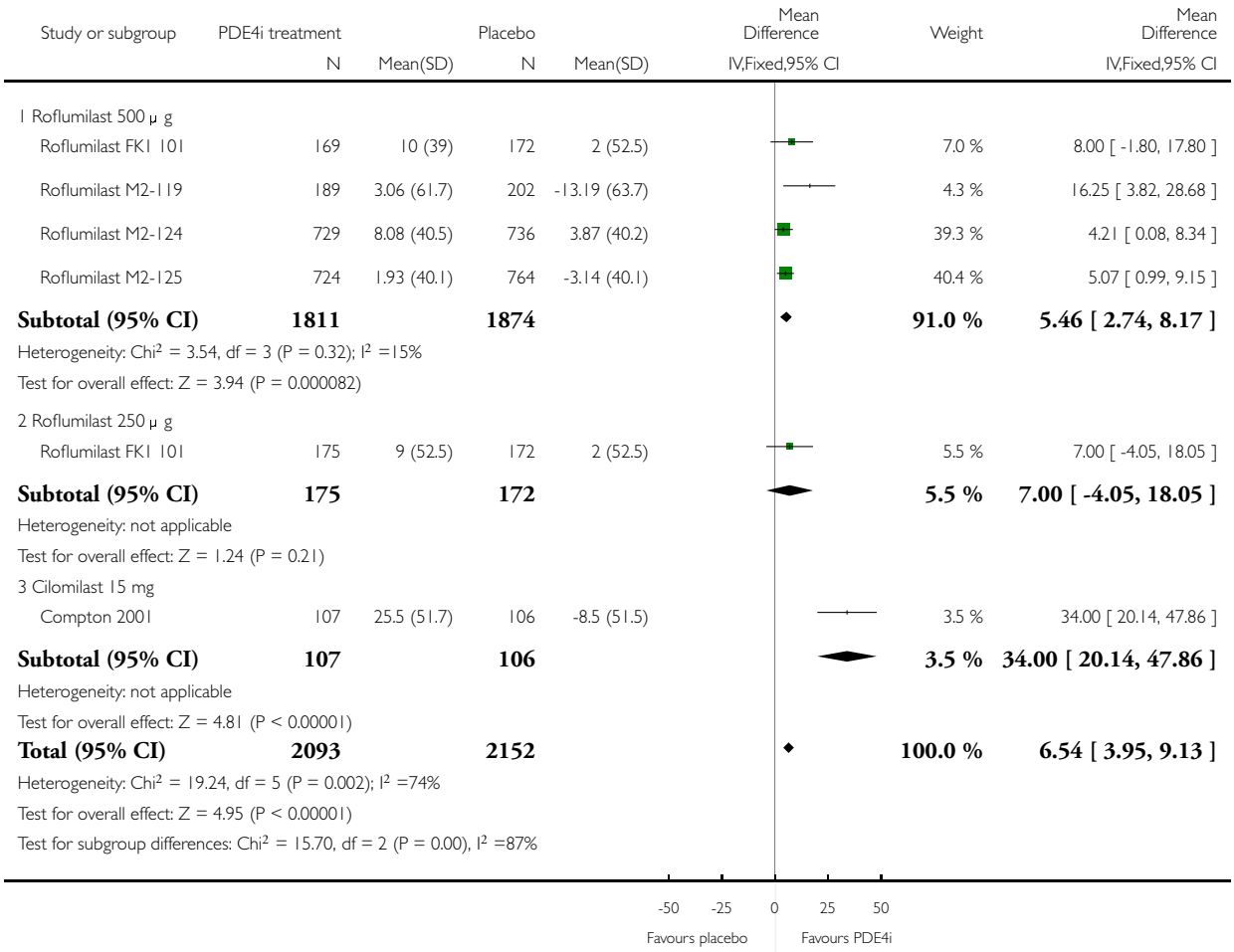
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 PDE4 inhibitor versus placebo, Outcome 10 PEF.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 10 PEF



Analysis 1.11. Comparison 1 PDE4 inhibitor versus placebo, Outcome 11 SGRQ total score.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 11 SGRQ total score

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Roflumilast 500 µ g							
Roflumilast DAL-MD-01	11	-7.5 (13.8)	16	-0.8 (13.8)		0.3 %	-6.70 [-17.29, 3.89]
Roflumilast M2-107	555	-3.5 (14.1)	140	-1.8 (9.5)		10.1 %	-1.70 [-3.66, 0.26]
Roflumilast M2-112	760	-1.7 (19.3)	753	-2 (19.2)		10.4 %	0.30 [-1.64, 2.24]
Subtotal (95% CI)	**1326**		**909**			**20.8 %**	**-0.79 [-2.16, 0.58]**
Heterogeneity: Chi^2 = 3.23, df = 2 (P = 0.20); I^2 =38%							
Test for overall effect: Z = 1.13 (P = 0.26)							
2 Roflumilast 250 µ g							
Roflumilast M2-107	576	-3.4 (14.4)	140	-1.8 (9.5)		10.1 %	-1.60 [-3.56, 0.36]
Subtotal (95% CI)	**576**		**140**			**10.1 %**	**-1.60 [-3.56, 0.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.60 (P = 0.11)							
3 Cilomilast 15 mg							
Cilomilast 039	310	-3.7 (12.32)	181	0.4 (10.76)		9.0 %	-4.10 [-6.18, -2.02]
Cilomilast 042	375	-4.2 (15.5)	190	-4.9 (13.8)		6.2 %	0.70 [-1.81, 3.21]
Cilomilast 091	369	-2.7 (21.1)	197	-2.3 (16.8)		3.8 %	-0.40 [-3.58, 2.78]
Cilomilast 103657	292	-1.8 (10.2)	310	-1.84 (10)		14.9 %	0.04 [-1.57, 1.65]
Cilomilast 121	580	-9 (14.7)	320	-8.7 (14.7)		9.7 %	-0.30 [-2.31, 1.71]
Cilomilast 156	304	-3.2 (10.5)	337	-1.3 (11)		14.0 %	-1.90 [-3.57, -0.23]
Cilomilast 157	347	-1.29 (14.9)	369	-1.49 (14.4)		8.4 %	0.20 [-1.95, 2.35]
Compton 2001	107	-3.9 (13.4)	106	0 (13.4)		3.0 %	-3.90 [-7.50, -0.30]
Subtotal (95% CI)	**2684**		**2010**			**69.1 %**	**-1.06 [-1.81, -0.31]**
Heterogeneity: Chi^2 = 17.26, df = 7 (P = 0.02); I^2 =59%							
Test for overall effect: Z = 2.76 (P = 0.0058)							
Total (95% CI)	**4586**		**3059**			**100.0 %**	**-1.06 [-1.68, -0.43]**
Heterogeneity: Chi^2 = 20.93, df = 11 (P = 0.03); I^2 =47%							
Test for overall effect: Z = 3.32 (P = 0.00091)							
Test for subgroup differences: Chi^2 = 0.44, df = 2 (P = 0.80), I^2 =0.0%							

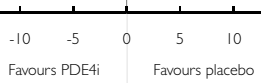
Analysis 1.12. Comparison 1 PDE4 inhibitor versus placebo, Outcome 12 SGRQ total score (by published versus unpublished).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 12 SGRQ total score (by published versus unpublished)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Published							
Cilomilast 039	310	-3.7 (12.32)	181	0.4 (10.76)		10.0 %	-4.10 [-6.18, -2.02]
Compton 2001	107	-3.9 (13.4)	106	0 (13.4)		3.3 %	-3.90 [-7.50, -0.30]
Roflumilast DAL-MD-01	11	-7.5 (13.8)	16	-0.8 (13.8)		0.4 %	-6.70 [-17.29, 3.89]
Roflumilast M2-107	555	-3.5 (14.1)	280	-1.8 (13.4)		11.3 %	-1.70 [-3.66, 0.26]
Roflumilast M2-112	760	-1.7 (19.3)	753	-2 (19.2)		11.5 %	0.30 [-1.64, 2.24]
Subtotal (95% CI)	**1743**		**1336**			**36.5 %**	**-1.98 [-3.07, -0.89]**
Heterogeneity: Chi^2 = 11.22, df = 4 (P = 0.02); I^2 =64%							
Test for overall effect: Z = 3.56 (P = 0.00037)							
2 Unpublished							
Cilomilast 042	375	-4.2 (15.5)	190	-4.9 (13.8)		6.9 %	0.70 [-1.81, 3.21]
Cilomilast 091	369	-2.7 (21.1)	197	-2.3 (16.8)		4.3 %	-0.40 [-3.58, 2.78]
Cilomilast 103657	292	-1.8 (10.2)	310	-1.84 (10)		16.6 %	0.04 [-1.57, 1.65]
Cilomilast 121	580	-9 (14.7)	320	-8.7 (14.7)		10.8 %	-0.30 [-2.31, 1.71]
Cilomilast 156	304	-3.2 (10.5)	337	-1.3 (11)		15.6 %	-1.90 [-3.57, -0.23]
Cilomilast 157	347	-1.29 (14.9)	369	-1.49 (14.4)		9.4 %	0.20 [-1.95, 2.35]
Subtotal (95% CI)	**2267**		**1723**			**63.5 %**	**-0.43 [-1.26, 0.40]**
Heterogeneity: Chi^2 = 4.44, df = 5 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 1.02 (P = 0.31)							
Total (95% CI)	**4010**		**3059**			**100.0 %**	**-1.00 [-1.65, -0.34]**
Heterogeneity: Chi^2 = 20.61, df = 10 (P = 0.02); I^2 =51%							
Test for overall effect: Z = 2.96 (P = 0.0030)							
Test for subgroup differences: Chi^2 = 4.94, df = 1 (P = 0.03), I^2 =80%							



Analysis 1.13. Comparison 1 PDE4 inhibitor versus placebo, Outcome 13 SGRQ total score (by duration).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 13 SGRQ total score (by duration)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Duration < 12 weeks							
Compton 2001	107	-3.9 (13.4)	106	0 (13.4)		3.3 %	-3.90 [-7.50, -0.30]
Roflumilast DAL-MD-01	11	-7.5 (13.8)	16	-0.8 (13.8)		0.4 %	-6.70 [-17.29, 3.89]
Subtotal (95% CI)	**118**		**122**			**3.7 %**	**-4.19 [-7.60, -0.78]**
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.62); I^2 =0.0%							
Test for overall effect: Z = 2.41 (P = 0.016)							
2 Duration 24 to 26 weeks							
Cilomilast 039	310	-3.7 (12.32)	181	0.4 (10.76)		10.0 %	-4.10 [-6.18, -2.02]
Cilomilast 042	375	-4.2 (15.5)	190	-4.9 (13.8)		6.9 %	0.70 [-1.81, 3.21]
Cilomilast 091	369	-2.7 (21.1)	197	-2.3 (16.8)		4.3 %	-0.40 [-3.58, 2.78]
Cilomilast 103657	292	-1.8 (10.2)	310	-1.84 (10)		16.6 %	0.04 [-1.57, 1.65]
Cilomilast 121	580	-9 (14.7)	320	-8.7 (14.7)		10.8 %	-0.30 [-2.31, 1.71]
Cilomilast 156	304	-3.2 (10.5)	337	-1.32 (11)		15.6 %	-1.88 [-3.55, -0.21]
Roflumilast M2-107	555	-3.5 (14.1)	280	-1.8 (13.4)		11.3 %	-1.70 [-3.66, 0.26]
Subtotal (95% CI)	**2785**		**1815**			**75.4 %**	**-1.18 [-1.94, -0.42]**
Heterogeneity: Chi^2 = 13.81, df = 6 (P = 0.03); I^2 =57%							
Test for overall effect: Z = 3.05 (P = 0.0023)							
3 Duration 52 weeks							
Cilomilast 157	347	-1.29 (14.9)	369	-1.49 (14.4)		9.4 %	0.20 [-1.95, 2.35]
Roflumilast M2-112	760	-1.7 (19.3)	753	-2 (19.2)		11.5 %	0.30 [-1.64, 2.24]
Subtotal (95% CI)	**1107**		**1122**			**20.9 %**	**0.26 [-1.18, 1.69]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
Total (95% CI)	**4010**		**3059**			**100.0 %**	**-0.99 [-1.65, -0.33]**
Heterogeneity: Chi^2 = 20.56, df = 10 (P = 0.02); I^2 =51%							
Test for overall effect: Z = 2.96 (P = 0.0031)							
Test for subgroup differences: Chi^2 = 6.50, df = 2 (P = 0.04), I^2 =69%							

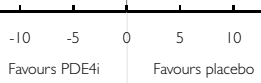
Analysis 1.14. Comparison 1 PDE4 inhibitor versus placebo, Outcome 14 SGRQ total score (by mean COPD severity).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 14 SGRQ total score (by mean COPD severity)

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 GOLD grade I and II							
Cilomilast 091	369	-2.7 (21.1)	197	-2.3 (16.8)		6.8 %	-0.40 [-3.58, 2.78]
Cilomilast 156	304	-3.2 (10.5)	337	-1.3 (11)		24.7 %	-1.90 [-3.57, -0.23]
Roflumilast M2-107	555	-3.5 (14.1)	280	-1.8 (13.4)		17.8 %	-1.70 [-3.66, 0.26]
Subtotal (95% CI)	**1228**		**814**			**49.3 %**	**-1.62 [-2.80, -0.44]**
Heterogeneity: Chi^2 = 0.68, df = 2 (P = 0.71); I^2 =0.0%							
Test for overall effect: Z = 2.70 (P = 0.0070)							
2 GOLD grade III and IV							
Cilomilast 039	310	-3.7 (12.32)	181	0.4 (10.76)		15.8 %	-4.10 [-6.18, -2.02]
Cilomilast 042	375	-4.2 (15.5)	190	-4.9 (13.8)		10.8 %	0.70 [-1.81, 3.21]
Compton 2001	107	-3.9 (13.4)	106	0 (13.4)		5.3 %	-3.90 [-7.50, -0.30]
Roflumilast DAL-MD-01	11	-7.5 (13.8)	16	-0.8 (13.8)		0.6 %	-6.70 [-17.29, 3.89]
Roflumilast M2-112	760	-1.7 (19.3)	753	-2 (19.2)		18.2 %	0.30 [-1.64, 2.24]
Subtotal (95% CI)	**1563**		**1246**			**50.7 %**	**-1.51 [-2.67, -0.34]**
Heterogeneity: Chi^2 = 14.87, df = 4 (P = 0.005); I^2 =73%							
Test for overall effect: Z = 2.54 (P = 0.011)							
Total (95% CI)	**2791**		**2060**			**100.0 %**	**-1.56 [-2.39, -0.74]**
Heterogeneity: Chi^2 = 15.57, df = 7 (P = 0.03); I^2 =55%							
Test for overall effect: Z = 3.70 (P = 0.00021)							
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.89), I^2 =0.0%							

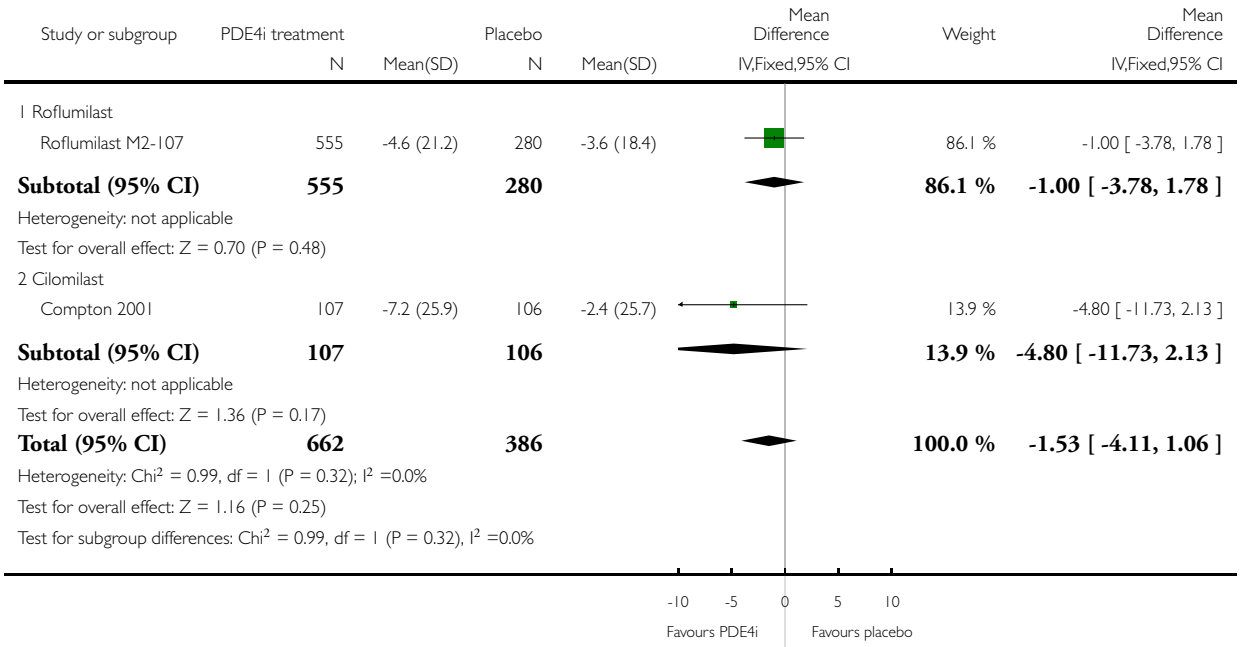


Analysis 1.15. Comparison 1 PDE4 inhibitor versus placebo, Outcome 15 SGRQ symptom score.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 15 SGRQ symptom score

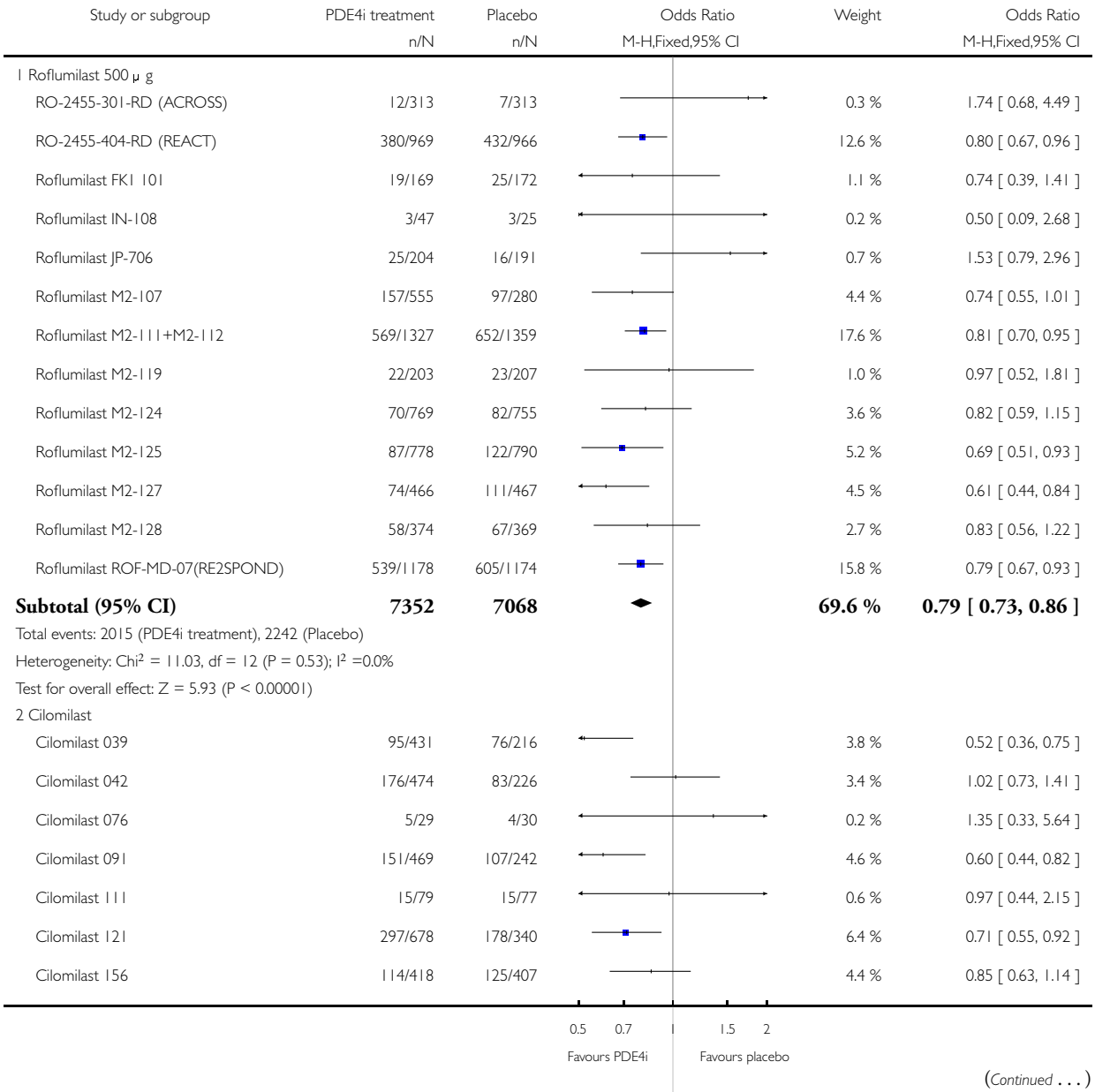


Analysis 1.16. Comparison 1 PDE4 inhibitor versus placebo, Outcome 16 Number of participants with one or more exacerbations (by drug).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 16 Number of participants with one or more exacerbations (by drug)



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Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 157	191/455	209/452		5.8 %	0.84 [0.65, 1.09]
Cilomilast 168	28/203	18/103		1.0 %	0.76 [0.40, 1.44]
Cilomilast 180	3/97	6/102		0.3 %	0.51 [0.12, 2.10]
Subtotal (95% CI)	**3333**	**2195**		**30.4 %**	**0.76 [0.67, 0.85]**
Total events: 1075 (PDE4i treatment), 821 (Placebo)					
Heterogeneity: Chi^2 = 12.00, df = 9 (P = 0.21); I^2 =25%					
Test for overall effect: Z = 4.64 (P < 0.00001)					
Total (95% CI)	**10685**	**9263**		**100.0 %**	**0.78 [0.73, 0.83]**
Total events: 3090 (PDE4i treatment), 3063 (Placebo)					
Heterogeneity: Chi^2 = 23.45, df = 22 (P = 0.38); I^2 =6%					
Test for overall effect: Z = 7.50 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.40, df = 1 (P = 0.53), I^2 =0.0%					

Analysis 1.17. Comparison 1 PDE4 inhibitor versus placebo, Outcome 17 Number of participants on roflumilast with one or more exacerbations (additional medication).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 17 Number of participants on roflumilast with one or more exacerbations (additional medication)

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Long-acting bronchodilators					
Roflumilast M2-127	74/466	111/467		6.4 %	0.61 [0.44, 0.84]
Roflumilast M2-128	58/374	67/369		3.9 %	0.83 [0.56, 1.22]
Subtotal (95% CI)	**840**	**836**		**10.3 %**	**0.69 [0.54, 0.88]**
Total events: 132 (PDE4i treatment), 178 (Placebo)					
Heterogeneity: Chi^2 = 1.47, df = 1 (P = 0.23); I^2 =32%					
Test for overall effect: Z = 2.93 (P = 0.0034)					
2 Corticosteroids					
Roflumilast M2-111+M2-112	569/1327	652/1359		25.3 %	0.81 [0.70, 0.95]
Subtotal (95% CI)	**1327**	**1359**		**25.3 %**	**0.81 [0.70, 0.95]**
Total events: 569 (PDE4i treatment), 652 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.65 (P = 0.0080)					
3 Treatment only					
Roflumilast FK1 101	19/169	25/172		1.5 %	0.74 [0.39, 1.41]
Roflumilast IN-108	3/47	3/25		0.3 %	0.50 [0.09, 2.68]
Roflumilast JP-706	25/204	16/191		1.0 %	1.53 [0.79, 2.96]
Roflumilast M2-107	157/555	97/280		6.4 %	0.74 [0.55, 1.01]
Roflumilast M2-119	22/203	23/207		1.4 %	0.97 [0.52, 1.81]
Roflumilast M2-124	70/769	82/755		5.2 %	0.82 [0.59, 1.15]
Roflumilast M2-125	87/778	122/790		7.4 %	0.69 [0.51, 0.93]
Subtotal (95% CI)	**2725**	**2420**		**23.1 %**	**0.79 [0.67, 0.93]**
Total events: 383 (PDE4i treatment), 368 (Placebo)					
Heterogeneity: Chi^2 = 5.59, df = 6 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 2.89 (P = 0.0038)					
4 Various concomitant treatments					
RO-2455-301-RD (ACROSS)	12/313	7/313		0.5 %	1.74 [0.68, 4.49]
RO-2455-404-RD (REACT)	380/969	432/966		18.1 %	0.80 [0.67, 0.96]
Roflumilast ROF-MD-07(RE2SPOND)	540/1178	605/1174		22.6 %	0.80 [0.68, 0.94]
Subtotal (95% CI)	**2460**	**2453**		**41.2 %**	**0.81 [0.72, 0.91]**

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Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 932 (PDE4i treatment), 1044 (Placebo)					
Heterogeneity: Chi^2 = 2.59, df = 2 (P = 0.27); I^2 =23%					
Test for overall effect: Z = 3.51 (P = 0.00045)					
Total (95% CI)	**7352**	**7068**	◆	**100.0 %**	**0.79 [0.73, 0.86]**
Total events: 2016 (PDE4i treatment), 2242 (Placebo)					
Heterogeneity: Chi^2 = 11.03, df = 12 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 5.91 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.41, df = 3 (P = 0.70), I^2 =0.0%					

Analysis 1.18. Comparison 1 PDE4 inhibitor versus placebo, Outcome 18 Exacerbation rate (inverse variance).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 18 Exacerbation rate (inverse variance)

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Roflumilast				
RO-2455-404-RD (REACT)	-0.1416 (0.0725)	■	15.5 %	0.87 [0.75, 1.00]
Roflumilast M2-111	-0.1508 (0.1001)	■	8.2 %	0.86 [0.71, 1.05]
Roflumilast M2-112	-0.0683 (0.0809)	■	12.5 %	0.93 [0.80, 1.09]
Roflumilast M2-124	-0.1625 (0.0717)	■	15.9 %	0.85 [0.74, 0.98]
Roflumilast M2-125	-0.1985 (0.0716)	■	15.9 %	0.82 [0.71, 0.94]
Roflumilast M2-127	-0.2357 (0.1586)	■	3.2 %	0.79 [0.58, 1.08]
Roflumilast M2-128	-0.1744 (0.1962)	■	2.1 %	0.84 [0.57, 1.23]
Roflumilast ROF-MD-07(RE2SPOND)	-0.0834 (0.065)	■	19.3 %	0.92 [0.81, 1.04]
Subtotal (95% CI)		◆	**92.7 %**	**0.87 [0.82, 0.92]**

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Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
Heterogeneity: Chi² = 2.71, df = 7 (P = 0.91); I² =0.0%				
Test for overall effect: Z = 4.64 (P < 0.00001)				
2 Cilomilast				
Cilomilast 157	-0.0473 (0.1057)		7.3 %	0.95 [0.78, 1.17]
Subtotal (95% CI)			**7.3 %**	**0.95 [0.78, 1.17]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.45 (P = 0.65)				
Total (95% CI)			**100.0 %**	**0.88 [0.83, 0.93]**
Heterogeneity: Chi² = 3.39, df = 8 (P = 0.91); I² =0.0%				
Test for overall effect: Z = 4.59 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² =0.0%				

Analysis 1.19. Comparison 1 PDE4 inhibitor versus placebo, Outcome 19 Borg Scale.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 19 Borg Scale

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Cilomilast							
Cilomilast 039	357	-0.13 (1.7)	196	0.19 (1.7)		22.8 %	-0.32 [-0.62, -0.02]
Cilomilast 042	422	-0.29 (2.1)	206	-0.11 (1.9)		18.6 %	-0.18 [-0.51, 0.15]
Cilomilast 091	417	0.03 (2.9)	223	0.21 (2.2)		12.4 %	-0.18 [-0.58, 0.22]
Cilomilast 111	73	0.03 (1.6)	69	-0.03 (1.7)		6.8 %	0.06 [-0.48, 0.60]
Cilomilast 156	347	-0.16 (1.7)	369	0.02 (1.5)		36.0 %	-0.18 [-0.42, 0.06]
Cilomilast 180	84	-0.1 (2.7)	97	0 (2.5)		3.4 %	-0.10 [-0.86, 0.66]
Total (95% CI)	**1700**		**1160**			**100.0 %**	**-0.19 [-0.33, -0.05]**

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Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Heterogeneity: Chi^2 = 1.62, df = 5 (P = 0.90); I^2 =0.0%							
Test for overall effect: Z = 2.68 (P = 0.0075)							
Test for subgroup differences: Not applicable							

Analysis 1.20. Comparison 1 PDE4 inhibitor versus placebo, Outcome 20 Summary symptom score.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 20 Summary symptom score

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Roflumilast							
RO-2455-404-RD (REACT)	969	-1.27 (4.8436)	966	-0.99 (4.718)		32.3 %	-0.06 [-0.15, 0.03]
Roflumilast ROF-MD-07(RE2SPOND)	1178	0 (4.3302)	1174	-0.06 (4.3302)		39.3 %	0.01 [-0.07, 0.09]
Subtotal (95% CI)	**2147**		**2140**			**71.6 %**	**-0.02 [-0.08, 0.04]**
Heterogeneity: Chi^2 = 1.43, df = 1 (P = 0.23); I^2 =30%							
Test for overall effect: Z = 0.63 (P = 0.53)							
2 Cilomilast							
Cilomilast 039	382	-0.21 (1.8)	202	-0.12 (1.7)		8.8 %	-0.05 [-0.22, 0.12]
Cilomilast 042	435	-0.41 (2.3)	212	-0.59 (1.9)		9.5 %	0.08 [-0.08, 0.25]
Cilomilast 091	437	-0.3 (2.7)	231	0.04 (2.3)		10.1 %	-0.13 [-0.29, 0.03]
Subtotal (95% CI)	**1254**		**645**			**28.4 %**	**-0.04 [-0.13, 0.06]**
Heterogeneity: Chi^2 = 3.43, df = 2 (P = 0.18); I^2 =42%							
Test for overall effect: Z = 0.72 (P = 0.47)							
Total (95% CI)	**3401**		**2785**			**100.0 %**	**-0.02 [-0.07, 0.03]**
Heterogeneity: Chi^2 = 4.93, df = 4 (P = 0.29); I^2 =19%							
Test for overall effect: Z = 0.92 (P = 0.36)							
Test for subgroup differences: Chi^2 = 0.08, df = 1 (P = 0.78), I^2 =0.0%							

Analysis 1.21. Comparison 1 PDE4 inhibitor versus placebo, Outcome 21 Shortness of breath questionnaire.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 21 Shortness of breath questionnaire

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Roflumilast M2-127	454	-0.6 (14.9)	461	-1.1 (15)		50.2 %	0.50 [-1.44, 2.44]
Roflumilast M2-128	359	-3.4 (13.3)	359	-0.7 (13.3)		49.8 %	-2.70 [-4.65, -0.75]
Total (95% CI)	**813**		**820**			**100.0 %**	**-1.09 [-2.47, 0.28]**

Heterogeneity: Chi^2 = 5.22, df = 1 (P = 0.02); I^2 =81%

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

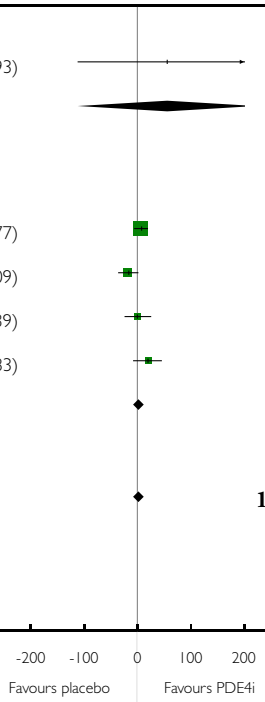
Analysis 1.22. Comparison 1 PDE4 inhibitor versus placebo, Outcome 22 6-minute walk test.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 22 6-minute walk test

Study or subgroup	PDE4i treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Roflumilast							
Roflumilast DAL-MD-01	11	55 (142)	16	0 (293)		0.3 %	55.00 [-111.29, 221.29]
Subtotal (95% CI)	**11**		**16**			**0.3 %**	**55.00 [-111.29, 221.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.65 (P = 0.52)							
2 Cilomilast							
Cilomilast 039	356	16.1 (79)	194	9 (77)		48.6 %	7.10 [-6.49, 20.69]
Cilomilast 042	423	5.8 (125)	207	22.2 (109)		24.8 %	-16.40 [-35.44, 2.64]
Cilomilast 091	408	5.4 (178)	218	4.6 (139)		14.1 %	0.80 [-24.47, 26.07]
Cilomilast 111	73	16.1 (82)	69	-3.7 (83)		12.2 %	19.80 [-7.35, 46.95]
Subtotal (95% CI)	**1260**		**688**			**99.7 %**	**1.92 [-7.58, 11.41]**
Heterogeneity: Chi^2 = 5.79, df = 3 (P = 0.12); I^2 =48%							
Test for overall effect: Z = 0.40 (P = 0.69)							
Total (95% CI)	**1271**		**704**			**100.0 %**	**2.09 [-7.39, 11.57]**
Heterogeneity: Chi^2 = 6.18, df = 4 (P = 0.19); I^2 =35%							
Test for overall effect: Z = 0.43 (P = 0.67)							
Test for subgroup differences: Chi^2 = 0.39, df = 1 (P = 0.53), I^2 =0.0%							

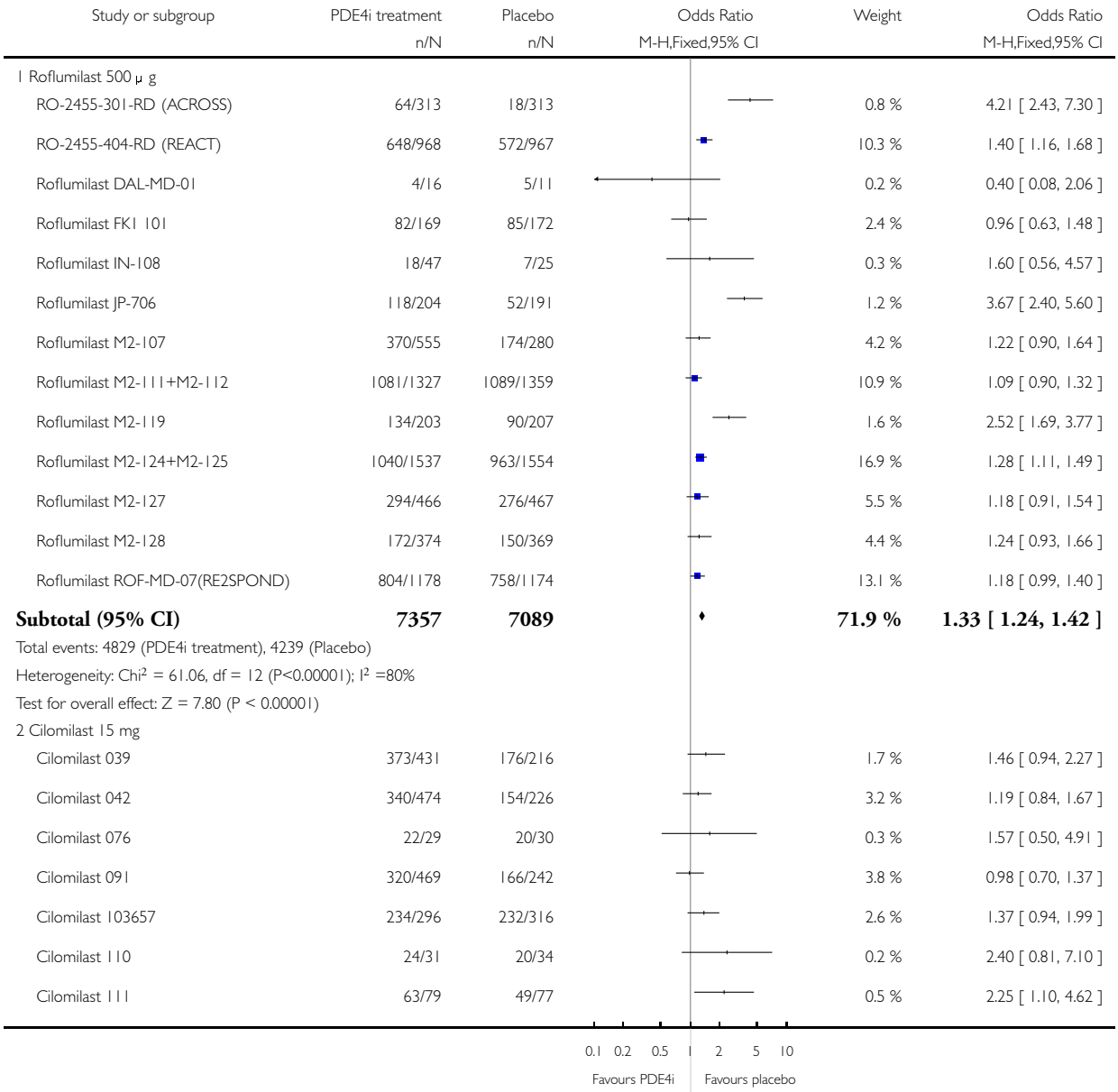


Analysis 1.23. Comparison 1 PDE4 inhibitor versus placebo, Outcome 23 Number of participants experiencing an adverse effect.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 23 Number of participants experiencing an adverse effect



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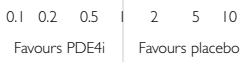
Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 121	518/678	245/340		4.2 %	1.26 [0.93, 1.69]
Cilomilast 156	364/418	339/407		2.4 %	1.35 [0.92, 1.99]
Cilomilast 157	351/455	343/452		4.3 %	1.07 [0.79, 1.46]
Cilomilast 168	136/203	76/103		1.8 %	0.72 [0.43, 1.22]
Cilomilast 180	65/97	68/102		1.2 %	1.02 [0.56, 1.83]
Cilomilast 181	41/65	36/62		0.7 %	1.23 [0.60, 2.52]
Compton 2001	64/105	55/105		1.2 %	1.42 [0.82, 2.45]
Subtotal (95% CI)	**3830**	**2712**		**28.1 %**	**1.21 [1.08, 1.36]**
Total events: 2915 (PDE4i treatment), 1979 (Placebo)					
Heterogeneity: Chi^2 = 12.53, df = 13 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.19 (P = 0.0014)					
Total (95% CI)	**11187**	**9801**		**100.0 %**	**1.29 [1.22, 1.37]**
Total events: 7744 (PDE4i treatment), 6218 (Placebo)					
Heterogeneity: Chi^2 = 75.16, df = 26 (P<0.00001); I^2 =65%					
Test for overall effect: Z = 8.32 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.84, df = 1 (P = 0.17), I^2 =46%					



Analysis 1.24. Comparison 1 PDE4 inhibitor versus placebo, Outcome 24 Number of participants experiencing an adverse event (Roflumilast 500 μg versus 250 μg).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 24 Number of participants experiencing an adverse event (Roflumilast 500 μg versus 250 μg)

Study or subgroup	Roflumilast 500 μg n/N	Roflumilast 250 μg n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Roflumilast FK1 101	82/169	85/175		20.4 %	1.00 [0.65, 1.52]
Roflumilast IN-108	18/47	17/46		5.0 %	1.06 [0.46, 2.45]
Roflumilast JP-706	118/204	76/205		15.2 %	2.33 [1.57, 3.46]
Roflumilast M2-107	370/555	382/576		59.4 %	1.02 [0.79, 1.30]
Total (95% CI)	**975**	**1002**		**100.0 %**	**1.21 [1.01, 1.46]**

Total events: 588 (Roflumilast 500 μg), 560 (Roflumilast 250 μg)

Heterogeneity: Chi^2 = 13.28, df = 3 (P = 0.004); I^2 =77%

Test for overall effect: Z = 2.08 (P = 0.037)

Test for subgroup differences: Not applicable

Analysis 1.25. Comparison 1 PDE4 inhibitor versus placebo, Outcome 25 Diarrhoea.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 25 Diarrhoea

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast					
RO-2455-301-RD (ACROSS)	19/313	3/313		0.9 %	6.68 [1.96, 22.80]
RO-2455-404-RD (REACT)	99/968	35/967		9.6 %	3.03 [2.04, 4.51]
Roflumilast DAL-MD-01	1/11	0/16		0.1 %	4.71 [0.18, 126.90]
Roflumilast M2-107	50/555	6/280		2.2 %	4.52 [1.91, 10.68]
Roflumilast M2-111+M2-112	161/1327	39/1359		10.4 %	4.67 [3.27, 6.69]
Roflumilast M2-119	23/203	1/207		0.3 %	26.32 [3.52, 196.86]
Roflumilast M2-124	63/769	26/755		7.4 %	2.50 [1.57, 4.00]
Roflumilast M2-125	67/778	23/790		6.4 %	3.14 [1.94, 5.10]
Roflumilast M2-127	38/466	16/467		4.5 %	2.50 [1.37, 4.56]
Roflumilast M2-128	33/374	2/369		0.6 %	17.76 [4.23, 74.57]
Roflumilast ROF-MD-07(RE2SPOND)	119/1178	38/1174		10.5 %	3.36 [2.31, 4.89]
Subtotal (95% CI)	**6942**	**6697**		**52.7 %**	**3.72 [3.15, 4.38]**
Total events: 673 (PDE4i treatment), 189 (Placebo)					
Heterogeneity: Chi^2 = 17.02, df = 10 (P = 0.07); I^2 =41%					
Test for overall effect: Z = 15.55 (P < 0.00001)					
2 Cilomilast					
Cilomilast 039	90/431	23/216		7.4 %	2.21 [1.36, 3.62]
Cilomilast 042	38/474	8/226		3.0 %	2.38 [1.09, 5.18]
Cilomilast 076	6/29	4/30		1.0 %	1.70 [0.42, 6.77]
Cilomilast 091	47/469	10/242		3.6 %	2.58 [1.28, 5.21]
Cilomilast 103657	50/296	20/316		4.9 %	3.01 [1.74, 5.19]
Cilomilast 110	4/31	2/34		0.5 %	2.37 [0.40, 13.96]
Cilomilast 111	14/79	3/77		0.8 %	5.31 [1.46, 19.31]
Cilomilast 121	94/678	20/340		7.0 %	2.58 [1.56, 4.25]
Cilomilast 156	82/418	44/407		11.0 %	2.01 [1.36, 2.99]
Cilomilast 157	33/455	13/452		3.7 %	2.64 [1.37, 5.09]

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Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 168	28/203	7/103		2.4 %	2.19 [0.92, 5.21]
Cilomilast 180	9/97	3/102		0.8 %	3.38 [0.89, 12.86]
Cilomilast 181	5/65	2/62		0.6 %	2.50 [0.47, 13.39]
Compton 2001	9/105	2/105		0.6 %	4.83 [1.02, 22.91]
Subtotal (95% CI)	**3830**	**2712**		**47.3 %**	**2.47 [2.05, 2.98]**
Total events: 509 (PDE4i treatment), 161 (Placebo)					
Heterogeneity: Chi^2 = 4.44, df = 13 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 9.40 (P < 0.00001)					
Total (95% CI)	**10772**	**9409**		**100.0 %**	**3.13 [2.76, 3.54]**
Total events: 1182 (PDE4i treatment), 350 (Placebo)					
Heterogeneity: Chi^2 = 29.35, df = 24 (P = 0.21); I^2 =18%					
Test for overall effect: Z = 18.01 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 10.17, df = 1 (P = 0.00), I^2 =90%					

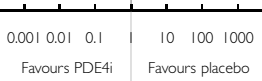
Analysis 1.26. Comparison 1 PDE4 inhibitor versus placebo, Outcome 26 Nausea.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 26 Nausea

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast 500 μ g					
RO-2455-301-RD (ACROSS)	3/313	0/313		0.3 %	7.07 [0.36, 137.40]
RO-2455-404-RD (REACT)	55/968	15/967		7.3 %	3.82 [2.14, 6.82]
Roflumilast DAL-MD-01	1/11	0/16		0.2 %	4.71 [0.18, 126.90]
Roflumilast M2-107	27/555	2/280		1.3 %	7.11 [1.68, 30.11]
Roflumilast M2-111+M2-112	80/1327	20/1359		9.6 %	4.30 [2.62, 7.05]
Roflumilast M2-124	41/769	15/755		7.4 %	2.78 [1.52, 5.06]
Roflumilast M2-125	21/778	15/790		7.5 %	1.43 [0.73, 2.80]
Roflumilast M2-127	25/466	1/467		0.5 %	26.42 [3.56, 195.79]
Roflumilast M2-128	11/374	4/369		2.0 %	2.77 [0.87, 8.76]
Roflumilast ROF-MD-07(RE2SPOND)	64/1178	30/1174		14.7 %	2.19 [1.41, 3.41]
Subtotal (95% CI)	**6739**	**6490**		**50.7 %**	**3.21 [2.57, 4.03]**
Total events: 328 (PDE4i treatment), 102 (Placebo)					
Heterogeneity: Chi^2 = 16.16, df = 9 (P = 0.06); I^2 =44%					
Test for overall effect: Z = 10.17 (P < 0.00001)					
2 Roflumilast 250 μ g					
Roflumilast M2-107	16/576	2/280		1.4 %	3.97 [0.91, 17.39]
Subtotal (95% CI)	**576**	**280**		**1.4 %**	**3.97 [0.91, 17.39]**
Total events: 16 (PDE4i treatment), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.83 (P = 0.067)					
3 Cilomilast 15 mg					
Cilomilast 039	82/431	10/216		5.6 %	4.84 [2.46, 9.54]
Cilomilast 042	56/474	9/226		5.5 %	3.23 [1.57, 6.65]
Cilomilast 076	3/29	2/30		0.9 %	1.62 [0.25, 10.45]
Cilomilast 091	34/469	9/242		5.7 %	2.02 [0.95, 4.29]
Cilomilast 103657	63/296	12/316		4.7 %	6.85 [3.61, 13.00]
Cilomilast 110	4/31	1/34		0.4 %	4.89 [0.52, 46.36]
Cilomilast 111	13/79	4/77		1.7 %	3.59 [1.12, 11.57]



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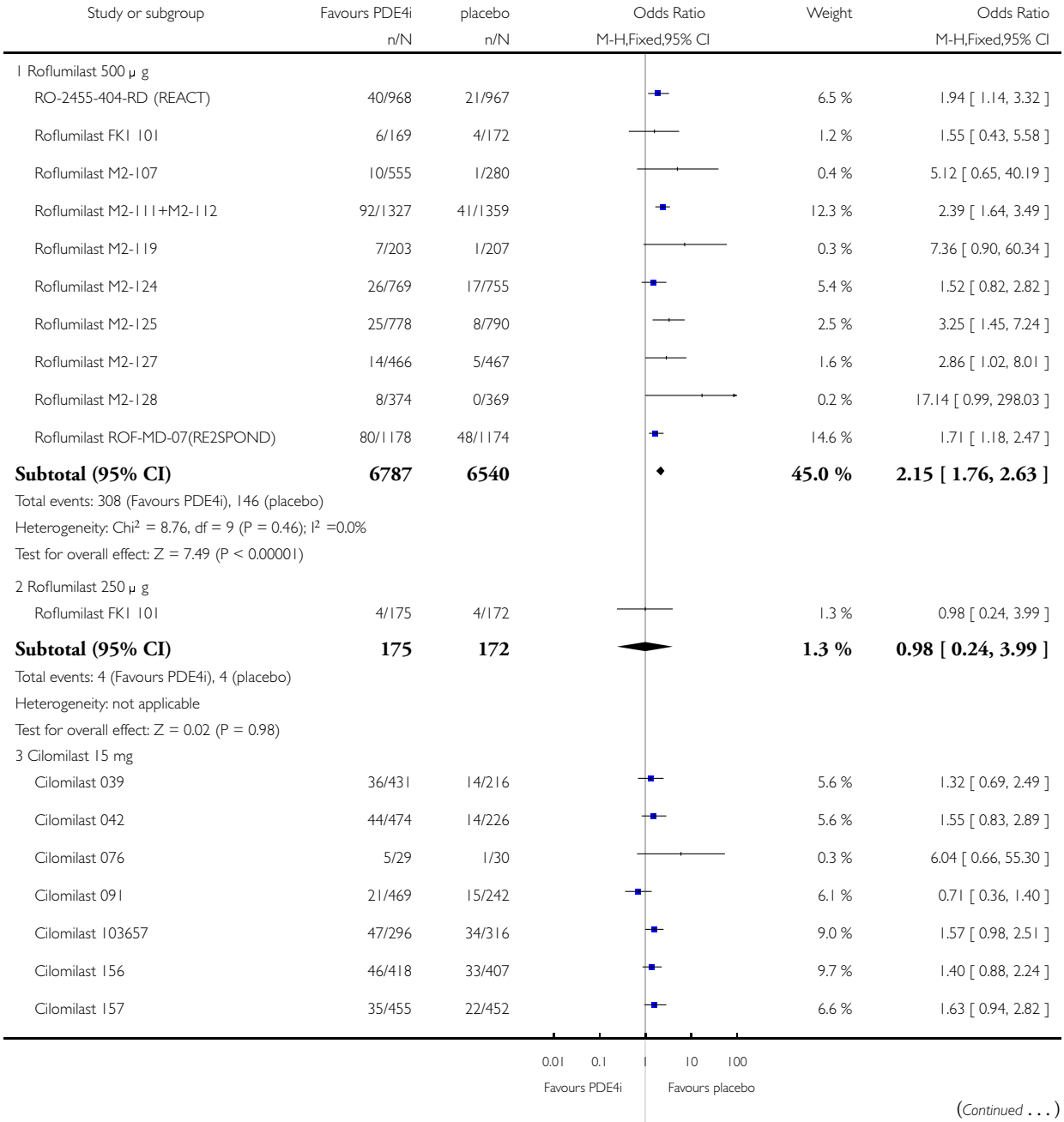
Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 121	39/678	3/340		1.9 %	6.86 [2.10, 22.35]
Cilomilast 156	109/418	27/407		10.4 %	4.96 [3.17, 7.76]
Cilomilast 157	44/455	14/452		6.5 %	3.35 [1.81, 6.20]
Cilomilast 168	28/203	2/103		1.2 %	8.08 [1.89, 34.63]
Cilomilast 180	11/97	2/102		0.9 %	6.40 [1.38, 29.65]
Cilomilast 181	6/65	4/62		1.9 %	1.47 [0.40, 5.50]
Compton 2001	12/105	1/105		0.5 %	13.42 [1.71, 105.19]
Subtotal (95% CI)	**3830**	**2712**		**48.0 %**	**4.37 [3.49, 5.47]**
Total events: 504 (PDE4i treatment), 100 (Placebo)					
Heterogeneity: Chi^2 = 14.16, df = 13 (P = 0.36); I^2 =8%					
Test for overall effect: Z = 12.87 (P < 0.00001)					
Total (95% CI)	**11145**	**9482**		**100.0 %**	**3.78 [3.23, 4.43]**
Total events: 848 (PDE4i treatment), 204 (Placebo)					
Heterogeneity: Chi^2 = 34.99, df = 24 (P = 0.07); I^2 =31%					
Test for overall effect: Z = 16.52 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 3.60, df = 2 (P = 0.17), I^2 =44%					

Analysis 1.27. Comparison 1 PDE4 inhibitor versus placebo, Outcome 27 Headache.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 27 Headache



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Study or subgroup	Favours PDE4i n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 168	8/203	4/103		1.7 %	1.02 [0.30, 3.45]
Cilomilast 180	16/97	14/102		3.7 %	1.24 [0.57, 2.70]
Cilomilast 181	9/65	12/62		3.4 %	0.67 [0.26, 1.72]
Compton 2001	7/105	7/105		2.1 %	1.00 [0.34, 2.96]
Subtotal (95% CI)	**3042**	**2261**		**53.8 %**	**1.32 [1.08, 1.62]**
Total events: 274 (Favours PDE4i), 170 (placebo)					
Heterogeneity: Chi^2 = 8.82, df = 10 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 2.69 (P = 0.0071)					
Total (95% CI)	**10004**	**8973**		**100.0 %**	**1.69 [1.47, 1.95]**
Total events: 586 (Favours PDE4i), 320 (placebo)					
Heterogeneity: Chi^2 = 28.09, df = 21 (P = 0.14); I^2 =25%					
Test for overall effect: Z = 7.29 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 11.83, df = 2 (P = 0.00), I^2 =83%					

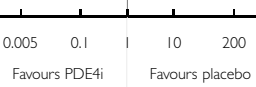
Analysis 1.28. Comparison 1 PDE4 inhibitor versus placebo, Outcome 28 Vomiting.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 28 Vomiting

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast					
Roflumilast M2-107	1/555	0/280		1.7 %	1.52 [0.06, 37.37]
Subtotal (95% CI)	**555**	**280**		**1.7 %**	**1.52 [0.06, 37.37]**
Total events: 1 (PDE4i treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.80)					
2 Cilomilast					
Cilomilast 039	37/431	6/216		19.1 %	3.29 [1.37, 7.91]
Cilomilast 042	17/474	0/226		1.7 %	17.33 [1.04, 289.44]
Cilomilast 076	4/29	0/30		1.1 %	10.76 [0.55, 209.55]
Cilomilast 091	22/369	1/242		3.0 %	15.28 [2.05, 114.12]
Cilomilast 103657	28/296	8/316		18.3 %	4.02 [1.80, 8.98]
Cilomilast 156	33/418	11/407		26.8 %	3.09 [1.54, 6.19]
Cilomilast 157	21/455	8/452		20.0 %	2.69 [1.18, 6.13]
Cilomilast 168	9/203	1/103		3.3 %	4.73 [0.59, 37.87]
Cilomilast 180	4/97	1/102		2.4 %	4.34 [0.48, 39.57]
Cilomilast 181	5/65	1/62		2.5 %	5.08 [0.58, 44.81]
Subtotal (95% CI)	**2837**	**2156**		**98.3 %**	**4.06 [2.83, 5.82]**
Total events: 180 (PDE4i treatment), 37 (Placebo)					
Heterogeneity: Chi^2 = 4.95, df = 9 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 7.60 (P < 0.00001)					
Total (95% CI)	**3392**	**2436**		**100.0 %**	**4.01 [2.80, 5.74]**
Total events: 181 (PDE4i treatment), 37 (Placebo)					
Heterogeneity: Chi^2 = 5.24, df = 10 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 7.59 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.36, df = 1 (P = 0.55), I^2 =0.0%					

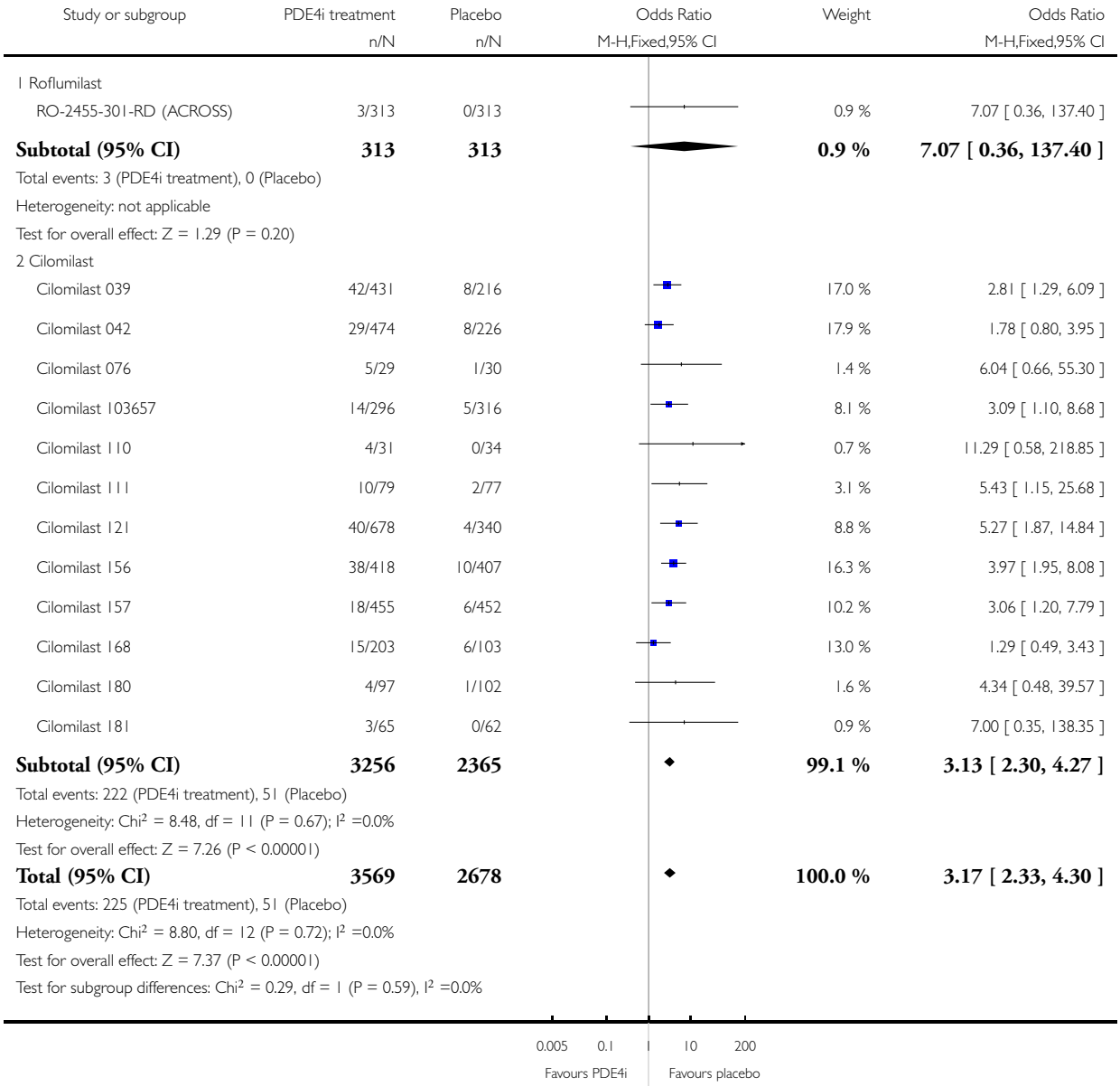


Analysis 1.29. Comparison 1 PDE4 inhibitor versus placebo, Outcome 29 Dyspepsia.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 29 Dyspepsia

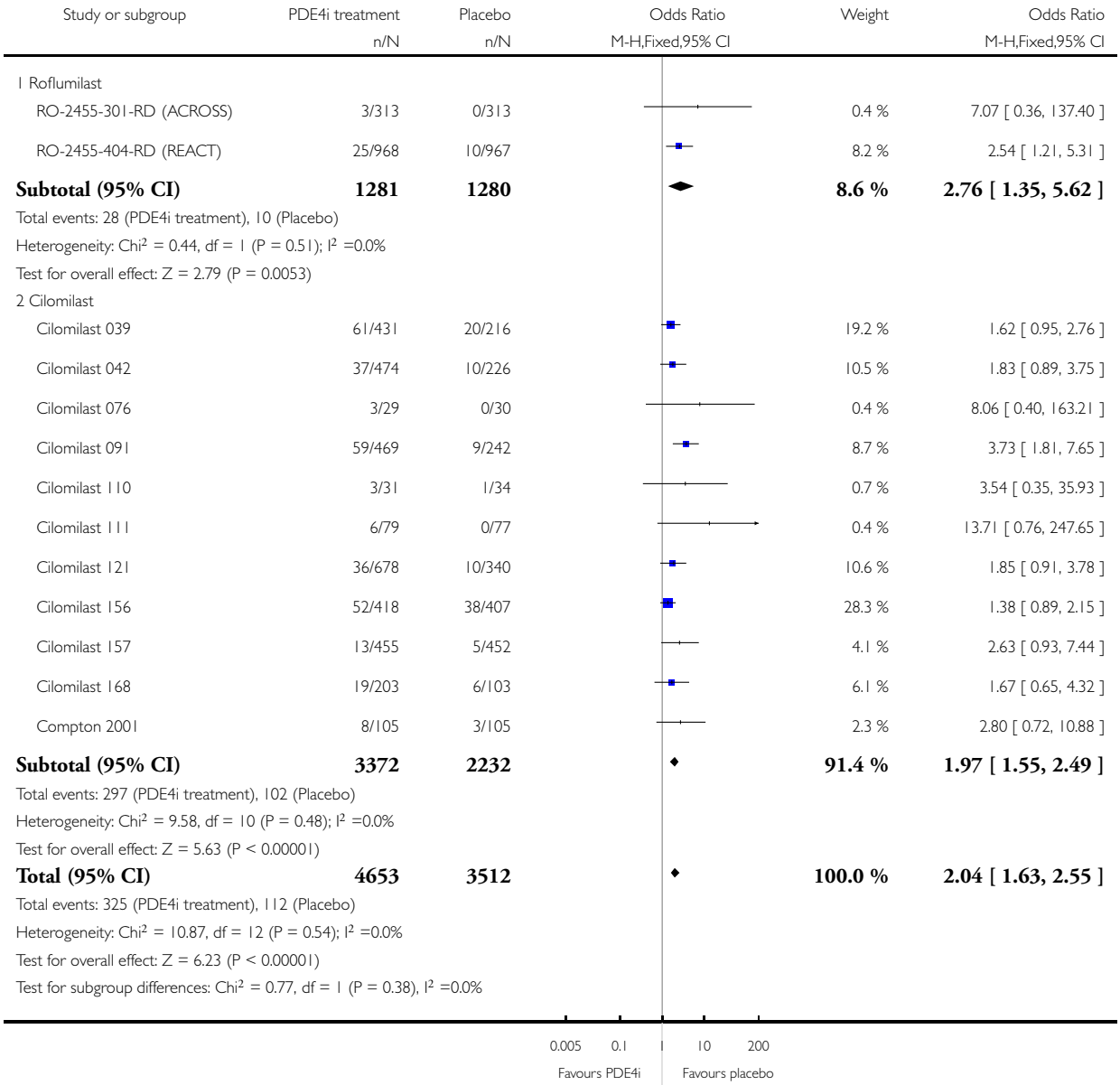


Analysis 1.30. Comparison 1 PDE4 inhibitor versus placebo, Outcome 30 Abdominal pain.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 30 Abdominal pain



Analysis 1.31. Comparison 1 PDE4 inhibitor versus placebo, Outcome 31 Weight loss.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 31 Weight loss

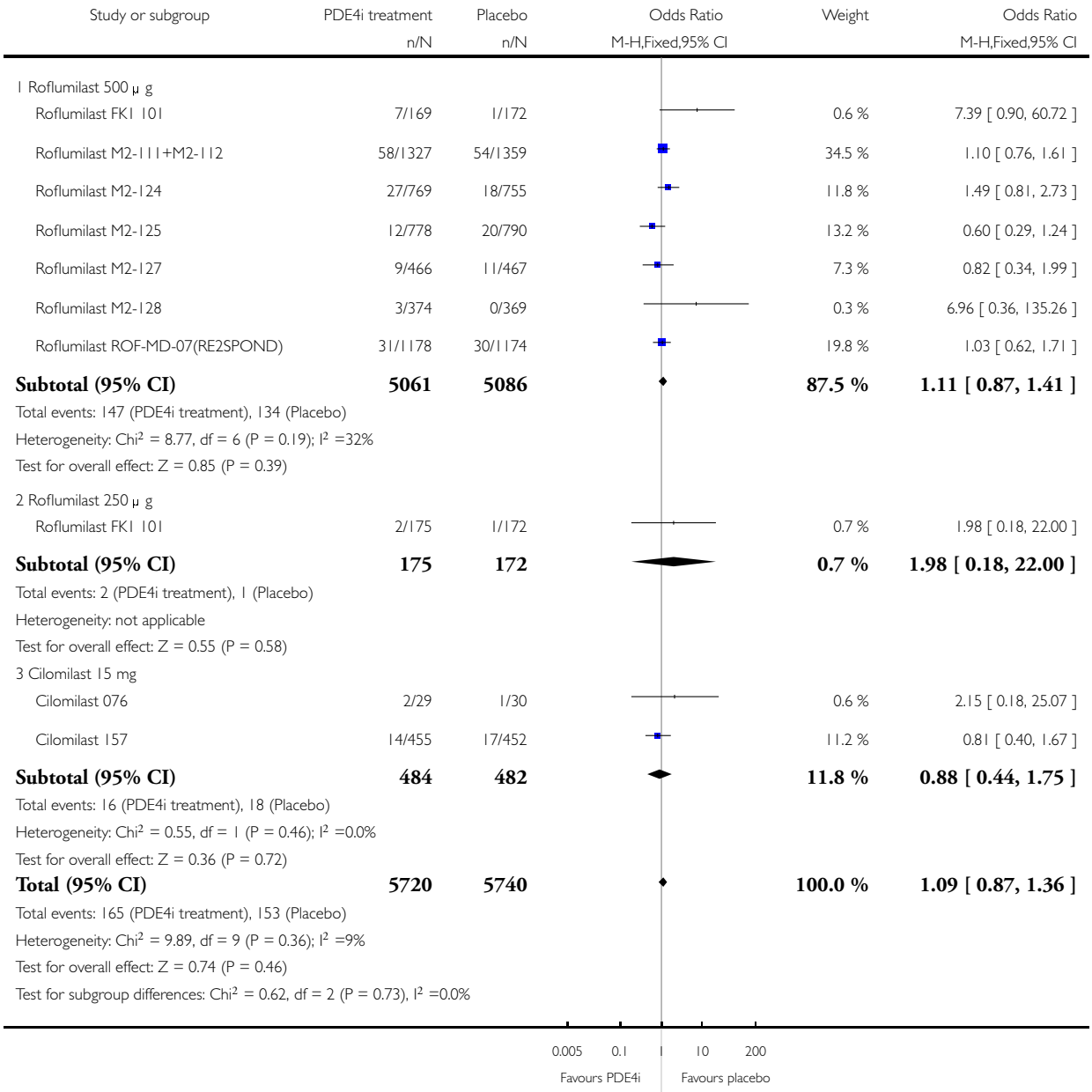
Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast					
RO-2455-404-RD (REACT)	88/968	27/967		18.5 %	3.48 [2.24, 5.41]
Roflumilast DAL-MD-01	1/11	0/16		0.3 %	4.71 [0.18, 126.90]
Roflumilast M2-111+M2-112	100/1327	38/1359		26.2 %	2.83 [1.93, 4.15]
Roflumilast M2-119	11/203	1/207		0.7 %	11.80 [1.51, 92.28]
Roflumilast M2-124	92/769	24/755		16.1 %	4.14 [2.61, 6.56]
Roflumilast M2-125	65/778	20/790		13.7 %	3.51 [2.10, 5.85]
Roflumilast M2-127	40/466	5/467		3.4 %	8.68 [3.39, 22.19]
Roflumilast M2-128	21/374	2/369		1.4 %	10.92 [2.54, 46.90]
Roflumilast ROF-MD-07(RE2SPOND)	91/1178	28/1174		19.5 %	3.43 [2.23, 5.28]
Total (95% CI)	**6074**	**6104**		**100.0 %**	**3.76 [3.11, 4.54]**
Total events: 509 (PDE4i treatment), 145 (Placebo)					
Heterogeneity: Chi^2 = 8.95, df = 8 (P = 0.35); I^2 =11%					
Test for overall effect: Z = 13.80 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 1.32. Comparison 1 PDE4 inhibitor versus placebo, Outcome 32 Influenza-like symptoms.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 32 Influenza-like symptoms



Analysis 1.33. Comparison 1 PDE4 inhibitor versus placebo, Outcome 33 Upper respiratory tract infection.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 33 Upper respiratory tract infection

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast 500 µ g					
Roflumilast DAL-MD-01	1/11	2/16		0.3 %	0.70 [0.06, 8.82]
Roflumilast FK1 101	26/169	27/172		4.5 %	0.98 [0.54, 1.75]
Roflumilast M2-107	23/555	14/280		3.6 %	0.82 [0.42, 1.62]
Roflumilast M2-111+M2-112	72/1327	86/1359		16.1 %	0.85 [0.62, 1.17]
Roflumilast M2-119	18/203	6/207		1.1 %	3.26 [1.27, 8.39]
Roflumilast M2-124	16/769	21/755		4.1 %	0.74 [0.38, 1.43]
Roflumilast M2-125	33/778	38/790		7.2 %	0.88 [0.54, 1.41]
Roflumilast M2-127	9/466	19/467		3.7 %	0.46 [0.21, 1.04]
Roflumilast M2-128	4/374	2/369		0.4 %	1.98 [0.36, 10.90]
Roflumilast ROF-MD-07(RE2SPOND)	60/1178	66/1174		12.5 %	0.90 [0.63, 1.29]
Subtotal (95% CI)	**5830**	**5589**		**53.6 %**	**0.90 [0.75, 1.07]**
Total events: 262 (PDE4i treatment), 281 (Placebo)					
Heterogeneity: Chi^2 = 11.18, df = 9 (P = 0.26); I^2 =20%					
Test for overall effect: Z = 1.25 (P = 0.21)					
2 Roflumilast 250 µ g					
Roflumilast FK1 101	22/175	27/172		4.8 %	0.77 [0.42, 1.42]
Roflumilast M2-107	27/576	14/280		3.6 %	0.93 [0.48, 1.81]
Subtotal (95% CI)	**751**	**452**		**8.4 %**	**0.84 [0.54, 1.31]**
Total events: 49 (PDE4i treatment), 41 (Placebo)					
Heterogeneity: Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					
3 Cilomilast 15 mg					
Cilomilast 039	68/431	33/216		7.4 %	1.04 [0.66, 1.63]
Cilomilast 042	29/474	11/226		2.8 %	1.27 [0.62, 2.60]
Cilomilast 076	4/29	1/30		0.2 %	4.64 [0.49, 44.27]
Cilomilast 091	14/469	7/242		1.8 %	1.03 [0.41, 2.59]
Cilomilast 103657	52/296	49/316		7.8 %	1.16 [0.76, 1.78]

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Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 110	3/31	4/34		0.7 %	0.80 [0.17, 3.91]
Cilomilast 111	8/79	5/77		0.9 %	1.62 [0.51, 5.20]
Cilomilast 156	46/418	61/407		11.0 %	0.70 [0.47, 1.06]
Cilomilast 168	18/203	18/103		4.4 %	0.46 [0.23, 0.93]
Cilomilast 180	2/97	6/102		1.1 %	0.34 [0.07, 1.71]
Subtotal (95% CI)	**2527**	**1753**		**38.1 %**	**0.92 [0.75, 1.13]**
Total events: 244 (PDE4i treatment), 195 (Placebo)					
Heterogeneity: Chi^2 = 12.11, df = 9 (P = 0.21); I^2 =26%					
Test for overall effect: Z = 0.78 (P = 0.44)					
Total (95% CI)	**9108**	**7794**		**100.0 %**	**0.90 [0.79, 1.02]**
Total events: 555 (PDE4i treatment), 517 (Placebo)					
Heterogeneity: Chi^2 = 23.59, df = 21 (P = 0.31); I^2 =11%					
Test for overall effect: Z = 1.61 (P = 0.11)					
Test for subgroup differences: Chi^2 = 0.14, df = 2 (P = 0.93), I^2 =0.0%					

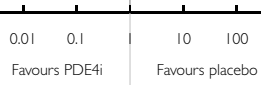
Analysis 1.34. Comparison 1 PDE4 inhibitor versus placebo, Outcome 34 Withdrawals due to adverse events.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 34 Withdrawals due to adverse events

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast 500 µ g					
RO-2455-301-RD (ACROSS)	19/313	6/313		0.8 %	3.31 [1.30, 8.39]
RO-2455-404-RD (REACT)	104/969	52/966		6.7 %	2.11 [1.50, 2.99]
Roflumilast DAL-MD-01	0/11	0/16			Not estimable
Roflumilast FK1 101	12/169	10/172		1.3 %	1.24 [0.52, 2.95]
Roflumilast IN-108	0/47	1/25		0.3 %	0.17 [0.01, 4.38]
Roflumilast JP-706	48/204	12/191		1.4 %	4.59 [2.35, 8.95]
Roflumilast M2-107	84/555	23/280		3.8 %	1.99 [1.23, 3.24]
Roflumilast M2-111+M2-112	235/1327	136/1359		16.0 %	1.94 [1.54, 2.43]
Roflumilast M2-119	20/203	7/207		0.9 %	3.12 [1.29, 7.56]
Roflumilast M2-124	119/766	78/759		9.6 %	1.61 [1.18, 2.18]
Roflumilast M2-125	101/773	83/798		10.3 %	1.29 [0.95, 1.76]
Roflumilast M2-127	77/466	45/467		5.4 %	1.86 [1.25, 2.75]
Roflumilast M2-128	33/371	20/372		2.6 %	1.72 [0.97, 3.05]
Roflumilast ROF-MD-07(RE2SPOND)	138/1178	64/1174		8.2 %	2.30 [1.69, 3.13]
Subtotal (95% CI)	**7352**	**7099**		**67.5 %**	**1.91 [1.71, 2.13]**
Total events: 990 (PDE4i treatment), 537 (Placebo)					
Heterogeneity: Chi^2 = 21.47, df = 12 (P = 0.04); I^2 =44%					
Test for overall effect: Z = 11.36 (P < 0.00001)					
2 Cilomilast 15 mg					
Cilomilast 039	94/431	35/216		5.3 %	1.44 [0.94, 2.21]
Cilomilast 042	71/474	22/226		3.7 %	1.63 [0.98, 2.71]
Cilomilast 076	4/29	0/30		0.1 %	10.76 [0.55, 209.55]
Cilomilast 091	78/469	32/242		5.1 %	1.31 [0.84, 2.04]
Cilomilast 103657	46/296	17/316		2.0 %	3.24 [1.81, 5.79]
Cilomilast 110	0/31	0/34			Not estimable
Cilomilast 111	14/79	8/77		1.0 %	1.86 [0.73, 4.72]



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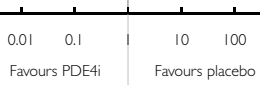
Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 121	49/678	8/340		1.4 %	3.23 [1.51, 6.91]
Cilomilast 156	80/418	42/407		5.0 %	2.06 [1.38, 3.07]
Cilomilast 157	80/455	46/452		5.5 %	1.88 [1.28, 2.78]
Cilomilast 168	36/203	8/103		1.3 %	2.56 [1.14, 5.73]
Cilomilast 180	9/97	6/102		0.8 %	1.64 [0.56, 4.78]
Cilomilast 181	6/65	3/62		0.4 %	2.00 [0.48, 8.38]
Compton 2001	14/107	8/106		1.0 %	1.84 [0.74, 4.60]
Subtotal (95% CI)	**3832**	**2713**		**32.5 %**	**1.90 [1.61, 2.24]**
Total events: 581 (PDE4i treatment), 235 (Placebo)					
Heterogeneity: Chi^2 = 11.81, df = 12 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 7.72 (P < 0.00001)					
Total (95% CI)	**11184**	**9812**		**100.0 %**	**1.90 [1.74, 2.09]**
Total events: 1571 (PDE4i treatment), 772 (Placebo)					
Heterogeneity: Chi^2 = 33.29, df = 25 (P = 0.12); I^2 =25%					
Test for overall effect: Z = 13.73 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 =0.0%					



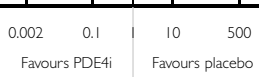
Analysis 1.35. Comparison 1 PDE4 inhibitor versus placebo, Outcome 35 Non-fatal serious adverse events.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 35 Non-fatal serious adverse events

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast 500 µ g					
RO-2455-404-RD (REACT)	249/969	285/966		19.0 %	0.83 [0.68, 1.01]
Roflumilast DAL-MD-01	0/16	0/11			Not estimable
Roflumilast FK1 101	9/169	11/172		0.9 %	0.82 [0.33, 2.04]
Roflumilast IN-108	1/47	1/25		0.1 %	0.52 [0.03, 8.71]
Roflumilast JP-706	20/204	12/191		1.0 %	1.62 [0.77, 3.41]
Roflumilast M2-107	53/555	21/280		2.3 %	1.30 [0.77, 2.21]
Roflumilast M2-111+M2-112	263/1327	264/1359		18.8 %	1.03 [0.85, 1.24]
Roflumilast M2-119	134/203	90/207		2.7 %	2.52 [1.69, 3.77]
Roflumilast M2-124+M2-125	301/1537	336/1554		24.1 %	0.88 [0.74, 1.05]
Roflumilast ROF-MD-07(RE2SPOND)	180/1178	162/1174		12.3 %	1.13 [0.90, 1.42]
Subtotal (95% CI)	**6205**	**5939**		**81.3 %**	**1.01 [0.93, 1.11]**
Total events: 1210 (PDE4i treatment), 1182 (Placebo)					
Heterogeneity: Chi^2 = 30.08, df = 8 (P = 0.00020); I^2 =73%					
Test for overall effect: Z = 0.30 (P = 0.77)					
2 Cilomilast 15 mg					
Cilomilast 039	24/431	25/216		2.8 %	0.45 [0.25, 0.81]
Cilomilast 042	28/474	13/226		1.5 %	1.03 [0.52, 2.03]
Cilomilast 076	2/29	1/30		0.1 %	2.15 [0.18, 25.07]
Cilomilast 091	23/469	19/242		2.1 %	0.61 [0.32, 1.13]
Cilomilast 103657	17/296	23/316		1.9 %	0.78 [0.41, 1.48]
Cilomilast 110	1/31	0/34		0.0 %	3.39 [0.13, 86.43]
Cilomilast 111	8/79	2/77		0.2 %	4.23 [0.87, 20.58]
Cilomilast 121	38/678	10/340		1.1 %	1.96 [0.96, 3.98]
Cilomilast 156	25/418	38/407		3.2 %	0.62 [0.37, 1.04]
Cilomilast 157	53/455	55/452		4.4 %	0.95 [0.64, 1.42]
Cilomilast 168	7/203	4/103		0.5 %	0.88 [0.25, 3.09]



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Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 180	6/97	7/102		0.6 %	0.89 [0.29, 2.76]
Cilomilast 181	2/65	1/62		0.1 %	1.94 [0.17, 21.91]
Compton 2001	4/107	3/106		0.3 %	1.33 [0.29, 6.11]
Subtotal (95% CI)	**3832**	**2713**		**18.7 %**	**0.87 [0.72, 1.06]**
Total events: 238 (PDE4i treatment), 201 (Placebo)					
Heterogeneity: Chi^2 = 19.12, df = 13 (P = 0.12); I^2 =32%					
Test for overall effect: Z = 1.34 (P = 0.18)					
Total (95% CI)	**10037**	**8652**		**100.0 %**	**0.99 [0.91, 1.07]**
Total events: 1448 (PDE4i treatment), 1383 (Placebo)					
Heterogeneity: Chi^2 = 51.49, df = 22 (P = 0.00037); I^2 =57%					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Chi^2 = 1.80, df = 1 (P = 0.18), I^2 =44%					

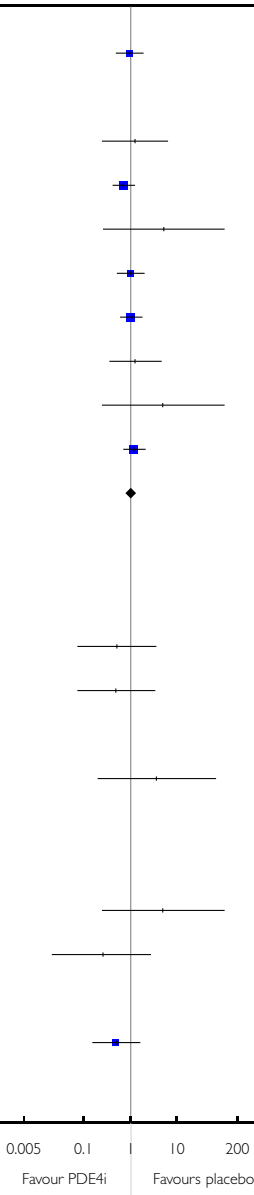
Analysis 1.36. Comparison 1 PDE4 inhibitor versus placebo, Outcome 36 Mortality.

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 36 Mortality

Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast					
RO-2455-404-RD (REACT)	17/969	18/966		12.8 %	0.94 [0.48, 1.84]
Roflumilast DAL-MD-01	0/16	0/11			Not estimable
Roflumilast M2-107	5/555	2/280		1.9 %	1.26 [0.24, 6.55]
Roflumilast M2-111+M2-112	22/1327	32/1359		22.5 %	0.70 [0.40, 1.21]
Roflumilast M2-119	2/203	0/207		0.4 %	5.15 [0.25, 107.91]
Roflumilast M2-124	17/765	17/758		12.1 %	0.99 [0.50, 1.96]
Roflumilast M2-125	25/772	25/796		17.2 %	1.03 [0.59, 1.81]
Roflumilast M2-127	5/466	4/467		2.9 %	1.26 [0.34, 4.70]
Roflumilast M2-128	2/374	0/369		0.4 %	4.96 [0.24, 103.66]
Roflumilast ROF-MD-07(RE2SPOND)	30/1178	25/1174		17.6 %	1.20 [0.70, 2.05]
Subtotal (95% CI)	**6625**	**6387**		**87.6 %**	**1.01 [0.78, 1.29]**
Total events: 125 (PDE4i treatment), 123 (Placebo)					
Heterogeneity: Chi^2 = 4.51, df = 8 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 Cilomilast					
Cilomilast 039	2/431	2/216		1.9 %	0.50 [0.07, 3.57]
Cilomilast 042	2/474	2/226		1.9 %	0.47 [0.07, 3.39]
Cilomilast 076	0/29	0/30			Not estimable
Cilomilast 091	3/469	0/242		0.5 %	3.64 [0.19, 70.73]
Cilomilast 103657	0/296	0/316			Not estimable
Cilomilast 110	0/31	0/34			Not estimable
Cilomilast 111	2/79	0/77		0.4 %	5.00 [0.24, 105.86]
Cilomilast 121	1/678	2/340		1.9 %	0.25 [0.02, 2.76]
Cilomilast 156	0/418	0/407			Not estimable
Cilomilast 157	4/455	8/452		5.7 %	0.49 [0.15, 1.65]
Cilomilast 168	0/203	0/103			Not estimable



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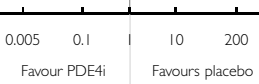
Study or subgroup	PDE4i treatment n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cilomilast 180	0/97	0/102			Not estimable
Cilomilast 181	0/65	0/62			Not estimable
Subtotal (95% CI)	**3725**	**2607**		**12.4 %**	**0.70 [0.34, 1.45]**
Total events: 14 (PDE4i treatment), 14 (Placebo)					
Heterogeneity: Chi^2 = 4.08, df = 5 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.95 (P = 0.34)					
Total (95% CI)	**10350**	**8994**		**100.0 %**	**0.97 [0.76, 1.23]**
Total events: 139 (PDE4i treatment), 137 (Placebo)					
Heterogeneity: Chi^2 = 9.80, df = 14 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.80)					
Test for subgroup differences: Chi^2 = 0.84, df = 1 (P = 0.36), I^2 =0.0%					

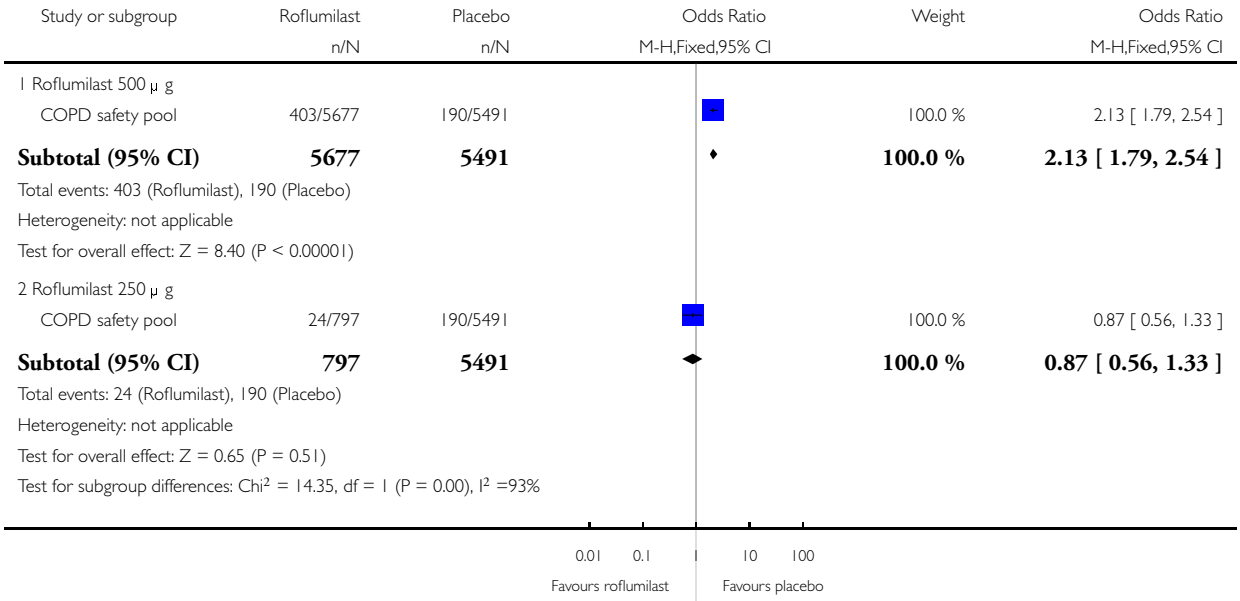


Analysis 1.37. Comparison 1 PDE4 inhibitor versus placebo, Outcome 37 All psychiatric disorders (roflumilast).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 37 All psychiatric disorders (roflumilast)

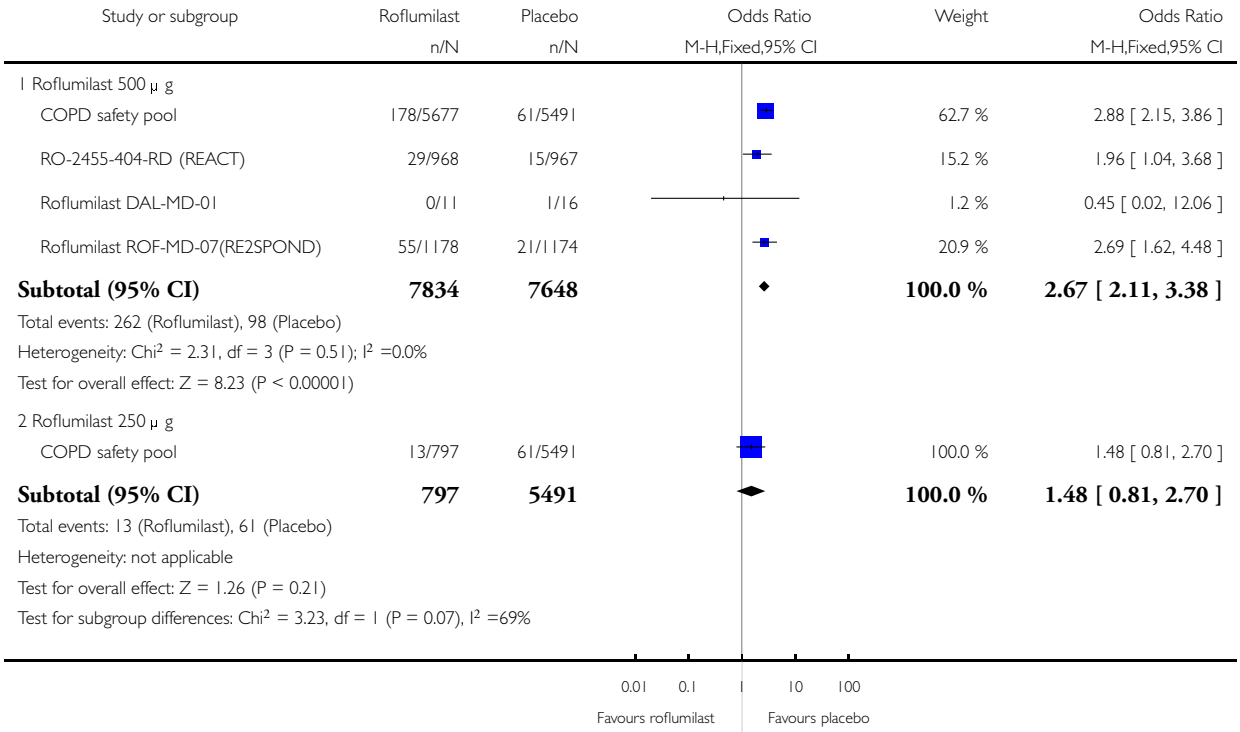


Analysis 1.38. Comparison 1 PDE4 inhibitor versus placebo, Outcome 38 Insomnia and sleep disorders (roflumilast).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 38 Insomnia and sleep disorders (roflumilast)



Analysis 1.39. Comparison 1 PDE4 inhibitor versus placebo, Outcome 39 Anxiety or anxiety disorder (roflumilast).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 39 Anxiety or anxiety disorder (roflumilast)

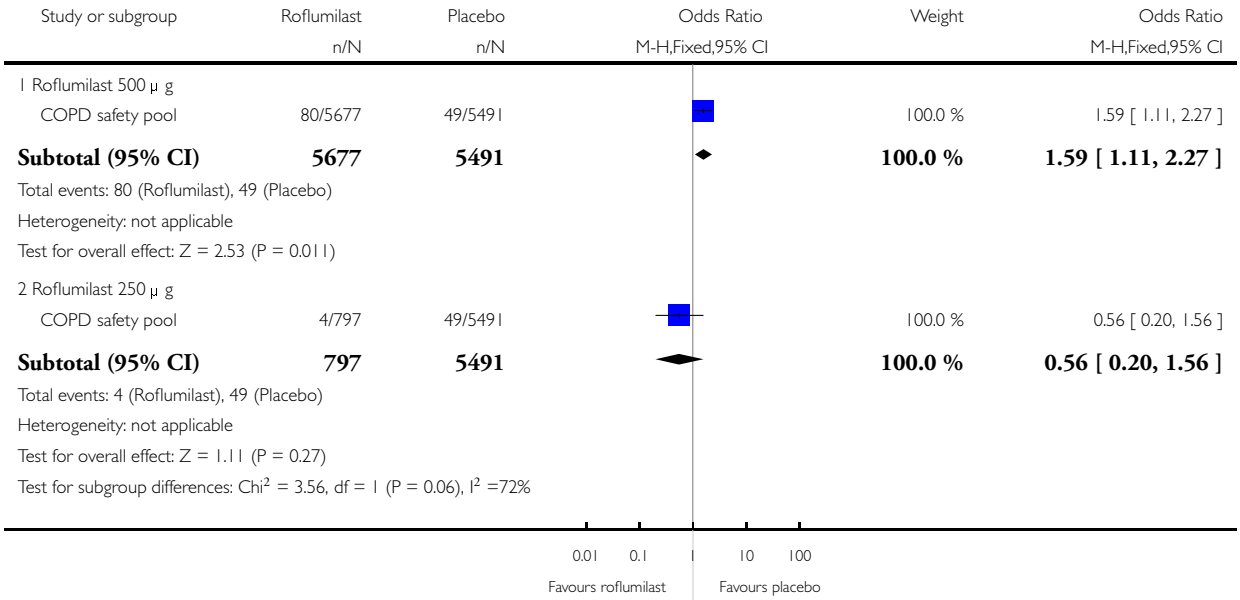
Study or subgroup	Roflumilast n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Roflumilast 500 µg					
COPD safety pool	82/5677	44/5491		100.0 %	1.81 [1.26, 2.62]
Subtotal (95% CI)	**5677**	**5491**		**100.0 %**	**1.81 [1.26, 2.62]**
Total events: 82 (Roflumilast), 44 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.17 (P = 0.0015)					
2 Roflumilast 250 µg					
COPD safety pool	6/797	44/5491		100.0 %	0.94 [0.40, 2.21]
Subtotal (95% CI)	**797**	**5491**		**100.0 %**	**0.94 [0.40, 2.21]**
Total events: 6 (Roflumilast), 44 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
Test for subgroup differences: Chi^2 = 1.92, df = 1 (P = 0.17), I^2 =48%					

Analysis 1.40. Comparison 1 PDE4 inhibitor versus placebo, Outcome 40 Depression (roflumilast).

Review: Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

Comparison: 1 PDE_4 inhibitor versus placebo

Outcome: 40 Depression (roflumilast)



ADDITIONAL TABLES

Table 1. Number of references for which we sought full text

Search date:	No. of references for which we sought full text
December 2008	53
January 2010	5
August 2010	12
June 2013	20
October 2016	28

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*the Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the Cochrane Airways Trials Register

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategy to identify relevant trials from the Cochrane Airways Trials Register

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Phosphodiesterase 4 Inhibitors
#8 Phosphodiesterase*
#9 PDE4*
#10 roflumilast
#11 rolipram
#12 cilomilast
#13 ariflo
#14 SB207499
#15 Tetomilast
#16 ORIC485
#17 Oglemilast
#18 GRC-3886
#19 QAK423
#20 Arofylline

#21 AWD12-281
#22 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 #6 and #22

Appendix 3. Airways Group Trials Register search strategy (sensitive search)

PDE* or phosphodiesterase* or isoenzyme* or theophylline or rolipram or pentoxifylline or papaverine or milrinone or etazolate or etazolate or dyphylline or dipyridamole or caffeine or amrinone or aminophylline or isobutylxanthine or cilomilast or ariflo or cilostazol or enoximone or milrinone or olprinone or roflumilast or sb207499 or zardaverine or cilostamide or enoximone or trequinsin or Telomilast or IC485 or Oglemilast or QAK423 or GRC-3886 or Arofylline or AWD12-281

WHAT'S NEW

Date	Event	Description
11 October 2016	New citation required but conclusions have not changed	Five new eligible studies of roflumilast 500 μg included RO-2455-301-RD (ACROSS); RO-2455-404-RD (REACT); Roflumilast DAL-MD-01; Roflumilast FLUI-2011-77; Roflumilast ROF-MD-07(RE2SPOND). No substantive changes to findings.
11 October 2016	New search has been performed	New literature search run.

HISTORY

Date	Event	Description
17 December 2013	Amended	Typo in plain language summary title amended
4 November 2013	Amended	Risk of bias for Cilomilast 076 added.
6 June 2013	New citation required and conclusions have changed	We included seven new studies in this update and excluded one cross-over trial. FDA report on psychiatric adverse events and suicides included Text revised to take account of Cochrane reporting standards 'Summary of findings' table added.
6 June 2013	New search has been performed	New literature search run.

CONTRIBUTIONS OF AUTHORS

Jimmy Chong: study selection, data extraction, review write up, leading update of review.

Phillippa Poole: protocol initiation and development, study selection, data extraction, review write up, all stages of update, corresponding author.

Bonnie Leung: study selection, data extraction, review write up.

DECLARATIONS OF INTEREST

Jimmy Chong: none known

Phillippa Poole: none known

Bonnie Leung: none known

SOURCES OF SUPPORT

Internal sources

- University of Auckland provided salary support for Professor Phillippa Poole, New Zealand.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the comparison between published and unpublished results when we discovered the large number of unpublished studies, but before we extracted the data from the studies and carried out the analysis.

We have excluded cross-over trials as carry-over effects and disease progression cannot be adequately controlled for in people with chronic obstructive pulmonary disease.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Aminopyridines [*administration & dosage; adverse effects]; Benzamides [*administration & dosage; adverse effects]; Cyclohexanecarboxylic Acids [*administration & dosage; adverse effects]; Cyclopropanes [administration & dosage; adverse effects]; Disease Progression; Forced Expiratory Volume [drug effects]; Nitriles [*administration & dosage; adverse effects]; Phosphodiesterase 4 Inhibitors [*administration & dosage; adverse effects]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans

CHEST

Prevention of Acute Exacerbations of COPD

American College of Chest Physicians and Canadian Thoracic Society Guideline

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PODCAST

BACKGROUND: COPD is a major cause of morbidity and mortality in the United States as well as throughout the rest of the world. An exacerbation of COPD (periodic escalations of symptoms of cough, dyspnea, and sputum production) is a major contributor to worsening lung function, impairment in quality of life, need for urgent care or hospitalization, and cost of care in COPD. Research conducted over the past decade has contributed much to our current understanding of the pathogenesis and treatment of COPD. Additionally, an evolving literature has accumulated about the prevention of acute exacerbations.

METHODS: In recognition of the importance of preventing exacerbations in patients with COPD, the American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) joint evidence-based guideline (AECOPD Guideline) was developed to provide a practical, clinically useful document to describe the current state of knowledge regarding the prevention of acute exacerbations according to major categories of prevention therapies. Three key clinical questions developed using the PICO (population, intervention, comparator, and outcome) format addressed the prevention of acute exacerbations of COPD: nonpharmacologic therapies, inhaled therapies, and oral therapies. We used recognized document evaluation tools to assess and choose the most appropriate studies and to extract meaningful data and grade the level of evidence to support the recommendations in each PICO question in a balanced and unbiased fashion.

RESULTS: The AECOPD Guideline is unique not only for its topic, the prevention of acute exacerbations of COPD, but also for the first-in-kind partnership between two of the largest thoracic societies in North America. The CHEST Guidelines Oversight Committee in partnership with the CTS COPD Clinical Assembly launched this project with the objective that a systematic review and critical evaluation of the published literature by clinical experts and researchers in the field of COPD would lead to a series of recommendations to assist clinicians in their management of the patient with COPD.

CONCLUSIONS: This guideline is unique because it provides an up-to-date, rigorous, evidence-based analysis of current randomized controlled trial data regarding the prevention of COPD exacerbations.

CHEST 2015; 147(4):894-942

ABBREVIATIONS: AECOPD = acute exacerbation of COPD; CB = consensus based; CDC = US Centers for Disease Control and Prevention; CHEST = American College of Chest Physicians; CRGC = Canadian Respiratory Guidelines Committee; CTS = Canadian Thoracic Society; GIN = Guidelines International Network; GOC = Guidelines Oversight Committee; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; NAC = N-acetylcysteine; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial; RR = rate ratio; S-CMC-lys = S-carboxymethylcysteine lysine salt; SGRQ = St. George's Respiratory Questionnaire; WHO = World Health Organization; WMD = weighted mean difference

Summary of Recommendations

PICO 1: Do Nonpharmacologic Treatments and Vaccinations Prevent/Decrease Acute Exacerbations of COPD?

1. In patients with COPD, we suggest administering the 23-valent pneumococcal vaccine as part of overall medical management but did not find sufficient evidence that pneumococcal vaccination prevents acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of pneumococcal vaccine for general health, and we endorse existing guidelines that recommend it for patients with COPD. Although evidence does not specifically support using the vaccine for the prevention of acute exacerbations, multiple bodies, including the US Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO), recommend the use of pneumococcal vaccine for all adults aged ≥ 65 years and in those aged 19 to 64 years with underlying medical conditions such as COPD that put them at greater risk of serious pneumococcal infection.

2. In patients with COPD, we recommend administering the influenza vaccine annually to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on the benefits of influenza vaccination for general health, the low risk of side effects, and the existing guidelines that recommend it for patients with COPD. Although the effect and evidence are moderate for the prevention of acute exacerbations of COPD, multiple bodies, including the CDC and WHO, recommend the use of a yearly influenza vaccine for all adults, including those with COPD.

3. In patients with COPD, we suggest including smoking cessation counseling and treatment using best practices as a component of a comprehensive clinical strategy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of smoking cessation for all individuals. In particular, it is the only evidence-based intervention that improves COPD prognosis by mitigating lung function decline and reduces symptoms. Although the effect and evidence for smoking cessation in the prevention of acute exacerbations of COPD are low, evidence supports smoking cessation for many reasons: smokers with mild COPD who produce cough and phlegm achieve substantial symptom reductions in the first year after smoking cessation with less lung function decline and less symptoms upon sustained cessation; cigarette smoking may be associated with infections such as pneumonia; among other general health benefits. The benefit from smoking cessation outweighs the risks, and a myriad of strategies have been summarized by other guidelines and reviews. In general, effective smoking cessation programs include behavioral, physiologic, and psychologic components comprising an acknowledgment of current smoking followed by advice to quit, pharmacologic therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), and counseling (in-person or telephone

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counseling), with cessation rates ranging from 8.8% to 34.5%. Smoking cessation that includes counseling and pharmacologic interventions are cost-effective.

4. In patients with moderate, severe, or very severe COPD who have had a recent exacerbation (ie, ≤ 4 weeks), we recommend pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

5. In patients with moderate, severe, or very severe COPD who have had an exacerbation greater than the past 4 weeks, we do not suggest pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

6. In patients with COPD, we suggest that education alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the motivational educational intervention because it is labor intensive compared with traditional education techniques.

7. In patients with COPD, we suggest that case management alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the lack of change in quality of life in either group because this information was present for only a small proportion of the entire sample.

8. In patients with COPD with a previous or recent history of exacerbations, we recommend education and case management that includes direct access to a health-care specialist at least monthly to prevent severe acute exacerbations of COPD, as assessed by decreases in hospitalizations (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

9. In patients with moderate to severe COPD, we suggest education together with an action plan but without case management does not prevent severe acute exacerbations of COPD, as assessed by a decrease in ED visits or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

10. For patients with COPD, we suggest education with a written action plan and case management for the prevention of severe acute exacerbations of COPD, as assessed by a decrease in hospitalizations and ED visits (Grade 2B).

Underlying Values and Preferences: This recommendation places high value on reducing COPD-related hospitalizations, as these are associated with increased morbidity and mortality. Hospitalizations were believed to best reflect exacerbations because increased physician visits or increased medication use could be a result of the intervention to prevent an exacerbation. High value was also placed on changes in individuals with a history of exacerbations and on outcomes that specifically identified COPD-related hospitalizations. The recommendation reflects the fact that one study reported increased mortality in the intervention group. Although we do not know the reason for increased mortality in this one study, patients with underlying severe disease and clinical instability need close attention and careful follow-up. This point emphasizes that a specially trained

staff is required to supervise this intervention and that patient selection must be individualized.

11. For patients with COPD, we suggest that telemonitoring compared with usual care does not prevent acute exacerbations of COPD, as assessed by decreases in emergency room visits, exacerbations, or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: There is insufficient evidence at this time to support the contention that telemonitoring prevents COPD exacerbations.

PICO 2: Does Maintenance Inhaled Therapy Prevent/Decrease Acute Exacerbations of COPD?

12. In patients with moderate to severe COPD, we recommend the use of long-acting β_2-agonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting β_2-agonist therapy improving quality of life and lung function compared with placebo. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting β_2-agonist therapy and placebo in this patient group.

13. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with placebo. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting muscarinic antagonists and placebo in this patient group.

14. In patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared with long-acting β_2-agonist to prevent moderate to severe acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting muscarinic antagonists having a lower rate of nonfatal serious adverse events compared with long-acting β_2-agonists. This comparative benefit may not apply with the new ultralong-acting β_2-agonists that are a once-daily medication. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. A lower value was placed on the lack of statistically significant differences in changes in lung function, quality of life, and patient symptoms between the two drug groups.

15. In patients with moderate to severe COPD, we suggest the use of a short-acting muscarinic antagonist compared with short-acting β_2-agonist monotherapy to prevent acute mild-moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist to reduce the risk of acute exacerbations of COPD together with the comparative benefit of a short-acting muscarinic antagonist improving quality of life and lung function compared with short-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that medication-related adverse events were fewer in the short-acting muscarinic antagonist than in the short-acting β_2-agonist group.

16. In patients with moderate to severe COPD, we suggest the use of short-acting muscarinic antagonist plus short-acting β_2-agonist compared with short-acting β_2-agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist plus short-acting β_2-agonist reducing the risk of acute exacerbations of COPD together with the comparative small benefits of a short-acting muscarinic

antagonist plus a short-acting β_2-agonist improving quality of life, exercise tolerance, and lung function compared with short-acting β_2-agonist alone. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of a short-acting muscarinic antagonist plus a short-acting β_2-agonist vs a short-acting β_2-agonist alone.

17. In patients with moderate to severe COPD, we suggest the use of long-acting β_2-agonist monotherapy compared with short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD in patients treated with long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy and the comparative value of long-acting β_2-agonist monotherapy improving lung function, quality of life, and dyspnea scores compared with short-acting muscarinic antagonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy.

18. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with a short-acting muscarinic antagonist to prevent acute moderate to severe exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on a long-acting muscarinic antagonist reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with a short-acting muscarinic antagonist. This recommendation also acknowledges that there were fewer nonfatal serious adverse events in subjects treated with a long-acting muscarinic antagonist than in those treated with a short-acting muscarinic antagonist.

19. In patients with moderate to severe COPD, we suggest the combination use of a short-acting muscarinic antagonist plus long-acting β_2-agonist compared with long-acting β_2-agonist monotherapy to prevent acute mild to moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on the combination of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD compared with the use of long-acting β_2-agonist therapy alone and the comparative value of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy improving lung function, quality of life, and dyspnea scores compared with long-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the combined use of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy vs long-acting β_2-agonist therapy alone.

20. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy (and not inhaled corticosteroid monotherapy) compared with placebo to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with slowing the rate of decline in health-related quality of life and a relatively lower value on the risks and consequences of oral candidiasis, hoarseness and dysphonia, bruising, and pneumonia.

21. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with long-acting β_2-agonist monotherapy to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with improved health-related quality of life, reduced dyspnea, less rescue medication use, and improved lung function and a relatively lower value on the risks and consequences of oral candidiasis, upper respiratory tract infections, and pneumonia.

22. For patients with stable moderate to very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with inhaled corticosteroid monotherapy to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with the comparative mortality benefit of combination inhaled corticosteroid/long-acting β_2-agonist therapy, acknowledging that there were no significant differences in serious adverse events or incidence of pneumonia between the groups. This recommendation does not support the use of inhaled corticosteroid monotherapy in COPD.

23. For patients with stable COPD, we recommend inhaled long-acting anticholinergic/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

24. For patients with stable COPD, we recommend maintenance combination of inhaled corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD and a relatively lower value on the risks and consequences of pneumonia.

25. For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

PICO 3: In Patients Aged > 40 Years Who Are Previous or Current Smokers With COPD, Does Oral Therapy Prevent/Decrease Acute Exacerbations of COPD?

26. For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long-term macrolide to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: This recommendation places high value on the prevention of COPD exacerbations. However, clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance. The duration and exact dosage of macrolide therapy are unknown.

27. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we suggest that systemic corticosteroids be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30 days following the initial exacerbation (Grade 2B).

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term corticosteroids to reduce acute exacerbations of COPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

28. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we recommend that systemic corticosteroids not be given orally or intravenously for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first 30 days following the initial acute exacerbation of COPD (Grade 1A).

Remark: This does not preclude the use of systemic corticosteroids for the treatment of acute exacerbations of COPD.

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term

corticosteroids to reduce acute exacerbations of COPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

29. For patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year, we suggest the use of roflumilast to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: Clinicians prescribing roflumilast need to advise their patients of the potential side effects of weight loss and diarrhea. Patients may have to discontinue the therapy because of side effects. The decision to prescribe this medication should also be informed by the fact that there are limited data for supplemental effectiveness in patients concurrently using inhaled therapies.

30. For stable patients with COPD, we suggest treatment with oral slow-release theophylline twice daily to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that theophylline may reduce the number of exacerbations. Patient decisions may also be informed by the relatively narrow therapeutic window with respect to adverse effects of treatment with theophylline. Physicians should use the lowest effective dose in prescribing theophylline in order to avoid adverse effects. Theophylline use requires vigilance on the part of the physician in order to avoid serious drug interactions, which lead to changes in serum theophylline levels. Patients should be advised that changes in tobacco use habits will affect serum theophylline levels and that they should inform their physicians if they stop smoking while taking theophylline.

31. For patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, we suggest treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that N-acetylcysteine may reduce the number of exacerbations. Patient decisions may also be informed by the low risk of adverse effects from treatment with N-acetylcysteine.

32. For stable outpatients with COPD who continue to experience acute exacerbations of COPD despite maximal therapy designed to reduce acute exacerbations of COPD, we suggest that oral carbocysteine could be used to prevent acute exacerbations where this therapy is available (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This suggestion places high value on preventing acute exacerbations of COPD, with minimal risks associated with carbocysteine. The main adverse events reported in studies were mild GI symptoms.

33. For patients with moderate to severe COPD who are at risk for COPD exacerbations, we do not recommend using statins to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: We place high value on reducing exacerbations in patients with COPD and, thus, do not recommend statins for preventing acute exacerbations. However, patients with COPD may meet accepted criteria for initiating statins because of the presence of cardiovascular risk factors.

Introduction

COPD is a common disease with substantial associated morbidity and mortality. Patients with COPD usually have a progression of airflow obstruction that is not fully reversible and can lead to a history of progressively worsening breathlessness, that can impact daily activities and health-related quality of life.[1-3] COPD is the fourth leading cause of death in Canada[4] and the third leading cause of death in the United States where it claimed 133,965 lives in 2009.[5] In 2011, 12.7 million US adults were estimated to have COPD.[6] However, approximately 24 million US adults have evidence of impaired lung function, indicating an underdiagnosis of COPD.[7] Although 4% of Canadians aged 35 to 79 years self-reported having been given a diagnosis of COPD, direct measurements of lung function from the Canadian Health Measures Survey indicate that 13% of Canadians have a lung function score indicative of COPD.[4]

COPD is also costly. In 2009, COPD caused 8 million office visits, 1.5 million ED visits, 715,000 hospitalizations, and 133,965 deaths in the United States.[8] In 2010, US costs for COPD were projected to be approximately $49.9 billion, including $29.5 billion in direct health-care expenditures, $8.0 billion in indirect morbidity costs, and $12.4 billion in indirect mortality costs.[9] Exacerbations account for most of the morbidity, mortality, and costs associated with COPD. The economic burden associated

with moderate and severe exacerbations in Canada has been estimated to be in the range of $646 million to $736 million per annum.[10] This value may be an underestimate given that the prevalence of moderate exacerbations is not well documented, COPD is underdiagnosed, and the rate of hospitalization due to COPD is increasing.[11]

Exacerbations are to COPD what myocardial infarctions are to coronary artery disease: They are acute, trajectory-changing, and often deadly manifestations of a chronic disease. Exacerbations cause frequent hospital admissions, relapses, and readmissions[12]; contribute to death during hospitalization or shortly thereafter[12]; reduce quality of life dramatically[12,13]; consume financial resources[12,14]; and hasten a progressive decline in pulmonary function, a cardinal feature of COPD. Hospitalization due to exacerbations accounts for > 50% of the cost of managing COPD in North America and Europe.[15,16]

COPD exacerbation has been defined as

> an event in the natural course of the disease characterized by a baseline change in the patient's dyspnea, cough, and/or sputum that is beyond the normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.[17,18]

Exacerbation in clinical trials has been defined for operational reasons on the basis of whether an increase in treatment beyond regular or urgent care is required in an ED or a hospital. Exacerbation treatment in clinical trials usually is defined by the use of antibiotics, systemic corticosteroids, or both.[19] The severity of the exacerbation is then ranked or stratified according to the outcome: mild, when the clinical symptoms are present but no change in treatment or outcome is recorded; moderate, when the event results in a change in medication such as the use of antibiotics and systemic corticosteroids; or severe, when the event leads to a hospitalization.[1]

Two-thirds of exacerbations are associated with respiratory tract infections or air pollution, but one-third present without an identifiable cause.[17] Exacerbations remain poorly understood in terms of not only cause but also treatment and prevention. Although the management of an acute exacerbation has been the primary focus of clinical trials, the prevention of acute exacerbations has not been a major focus until recently. Most current COPD guidelines focus on the general diagnosis and evaluation of the patient with COPD, the management of stable disease, and the diagnosis and management of acute exacerbations.[1,20] Although current COPD guidelines state that prevention of exacerbations is possible, little guidance is provided to the clinician regarding current available therapies for the prevention of COPD exacerbations.[1,20] Moreover, recent new therapies have promise in preventing acute exacerbations of COPD (AECOPDs) and would benefit from critical review of their efficacy in the exacerbation prevention management.[21-23] The American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) jointly commissioned this evidence-based guideline on the prevention of COPD exacerbations to fill this important void in COPD management.

The overall objective of this CHEST and CTS joint evidence-based guideline (AECOPD Guideline) was to create a practical, clinically useful document describing the current state of knowledge regarding the prevention of acute exacerbations of COPD according to major categories of prevention therapies. We accomplished this by using recognized document evaluation tools to assess and choose the most appropriate studies and evidence to extract meaningful data and to grade the level of evidence supporting the recommendations in a balanced and unbiased fashion. The AECOPD Guideline is unique not only for its topic, but also for the first-in-kind partnership between two of the largest thoracic societies of North America. The CHEST Guidelines Oversight Committee (GOC) in partnership with the CTS COPD Clinical Assembly launched this project with the objective that a systematic review and critical evaluation of the published literature by clinical experts and researchers in the field of COPD would lead to a series of recommendations to assist clinicians in their management of the patient with COPD. This guideline is unique because a group of interdisciplinary clinicians who have special expertise in COPD clinical research and care led the development of the guideline process with the assistance of methodologists.

Materials and Methods

Expert Panel Composition

Members from CHEST and CTS were selected to participate on the AECOPD Guideline panel based on their expertise in the field. CTS representatives were members of the CTS COPD Clinical Assembly. Members who were interested in serving on the guideline panel were asked to submit their curriculum vitae, statement of interest, and conflict of interest disclosure form to the CHEST GOC for review. The final panel comprised a chair from CHEST and vice-chair from CTS as well as eight panelists from CHEST and nine from CTS who are experts in pulmonology and respiratory therapy. Panelists were assigned to one of three writing groups that addressed each key question. The groups were referred to as PICO groups because the key questions were developed using the PICO format, which defines the population, intervention, comparator, and outcome of interest.

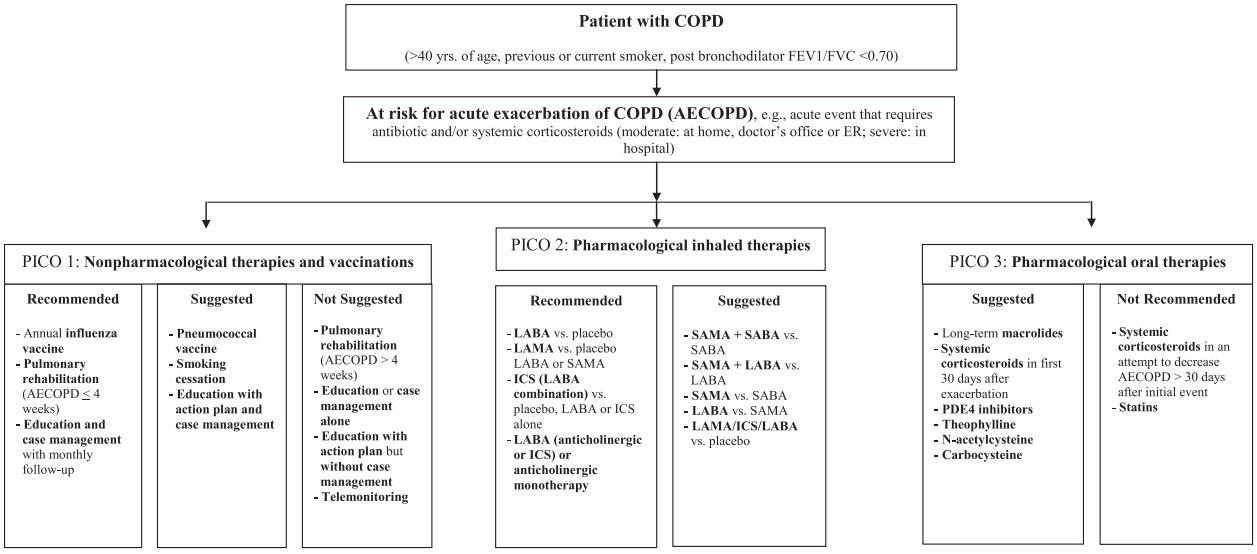

Figure 1 – *Decision tree for prevention of AECOPD according to three key clinical questions using the PICO format: nonpharmacologic therapies, inhaled therapies, and oral therapies. Note that the wording used is "recommended or not recommended" when the evidence was strong (level 1) or "suggested or not suggested" when the evidence was weak (level 2). AECOPD = acute exacerbation of COPD; ER = emergency room; ICS = inhaled corticosteroid; LABA = long-acting* β_2*-agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase 4; PICO = population, intervention, comparator, outcome; SABA = short-acting* β_2*-agonist; SAMA = short-acting muscarinic antagonist.*

Conflicts of Interest

The CHEST GOC reviewed all panel nominees, including the three methodologists, for their conflicts of interest. After review, nominees who reported no substantial conflicts of interest were approved, and nominees with potential conflicts of interest deemed to be manageable were "approved with management." Panelists approved with management were prohibited from writing and voting on treatment-related recommendations. They were allowed to contribute to writing the background sections of the guidelines and to participate in discussions of controversial recommendations. The chair was charged with reviewing any writing submitted by panelists who were approved with management. A grid tracking the conflicts of interest for each recommendation was created for each PICO writing group at the time of voting on the controversial recommendations. The three conflict of interest grids can be found in e-Tables 1 to 3.

Formulation of Key Questions

The AECOPD Guideline Executive Committee developed three key questions using the PICO format, which were then reviewed and revised by each PICO writing group. The three PICO questions that addressed the prevention of acute exacerbations of COPD were nonpharmacologic therapies, inhaled therapies, and oral therapies (Table 1). The outcome of interest was preventing acute exacerbations, including those requiring change in medication (antibiotic, prednisone, or both), ED visits and hospital admissions and readmissions, unscheduled physician visits, change in location of care, time to first exacerbation, or exacerbation rate. Systematic reviews were conducted for interventions identified in each PICO question, starting with a search for guidelines and systematic reviews. A further explanation of these processes was published separately.[24]

Definitions of Exacerbations

Exacerbation and COPD severity is noted when data were available to characterize the level of impairment or exacerbation severity. Exacerbations were defined as events that required a medication intervention with antibiotics, systemic corticosteroids, or both, and the severity of exacerbations was characterized by the location of care (home, ED, or hospital). Mild exacerbations were defined by adjustments in bronchodilator or inhaled corticosteroid therapy; moderate exacerbations were lower respiratory tract events treated with antibiotics, corticosteroids, or both agents; and severe exacerbations required ED visits or hospitalization. For the purpose of these guidelines, COPD was defined as a postbronchodilator $FEV_1/FVC < 0.7$. Mild COPD was further stratified by an $FEV_1 \geq 80\%$ predicted, moderate COPD by an FEV_1 50% to < 79% predicted, severe COPD by an FEV_1 30% to 49% predicted, and very severe COPD by an $FEV_1 < 30\%$ predicted.

Literature Searches

All panelists reviewed the PICO questions and finalized the search terms, inclusion and exclusion criteria, and databases that would be searched (Table 2). The Guidelines International Network (GIN) Library and National Guideline Clearinghouse were used to search for guidelines on COPD, and PubMed and the Cochrane Library were used to search for systematic reviews and primary literature.

The searches for guidelines were conducted on January 30, 2013, and included all guidelines published up to that date. The GIN search netted 26 guidelines, whereas the National Guidelines Clearinghouse search netted 24; only six of these were not found in the GIN search. In total, eight guidelines were considered relevant and were assessed for quality using the AGREE (Appraisal of Guidelines Research & Evaluation) II instrument.[25] Guidelines were excluded if they did not cover one of the three interventions (nonpharmacologic therapies, inhaled therapies, and oral therapies), did not cover the outcome of interest (prevention of acute exacerbations of COPD), or were not an evidence-based guideline.

The Cochrane search for systematic reviews took place on April 25, 2013, and was limited to systematic reviews published between 2007 and 2013. The PubMed search was conducted on April 29, 2013, and was limited to reviews published between 2008 and 2013. The search of the Cochrane Library resulted in 127 systematic reviews, and an additional 14 systematic reviews were found in the PubMed search. The systematic reviews were categorized by topic and sent to the three PICO groups for study selection. Relevant systematic reviews were assessed for quality using the DART (Documentation and Appraisal Review Tool)[26] to further determine whether they would be used to directly inform the evidence base for recommendations. Any fair- or good-quality

TABLE 1] PICO Questions

Section	Population	Intervention	Comparator	Outcome
Key question 1: In patients aged > 40 y who are previous or current smokers with COPD, do nonpharmacologic treatments and vaccinations prevent acute exacerbations?				
Nonpharmacologic treatment and vaccinations	• Adults with COPD aged > 40 y • Previous or current smoker • Diagnosis confirmed by spirometry $FEV_1/FVC < 0.70$	• Nonpharmacologic treatment and vaccinations (includes self-management, intensive education, vaccinations, rehabilitation, telemedicine, and integration of information technology platforms) • Education: educational sessions on COPD without support intervention other than physician visits • Self-management: —Educational sessions on COPD with ongoing support/empowerment from a case manager or COPD educator through visits, telephone calls, or information technology —Educational sessions on COPD with telemedicine-based programs without support intervention, such as the presence of a case manager (telemonitoring, teleintervention), that include stationary and mobile device applications —In-home monitoring without an educational component • Pulmonary rehabilitation (inpatient and outpatient): educational sessions on COPD with an exercise training program (home, community, outpatient, or inpatient) for minimum of 4 wk or 12 sessions • Vaccinations: influenza and pneumococcal vaccination • Smoking cessation	• Usual care and community standard of care at that time	• Exacerbations requiring change in medication (antibiotics, prednisone, or both) • ED visits and hospital admissions and readmissions • Unscheduled physician visits • Change in location of care • Time to first exacerbation • Exacerbation rate

(Continued)

TABLE 1] *(continued)*

Section	Population	Intervention	Comparator	Outcome
Key question 2: In patients aged > 40 y who are previous or current smokers with COPD, does maintenance inhaled therapy prevent acute exacerbations?				
Maintenance inhaled therapy	• Adults with COPD aged > 40 y • Previous or current smoker • Diagnosis confirmed by spirometry $FEV_1/FVC < 0.70$	Maintenance inhaled therapy: • Long-acting anticholinergics • Short-acting anticholinergics alone and in combination with short-acting β_2-agonists • ICSs • Long-acting β_2-agonists (formoterol, salmeterol, indacaterol) • Combination of long-acting anticholinergics, ICSs, and long-acting β_2-agonists • Should not include short-acting reliever medications (short-acting β_2-agonists alone)	• Short-acting bronchodilators • Combination therapies compared with single modality • Studies where control arm includes treatment • Head-to-head comparison	• Exacerbations requiring change in medication (antibiotics, prednisone, or both) • ED visits and hospital admissions and readmissions • Unscheduled physician visits • Change in location of care • Time to first exacerbation • Exacerbation rate
Key question 3: In patients aged > 40 y who are previous or current smokers with COPD, does oral therapy prevent acute exacerbations?				
Oral therapy	• Adults with COPD aged > 40 y • Previous or current smoker • Diagnosis confirmed by spirometry $FEV_1/FVC < 0.70$	Oral therapy: • Chronic antibiotic therapy • Phosphodiesterase 4 inhibitors • Statins • Oral or systemic corticosteroid therapy • Mucolytics (erdosteine, carbocysteine, N-acetylcysteine) • Theophyllines	• Study-defined placebo	• Exacerbations requiring change in medication (antibiotics, prednisone, or both) • ED visits and hospital admissions and readmissions • Unscheduled physician visits • Change in location of care • Time to first exacerbation • Exacerbation rate

ICS = inhaled corticosteroid; PICO = population, intervention, comparator, outcome.

TABLE 2] Study Methods

Section	Type of Study	Search Terms	Inclusion/Exclusion Criteria	Databases Searched
Key question 1: In patients aged > 40 y who are previous or current smokers with COPD, do nonpharmacologic treatments and vaccinations prevent acute exacerbations?				
Nonpharmacologic treatment and vaccinations	• Systematic reviews/ meta-analyses • RCTs (if available) • Otherwise cohort studies, case series studies, prospective studies, retrospective studies	• Acute exacerbations • COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive) • Chronic disease management, prevention • Nonpharmacologic therapies, education • Self-management • Case management • Action plans • In-home monitoring • Tele-intervention, telehealth, tele-health, Ehealth, e-health, telehealthcare, telecare, telemedicine, tele-monitoring, Emedicine, telecommunications and medicine, teleconsult • Respiratory rehabilitation pulmonary rehabilitation, (exercise, exercise training, activity, physical activity, exercise movement techniques, muscle training, kinesiotherapy, strength, training, walking, ambulation, mobilization, mobility, fitness exercise)—only if exercise is included • Immunizations, vaccination, influenza prevention, pneumococcal prevention • Smoking cessation	• English-language studies • No date restrictions • Studies included based on PICO • Included studies with follow-up duration ≥ 3 mo and studies with follow-up duration ≥ 6 mo • Primary and secondary outcomes included. If studies included that examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes was carefully examined and the body of evidence downgraded for risk of bias, if deemed necessary.	• National Guidelines Clearinghouse • Guidelines International Network • PubMed • Cochrane Library
Key question 2: In patients aged > 40 y who are previous or current smokers diagnosed with COPD, does maintenance inhaled therapy prevent acute exacerbations?				

(Continued)

TABLE 2] *(continued)*

Section	Type of Study	Search Terms	Inclusion/Exclusion Criteria	Databases Searched
Maintenance inhaled therapy	• Systematic reviews/ meta-analyses • RCTs (if available) • Otherwise cohort studies, case series studies, prospective studies, retrospective studies	• Acute exacerbations • COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive) • Chronic disease management, prevention • Inhaled therapy • Long acting β agonists • Long acting anticholinergics • Short acting anticholinergics • Inhaled corticosteroids	• English-language studies • No date restrictions • Studies included based on PICO • Included studies with follow-up duration ≥ 3 mo and studies with follow-up duration ≥ 6 mo • Primary and secondary outcomes included. If studies included that examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes was carefully examined and the body of evidence downgraded for risk of bias, if deemed necessary.	• National Guidelines Clearinghouse • Guidelines International Network • PubMed • Cochrane Library
Key question 3: In patients aged > 40 y who are previous or current smokers with COPD, does oral therapy prevent acute exacerbations?				
Oral therapy	• Systematic reviews/ meta-analyses • RCTs (if available) • Otherwise cohort studies, case series studies, prospective studies, retrospective studies	• Acute exacerbations • COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive) • Chronic disease management, prevention • Oral therapy • Antibiotics • Erdosteine • Carbocisteine • N-acetylcysteine • Phosphodiesterase-4 inhibitors • Statins • Oral or systemic corticosteroids • Mucolytics • Theophyllines	• English-language studies • No date restrictions • Studies included based on PICO • Included studies with follow-up duration ≥ 3 mo and studies with follow-up duration ≥ 6 mo • Primary and secondary outcomes included. If included studies examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes was carefully examined and the body of evidence downgraded for risk of bias, if deemed necessary.	• National Guidelines Clearinghouse • Guidelines International Network • PubMed • Cochrane Library

RCT = randomized controlled trial. See Table 1 legend for expansion of other abbreviation.

systematic reviews used in this manner were updated through the search strategies used by the review authors. Systematic reviews were also scanned for references that could further inform the primary literature searches.

Literature Searches by PICO Group

The PICO 1 nonpharmacologic therapies group reviewed 49 systematic reviews and determined that 15 were relevant. Of the 15 systematic reviews, four were used to directly inform the evidence base. The PICO 1 group conducted primary literature searches and reviews for the questions on education, action plans, case management, and smoking cessation because existing systematic reviews did not meet the predefined definitions for these interventions. The PICO 2 inhaled therapies group reviewed 49 systematic reviews and determined that 30 were relevant. Of the 30 systematic reviews, 11 were used to directly inform the evidence base. The PICO 3 oral therapies group reviewed 27 systematic reviews and determined that eight were potentially relevant. The PICO 3 group also conducted primary literature reviews because the extracted systematic reviews did not sufficiently address all the drug classes. Additional details on literature searches and study selection can be found in e-Appendix 1.

Study Selection and Data Extraction

A methodologist assigned to each PICO group conducted the initial literature searches and the first-round title and abstract review to exclude studies not related to COPD based on the inclusion and exclusion criteria shown in Table 2. The panelists reviewed the studies identified for exclusion and divided into pairs to apply the inclusion and exclusion criteria to the studies initially screened for inclusion. All recommendations were made independently in parallel and then compared. Disagreements were resolved through discussion and further consultation with the methodologist if needed. Panelists were divided into pairs for data extraction, with one performing data extraction and the other independently reviewing the initial data extraction. The methodologists assisted in building evidence tables and added data necessary for conducting any meta-analyses. Data from new studies identified in updated searches of published systematic reviews and data from de novo reviews were extracted into evidence tables (e-Tables 4, 5).

Quality Assessment

The methodologists assessed the quality of the guidelines using AGREE II[25] and DART.[26] Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool.[27] R. D. developed a quality assessment tool for intervention studies, including RCTs and observational studies, that was used to assess the quality of any observational studies included in the evidence reviews.[28,29] As the methodologists were assessing the quality of the studies, they also considered how exacerbations were counted[30] and whether the outcomes were treated as primary or secondary outcomes.

Meta-analyses and Evidence Profiles

Upon completion of the evidence tables and quality assessment, Review Manager version 5.1 software (The Cochrane Collaboration) was used to create meta-analyses on topics where data were homogeneous and poolable based on the measured outcomes. Studies with a shorter follow-up period (ie, 3-4 months) were examined separately from those with a longer follow-up period (ie, $\geq$ 6 months). When possible, meta-analyses included studies from published systematic reviews as well as new studies identified through updated searches. Meta-analyses were also used for data compiled from de novo reviews. Heterogeneity of the pooled results was assessed using a χ^2 test and Higgins I^2, and a forest plot was examined for consistency of the results. A Higgins $I^2 \geq 50\%$ and $P < .05$ indicated statistically significant heterogeneity. The random-effects model was chosen a priori as the appropriate model for pooling data. Results from the meta-analyses can be found in e-Tables 6 and 7.

Grading the Evidence Profiles

Evidence profiles were produced using GRADEpro software (GRADE Working Group). The GRADEpro software ranked the quality of the body of evidence using four categories: high, moderate, low, and very low (Table 3).[31] The quality of the evidence was then used to determine the strength of the supporting evidence that informed a recommendation (see the next section, Recommendations, for more information on grading recommendations). Additional information on grading the body of evidence can be found in "Methodologies for the Development of CHEST Guidelines and Expert Panel Reports."[24] Evidence profiles can be found in e-Tables 8 to 10.

Recommendations

Evidence tables, meta-analyses, evidence profiles, and all the studies included in the evidence review informed the recommendations and their associated grades. Recommendations were graded using the CHEST grading system (Table 4).[24,32] Values and preferences statements are considered part of a recommendation, and they appear with the recommendation in the main text of the guideline as well as in the summary of recommendations and executive summary. Panelists who were approved with management refrained from writing treatment-related recommendations and were assigned to drafting supporting text. Only one panelist in the PICO 1 nonpharmacologic therapies group was prohibited from writing treatment-related recommendations. Two panelists in the PICO 2 inhaled therapies group were permitted to write recommendations, and they worked with the other panelists in the group to draft supporting text. Three panelists in the PICO 3 oral therapies group were permitted to write recommendations, and they worked with the other panelists to draft the supporting text. Recommendations were not made in instances where the panelists believed the data insufficient or inconclusive to warrant a recommendation. In instances where there was insufficient evidence but a recommendation was still warranted, a weak suggestion was developed, and consensus based (CB) replaced the grade. Completed recommendations/suggestions and supporting text were reviewed by each PICO group and revised before shared with the entire panel.

Recommendations/suggestions and supporting text were sent to the panelists along with a survey of the recommendations/suggestions asking panelists to identify any recommendations deemed controversial based on wording, grade, or both. Any recommendations identified as

TABLE 3] Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

Definitions adapted from Balshem et al.[31]

TABLE 4] American College of Chest Physicians Grading System

Grade of Recommendation	Balance of Benefit vs Risk and Burdens (Strength of the Recommendation: Level 1 or 2)	Methodological Strength of Supporting Evidence (Quality of Body of Evidence: A, B, C, or CB)	Implications
Graded evidence-based guideline recommendations			
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balance with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ, depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balance with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies	Best action may differ, depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Nongraded consensus-based suggestions			
Consensus based	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on confidence in the estimate of effect and may change the estimate.

CB = consensus based. See Table 2 legend for expansion of abbreviation.

controversial in the survey as well as any CB suggestions were presented and discussed during a live webinar. Panelists were then sent an additional survey with the revised statements resulting from the discussions and asked to vote on the recommendations/suggestions. The conflict of interest grids were sent with the voting survey, and panelists approved with management were on the honor system to refrain from voting on any treatment-related recommendations. Based on CHEST policy, 75% participation and 80% consensus were required for recommendations/suggestions to pass. Any recommendations/suggestions that did not pass were revised based on feedback included in the voting survey, and a new survey was sent with the incorporated changes.

Review Process

After the AECOPD Guideline Executive Committee provided final approval, the manuscript was sent to the Executive of the Canadian Respiratory Guidelines Committee (CRGC), CTS Executive, and CHEST reviewers representing the GOC, Board of Regents, and NetWorks. The CHEST NetWorks of interested members in the areas of airways disorders and clinical pulmonary medicine reviewed the manuscript content. All reviewed both content and methods for consistency, accuracy, and completeness. The *CHEST* Journal peer-review process was integrated with these reviews. All ideas for modification were marked as mandatory or suggested by the GOC, responded to or justified by the authors, and tracked through multiple rounds of review.

Dissemination, Implementation, and Knowledge Translation

After publication, the guidelines were promoted by both CHEST and CTS to a wide audience of physicians, other health-care providers, and the public through multiple avenues. Joint press releases were made to both the lay and the medical media, with major outreach efforts to all relevant print, broadcast, and Internet media. Panelists located in various large media markets were identified as potential spokespersons for interviews. In addition to the guidelines, a companion article was prepared to help with implementation.

American College of Chest Physicians: Social media promotion was facilitated over Twitter, Facebook, CHEST e-Communities, internal and external blogs, and other communication routes. Blast communications were sent to CHEST members with links to the publication and postings on the CHEST website.

In addition to publication in *CHEST*, other derivative products were prepared to help with implementation, including slide sets, algorithms, and other clinical tools. These derivative products were posted on the CHEST website and made available in CHEST Guidelines expected to launch at a later date. CHEST Guidelines will be the repository for the most current recommendations/suggestions from all CHEST guidelines, consensus statements, and hybrid documents. This online repository will also house a collection of related resources.

Canadian Thoracic Society: The knowledge translation plan was developed by (1) identifying key messages from the guideline recommendations, (2) determining the target audiences for each message, (3) seeking out the most credible messenger and engaging his or her interest in becoming involved in the communication, and (4) launching a knowledge translation strategy grounded in the best available research evidence. The CTS has a framework for guideline dissemination and implementation, with concurrent evaluation led by the CRGC based on the Knowledge-to-Action Framework.[33] Traditional knowledge diffusion avenues, such as presentations at scientific meetings and publication in peer-reviewed journals, will be used. The guideline was promoted through the CRGC website (www.respiratoryguidelines.ca). Targeted promotional communications were sent to provincial lung associations across Canada and distributed through CTS e-bulletins to individuals and organizations with an interest in this topic area.

CTS used other modes of communication such briefing notes, websites, creative media, and emerging online technologies (eg, podcasting, accredited webinars). To disseminate more broadly to the general public, traditional media and social media were engaged. Point-of-care tools for implementation of guideline recommendations were developed, including a trifold pocket brochure (Slim Jim) and electronic versions of the guideline for the smart phone and tablet. A slide kit for teaching and self-directed learning were posted for viewing and downloading on the CRGC website.

Endorsement

Associations were invited to consider endorsing the approved guideline for listing in the final publication. These organizations were requested to help to promote the publication to their memberships through newsletters, websites, and other means.

Updating

CHEST guidelines and consensus statements are living documents subject to updating as necessary. Annual reviews begin 1 year after publication. The CHEST GOC and CTS CRGC have established criteria to select and prioritize projects for updating, including the publication of new studies where the results might affect either the direction or the strength of the existing recommendations. Other criteria focus on new interventions or changes in practice that might require updating existing recommendations. The long-term goal is to maintain the currency of the guidance documents.

Recommendations for the Prevention of Acute Exacerbations of COPD

PICO 1: Do Nonpharmacologic Treatments and Vaccinations Prevent/Decrease Acute Exacerbations of COPD?

Effective support and management of individuals at risk for an AECOPD demands a comprehensive and patient-centered approach. The widely adopted Chronic Care Model[34,35] recognizes that improvements in care require approaches incorporating patient-, provider-, and system-level interventions. Key elements of the Chronic Care Model are the health system, delivery system design (including case management), decision support, clinical information systems, self-management support (including assessment, goal setting, action planning, problem solving, and follow-up), and community. The importance of incorporating nonpharmacologic approaches into the care of this population is reflected in international guidelines for COPD management.[20,36,37]

PICO question 1 addresses the following categories: (1) pneumococcal vaccinations; (2) influenza vaccinations; (3) smoking cessation programs; (4) pulmonary rehabilitation; (5) education, action plans, and case management; and (6) telemonitoring (Table 1). A definition of each intervention is specified in the text

that accompanies each recommendation. The present taxonomy and definitions of interventions differ from that of several other publications[38-40] related to nonpharmacologic management. We chose to create exclusive, clearly defined, and comparable categories and to characterize evolving technologies, such as telemonitoring.

These topics may be considered complex interventions[41] in that they contain multiple interacting components and possess nonlinear causal pathways subject to a host of variables.[42] Rigorous evaluation of complex interventions can be complicated by numerous factors, including the need to adapt interventions to local contexts and issues of feasibility and acceptability.[43] Many of the nonpharmacologic trials have limitations with respect to such methodological aspects as how the intervention was standardized and the details of the experimental treatment and comparator as they were implemented. Prevention of exacerbations often was not the primary outcome for many studies examining the efficacy and effectiveness of nonpharmacologic interventions, thus limiting our ability to make definitive recommendations. We recognize that some interventions may have beneficial outcomes relevant to overall health and quality of life but are insufficient to recommend their use to prevent exacerbations.

Pneumococcal Vaccine: The presence of underlying medical conditions such as COPD increases the risk for pneumococcal disease and its complications. Hospitalization rates for pneumococcal pneumonia are higher in patients with COPD than in the general population.[44,45] Pneumococcal vaccinations are effective for reducing the risk of infectious disease and may be beneficial in reducing infectious-related exacerbations in COPD.[46] Patients with COPD with persistent lower-airway bacterial colonization, those with *Streptococcus pneumoniae* in sputum, and those with newly acquired *Streptococcus* pneumonia have a significantly increased risk of COPD exacerbation.[47-49] COPD exacerbations associated with pneumococcal infection result in longer hospitalizations and greater impairment of lung function compared with noninfectious exacerbations.[50] Multiple guidelines, including those of the US Centers for Disease Control and Prevention (CDC) and Health Canada, recommend the use of pneumococcal vaccine for all adults aged ≥ 65 years and those aged 19 to 64 years with underlying medical conditions that put them at greater risk for serious pneumococcal infection, including those with COPD.[20,37,44,46,51]

Although existing recommendations support vaccination in patients with COPD in general, no clear evidence supports its use to prevent acute exacerbations of COPD as summarized in a Cochrane review.[52] Seven studies met inclusion criteria; two older trials used a 14-valent vaccine, and five more-recent trials used a 23-valent vaccine. Improvement in pneumonia rates in patients with COPD (six studies involving 1,372 individuals) did not achieve statistical significance for vaccination vs control (OR, 0.72; 95% CI, 0.51-1.01). The likelihood of acute exacerbations of COPD (two studies involving 216 individuals) was not different between the vaccination vs no vaccination groups (OR, 0.58; 95% CI, 0.30-1.13). Analysis of secondary outcomes found no statistically significant reduction in hospital admissions or ED visits. In pooled results from three studies (n = 888), there was no significant reduction in all-cause mortality for periods up to 48 months postvaccination (OR, 0.94; 95% CI, 0.67-1.33).

The COPD Clinical Research Network evaluated the safety and immunogenicity of a 7-valent protein-conjugated vs 23-valent polysaccharide pneumococcal vaccine in a randomized open-label trial in patients with COPD.[53] Both vaccines resulted in significant increases in postvaccination IgG levels for all serotypes compared with baseline; however, there were greater antibody responses in five of seven serotypes using the 7-valent protein-conjugated vs the 23-valent polysaccharide vaccine. No differences (hazard ratio [HR], 0.91; $P = .66$) were noted in the time to first exacerbation of COPD or in the number of exacerbations, cases of pneumonia, or hospitalizations, but the study was not powered to address these issues.

We also found one study that examined the additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbations in patients with chronic lung diseases.[54] In this open-label RCT in 167 subjects randomly assigned to both vaccines compared with influenza vaccine alone, fewer episodes of infectious-related acute exacerbations were experienced over a 2-year period ($P = .022$).

1. In patients with COPD, we suggest administering the 23-valent pneumococcal vaccine as part of overall medical management but did not find sufficient evidence that pneumococcal vaccination prevents acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of pneumococcal vaccination for general health, and we endorse existing guidelines that recommend it for patients with COPD. Although evidence does not specifically support using the vaccine for the prevention of acute exacerbations, multiple bodies, including the CDC and World Health

Organization (WHO), recommend the use of pneumococcal vaccine for all adults aged ≥ 65 years and in those aged 19 to 64 years with underlying medical conditions such as COPD that put them at greater risk of serious pneumococcal infection.

Influenza Vaccine: Annual influenza vaccination is the primary means of influenza prevention and has been recommended since 2010 for all persons aged ≥ 6 months who do not have contraindications.[55] Influenza infection is associated with excessive mortality and morbidity in COPD that include detrimental effects on disease progression and increased risk of hospitalization.[1,20,36,37,56,57]

The evidence supporting the recommendation for influenza vaccine use in COPD was primarily derived from a Cochrane review last updated in May 2009.[58] This systematic review evaluated the evidence from RCTs regarding treatment effects of influenza vaccination in subjects with COPD, including exacerbation rates, hospitalizations, mortality, lung function, and adverse effects.[58] Eleven studies were included in this systematic, evidence-based review, with six specifically performed in patients with COPD and two evaluating exacerbation rates using inactivated virus vaccination.[59,60] These studies defined COPD minimally by specified COPD clinical diagnosis and measured exacerbations determined clinically without rigorous or adjudicated definitions. In a pooled analysis across 180 subjects, inactivated influenza vaccine in patients with COPD resulted in a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo (weighted mean difference [WMD], −0.37; 95% CI, −0.64 to −0.11; $P = .006$). The effect was further to occur only after 3 to 4 weeks, defined as late exacerbations (WMD, −0.39; 95% CI, −0.61 to −0.18; $P = .0004$). Both studies found a reduction in influenza-related respiratory infections (WMD, 0.19; 95% CI, 0.07-0.48; $P = .0005$).

Additional analyses in the Cochrane review[58] of other secondary outcomes found no effect on reduced hospitalization (OR, 0.33; 95% CI, 0.09-1.24; $P = .52$). Analyses of a broader pool of patients with COPD and in elderly patients in general (only a minority of whom had COPD) found a significant increase in the occurrence of local adverse reactions with vaccines, but the effects were generally mild and transient. There was no evidence of an effect of intranasal live attenuated virus when added to an inactivated intramuscular vaccination. The studies were reported to be too small to have detected any effect on mortality.

2. In patients with COPD, we recommend administering the influenza vaccine annually to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on the benefits of influenza vaccination for general health, the low risk of side effects, and the existing guidelines that recommend it for patients with COPD. Although the effect and evidence are moderate for the prevention of acute exacerbations of COPD, multiple bodies, including the CDC and WHO, recommend the use of a yearly influenza vaccine for all adults, including those with COPD.

Smoking Cessation: International organizations, including the CTS, WHO, National Institute for Health and Clinical Excellence, Burden of Chronic Obstructive Lung Disease, and US Preventive Services Task Force, recommend tobacco cessation for all adults with COPD, citing it as the most effective intervention in reducing COPD progression and morbidity. Smoking cessation is the only evidence-based intervention that improves COPD prognosis[61,62] by ameliorating the annual decline in lung function,[63] reducing cough and sputum production,[64] improving health-related quality of life, and reducing COPD exacerbations. Exacerbation frequency and active smoking may independently result in lung function decline.[65] Smoking cessation attempts may be difficult and frequently unsuccessful for patients with COPD who have prolonged exposure to tobacco smoke.[66,67] An effective smoking cessation program should address the behavioral, physiologic, and psychologic consequences of smoking; be cognizant of prior unsuccessful quit attempts; and target high-risk smokers. Smoking cessation programs that range from simple strategies to intensive, multicomponent programs have been tested in patients with COPD. These programs may comprise acknowledging current smoking followed by advice to quit, pharmacologic therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), or counseling (in-person or telephone counseling). These strategies have been used alone or in combination with varying success. Smoking cessation rates ranging from 8.8% to 34.5% have been reported and vary according to the strategy implemented, such as low-intensity counseling vs combination strategies that include psychosocial and pharmacologic interventions.[68] Most authors recommend a combination of pharmacologic and behavioral strategies for smokers with COPD.[68-70]

We identified two observational evaluations of tobacco cessation effects on COPD exacerbations and two RCTs

that were limited by quality and bias. Au et al[71] evaluated whether smoking status and duration of abstinence affected the risk for COPD exacerbations in a cohort of 23,971 current and former smokers from the Department of Veterans Affairs. Using Cox proportional hazards regression adjusting for age, comorbidity, markers of COPD severity, and socioeconomic status, smoking cessation was associated with a reduced risk for COPD exacerbations (adjusted HR, 0.78; 95% CI, 0.75-0.87). The magnitude of the reduced risk depended on the duration of smoking abstinence (adjusted HR: quit < 1 year, 1.04 [95% CI, 0.87-1.26]; quit 1-5 years, 0.93 [95% CI, 0.79-1.08]; quit 5-10 years, 0.84 [95% CI, 0.70-1.00]; quit ≥ 10 years, 0.65 [95% CI, 0.58-0.74]; linear trend $P < .001$). A cost-effectiveness analysis was performed on a randomized clinical trial comparing the effectiveness of a high-intensity smoking cessation intervention vs a medium-intensity strategy.[72] After 1 year, the high-intensity strategy (individual counseling sessions, telephone contacts, small-group counseling sessions, and pharmacologic support) was associated with a higher continuous abstinence rate (salivary cotinine-validated abstinence at 6 and 12 months, 19% vs 9%, respectively; relative risk, 2.22; 95% CI, 1.06-4.65; $P = .03$). Additionally, the high-intensity strategy was associated with lower cost (€581 vs €595), a lower average number of exacerbations (0.38 vs 0.60), and a reduced number of hospital days (0.39 vs 1.00) per patient.

In a single-center study, Borglykke et al[73] randomized 223 smokers hospitalized with symptoms consistent with a COPD exacerbation to a smoking cessation program vs usual care. After 1 year, the 48 subjects enrolled in the intervention group were more likely to be abstinent (30% vs 13%; OR, 2.83; 95% CI, 1.40-5.74). After 3 years, the intervention group had fewer hospital admissions and number of days admitted, although these differences were not statistically significant.

Hospital admission following a smoking cessation intervention was evaluated in 19,709 participants from three prospective population studies in Copenhagen, Denmark.[74] Compared with current smokers, former smokers had a significant reduction in the risk of hospital admission (HR, 0.57; 95% CI, 0.33-0.99). Smoking cessation was demonstrated to be effective in reducing hospital admissions, but reduction in smoking was not associated with a significantly lower risk of hospitalization (HR, 0.93; 95% CI, 0.73-1.18).

The strength of the data is low; therefore, the benefits compared with risk for this outcome are uncertain. However, the additional benefits achieved from smoking cessation, such as reduction in precancerous lesions and reduction in lung cancer risk,[75] and other outcomes associated with improved COPD symptoms support this recommendation. Additionally, a consortium of specialty and primary care organizations comprising the American College of Physicians, CHEST, American Thoracic Society, and European Respiratory Society recommended smoking cessation for patients with COPD in a clinical practice guideline update published in 2011.[20]

3. In patients with COPD, we suggest including smoking cessation counseling and treatment using best practices as a component of a comprehensive clinical strategy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of smoking cessation for all individuals. In particular, it is the only evidence-based intervention that improves COPD prognosis by mitigating lung function decline and reduces symptoms. Although the effect and evidence for smoking cessation in the prevention of acute exacerbations of COPD are low, evidence supports smoking cessation for many reasons. Among general health benefits, smoking cessation in patients with mild COPD who produce cough and phlegm leads to substantial symptom reduction in the first year, with less lung function decline and fewer symptoms upon sustained cessation as well as leads to a decreased risk for infections such as pneumonia, which has been associated with cigarette smoking. The benefit from smoking cessation outweighs the risks, and a myriad of strategies have been summarized by other guidelines and reviews. In general, effective smoking cessation programs include behavioral, physiologic, and psychologic components comprising an acknowledgment of current smoking followed by advice to quit, pharmacologic therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), and counseling (in-person or telephone counseling) with cessation rates ranging from 8.8% to 34.5%. Smoking cessation that includes counseling and pharmacologic interventions are cost-effective.

Pulmonary Rehabilitation: Pulmonary rehabilitation has been recently defined as "a comprehensive intervention based on exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."[76] The benefits of pulmonary rehabilitation in patients with COPD are considerable,[76-78] and rehabilitation has been shown to be the most effective therapeutic

strategy to improve shortness of breath, health-related quality of life, and exercise tolerance.[79,80] Pulmonary rehabilitation is a prominent component of integrated COPD care[81] and is considered a standard-of-care intervention for individuals with COPD who remain symptomatic despite optimal bronchodilator therapy.[37,77,78]

For this analysis, we assumed that an all-cause hospitalization reflected a COPD-specific hospitalization. In a pooled analysis across 623 patients with COPD from all nine studies,[82-90] pulmonary rehabilitation resulted in a significant reduction in hospitalizations compared with conventional care (OR, 0.45; 95% CI, 0.22-0.91; $P = .03$). Overall, the quality of evidence was rated low to very low due to risk of bias, inconsistency, and imprecision. Minimal harms were noted with participation in rehabilitation, with no serious adverse events reported. Considerable heterogeneity was observed between studies, with three of the nine showing a significant reduction in hospitalizations following rehabilitation ($P = .03$, $I^2 = 52\%$). In an attempt to examine study heterogeneity, the studies were further categorized based on whether pulmonary rehabilitation was given immediately (ie, <1 month) following a recent COPD hospitalization (unstable state or recovery phase) or in patients with stable disease. In the studies that examined the effect of pulmonary rehabilitation given immediately after a COPD hospitalization, the data show a reduction in COPD rehospitalizations following rehabilitation[82-84,87,88] (OR, 0.24; 95% CI, 0.07-0.88; $P = .03$). These findings are consistent with an earlier Cochrane review by Puhan et al.[91] Of note, grade 1C was given because the studies examining pulmonary rehabilitation immediately after an acute exacerbation were judged to be of low or very-low quality, and significant heterogeneity was observed between studies ($P = .008$, $I^2 = 71\%$).

In the four studies examining patients without a recent history of exacerbation (stable state), pulmonary rehabilitation consistently did not reduce COPD hospitalizations (OR, 0.79; 95% CI, 0.42-1.5; $P = .47$).[85,86,89,90] However, as previously mentioned, among patients with a recent exacerbation (≤ 4 weeks from prior hospitalization), pulmonary rehabilitation has shown benefit in reducing COPD hospitalizations, adding to the growing literature detailing the considerable patient benefits from pulmonary rehabilitation and supporting earlier statements advocating for greater access to pulmonary rehabilitation for patients with COPD.[76,77] The recommendation would be strengthened by consistent, high-quality, large RCTs that specifically track both acute exacerbations and exacerbation-related hospitalizations.

4. In patients with moderate, severe, or very severe COPD who have had a recent exacerbation (ie, ≤ 4 weeks), we recommend pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

5. In patients with moderate, severe, or very severe COPD who have had an exacerbation greater than the past 4 weeks, we do not suggest pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

Education, Action Plans, and Case Management: Education, action plans, and case management are interventions that directly relate to the tenets of the Chronic Care Model.[92] They focus on enabling patients to be knowledgeable about COPD, to have the necessary skills to manage their chronic disease, and to be motivated to take an active part in their health care in partnership with an experienced and engaged health-care team. There is no consensus on the definition of education, action plans, and case management in COPD care. We defined education as formal delivery of information on topics related to COPD with the aim of improving the knowledge and understanding of COPD. Patient education was categorized as self-management education (eg, education aiming at patient self-management). An

action plan was defined as a written plan produced for the purpose of patient self-management of COPD exacerbations. Case management was defined as "a collaborative process of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an individual's and family's comprehensive health needs through communication and available resources to promote quality, cost-effective outcomes."[93] In this review, case management was identified as structured follow-up, communication, or both with a health-care professional with a particular focus on changes in the patient's signs and symptoms; advice on appropriate interventions; referral to physicians; and recommendations for the initiation of therapy to prevent or reduce the risk of a serious AECOPD. The communication could be in person or through telephone or other teletechnology but did not include biomonitoring with data transferred over teletechnology.

This systematic review was completed before the 2014 Cochrane review on self-management for patients with COPD by Zwerink et al[94] and differs from that review in several important ways. Zwerink et al[94] searched the literature from 1994 to 2011, whereas the current literature review was not limited by publication date. The Cochrane review did not focus specifically on prevention of acute exacerbations of COPD and used a broad definition of self-management that included smoking cessation, self-recognition, and self-treatment of acute exacerbations of COPD; exercise and physical activity; action plans; and advice on diet, medication, and coping with dyspnea. In the present review, we chose to examine the effects of many of these interventions separately because these interventions often are delivered separately in current clinical practice.

Education Alone: One RCT[95] investigated the benefits of pharmacist-delivered patient education on health-related quality of life. Using the motivational interviewing technique, pharmacists in an outpatient clinic delivered one-on-one education with study participants on disease management topics, including medications, the importance of exercise, and airway clearance. Neither the duration of the intervention nor the number of sessions was reported. The primary outcome measure was improvement in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ). Prevention of COPD-related ED visits and hospitalizations were secondary outcome measures. The method of measuring ED visits and hospitalizations was done through patient interview, medical records, and hospital databases. In this study of 133 patients (61% women; FEV_1, 54% predicted; 66 in intervention arm; 67 in control arm), patient education delivered by a pharmacist resulted in a statistically significant reduction in COPD-related hospitalizations over a 6-month follow-up period. Based on the published data, we calculated an OR of 0.24 (95% CI, 0.06-0.91).

There is lack of data to recommend education alone to prevent COPD exacerbations. Only one study was conducted in a single hospital with a small sample size. Furthermore, the lack of information on the implementation of the patient education limits the ability of other investigators to replicate this intervention.

6. In patients with COPD, we suggest that education alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the motivational educational intervention because it is labor intensive compared with traditional education techniques.

Case Management Alone: One RCT[96] investigated the benefits of a 1-year period of case management alone on health-care use, which was a prespecified secondary outcome of the study. The method of measuring ED visits, hospital admissions, and number of hospital days was not specified. In this study, 122 patients who had been receiving long-term oxygen therapy for at least 6 months and who had a mean FEV_1 of 28% predicted were randomly assigned to an intervention or a usual-care group. The intervention combined home care management and easy access to hospital resources. It included a monthly telephone call and a home visit every 3 months as well as a rapid response to patient requests for assistance with respiratory issues over the 1-year study period. The intervention was associated with a highly significant reduction in the number of hospitalizations (intervention group, 0.5 ± 0.86; control group, 1.29 ± 1.7; Mann-Whitney U test $P = .001$), ED visits (intervention group, 0.45 ± 0.83; control group, 1.58 ± 1.96; Mann-Whitney U test $P = .0001$), and hospitalization days (intervention group, 7.43 ± 15.6; control group, 18.20 ± 24.55; t test $P = .01$). The study had a high risk of bias related to unclear randomization techniques, incomplete outcome data, lack of blinded assessments, and low number of participants. Furthermore, it is not clear how the intervention affected acute exacerbations of COPD.

Although the intervention resulted in a statistically significant reduction in ED visits, hospitalizations, and hospitalization days, this evidence was from one study with a high risk of bias. Therefore, because of the lack of sufficient evidence for a graded recommendation, there is uncertainty about the effect of case management alone to prevent acute exacerbations of COPD.

7. In patients with COPD, we suggest that case management alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the lack of change in quality of life in either group because this information was present for only a small proportion of the entire sample.

Education and Case Management (Without Action Plan): Three studies[97-99] met our inclusion criteria and assessed changes in hospitalizations, although not always as the primary outcome measure. None of these studies included an action plan in the intervention. Other outcome measures included visits to the physician's office, clinic, or ED. Two studies[97,99] reported a decrease in hospitalizations in the intervention group, whereas the other found no difference between groups.[98] The data from two studies[97,98] were combined in a meta-analysis to assess the effect on hospitalizations. The results demonstrated no statistically significant differences between groups. After a 6-month follow-up period, Lainscak et al[97] reported a 14% hospitalization rate for the intervention group vs 31% for the control group, whereas Smith et al[98] reported that 70% of participants in the intervention group and 55% in the control group had one or more respiratory-related hospitalization. The pooled OR was 0.82 (95% CI, 0.17-3.99), with significant heterogeneity between studies ($P = .003$, $I^2 = 89\%$). The study by Soler et al[99] reported a significant decrease in hospitalizations. Smith et al reported no impact of education and case management on hospitalizations, hospital length of stay, or ED visits; however, these results must be viewed with caution because the sample size was small and the dropout rate high and the data were missing in one-third of the study participants.

Heterogeneity in participant characteristics and study methodology affected our conclusion about the effect of education and case management on exacerbations. Although patients in all three studies had moderate to severe disease, their exacerbation histories differed. The studies by Lainscak et al[97] and Soler et al[99] recruited participants with a history of exacerbations and reported decreases in hospitalizations, whereas Smith et al[98] did not specify an exacerbation history as an inclusion criterion and found that the intervention did not affect hospitalizations. The intensity, content, and duration of the intervention also varied among the three studies. Smith et al[98] reported on respiratory-specific hospitalizations, whereas Lainscak et al[97] and Soler et al[99] used all-cause hospitalization data. All studies had small participant numbers. Only Lainscak et al[97] had $>$ 100 participants per group. The other studies had $<$ 50 participants per group.

8. In patients with COPD with a previous or recent history of exacerbations, we recommend education and case management that includes direct access to a health-care specialist at least monthly to prevent severe acute exacerbations of COPD, as assessed by decreases in hospitalizations (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

Education and Action Plan: Four studies[100-103] met our inclusion criteria and assessed the effect of structured education and action plans on the prevention of acute exacerbations of COPD. Two studies[102,103] assessed changes in mean ED visits and mean hospitalizations, whereas the other two[100,101] assessed hospitalization rates. None of the studies assessed ED visits or hospitalizations as the primary outcome measure.

The inclusion criteria varied among the studies. McGeoch et al[101] required a previous history of an AECOPD within the past year, whereas the other three studies did not have this criterion. Gallefoss[100] required an FEV_1 between 40% and 80% predicted; Wood-Baker et al[103] required an $FEV_1 < 65\%$ predicted; and Wakabayashi et al[102] and McGeoch et al[101] had no FEV_1 percent predicted requirement. The number of participants in the study ranged from 52 in Gallefoss[100] to 154 in the intervention reported by McGeoch et al.[101] The number of events or the event rates were low in the four studies. The data from all studies were combined in separate meta-analyses to assess the effect of education combined with an action plan on ED visits and hospitalizations. These studies demonstrated no effect on mean ED visits, mean hospitalizations, or hospitalization rates. Gallefoss[100] and Wood-Baker et al[103] also assessed the impact of the intervention on general practitioner visits. Gallefoss[100] reported that the intervention reduced the

number of nonacute general practitioner visits, but there was no difference in the number of acute care visits. Wood-Baker et al[103] reported no differences between the groups in general practitioner visits. None of the studies reported any adverse events related to the intervention. The risk of bias was rated serious to very serious in all the studies.

9. In patients with moderate to severe COPD, we suggest education together with an action plan but without case management does not prevent severe acute exacerbations of COPD, as assessed by a decrease in ED visits or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

Education and Action Plan and Case Management: We identified 16 studies that met our inclusion criteria. Twelve presented original data that assessed the effect of education combined with a written action plan and individualized case management on hospital admissions and ED visits. The results of eight studies[104-111] were combined in a meta-analysis to assess the effect of the intervention on hospitalizations. Four of these studies[104,107-109] provided data for a meta-analysis of the effect of the intervention on ED visits. An additional four studies[112-115] addressed outcomes of interest but could not be included in the meta-analyses.

Six studies[104-106,109,114,115] specifically recruited participants with a history of exacerbations. Two studies[114,115] measured differences in all-cause hospitalizations and ED visits, whereas the other studies focused on acute exacerbations of COPD. Seven studies included in the meta-analysis reported the effect of a 12-month intervention on hospitalizations,[104-109,111] and one study assessed a 6-month intervention.[110]

In the meta-analysis assessing hospitalizations, 1,094 individuals received the intervention and 1,107 received usual care. Eight studies[104-111] favored the intervention (pooled OR, 0.64; 95% CI, 0.46-0.90). There was heterogeneity in the study results ($P = .05$, $I^2 = 51\%$), with three studies[106,110,111] showing nonsignificant effects. The study by Fan et al[106] was stopped early due to excess mortality in the intervention group. Three studies[113-115] could not be included in the meta-analysis. These studies assessed hospitalizations at 3,[115] 6,[113] and 12[114] months. None of the studies demonstrated a difference in hospitalizations between groups. Eight studies[104,106-108,110-112,114] had a low risk of bias, and the risk of bias was unclear in the rest.

Seven studies[104,107-109,113-115] examined the effect of interventions on ED visits. Four of these[104,107-109] were combined in a meta-analysis, and the others[113-115] were considered separately. One-half of the studies[104,109] in the meta-analysis recruited participants who had a history of exacerbations, and three[104,108,109] reported COPD-specific results. The results of the meta-analysis clearly favored the 12-month intervention (pooled OR, 0.48; 95% CI, 0.36-0.63). The study by Rice et al[109] showed a positive effect and contributed 54% of the total weight. Of the three studies not included in the meta-analysis, only Gadoury et al[114] reported a reduction in all-cause visits. Participants had a history of exacerbations on entry into the study, and the study itself had a low risk of bias.

One study[112] assessed the effects of an intervention on the frequency of exacerbations over a 24-month intervention period. Participants were randomized into a usual-care, routine monitoring, or self-management group. Randomization included stratification for disease severity and the frequency of exacerbation in the 24 months prior to entering the study. Most of the study participants had mild to moderately severe disease. There was no difference in unscheduled medical contact between the groups during the first month (OR, 1.09; 95% CI, 0.42-2.81) or the subsequent 12 months (OR, 2.07; 95% CI, 0.60-7.15). There were no differences in the frequency of exacerbations at 12 (RR, 1.10; 95% CI, 0.86-1.40) or 24 (OR, 1.16; 95% CI, 0.81-1.67) months.

The study by Fan et al,[106] a large, multisite study conducted in the Veterans Administration system, was stopped early due to excess mortality in the intervention group. At study termination, 426 individuals had been randomized to the usual-care or intervention group. There was no difference in COPD-related exacerbations over the mean follow-up period of 250 days, but there were 28 deaths in the intervention group compared with 10 in the usual-care group. Deaths due to COPD accounted for the largest difference between the groups. Despite careful analysis, the authors were not able to explain the difference in mortality between the groups. Comparison with large studies with similar interventions[104,109] did not help to explain the higher mortality in the case management group. These unexpected results demonstrate that we do not yet fully understand the effects of this type of intervention.

10. For patients with COPD, we suggest education with a written action plan and case management for the prevention of severe acute exacerbations of COPD as assessed by a decrease in hospitalizations and ED visits (Grade 2B).

Underlying Values and Preferences: This recommendation places high value on reducing COPD-related hospitalizations, as these are associated with increased morbidity and mortality. Hospitalizations were believed to best reflect exacerbations because increased physician visits or increased medication use could be a result of the intervention to prevent an exacerbation. High value was also placed on changes in individuals with a history of exacerbations and on outcomes that specifically identified COPD-related hospitalizations. The recommendation reflects the fact that one study reported increased mortality in the intervention group. Although we do not know the reason for increased mortality in this one study, patients with underlying severe disease and clinical instability need close attention and careful follow-up. This point emphasizes that a specially trained staff is required to supervise this intervention and that patient selection must be individualized.

Telemonitoring: Information and communications technologies have rapidly developed the potential to contribute to the delivery of accessible, cost-effective, high-quality health-care services, although evaluation of these services is still at an early stage.[116] Although there is no single definitive definition of telemedicine, the American Telemedicine Association defines it as "the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status."[117] "Telemedicine" is a broad term that encompasses a wide range of services, including video conferencing; e-health, such as patient portals; transmission of still images; continuing medical education; consumer-focused wireless applications; and remote monitoring of vital signs.[117]

Given the range of telemedicine options, we have restricted our review to studies dealing with telemonitoring to provide care for patients at risk for acute exacerbations of COPD. We defined telemonitoring as comprising the following elements: (1) electronic transfer of self-report or biometric data (eg, oxygen saturation, pulse rate, BP) over a distance; (2) use of a device located in the patient's home or on his or her person (mobile device); and (3) personalized feedback from a health-care professional who exercises his or her skills and judgment in the provision of tailored advice to the patient or automated feedback based on a predetermined algorithm.

Our recommendation is based on three RCTs[118-120] from one systematic review[121] that met our definition and 18 additional RCTs.[122-139] Of these, only six studies[127,130-134] in 707 subjects were poolable, although we did take into account the findings of studies not included in the meta-analysis in making our recommendation. In the excluded studies, telemonitoring was demonstrated to be feasible and acceptable to patients[122,123,136,139] and providers.[136] Evidence on the association between telemonitoring and hospital admissions was mixed,[122,124,135,137,138] as was evidence on cost-effectiveness,[126,128] likely reflecting the variability in program implementation. We examined the outcomes of telemonitoring on the number of ED visits, exacerbations, and hospitalizations. No statistically significant results were found for any of these outcomes. For ED visits within 3 to 6 months,[120,130,131,133] the pooled OR was 0.45 (95% CI, 0.18-1.12), with nonsignificant heterogeneity between studies ($P = .14$, $I^2 = 46\%$). For ED visits within 12 months,[118,119] the pooled OR was 0.19 (95% CI, 0.03-1.27), with significant heterogeneity between studies ($P = .004$, $I^2 = 88\%$). For exacerbations within 4 to 9 months of implementing the telemonitoring intervention,[127,134] the OR was 0.58 (95% CI, 0.30-1.12), with nonsignificant heterogeneity between studies ($P = .67$, $I^2 = 0\%$). In terms of hospitalizations within a 3-month time frame,[130,131] the OR was 0.87 (95% CI, 0.18-4.20), with nonsignificant heterogeneity between studies ($P = .25$, $I^2 = 26\%$), whereas the OR was 0.63 (95% CI, 0.40-1.01) for hospitalizations within a 6- to 12-month time frame,[118,119,132,133] with nonsignificant heterogeneity between studies ($P = .32$, $I^2 = 15\%$).

Importantly, there was substantial variability in the telemonitoring interventions and equipment used, which included recording and electronic transmission of vital signs (spirometry, pulse oximetry, heart rate, and BP)[130,131]; a technology platform for delivery of education and transmission of pedometer results[131]; a hand-held monitor, self-reported symptoms, and manually entered temperature and oximetry[132]; sensor-containing wristbands for heart rate, physical activity, near body temperature, and galvanic skin response; a commercial oximeter and cell phone coupled with a wristband[134]; self-report data (EXACT-PRO [Exacerbations of Chronic Pulmonary Disease Tool Patient-Oriented Outcome] questionnaire) transmitted through cell phones; and automated alert calls based on winter weather conditions.[127] The variability among the telemonitoring applications precludes accurate comparison between studies.

A review by Wootton[140] noted that the majority of RCTs on telemedicine for chronic disease management reported positive effects, raising the possibility that a publication bias exists favoring only positive results. Wootton further suggested that understanding the true effects of any intervention to improve chronic illness care will require interventions lasting years rather than

weeks or months. Although telemonitoring holds promise for COPD management, there is no evidence at this time that telemonitoring significantly reduces acute exacerbations of COPD, and in many countries, it is too expensive.

11. For patients with COPD, we suggest that telemonitoring compared with usual care does not prevent acute exacerbations of COPD, as assessed by decreases in emergency room visits, exacerbations, or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: There is insufficient evidence at this time to support the contention that telemonitoring prevents COPD exacerbations.

PICO 2: Does Maintenance Inhaled Therapy Prevent/Decrease Acute Exacerbations of COPD?

An extensive amount of data is available regarding the effects of inhaled therapy on the treatment and prevention of acute exacerbations of COPD. To examine this area in a systematic fashion, we organized the analysis of the efficacy of inhaled therapy to prevent COPD exacerbations into separate analyses of short-acting β_2-agonists and short-acting muscarinic antagonists vs placebo and long-acting β_2-agonists and long-acting muscarinic antagonists vs placebo with each other and in combination. Similarly, we compared inhaled corticosteroids with placebo and the combination of long-acting β_2-agonists plus inhaled corticosteroids with placebo and vs long-acting muscarinic antagonists and the combination of all three inhaled agents with placebo to prevent COPD exacerbations (Table 1).

Long-Acting Bronchodilators Compared With Placebo or Monotherapy: Inhaled long-acting β_2-agonists are an important therapeutic option for patients with COPD. They lead to the activation of the β_2-receptors lining the airway smooth muscle, resulting in bronchodilation. The majority of long-acting β_2-agonists are 12-h medications, thus requiring a twice-daily dosing regimen. This distinguishes them from ultralong-acting β_2-agonists that are once-daily medications. A recent systematic review of long-acting β_2-agonist in COPD[141] evaluating salmeterol (50 μg bid) and two doses of formoterol (12 and 24 μg bid) demonstrated a benefit of long-acting β_2-agonist vs placebo in reducing exacerbation rates. Data from seven studies enrolling 2,859 patients were combined to assess the rate of severe exacerbations requiring hospitalizations. For severe exacerbations, the OR was 0.73 (95% CI, 0.56-0.95). The overall quality of evidence was moderate due to risk of publication bias. Several studies did not report exacerbations in a form that could be included in any of the outcomes. The authors found no difference in the long-acting β_2-agonist or dose used for the effect. For assessing the impact of long-acting β_2-agonists on moderate exacerbations (requiring a course of antibiotics, oral steroids, or both), seven studies enrolling 3,375 patients were reviewed. For moderate exacerbations, the OR was 0.73 (95% CI, 0.61-0.87). The quality of evidence was deemed moderate due to risk of publication bias. However, for the lower dose of formoterol (12 μg bid), no benefit was seen (OR, 0.78; 95% CI, 0.56-1.07).

The review highlights other benefits of treatment with a long-acting β_2-agonist. There were significant improvements in quality of life as measured by the SGRQ. The SGRQ score improved by −2.32 (95% CI, −3.09 to −1.54) in the patients treated with long-acting β_2-agonists. Furthermore, more patients reached the minimally clinically important difference of −4 units on the SGRQ in the long-acting β_2-agonist vs placebo group (OR, 1.58; 95% CI, 1.32-1.90). Again, there was no difference between the drug and dose used in the studies.

The safety of this class of medications was evident. When all studies were pooled and analyzed, the rate of adverse events was similar between the long-acting β_2-agonist and placebo arms (OR, 0.97; 95% CI, 0.83-1.14). The long-acting β_2-agonist arm did not affect mortality (OR, 0.90; 95% CI, 0.75-1.08). In summary, patients with moderate to severe COPD had reduced rates of exacerbations (both moderate and severe) with a long-acting β_2-agonist vs placebo. Benefits in other aspects of COPD management were demonstrated, with strong safety data.

12. In patients with moderate to severe COPD, we recommend the use of long-acting β_2-agonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting β_2-agonist therapy improving quality of life and lung function compared with placebo. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting β_2-agonist therapy and placebo in this patient group.

Long-Acting Muscarinic Antagonists Compared With Placebo: Tiotropium is an inhaled long-acting muscarinic antagonist used in the treatment of COPD.

Tiotropium inhibits the release of acetylcholine at the receptor level by binding to the M2- and M3-muscarinic receptors that line the airway. The resulting bronchodilation has improved outcomes, including quality of life, increased exercise capacity, and a reduction in exacerbations.[23,142,143] Furthermore, its safety has been reviewed in several analyses, all of which demonstrate an acceptable safety profile. Until recently, tiotropium had only been delivered as a dry powder through the HandiHaler (Boehringer Ingelheim GmbH). The large majority of studies assessing the efficacy of tiotropium involved the use of the dry powder inhaler in the treatment arm. Respimat (Boehringer Ingelheim GmbH) is a novel delivery system using a soft mist rather than a dry powder as the means of delivering tiotropium.

There has been some concern regarding the safety of tiotropium delivered through Respimat[144] because studies have demonstrated an increase in associated mortality. To address this question, a large RCT assessing the safety of tiotropium delivered through the Respimat system has recently been published,[145] and this will be further in this guideline.

A systematic review[146] assessing the effectiveness of tiotropium vs placebo included 22 studies enrolling 22,309 patients. Nineteen studies assessed tiotropium 18 μg daily delivered by the HandiHaler. Three studies assessed tiotropium delivered by the Respimat system. One study examined a dose of 5 μg, and the other two examined doses of 5 and 10 μg. There was a reduction in the rate of acute exacerbations in the tiotropium arm compared with the placebo arm (OR, 0.78; 95% CI, 0.70-0.87; number needed to treat, 16). This was deemed high-quality evidence with no risk of bias. Furthermore, 21 studies enrolling 22,852 patients examined the rate of exacerbations requiring hospitalizations. Tiotropium treatment was associated with fewer hospitalizations due to exacerbations (OR, 0.85; 95% CI, 0.72-1.00), but there was no statistically significant difference in all-cause hospitalizations (OR, 1.00; 95% CI, 0.88-1.13) or nonfatal serious adverse events (OR, 1.03; 95% CI, 0.97-1.10).[146] The quality of evidence was deemed moderate due to imprecision because the CIs around the effect estimates were very wide. Regarding mortality, tiotropium delivered through the HandiHaler was associated with fewer deaths than placebo, but this was not statistically significant (OR, 0.92; 95% CI, 0.8-1.05). However, tiotropium delivered by the Respimat system had more associated deaths than placebo (OR, 1.47; 95% CI, 1.04-2.08). The authors recognized that the event rates were low and that this may have been affected by withdrawal rates, which were higher than mortality rates.

Since the publication of this systematic review, a large RCT (TIOSPIR [Tiotropium Safety and Performance in Respimat]) examining Respimat vs HandiHaler has been published. The study randomized 17,183 patients to Respimat 2.5 μg, Respimat 5.0 μg, or HandiHaler 18 μg. The primary safety outcome was time to death from any cause. The primary efficacy outcome was time to first COPD exacerbation. The HR for time to death with Respimat 5 μg vs HandiHaler was 0.96 (95% CI, 0.84-1.09) and for the Respimat 2.5 μg vs HandiHaler, 1.00 (95% CI, 0.87-1.14). Both were not statistically significant. Although this is reassuring, safety issues remain a concern with the Respimat system in secondary analysis of TIOSPIR data, especially in patients with renal disease (who were excluded from this study).

13. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with placebo. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting muscarinic antagonists and placebo in this patient group.

Long-Acting Muscarinic Antagonists Compared With Long-Acting β_2-Agonists: Pharmacologic therapy for COPD is implemented in a stepwise fashion.[142,147] Patients should be started initially on short-acting bronchodilators, and if symptoms persist, introduction of long-acting bronchodilators is recommended. The two classes of long-acting agents used in the treatment of COPD are long-acting muscarinic antagonists and long-acting β_2-agonists. Both classes have independent mechanisms of action, producing a bronchodilator effect resulting in improved symptoms, quality of life, and exercise tolerance.[148-150] In addition, each

class has been shown to reduce the rate of acute exacerbations.[23,151] However, the question remains about whether a difference exists between these classes of medications in their ability to reduce the risk of an exacerbation.

A systematic review by Chong et al[152] specifically addressed this question. This systematic review compared tiotropium (the most commonly used long-acting muscarinic antagonist in COPD) vs long-acting β_2-agonists in the treatment of stable COPD. The long-acting β_2-agonists reviewed were salmeterol, formoterol, and indacaterol. The authors included six studies enrolling 12,123 patients. The length of the studies varied from 3 to 12 months. In all the studies, patients in the tiotropium arm received the 18-μg dose administered through the HandiHaler. Three studies compared tiotropium to salmeterol 50 μg bid, and one study used formoterol 10 μg bid. For indacaterol, one dose-finding study used open-label tiotropium 150 and 300 μg; where possible, the results of the two doses were pooled. The other study was a double-dummy RCT using 150 μg indacaterol. It is important to note that in all the studies, patients were allowed to use inhaled corticosteroids at a stable dose.

Most studies used similar definitions of acute exacerbation, which was an increase in symptoms for at least 3 consecutive days resulting in additional treatment. Tiotropium was associated with a lower rate of exacerbations compared with long-acting β_2-agonists. Tiotropium had an OR of 0.86 (95% CI, 0.79-0.93). The strength of this evidence was deemed moderate because of a serious risk of bias. In the four studies that reported COPD hospitalization as an outcome, the number of participants requiring hospitalization for a COPD exacerbation was significantly lower in those who received tiotropium compared with those who received a long-acting β_2-agonist (OR, 0.87; 95% CI, 0.77-0.99; analysis, 1.15[152]). In three studies that allowed comparison of all-cause hospitalization, there was no statistical difference in hospitalizations between tiotropium and long-acting β_2-agonists (OR, 0.93; 95% CI, 0.57-1.54).[140]

The authors recognized that the largest and longest study comparing tiotropium to salmeterol had a statistically significant difference in the rate of exacerbation.[153] All the other studies reviewed did not demonstrate that tiotropium was significantly better at preventing exacerbations than long-acting β_2-agonists, which one must keep in mind while interpreting the recommendation. Furthermore, a large majority of patients were using inhaled corticosteroids during the study. The impact that this may have on the exacerbation rate is difficult to determine.

14. In patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared with long-acting β_2-agonist to prevent moderate to severe acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting muscarinic antagonists having a lower rate of nonfatal serious adverse events compared with long-acting β_2-agonists. This comparative benefit may not apply with the new ultralong-acting β_2-agonists that are a once-daily medication. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. A lower value was placed on the lack of statistically significant differences in changes in lung function, quality of life, and patient symptoms between the two drug groups.

Short-Acting Muscarinic Antagonist Compared With Short-Acting β_2-Agonist Monotherapy: Based on the available data, comparing treatment with short-acting β_2-agonist monotherapy with ipratropium alone (short-acting muscarinic antagonist) for 1 to 3 months resulted in no significant improvement in postbronchodilator FEV_1 measurement, but there was a small benefit in prebronchodilator FEV_1 of borderline statistical significance. There was a small increase in prebronchodilator FVC and a postbronchodilator increase in the FVC area under the curve over 8 h, and this approached statistical significance. These data suggest that the beneficial effects of a short-acting muscarinic antagonist over short-acting β_2-agonist are small in terms of lung function.[154-160]

There was no study evaluating exacerbation as a primary end point. However, four studies enrolling 1,218 patients with a serious risk of bias and overall moderate quality of evidence examined the number of subjects who had to add or increase systemic oral corticosteroids, which could be interpreted as a surrogate marker for exacerbations.[157,161-163] Meta-analysis of the four studies indicated that significantly fewer subjects receiving short-acting muscarinic antagonist therapy added or increased use of oral steroids compared with

those receiving short-acting β_2-agonist therapy (OR, 0.52; 95% CI, 0.37-0.74). This would give a number needed to treat of 15 patients treated with short-acting muscarinic antagonist therapy compared with 28 patients treated with short-acting β_2-agonist therapy to prevent the need for oral steroids.

Therefore, this treatment comparison receives a grade 2C recommendation based on the body of reported evidence. The grade 2C categorization is weak, with low- or very-low-quality evidence and uncertainty in the estimates of the benefits, risks, and burdens, all of which are closely balanced. However, there is evidence of benefit for at least one critical outcome (addition or increase in the use of oral steroids) that may be considered a surrogate marker of a moderate exacerbation. Higher-quality research may have an important impact on the confidence of estimated effect in the future. Patient preference and cost should be taken into consideration. Future studies could incorporate measures of health-care use and be of longer duration to capture the effects on exacerbation rates.

15. In patients with moderate to severe COPD, we suggest the use of a short-acting muscarinic antagonist compared with short-acting β_2-agonist monotherapy to prevent acute mild-moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist reducing the risk of acute exacerbations of COPD together with the comparative benefit of a short-acting muscarinic antagonist improving quality of life and lung function compared with short-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that medication-related adverse events were fewer in the short-acting muscarinic antagonist than in the short-acting β_2-agonist group.

Short-Acting Muscarinic Antagonist Plus Short-Acting β_2-Agonist Compared With Short-Acting β_2-Agonist: Stepwise pharmacologic therapy, particularly when two different agents with different mechanisms of action are used, is the standard therapy for asthma and COPD care in all guidelines. Long-term combination therapy of a short-acting muscarinic antagonist and a short-acting β_2-agonist over 12 weeks with ipratropium plus a short-acting β_2-agonist is associated with some clinically meaningful postbronchodilator outcomes compared with β_2-agonist treatment alone, but these outcomes were not reflected in subjective improvements in quality of life or symptom scores.[154] The evidence for this combined therapy vs monotherapy using short-acting bronchodilators to reduce exacerbations is either weak or lacking.

There has been only one study with exacerbation as an end point, and that favored the combination (ipratropium plus short-acting β_2-agonist).[164] The study had serious bias and inconsistency. The evidence, therefore, was rated as overall low quality. Five additional studies enrolling 1,591 patients from 42 to 85 days recorded the addition of or increase in oral steroids as an end point.[157,160-167] These studies in aggregate had no serious inconsistencies in quality assessment and an overall moderate quality of evidence. We have given this recommendation a grade 2B, which is weak with moderate-quality evidence because of the long history of safety and clinical guideline data formulated throughout the years.

The patient's preference is an important factor that requires consideration in using these agents, and generally, these agents are first line because of their safety profile and ease of use. Future studies should be of longer duration to more robustly capture the effects of these agents on exacerbation rates and incorporate outcomes that measure health-care use.

16. In patients with moderate to severe COPD, we suggest the use of short-acting muscarinic antagonist plus short-acting β_2-agonist compared with short-acting β_2-agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist plus a short-acting β_2-agonist reducing the risk of acute exacerbations of COPD together with the comparative small benefits of a short-acting muscarinic antagonist plus a short-acting β_2-agonist improving quality of life, exercise tolerance, and lung function compared with a short-acting β_2-agonist alone. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of a short-acting muscarinic antagonist plus a short-acting β_2-agonist vs a short-acting β_2-agonist alone.

Short-Acting Muscarinic Antagonists Compared With Long-Acting β_2-Agonist Monotherapy: The primary classes of bronchodilators used in the treatment of COPD have both short-acting and long-acting formulations. Current guidelines suggest that patients with moderate to severe COPD use the short-acting formulations for rescue and the long-acting bronchodilators as maintenance therapy.[142,147] This recommendation is based on several advantages the long-acting formulations have over the short-acting agents, including

sustained bronchodilation, improved quality of life, and improved compliance.[168-170]

A systematic review comparing short-acting muscarinic antagonist (ipratropium) monotherapy vs long-acting β_2-agonist therapy assessed change in lung function, quality of life, symptom scores, and exacerbation rates.[154] This analysis included four studies comparing ipratropium 42 μg with salmeterol 50 μg and placebo. As well, one study comparing ipratropium 80 μg tid with formoterol 18 μg bid and placebo and another comparing ipratropium 40 μg qid with formoterol 12 or 24 μg and placebo were included for analysis.

For the ipratropium vs salmeterol studies, there was no significant difference in the patients experiencing one or more exacerbations (OR, 1.23; 95% CI, 0.84-1.80). The quality of evidence was low given inconsistency and imprecision. For the formoterol studies, there was no significant difference in exacerbation rates, but values were not provided. The studies used in the systematic review had varying inclusion criteria, used unconventional dosing for both ipratropium and the long-acting β_2-agonists, and did not provide clear definitions for exacerbations. Given the poor evidence addressing the question of ipratropium vs long-acting β_2-agonists for the prevention of acute exacerbations, the current recommendation is made based on the known benefits of long-acting β_2-agonists in patients with COPD.[141]

17. In patients with moderate to severe COPD, we suggest the use of long-acting β_2-agonist monotherapy compared with short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD in patients treated with long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy and the comparative value of long-acting β_2-agonist monotherapy improving lung function, quality of life, and dyspnea scores compared with short-acting muscarinic antagonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy.

Long-Acting Muscarinic Antagonist Compared With Short-Acting Muscarinic Antagonist: The airflow obstruction associated with moderate to severe COPD results in exercise limitation, poor quality of life, and a predisposition to exacerbations. Bronchodilators, both short-acting and long-acting, play an important role in helping patients with COPD to cope with the disease by improving many of the physiologic limitations that develop with activity in these patients.[148,150,171] Inhaled muscarinic antagonists (or anticholinergics) have long been recognized as an important pharmacologic class of bronchodilators that result in improved quality of life, symptom limitation, and reduced rate of exacerbations.[146,172]

Ipratropium is a short-acting muscarinic antagonist that nonspecifically binds to airway muscarinic receptors. Tiotropium is a long-acting muscarinic antagonist that selectively binds to M1- and M3-muscarinic receptors in the airway. Until recently, it has been the only inhaled muscarinic antagonist available for treating COPD.[142,147] Newer muscarinic antagonists are now available, including aclidinium bromide, glycopyrronium bromide, and umeclidinium bromide. The majority of studies involving these newer compounds compared efficacy to either placebo or tiotropium and not to ipratropium. Furthermore, there is no meta-analysis comparing these compounds with ipratropium. Thus, for the question of the benefit of a long-acting muscarinic antagonist vs short-acting muscarinic antagonist for the prevention of an exacerbation, the evidence for tiotropium vs ipratropium was assessed.

A recent systematic review compared tiotropium and ipratropium in the treatment of stable COPD.[173] The review included two studies enrolling 1,073 patients. One study randomized patients to tiotropium 18 μg delivered by HandiHaler, and the other used tiotropium 5 and 10 μg delivered by the Respimat system. Both studies used an ipratropium metered-dose inhaler as the comparator arm. In both studies, the rates of acute exacerbations and COPD hospitalizations were secondary outcomes. Tiotropium was superior to ipratropium in exacerbation prevention (OR, 0.71; 95% CI, 0.52-0.95). The quality of the evidence was high, and there was no risk of bias. Furthermore, use of tiotropium resulted in a lower rate of hospitalization due to exacerbation compared with ipratropium (OR, 0.56; 95% CI, 0.31-0.99). The quality of evidence for this outcome was also deemed to be high with no risk of bias. The superiority of tiotropium over ipratropium was also seen in trough FEV_1 values and quality of life. There were insufficient data available to recommend one delivery device for tiotropium over another; however, no harm was demonstrated in the study using the Respimat delivery system.

The authors supported the use of tiotropium over ipratropium in the treatment of stable COPD because physiologic and clinical benefits, including reduced rates of exacerbation, were seen in the patients randomized to tiotropium. Their conclusion supports current clinical thinking and guideline recommendations.[142,147] In addition to a clinical benefit, the once-daily dosing of tiotropium is associated with improved compliance compared with ipratropium.[170] The safety of the Respimat system used to deliver tiotropium remains controversial.[144] In this review, no conclusions could be made regarding the superiority of one delivery device over the other, and no safety concerns were noted. Concern regarding safety of tiotropium delivered through the Respimat system has been well documented. A recent multicenter international RCT demonstrated the safety of the Respimat delivery system for tiotropium vs HandiHaler.[145] However, controversy still remains because a secondary analysis of the RCT data suggests that specific patient populations may be at risk for adverse events or higher mortality.[174-176]

18. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with a short-acting muscarinic antagonist to prevent acute moderate to severe exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on a long-acting muscarinic antagonist reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with a short-acting muscarinic antagonist. This recommendation also acknowledges that there were fewer nonfatal serious adverse events in subjects treated with a long-acting muscarinic antagonist than in those treated with a short-acting muscarinic antagonist.

Short-Acting Muscarinic Antagonist Plus Long-Acting β_2-Agonist Compared With Long-Acting β_2-Agonist Monotherapy: The natural progression of COPD results in increased symptoms, a decline in quality of life, and an increased risk of exacerbations. As the disease progresses and the patient's needs change, current guidelines recommend add-on pharmacotherapy to address the symptoms. One option is the addition of regular ipratropium, a short-acting muscarinic antagonist, to a long-acting β_2-agonist. Using bronchodilators that target different receptors may improve clinical symptoms and, therefore, may prevent exacerbations. Although this combination may be viewed as unique, some studies assessed its effectiveness in patients with COPD. A meta-analysis reviewed the available data comparing ipratropium plus long-acting β_2-agonist vs long-acting β_2-agonist alone in the treatment of stable COPD.[154] This analysis highlighted that few studies (two unpublished and one published) exist on this therapeutic strategy for COPD. The one published study examined the impact that the ipratropium and long-acting β_2-agonist combination has on the prevention of exacerbations. The 12-week study enrolled 94 patients who were randomized to ipratropium plus salmeterol vs salmeterol alone. Patients were allowed to use a short-acting β_2-agonist for rescue. The combination therapy demonstrated a lower rate of exacerbations but was not statistically significant (OR, 0.49; 95% CI, 0.17-1.40). However, there was a low rate of exacerbation in both groups and improvements in lung function and quality of life with the combination vs lone long-acting β_2-agonist therapy. The long-acting β_2-agonist used in this study was salmeterol, and currently, no other published studies used other long-acting β_2-agonists in combination with ipratropium. The authors concluded that more studies are needed to examine this combination because of some suggestion of benefit.

We recognize that with the development of new long-acting β_2-agonists and long-acting muscarinic antagonists to treat COPD, including the combination of long-acting β_2-agonist and long-acting muscarinic antagonist in a single inhaler, the utility of ipratropium plus long-acting β_2-agonist is limited, which may explain the limited number of studies examining this combination. However, availability of these novel therapies, especially in resource-limited settings, can affect one's approach to therapy. Therefore, having multiple therapeutic options that may provide similar outcomes for a global population would be ideal. For the combination of ipratropium plus long-acting β_2-agonist vs long-acting β_2-agonist alone for the prevention of acute exacerbations of COPD, a grade 2C recommendation favoring the combination is given. This is based on the demonstrated safety of this combination, the improvements in functional and quality-of-life measures, and an indication of benefit in reducing the frequency of exacerbations.

19. In patients with moderate to severe COPD, we suggest the combination use of a short-acting muscarinic antagonist plus long-acting β_2-agonist compared with long-acting β_2-agonist monotherapy to

prevent acute mild to moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on the combination of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD compared with the use of long-acting β_2-agonist therapy alone and the comparative value of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy improving lung function, quality of life, and dyspnea scores compared with long-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the combined use of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy vs long-acting β_2-agonist therapy alone.

Inhaled Corticosteroids Compared With Placebo or Other Monotherapy: Airway inflammation plays an important role in the pathophysiology of COPD,[177] which has suggested a potential role for inhaled corticosteroids in the treatment of this disease and has led to their excessive use in clinical practice.[178,179] However, although inhaled corticosteroids have significant effects in suppressing airway inflammation in asthma, their antiinflammatory effects in COPD are debatable.[180-182] The reported relative resistance to the antiinflammatory effects of corticosteroids observed in COPD may be attributed to oxidative stress from smoke exposure or from neutrophilic inflammation. In vitro and in vivo evidence suggest that histone deacetylase 2 enzyme activity and expression are suppressed in patients with COPD, thus blunting the antiinflammatory effects of corticosteroids.[180-185] Nevertheless, a meta-analysis of eight RCTs that used bronchial biopsy specimens and BAL fluid to evaluate the effects of inhaled corticosteroids in stable COPD showed that inhaled corticosteroids reduce lymphocytic inflammation in COPD.[186] These findings suggest that antiinflammatory effects of inhaled corticosteroids may be more pronounced in patients with predominant lymphocytic airway inflammation.

Several short- and long-term studies (up to 3 years) evaluated the efficacy and safety of inhaled corticosteroids when used in combination with inhaled long-acting β_2-agonists.[22,151,187-199] In addition, several systematic reviews and meta-analyses have been published on the topic.[200-204] These studies evaluated several important outcomes, including lung function, mortality, exacerbations, health-related quality of life, and symptoms. Despite the plethora of studies, the precise role of role of inhaled corticosteroids in improving lung function and other patient outcomes in COPD is still controversial. Furthermore, predictors of response to inhaled corticosteroids in COPD have not been fully evaluated, and existing evidence is based on few studies in the general COPD population. Because the use of inhaled corticosteroids may be associated with potential local and systemic adverse effects, careful evaluation of the benefit and risk ratio is essential.

Long-Term Effects of Inhaled Corticosteroids Compared With Placebo: A systematic review evaluated the role of inhaled corticosteroids vs placebo in COPD by examining data from 55 primary studies enrolling 16,154 participants.[204] Long-term use of inhaled corticosteroids reduced the mean rate of exacerbations in those studies where pooling of data was possible (generic inverse variance analysis using the total exacerbations per patient per year and SE from each study: relative effect, −0.26 exacerbations/patient/year [95% CI, −0.37 to −0.14; 2,586 participants]; moderate overall quality of evidence due to risk of bias by pooled means analysis: relative effect, −0.19 exacerbations/patient/year [95% CI, −0.30 to −0.08; 2,253 participants]; overall quality of evidence low due to risk of bias and inconsistency). Response to inhaled corticosteroids was not predicted by oral steroid response, bronchodilator reversibility, or bronchial hyperresponsiveness in patients with COPD. Studies of < 1,000 μg beclomethasone dipropionate equivalents per day did not show a statistically significant difference compared with placebo.

There was an increased risk of oropharyngeal candidiasis (OR, 2.65; 95% CI, 2.03-3.46; 5,586 participants) and hoarseness. In the long-term studies, the rate of pneumonia was increased in the inhaled corticosteroid group compared with the placebo group in studies that reported pneumonia as an adverse event (OR, 1.56; 95% CI, 1.30-1.86; 6,235 participants). The long-term studies that measured bone effects generally showed no major effect on fractures and bone mineral density over 3 years.

Inhaled Corticosteroids Compared With Long-Acting β_2-Agonists: Both long-acting β_2-agonists and inhaled corticosteroids are used in the treatment of COPD. Although these treatments can sometimes be taken together, the value of the two individual components is unclear. To evaluate the efficacy and safety of inhaled corticosteroids vs long-acting β_2-agonists in COPD, a review examined data from seven randomized trials (5,997 participants) of good quality with a duration of 6 months to 3 years.[202] All the trials compared inhaled

corticosteroid/long-acting β_2-agonist combination inhalers with long-acting β_2-agonist and inhaled corticosteroid as individual components.

Four studies (4,750 participants) reported exacerbation RRs between inhaled corticosteroid or long-acting β_2-agonist and placebo or an inhaled corticosteroid/long-acting β_2-agonist combination.[22,151,190,199] The RR between inhaled corticosteroid and long-acting β_2-agonist was not statistically significant (0.96; 95% CI, 0.89-1.02), which suggests moderate overall quality of evidence due to risk of bias. There was no statistically significant difference in exacerbation RR between studies of 1 year and > 1 year of treatment ($\chi^2 = 0.11$, degrees of freedom = 1, $P = .75$). Two studies comparing fluticasone with salmeterol reported the number of patients experiencing exacerbations requiring treatment with antibiotics, corticosteroids, or both or hospitalization during the treatment period (688 participants).[193,196] In these studies, although more patients on inhaled corticosteroids (136 of 351) experienced exacerbations than those on long-acting β_2-agonists (115 of 337), there was no statistically significant difference between the groups (OR, 1.22; 95% CI, 0.89-1.67).

Exacerbations leading to hospitalizations were only reported in a single trial with 3,093 participants.[151] A comparison of RRs showed no significant difference in the risk of hospitalization due to exacerbation between fluticasone and salmeterol (RR, 1.07; 95% CI, 0.91-1.26). The incidence of pneumonia was significantly higher among patients on inhaled corticosteroids than on long-acting β_2-agonists whether classified as an adverse event (OR, 1.38; 95% CI, 1.10-1.73) or serious adverse event (OR, 1.48; 95% CI, 1.13-1.93).

Budesonide Compared With Formoterol or Fluticasone Compared With Salmeterol: Four of the trials included in the aforementioned review evaluated fluticasone and salmeterol monotherapy components, and the remaining three included budesonide and formoterol monotherapy components.[202] There was no evidence of a class effect between the fluticasone/salmeterol and budesonide/formoterol trials in a subgroup analysis ($\chi^2 = 1.57$, degrees of freedom = 1, $P = .21$).

In summary, there was no statistically significant differences in the number of patients experiencing exacerbations (OR, 1.22; 95% CI, 0.89-1.67) or the rate of exacerbations per patient year (RR, 0.96; 95% CI, 0.89-1.02) between inhaled corticosteroids and long-acting β_2-agonists. Both inhaled corticosteroids and long-acting β_2-agonists contribute to a decrease in exacerbation rates, but there is insufficient evidence to recommend maintenance inhaled corticosteroid therapy over maintenance long-acting β_2-agonist therapy in preventing acute exacerbations of COPD. Although inhaled corticosteroid therapy may benefit some patients with COPD, it also increases the risk of systemic adverse effects, including pneumonia.

Combination Inhaled Therapies: Long-Acting Muscarinic Antagonists, Inhaled Corticosteroids, and Long-Acting β_2-Agonists: *Long-Acting Bronchodilator and Corticosteroid Therapy:* The past decades have seen a significant increase in the number of pharmacologic agents available to treat patients with COPD. However, they are basically longer-acting variations of the primary agents long-acting muscarinic antagonists[18,23,205-208]; long-acting β_2-agonists[209-211] and ultralong-acting β_2-agonists[212-214] that have a 12- or 24-h administration regimen, respectively; and 12- and 24-h inhaled corticosteroids.[215-218] Each agent, singularly or in combination, has been shown to improve lung function (degree of obstruction and decrease static and dynamic hyperinflation), relieve symptoms, and improve health-related quality of life and exercise endurance.

Double or Triple Therapy: Existing national and international COPD guidelines have recommended that if COPD symptoms are not well controlled with single agents, the combination of two or more agents in a stepwise manner is reasonable.[17,142,147] The effect of combination therapy has proven beneficial for lung function and health-related quality of life, but the effectiveness on exacerbations remains less clear.[219,220] In its most recent iteration,[142] the GOLD (Global Initiative for Chronic Obstructive Lung Disease) grades disease severity using the number of exacerbations as a risk categorization and recommends combination therapy for patients with two or more exacerbations (categories C and D). Exacerbations were also highlighted and specifically targeted for combination therapy in prior CTS practice guidelines.[147] The combination includes primarily an inhaled corticosteroid and a long-acting β_2-agonist, although potential use of a long-acting muscarinic antagonist plus a long-acting β_2-agonist is also recommended based primarily on consensus. In patients with more severe COPD (GOLD category D), triple therapy is considered appropriate.

Evidence for Combination Inhaled Corticosteroid/Long-Acting β_2-Agonist Compared With Single Bronchodilator: Relatively few long-term studies have compared combination inhaled corticosteroid and

long-acting β_2-agonist with single drugs, with exacerbations as the main outcome. A Cochrane meta-analysis[220] found 14 studies that met these inclusion criteria, randomizing 11,794 patients with severe COPD. The review evaluated 10 studies assessing fluticasone plus salmeterol and four studies assessing budesonide plus formoterol separately. The studies were well designed with a low risk of bias for randomization and blinding, but they had high rates of attrition, which reduced confidence in the results for outcomes. The reviewers concluded that the combination inhaled corticosteroid/long-acting β_2-agonist therapy reduced the number of exacerbations but did not affect the rate of hospitalizations compared with long-acting β_2-agonist therapy alone. The combination did result in better lung function, health-related quality of life, dyspnea, and reduced use of rescue medication, but the differences did not reach clinical significance. There was a 4% increased risk of pneumonia in the combination therapy group compared with the long-acting β_2-agonist alone group. There are no head-to-head comparisons of the newer combinations (once-a-day formulations) that provide firm recommendations regarding their use and indications. However, the studies of the once-a-day single delivery combination of inhaled corticosteroid and long-acting β_2-agonist again show better lung function and less dyspnea and rescue medication use with a small effect on exacerbations and no effect on hospitalizations over bronchodilators alone.[191,221]

There are few data comparing triple therapy with double or single therapy. A systematic review compared the efficacy of three therapeutic approaches: tiotropium plus long-acting β_2-agonist (dual therapy), long-acting β_2-agonist plus inhaled corticosteroid (combined therapy), and tiotropium plus inhaled corticosteroid plus long-acting β_2-agonist (triple therapy), each compared with tiotropium single therapy.[214] Twenty trials enrolling 6,803 patients were included in the review. The authors concluded that dual therapy improved lung function and health-related quality of life but failed to decrease exacerbation frequency compared with tiotropium monotherapy. Combined therapy also improved lung function, health-related quality of life, and dyspnea without a significant impact on risk of exacerbations. Again, the authors observed an increased risk of adverse events in patients receiving this therapy. Triple therapy increased lung function and improved health-related quality of life (reaching minimally important clinical thresholds in both outcomes) and marginally improved risk for exacerbations. However, the authors still concluded that the data were insufficient to make strong recommendations.

In some of these studies, the responses or benefits in end points, such as lung function, health-related quality of life, and dyspnea, do not always parallel the observed responses in reducing acute exacerbations. Although the reasons for these occasional dissimilar responses are not clearly obvious, it appears reasonable to independently assess the specific impact of these interventions on reducing exacerbations.

20. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance, combination inhaled corticosteroid/long-acting β_2-agonist therapy (and not inhaled corticosteroid monotherapy) compared with placebo to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with slowing the rate of decline in health-related quality of life and a relatively lower value on the risks and consequences of oral candidiasis, hoarseness and dysphonia, bruising, and pneumonia.

21. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with long-acting β_2-agonist monotherapy to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with improved health-related quality of life, reduced dyspnea, less rescue medication use, and improved lung function and a relatively lower value on the risks and consequences of oral candidiasis, upper respiratory tract infections, and pneumonia.

22. For patients with stable moderate to very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with inhaled corticosteroid monotherapy to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with the comparative mortality benefit of combination inhaled corticosteroid/long-acting β_2-agonist therapy, acknowledging that there were no significant differences in serious adverse events or incidence of pneumonia between the groups.

This recommendation does not support the use of inhaled corticosteroid monotherapy in COPD.

23. For patients with stable COPD, we recommend inhaled long-acting anticholinergic/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

24. For patients with stable COPD, we recommend maintenance combination of inhaled corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD and a relatively lower value on the risks and consequences of pneumonia.

25. For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

PICO 3: In Patients Aged > 40 Years Who Are Previous or Current Smokers With COPD, Does Oral Therapy Prevent/Decrease Acute Exacerbations of COPD?

In the administration of treatment medication for COPD, the inhalation route has been favored for the past 30 years. This technique enables the drugs to act directly on the airways, provided that the inhalation device is used correctly. Although inhaled medications are not without adverse effects, they often are seen as having a better tolerability and safety profile than oral medications. Some medications can only be administered orally. Selecting drugs that are orally administered depends on the type of drug and the patient. Furthermore, poor access to inhaled medications can be a problem in some countries. We chose to organize the review of oral therapy by the following categories: antibiotics, oral corticosteroids, phosphodiesterase inhibitors (roflumilast, theophylline), mucolytic agents (N-acetylcysteine [NAC], erdosteine, and carbocysteine), and statins (Table 1).

Some of the oral medications (eg, antibiotics, corticosteroids) are primarily prescribed to treat acute exacerbations of COPD. In this review, we did not assess the interventions used to treat acute exacerbations; we evaluated the evidence around the use of the interventions to prevent or decrease acute exacerbations.

Antibiotics: Macrolide antibiotics have a number of antimicrobial, antiinflammatory, and immunomodulating effects and have been used for many years in the management of other chronic airway diseases, including diffuse panbronchiolitis and cystic fibrosis. Given this successful use and the significant role airway inflammation and bacterial infection play in the pathogenesis of COPD exacerbations, there has been increasing interest in the use of macrolides to prevent these events.

Five RCTs comparing the administration of a macrolide vs placebo or another agent were identified for final inclusion of which three were ultimately included in the analysis on the basis of matched outcomes.[21,222,223] Seemungal et al[223] conducted a double-blind, randomized, placebo-controlled study of erythromycin 250 mg bid in 109 patients with moderate to severe COPD and found that the frequency of acute exacerbations of COPD was significantly reduced in the erythromycin group (RR, 0.648; 95% CI, 0.489-0.859; $P = .003$). A similar randomized, placebo-controlled study by He et al[222] using erythromycin 125 mg tid found a comparable protective effect on exacerbation risk (RR, 0.554; 95% CI, 0.314-0.979; $P = .042$). Albert et al[21] conducted the largest RCT of macrolides to date (n = 1,142) and compared azithromycin 250 mg daily with placebo for 1 year in patients with moderate to severe COPD who had either suffered a similar event in the year prior to enrollment or who were on long-term oxygen therapy. The number of patients who were enrolled based solely on meeting the oxygen requirement was only 12%. The exacerbation rate was significantly reduced from 1.83 to 1.48 acute exacerbations of COPD per patient-year (RR, 0.83; 95% CI, 0.72-0.95; $P = .01$), and this remained significant after adjustment for sex, FEV_1, age, and smoking status. Given the similar patient populations and comparable effect sizes, the pooled effects (RR, 0.73; 95% CI, 0.58-0.91) provide high-quality evidence to support the use of macrolides for the prevention of acute exacerbations. In the study by Albert et al,[21] fewer patients in the azithromycin group developed nasopharyngeal colonization during the study with common respiratory pathogens, but those who did were more likely to become

colonized with organisms that were resistant to azithromycin. The significance of these findings is uncertain because colonization was not associated with an increase in COPD exacerbations or pneumonia. There was also a modest increase in the risk of hearing loss in those assigned to azithromycin, although this often was reversible. Although there was no increase in the risk of adverse cardiovascular events in patients taking azithromycin in the study by Albert et al,[21] other large population-based studies suggested that the drug may increase the risk of cardiac death, and thus, patients should be carefully evaluated for predisposing conditions or medications before initiating therapy. The cardiac safety of azithromycin in the study by Albert et al[21] may be partly due to excluding patients with QT prolongation or who were taking other drugs that could prolong the QT interval. The data from the available clinical trials demonstrate that regular macrolide therapy definitively reduces the risk of acute exacerbations. Although these results are robust and would support a level 1 recommendation, safety data from the largest of these studies (Albert et al[21]) raise concerns about the development of antibiotic resistance as well as hearing loss. In addition, data from large observational studies in other populations suggest the potential for cardiovascular side effects, including prolongation of the QT interval, although these were not observed in the randomized trials reviewed for these guidelines. Based on these potential safety concerns, macrolide therapy is suggested (grade 2A) as a therapeutic option in patients with a history of exacerbations, and clinicians should be aware of the potential for adverse effects. The duration and exact dosage of macrolide therapy is unknown, but given the efficacy of the macrolides, strategies to mitigate these potential adverse effects are recommended.

26. For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long-term macrolide to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: This recommendation places high value on the prevention of COPD exacerbations. However, clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance. The duration and exact dosage of macrolide therapy are unknown.

Corticosteroids: Systemic oral corticosteroids for the long-term treatment of COPD are not recommended (GOLD guidelines), but their use is recommended for treating acute exacerbations of COPD (GOLD guidelines).[1] Systemic corticosteroids have been shown to improve symptoms and lung function, reduce treatment failure, and shorten length of hospital stay.[224-227] The effect of preventing a subsequent exacerbation is more controversial and was the focus of our review.

Four studies addressed hospitalization within 30 days following an exacerbation,[224,226,228,229] whereas two studies addressed hospitalization for acute exacerbations of COPD at 6 months.[226,230] Aggarwal et al[228] compared 2 weeks of either hydrocortisone or methylprednisolone along with standard therapy in patients treated for acute exacerbations of COPD in the ED. They found no difference in the readmission rate between the two groups during the 2-week follow-up period (OR, 0.18; 95% CI, 0.01-3.85). Niewoehner et al[226] randomized patients hospitalized for acute exacerbations of COPD to 8 weeks of corticosteroids, 2 weeks of corticosteroids with 6 weeks of placebo, or 8 weeks of placebo. Compared with placebo, there was a reduction in treatment failure for the combined corticosteroid group at 30 days (23% vs 33%, $P = .04$), but there was no difference in the 30-day readmission rates between the corticosteroid and placebo groups (4% vs 5%), leading to a nonsignificant OR of 0.54 (95% CI, 0.10-2.88). Ställberg et al[229] treated outpatients with COPD for an acute exacerbation with either high-dose inhaled budesonide/formoterol or 30 mg prednisolone daily and inhaled formoterol bid for 2 weeks. Three patients (5.6%) in the prednisolone group and one (1.8%) in the inhaled therapy group required hospitalization during the 12-week follow-up period, providing a nonsignificant OR for hospitalization of 1.02 (95% CI, 0.06-16.71). Aaron et al[224] treated patients presenting to the ED with an AECOPD not requiring admission with either prednisone 40 mg daily or placebo once daily for 10 days. Prednisone reduced the 30-day risk of the combined end point of unscheduled physician visit or return to the ED compared with placebo (27% vs 43%, $P = .05$), and there was a trend toward lower hospitalization in the prednisone group (11% vs 21%, $P = .11$). The calculated OR for hospitalization favored the prednisone group in this study (0.40; 95% CI, 0.16-0.99). The pooled data from these studies suggest that systemic corticosteroids used to treat an AECOPD can reduce 30-day readmission rates due to recurrent AECOPD (OR, 0.43; 95% CI, 0.20-0.91).

Rice et al[230] randomly assigned patients with COPD on long-term corticosteroid therapy to either their usual dose of corticosteroids for 6 months or gradual tapering

of corticosteroid therapy at a rate of 5 mg/wk. The primary outcome of the study was the average number of AECOPD during the 6-month treatment period. There was no difference in the number of exacerbations between the two groups. Additionally, there were three admissions (15%) in the usual dose group and none in the tapering group (OR, 7.40; 95% CI, 0.36-153.8). The previously discussed Niewoehner et al[226] trial also failed to show a reduction in 6-month hospitalizations between placebo group and group treated with 8 weeks of systemic corticosteroids (OR, 1.07; 95% CI, 0.49-2.36). Pooling the data from these studies shows no support for treating an AECOPD with systemic corticosteroids to reduce future exacerbations during the following 6 months (OR, 1.6; 95% CI, 0.34-7.51). This would not preclude the short-term use of systemic corticosteroids for treating an AECOPD in either the outpatient or the inpatient setting.

27. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we suggest that systemic corticosteroids be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30 days following the initial exacerbation (Grade 2B).

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term corticosteroids to reduce acute exacerbations of COPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

28. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we recommend that systemic corticosteroids not be given orally or intravenously for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first 30 days following the initial acute exacerbation of COPD (Grade 1A).

Remark: This does not preclude the use of systemic corticosteroids for the treatment of acute exacerbations of COPD.

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term corticosteroids to reduce AECOPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

Phosphodiesterase 4 Inhibitor: The phosphodiesterase 4 inhibitor roflumilast has been evaluated for its ability to prevent future exacerbations in patients with moderate to severe COPD with a history of chronic cough and sputum production and exacerbations. Two of the included studies[231,232] were large, placebo-controlled, multicenter trials. The results from the centers participating in the Calverley et al[231] trial were pooled because the protocols were identical for the participating centers. Fabbri et al[232] conducted four studies comparing roflumilast with placebo; one compared roflumilast and either salmeterol or tiotropium with bronchodilator alone and, therefore, was analyzed as two separate studies. One study[221] was actually a post hoc analysis of the two studies reported in Calverley et al[231] and looked at the value of roflumilast in reducing the frequency of COPD exacerbations in the frequent exacerbator phenotype (two or more exacerbations in the previous year) compared with the infrequent exacerbator phenotype. One study[233] had FEV_1 as a primary outcome and COPD exacerbations as a secondary outcome. Because the study was only 12 weeks long and the number of exacerbations was low in both the placebo and the roflumilast groups, this study was excluded from the pooled data.

We were able to match three studies, one from Calverley et al[231] and two from Fabbri et al[232] reporting the median time to first COPD exacerbation. The mean HR was 0.87 (95% CI, 0.80-0.95) for roflumilast. Two studies[151,221] reported the number of subjects experiencing two or more exacerbations per year. The HR for roflumilast was 0.95 (95% CI, 0.83-1.08). Two studies from Calverley et al and two from Fabbri et al were matched to report the mean rate of exacerbations per year, although the two Fabbri et al studies included mild exacerbations in addition to the moderate and severe exacerbations counted in the Calverley et al studies.[151,231] The HR for roflumilast was 0.85 (95% CI, 0.79-0.92).

Each included trial for the pooled exacerbation data was large and well designed. However, they only included a subset of patients with COPD with grade III or IV obstruction ($FEV_1 < 50\%$ predicted), a history of chronic bronchitis, and at least one reported exacerbation requiring treatment or hospitalization in the previous year. There were a number of medication exclusions for the trials. Most excluded the use of theophylline and inhaled corticosteroids.[221,231,232] More than 40% of patients in the roflumilast and placebo groups had been treated with long-term inhaled corticosteroids prior to the studies, and previous studies suggested that inhaled corticosteroid withdrawal may be associated with an increased subsequent risk of exacerbations. Long-term use of inhaled corticosteroids up to 2,000 μg beclomethasone equivalents was allowed in the study by Calverley et al.[151] This may explain the somewhat lower mean exacerbation rate in both the placebo and the roflumilast groups in this study compared with the other studies that excluded inhaled corticosteroids. However, the benefit of roflumilast in reducing exacerbations was similar between subjects previously on inhaled corticosteroids and those who were not in the latter studies.

The use of long-acting muscarinic agents was excluded in each study aside from Fabbri et al,[232] which specifically looked at the benefit of roflumilast vs placebo added to tiotropium. The use of long-acting β-agonists was excluded from the study by Calverley et al.[151] Each study had a number of secondary end points, including prebronchodilator and postbronchodilator FEV_1, both values of which increased by a statistically significant amount. The improvements in prebronchodilator FEV_1 between the roflumilast and placebo groups ranged from 39[151] to 80 mL when added to tiotropium.[232] The postbronchodilator improvement ranged from 36[151] to 81 mL when added to tiotropium.[232] In a smaller study by Lee et al[233] looking at the benefit of roflumilast vs placebo in Asian patients with COPD with slightly less severe airflow obstruction compared with those enrolled in the exacerbation studies, improvements in prebronchodilator FEV_1 averaged 95 mL and postbronchodilator FEV_1 79 mL (both $P < .0001$).

Side effects of nausea, diarrhea, headache, and weight loss averaging about 2.1 kg were more common in the roflumilast-treated patients and led to increased patient withdrawals from the study, particularly in the first 3 to 4 weeks. The side effects may limit the use of this medication in the clinical setting.

29. For patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year, we suggest the use of roflumilast to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: Clinicians prescribing roflumilast need to advise their patients of the potential side effects of weight loss and diarrhea. Patients may have to discontinue the therapy because of side effects. The decision to prescribe this medication should also be informed by the fact that there are limited data for supplemental effectiveness in patients concurrently using inhaled therapies.

Theophylline: Theophylline has been used to treat airway diseases for decades. Its bronchodilator effects are mediated through inhibition of phosphodiesterase 3,[234] although this requires fairly high serum levels, which are associated with frequent side effects of nausea, vomiting, and gastroesophageal reflux as well as headache. At lower doses, theophylline also likely has antiinflammatory effects, although these may be mediated through phosphodiesterase 4 inhibition and activation of histone deacetylase 2, which downregulates a number of inflammatory genes. The drug is metabolized by the hepatic cytochrome p450 system and, thus, has a number of important drug interactions. As a bronchodilator in patients with COPD, theophylline improves lung function when added to long-acting β-agonists, and there is some evidence that it may reverse corticosteroid resistance in this group.

Of the 18 studies of oral theophylline compared with placebo, an active comparator, or both, two met criteria for further review.[235,236] Rossi et al[235] randomized 854 patients with COPD ($FEV_1 < 70\%$ predicted) to one of two doses of formoterol (12 or 24 μg bid), oral slow-release theophylline twice daily and titrated to 8 to 20 mg/L 3 to 4 h after dosing, or placebo for 1 year. The primary end point was FEV_1, but the number of patients experiencing moderate to severe exacerbations was also assessed and shown to be reduced in both the formoterol dosage arms compared with placebo. There was no difference in the number of patients with exacerbations in the theophylline vs placebo arms. GI side effects were threefold higher in those receiving theophylline than either formoterol arm, and this led to a 27% withdrawal rate in the first 3 months of the study. Zhou et al[236] performed a 1-year randomized, double-blind, parallel group and placebo-controlled trial of slow-release theophylline 100 mg bid in 110 patients with COPD ($FEV_1 > 30\%$ predicted but poor response to short-term bronchodilators). The odds of exacerbation in the theophylline group were reduced (0.73) vs placebo,

although the risk of GI side effects was also higher in those receiving theophylline. The pooled analysis of these two studies revealed an effect estimate of 0.83 (95% CI, 0.47-1.47), suggesting moderate-quality evidence supporting theophylline in the prevention of acute exacerbations. From a clinical standpoint, there are no studies examining the role of theophylline as add-on therapy in patients with ongoing exacerbations despite inhaled therapies, although this is a common manner in which the drug is used. The unfavorable side effect profile of theophylline compared with inhaled agents that more clearly reduce exacerbations also makes treatment with the drug less useful.

30. For stable patients with COPD, we suggest treatment with oral slow-release theophylline twice daily to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that theophylline may reduce the number of exacerbations. Patient decisions may also be informed by the relatively narrow therapeutic window with respect to adverse effects of treatment with theophylline. Physicians should use the lowest effective dose in prescribing theophylline in order to avoid adverse effects. Theophylline use requires vigilance on the part of the physician in order to avoid serious drug interactions, which lead to changes in serum theophylline levels. Patients should be advised that changes in tobacco use habits will affect serum theophylline levels and that they should inform their physicians if they stop smoking while taking theophylline.

N-acetylcysteine: Patients with COPD and chronic bronchitis may experience exacerbations of their condition because of thick secretions that are difficult to eliminate from the tracheobronchial tree. NAC has been proposed as an agent that may act as a mucolytic in the respiratory tract and aid in the elimination of secretions. NAC reduces the viscosity of respiratory secretions as a result of the cleavage of disulfide bonds.[237] In patients with COPD and chronic bronchitis, oral NAC has been proposed as a mucolytic agent because it is rapidly absorbed from the GI tract, has been reported to be rapidly present after ingestion in an active form in lung tissue and respiratory secretions, and is well tolerated except for in rare patients with adverse GI effects.[238] Investigators first suggested that NAC might be effective in reducing exacerbations of COPD more than 3 decades ago.[238,239]

We identified 11 RCTs comparing the administration of NAC with placebo or another agent, of which three were ultimately included in the meta-analysis based on matched outcomes.[240-242] The other studies[243-248] were either not conducted at the patient level but, instead, at the exacerbation count level or had exacerbations as a secondary outcome measure.

Hansen et al[240] randomized 129 patients to a prospective, placebo-controlled, double-blind study with oral NAC administered twice daily as the study intervention. The authors found an improvement in subjective complaints using the General Health Score, an established psychiatric instrument measuring symptomatic well-being. This finding was mitigated by scores being different between the two groups at baseline. The number of exacerbations in the NAC group was not significantly different from that in the placebo group.

Pela et al[241] studied 169 patients randomized to receive oral NAC 600 mg once daily vs placebo. The primary outcome measurement was the rate of COPD exacerbations, which was reduced by 41% in the intervention group compared with the control group. The study drug reduced the number of patients having multiple exacerbations, and pulmonary function measurements were slightly, but significantly improved. NAC was well tolerated, with no difference in adverse events between groups.

In the largest study to date by Zheng et al[242] randomized 1,006 patients to receive oral NAC 600 mg bid vs placebo. This study was a large, multicenter, prospective, placebo-controlled, parallel group trial performed in China. Patients were selected if they had moderate to severe COPD based on spirometric measurements, were aged 40 to 80 years, and had at least two COPD exacerbations within the 2 years prior to enrollment. Patients were also stratified according to their use of inhaled corticosteroids. The exacerbation rate was 1.16 in the NAC group vs 1.49 in the placebo group (RR, 0.78 for the NAC group). Time to first exacerbation was not different between the study and placebo groups, but time to second and third exacerbations was shorter in the placebo arm. NAC appeared to be more effective in patients with GOLD II COPD compared with those with GOLD III, with time to first exacerbation being longer in the GOLD II group than in the GOLD III group. The incidence of adverse effects attributed to the study drug did not differ between the NAC and placebo groups.

When examined together, the combined data from these studies[240-242] demonstrate a reduction in the rate of exacerbations in COPD associated with the use of NAC

compared with placebo (OR, 0.61; 95% CI, 0.37-0.99). Although conclusions are limited by the sample size of the studies assessed, oral NAC is well tolerated and appears to represent a low risk to patients.

31. For patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, we suggest treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that N-acetylcysteine may reduce the number of exacerbations. Patient decisions may also be informed by the low risk of adverse effects from treatment with N-acetylcysteine.

Erdosteine: Erdosteine, a mucolytic, has potential to reduce exacerbations in patients with COPD. The only study identified in the systematic review was a small RCT in 124 patients over 8 months.[249] Therefore, we determined that insufficient evidence supports a recommendation about the use of erdosteine for the prevention of COPD exacerbations.

Carbocysteine: S-carboxymethylcysteine (carbocysteine or S-CMC) is a thiol derivative of L-cysteine and is available as carbocysteine or its lysine salt (S-CMC-lys), which is cleaved in the GI tract to the active drug carbocysteine. This drug is a mucolytic agent available in Europe and Asia that has been demonstrated to reduce sputum viscosity and increase mucociliary transport.[250]

Only three studies[251-253] were deemed to be of sufficient quality to be included, but a pooled analysis could not be performed because of the heterogeneous nature of the studies. S-CMC-lys was given to patients in a multicenter randomized placebo-controlled trial performed in 662 outpatients with chronic obstructive bronchitis.[252] Patients were randomized to S-CMC-Lys daily, placebo, or intermittent treatment with alternating 1-week courses of S-CMC-Lys and placebo for 6 months. The percentage of patients who were exacerbation free during the 6-month trial was significantly greater in the group randomized to once daily S-CMC-Lys compared with placebo (70.4% vs 54.1%, $P = .001$), and the time to a first AECOPD was prolonged compared with placebo. Another trial enrolled 109 patients with obstructive chronic bronchitis to either carbocysteine or placebo for a 6-month winter period, but the investigators found no difference in the number of acute exacerbations of chronic bronchitis between the two groups.[252] The largest study to date has been the PEACE Study (Effect of Carbocysteine on Acute Exacerbation of COPD), which randomized 709 outpatients with COPD with a history of at least two acute exacerbations of COPD in the previous 2 years to either placebo or carbocysteine for 1 year. There was a significant reduction in the number of exacerbations in the carbocysteine group compared with the placebo group (RR, 0.75; 95% CI, 0.62-0.92) with the difference becoming significant after 6 months of therapy.[253] These studies did not permit a pooled analysis; therefore, we can only suggest that carbocysteine may be beneficial in reducing acute exacerbations of COPD, but more data from randomized placebo-controlled clinical trials are needed before an evidence-based recommendation can be made.

32. For stable outpatients with COPD who continue to experience acute exacerbations of COPD despite maximal therapy designed to reduce acute exacerbations of COPD, we suggest that oral carbocysteine could be used to prevent acute exacerbations where this therapy is available (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This suggestion places high value on preventing acute exacerbations of COPD, with minimal risks associated with carbocysteine. The main adverse events reported in studies were mild GI symptoms.

Statins: Statins are well-known and widely prescribed for their lipid-lowering effects and improved outcomes related to cardiovascular disease. Statins are also known for their pleotropic effects, which include an antiinflammatory effect. In view of this attribute, statins have been evaluated for their role in preventing COPD exacerbations.

We found five observational studies[254-258] that explored the impact of statins on COPD exacerbations as reflected in large patient databases. Hospitalizations decreased for the patients receiving statins in three studies (RR, 0.66 [95% CI, 0.51-0.85]; OR, 0.68 [95% CI, 0.44-1.04]; HR, 0.66 [95% CI, 0.60-0.74]).[256-258] Two studies were pooled on COPD exacerbations, resulting in a pooled effect estimate OR of 0.58 (95% CI, 0.45-0.74)[255,258] in favor of statins. These observational studies all significantly supported an effect of statins on reducing COPD exacerbations. However, the authors of these studies concluded that an RCT would be needed to support the results.

A prospective RCT by Criner et al[259] included 885 patients with moderate to severe COPD who met at least one of the following criteria within the previous year: use of

supplemental oxygen, receipt of systemic glucocorticoids or antibiotics, ED visits, or hospital admissions for COPD exacerbations. Patients who had known cardiovascular risk factors and met criteria for statin use based on current guidelines were excluded. After recruitment of 885 of the anticipated 1,200 patients who were to be treated for 12 to 36 months, the trial was stopped due to futility by the data safety and monitoring board, which concluded that there was no signal for an immediate or delayed effect in an intention-to-treat analysis of the entire cohort or in any subgroup analyses. The COPD exacerbation rate was 1.36 ± 1.61 and 1.39 ± 1.73 per person-year ($P = .54$) in the statin and placebo groups, respectively. There was no effect on ED visits, unscheduled physician visits, or severity of exacerbations. Furthermore, no effect was seen in reducing severe exacerbations or hospitalizations. This RCT was determined to have a low risk of bias from the Cochrane Risk of Bias Tool. Accordingly, the highest level of evidence did not support the use of statins in COPD in preventing exacerbations.

33. For patients with moderate to severe COPD who are at risk for COPD exacerbations, we do not recommend using statins to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: We place high value on reducing exacerbations in patients with COPD and, thus, do not recommend statins for preventing acute exacerbations. However, patients with COPD may meet accepted criteria for initiating statins because of the presence of cardiovascular risk factors.

Novel Therapies Not Included in the Guidelines

Several novel therapies are now in various stages of development for use alone or in combination with other agents in the management of COPD. Studies examining the effect of these agents on COPD exacerbations are either nonexistent or too small to include in the current guidelines. A short description of such agents is included here.

Most of the novel agents that have been recently approved or are in late stages of development include once-daily long-acting β_2-agonists olodaterol and vilanterol and long-acting muscarinic antagonists umeclidinium and glycopyrronium delivered through novel delivery devices. Olodaterol, recently approved by the US Food and Drug Administration for COPD is a new inhaled ultralong-acting β-agonist that offers the potential adherence and therapeutic advantage of once-daily therapy.[260,261] Additionally, multiple formulations of once-daily agents that use combinations of long-acting β_2-agonists and long-acting muscarinic antagonists (vilanterol/umeclidinium, tiotropium/olodaterol, aclidinium/formoterol, glycopyrronium/indacaterol, glycopyrronium/formoterol) are under development.[221,262-274] One such combination is vilanterol/umeclidinium that was recently approved by the Food and Drug Administration for COPD as once-daily combination bronchodilator therapy.[275-278] Similarly, once-daily long-acting β_2-agonist/inhaled corticosteroid formulations are being investigated. One such agent recently approved is fluticasone furoate/vilanterol, and several studies reported that this combination improves lung function and reduces exacerbations more effectively than either of its monocomponents.[188,191,194,197,279,280]

A large long-term study investigating fluticasone furoate/vilanterol in patients with cardiovascular risk factors (SUMMIT [Study to Understand Mortality and Morbidity in COPD]) is currently under way.[281] Other novel agents in early development are those that target airway inflammation in COPD, such as adenosine A2A-receptor agonists, inhibitors of proinflammatory pathways, and activators of antiinflammatory pathways. Among these are mimics of IL-10 and inhibitors of (1) tumor necrosis factor-α, (2) chemokines, (3) nuclear factor-κB; (4) p38 mitogen-activated protein kinase, (5) phosphoinositide 3-kinase, and (6) leukotriene B4. Other drugs under investigation include those with antioxidant effects and that may have effects on lung regeneration (retinoids) as well as mucoactive drugs.[184,185,270,282-285]

Conclusions

These guidelines provide the clinician with evidence-based information on therapies to prevent COPD exacerbations using an objective, rigorous, evidence-based approach to the assessment of the existing literature regarding nonpharmacologic inhaled and oral therapies (Fig 1). We have avoided providing opinions, instead using objective assessment of each recommendation where the data are robust enough to provide a meaningful conclusion based on the available data. This assessment also highlights areas where more research is needed as demonstrated by CB recommendations as well as recommendations given a grade of C. It is clear that large gaps in knowledge currently exist about exacerbation prevention that limit our ability to prioritize one type of therapy over another or make recommendations about combinations of therapy to prevent exacerbations. Hopefully, future research will evaluate combinations of

therapies across PICO groups and their impact on exacerbation prevention. Newer therapies that are soon to be released for clinical use or that are currently under investigation that focus on the prevention of COPD exacerbations also promise to rapidly improve the future armamentarium for the treatment of the patient with COPD.

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Dr Hernandez reports that his institution has received pharmaceutical company grant monies for research studies on which he has been an investigator, including CSL Behring, Boehringer Ingelheim GmbH, and Grifols International SA. His institution also has received grant monies for research studies for which he has been an investigator, including CIHR and Lung Association of Nova Scotia. He has participated in speaking activities, industry advisory committees, and other activities related to industry sources with the following pharmaceutical companies: Actelion Pharmaceuticals US, Inc; Almirall, SA; AstraZeneca; Boehringer Ingelheim GmbH; GlaxoSmithKline plc; Grifols; Intermune; Merck Sharp & Dohme Corp; and Novartis AG. Dr Balter has served over the past 3 years on advisory boards for and has presented at continuing education meetings for Almirall, SA; AstraZeneca; Boehringer Ingelheim GmbH; GlaxoSmithKline plc; Merck Frosst Canada Inc; Novartis AG; and Takeda Pharmaceutical Company Limited. Dr Bhutani receives university grant money, pharmaceutical grant money, grant money from government organizations in Canada and participates in speakers bureaus and speaks publicly on the topic of acute exacerbations of COPD. Dr Camp has received operating grant funding from CIHR, Canadian Lung Association, and Physiotherapy Foundation of Canada. She has received research infrastructure funding from the Canadian Foundation of Innovation and the British Columbia Lung Association and a scholar award from the Michael Smith Foundation of Health Research. She has received honoraria for speaking engagements from the Canadian Lung Association and the University of British Columbia Respiratory Division. 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Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

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The Chronic Bronchitis Phenotype in COPD: Features and Implications

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Abstract

Purpose of Review—Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem that is projected to rank fifth worldwide in terms of disease burden and third in terms of mortality. Chronic bronchitis (CB) is associated with multiple clinical consequences, including hastening lung function decline, increasing risk of exacerbations, reducing health related quality of life, and possibly raising all-cause mortality. Recent data suggests greater elucidation on the risk factors, radiologic characteristics, and treatment regimens. Our goal was to review the literature on chronic bronchitis that has been published in the last few years.

Recent Findings—A growing body of literature that more carefully describes environmental risk factors, epidemiology, and genetics associated with CB. In addition, as computed tomography technology continues to improve, the radiologic phenotype associated with CB is better understood.

Summary—With these new data, the clinician can recognize the newly described risk factors and the associated phenotype for chronic bronchitis and entertain new treatment options for this high risk population.

Keywords

Chronic Obstructive Pulmonary Disease; Chronic Bronchitis; Genetics; Airway disease; N-Acetylcysteine

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem that is projected to rank fifth worldwide in terms of disease burden and third in terms of mortality.(1) Chronic bronchitis (CB) is a common clinical phenotype in COPD and is classically defined as chronic cough and sputum production for 3 months a year for 2 consecutive years,(2) but many studies have used different definitions to define it. However it is described, it is clear that CB is associated with multiple clinical consequences, including hastening lung function decline, increasing risk of exacerbations, reducing health related quality of life, and possibly raising all-cause mortality.(3-8) Despite its clinical consequences, the literature regarding its pathophysiology, radiologic characteristics, and clinical phenotype has been sparse. Recently, however, there has been a growing body of literature that more carefully describes environmental risk factors, epidemiology, and genetics associated with CB. In addition, as computed tomography technology continues to improve, the radiologic phenotype associated with CB is better understood. Herein, we will describe our current understanding of CB in COPD, with an emphasis on recent literature.

Epidemiology

CB is surprisingly common in the general population, seen in 3.4-22.0% of adults.(9-21). This wide range of prevalence estimates may be due to varying definitions of CB (i.e. chronic phlegm versus chronic cough and phlegm) as well as the possible inclusion of subjects with bronchiectasis. Table 1 provides an overview of the prevalence of cough and sputum production in population based studies.

According to recent statistics, chronic bronchitis (CB) affects approximately 10 million people in the United States, the majority of which are between 44-65 years of age.(24) 24.3% of individuals with CB are older than 65, and surprisingly 31.2% are between the ages of 18 and 44.

The numbers affected by CB dramatically increase with smoking. Pelkonen et al. followed 1,711 Finnish men in rural communities for 30 years and found the incidence of CB was 42% in continuous smokers, 26% in ex-smokers, and 22% in never smokers.(20) A recent cross sectional study of over 5,000 adult current or ex-smokers with over a 10 pack year history, the prevalence of CB, using the classic definition, was a striking 34.6%.(21) The prevalence of CB is higher in COPD patients, affecting 14-74% of all COPD patients.(25-28)

CB seems to affect whites more than blacks, but the majority of studies have been comprised of mostly whites.(11, 14, 19, 20, 29) A recent study of non-Hispanic whites and blacks found that COPD subjects were more likely to be white than black, but the differences in racial distribution between those with and without CB were small.(28) Gender has also been a matter of debate. Many studies have found that CB affects men more than women.(27, 28, 30, 31) However, according to the 2013 American Lung Association report, the prevalence rates of CB in women were nearly twice that of men (59.7 vs. 29.6 per 1000 persons).(24) A 10-year study of Danish 21,130 patients showed that the cumulative prevalence of chronic mucus secretion was 10.7% in females vs. 8.7% in males.(19) The

reasons for the higher prevalence of CB in females compared to males is unclear, but may be due to hormonal influences, gender differences in symptom reporting, and gender diagnostic bias; for example, in the EUROSCOP study, women reported more dyspnea and cough but less phlegm symptoms than men.(32)

Recent evidence has suggested that CB may be underdiagnosed, likely related to the various definitions used for CB. Using a definition of chronic phlegm alone for most days, 3 months a year, for 2 years, the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study estimated a CB prevalence of 14.4 and 6.2% in those with and without COPD, respectively.(27) When using the classic definition, however, the prevalence fell to 7.4 and 2.5%, respectively. In the Genetic Epidemiology of COPD (COPDGene) study,(33) the prevalence of CB was 26.2% in GOLD 1-4 subjects using the classic definition, but was 39% when using a novel definition of cough and phlegm using the Saint George's Respiratory Questionnaire.(unpublished data) A large epidemiologic survey of the French general population showed a CB prevalence of 3.5%, but only 28.6% of these subjects reported a history of respiratory disease.(34) These data highlight the need to ask the appropriate questions when interviewing patients at risk for CB and the need of a more uniform definition across studies.

Risk Factors

The primary risk factor of CB is smoking. As mentioned earlier, the cumulative 30-year incidence of CB in current smokers is 42%.(20) A 2011 meta-analysis has found that ever smoking conferred a 2.69, (95% CI 2.50-2.90), and current smoking was associated with a relative risk of 3.41 (95% CI 3.13-3.72).(35) More recent literature has supported the increased risk of CB conferred by smoking.(28, 36) Sumner et al. objectively measured cough in those with and without COPD with 24 hour cough monitoring and found that the greatest cough frequency was in COPD current smokers, followed by COPD ex-smokers and healthy current smokers.(37) In addition, in this study reported sputum production, smoking history, and current smoking predicted cough frequency. However, CB has been described in 4-22% of never smokers,(16, 20) suggesting that other risk factors may exist. Interestingly, two cross sectional studies showed stable rates of CB of 12.5 to 12.6% in young adults, even though the rates of smoking decreased from 33.6% to 26.9%.(38) Recent literature has highlighted that occupational exposures, biomass fuels, dusts, and chemical fumes place individuals at risk for developing CB.

While a significant body of literature exists that ties occupational exposures with worsening asthma control and bronchial hyperresponsiveness, the link between CB and occupational exposures is just beginning to emerge. A study involving 338 hospitalized COPD subjects in 9 Spanish hospitals found that high exposure to gases or fumes was associated with CB symptoms.(39) Dijkstra et al. found that exposures to mineral dusts and gases and fumes was associated with an odds ratio of 1.38 and 2.19, respectively, in 8529 subjects without COPD.(36) There were also significant interactions found between the presence of COPD and exposures to gases, fumes, and aromatic solvents in this cohort, comprised of an additional 1479 subjects with COPD diagnosed by spirometry. Exposure to both dusts and fumes was associated with an increased risk of chronic cough and chronic phlegm (odds

ratios 1.83 and 1.82, respectively) after adjustment for demographic factors and smoking in the COPDGene cohort, a study that involved more than 9600 subjects with and without COPD.(40) These associations show that, regardless of the presence of airflow obstruction, significant gas and fume exposure can result in chronic cough and sputum production. The specific gases or fumes, as well as the amount of exposure necessary, remains unclear and deserves further investigation.

In the last decade it has become apparent that exposure to biomass fuels, such as wood, dung, and crop residues, is a significant risk factor for COPD. Biomass smoke exposure predominantly affects women in rural areas who use these fuels for cooking. With the increasing understanding of the risk of developing COPD conferred by biomass smoke, it is apparent that it also increases risk for developing CB. Compared to COPD due to tobacco smoking, those with COPD related to biomass smoke exposure have more cough, phlegm symptoms and air trapping on CT scan.(41) Two recent studies comparing radiologic phenotypes between tobacco smoke-exposed and biomass smoke-exposed subjects matched for lung function found that the biomass group had more air trapping or peribronchial thickening and less emphysema than the tobacco group, suggesting an airway predominant phenotype.(42, 43) Another study of wood smoke-exposed women with COPD, the most common findings on HRCT scans were bronchial wall thickening, bronchiectasis, mosaic perfusion pattern, parenchymal bands, and tree-in-bud opacities.(44) These radiologic findings suggest a bronchitic clinical phenotype, as CB is associated with greater airway wall thickening and gas trapping on CT scan.(28)

Air pollution is another risk factor for worsening of CB symptoms and exacerbations. Ozone studies have shown diminished lung function, reduced exercise capacity, and lung inflammation at levels at or below the National Ambient Air Quality Standards of air quality.(45) To make matters worse, ambient ozone levels are expected to increase in the upcoming decades.(46) A study of over ten years of ambient ozone levels found that increased ozone levels were associated with greater emergency department visits for CB.(47) In a meta-analysis of 23 studies examining all-cause mortality associated with outdoor fine particulate matter (particles with a median diameter <2.5 μm (PM2.5)) air pollution, a 10 mg/m^3 increment in PM2.5 was associated with an increase in the risk of death, particularly respiratory causes of death (1.51%, 95% CI 1.01-2.01).(48) There is also supportive literature that air pollution increases systemic biomarkers of inflammation in COPD subjects, particularly interleukin 8, C-reactive protein, fibrinogen, and hepatocyte growth factor.(Dadvand) Systemic levels of C-reactive protein and fibrinogen have been shown in univariate analysis to be greater in COPD subjects with CB in the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS).(49) Other studies, however, have not been as supportive of the association between air pollution with CB. A meta-analysis of 5 cross-sectional studies in Europe found no statistically significant associations between any air pollutant and CB except in never smokers (OR 1.31 for PM_{coarse}).(50)

Recently more data have emerged linking the CB phenotype with upper airway symptoms. An analysis of two large epidemiologic cross sectional surveys of young adults conducted at different times (1998/2000 and 2007/2010) found that the likelihood of having CB was significantly higher in subjects with allergic rhinitis.(38) This study also revealed that

although the prevalence of CB remained stable, the rates of current smoking dropped over the timespan between the two surveys and the prevalence of allergic rhinitis increased, strengthening the association between upper airway and lower airway symptoms. In an analysis of the National Health and Nutrition Survey III (NHANES III), the presence of self-reported doctor-diagnosed hay fever or allergic upper respiratory symptoms (21.4% of 1381 subjects) was independently associated with chronic cough and phlegm.(51) Exacerbation rates were greater in those with an allergic phenotype compared to those without it. In the COPDGene cohort, those with COPD and CB (24.5% of 2703 subjects) were more likely to have allergic nasal and ocular symptoms and exacerbation frequency compared to COPD subjects without CB.(28)

Genetics

As CB exists in those without airflow obstruction, and not everyone with COPD develops CB, it is clear that predisposing factors in combination with exposures lead to CB. Recent data have revealed possible genetic predispositions. In a population based study of 13649 twins, from the Danish Twin Registry, CB showed moderate familial aggregation especially in women.(52) Genome wide association analysis in the Netherlands of chronic mucus hypersecretion showed a strong association with a SNP on chromosome 3.(53) An simultaneous analysis of three different cohorts, COPDGene (non-Hispanic whites and blacks), GenKOLS (Bergen, Norway), and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) found a new genome-wide locus of chromosome 11p15.5 in COPD subjects with CB compared to smoking controls.(54) As the understanding of COPD genetics increases, perhaps we will be able to elucidate the gene-environment interactions responsible for the development of CB.

Radiologic features

CB is associated with greater airway disease on CT scan. One of the first studies that compared 20 COPD subjects with CB and 22 COPD subjects without CB found significantly higher bronchial wall percentage areas and thickness-to-diameter ratios in those with CB compared to subjects without CB.(55) More recent studies have corroborated these initial findings in different cohorts and using different quantitative techniques. A recent study showed that sputum purulence in combination with lung function measures strongly predicted airway wall thickness of 10mm airways (Pi10) in 373 COPD subjects.(56) In the COPDGene study, which involved over 2700 COPD subjects with complete radiographic analysis and pertinent clinical histories, airway wall thickness in combination with lung function, smoking history, allergic symptoms, and gastroesphageal reflux was predictive of CB in a multivariate model.(28)

Clinical Features

Table 2 summarizes the current data regarding the outcomes associated with CB. Multiple studies have shown that CB accelerates lung function decline,(3, 57) worsen health related quality of life,(26-28) may increase mortality,(4, 5, 30, 61) and increases the risk of exacerbations.(3, 25, 27) Some literature on exacerbations leaves the link with exacerbations and CB debatable. In the ECLIPSE study, CB defined as chronic cough was a significant

predictor of exacerbations but only on univariate analysis.(66) Another study of smokers without spirometric evidence of COPD found CB to again be a significant risk factor for respiratory exacerbations but only on univariate analysis.(67)

However, recent data has more firmly established the link between CB and exacerbations. A multicenter cross sectional study of 975 GOLD 2-4 COPD subjects, where the prevalence of CB was 64%, found that the CB group had more exacerbations (2.08±2.78 vs. 1.05±1.71 exacerbations/patient/year, $p<0.0001$), a higher percentage of subjects with frequent exacerbations (37.3 vs. 14.2%, $p<0.0001$), more hospital admissions due to COPD (0.28±0.75 vs. 0.15±0.43 hospitalizations/patient/year, $p=0.0027$), and more all cause hospitalizations (0.52±0.91 vs. 0.38±0.83 hospitalizations/patient/year, $p=0.0185$).(60) An analysis of the COPDGene study (cross sectional, multicenter) of GOLD 1-4 subjects found similar trends in total exacerbation frequency (0.96±1.46 vs 0.52±1.04 exacerbations in the past year, $p<0.0001$) and history of severe exacerbations (24.2 vs. 15.2%, $p<0.0001$).(28) An analysis of the GOLD 0 subjects from the COPDGene study also found that those with CB (12.2% of 4880 subjects) had an increased rate of respiratory exacerbations.(68) In long term follow-up of 8246 subjects in the COPDGene study, CB was independently associated with exacerbation risk in all subjects (HR 1.15, 95% CI 1.03-1.28), including GOLD 0 and GOLD U (undefined, indicating smokers at risk for COPD with restrictive lung disease on spirometry).(69) Similar trends were seen in the COPD Clinical Research Network Azithromycin trial (MACRO) and the SPIROMICS cohorts.(49, 70) Using a novel definition of severe CB, defined as chronic cough, phlegm, and chest trouble, we found that severe CB was associated with increased mortality and all-cause hospitalizations in the National Emphysema Treatment Trial cohort.(71)

Implications for treatment

Treatment for COPD and CB is multifold and includes both pharmacologic and nonpharmacologic strategies. Please refer to a recent review for more extensive discussion on this topic.(72) Exacerbation rates remain high in those with CB, despite treatment with COPD maintenance medications.(73) Therefore, the primary focus in recent research has been on reducing exacerbations in this high risk population.

Macrolide antibiotics have been shown to have anti-inflammatory properties and have been used to decrease COPD exacerbations. Independent of their antibiotic properties, macrolides have been shown to reduce neutrophil-elastase induced mucus stasis, suggesting benefit in CB.(74) The effect of chronic macrolide therapy on COPD exacerbations was assessed in 109 patients randomly assigned to receive erythromycin 250 mg or placebo twice daily for 1 year.(75) The erythromycin group had significantly fewer exacerbations than the placebo group. A recent large, prospective, placebo-controlled, randomized trial on the use of azithromycin (250 mg daily for 1 year) to prevent acute exacerbations of COPD showed that azithromycin was associated with a significant decrease in exacerbation frequency and an improvement in HRQoL.(76) There was, however, no additional benefit conferred to those with CB.(77) What future studies with macrolides will show in those with CB remains to be determined.

Phosphodiesterase-4 inhibitors, particularly roflumilast, may be beneficial in the treatment of CB. Acquired dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) in airway epithelial cells can delay mucociliary transport, and has been associated with CB.(78) Moreover, roflumilast activates CFTR-mediated anion transport,(79) which may be at least one mechanism of its benefit in CB. In two 24-week trials, 933 patients with moderate to severe COPD were randomly assigned to roflumilast plus salmeterol or salmeterol alone, and 743 patients were randomly assigned to roflumilast plus tiotropium or tiotropium alone.(80) The overwhelming majority of patients (78–100%) endorsed chronic cough and sputum production. In both trials, roflumilast significantly reduced exacerbation rate. Thus, as CB increases risk for exacerbation, roflumilast may play a preferential role in preventing exacerbations in patients with CB and COPD. The Global Initiative on Obstructive Lung Disease (GOLD) currently recommends roflumilast for those with CB and in those with frequent exacerbations as second line therapy.(1)

As oxidative stress is crucial to the pathogenesis of COPD, antioxidant therapy may be of benefit in COPD treatment. The two most extensively studied antioxidant medications for COPD are N-acetylcysteine (NAC) and carbocysteine. Unfortunately, the two largest trials showed either no or weak reductions in exacerbations in long term follow-up.(81, 82) A more recent study, High-Dose N-Acetylcysteine in Stable COPD (HIACE) study, enrolled 120 subjects with stable COPD from one center and randomized them to receive NAC 600mg twice daily or placebo for one year.(83) The NAC group had a statistically significant increase in small airways function as measured by FEF_{25-75} compared to placebo but there was no difference in exacerbation frequency. A larger multicenter randomized controlled trial randomized 1006 subjects to the same NAC regimen or placebo and found significant reductions in exacerbation frequency (risk ratio 0.78, 95% CI 0.67-0.90).(84)

Conclusions

The recent data on chronic bronchitis has shed more light on the epidemiology, risk factors, radiologic features, genetic influences, and therapeutic strategies. This should influence the clinician to maintain a higher index of suspicion for chronic bronchitis given the recent growing body of literature on risk factors and phenotype. However, more study is needed to determine why some smokers develop CB and others do not and on how smoking cessation affects its natural history. In addition, more research on the pathophysiology of this disease process will help development of better therapies that directly target CB in order to improve quality of life, decrease exacerbations, and reduce mortality.

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Key Points

1. The main risk factor for chronic bronchitis remains current smoking but exposure to air pollution, dusts and fumes and biomass fuels are newly described risk factors.
2. Chronic bronchitis significantly increases the rate of COPD exacerbations.
3. Chronic bronchitis is seen variably in smokers but also is seen to a surprising degree in nonsmokers, suggesting other risk factors are significant.
4. New treatments like N-Acetyl Cysteine may be beneficial in those with chronic bronchitis.

Table 1

Prevalence of Chronic Bronchitis in Multiple Studies.

Study	Subjects	Findings
Lange 1989[9]	General population, Copenhagen; 12,698 adults	Bronchial hypersecretion: 10.1%
Sobradillo 1999[22]	General population, Spain; 4035 adults aged 40-69 years	Cough: 13.5% Expectoration: 10.7% Chronic Bronchitis: 4.8%
Pallasaho 1999[10]	Random sample, Finland; 8000 subjects aged 20-69 years	Productive cough: 27%
von Hertzen 2000[11]	Random subjects, Finland; 7217 subjects age >30 years	Chronic bronchitis and/or emphysema: 22% in men, 7% in women
Cerveri 2001[12]	General population, Europe; 17,966 subjects aged 20-44 years	Chronic Bronchitis: 2.6% (range 0.7-9.7% across countries)
Janson 2001[13]	Multinational; 18,277 subjects aged 20-48 years	Productive cough: 10.2%
Huchon 2002[14]	General population, France; 14,076 subjects	Chronic bronchitis: 4.1% Chronic cough and/or expectoration: 11.7%
Lundback 2003[15]	5892 subjects from OLIN Study cohort	Chronic productive cough: 60% in COPD subjects
Miravitlles 2006[16]	General population, Spain; 6758 adults aged >40 years	Cough: 5% in never smokers, 11% in smokers or ex-smokers Expectoration: 4% in never smokers, 11% in smokers and ex-smokers
Pelkonen 2006[20]	Finnish cohort of 1711 adult men aged 40-59	Incidence of chronic productive cough: 42% current smokers, 26% past smokers, 22% never smokers
De Marco 2007[17]	International cohort of 5002 subjects aged 20-44 years with normal lung function	Chronic cough/phlegm production: 9.2%
Miravitlles 2009[18]	Population based sample, Spain; 4274 adults aged 40-80 years	Chronic cough: 3.4% Chronic sputum production: 11.7%
Harmsen 2010[19]	Danish cohort of 29180 (in 1994) and 21130 (in 2004) twins aged 12-41 years	Cumulative prevalence of chronic mucus secretion over 10 years of study, 10.7% in females and 8.7% in males
Martinez 2014[21].	United States cohort of 5858 adult past or previous smokers without airflow obstruction	Chronic bronchitis: 34.6%

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Table 2

Summary of the Effects of Chronic Bronchitis on Outcomes.

Outcome	Study	Subjects	Important Findings
Lung Function	Sherman et al. 1992.[57]	3,948	Adjusted FEV1 decline: 4.5 mL per year ± 2 (SE) in males *; 1.7 mL per year ± 1.5 (SE) in females
	Vestbo et al. 1996.[3]	9,435	Adjusted FEV1 decline: 22.8 ml/year (95% CI 8.2 to 37.4) in males*; 12.6 ml/year (95% CI 0.7 to 24.6) in females
	Lindberg et al. 2006.[58]	963	FEV1/FVC<0.7 and FEV1<80% predicted, OR: 2.56 (95% CI 1.32 to 4.95)*
	de Marco et al. 2007.[59]	5,002	FEV1/FVC<0.7, IRR: 1.85 (95% CI 1.17 to 2.93)*
	Guerra et al. 2008.[5]	1,412	FEV1/FVC<0.7, HR: 2.2 (95% CI 1.3 to 3.8) in <50 years*; 0.9 (95% CI 0.6 to 1.4) in ≥50 years
Health Related Quality of Life	Agusti et al. 2010.[26]	2,164	CB+ vs CB-: GOLD II: SGRQ total 50.3±18 vs 38.9±20.5*; mMRC 1.5±1 vs 1.3±1* GOLD III: SGRQ total 58.8±17.6 vs 51.2±18.2*; mMRC 1.8±1 vs 1.8±1.1 GOLD IV: SGRQ total 65±16.5 vs 59.4±15.2*; mMRC 2.4±1 vs 2.3±1
	de Oca et al. 2012.[27]	759	CB+ vs CB-: Short Form-12 physical score 44.6±1.01 vs 49.5±0.36* Limitation due to physical health 39(40.6) vs 148(22.4)*
	Kim et al. 2014.[28]	2,703	CB+ vs CB-: SGRQ total 48.0±21.3 vs 30.6±21.8* mMRC 2.3±1.4 vs 1.6±1.5*
COPD Exacerbations and Hospitalizations	Vestbo et al. 1996.[3]	9,435	COPD-related hospitalization, RR: 2.4 (95% CI 1.3 to 4.5) in males*; 2.6 (95% CI 1.2 to 5.3) in females*
	Burgel et al. 2009.[25]	433	All exacerbations: OR 4.15 (95% CI 2.43 to 7.08)* Moderate exacerbations: OR 4.65 (95% CI 2.54 to 8.48)* Severe exacerbations: OR 4.08 (95% CI 1.18 to 14.09)*
	Agusti et al. 2010.[26]	2,164	CB+ vs CB-, exacerbations in past year: GOLD II: 0.7±1.1 vs 0.6±1 GOLD III: 1±1.2 vs 1±1.4 GOLD IV: 1.2±1.6 vs 1.2±1.3

Outcome	Study	Subjects	Important Findings
	de Oca et al. 2012.[27]	759	CB+ vs CB-, exacerbations in past year: 5.3±3.83 vs 2.1±0.95
	Corhay et al. 2013.[60]	974	CB+ vs CB-, exacerbations per patient per year: 2.08±2.78 vs. 1.05±1.71*
	Kim et al. 2014.[28]	2,703	CB+ vs CB-, exacerbations in past year: Total, number/patient: 0.96±1.46 vs 0.52±1.04* Severe, %: 24.2 vs 15.2*
Mortality	Annesi et al. 1986.[61]	1,061	All-cause, RR: 1.35±0.111*
	Speizer et al. 1989.[30]	8,427	COPD-related, OR: 3.75 (95% CI 1.28 to 11) in males*; 11.04 (95% CI 2.52 to 48.5) in females* All-cause, OR: 1.37 (95% CI 1.09 to 1.72) in males*; 0.98 (95% CI 0.68 to 1.41) in females
	Tockman et al. 1989.[62]	884	All cause, RR: 1.65 (95% CI 0.95 to 2.89)
	Lange el al. 1990.[29]	13,756	All-causes, RR: 1.3 (95% CI 1.1 to 1.4) in males* and 1.1 (95% CI 0.9 to 1.3) in females
	Prescott et al. 1995.[63]	14,223	COPD-related with pulmonary infection, RR: 3.5 (95% CI 1.8 to 7.1)* COPD-related without pulmonary infection, RR: 0.9 (95% CI 0.5 to 1.8)
	Mannino et al. 2003.[64]	5,542	All-cause, RR: 1.2 (95% CI 0.97 to 1.4)
	Pelkonen et al. 2006.[4]	1,711	Respiratory-related, HR: 2.54 (95% CI 1 to 6.46)* All-cause, HR: 1.64 (95% CI 1.23 to 2.19)*
	Guerra et al. 2009.[5]	1,412	All-cause mortality, HR: 2.2 (95% CI 1.3 to 3.8) in <50 years*; 1 (95% CI 0.7 to 1.3) in ≥50 years

*Statistically significant. Data are presented as mean±SD or number (percentage) except as indicated. Incident rate ratio, odds ratio, relative risk, and hazard ratio are all from multivariate analysis with adjustments for covariates.

FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, SE = standard error, CI = confidence interval, HR = hazard ratio, RR = relative risk, OR = odds ratio, CB+ = group with chronic bronchitis, CB - = group without chronic bronchitis, SGRQ = St. George's Respiratory Questionnaire, and mMRC = modified Medical Research Council. Updated and modified from Ramos F, Krahnke J, Kim V. Clinical Issues of Mucus Accumulation in COPD. *IJCOPD* 2014:9 139–150.(65) With permission.

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ORIGINAL RESEARCH

Impact of roflumilast on exacerbations of COPD, health care utilization, and costs in a predominantly elderly Medicare Advantage population

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Background: Chronic obstructive pulmonary disease (COPD) exacerbations are associated with declining lung function and health-related quality of life, and increased hospitalization and mortality. Clinical trials often poorly represent the elderly and thus have only partial applicability to their clinical care.

Objective: To compare exacerbations, COPD-related health care utilization (HCU), and costs in a predominantly elderly Medicare COPD population initiated on roflumilast versus those not initiated on roflumilast.

Methods: Deidentified administrative claims data from a large, national payer were utilized. Medicare patients aged 40–89 years with at least one COPD diagnosis from May 1, 2010 to December 31, 2012 were included. Members with at least one roflumilast pharmacy claim (index) were assigned to the roflumilast group and those without were assigned to the non-roflumilast group. Proxy index dates for the non-roflumilast group were randomly assigned for similar distribution of all patients' time at risk. Subjects with at least one pre-index COPD exacerbation had to be continuously enrolled for ≥365 days pre-index and post-index. Unadjusted and adjusted difference-in-difference (DID) analyses contrasted pre-index with post-index changes in exacerbations, HCU, and costs of roflumilast treatment compared with non-roflumilast treatment.

Results: A total of 500 roflumilast and 60,145 non-roflumilast patients were included (mean age 69.7 and 72.3 years, respectively; $P<0.0001$). Unadjusted DID favored roflumilast for all exacerbations, with greater pre-index to post-index reductions in mean per 30-day COPD-related hospitalizations (–0.0182 versus –0.0013, $P=0.009$), outpatient visits (–0.2500 versus –0.0606, $P<0.0001$), and COPD-related inpatient costs (–US$141 versus –US$11, $P=0.0346$) and outpatient costs (–US$31 versus –US$4, $P<0.0001$). Multivariate analyses identified significantly improved pre-index to post-index COPD-related total costs ($P=0.0005$) and total exacerbations ($P<0.0001$) for the roflumilast group versus non-roflumilast group.

Conclusion: In a predominantly elderly Medicare COPD population, newly initiated roflumilast patients displayed similar or significantly better unadjusted reductions in all exacerbation-related, COPD-related HCU-related, and COPD-related costs outcomes compared with non-roflumilast patients. These analyses also suggest better adjusted COPD-related costs and total exacerbations for roflumilast-initiated patients.

Keywords: COPD, roflumilast, exacerbations, health care utilization, Medicare

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by persistent airflow limitation, chronic and progressive dyspnea, cough, and sputum production, and is often complicated by exacerbations. COPD-related exacerbations have serious health consequences and are associated with declines in lung function,

reduction in health-related quality of life, and hospitalization and mortality.[1] The economic impact of exacerbations is evidenced by the cost of COPD exacerbation-related hospitalizations, accounting for the largest share of direct medical costs associated with COPD.[2] The elderly COPD population poses an ever more common challenge with regard to diagnosis and treatment.[3] COPD is often underdiagnosed in elderly patients due in part to concurrent age-related changes in lung function.[4] The increased prevalence of comorbid conditions in the elderly COPD patient can also contribute to the difficulty of diagnosis and treatment selection.[3,5,6] Clinical trials upon which new COPD treatments are approved by the US Food and Drug Administration are often poorly representative of the real-world elderly population and thus have only partial applicability to the clinical care of an elderly patient.[6]

Until recently, therapy for COPD patients of all ages had been guided primarily by airflow limitation and as such provided limited clinical guidance for a disease that is accepted as heterogeneous and complex.[7,8] The most recent iteration of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment guidelines allow for patient assessment based not only on forced expiratory volume in one second values, but also patient-specific symptomology and exacerbation history, and assigns patient categorization and treatment according to four groups (A, B, C, and D).[9] Current COPD treatment options recommended by the GOLD treatment guidelines to relieve symptoms and prevent exacerbations include smoking cessation, long-term oxygen therapy, inhaled corticosteroids (ICS), oral corticosteroids, bronchodilator therapy, and roflumilast, a phosphodiesterase-4 inhibitor available on the US market.[9]

Roflumilast is indicated as a treatment option to reduce the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[10] This agent has been shown to reduce exacerbation frequency in patients with severe airflow limitation, history of exacerbations, and chronic cough and sputum,[11,12] as would typically be found in the severe group D GOLD classification. While greater sensitivity of elderly patients to roflumilast cannot be explicitly ruled out, no differences in safety or effectiveness have been observed between older and younger clinical trial subjects.[10]

An assessment of real-world utilization of roflumilast is essential to better understand the characteristics of COPD patients for whom it is prescribed, the appropriateness of its use, and associated outcomes, as measured by health care utilization (HCU) and exacerbation occurrence. To date, there is no description of an elderly COPD population within which roflumilast is being utilized in actual clinical practice. This study endeavored to characterize a predominantly elderly Medicare COPD population initiated on roflumilast and to compare post-initiation outcomes with a population not initiated on roflumilast.

Materials and methods

Study design and subject selection

This retrospective study utilized deidentified health care claims from a large Medicare Advantage Prescription Drug health plan. Medical and pharmacy claims data were extracted from May 1, 2010 to December 31, 2012, and were used to identify potential subjects, to measure baseline characteristics, and to examine the outcomes of interest. Medicare Advantage Prescription Drug plan members between 40 and 89 years of age with at least one COPD diagnosis, as identified by the ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) diagnosis codes of 491.x, 492.x, or 496.x, were identified as potential subjects. From this pool of potential subjects, members with at least one pharmacy claim for roflumilast were identified and the first observed roflumilast claim was assigned as the index date. Subjects in the "roflumilast-treated group" were required to have 12 months of continuous pre-index enrollment, 12 months of continuous post-index enrollment, and at least one pre-index COPD exacerbation of any severity (see Table 1 for exacerbation definition algorithm).[13,14] The remaining pool of initially identified potential subjects was eligible for inclusion in the "non-roflumilast treated group". Proxy index dates, based on the distribution of the difference between pre-index exacerbation date and index date of the roflumilast-treated group, were randomly assigned to the non-roflumilast subjects so that the distribution of all non-roflumilast subjects' time at risk was similar to that in the roflumilast-treated group.[15] Once proxy index dates were assigned, continuous enrollment criteria, age requirements at index date, and pre-index exacerbation criteria were applied and the final non-roflumilast-treated group was identified. The research protocol was reviewed and received approval by an independent institutional review board prior to initiation of the study. A waiver of informed consent and a waiver of authorization to use protected health information were granted.

Subject characteristics

Subject enrollment data provided sex, race/ethnicity, low income subsidy status (defined as Medicare beneficiaries with income below 150% of poverty level), and Medicare dual

Table 1 Exacerbation type definitions and identification algorithm

Exacerbation type (ranked by decreasing severity)	Identification method
Inpatient hospitalized exacerbation (a variation of criteria used by Lindenauer et al[13])	Presence of an inpatient hospital stay with a principal diagnosis of COPD with acute exacerbation (ICD-9-CM codes 491.21, 491.22, 493.22), emphysema (ICD-9-CM, 492.8), or if they had a principal diagnosis of respiratory failure (ICD-9-CM codes 518.81, 518.82, 518.84) combined with a secondary diagnosis of COPD with acute exacerbation or emphysema.
Exacerbation requiring an emergency room visit[14]	Presence of an emergency room visit with a primary diagnosis of COPD (ICD-9-CM code 491.x, 492.x, or 496.x).
Ambulatory exacerbation identified by qualifying diagnosis[14]	Presence of an office or outpatient non-emergency room visit with any of the following ICD-9-CM diagnosis codes in the first position: 136.3, 466–466.19, 480–486, 487.0, 490, 491.21, 491.22, 493.02, 493.12, 493.22, 493.92, 494.1, 506.0–506.3, 507–507.8, 511.0–511.1, 512–512.8, 517.1, 518.0, 518.81, 518.82, 518.84, 770.84.
Ambulatory exacerbation identified by qualifying antibiotic[14]	Presence of a pharmacy claim for the following oral antibiotics commonly used for respiratory infections amoxicillin, beta-lactamase inhibitors, second or third-generation cephalosporins, macrolides, or doxycycline.
Ambulatory exacerbation identified by qualifying systemic steroid[14]	Presence of a pharmacy claim for systemic steroids (oral, intramuscular, or intravenous).

Abbreviations: COPD, chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

eligibility status. Age was calculated as of the index date. Geographic region was based on the subject's state of residence on the index date. Comorbidity burden was measured by the Deyo-Charlson Comorbidity Index (DCCI). The DCCI uses 17 categories of comorbidity to calculate a score that reflects the cumulative increased likelihood of 1-year mortality and is based on ICD-9 diagnoses and procedure codes, and their associated weights.[16,17] In addition to the DCCI score, other comorbid respiratory conditions of interest were identified by their associated ICD-9-CM codes. These conditions included respiratory tract cancer, cystic fibrosis, fibrosis from tuberculosis, bronchiectasis, pneumoconiosis, pulmonary fibrosis, pulmonary tuberculosis, and pulmonary sarcoidosis.

Pre-index and post-index medication utilization was measured based on pharmacy or J-coded medical claims adjudicated during the respective period. Respiratory-related medication use patterns were measured for the following classes: short-acting β2-agonists, long-acting β-agonists (LABAs), ICS, ICS/LABA combination products, short-acting anticholinergics, long-acting muscarinic antagonists (LAMAs), methylxanthines, and oral or intravenous corticosteroids. The combination regimen of ICS, LABA, and LAMA was also identified for subjects utilizing each of those three classes at least once during the respective period. Lastly, baseline antibiotic use and long-term oxygen use were identified.

Outcomes

The quantity and costs of COPD-related and total inpatient and outpatient services received, including inpatient hospitalizations, emergency room visits, outpatient office visits, and pharmacy claims, were assessed for both the 12-month pre-index and 12-month post-index periods. Medical claim place of service and current procedural terminology (CPT) codes were used to assign inpatient, emergency room, or outpatient office visit utilization and costs. Total pharmacy costs were defined as the sum of plan-paid and member-paid costs associated with all paid pharmacy claims. Total all-cause health care costs were defined as the sum of the respective total medical cost and total pharmacy cost components. All cost calculations included both member-paid and plan-paid components.

The proportion of subjects with inpatient hospitalized exacerbation, emergency room visit exacerbation, an ambulatory exacerbation identified by qualifying diagnosis, or an ambulatory exacerbation identified by qualifying steroid were assessed. Complete operational definitions of each exacerbation type can be found in Table 1. In the event that a patient had multiple exacerbation events and the time between each event was less than 14 days, the exacerbation "episode" would continue until there was a greater than 14-day space without exacerbation. Only the most severe exacerbation type within that episode was recorded. Any exacerbation occurring after that 14-day window would be a separated exacerbation episode. The occurrence of the aforementioned exacerbation types during the pre-index period was also assessed. The total number of exacerbations (any severity excluding those identified by qualifying antibiotic) experienced by each subject for both the pre-index and post-index periods was determined.

Statistical analysis

Members' baseline demographics, comorbidities, medication used, exacerbations of different severity, HCU, and health care costs were summarized and compared across groups. Post-index exacerbations of different severity, HCU, and health care costs were also summarized and compared. Counts and percentages for categorical variables were calculated. For continuous variables, means and standard deviations were calculated. Bivariate comparisons of baseline characteristics between the roflumilast-treated group and non-roflumilast-treated group were conducted. Chi-square or Fisher's exact tests and Wilcoxon rank sum tests were used to evaluate the statistical significance of differences in categorical and continuous variables, respectively.

A difference-in-difference (DID) analytic approach was utilized to contrast changes (12 months before versus 12 months after the index date) in HCU, costs, and exacerbations of the roflumilast-treated group compared with non-roflumilast-treated group. The DID analyses were conducted as univariate analyses for all utilization, cost, and exacerbation outcomes and as multivariate analyses for total COPD-related costs, number of total exacerbations, and number of severe exacerbations. For the univariate DID analyses, all utilization, cost, and exacerbation variables were normalized to a "per 30-day" value due to the allowed variance in member post-index follow-up time (at least 1 year). The 12-month pre-index versus 12-month post-index differences in exacerbation, cost, and utilization variables within each group were calculated and then the net differences (the DID) between the groups were determined and compared using a *t*-test with unequal variances assumed. Multivariate DID analyses were also conducted to adjust for any baseline differences (eg, comorbidities, baseline medication use) between the two cohorts and validate the respective univariate findings. For the multivariate DID analyses, a generalized linear model with a gamma distribution and log link was fitted to model total COPD costs. A generalized linear model with a negative binomial distribution and log link was fitted to model total exacerbations and severe exacerbations. The generalized estimating equation method was used to account for repeated measures of the same member. Several variables were entered into the three models, including index treatment group (roflumilast or non-roflumilast), demographic characteristics, baseline medical conditions, pre-index medication utilization, and pre-index all-cause health care costs. The total COPD costs model also adjusted for differences in baseline number of each exacerbation type.

All analyses of data were conducted using SAS version 9.3 and SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC, USA). The a priori alpha level for all comparative analyses was 0.05 and all statistical tests were two-tailed.

Results

Study populations and baseline characteristics

After application of the study inclusion and exclusion criteria, a total of 60,645 Medicare Advantage Prescription Drug members were identified, comprising 500 for the roflumilast-treated group and 60,145 for the non-roflumilast-treated group (Table 2). Significant differences between the roflumilast and non-roflumilast-treated groups were observed for age and low income subsidy. The roflumilast-treated group was younger on average relative to the non-roflumilast-treated group (69.7 versus 72.3 years, $P<0.0001$). A greater proportion of roflumilast subjects qualified for a low income subsidy relative to non-roflumilast subjects (48.60% versus 25.03%, $P<0.0001$). No statistically significant differences were observed for sex, race/ethnicity, or geographic region of residence.

The baseline comorbidities of the study groups are described in Table 3. There was no significant difference between the roflumilast-treated group and the non-roflumilast-treated group in baseline DCCI score (2.62 versus 2.63, respectively, $P=0.8569$). Relative to the non-roflumilast-treated group, the roflumilast-treated group had a significantly greater prevalence of congestive heart failure (CHF), bronchiectasis, pneumoconiosis, and pulmonary fibrosis. The non-roflumilast-treated group had a greater prevalence of diabetes with complications, renal disease, and metastatic carcinoma.

Significant differences in baseline medication utilization between the roflumilast-treated group and non-roflumilast-treated group were observed across all COPD medication classes and therapy combinations examined (Table 4). Subjects who had been initiated on roflumilast were significantly greater baseline utilizers of COPD medications and therapy combinations compared with their non-roflumilast counterparts. A combination regimen of interest, comprised of ICSs, LABAs, and LAMAs, was used to a far greater extent during the pre-index period by the roflumilast-treated group relative to the non-roflumilast-treated group (50.60% versus 6.75%, respectively, $P<0.0001$).

Significant differences between the roflumilast-treated group and the non-roflumilast-treated group were observed across all forms of pre-index all-cause and COPD-related HCU, with the roflumilast-treated group exhibiting

Table 2 Baseline demographics of subjects initiated on roflumilast and subjects not initiated on roflumilast

Trait	Roflumilast-treated group n=500	Non-roflumilast-treated group n=60,145	*P*-value[a]
Age, years, mean (SD)	69.7 (8.3)	72.3 (9.1)	<0.0001
Age category, n (%)			
40–49	7 (1.40%)	1,064 (1.77%)	<0.0001
50–59	50 (10.00%)	4,711 (7.83%)	
60–69	181 (36.20%)	14,540 (24.17%)	
70–79	204 (40.80%)	26,165 (43.50%)	
80–89	58 (11.60%)	13,665 (22.72%)	
Sex, female, n (%)	271 (54.20%)	33,758 (56.10%)	0.3870
Race/ethnicity, n (%)			
White	451 (90.20%)	52,948 (88.03%)	0.1471
Black	39 (7.80%)	5,265 (8.75%)	
Hispanic	2 (0.40%)	974 (1.62%)	
Other	8 (1.60%)	958 (1.59%)	
Geographic region, n (%)			
Northeast	11 (2.20%)	954 (1.59%)	0.0825
Midwest	111 (22.20%)	13,674 (22.74%)	
South	354 (70.80%)	40,985 (68.14%)	
West	24 (4.80%)	4,532 (7.54%)	
Low income subsidy, n (%)	243 (48.60%)	15,052 (25.03%)	<0.0001

Notes: [a]Continuous variables compared via Wilcoxon rank sum test, categorical variables compared via Chi-square or Fisher's exact test, as appropriate.
Abbreviation: SD, standard deviation.

Table 3 Baseline comorbid conditions of subjects initiated on roflumilast and subjects not initiated on roflumilast

Trait	Roflumilast-treated group n=500	Non-roflumilast-treated group n=60,145	*P*-value[a]
DCCI score, mean (SD)	2.63 (1.84)	2.61 (2.31)	0.8569
Comorbidity, n (%)			
Myocardial infarction	60 (12.00%)	5,956 (9.90%)	0.1182
Congestive heart failure	120 (24.00%)	10,553 (17.55%)	0.0002
Peripheral vascular disease	70 (14.00%)	8,000 (13.3%)	0.6468
Cerebrovascular disease	53 (10.60%)	8,112 (13.49%)	0.0596
Dementia	8 (1.60%)	740 (1.23%)	0.4123
Chronic pulmonary disease	485 (97.00%)	39,431 (65.56%)	<0.0001
Connective tissue disease	23 (4.60%)	3,193 (5.31%)	0.4812
Peptic ulcer disease	11 (2.20%)	1,089 (1.81%)	0.5159
Mild liver disease	7 (1.40%)	606 (1.01%)	0.3623
Diabetes without complications	160 (32.00%)	20,217 (33.61%)	0.4468
Diabetes with complications	27 (5.40%)	7,039 (11.70%)	<0.0001
Paraplegia and hemiplegia	3 (0.60%)	521 (0.87%)	0.8055
Renal disease	64 (12.80%)	11,739 (19.52%)	0.0002
Cancer (including leukemia and lymphoma)	52 (10.40%)	7,146 (11.98%)	0.3078
Moderate or severe liver disease	2 (0.40%)	249 (0.41%)	1.0000
Metastatic carcinoma	1 (0.20%)	820 (1.36%)	0.0175
Acquired immunodeficiency syndrome	2 (0.40%)	98 (0.16%)	0.1997
Respiratory tract cancer	16 (3.20%)	1,490 (2.48%)	0.3011
Cystic fibrosis	0 (0.00%)	24 (0.04%)	1.0000
Fibrosis from tuberculosis	0 (0.00%)	4 (0.01%)	1.0000
Bronchiectasis	31 (6.20%)	1,128 (1.88%)	<0.0001
Pneumoconiosis	16 (3.20%)	1,076 (1.79%)	0.0181
Pulmonary fibrosis	50 (10.00%)	2,693 (4.48%)	<0.0001
Pulmonary tuberculosis	1 (0.20%)	86 (0.14%)	0.5136
Pulmonary sarcoidosis	2 (0.40%)	49 (0.08%)	0.0664

Notes: [a]Continuous variables compared via Wilcoxon rank sum test, categorical variables compared via Chi-square or Fisher's exact test, as appropriate.
Abbreviations: DCCI, Deyo-Charlson Comorbidity Index; SD, standard deviation.

Table 4 Baseline COPD treatment medications of subjects initiated on roflumilast and subjects not initiated on roflumilast

Trait	Roflumilast-treated group n=500	Non-roflumilast-treated group n=60,145	*P*-value[a]
COPD medication class of interest, n (%)[b]			
Short-acting β2-agonists	449 (89.80%)	25,608 (42.58%)	<0.0001
LABA	55 (11.00%)	658 (1.09%)	<0.0001
ICS + LABA combination product	345 (69.00%)	12,629 (21.00%)	<0.0001
Anticholinergics (short-acting)	259 (51.80%)	9,424 (15.67%)	<0.0001
LAMA	308 (61.60%)	7,216 (12.00%)	<0.0001
Methylxanthines	90 (18.00%)	1,404 (2.33%)	<0.0001
Oral/intravenous corticosteroids	446 (89.20%)	34,643 (57.60%)	<0.0001
ICS	99 (19.80%)	3,389 (5.63%)	<0.0001
Antibiotics	477 (95.40%)	53,503 (88.96%)	<0.0001
Long-term oxygen use	330 (66.00%)	10,607 (17.64%)	<0.0001
Combination regimen of interest, n (%)			
ICS + LABA + LAMA combination[c]	253 (50.60%)	4,057 (6.75%)	<0.0001

Notes: [a]Categorical variables compared via Chi-square or Fisher's exact test, as appropriate; [b]not mutually exclusive; [c]ICS + LABA + LAMA combination use indicates that a member utilized each of these drug classes at least once during the pre-index period. Concomitant use was not required. Use of individual drug classes (ICS, LABA, and/or LAMA) is reflected under COPD medication class of interest.

Abbreviations: COPD, chronic obstructive pulmonary disease; LABA, long-acting β-agonist; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist.

greater utilization (Table 5). The lone exception was the use of all-cause outpatient services, where there was no difference between groups in the proportion of members with at least one visit in the pre-index period. Roflumilast-treated subjects were far greater utilizers of COPD-related inpatient services during the pre-index period, as measured by members with at least one visit, compared with the non-roflumilast-treated group (40.80% versus 7.89%, respectively, $P<0.0001$). This finding aligns with more subjects in the roflumilast-treated group experiencing at least one severe pre-index exacerbation (37.40% versus 6.25%, $P<0.0001$) and having a greater mean number of total pre-index exacerbations (6.02 versus 2.13, $P<0.0001$) than subjects with a recent exacerbation but not subsequently initiated on roflumilast (Table 5).

Significant differences between the roflumilast-treated group and the non-roflumilast-treated group were observed across the various pre-index all-cause and COPD-related costs, with the roflumilast-treated group exhibiting greater costs (Table 5). Of note, the subjects who initiated roflumilast following an exacerbation had significantly greater pre-index COPD-related inpatient costs ($7,160 versus $960, $P<0.0001$) and pre-index COPD-related total pharmacy costs ($3,999 versus $714, $P<0.0001$) compared with subjects who did not initiate roflumilast after a recent exacerbation.

HCU and cost outcomes

The only significant HCU, univariate DID between the roflumilast-treated group and non-roflumilast-treated group was found in the mean number of COPD-related hospitalizations per 30 days and in the mean number of COPD-related outpatient visits per 30 days (Table 6). The results of the univariate DID analyses for changes in all-cause health care costs and in COPD-related health care costs are also presented in Table 6. There were no significant univariate DID comparisons for any of the all-cause health care cost measures. The changes in mean COPD-related inpatient costs per 30 days was significantly different between the two groups (−$130, $P=0.0346$). The pre-index mean COPD-related inpatient costs for the roflumilast-treated group were $588 per 30 days (rounded to nearest whole dollar) while the post-index COPD-related inpatient costs were $447 per 30 days. This equates to an absolute change (ie, difference) of −$141. The corresponding absolute change for the non-roflumilast-treated group in mean COPD-related inpatient costs was −$11. The DID in these absolute pre-index to post-index changes was significant ($P=0.0346$) and equal to −$130. Additionally, a significant DID between the roflumilast-treated group and non-roflumilast-treated group was found in outpatient COPD-related costs per 30 days (−$26, $P<0.0001$). While no significant univariate DID comparison was found for mean total COPD-related costs (−$43, $P=0.2580$), the multivariate DID analysis did reveal that the covariate-adjusted pre-index to post-index period change in costs for the roflumilast-treated group was significantly different ($P=0.0005$) and favorable in comparison with the covariate-adjusted change in costs for the non-roflumilast-treated group (parameter estimate, −0.2754; 95% confidence interval [CI], −0.4294, −0.1215).

Table 5 Twelve-month baseline health care utilization, costs, and exacerbation frequency of subjects initiated on roflumilast and subjects not initiated on roflumilast

Measure	Roflumilast-treated group n=500	Non-roflumilast-treated group n=60,145	*P*-value[a]
All-cause hospitalizations			
Members with hospitalization, n (%)	298 (59.60%)	25,672 (42.68%)	<0.0001
Hospitalizations per member, mean (SD)	1.82 (3.46)	1.05 (2.93)	<0.0001
All-cause 30-day readmission			
Members with 30-day readmit, n (%)	93 (18.60%)	7,040 (11.71%)	<0.0001
All-cause ER visits			
Members with visit, n (%)	232 (46.40%)	23,337 (38.80%)	0.0005
Visits per member, mean (SD)	1.55 (3.51)	0.98 (2.31)	<0.0001
All-cause outpatient visits			
Members with visit, n (%)	500 (100.00%)	60,051 (99.84%)	1.0000
Visits per member, mean (SD)	42.21 (29.16)	38.38 (31.54)	<0.0001
COPD-related hospitalizations			
Members with hospitalization, n (%)	204 (40.80%)	4,745 (7.89%)	<0.0001
Hospitalizations per member, mean (SD)	0.90 (1.83)	0.11 (0.52)	<0.0001
COPD-related 30-day readmission			
Members with 30-day readmit, n (%)	40 (8.00%)	434 (0.72%)	<0.0001
COPD-related emergency room visits			
Members with visit, n (%)	87 (17.40%)	1,878 (3.12%)	<0.0001
Visits per member, mean (SD)	0.41 (1.41)	0.05 (0.34)	<0.0001
COPD-related outpatient visits			
Members with visit, n (%)	482 (96.40%)	41,920 (69.70%)	<0.0001
Visits per member, mean (SD)	9.22 (8.56)	2.59 (3.74)	<0.0001
All-cause health care costs, mean (SD)			
Total costs	$33,690.05 ($33,273.90)	$21,967.55 ($30,919.68)	<0.0001
Outpatient-related	$6,283.36 ($6,568.52)	$6,413.58 ($11,178.01)	<0.0001
Inpatient-related	$13,366.39 ($27,547.76)	$8,827.20 ($22,072.91)	<0.0001
ER-related	$790.03 ($1,885.93)	$533.23 ($1,375.83)	<0.0001
Pharmacy costs	$9,319.39 ($8,557.79)	$4,373.33 ($7,738.44)	<0.0001
COPD-related health care costs, mean (SD)			
Total costs	$10,260.01 ($9,767.42)	$1,583.64 ($4,058.56)	<0.0001
Outpatient-related	$898.97 ($1,685.18)	$176.31 ($474.04)	<0.0001
Inpatient-related	$7,160.63 ($15,873.57)	$960.33 ($5,988.98)	<0.0001
ER-related	$226.55 ($769.76)	$26.36 ($213.14)	<0.0001
Pharmacy costs	$3,999.77 ($3,160.50)	$714.27 ($1,503.25)	<0.0001
Exacerbations			
Severe, n (%)	187 (37.40%)	3,760 (6.25%)	<0.0001
Moderate-ER, n (%)	83 (16.60%)	1,752 (2.91%)	<0.0001
Moderate-outpatient by qualifying diagnosis, n (%)	319 (63.80%)	21,213 (35.27%)	<0.0001
Moderate-outpatient by qualifying steroid, n (%)	395 (79.00%)	30,739 (51.11%)	<0.0001
Any severity, n (%)	467 (93.40%)	42,182 (73.13%)	<0.0001
Number per member, mean (SD)	6.02 (5.04)	2.13 (2.84)	<0.0001

Notes: [a]Continuous variables compared via Wilcoxon rank sum test, categorical variables compared via Chi-square or Fisher's exact test, as appropriate. Currency is US dollars.

Abbreviations: SD, standard deviation; ER, emergency room; COPD, chronic obstructive pulmonary disease.

Exacerbation outcomes

Post-index reductions in mean COPD exacerbations per 30 days were seen for both the roflumilast-treated and non-roflumilast-treated groups (Table 6). The univariate DID analyses revealed that the roflumilast-treated group experienced a significantly greater absolute pre-index to post-index reduction in the following exacerbation types, based on mean number of exacerbations per 30 days: overall exacerbations; severe exacerbations; moderate exacerbations presenting in the emergency room; moderate exacerbations presenting to an outpatient facility; and moderate exacerbations prescribed steroid treatment. The multivariate DID analyses for total

Table 6 Univariate difference-in-difference analyses of health care utilization, costs, and exacerbations for roflumilast (n=500) and non-roflumilast (n=60,145) groups

Measure	Roflumilast-treated group			Non-roflumilast-treated group			Roflumilast change minus non-roflumilast change	
	Pre-index period	Post-index period	Change	Pre-index period	Post-index period	Change	DID[a]	*P*-value[b]
All-cause utilization per 30 days, mean (SD)								
Hospitalizations	0.1494 (0.2842)	0.1239 (0.2121)	−0.0255 (0.2264)	0.0866 (0.2410)	0.0792 (0.2441)	−0.0074 (0.2255)	−0.0181	0.0762
ER visits	0.1277 (0.2882)	0.1023 (0.2041)	−0.0254 (0.2262)	0.0807 (0.1902)	0.0657 (0.1579)	−0.0149 (0.1646)	−0.0105	0.3017
Outpatient visits	3.4692 (2.3965)	2.5558 (2.0372)	−0.9133 (1.9193)	3.1545 (2.5924)	2.4014 (2.1859)	−0.7531 (2.0756)	−0.1603	0.0637
COPD-related utilization per 30 days, mean (SD)								
Hospitalizations	0.0740 (0.1503)	0.0557 (0.1093)	−0.0182 (0.1444)	0.0092 (0.0426)	0.0079 (0.0391)	−0.0013 (0.0441)	−0.0169	0.009
ER visits	0.0335 (0.1159)	0.0254 (0.0904)	−0.0081 (0.1153)	0.0040 (0.0277)	0.0035 (0.0244)	−0.0005 (0.0318)	−0.0076	0.1434
Outpatient visits	0.7575 (0.7032)	0.5075 (0.4967)	−0.2500 (0.6264)	0.2129 (0.3073)	0.1523 (0.2519)	−0.0606 (0.2945)	−0.1894	<0.0001
All-cause costs per 30 days, mean (SD)								
Total costs	$2,769 ($2,734)	$2,484 ($2,883)	−$284 ($3,054)	$1,805 ($2,541)	$1,437 ($2,196)	−$367 ($2,563)	$84	0.5422
Outpatient-related costs	$516 ($539)	$404 ($530)	−$111 ($549)	$527 ($918)	$396 ($722)	−$130 ($844)	$19	0.4513
Inpatient-related costs	$1,098 ($2,264)	$1,072 ($2,366)	−$26 ($2,808)	$725 ($1,814)	$606 ($1,591)	−$119 ($2,122)	$93	0.4602
ER-related costs	$64 ($155)	$55 ($117)	−$9 ($137)	$44 ($113)	$36 ($91)	−$8 ($115)	−$1	0.8470
Pharmacy costs	$765 ($703)	$654 ($665)	−$111 ($497)	$359 ($636)	$269 ($513)	−$90 ($389)	−$21	0.3385
COPD-related costs per 30 days, mean (SD)								
Total costs	$843 ($802)	$780 ($797)	−$62 ($850)	$130 ($333)	$110 ($280)	−$19 ($314)	−$43	0.2580
Outpatient-related costs	$74 ($52)	$43 ($119)	−$ 31 ($52)	$14 ($38)	$9 ($25)	−$4 ($40)	−$26	<0.0001
Inpatient-related costs	$588 ($1,304)	$447 ($1,015)	−$141 ($1,371)	$78 ($492)	$67 ($462)	−$11 ($593)	−$130	0.0346
ER-related costs	$18 ($63)	$14 ($53)	−$4 ($63)	$2 ($17)	$2 ($15)	$0 ($20)	−$4	0.1529
Pharmacy costs	$328 ($259)	$330 ($250)	$2 ($203)	$58 ($123)	$51 ($105)	−$7 ($70)	$9	0.2840
Exacerbations per 30 days, mean (SD)								
Number of exacerbations	0.4955 (0.4144)	0.3382 (0.3006)	−0.1573 (0.3407)	0.1753 (0.2337)	0.1215 (0.1815)	−0.0538 (0.1819)	−0.1035	<0.0001
Number of severe exacerbations	0.0593 (0.1121)	0.0451 (0.0866)	−0.0143 (0.1064)	0.0068 (0.0313)	0.0056 (0.0261)	−0.0011 (0.0327)	−0.0131	0.0060
Number of moderate exacerbations, ER	0.0237 (0.0790)	0.0145 (0.0447)	−0.0091 (0.0693)	0.0029 (0.0185)	0.0024 (0.0155)	−0.0005 (0.0208)	−0.0087	0.0055
Number of moderate exacerbations, OP	0.1373 (0.1847)	0.0829 (0.1167)	−0.0544 (0.1517)	0.0487 (0.0878)	0.0318 (0.0646)	−0.0169 (0.0888)	−0.0375	<0.0001
Number of moderate exacerbations, steroid	0.2752 (0.3217)	0.1957 (0.2360)	−0.0794 (0.2611)	0.1169 (0.2053)	0.0816 (0.1556)	−0.0353 (0.1562)	−0.0442	0.0002

Notes: [a]Roflumilast-treated group mean difference minus non-roflumilast-treated group mean difference; positive DID values favor non-roflumilast-treated group; [b]*t*-test, unequal variances assumed. Currency is US dollars.
Abbreviations: DID, difference-in-difference; SD, standard deviation; ER, emergency room; COPD, chronic obstructive pulmonary disease; OP, outpatient.

number of exacerbations and number of severe exacerbations support the corresponding univariate findings. The covariate-adjusted pre-index to post-index period change in mean number of total exacerbations for the roflumilast-treated group was significantly different ($P<0.0001$) and favorable in comparison with the covariate-adjusted change in costs for the non-roflumilast-treated group (parameter estimate, –0.1299; 95% CI –0.1930, –0.0669). The covariate-adjusted reduction in mean number of severe exacerbations for the roflumilast-treated group exhibited a borderline significant difference ($P=0.0582$) and favorable comparison with the covariate-adjusted change in severe exacerbations for the non-roflumilast-treated group (parameter estimate, –0.1801; 95% CI –0.3664, 0.0062).

Discussion

Roflumilast, an anti-inflammatory phosphodiesterase-4 inhibitor, has been shown in clinical trials to reduce exacerbation rates and improve lung function in patients with COPD.[11,12,18] A post hoc analysis revealed that the mean annual exacerbation rate in patients with very severe COPD (GOLD stage IV) a mean age of 65 years, and treated with roflumilast was 36% lower than in patients treated with placebo (1.01 versus 1.59 mean exacerbations per year, respectively, $P=0.024$).[19] Further, a post hoc analysis of patients with GOLD stage III–IV disease found that treatment with roflumilast shifts patients from a baseline frequent exacerbator state (defined as two or more events per year) to a less frequent exacerbation state (zero or one events).[20] While the necessity of targeting roflumilast to subgroups of COPD patients with a greater likelihood of treatment benefit is evident,[21] there is little information regarding the use of roflumilast in actual clinical practice. In this study, the authors examined the baseline characteristics of a predominantly elderly Medicare beneficiary population with at least one exacerbation in the year prior to roflumilast initiation. Patient characteristics, 12-month post-initiation HCU, costs, and exacerbation occurrence in this roflumilast population were contrasted with a non-roflumilast population also with a recent exacerbation.

Several key findings are noted when contrasting the post-initiation HCU, costs, and exacerbation occurrence of the roflumilast-treated group with the non-roflumilast-treated group. Mean 30-day, all-cause total health care costs decreased post-index for both the roflumilast-treated and non-roflumilast-treated groups. However, there were no significant DID comparisons for any of the all-cause health care cost measures. Similarly, while within-group decreases in all-cause HCU were observed for both the roflumilast-treated group and the non-roflumilast-treated group, no significant DID comparisons for any of the all-cause utilization measures were identified. Conversely, mean COPD-related inpatient hospitalizations per 30 days and COPD-related outpatient visits per 30 days displayed a significant DID favorable to the roflumilast-treated group. For example, in the roflumilast-treated group, the pre-index mean number of COPD-related outpatient visits per 30 days was 0.7575 (approximately one visits per 40 days) while the post-index mean per 30 days was 0.5075 (approximately one visits per 60 days). This equates to an absolute change (ie, difference) of –0.2500, with a negative value indicating clinical improvement. The corresponding absolute change for the non-roflumilast-treated group in mean COPD-related outpatient visits per 30 days was –0.0606. The DID in these absolute pre-index to post-index changes was significant ($P<0.0001$) and equal to –0.1894 (roflumilast change minus non-roflumilast change), with the negative value favorable to the roflumilast-treated group. The HCU findings align with the only significant DID cost comparisons found, ie, mean 30-day COPD-related inpatient costs and mean 30-day COPD-related outpatient costs.

Post-index reductions in mean COPD exacerbations per 30 days, of all severities, were seen for both the roflumilast-treated and non-roflumilast-treated groups. The roflumilast-treated group experienced a significantly greater absolute pre-index to post-index reduction in all exacerbation types, with the exception of those defined by antibiotic use. For example, in the roflumilast-treated group, the pre-index mean number of overall exacerbations per 30 days was 0.4955 (approximately one exacerbation of any severity every 45 days) while the post-index mean per 30 days was 0.3382 (approximately one exacerbation of any severity every 65 days). This equates to an absolute change (ie, difference) of –0.1573, with a negative value indicating clinical improvement. The corresponding absolute change for the non-roflumilast-treated group in mean number of overall exacerbations per 30 days was –0.0538. The DID in these absolute pre-index to post-index changes was significant ($P<0.0001$) and equal to –0.1035 (roflumilast change minus non-roflumilast change), with the negative value favorable to roflumilast. This finding, as with the utilization and cost findings, is tempered by the likelihood that the non-roflumilast-treated group had less severe COPD relative to the roflumilast-treated group and any post-index change in therapy amongst the non-roflumilast-treated group was not assessed. However, the desired directional decrease in the

majority of exacerbation types for the roflumilast-treated group was observed and in accordance with previous findings in severe to very severe COPD patients initiated on roflumilast.[18,20]

An inherent challenge in retrospective administrative claims analysis of roflumilast use, and comparative effectiveness research in general,[22] is the difficulty in identifying an appropriate comparator group. This challenge is reflected in the lack of peer-reviewed, retrospective, administrative claims-based cost studies comparing roflumilast with different treatment regimens. Published economic evaluations of roflumilast are model-based[23–25] or were conducted in parallel with prospective clinical trials.[26] This challenge applies to the aforementioned univariate analyses of the present study and manifests in two ways, ie, determination of and comparator group selection by COPD severity and comorbidity burden. While administrative claims can provide information on key variables indicative of COPD severity, such as severity of baseline exacerbations and frequency and HCU, it cannot provide several variables that are recommended for use in the clinical setting to assign disease severity and guide treatment decisions. Such variables include smoking status, airflow limitations (as measured by forced expiratory volume in one second), and patient-reported outcomes such as symptom frequency and severity, all of which are key variables utilized in the most recent GOLD treatment guidelines.[9] Secondly, comparator selection based on similar concomitant disease states, while amenable to administrative claims analyses, is challenging when the treatment group consists of roflumilast-treated, likely severe COPD patients. For example, a higher incidence of CHF was found in the roflumilast-treated group compared with the non-roflumilast-treated group (24.0% versus 17.6%, respectively, $P<0.0002$). The incidence rate in both groups is similar to findings (11%–52%) in other studies.[27] Both CHF and COPD are chronic progressive diseases complicated by exacerbations. CHF may manifest both obstructive and restrictive ventilatory defects, thereby amplifying or masking the characteristic airflow limitation of COPD.[27] The favorability in COPD-related outcome measures, relative to the all-cause outcome measures, for roflumilast treatment compared with non-roflumilast treatment as found in the univariate DID analyses may be due to the presence of comorbid conditions, such as CHF, that independently require high levels of HCU and costs.[28]

With the aforementioned challenge in mind and in an effort to validate the univariate DID findings, multivariate models adjusted for pre-index concomitant disease (eg, CHF) and available COPD severity markers (eg, use of inhaled steroids, oxygen therapy), as well as other baseline covariates, were applied to total COPD-related costs, number of total exacerbations, and number of severe exacerbations. The multivariate DID models largely validated the corresponding univariate analyses of these three outcome measures, because the roflumilast-treated group in comparison with the non-roflumilast-treated group exhibited a statistically significant ($P<0.0001$) greater pre-index to post-index decrease in number of total exacerbations and a borderline statistically significant ($P=0.0582$) greater pre-index to post-index decrease in number of severe exacerbations. While the univariate DID found no significant difference in COPD-related costs between the two groups, the multivariate DID exhibited a statistically significant ($P=0.0005$) greater pre-index to post-index decrease for the roflumilast-treated group compared with the non-roflumilast-treated group. The multivariate DID findings, combined with the univariate findings, of this real-world roflumilast utilization and COPD outcomes study align with prior clinical trial-based studies that found roflumilast to significantly decrease COPD exacerbations[11,12,18] and health care costs.[26] This study also substantiates other real-world studies utilizing administrative claims data that have shown roflumilast to either significantly decrease[29,30] or trend toward a significant decrease[31] in exacerbations, health care costs, or HCU. The value of these findings for health care decision-makers lies in the ability to discern changes in COPD resource utilization and costs compared with overall HCU and costs. Further, these findings provide further insight into the beneficial impact of roflumilast in a predominantly elderly population with severe COPD. Ongoing clinical trials will further assess the benefits of roflumilast, as an addition to other standards of therapy, in patients with severe COPD and frequent exacerbations.[32]

Several limitations to this study, in addition to those already discussed, are worth noting. While multivariate regression modeling was utilized to reduce selection bias or strengthen any causal inferences, its ability to do so is limited to the covariates included in the model. As with all claims-based studies, the validity of subject identification and diagnostic classification, as well as the identification of disease-related utilization and costs, may be impacted by provider, region, or site-specific coding practices.

Conclusion

This study describes a predominantly elderly Medicare population with recent exacerbation who had been initiated on roflumilast. This population displayed several

baseline characteristics that coincide with a severe COPD population including, but not limited to, a high utilization rate of ICS/LABA/LAMA combination therapy, frequent hospitalizations, and frequent exacerbations. Univariate analyses of 12-month post-initiation of roflumilast revealed decreases in exacerbations and some markers of HCU, notably severe exacerbations requiring hospitalization. Multivariate analyses identified statistically significant improved outcomes for roflumilast patients compared with non-roflumilast patients for COPD-related costs and number of total exacerbations. These findings align with and/or augment prior clinical trials and real-world studies that also found favorable outcomes for roflumilast compared with alternative standards of care. Future research should endeavor to identify methods to combine the robust patient populations found via administrative claims-based research and validated COPD severity assessments found in patient-reported outcomes methodologies, as well as further explore the HCU effects of CHF in patients with COPD.

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Disclosure

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ORIGINAL RESEARCH

Lower 30-day readmission rates with roflumilast treatment among patients hospitalized for chronic obstructive pulmonary disease

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Background: Few data exist related to the impact of roflumilast on health care utilization. This retrospective study estimated 30-day hospital readmission rates between patients who did and did not use roflumilast among those with COPD hospitalizations.

Methods: Data were from MarketScan, a large US commercial health insurance claims database. Patients aged ≥40 years with at least one hospitalization for COPD between 2010 and 2011 were included. The roflumilast group included patients who used roflumilast within 14 days after the first hospitalization (index), while the comparison group (non-roflumilast) included patients who did not use roflumilast during the study period. Continuous enrollment for at least 6 months before and 30 days after the index date was required. The 30-day hospitalization rate was calculated after the index hospitalization. Conditional logistic regression with propensity score 1:3 matching was employed to assess the difference in 30-day hospital readmission rates between the roflumilast and non-roflumilast groups, adjusting for baseline characteristics, comorbidity, health care utilization, and COPD medication use within 14 days after the index date.

Results: A total of 15,755 COPD patients met the selection criteria, ie, 366 (2.3%) in the roflumilast group and 15,389 (97.7%) in the non-roflumilast group. The mean (± standard deviation) age was 71±12.5 years and 52% were female. After propensity score matching, all-cause 30-day hospitalization rates were 6.9% and 11.1% in the roflumilast and non-roflumilast groups, respectively. COPD-related 30-day hospitalization rates were 6.3% and 9.2% in the roflumilast and non-roflumilast groups, respectively. Conditional logistic regression identified a significantly lower likelihood of all-cause 30-day readmission (odds ratio 0.59, 95% confidence interval 0.37–0.93, P=0.023) for roflumilast patients relative to non-roflumilast patients.

Conclusion: This study showed, in a real-world setting, that use of roflumilast was associated with a lower rate of hospital readmission within 30 days among patients hospitalized for COPD.

Keywords: chronic obstructive pulmonary disease, roflumilast, health care utilization, hospital readmission

Introduction

COPD is a progressive lung condition characterized by persistent airflow limitation, chronic and progressive dyspnea, cough, and sputum production, and is often complicated by exacerbations.[1] COPD affects approximately 24 million US adults, including 12 million diagnosed patients and 12 million undiagnosed,[2] and is the third leading cause of death in the USA.[3] The annual cost of COPD was estimated at $49.9 billion in 2010, with $29.5 billion attributable to direct health care costs, in which hospital care cost accounted for the largest share of the total.[2]

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Reducing COPD exacerbations is an important goal of COPD management, given that exacerbations have serious health consequences and are associated with declines in lung function, reduction in health-related quality of life, and increased hospitalization and mortality.[4] Exacerbation is also one of the primary reasons for the significant economic burden of COPD, as it accounts for up to 45% of the total cost for treating COPD.[4,5] Roflumilast, an oral, once-daily, selective phosphodiesterase-4 inhibitor that reduces moderate and severe exacerbation rates and improves lung function in patients with COPD,[6,7] is indicated as a treatment to reduce the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It was approved by the US Food and Drug Administration (FDA) in February 2011.[8,9]

To better understand the medical care utilization associated with use of roflumilast in the real-world setting, we conducted a retrospective cohort study to compare all-cause and COPD-related hospital readmission rates within 30 days between patients who used roflumilast and those who did not.

Materials and methods

Data source

This study used longitudinal, integrated medical and pharmacy claims data from MarketScan databases: Commercial Claims and Encounters (Commercial) and the Medicare Supplemental and Coordination of Benefits (Medicare Supplemental). The MarketScan database includes patient-level, paid and adjudicated medical and pharmacy claims histories of 110 million covered lives belonging to 12 national and regional health plans in the USA.[10,11] The database captures the full continuum of care in all settings, including physician office visits, hospital stays, and outpatient pharmacy claims. These data are a good representation of the US national, commercially insured population and those who have both Medicare coverage and supplemental employer-sponsored coverage.

In the MarketScan database, each medical service claim has its date of service, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and procedure codes. There is also the National Drug Code and days of medication therapy supplied information available for pharmacy records. The date-of-service variable is important to identify temporal relationship and define medication treatments.

Study design

This was a retrospective matched-cohort study using the MarketScan claims database. We included patients aged 40 years or older with at least one hospitalization for COPD, identified as inpatient claims with a COPD diagnosis (ICD-9-CM 491, 492, or 496).[7] The roflumilast patient group was defined as those who had the drug within the first 14 days after the hospitalization for COPD, with the discharge date defined as the index date between July 1 and December 31, 2011. We selected a historic comparison group (non-roflumilast patients), defined as hospitalization for COPD with discharge date (index date) between July 1 and December 31, 2010. Because roflumilast was approved by the FDA in February 2011,[8,9] this approach ensures that the comparison group received no roflumilast treatment following hospitalizations during the study period. The reason we applied a historic comparison group was to reduce confounding by indication, as roflumilast is indicated for exacerbations in patients with severe COPD.[7]

Continuous enrollment of at least 6 months before and 30 days after the index date was required. We excluded patients with cystic fibrosis (ICD-9-CM 277.0x) or lung cancer (ICD-9-CM 162.xx) within the 6 months before the index date (baseline). To minimize misclassification bias, we also excluded patients with hospital readmission prior to their use of roflumilast.

Variables

We calculated all-cause and COPD-related hospitalization readmission rates within 30 days after the index date. In order to reduce sample selection bias, we adjusted for a list of covariates using a propensity score matching approach. The adjusted covariates included patient demographics, clinical characteristics, and health care utilization at baseline and COPD medication use within a 14-day follow-up period after the index date. Demographic variables included age, sex, geographic region, rural/urban setting, and type of health insurance (Medicare or not). The geographic regions were northeast, north central, west, and south. To control for comorbidities, a Charlson Comorbidity Index[12] was constructed for each subject based on the ICD-9-CM diagnosis codes of all claims within the 6 months before the index date. We excluded patients with moderate to severe liver disease because roflumilast is specifically contraindicated in these patients and this condition is a category included in the original Charlson Comorbidity Index. We also identified comorbid asthma (ICD-9-CM 493.xx) to further account for this clinically related condition.

To adjust for disease severity, we calculated variables for COPD exacerbations including the total number of severe exacerbation events and the proportion of patients who

experienced moderate exacerbations within the 6-month baseline period. Exacerbations were identified using medical and pharmacy claims following Lindenauer et al and Mapel et al.[13,14] A severe exacerbation was defined as a hospital admission for a primary COPD diagnosis with acute exacerbation (ICD-9-CM codes 491.21, 491.22, 493.22, 492.8), or a primary diagnosis of respiratory failure (518.81, 518.82, 518.84) combined with a secondary diagnosis of COPD with acute exacerbation or emphysema (491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, or 496).[13] A moderate exacerbation was identified by: an emergency room visit with the same diagnosis codes as severe exacerbation; at least one medical claim for diagnosis codes of 136.3, 466–466.19, 480–486, 487.0, 490, 491.21, 491.22, 493.02, 493.12, 493.22, 493.92, 494.1, 506.0–506.3, 507–507.8, 511.0–511.1, 512–512.8, 517.1, 518.0, 518.81, 518.82, 518.84, and 770.84 in a physician office or outpatient non-emergency room visit;[14] at least one pharmacy claim for systemic steroids; or at least one pharmacy claim for oral antibiotics commonly used for respiratory infections.

Health care utilization was summarized for each subject, including numbers of all medical service (non-COPD specific) and COPD-related utilizations. Each category included numbers for inpatient, emergency room, outpatient visits, and COPD medications within the 6-month baseline period. COPD medication variables were defined as numbers of medications including long-acting β_2-agonists, long-acting muscarinic antagonists, inhaled corticosteroids, inhaled corticosteroid-long-acting β_2-agonist combinations, or theophylline. Numbers of COPD medication by type were also summarized for the 14 days after the index date, and were adjusted for the propensity score analysis.

Statistical analysis

Patient demographics, clinical characteristics, health care utilization, and the 30-day post-index hospital readmission rate were compared between the roflumilast cohort and the comparison cohort (non-roflumilast patients). Continuous variables are reported as the mean ± standard deviation; categorical variables are summarized as percentages. Comparisons were made using appropriate statistical tests (Student's *t*-test for continuous data and Chi-square or Fisher's Exact test for categorical data).

To better balance the characteristics between the roflumilast-treated group and the non-roflumilast comparison group, we used the propensity score matching approach. Variables in the propensity score predictive equation included all patient demographics, clinical characteristics, and health care utilization. We used the greedy matching algorithm[15] to create the 1:3 matched roflumilast-treated and comparison groups. The matched subsamples were used as the final analytic dataset. We applied conditional logistic regressions to evaluate the odds of having post-index all-cause and COPD-related hospital readmissions between the roflumilast and non-roflumilast groups. Conditional logistic regression is used to take into consideration the quadruplets of patients after matching (every roflumilast-treated patient matched with three non-roflumilast comparison patients).[16]

Results

Table 1 gives the descriptive comparison of characteristics between patients with and without roflumilast before and after the propensity score matching. Based on the inclusion criteria, a total of 15,755 COPD patients, including 366 (2.3%) roflumilast and 15,389 (97.7%) non-roflumilast patients, were selected. Roflumilast patients were younger (mean 68±10.9 versus 72±11.4 years), with a higher percentage from the Southern US region (37% versus 29%), and a lower percentage under Medicare insurance (53% versus 71%) relative to non-roflumilast patients. Roflumilast patients were more likely to have asthma (30% versus 17%) and more severe COPD, represented by severe exacerbation frequency (0.45 versus 0.12) and moderate exacerbation (85% versus 58%) compared with non-roflumilast patients. Health care utilization variables showed that roflumilast patients used more medical services than non-roflumilast patients within the 6-month baseline period (all-cause hospitalizations [0.71 versus 0.44], all-cause ER visits [0.91 versus 0.26], all-cause outpatient visits [20 versus 18], COPD-related hospitalizations [0.58 versus 0.21], COPD-related emergency room visits [0.86 versus 0.24], and COPD-related outpatient visits [9.0 versus 4.6]). Roflumilast patients also used more COPD medications both within the 6-month baseline period and the 14-day post-index period. Numbers of these medications were included in the propensity score matching and were presented in Table 1. Percentages of use for these medications were not included in matching and were presented in Table S1.

Propensity score matching resulted in balanced groups in terms of these measured characteristics (Table 1). All of the variables that had statistically significant differences before matching had no significant differences after matching. Roflumilast patients on average had roflumilast 5.8±4.8 days after their index hospital discharge. The number of days from the index discharge to hospital readmission was not significantly different between roflumilast and non-roflumilast patients (16.5±8.1 and 13.3±8.3, respectively, P=0.10) among those

Table 1 Patient characteristics between roflumilast-treated group and comparison group

	Before matching			After matching		
	Roflumilast	**Non-roflumilast**	***P*-value**	**Roflumilast**	**Non-roflumilast**	***P*-value**
n	366	15,389		350	1,050	
Baseline characteristics						
Age at index date, years, mean ± SD	67.9±10.9	71.5±11.4	<0.0001	68.2±11.1	68.2±11.5	0.95
Female	54.4%	52.9%	0.58	54.0%	53.4%	0.85
Rural (versus urban)	20.5%	18.9%	0.33	20.9%	21.1%	0.91
Geographic region						
Northeast	17.5%	18.1%	<0.0001	16.0%	17.0%	0.06
North central	32.8%	38.3%		34.0%	32.5%	
South	37.2%	29.1%		37.4%	39.8%	
West	10.4%	14.3%		10.6%	10.4%	
Medicare insurance	52.7%	70.8%	<0.0001	54.6%	55.3%	0.80
CCI	1.899	2.257	<0.0001	1.897	1.846	0.55
Asthma	29.5%	17.0%	<0.0001	28.0%	29.3%	0.63
Severe exacerbation frequency per patient	0.45	0.12	<0.0001	0.38	0.41	0.59
Moderate exacerbation (yes/no)	85.2%	57.5%	<0.0001	84.6%	88.0%	0.10
COPD medications within 6-month baseline period						
LABAs (n)	0.38	0.06	<0.0001	0.35	0.25	0.18
LAMAs (n)	1.64	0.49	<0.0001	1.53	1.47	0.62
ICS (n)	0.49	0.19	<0.0001	0.42	0.40	0.81
ICS-LABA combinations (n)	1.49	0.58	<0.0001	1.40	1.41	0.89
Theophylline medications	0.33	0.09	<0.0001	0.30	0.26	0.55
Health care utilization within 6-month baseline period						
COPD-related inpatient visits (n)	0.58	0.21	<0.0001	0.50	0.52	0.76
COPD-related ER visits (n)	0.86	0.24	<0.0001	0.65	0.72	0.54
COPD-related outpatient visits (n)	9.03	4.64	<0.0001	8.47	8.50	0.96
All medical service inpatient visits (n)	0.71	0.44	<0.0001	0.63	0.65	0.79
All medical service ER visits (n)	0.91	0.26	<0.0001	0.70	0.77	0.53
All medical service outpatient visits (n)	19.81	17.57	0.007	19.30	19.61	0.74
COPD medications within 14 days after the index date						
LABAs (n)	0.05	0.01	<0.0001	0.05	0.03	0.36
LAMAs (n)	0.26	0.07	<0.0001	0.23	0.22	0.66
ICS (n)	0.09	0.03	0.0001	0.09	0.07	0.52
ICS-LABA combinations (n)	0.24	0.09	<0.0001	0.23	0.24	0.73
Theophylline medications (n)	0.07	0.01	<0.0001	0.07	0.05	0.44

Note: The data are presented as the mean or percentage, before and after 1:3 propensity score matching.
Abbreviations: CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ER, emergency room; SD, standard deviation; LABAs, long-acting β_2-agonists; LAMAs, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

who were readmitted. The all-cause hospital readmission rate within 30 days was significantly lower for roflumilast patients than for non-roflumilast patients (6.9% versus 11.1%, *P*=0.021) within the propensity score matched sample. The COPD-related hospital readmission rate was lower, but did not reach statistical significance (6.3% versus 9.2%, *P*=0.086).

Conditional logistic regression results for the propensity score matched sample are reported in Table 2. Roflumilast patients had a lower likelihood of all-cause hospital readmission within 30 days than non-roflumilast patients (odds ratio 0.59, 95% confidence interval 0.37–0.93, *P*=0.023). The regression result for 30-day COPD-related hospital

Table 2 Conditional logistic regressions for all-cause or COPD-related hospitalization within 30 days among the propensity score matched sample (n=1,400)

	Odds ratio	**95% CI**	***P*-value**
All-cause hospitalization within 30 days	0.59	0.37–0.93	0.023
COPD-related hospitalization within 30 days	0.66	0.41–1.07	0.089

Notes: Each row represents a separate regression. Independent variable of interest is roflumilast-treated (versus non-treated).
Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence interval.

readmission shows the same trend, but is not statistically significant (odds ratio 0.66, 95% confidence interval 0.41–1.07, *P*=0.089).

Discussion

This study estimated, in a real-world setting, that use of roflumilast is associated with a lower likelihood of all-cause 30-day hospital readmission for patients who were previously hospitalized for COPD. Our study is one of the first to focus on health care utilization outcomes for patients with roflumilast in a commercially insured US population.

Exacerbations of COPD are major clinical events that are associated with hospitalization and risk of dying.[4] Many exacerbations require hospitalization, and account for a large share of health care expense for COPD patients.[2] Roflumilast is an anti-inflammatory medication that improves lung function in patients with COPD. In clinical trials, roflumilast reduces the frequency of exacerbations in patients with severe airway obstruction, clinical features of chronic bronchitis, and a history of exacerbations.[6,7,17] It is also recommended as a second or alternative choice combined with a long-acting bronchodilator in COPD patients at high risk for hospitalization.[18] Thus, it is sensible to infer that roflumilast may reduce exacerbation-related hospitalizations. However, the evidence from clinical trials may not represent the community population. Results from a pooled data analysis of trials indicated that roflumilast leads to reduction in severe exacerbations, and possibly related hospitalizations.[19] Another review paper concluded that roflumilast did not reduce the frequency of hospitalization for exacerbations, even in the most favorable trials.[20] On the other hand, trial results may lack generalizability because they typically enroll a relatively healthier patient population (patients with comorbid conditions are commonly excluded from trials) compared with general practice. Our study fills this research gap by providing real-world empirical results as supportive evidence in a large, national, commercially insured US population and those who have Medicare coverage or supplemental employer-sponsored coverage.

We identified that use of roflumilast is associated with lower likelihood of all-cause 30-day hospital readmission. However, the results for COPD-related readmission did not reach statistical significance, although there was a trend for a decreased rate with roflumilast use. This is primarily due to the shorter time and limited data available after FDA approval for roflumilast when we conducted the analysis. This resulted in a small sample for the roflumilast group. Analysis based on more recent data should provide a larger sample size.

Our analysis has several strengths. First, our data are from a geographically diverse population covered by large employer-sponsored private health insurance programs in the USA,[10] which makes our study results more generalizable to community practice than trials. Second, the MarketScan data are contributed by employers. As long as these patients remain with the same employer, the data capture the full continuum of care and claims in all settings, even though the patients might switch their health plans. An individual usually stays longer with an employer than with a health insurance plan. Third, we applied a historic comparison group to reduce confounding by indication, as roflumilast is indicated for exacerbations in patients with severe COPD.[7] Additionally, we selected the comparison group from the same calendar months (July to December) as the roflumilast group in order to minimize the seasonal effect linked to respiratory conditions such as COPD.[21,22]

Some limitations of the study should also be noted. First, we defined roflumilast use within 14 days after inpatient discharge to allow a period of time between use of roflumilast and hospital readmission within 30 days. Our results are also limited to those who survived at least 30 days after a COPD hospital discharge. Patients who started roflumilast after 14 days, died within 30 days, or had follow-up data for less than 30 days were excluded from our study. By design, roflumilast patients could not have been readmitted prior to their first roflumilast prescription (within first 14 days post-discharge), while non-roflumilast patients did not need to meet any prescription requirement within the first 14 days post-discharge. This may lead to immortal time bias.[23] Nonetheless, this bias is not a concern here because the number of days from the index discharge to hospital readmission was not significantly different between roflumilast and non-roflumilast patients. Second, COPD exacerbations are events in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum production that is beyond normal day-to-day variations.[24] Due to the absence of a clinical measure of COPD exacerbation severity and lung function in the claims dataset, we defined exacerbation following Lindenauer et al and Mapel et al.[13,14] Third, information on patient race/ethnicity, education, income, and clinical measures such as laboratory values were not recorded in the claims database. Not controlling for these unmeasured covariates may lead to biased estimates for the effect of roflumilast on readmission rate. Fourth, all identified medical conditions were based on ICD-9 diagnosis codes in medical claims. Medical conditions not recorded in the claims (such as under-diagnosis) cannot be identified.

Meanwhile, consumption of medication was assessed using the pharmacy claims record. Whether a patient actually took the medication cannot be confirmed. Finally, there is no way to identify whether our patients participated in clinical trials involving roflumilast, which could lead to misclassification bias, although such a chance should be low.

In summary, our study showed, in a real-world setting, that use of roflumilast is associated with a lower 30-day hospital readmission rate in patients hospitalized for COPD. Such results complement the clinical trials by providing health care utilization outcomes at the population level. Pharmacotherapies such as roflumilast may be an effective option to decrease hospitalizations for patients with COPD exacerbations.

Disclosure

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Supplementary material

Table S1 Additional patient characteristics that are not included in the propensity score matching

	Before matching			After matching		
	Roflumilast	**Non-roflumilast**	***P*-value**	**Roflumilast**	**Non-roflumilast**	***P*-value**
n	366	15,389		350	1,050	
COPD medications within 6-month baseline period						
LABA use	11.5%	2.5%	<0.0001	11.1%	8.0%	0.07
LAMA use	58.2%	20.3%	<0.0001	56.9%	45.7%	0.05
ICS use	18.9%	9.5%	<0.0001	18.0%	15.9%	0.36
ICS-LABA combination use	59.8%	25.8%	<0.0001	58.9%	49.3%	0.12
Theophylline	12.0%	3.5%	<0.0001	12.0%	8.6%	0.06
COPD medications within 14 days after the index date						
LABAs	5.5%	0.7%	<0.0001	4.6%	3.3%	0.28
LAMAs	25.4%	6.8%	<0.0001	23.1%	22.0%	0.66
ICS	8.5%	2.7%	<0.0001	8.3%	6.8%	0.34
ICS-LABA combination	23.2%	8.3%	<0.0001	22.3%	23.1%	0.74
Theophylline	6.6%	1.2%	<0.0001	6.6%	5.2%	0.35

Abbreviations: COPD, chronic obstructive pulmonary disease; LABAs, long-acting β_2-agonists; LAMAs, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial

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Summary

Background Macrolide resistance is an increasing problem; there is therefore debate about when to implement maintenance treatment with macrolides in patients with chronic obstructive pulmonary disease (COPD). We aimed to investigate whether patients with COPD who had received treatment for three or more exacerbations in the previous year would have a decrease in exacerbation rate when maintenance treatment with azithromycin was added to standard care.

Methods We did a randomised, double-blind, placebo-controlled, single-centre trial in the Netherlands between May 19, 2010, and June 18, 2013. Patients (≥18 years) with a diagnosis of COPD who had received treatment for three or more exacerbations in the previous year were randomly assigned, via a computer-generated randomisation sequence with permuted block sizes of ten, to receive 500 mg azithromycin or placebo three times a week for 12 months. Randomisation was stratified by use of long-term, low-dose prednisolone (≤10 mg daily). Patients and investigators were masked to group allocation. The primary endpoint was rate of exacerbations of COPD in the year of treatment. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00985244.

Findings We randomly assigned 92 patients to the azithromycin group (n=47) or the placebo group (n=45), of whom 41 (87%) versus 36 (80%) completed the study. We recorded 84 exacerbations in patients in the azithromycin group compared with 129 in those in the placebo group. The unadjusted exacerbation rate per patient per year was 1·94 (95% CI 1·50–2·52) for the azithromycin group and 3·22 (2·62–3·97) for the placebo group. After adjustment, azithromycin resulted in a significant reduction in the exacerbation rate versus placebo (0·58, 95% CI 0·42–0·79; p=0·001). Three (6%) patients in the azithromycin group reported serious adverse events compared with five (11%) in the placebo group. During follow-up, the most common adverse event was diarrhoea in the azithromycin group (nine [19%] patients *vs* one [2%] in the placebo group; p=0·015).

Interpretation Maintenance treatment with azithromycin significantly decreased the exacerbation rate compared with placebo and should therefore be considered for use in patients with COPD who have the frequent exacerbator phenotype and are refractory to standard care.

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See Comment page 340

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Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) have important implications for the natural course of COPD and cause high mortality rates in patients with COPD.[1] Patients with three or more exacerbations for which hospital admission is needed have a risk of mortality that is four times higher than those with no exacerbations.[2] Prevention of exacerbations is therefore an essential strategy, not only for improvement of mortality rates, but also for improvement of health-related quality of life[3] and deceleration of further decline of lung function in patients with COPD.[4]

Prevention of acute exacerbations of COPD with long-term macrolide treatment is a recent development and the beneficial effect of this treatment has been postulated to result from both an antimicrobial and an immunomodulatory effect.[5] The largest study to date of this approach showed that long-term treatment with daily azithromycin significantly decreased the frequency of acute exacerbations of COPD.[6] However, this study included patients with at least one exacerbation within the previous year and those who were receiving continuous supplemental oxygen without having had any exacerbation. Implementation of this strategy in clinical practice might result in an excessive use of macrolides in patients with COPD. However, the main risk of the increasing consumption of azithromycin is the induction of macrolide resistance in a large group of patients, with the additional risk of induction of resistance to the general population.[7] To benefit maximally from macrolide treatment and to reduce the risk of resistance simultaneously, restrictive use of azithromycin is presently

warranted.[7] Proposals have been made to reserve long-term macrolide treatment for patients with two or more COPD exacerbations;[7,8] however, this recommendation was not supported by findings from clinical studies.

We did the COpd: infLUence of Macrolides on exacerBation freqUency in patientS (COLUMBUS) trial to investigate whether patients with COPD who had three or more exacerbations in the previous year would have a decreased rate of exacerbation when maintenance macrolide treatment was added to standard care.

Methods

Study design and participants

For the **study protocol** see http://www.erasmusmc.nl/longziekten/research/COPD/4549112/

The study protocol has been published elsewhere.[9] We undertook this prospective, randomised, double-blind, placebo-controlled, single-centre trial at the Amphia Hospital (Breda, the Netherlands) between May 19, 2010, and June 18, 2013. Eligible patients were 18 years or older, had been diagnosed with COPD according to the guidelines of the Global initiative for chronic Obstructive Lung Disease,[10] and had received treatment for three or more exacerbations of COPD in the previous year for which they received steroids or antibiotic treatment. Patients had to be clinically stable and could not have had a COPD exacerbation or respiratory-tract infection in the month before involvement in the study.

Exclusion criteria were a history of other clinically significant respiratory diseases (eg, asthma, cystic fibrosis); presence of bronchiectasis, as assessed by CT scan; maintenance antibiotic treatment; use of more than 10 mg prednisolone a day; allergy to macrolides; pregnancy or lactation in women; liver disease (alanine transaminase or aspartate transaminase concentrations that were two or more times the upper limit of normal); malignant disease of any kind for which the patient received treatment or was being monitored as part of follow-up after treatment; heart failure; and the use of drugs that could adversely interact with macrolides and for which therapeutic monitoring could not be undertaken.

All participants provided written informed consent. The study was approved by independent and local ethics committees.

Randomisation and masking

An independent pharmacy randomly assigned patients (1:1), via a computer-generated randomisation sequence with permuted blocks of ten (five per treatment group), to receive either azithromycin dihydrate 500 mg (Teva Pharmachemie, Haarlem, the Netherlands) or placebo, three times a week (Monday, Wednesday, and Friday) for 12 months. Randomisation was stratified by use of long-term, low-dose prednisolone (≤10 mg daily). The randomisation list was retained by the clinical trials pharmacist of the Amphia Hospital. Patients were enrolled by SU, RSD, and JGJVA, and were automatically given the next allocated treatment by clinical trials staff at the hospital pharmacy. Participants and investigators were masked to treatment allocation throughout the study. After data collection and data cleaning were completed, and after final database lock, investigators were unmasked and could assess outcomes and complete the data analysis.

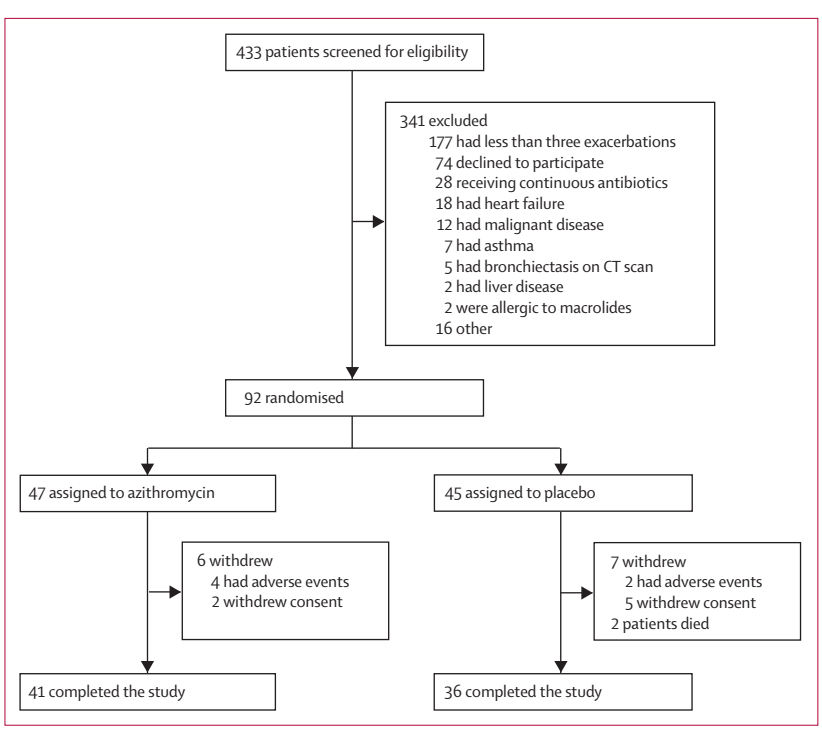

Figure 1: **Trial profile**

Procedures

Participants were followed up at the outpatient department at scheduled visits at months 3, 6, 9, and 12. During these visits, we obtained data for spirometry, the 6 min walk test, white-blood-cell count, concentrations of C-reactive protein, mid-regional pro-adrenomedullin, erythrocyte sedimentation rate, interleukin-6, and cytokine profiles of T-cell subsets. Additionally, patients completed the 12-Item Short-Form Health Survey (SF-12), the Hospital Anxiety and Depression Scale, and the St George's Respiratory Questionnaire at baseline and every 3 months. The type-D scale—a 14-item questionnaire to assess type D personality—was completed at baseline and at 12 months. Sputum samples were obtained for culture at baseline and at every scheduled visit. Sputum samples were processed according to American Society of Microbiology guidelines.[11] Sputum samples were additionally washed in sterile saline to avoid possible contamination from the oropharynx. We regarded a sputum sample as representative when more than 25 polymorphonuclear leucocytes and less than ten squamous cells per low-power field were identified by Gram stain. We established antibiotic susceptibility with breakpoints from the European Committee on Antimicrobial Susceptibility Testing.[12]

In case of an exacerbation, patients were seen and treated by the study investigators unless the patient chose to visit their family doctor. All exacerbations were defined according to Anthonisen criteria, and whether the patient needed treatment with steroids or antibiotics, or both.[13] An exacerbation was regarded as severe when hospital admission was necessary, and mild when it was treated at the outpatient department by the study investigators or the patient's family doctor.

Outcomes

The primary endpoint was rate of exacerbations of COPD in the year of treatment. Secondary outcomes were time to first exacerbation; hospital admission for acute exacerbations; change in proportion of exacerbations needing admission to hospital versus treatment in an outpatient department compared with the previous year; treatment for an acute exacerbation of COPD; forced expiratory volume in 1 s (FEV_1) after bronchodilation; forced vital capacity after bronchodilation; 6 min walking test; quality of life, as assessed by the SF-12 and the St George's Respiratory Questionnaire; acquisition of macrolide resistant microorganisms in sputum; and adverse events. Results of mid-regional pro-adrenomedullin, erythrocyte sedimentation rate, interleukin-6, cytokine profiles of T-cell subsets, the Hospital Anxiety and Depression Scale, and the type-D scale will be presented elsewhere.

Statistical analysis

The sample size was calculated with the assumption that the number of exacerbations followed a Poisson distribution with a mean rate of three exacerbations per patient per year in the placebo group. With 33 participants per treatment group followed up for 1 year, a 50% reduction was detectable with 90% power (two-sided α of 0·05). The calculation was based on an exact conditional binomial test, allowing exact inference on the rate ratio. To account for possible zero inflation, overdispersion, and participants dropping out earlier than 1 year after start of the study, the sample size was augmented by 40%, to 46 individuals per treatment group.

We analysed exacerbation rate with Poisson regression, with a log-link function and the log of time-in-study as an offset variable, and with covariates of long-term, low-dose prednisolone use, number of exacerbations in the preceding year, age, sex, smoking, and FEV_1. We corrected for overdispersion by multiplying the standard errors by the square root of the ratio of the Pearson χ^2 value to its number of degrees of freedom. We included all randomly assigned patients in the intention-to-treat analysis; for the per-protocol analysis we included only those who completed follow-up. The exacerbation rate ratio of azithromycin versus placebo treatment was tested for significance at the 5% level (two sided). Interaction between treatment and long-term, low-dose prednisolone use was also examined in an exploratory analysis.

Time to first exacerbation was analysed with Kaplan-Meier survival analysis and log-rank test. To investigate the effect of treatment, with discrimination between occurrences of mild and severe exacerbations, we used generalised linear modelling with a logit-link function and a robust variance estimator to analyse the probability

	Azithromycin (n=47)	Placebo (n=45)
Men	22 (47%)	18 (40%)
Age (years)	64·7 (10·2)	64·9 (10·2)
Present smoker	20 (43%)	9 (20%)
Body-mass index (kg/m²)	25·9 (4·6)	26·3 (5·7)
Acute exacerbations of COPD in the past year	4·0 (1·2)	4·0 (1·1)
Hospital admissions due to acute exacerbations of COPD	1·0 (1·1)	0·7 (0·8)
Symptoms		
Cough	28 (60%)	34 (76%)
Sputum production	29 (62%)	32 (71%)
Spirometry after bronchodilation		
FEV_1 (L)	1·1 (0·47)	1·1 (0·43)
FEV_1 (% of predicted)	44·2 (19·3)	45·0 (19·5)
FVC (L)	2·9 (0·8)	2·7 (0·92)
FVC (% of predicted)	92·5 (22·2)	88·9 (20·3)
FEV_1/FVC (%)	38·0 (11·7)	40·3 (12·4)
GOLD stages		
I	2 (4%)	3 (7%)
II	14 (30%)	12 (27%)
III	18 (38%)	20 (44%)
IV	13 (28%)	10 (22%)
6 min walk test (m)	402 (101)	365 (136)
6 min walk test (% of predicted)	79 (20)	74 (27)
Drugs		
LABA	45 (96%)	41 (91%)
LAMA	42 (89%)	32 (71%)
Inhaled corticosteroids	42 (89%)	43 (96%)
SABA	32 (68%)	33 (73%)
Prednisolone	11 (23%)	9 (20%)
Influenza vaccination in past year		
Yes	34 (72%)	41 (91%)
No	5 (11%)	1 (2%)
Not registered	8 (17%)	3 (7%)
SGRQ total score	57·4 (14·7)	57·6 (14·7)
Symptoms	61·4 (19·1)	61·9 (16·4)
Activity	77·7 (20·6)	75·0 (19·5)
Impacts	43·3 (15·2)	45·8 (17·2)
SF-12		
Physical component score	33·9 (10·0)	33·5 (9·0)
Mental component score	37·4 (12·7)	39·9 (11·4)
C-reactive protein (mg/L)	2 (1–180)	4 (1–42)
Leucocytes (×10⁹/L)	8·1 (5·8–17·1)	8·4 (5·1–17·4)

Data are n (%), mean (SD), or median (range), unless otherwise indicated. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. GOLD=Global Initiative for Chronic Obstructive Lung Disease. LABA=longacting beta agonist. LAMA=longacting muscarinic antagonist. SABA=shortacting beta agonist. SGRQ=St George's Respiratory Questionnaire. SF-12=12-Item Short-Form Health Survey.

***Table 1*: Baseline characteristics**

of hospital admission due to a given acute exacerbation of COPD; treatment was the only variable entered in this model. We did a similar analysis for the proportion of patients' exacerbations treated with antibiotics. Furthermore, the effect of treatment on the difference in the proportion of exacerbations requiring hospital admission versus outpatient treatment between the treatment year and the previous year was analysed with similar generalised linear modelling, whereby the correlation between the hospital proportions of the previous and treatment year was accounted for through the generalised estimation equations method. Secondary continuous outcome variables measured at baseline and at months 3, 6, 9, and 12 were analysed with linear mixed modelling. In addition to treatment, the baseline measurement of the outcome variable of interest was included as a covariate. Missing values over time for lung function parameters, 6 min walking test, C-reactive protein, and white-blood-cell count, caused by patients who withdrew before the end of the study, were appropriately imputed by the maximum likelihood estimation procedure used in linear mixed modelling, on the basis of the multivariate structure of the available measurements in time. Treatment effects were estimated by visit and overall across visits if the treatment-by-visit interaction was not significant (p>0·01).

For adverse events and baseline characteristics, comparisons of parameters between treatment groups were calculated with a *t* test if normally distributed and with a Mann-Whitney U test if not. We compared categorical data between the treatment groups with the exact χ^2 trend or Fisher's test, as appropriate. Statistical analysis was done with SPSS (version 21).

This study is registered with ClinicalTrials.gov, number NCT00985244.

	Acute exacerbations of COPD in the azithromycin group	Acute exacerbations of COPD in the placebo group
Total exacerbations	N=84	N=129
Severe exacerbation	25 (30%)	31 (24%)
Prednisolone	9 (11%)	5 (4%)
Antibiotics	0	0
Prednisolone and antibiotics	16 (19%)	26 (20%)
Mild exacerbation	59 (70%)	98 (76%)
Prednisolone	36 (43%)	25 (19%)
Antibiotics	0	16 (12%)
Prednisolone and antibiotics	23 (27%)	57 (44%)

Data are n (%), unless otherwise indicated. COPD=chronic obstructive pulmonary disease. Severe exacerbation was defined as an exacerbation for which hospital admission was necessary. Mild exacerbation was defined as an exacerbation treated at the outpatient department by the study investigators or the patient's family doctor.

***Table 2*: Exacerbations and given treatments during the study**

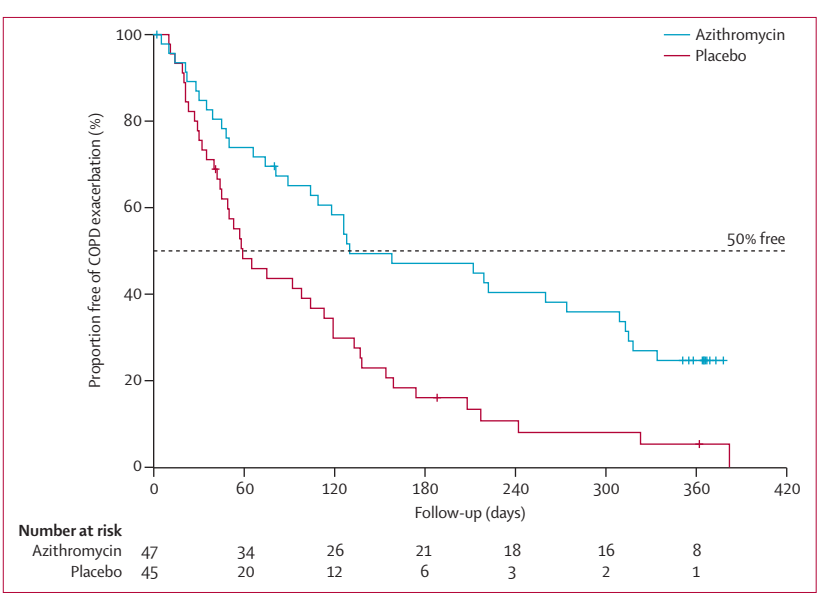

***Figure 2*: Proportion of patients free from acute exacerbations of COPD**
COPD=chronic obstructive pulmonary disease.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We randomly assigned 92 patients to the azithromycin group (n=47) or the placebo group (n=45), of whom 41 (87%) versus 36 (80%) completed the study. All 92 patients received at least one dose of the assigned treatment (figure 1). In 91 (99%) patients bronchiectasis was excluded by chest CT scan. Table 1 shows baseline characteristics.

We recorded 84 exacerbations in patients in the azithromycin group compared with 129 in those in the placebo group (table 2). 13 (28%) participants in the azithromycin group did not have any exacerbation compared with three (7%) participants in the placebo group. The unadjusted exacerbation rate per patient per year was 1·94 (95% CI 1·50–2·52) for the azithromycin group and 3·22 (2·62–3·97) for the placebo group. The rate ratio (RR) of azithromycin to placebo was 0·60 (95% CI 0·43–0·84; p=0·003). After adjustment for covariates, the analysis remained significant (azithromycin versus placebo 0·58, 0·42–0·79; p=0·001). Results from the unadjusted (RR 0·60, 95% CI 0·42–0·85; p=0·004) and adjusted (0·58, 0·42–0·79; p=0·001) per-protocol analyses were almost identical to those from the intention-to-treat analysis. No statistically significant difference was shown in the exacerbation rate ratio of azithromycin treatment to placebo between patients who did and did not already receive long-term, low-dose prednisolone treatment (p=0·12).

The median time to first exacerbation was 59 days (95% CI 31–87) in the placebo group and 130 days

(28–232) in the azithromycin group (p=0·001; figure 2). A post-hoc analysis showed that the probability of remaining free of exacerbations of COPD at 6 months was 0·14 (95% CI 0·04–0·24) in the placebo group and 0·47 (0·32–0·62) in the azithromycin group (p=0·0005). In the year of treatment the odds ratio for hospital admission due to acute exacerbations of COPD did not differ between groups (OR 1·34, 95% CI 0·67–2·70; p=0·41). To assess whether this result was affected by only a few patients needing frequent admission, we did a post-hoc analysis in which no difference in mean time-to-first admission was noted between patients in the azithromycin group and those in the placebo group (282 days *vs* 258 days; p=0·48). Furthermore, no difference was shown between groups in change of rate of hospital admission for acute exacerbations versus exacerbations treated in the outpatient department (azithromycin to placebo ratio of the OR of changes 0·86, 95% CI 0·35–2·07; p=0·73; appendix). We noted no difference between groups in treatment of severe exacerbations with additional antibiotics (OR 0·34, 95% CI 0·10–1·14; p=0·08). Mild exacerbations in the azithromycin group were treated significantly less often with additional antibiotics than were those in the placebo group (OR 0·20, 0·08–0·49; p=0·0001; table 2). During the study, macrolides were prescribed to four (9%) patients in the placebo group and to none in the azithromycin group.

No significant changes took place between groups in postbronchodilator forced vital capacity, FEV_1, and 6 min walking test from baseline to 12 months (table 3). The mean change in total score on the St George's Respiratory Questionnaire differed significantly between groups at 3 months in favour of azithromycin (–4·2, 95% CI –8·3 to –0·1; p=0·043), but this change did not persist at 12 months (table 3). No differences between groups were noted in mean change from baseline in the component scores at 12 months (table 3). However, after undertaking an estimation of the overall treatment effect across all visits, we recorded a significant difference in symptom score on the St George's Respiratory Questionnaire between patients in the azithromycin group and those in the placebo group, but not in the total score or component scores of activities and impacts (table 3). The SF-12 showed a significant difference in mean change in the mental component score at 3 months in favour of azithromycin (6·6, 95% CI 1·4–11·8; p=0·013), but not at 12 months (table 3). No differences were shown between groups in mean change in the physical component score at 3 months (data not shown) or 12 months (table 3). No significant changes were recorded between groups in concentrations of C-reactive protein and white-blood-cell counts at 12 months compared with baseline (table 3). However, across all visits, significantly lower concentrations were noted in patients in the azithromycin group for both C-reactive protein and white-blood-cell counts than in those in the placebo group (table 3).

See Online for appendix

One or more sputum samples were obtained in 32 (68%) of the 47 patients in the azithromycin group, and in 32 (71%) of the 45 patients in the placebo group. At

	At 12 months		Change from baseline at 12 months*				Overall effect	
	Azithromycin (n=41)	Placebo (n=36)	Azithromycin (n=47)	Placebo (n=45)	Difference (95% CI)	p value	Difference (95% CI)	p value
Spirometry after bronchodilation								
FEV1 (L)	1·1 (0·47)	1·0 (0·42)	–0·03	–0·07	0·03 (–0·04 to 0·11)	0·37	0·03 (–0·02 to 0·08)	0·19
FEV1 (% of predicted)	43·4 (17·9)	44·2 (20·1)	–1·13	–1·80	0·67 (–2·36 to 3·71)	0·66	0·86 (–1·14 to 2·85)	0·40
FVC (L)	2·9 (0·93)	2·7 (0·79)	–0·04	–0·12	0·08 (–0·09 to 0·25)	0·35	0·05 (–0·06 to 0·17)	0·35
FVC (% of predicted)	91·0 (23·5)	88·9 (20·9)	–0·73	–1·21	0·48 (–4·86 to 5·82)	0·86	0·22 (–3·33 to 3·78)	0·90
6 min walk test (m)	415 (108)	379 (121)	–1·5	–20·8	19·3 (–17·8 to 56·5)	0·31	8·4 (–15·2 to 31·9)	0·48
6 min walk test (% of predicted)	82 (20)	76 (23)	0·42	–3·55	3·97 (–3·66 to 11·60)	0·31	1·40 (–3·32 to 6·13)	0·56
SGRQ total score	56·2 (17·2)	57·3 (15·2)	–1·05	–0·44	–0·61 (–5·75 to 4·53)	0·82	–1·12 (–4·37 to 2·23)	0·49
Symptoms	57·3 (18·0)	63·0 (14·4)	–4·97	1·80	–6·77 (–14·22 to 0·67)	0·075	–5·06 (–9·64 to –0·49)	0·030
Activity	75·5 (22·4)	76·1 (19·9)	–1·66	–1·37	–3·02 (–8·72 to 2·67)	0·30	–2·91 (–6·32 to 0·49)	0·09
Impacts	44·6 (17·8)	44·5 (18·3)	1·12	–1·19	2·31 (–4·43 to 9·05)	0·50	0·89 (–3·19 to 4·96)	0·67
SF-12								
Physical component score	32·3 (10·7)	32·7 (10·3)	–0·76	1·13	–1·89 (–6·13 to 2·36)	0·38	1·30 (–1·26 to 3·86)	0·31
Mental component score	36·8 (11·7)	35·9 (13·1)	–0·04	–1·80	1·76 (–4·02 to 7·53)	0·55	2·68 (–0·51 to 5·87)	0·10
C-reactive protein (mg/L)	2 (1–30)	3 (1–90)	–20·6%	–2·1%	–18·9 (–50·6 to 33·2)	0·41	–27·1 (–42·3 to –8·0)	0·008
Leucocytes (×10⁹/L)	8·5 (3·1–16·2)	8·9 (4·8–16·3)	2·6%	9·9%	–6·7 (–17·2 to 5·1)	0·25	–8·4 (–14·2 to–2·3)	0·008

Data are mean (SD) or median (range), unless otherwise indicated. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. SGRQ=St George's Respiratory Questionnaire. SF-12=12-Item Short-Form Health Survey. *Computed by mixed model analysis with missing data accounted for by imputation.

***Table 3*: Secondary outcome variables at 12 months**

baseline, 42 sputum samples were obtained (22 in the azithromycin group and 20 in the placebo group), and 108 samples (51 *vs* 57) were obtained during 1 year of follow-up (appendix). The most commonly cultured bacteria in the azithromycin and placebo groups at baseline were *Haemophilus influenzae* (n=3 *vs* n=2), *Streptococcus pneumoniae* (n=2 *vs* n=3), and *Pseudomonas aeruginosa* (n=2 *vs* n=0). During follow-up, fewer patients in the azithromycin group had positive sputum cultures with new respiratory pathogens compared with those in the placebo group (n=4 *vs* n=12; p= 0·044; appendix). Acquisition of macrolide-resistant bacteria was noted in three (6%) patients in the azithromycin group compared with 11 (24%) patients in the placebo group (p=0·036; appendix).

No significant differences were shown in the frequency of adverse events or serious adverse events between treatment groups (table 4). During treatment, three (6%) patients in the azithromycin group had serious adverse events (table 4): two were diagnosed with lung carcinoma and a third had an acute coronary syndrome. Five (11%) patients in the placebo group had serious adverse events (table 4): two developed respiratory failure due to an acute exacerbation of COPD, both of whom died; the third patient had a transient ischaemic attack, the fourth had an acute coronary syndrome, and the fifth had cholecystitis for which a cholecystectomy was done. Four (9%) patients in the azithromycin group and two (4%) patients in the placebo group discontinued the study because of side-effects (figure 1). More patients had diarrhoea in the azithromycin group than in the placebo group (p=0·015; table 4).

	Azithromycin (n=47)	Placebo (n=45)
Any adverse events	68	74
Serious adverse events	3 (6%)	5 (11%)
Most frequent adverse events*		
Gastrointestinal		
Diarrhoea	9 (19%)	1 (2%)
Nausea or vomiting	3 (6%)	2 (4%)
Other	4 (9%)	7 (16%)
Laboratory investigations		
Creatinine increase	7 (15%)	3 (7%)
Elevated blood urea nitrogen	4 (9%)	10 (22%)
Hyperchloraemia	6 (13%)	5 (11%)
Alkaline phosphatase increase	4 (9%)	1 (2%)
ALT increase	5 (11%)	4 (9%)
AST increase	3 (6%)	3 (7%)
Gamma-glutamyltransferase increase	6 (13%)	1 (2%)
LDH increase	3 (6%)	4 (9%)
Other	9 (19%)	17 (38%)

Data are n (%), unless otherwise indicated. Diarrhoea was the only event that differed significantly between groups (p=0·015). ALT=alanine aminotransferase. AST=aspartate aminotransferase. LDH=lactate dehydrogenase. *Events with an incidence of 2·5% or higher.

Table 4: **Adverse events**

Discussion

This study is the first to investigate macrolide treatment in patients with frequent exacerbations of COPD. Our findings show that treatment with azithromycin for 12 months decreased the rate of exacerbations and increased time to first exacerbation compared with placebo (panel).

We examined a COPD population who were refractory to usual care. The proportions of patients who received treatment with inhaled corticosteroids (92%), long-acting beta agonists (LABAs) (93%), and long-acting muscarinic antagonists (LAMAs) (80%) were substantially higher in our study than in two prospective randomised trials investigating the effect of long-term macrolide treatment in patients with COPD.[6,14] In Albert and colleagues' study,[6] inhaled corticosteroids were prescribed in 77% of the patients, LABAs in 74%, and LAMAs in 63%, whereas in Seemungal and colleagues' study,[14] 78% of patients received inhaled corticosteroids, 63% received LABAs, and 33% received LAMAs.

Our main inclusion criterion was the presence of three or more acute exacerbations of COPD in the preceding 12 months. This criterion is in contrast with that of Albert and colleagues' trial,[6] in which 12% of patients did not have any exacerbations in the year before inclusion, and that of Seemungal and colleagues' trial, in which 65% of patients had fewer than three exacerbations in the year before inclusion.[14] Therefore, our main outcome cannot be directly compared with those from these two studies. We recorded a higher relative reduction (42%) in exacerbation rate than in Albert and colleagues' trial (27%)[6] and Seemungal and colleagues' trial (35%).[14] Furthermore, median time to first exacerbation in the azithromycin (130 days) and placebo groups (59 days) in the COLUMBUS study was substantially shorter than that in the trials by Albert and colleagues[6] (azithromycin 266 days [95% CI 227–313], placebo 174 days [143–215]) and Seemungal and colleagues (erythromycin 271 days, placebo 89 days).[14] Another important finding is that 7% of patients in our control group did not have any exacerbation, compared with 32% of those in Albert and colleagues' control group.[6] This result suggests that use of a criterion of three or more exacerbations exposes fewer patients to redundant macrolide treatment, which consequently reduces the possibility of side-effects and the development of macrolide resistance. An additional difference between our study and that by Albert and colleagues was our use of a thrice-weekly regimen compared with their use of daily azithromycin.[6] When designing the study protocol, most data of long-term treatment with azithromycin were for thrice-weekly regimens in studies of patients with cystic fibrosis.[19,20] Until now, no study has been done comparing a daily dosage with a thrice-weekly schedule.

Azithromycin did not improve generic and disease-specific health-related quality of life, as assessed by SF-12 and the St George's Respiratory Questionnaire. However, we noted a clinically and statistically significant

average treatment effect in the symptom component score of the St George's questionnaire in patients in the azithromycin group compared with those in the placebo group at 12 months. This improvement in symptom score might be attributable to the reduction in exacerbations. In a 2 year study done to assess exacerbations and their effect on health-related quality of life in patients with COPD, Miravitlles and colleagues showed that the greatest differences between frequent and infrequent exacerbators in the St George's Respiratory Questionnaire were in the symptoms scale.[21]

Macrolide treatment is an important cause of the development of macrolide resistance in oral commensal streptococcal flora.[22] We identified acquisition of macrolide-resistant bacteria in sputum; however, the number of positive sputum cultures was low. In line with Albert and colleagues' findings, patients in the azithromycin group were less likely to become colonised with respiratory pathogens than were those in the placebo group.[6] Furthermore, azithromycin significantly reduced acquisition of macrolide-resistant bacteria in sputum compared with placebo. In Albert and colleagues' study, fewer patients (in absolute numbers) given azithromycin were colonised with macrolide-resistant respiratory pathogens compared with those given placebo.[6,23] In our study, we could not explain the increase in acquisition of macrolide-resistant bacteria in the placebo group by additional use of macrolides during follow-up for any indication.

Several randomised trials have proven the effectiveness of maintenance macrolide treatment for the prevention of exacerbations of non-cystic-fibrosis bronchiectasis.[24–26] Inclusion of patients with COPD with bronchiectasis in our study could have resulted in substantial bias because the achieved results could have been affected by patients with non-cystic-fibrosis bronchiectasis. Therefore, we chose to exclude these patients. During the screening period, we excluded five of 433 patients because of bronchiectasis. This number is relatively low compared with that in a study by Martinez-Garcia and colleagues in which almost 58% of the patients with COPD had bronchiectasis.[27] However, in that study, patients with COPD with and without previous exacerbations were included. Another notable observation in our study was the presence of a larger number of female than male patients with COPD. Additionally, in the ECLIPSE and POET studies, women had a higher tendency of exacerbating more frequently than did men.[28–30]

Macrolides have been extensively investigated on the basis of their postulated immunomodulatory effects. Evidence suggests that macrolides decrease the production of pro-inflammatory cytokines in response to viral infections,[31] decrease the hypersecretion of pro-inflammatory cytokines and chemokines,[32] improve alveolar macrophage phagocytosis function,[33] and maintain integrity of the airway epithelium.[34] In addition to the immunomodulatory effects, the decrease in airway bacterial colonisation in patients receiving azithromycin as shown in our study might also be associated with reduction in systemic inflammation.[35]

Azithromycin was well tolerated in our trial. Adverse events were mostly gastrointestinal, with roughly a fifth of patients in the azithromycin group reporting diarrhoea, a finding similar to that seen in other studies of azithromycin.[16,24,25] However, in Albert and colleagues' study, only 5% of patients in the azithromycin group reported gastrointestinal complaints.[6] Although, by contrast with erythromycin and clarithromycin, azithromycin does not change the concentrations of theophylline, we therapeutically monitored theophylline as described in the study protocol.[9,36] We did not record theophylline concentrations greater than the therapeutic range.

Our study has some limitations. First, we had small numbers of culture-positive sputum samples for assessment of the development of antimicrobial resistance. We did not assess macrolide resistance in oral commensal flora; therefore, our results might underestimate macrolide resistance in vivo. Second, although patients were actively asked about hearing loss, no standard audiometry was done. In several studies done with macrolides, no reports of hearing loss were made.[24,25,37] At the end of our study, one patient in the placebo group reported hearing loss. Third, electrocardiographs were not done as standard before and during the study. However, apart from two patients, one in each treatment group, who had an acute coronary syndrome, no other cardiovascular-related events or deaths were reported.

Panel: Research in context

Systematic review

We searched PubMed, with no language restrictions, for randomised controlled trials done in adults and published before Oct 31, 2013. We used the search terms "COPD", "therapy", and "macrolides". Of the 43 results we identified six clinical trials[6,14,15–18] that prospectively investigated long-term macrolide treatment (erythromycin,[14,16,18] clarithromycin,[15] and azithromycin[6,17]) in patients with exacerbations of chronic obstructive pulmonary disease (COPD). None of the six trials included a chest CT scan to screen for bronchiectasis, or had a minimum requirement for exacerbations as main inclusion criterion. One double-blind randomised controlled trial of fairly short duration (3 months) was done in patients with stable COPD and showed no reduction in exacerbations of COPD.[15] Three other trials showed that macrolides reduced exacerbations of COPD,[16–18] and in two of these trials,[16,17] time to first exacerbation was also delayed. However, two of these trials were quite small (22 and 36 patients) and of fairly short duration (6 months),[16,17] and two trials were open-label.[17,18] A study by Seemungal and colleagues[14] showed that patients given 250 mg erythromycin twice daily had fewer exacerbations than did those given placebo, and that time to first exacerbation was delayed in the treatment group. A trial by Albert and colleagues[6] likewise showed a reduction in exacerbations and an increased time to first exacerbation in patients given daily 250 mg azithromycin compared with placebo.

Interpretation

Our results show that azithromycin treatment for 12 months decreased the exacerbation rate and increased the time to first exacerbation compared with placebo in patients who did not have bronchiectasis and who had received treatment for at least three exacerbations of COPD in the previous year. These results support the use of long-term macrolide treatment in patients with the frequent exacerbator phenotype who are refractory to standard care.

In summary, our results show that long-term treatment with azithromycin could be recommended in patients with COPD with the frequent exacerbator phenotype who are refractory to standard care. However, careful monitoring of the emergence of macrolide resistance is warranted.

Contributors

SU, RSD, JAJWK, PGHM, NEvV, HCH, JGJVA, and MMvdE contributed to the study design. SU, RSD, JAJWK, PGHM, AJP, JGJVA, and MMvdE participated in data interpretation. SU, RSD, JAJWK, PGHM, NEvV, AAME, AJP, HCH, JGJVA, and MMvdE edited the manuscript. SU, RSD, PGHM, JGJVA and MMvdE wrote the manuscript. PGM did the statistical analysis. SU contributed to data collection. SU and MMvdE did the literature search. SU, RSD, and JGJVA enrolled the study participants. JAJWK was responsible for the microbiological analysis. NEvV contributed to random assignment of the patients. AAME coordinated the laboratory tests. AJP contributed to the study protocol. JGJVA and MMvdE contributed equally to this manuscript.

Declaration of interests

We declare that we have no competing interests.

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CHEST

Original Research

COPD

The Chronic Bronchitic Phenotype of COPD

An Analysis of the COPDGene Study

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Background: **Chronic bronchitis (CB) in patients with COPD is associated with an accelerated lung function decline and an increased risk of respiratory infections. Despite its clinical significance, the chronic bronchitic phenotype in COPD remains poorly defined.**

Methods: **We analyzed data from subjects enrolled in the Genetic Epidemiology of COPD (COPDGene) Study. A total of 1,061 subjects with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II to IV were divided into two groups: CB (CB+) if subjects noted chronic cough and phlegm production for ≥ 3 mo/y for 2 consecutive years, and no CB (CB−) if they did not.**

Results: **There were 290 and 771 subjects in the CB+ and CB− groups, respectively. Despite similar lung function, the CB+ group was younger (62.8 ± 8.4 vs 64.6 ± 8.4 years, *P* = .002), smoked more (57 ± 30 vs 52 ± 25 pack-years, *P* = .006), and had more current smokers (48% vs 27%, *P* < .0001). A greater percentage of the CB+ group reported nasal and ocular symptoms, wheezing, and nocturnal awakenings secondary to cough and dyspnea. History of exacerbations was higher in the CB+ group (1.21 ± 1.62 vs 0.63 ± 1.12 per patient, *P* < .027), and more patients in the CB+ group reported a history of severe exacerbations (26.6% vs 20.0%, *P* = .024). There was no difference in percent emphysema or percent gas trapping, but the CB+ group had a higher mean percent segmental airway wall area (63.2% ± 2.9% vs 62.6% ± 3.1%, *P* = .013).**

Conclusions: **CB in patients with COPD is associated with worse respiratory symptoms and higher risk of exacerbations. This group may need more directed therapy targeting chronic mucus production and smoking cessation not only to improve symptoms but also to reduce risk, improve quality of life, and improve outcomes.**

Trial registry: **ClinicalTrials.gov; No.: NCT00608764; URL: www.clinicaltrials.gov**

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Abbreviations: AWT = airway wall thickness; BODE = BMI, airway obstruction, dyspnea, exercise capacity; CB = chronic bronchitis; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MMRC = Modified Medical Research Council; SGRQ = St. George Respiratory Questionnaire; WA% = wall area percent

Chronic cough and sputum production are common, but symptoms vary in patients with COPD.[1] They result from goblet cell hyperplasia in both large and small airways,[2-4] and the subsequent mucus hypersecretion worsens airflow obstruction and predisposes to bacterial colonization.[5] Mucus overproduction may develop as a consequence of cigarette smoke exposure,[6,7] acute and chronic viral infection,[8] or inflammatory cell activation of mucin gene transcription[9] and is compounded by difficulty in clearing secretions because of poor ciliary function, distal airway occlusion, and ineffective cough.[2,9,10]

Chronic mucus hypersecretion has been shown in some large epidemiologic studies to be associated with an accelerated lung function decline, increased risk for respiratory infection,[11,12] and higher mortality.[13-15] Several studies have demonstrated an increased risk of COPD exacerbation.[16-19] Goblet cell hyperplasia also has prognostic value as it has been associated with an increased risk of mortality and a lack of improvement in lung function after lung reduction surgery.[20,21] Despite these clinical and pathologic correlates of chronic bronchitis (CB) to various clinical outcomes, the current literature is limited regarding

the clinical and radiographic characteristics of CB in patients with COPD.

We analyzed 1,061 patients with moderate to severe COPD in the first 2,500 subjects enrolled in the Genetic Epidemiology of COPD (COPDGene) Study. We specifically sought to carefully characterize those with CB symptoms and compare them to those without these symptoms. We hypothesized that chronic cough and sputum production in patients with COPD are associated with a greater exacerbation frequency, heightened respiratory symptoms, and worse health-related quality of life compared with those without CB symptoms.

Materials and Methods

Patient Selection

The COPDGene Study is a multicenter observational study to analyze genetic susceptibility for the development of COPD. This study met all criteria for institutional review board approval (Temple IRB #11369). Inclusion and exclusion criteria and protocol have been described previously.[22] Briefly, enrollees are blacks or non-Hispanic whites aged 45 to 80 years with at least a 10-pack-year smoking history. Exclusion criteria include pregnancy, history of other lung disease except asthma, prior lobectomy or lung volume reduction, active cancer undergoing treatment, or known or suspected lung cancer.

Subjects were asked whether they had cough, and if they responded yes, they were asked whether they coughed on most days for ≥ 3 consecutive mo/y and for how many years. Similar questions were asked regarding phlegm production. Subjects were placed in the CB+ group if they had chronic cough and phlegm production for ≥ 3 mo/y for at least 2 consecutive years or in the CB− (no CB) group if these criteria were not satisfied.

Clinical Characterization

Dyspnea and health-related quality of life were assessed using the Modified Medical Research Council (MMRC) scale and St. George Respiratory Questionnaire (SGRQ). Upper- and lower-respiratory tract symptoms were collected using a modified form of the American Thoracic Society Diffuse Lung Disease Respiratory Epidemiology questionnaire.[23] Medical comorbidities were assessed based on subject self-report. Subjects were asked whether they experienced COPD exacerbations in the past year and to quantify the number of episodes. They also were asked whether they had been to the ED or hospitalized for an exacerbation in the past year. These answers were used to determine exacerbation history and history of severe exacerbations, respectively.

Each subject underwent prebronchodilater and postbronchodilator spirometry using an EasyOne spirometer (Welch-Allyn Switzerland GmbH; Vaud, Switzerland). Predicted values were obtained using National Health and Nutrition Examination Survey III data.[24] Six-min walk distance was measured in the standard fashion.[25]

CT Imaging

Volumetric CT scan acquisitions were obtained at full inspiration (200 mA) and at the end of normal expiration (50 mA). Thin-slice collimation with slice thickness and intervals of < 1 mm was used to enhance spatial resolution. Quantitative image analysis to calculate lung volumes, percent emphysema, and percent gas trapping was performed using VIDA (VIDA Diagnostics, Inc; Coralville, Iowa) and 3DSlicer (available at http://www.slicer.org) software.[26] Percent emphysema was defined as the total percentage of both lungs with attenuation values < −950 Hounsfield units on inspiratory images, and percent gas trapping was defined as the total percentage of both lungs with attenuation values < −856 Hounsfield units on expiratory images. These percentages were adjusted for type of CT scanner. Total lung capacity and functional residual capacity were calculated based on inspiratory and expiratory CT images, respectively. Airway disease was quantified in a subset of each group as wall area percent (WA%) [(wall area/total bronchial area) × 100)] and airway wall thickness (AWT).[27] The mean WA% and AWT were calculated as the average of the values for six segmental bronchi in each subject. Using 3DSlicer, we also expressed AWT as the square root of the wall area of a theoretical 10-mm diameter airway as previously described.[28]

Statistical Analysis

Analysis was performed using JMP, version 8.0.1 (SAS Inc; Cary, North Carolina). Values are expressed as mean ± SD, unless stated otherwise. Categorical variables (eg, sex, race, presence of ocular or nasal symptoms) were compared between groups using χ^2 test. Continuous variables (eg, age, smoking history, exacerbation history) were evaluated using one-way analysis of variance or two-tailed unpaired t test. Wilcoxon rank sum test was used for nonnormally distributed data. $P < .05$ was considered statistically significant. Multiple logistic regressions were performed to assess the independent effects of CB, sex, age, current smoking, and total pack-year history of smoking on symptoms.

Results

Participant demographics and medications are summarized in Table 1. Of the 1,061 subjects with COPD analyzed, CB was reported in 27.3% (CB+ group, n = 290; CB− group, n = 771). The percentage of subjects with CB in each GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage was similar (GOLD stage II, 27.3%; GOLD stage III, 28.7%; GOLD stage IV, 25.0%; $P = .650$). In the entire cohort, the CB+ group was younger (62.8 ± 8.4 vs 64.6 ± 8.4 years, $P = .002$) and had a greater

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Table 1—*Patient Characteristics and Medication Usage*

Variable	CB+ (n = 290)	CB− (n = 771)	*P* Value
Demographic			
Age, y	62.8 ± 8.4	64.6 ± 8.4	.002[a]
Smoking history, pack-y	57 ± 30	52 ± 25	.006[a]
Current smoker, %	48	27	< .0001[a]
Sex, %			.027[a]
Male	57	50	
Female	43	50	
Race, %			.034[a]
White	86	80	
Black	14	20	
FEV_1, % predicted	48.5 ± 17.6	48.7 ± 18.4	.904
FVC, % predicted	77.7 ± 18.2	75.6 ± 17.7	.106
FEV_1/FVC	0.47 ± 0.12	0.48 ± 0.13	.088
6MWD, m	342 ± 8	348 ± 5	.540
Height, cm	170 ± 10	169 ± 10	.055
BMI, kg/m^2	28.0 ± 6.3	28.0 ± 6.2	.770
BODE score[b]	3 (2-5)	3 (1-5)	.033[a]
Medications, % pts use			
SABD	92.7	82.1	.003[a]
LABA	12.2	10.8	.626
LAMA	52.5	57.4	.218
ICS	18.6	13.8	.086
OCS	7.7	7.8	.888
Combo ICS/LABA	50.0	57.6	.047[a]
Theophylline	10.1	6.9	.150
Oxygen	27.0	33.4	.054
Comorbidities, % pts			
Angina	9.0	4.5	.016[a]
Asthma	30.0	25.1	.229
Congestive heart failure	5.2	5.2	.990
Coronary artery disease	8.3	8.0	.900
Diabetes	16.2	10.3	.010[a]
Hypertension	49.3	47.0	.535
Hypercholesterolemia	44.5	39.3	.141
Stroke	2.4	3.9	.227
Gastroesophageal reflux	34.6	27.6	.029[a]
Compression fractures	9.7	5.6	.027[a]
Hip fracture	2.8	2.7	.979
Osteoarthritis	25.9	18.3	.008[a]
Osteoporosis	14.8	14.9	1.000
Sleep apnea	22.4	14.4	.002[a]

Data are presented as mean ± SD or as a percentage of the group. 6MWD = 6-min walk distance; BODE = BMI, airway obstruction, dyspnea, exercise capacity; CB = chronic bronchitis; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; OCS = oral corticosteroid; pt = patient; SABD = short-acting bronchodilator.

[a]*P* < .05.

[b]Expressed as median (interquartile range).

percentage of whites (86% vs 80%, *P* = .034) and men (57% vs 50%, *P* = .027). The CB+ group had a greater pack-year smoking history (57 ± 30 pack-years vs 52 ± 25 pack-years, *P* = .006) and had more current smokers (48% vs 27%, *P* < .0001). There was no difference in lung function, 6-min walk distance, height, or BMI between the two groups. The OR for CB from current smoking was 2.56 (95% CI, 1.93-3.39). Comparing current smokers with ex-smokers within the CB+ group, current smokers were younger (59.6 ± 7.6 years vs 65.8 ± 8.1 years, *P* < .0001), were thinner (BMI, 27.0 ± 5.8 kg/m^2 vs 28.9 ± 6.7 kg/m^2, *P* = .0127), and had better lung function (FEV_1, 54.3% ± 15.6% vs 43.3% ± 17.8%, *P* < .0001). The CB+ group reported greater use of short-acting bronchodilators (92.7% vs 82.1%, *P* = .003) and lesser use of combination inhaled steroid/long-acting β-agonists (50.0% vs 57.6%, *P* = .047). There were no differences in other respiratory medication usage between groups.

Comorbidities also are listed in Table 1. Compared with the CB− group, a greater number of subjects in the CB+ group reported a history of angina (9.0% vs 4.5%, *P* = .011), diabetes (16.2% vs 10.3%, *P* = .010), gastroesophageal reflux (34.6% vs 27.6%, *P* = .029), compression fractures (9.7% vs 5.6%, *P* = .027), osteoarthritis (25.9% vs 18.3%, *P* = .008), and sleep apnea (22.4% vs 14.4%, *P* = .002). There were no differences in asthma, congestive heart failure, coronary artery disease, myocardial infarction, hypertension, hypercholesterolemia, stroke, and osteoporosis. When the incidence of angina was controlled for other cardiac risk factors (hypertension, pack-year smoking history, hypercholesterolemia, and diabetes), the presence of CB was still associated with an increased incidence of angina (OR, 1.92; *P* = .02).

Table 2 summarizes symptoms, quality of life, and exacerbation history. The subjects in the CB+ group were more symptomatic than those in the CB− group. MMRC, SGRQ, and BODE (BMI, airflow obstruction, dyspnea, exercise capacity) index scores were greater in the CB+ group (MMRC, 2.55 ± 1.31 vs 2.11 ± 1.41, *P* < .0001; SGRQ, 49.9 ± 19.7 vs 36.6 ± 20.0, *P* < .0001; BODE index, 3.35 ± 2.04 vs 3.05 ± 2.11, *P* = .033) (Fig 1). Upper-respiratory tract symptoms were greater in the CB+ group (eg, nasal congestion, rhinorrhea) (69.3% vs 53.4%, *P* < .0001) as were allergic ocular symptoms (eg, itchy, watery eyes) (52.8% vs 40.2%, *P* < .0001). There was also a greater history of wheezing (86.5% vs 67.6%, *P* < .0001), nocturnal awakenings secondary to cough (45.9% vs 19.1%, *P* < .0001), and nocturnal awakenings secondary to dyspnea or chest tightness (39.3% vs 24.4%, *P* < .0001) in the CB+ group.

In the entire cohort, current smoking was not associated with respiratory symptoms or SGRQ scores in multivariate analysis. Subjects who reported the use of supplemental oxygen had higher MMRC scores (2.94 ± 1.02 vs 1.90 ± 1.43, *P* < .0001) and more nasal symptoms (62% vs 56%, *P* = .044) than those who did not use oxygen but not other symptoms. When the presence of CB was factored into multivariate analysis, oxygen use did not have a statistically significant impact on any respiratory symptoms. The use of oxygen was associated with higher SGRQ scores (49.1 ± 17.1 vs 35.9 ± 21.3, *P* < .0001), which was

Table 2—*Symptoms, Quality of Life, Exacerbation History, and Radiology*

Variable	CB+	CB−	*P* Value
Symptoms and quality of life			
MMRC dyspnea score[a]	3 (2-4)	2 (1-3)	< .0001[b]
SGRQ, total	49.9 ± 19.7	36.6 ± 20.0	< .0001[b]
SGRQ, respiratory	62.5 ± 19.0	38.0 ± 22.4	< .0001[b]
Nasal symptoms, %	69.3	53.4	< .0001[b]
Ocular symptoms, %	52.8	40.2	< .0001[b]
Wheezing, %	86.5	67.6	< .0001[b]
Awakened by cough, %	45.9	19.1	< .0001[b]
Awakened by dyspnea, %	39.3	24.4	< .0001[b]
Exacerbations in the previous year			
Total exacerbations, No./pt	1.21 ± 1.62	0.63 ± 1.12	.027[b]
History of severe exacerbations, %	26.6	20.0	.024[b]
Radiology			
% Emphysema[c]	14.2 ± 13.0	16.0 ± 13.4	.212
% Gas trapping	42.0 ± 20.0	42.8 ± 20.3	.593
Total lung capacity,[d] L	6.30 ± 1.50	5.88 ± 1.40	.0004[b]
Functional residual capacity,[d] L	4.22 ± 1.19	3.92 ± 1.28	.002[b]
Mean segmental WA%[e]	63.2 ± 2.9	62.6 ± 3.1	.013[b]
Mean segmental AWT,[e] mm	1.60 ± 0.21	1.60 ± 0.22	.700
Pi10,[d] mm	3.800 ± 0.129	3.798 ± 0.126	.816

Data are presented as mean ± SD or as a percentage of the group. AWT = airway wall thickness; MMRC = Modified Medical Research Council; Pi10 = 10-mm diameter airway; SGRQ = St. George Respiratory Questionnaire; WA% = wall area percent. See Table 1 legend for expansion of other abbreviations.

[a]Expressed as median (interquartile range).

[b]$P < .05$.

[c]Percent emphysema was adjusted for type of CT scanner at different institutions.

[d]Total lung capacity and functional residual capacity were adjusted for height, age, sex, and race in multivariate analysis.

[e]Airway data performed in a subset of patients (CB+, n = 242; CB− n = 620).

an independent association on multivariate analysis. In multivariate analysis with multiple logistic regression, CB was independently associated with increased respiratory symptoms when adjusting for age, current smoking, pack-year history of smoking, sex, and race (Table 3).

The CB+ group had a greater history of exacerbations in the previous year (1.21 ± 1.62 vs 0.63 ± 1.12 per patient, $P = .027$), and more patients in the CB+ group reported a history of severe exacerbations in the previous year (26.6% vs 20.0%, $P = .024$) (Fig 2). The increased exacerbation history in the CB+ group was statistically significant in multivariate analysis controlling for age, current smoking, pack-year history of smoking, sex, and race (all exacerbations prevalence ratio, 1.60; 95% CI, 1.41-1.82; severe exacerbations prevalence ratio, 1.39; 95% CI, 1.24-1.56). Within each GOLD stage, the CB+ group had a significantly greater exacerbation history. The difference in total exacerbation history was greatest in the subgroup with GOLD stage IV disease (GOLD stage II, 0.83 ± 1.24 vs 0.42 ± 0.82 per patient; GOLD stage III, 1.44 ± 1.81 vs 0.78 ± 1.30 per patient; GOLD stage IV, 1.89 ± 1.91 vs 0.93 ± 1.21 per patient). Current smokers in the CB+ group had fewer exacerbations than ex-smokers (0.9 ± 1.6 vs 1.5 ± 1.6 per patient, $P = .0031$).

Radiographic measurements are summarized in Table 2. Percent gas trapping (CB+, 42.0% ± 20.0%; CB−, 42.8% ± 20.3%; $P = .593$) and percent emphysema (CB+, 14.2% ± 13.0%; CB−, 16.0% ± 13.4%, $P = .212$) were similar in each group. Total lung capacity (6.30 ± 1.50 L vs 5.88 ± 1.40 L, $P = .0001$) and functional residual capacity (4.22 ± 1.19 L vs 3.92 ± 1.28 L, $P = .002$) were greater in the CB+ group. When lung volumes were adjusted for age, height, race, and sex in multivariate analysis, the differences in total lung capacity between groups remained statistically significant (point estimate, 1.08; 95% CI, 1.05-1.12). Functional residual capacity, however, only tended to be different between groups after these adjustments (point estimate, 1.07; 95% CI, 0.99-2.29). There were 242 subjects in the CB+ group and 620 in the CB− group with available data on radiographic airway measurements. The CB+ group had a higher mean WA% (63.2% ± 2.9% vs 62.6% ± 3.1%, $P = .013$), but there was no difference in mean AWT (1.60 ± 0.21 mm vs 1.60 ± 0.22 mm, $P = .700$) or 10-mm diameter airway (3.800 ± 0.129 mm vs 3.798 ± 0.126 mm, $P = .816$).

Discussion

In this large, cross-sectional, multicenter study, we describe with great precision the clinical phenotype

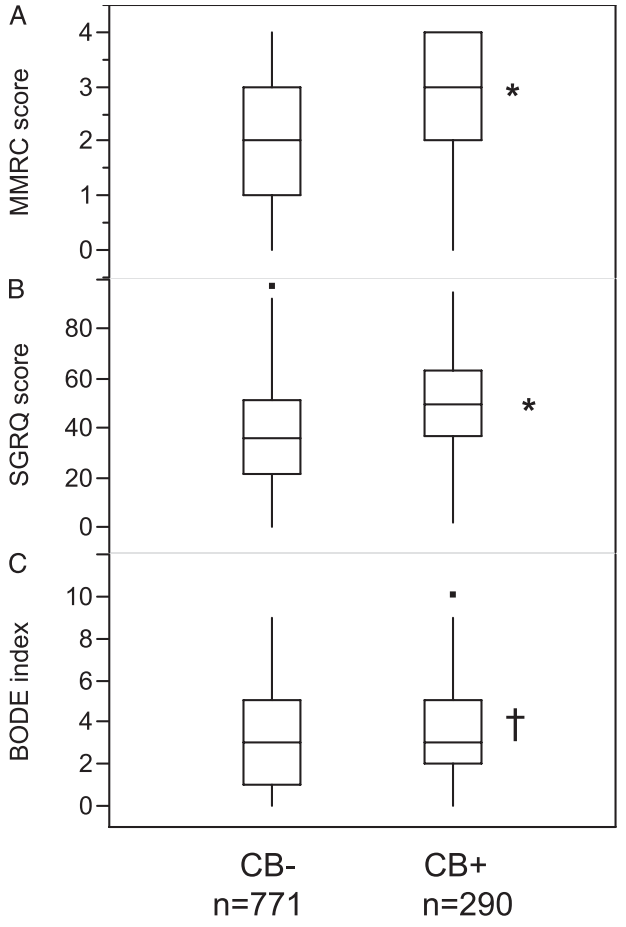

FIGURE 1. Dyspnea, quality of life, and BODE index in each group. A, MMRC scores. B, SGRQ scores. C, BODE index scores. MMRC scores, SGRQ scores, and BODE index scores in the CB+ group were significantly higher than in the CB− group. Data are presented as median (interquartile range). *$P < .0001$. †$P = .033$. BODE = BMI, airway obstruction, dyspnea, exercise capacity; CB = chronic bronchitis; MMRC = Modified Medical Research Council; SGRQ = St. George Respiratory Questionnaire.

of patients with COPD and CB. With similar lung function, we found subjects with CB to be younger, have a greater smoking history, and have a greater likelihood of current smoking history than subjects without CB. Moreover, those with CB had higher SGRQ scores, a greater degree of breathlessness, and more upper-airway symptoms. These differences in health-related quality of life and dyspnea are equal to or greater than the minimal clinically important difference thresholds for COPD.[29] BODE scores were higher in the CB+ group most likely because of the higher MMRC scores. Finally, there was a higher exacerbation history in the CB+ group, and more subjects in the CB+ group reported severe exacerbations that required hospitalization or urgent care visits. This difference in exacerbation history was most significant in subjects with GOLD stage IV disease.

Table 3—*Independent Effects of CB on Respiratory Symptoms*

Variable	Prevalence Ratio	95% CI
Nasal symptoms	1.55	1.28-1.87
Ocular symptoms	1.32	1.17-1.52
Wheezing	2.36	1.72-3.23
Awakened by cough	1.30	1.18-1.43
Awakened by dyspnea	1.19	1.07-1.31

Prevalence ratios of CB on respiratory symptoms in multivariate analysis, adjusting for age, current smoking, pack-year history of smoking, sex, and race. See Table 1 for expansion of abbreviation.

Exacerbation frequency has been shown to be greater in patients with COPD and CB.[16,17,30] Seemungal et al[16] found that CB significantly increased the odds of having frequent exacerbations in a group of 70 patients. A cross-sectional analysis of 433 patients also similarly found an increased risk of exacerbation.[17] The present study validates these prior findings in a much larger cohort, making the relationship between CB and risk of exacerbation more relevant to the general COPD population. We also demonstrate that the greatest difference in exacerbation history was in the patients with the worst disease severity. Although the assessment of exacerbations lacked validation from medical records and was based on patient reporting of episodes within the year prior to enrollment, the large number of patients in this study adds strength to the conclusion that CB is associated with an increased risk of exacerbation.

Another recent large observational study found a significant, but weak relationship between chronic cough and exacerbation rate.[31] In comparison, the link between CB and exacerbations found in the present study is more significant. Although the cohorts had similar lung function and demographics, the aforementioned study enrolled more patients with frequent exacerbations (47% of entire cohort, compared with 39% in the present one), and the incidence of CB in their cohort is unclear. These differences in subject characteristics are most likely to be responsible for the disparity in results.

Of interest, subjects with CB were more likely to be current smokers. We analyzed the effects of current smoking and found no effect on respiratory symptoms or health-related quality of life and found a lower exacerbation history than in ex-smokers. Therefore, the differences seen in symptoms and SGRQ scores between the CB+ and CB− groups cannot be attributed to current smoking alone, and the fewer exacerbations in the current smokers may have been related to better lung function. In addition, there was a trend toward greater use of oxygen in subjects without CB. Although it is established that oxygen supplementation reduces breathlessness in healthy subjects and those with COPD,[32-34] the use of oxygen in the present cohort did not affect respiratory symptoms and actually was

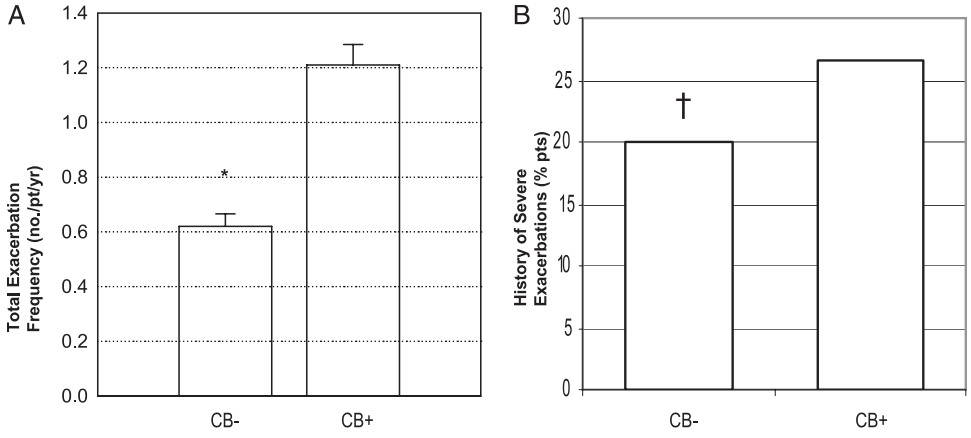

FIGURE 2. Exacerbation rate in each group. A, Total exacerbation rate. B, History of severe exacerbations. Both total exacerbation rate (data are presented as mean ± SE) and history of severe exacerbations were significantly greater in the CB+ group than in the CB− group. *$P < .0001$. †$P = .0238$. pt = patient. See Figure 1 legend for expansion of other abbreviation.

associated with higher SGRQ scores, so the lower percentage of respiratory symptoms and lower SGRQ scores in the CB− group is not explained by oxygen use.

Whether the differences in respiratory symptoms between the two groups represent a true relationship with CB is a matter of debate. It is likely that chronic sputum production has significant physiologic effects on airflow, causing greater dyspnea and worse health-related quality of life. Indeed, we have shown that in high-risk patients with severe COPD, chronic sputum production was associated with a lower peak expiratory flow when measured daily for up to 2 years as well as with more breathlessness and more frequent exacerbations.[18] Alternatively, it is possible that patients who have complaints of chronic cough and sputum production are simply more likely to describe worse respiratory symptoms to health-care providers without any quantifiable difference in airway inflammation or disease severity. We also did not collect information on use of intranasal steroids or leukotriene antagonists, so it is possible that the CB+ group described more upper-respiratory symptoms as a result of underuse of these medications. Finally, no adjustment was made for multiple comparisons, thereby raising the possibility that by chance alone a few comparisons were spuriously statistically significant. However, the differences in symptoms between the two study groups are large and highly statistically significant (P values often $< .0001$), and their presence in this large COPD cohort suggests that the differences are indeed real. Furthermore, the greater symptoms coupled with more exacerbations in subjects with CB underscore their clinical significance.

Interestingly, the degree of emphysema and gas trapping were similar in each group, which was not consistent with the study hypothesis. We expected that for a given degree of airflow obstruction, subjects with CB would have a greater proportion of expiratory flow limitation caused by airway disease and, therefore, less emphysema and more gas trapping. Although segmental airway WA% was greater in subjects with CB, there were no statistically significant differences in the other two measures of airway disease. This inconsistency suggests that either WA% is a better barometer of airway inflammation than the other measures or that the detected differences are not true, thereby implying that CB may be related more to large airways disease and not to the small airways. This finding also implies that the phenomenon of CB occurs independently from the presence or degree of emphysema. Alternatively, it is possible that our current means of airway radiographic measurement are not sensitive enough to detect real differences in airway pathology or that radiographically quantifiable differences in morphology do not exist, despite at least qualitative differences in airway inflammation. This issue can be clarified with further analysis of our current radiographic data, advances in technology, and the development of different means of quantifying airway pathology.

The higher lung volumes in the CB+ group were also curious findings. These differences could not be completely explained by the differences in age, sex, and race between the two groups.[24,35] However, it should be realized that these values were based on radiographic measurements, and lung volumes measured by plethysmography were not available in this study. At this time, the significance of this finding is uncertain.

Nevertheless, this large cross-sectional analysis of subjects with COPD and a broad spectrum of disease severity shows with greater precision how subjects with COPD and CB are phenotypically different from subjects with COPD without CB. They are younger, more commonly men, more likely to be current

smokers, and more symptomatic and have more frequent comorbidities. Eliciting a history of CB can identify a group with worse lower- and upper-airway symptoms, greater risk of exacerbation, and worse prognosis. The clinician also should maintain a heightened suspicion for diabetes, coronary heart disease, osteoporosis, and sleep apnea in this patient population. This group may need more directed therapy targeting chronic mucus production and smoking cessation not only to improve symptoms but also to reduce risk, improve quality of life, and improve outcomes.

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Dr Kim: contributed to the study design, data collection and analysis, and writing of the manuscript.
Dr Han: contributed to the study design, data collection and analysis, and writing of the manuscript.
Ms Vance: contributed to the study design, data collection and analysis, and writing of the manuscript.
Dr Make: contributed to the study design, data collection and analysis, and writing of the manuscript.
Dr Newell: contributed to the study design, data collection and analysis, and writing of the manuscript.
Dr Hokanson: contributed to the study design, data collection and analysis, and writing of the manuscript.
Dr Hersh: contributed to the study design, data collection and analysis, and writing of the manuscript.
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RESPIRATORY RESEARCH

RESEARCH Open Access

Reduction of exacerbations by the PDE4 inhibitor roflumilast - the importance of defining different subsets of patients with COPD

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Abstract

Background: As chronic obstructive pulmonary disease (COPD) is a heterogeneous disease it is unlikely that all patients will benefit equally from a given therapy. Roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor, has been shown to improve lung function in moderate and severe COPD but its effect on exacerbations in unselected populations was inconclusive. This led to the question of whether a responsive subset existed that could be investigated further.

Methods: The datasets of two previous replicate, randomized, double-blind, placebo-controlled, parallel-group studies (oral roflumilast 500 μg or placebo once daily for 52 weeks) that were inconclusive regarding exacerbations were combined in a post-hoc, pooled analysis to determine whether roflumilast reduced exacerbations in a more precisely defined patient subset.

Results: The pooled analysis included 2686 randomized patients. Roflumilast significantly decreased exacerbations by 14.3% compared with placebo (p = 0.026). Features associated with this reduction were: presence of chronic bronchitis with or without emphysema (26.2% decrease, p = 0.001), presence of cough (20.9% decrease, p = 0.006), presence of sputum (17.8% decrease, p = 0.03), and concurrent use of inhaled corticosteroids (ICS; 18.8% decrease, p = 0.014). The incidence of adverse events was similar with roflumilast and placebo (81.5% vs 80.1%), but more patients in the roflumilast group had events assessed as likely or definitely related to the study drug (21.5% vs 8.3%).

Conclusions: This post-hoc, pooled analysis showed that roflumilast reduced exacerbation frequency in a subset of COPD patients whose characteristics included chronic bronchitis with/without concurrent ICS. These observations aided the design of subsequent phase 3 studies that prospectively confirmed the reduction in exacerbations with roflumilast treatment.

Trials registration: ClinicalTrials.gov identifiers: NCT00076089 and NCT00430729.

Background

Chronic obstructive pulmonary disease (COPD) is a highly prevalent condition and a major cause of morbidity and mortality worldwide [1-3]. As the disease progresses, patients with COPD report more frequent exacerbations, which are associated with an increased mortality risk and greater health care utilization, hospital admissions and costs [4]. Worse, frequent exacerbations are associated with a faster decline in lung function and increased mortality [5].

Phosphodiesterase 4 (PDE4) inhibitors are effective anti-inflammatory agents in animal models and have been shown to reduce markers of inflammation in COPD [6,7]. In a 6-month study in patients with moderate-to-severe COPD (post-bronchodilator mean forced expiratory volume in 1 second [FEV_1] 54% predicted [8]), the PDE4 inhibitor roflumilast improved lung function and reduced exacerbations [9]. This led to two subsequent 12-month studies (M2-111, reported here for the first time, and M2-112 [10]) in patients with severe-

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to-very-severe COPD, which confirmed the positive effect of roflumilast on lung function. Although neither study demonstrated a significant effect on exacerbations, which was a co-primary endpoint, a trend towards lower overall exacerbation rates with roflumilast was seen in each study.

As COPD is a highly heterogeneous disease [11], the possibility that a subset of the COPD population might be more responsive to roflumilast-induced reduction in exacerbations was entertained. To test this hypothesis, the results from the two 12-month studies, that were inconclusive with regard to exacerbations, were pooled and a series of post-hoc analyses performed. The results of these analyses are presented in the current report. The heterogeneity of the COPD patient population is well recognized. However, clinically meaningful subsets of patients with COPD have been difficult to define and several large observational studies are currently underway to attempt to address this problem [12-14]. The current post-hoc analysis of pooled clinical trial data was conducted in order to define a subset of patients with COPD who are likely to respond to a specific therapy - a 'hypothesis-generating' exercise that has been confirmed in subsequent clinical trials [15]. The approach described in the current study may be applicable to define other meaningful subsets of patients with COPD.

Methods

Patients and study design

M2-111 was conducted between December 2003 and December 2005 in 188 centers in 6 countries, and M2-112 between January 2003 and October 2004 in 159 centers in 14 countries. Full details of the methodology, patient selection and efficacy assessments have been published previously for M2-112 [10]. (For details of the clinical design of both trials, and a CONSORT diagram for the unpublished study M2-111, see Additional file 1, Appendix 1, and Additional file 1, Figure S1).

The studies were approved by local ethical review committees (see Additional file 1, Appendix 2 for a list of committee names and approval numbers) and performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Statistical analysis

The statistical analysis was performed as described previously [10] with some modifications (i.e., all data were re-analyzed based on the methods used in two other 52-week studies) [15]. The primary endpoint (pre-bronchodilator FEV_1) and main secondary lung function endpoint (post-bronchodilator FEV_1) were evaluated using a repeated measures analysis of covariance (ANCOVA, mixed effects model). This model is able to handle missing data points by taking into account all available data from scheduled visits of the treatment period and the correlation in repeated measurements. The co-primary endpoint of rate of moderate or severe exacerbations per patient per year was defined by the need for oral or parenteral corticosteroid treatment, hospitalization, or death, and was evaluated using a Poisson regression model with a correction for over-dispersion. The natural logarithm of the trial duration, in terms of years, was included in this model as an off-set variable to correct for the time a patient participated in the trial. Rate ratios from this model were expressed as percent reductions. Time to onset of exacerbations was analyzed using a Cox proportional hazards regression model. For the regression models (ANCOVA, Poisson, and Cox), the covariates included treatment (roflumilast/placebo), age, sex, smoking status (current/former smoker), study, concomitant treatment with inhaled corticosteroids (ICS) and country pool (only for the overall population). In the Poisson regression analysis, baseline post-bronchodilator FEV_1 (% of predicted value) was also included as a covariate. Adverse events were analyzed using descriptive statistics.

Data are presented as mean and standard deviation (SD), unless otherwise indicated. Safety endpoints were analyzed using descriptive statistics. Results are presented as mean ± SD or standard error (SE) as appropriate, with data derived from the statistical modeling being adjusted means. All p values are reported two-sided with a level of significance of 0.05.

To identify subpopulations, the two primary endpoints were analyzed additionally in subgroups stratified by sex, smoking status, concomitant use of ICS, concomitant use of anticholinergics, study completion status, COPD severity (severe, very severe), history of chronic bronchitis or emphysema (investigator-diagnosed), as well as cough and sputum score during the week before randomization.

Results

Patients

Of 3630 patients enrolled into the run-in period, 2686 patients met the inclusion criteria and were randomized to treatment; 1905 patients completed the studies (Figure 1). The reasons for withdrawal were similar between groups except for adverse events, which occurred more frequently with roflumilast.

Demographics and baseline characteristics of the randomized patients were comparable between treatments (Table 1). Patients were predominantly male, and spirometric severity was consistent with severe-to-very-severe disease [8]. FEV_1 reversibility to short-acting β_2-agonists was similar in both treatment groups. As the inclusion criterion of FEV_1 reversibility to short-acting β_2-agonists

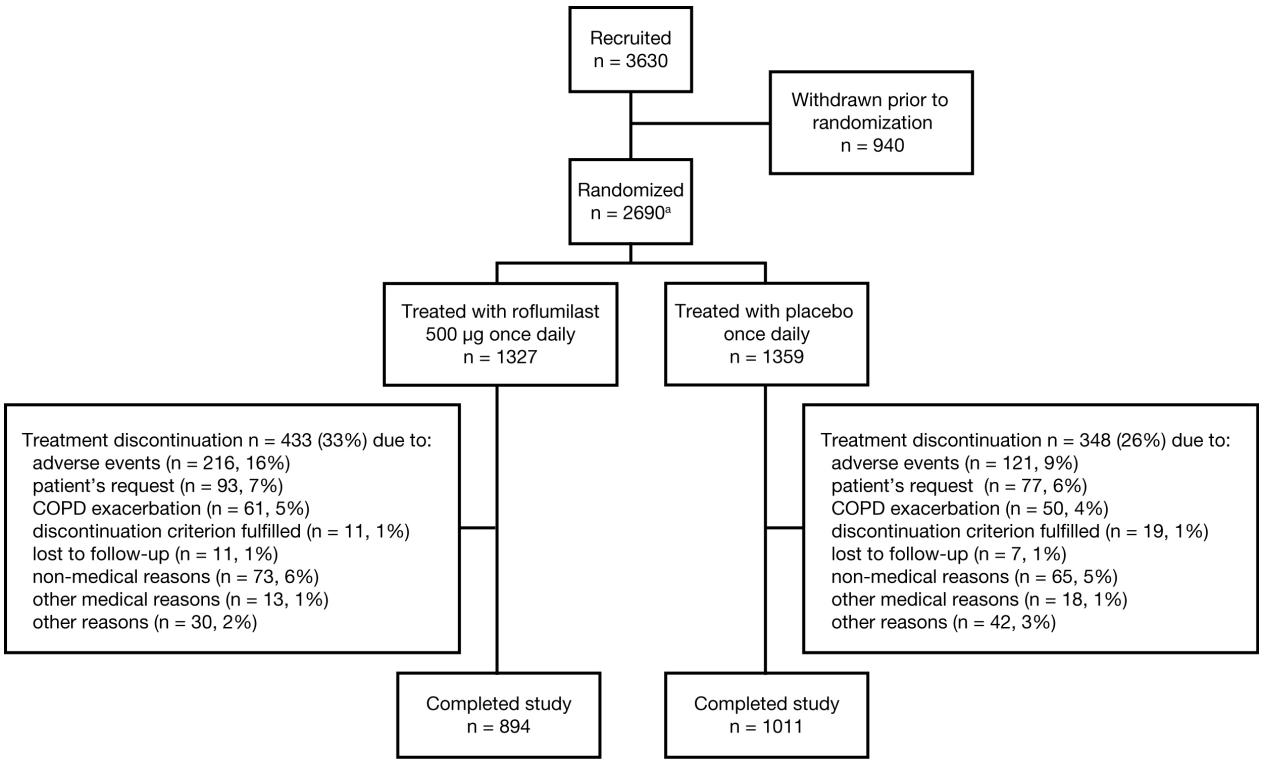

Figure 1 Trial profiles of M2-111 and M2-112. Percentages are based on the number of randomized patients in a treatment group.

≤15% was defined only in study M2-112, mean reversibility was lower in M2-112 (11%) than in M2-111 (19%). All other demographic and baseline characteristics were comparable (or with only small differences not considered clinically relevant) between the two studies. On study entry and during the course of the studies, about 60% of the patients continued to receive ICS, while 60% continued to receive short-acting anticholinergics (Table 1).

Exacerbations

The rate of moderate-to-severe exacerbations in the pooled analysis was 14.3% lower with roflumilast compared with placebo (0.52 vs 0.61 exacerbations per year; p = 0.026, Table 2 and Figure 2). However, the median time to first moderate or severe exacerbation was comparable in the roflumilast and placebo groups (120 and 126 days, respectively, p = 0.236).

There were several subgroups in which the exacerbation rate appeared lower with roflumilast compared with placebo (Table 2), including patients with chronic bronchitis with or without emphysema (26.2% reduction in exacerbation rate vs placebo; p = 0.001). Other subgroups, such as current vs former smokers or those based on spirometrically defined COPD severity, showed no or little difference in the exacerbation rate with roflumilast. Patients receiving concomitant ICS experienced an 18.8% reduction in exacerbations compared with placebo (p = 0.014). Patients not receiving ICS exhibited no clinical benefit compared with placebo (Table 2). A significant reduction in exacerbation rate in favor of roflumilast was also seen in the subgroup of patients receiving concomitant short-acting anticholinergic treatment (18.3%, p = 0.012).

Lung function

Treatment with roflumilast resulted in significant improvement in pre-bronchodilator FEV_1 compared with placebo. In the combined analysis, the improvement was evident at Week 4 (first measured time point) and maintained throughout the 52 weeks of the studies. After 52 weeks, the change in pre-bronchodilator FEV_1 from baseline with roflumilast versus placebo was 51 mL (SE 7 mL, p < 0.0001), while the change in post-bronchodilator FEV_1 with roflumilast vs placebo was 53 mL (SE 8 mL, p < 0.0001) (Figure 3; and see Additional file 1, Table S1). In contrast to the effect on exacerbations, roflumilast consistently showed a significant improvement compared with placebo in pre-bronchodilator FEV_1 in all subgroups; the same was

Table 1 Demographics and baseline characteristics

	Pooled study population		M2-111		M2-112	
Characteristics	**Roflumilast**	**Placebo**	**Roflumilast**	**Placebo**	**Roflumilast**	**Placebo**
No. of patients	1327	1359	567	606	760	753
Age (years)	64.7 (9.2)	64.4 (8.9)	64 (8.7)	64 (8.8)	65 (9.6)	64 (9.1)
Male sex, n (%)	958 (72.2)	974 (71.7)	387 (68.3)	400 (66.0)	571 (75.1)	574 (76.2)
Body mass index, kg/m^2	25.7 (5.3)	25.7 (5.4)	26.0 (5.7)	25.8 (5.7)	25.4 (5.0)	25.6 (5.1)
Smoking status						
Current smokers, n (%)	529 (40)	530 (39)	240 (42)	265 (44)	289 (38)	265 (35)
Former smokers, n (%)	798 (60)	829 (61)	327 (58)	341 (56)	471 (62)	488 (65)
Pack-years (± SD)	46 (25.6)	48 (26.6)	50 (28.2)	51 (26.7)	42 (22.9)	45 (26.2)
Pre-bronchodilator FEV_1 (L)	1.0 (0.4)	1.0 (0.3)	0.96 (0.4)	0.93 (0.3)	1.04 (0.4)	1.06 (0.3)
Post-bronchodilator FEV_1 (L)	1.13 (0.4)	1.13 (0.4)	1.12 (0.4)	1.09 (0.4)	1.13 (0.4)	1.15 (0.4)
Post-bronchodilator FEV_1 (% predicted)	37.1 (10.5)	36.8 (9.9)	36.8 (10.7)	36.1 (9.7)	37.3 (10.3)	37.3 (9.9)
Reversibility:						
Change in FEV_1 (mL)	126.9 (140.1)	125.8 (149.1)	165.6 (142.8)	160.9 (150.0)	98.1 (130.9)	97.6 (142.4)
Change in FEV_1 (%)	14.6 (16.4)	14.4 (16.4)	19.4 (17.1)	19.1 (17.6)	11.0 (14.8)	10.6 (14.4)
FEV_1/FVC (%)	41.8 (11.3)	41.8 (10.7)	43.3 (10.7)	43.1 (10.1)	40.6 (11.5)	40.7 (11.2)
COPD severity, n (%)						
Very severe COPD	329 (24.8)	345 (25.4)	148 (26.1)	169 (27.9)	181 (23.8)	176 (23.4)
Severe COPD	864 (65.1)	909 (66.9)	356 (62.8)	399 (65.8)	508 (66.8)	510 (67.7)
COPD history, n (%)						
Emphysema	352 (26.5)	413 (30.4)	193 (34.0)	234 (38.6)	159 (20.9)	179 (23.8)
Chronic bronchitis ± emphysema	817 (61.6)	847 (62.3)	374 (66.0)	372 (61.4)	443 (58.3)	475 (63.1)
Pre-study medication for COPD, n (%)*	1273 (96)	1291 (95)	537 (95)	557 (92)	736 (97)	734 (98)
Inhaled short-acting β agonists	729 (55)	734 (54)	315 (56)	333 (55)	414 (55)	401 (53)
Inhaled corticosteroids	579 (44)	588 (43)	218 (38)	225 (37)	361 (48)	363 (48)
Inhaled short-acting anticholinergics	549 (41)	570 (42)	189 (33)	192 (32)	360 (47)	378 (50)
Inhaled long-acting β_2-agonists	353 (27)	379 (28)	143 (25)	140 (23)	210 (28)	239 (32)
Xanthines	320 (24)	316 (23)	113 (20)	118 (20)	207 (27)	198 (26)
Inhaled combination of β_2-agonists and short-acting anticholinergics	323 (24)	314 (23)	168 (30)	174 (29)	155 (20)	140 (19)
Inhaled combination of corticosteroids and long-acting β_2-agonists	260 (20)	263 (19)	131 (23)	139 (23)	129 (17)	124 (17)
Concomitant short-acting anticholinergics, n (%)	786 (59)	818 (60)	334 (59)	350 (58)	452 (60)	468 (62)
Concomitant inhaled corticosteroids, n (%)	809 (61)	813 (60)	328 (58)	332 (55)	481 (63)	481 (64)

Data are expressed as mean (SD), unless otherwise stated.

* Patients could have received more than one of these medications.

seen for post-bronchodilator FEV_1 (see Additional file 1, Table S1). In the group of patients with COPD associated with chronic bronchitis or combined emphysema and chronic bronchitis, those patients receiving concomitant ICS showed a greater improvement from baseline with roflumilast vs placebo (see Additional file 1, Table S1).

Health status

In the combined analysis, treatment with roflumilast resulted in no significant improvement in St George's Respiratory Questionnaire (SGRQ) total score compared with placebo. In contrast, in the subgroup analysis (Figure 4; and see Additional file 1, Table S2), a significant improvement in SGRQ total score was observed for individuals with chronic bronchitis ($p = 0.0265$). This difference was also evident in patients with chronic bronchitis who were concurrently treated with ICS ($p = 0.0397$).

Safety

Adverse events were similar to those reported for roflumilast in previous studies (see Additional file 1, Appendix 3). Importantly, roflumilast (compared with placebo)

Table 2 Analysis of exacerbations (moderate to severe)

	Roflumilast		Placebo		Effect size		
Characteristic	**n**	**Rate**	**n**	**Rate**	**Rate ratio (SE)**	**Change (%)**	**p value**
M2-111	567	0.595	606	0.692	0.860 (0.085)	-14.0	0.129
M2-112	760	0.455	753	0.537	0.848 (0.081)	-15.2	0.085
Pooled results							
Overall	1327	0.523	1359	0.610	0.857 (0.059)	-14.3	0.026
Sex							
Female	369	0.612	385	0.648	0.943 (0.117)	-5.7	0.637
Male	958	0.495	974	0.609	0.813 (0.071)	-18.7	0.018
Smoking status							
Current smoker	529	0.529	530	0.643	0.823 (0.094)	-17.7	0.086
Former smoker	798	0.568	829	0.663	0.857 (0.078)	-14.3	0.092
Concomitant treatment							
ICS	809	0.720	813	0.886	0.812 (0.068)	-18.8	0.014
No ICS	518	0.424	546	0.460	0.923 (0.124)	-7.7	0.550
Concomitant treatment							
Short-acting anticholinergics	786	0.706	818	0.864	0.817 (0.066)	-18.3	0.012
No short-acting anticholinergics	541	0.368	541	0.370	0.995 (0.147)	-0.5	0.974
COPD severity							
Very severe COPD	329	0.738	345	0.885	0.833 (0.101)	-16.7	0.132
Severe COPD	864	0.526	909	0.609	0.864 (0.080)	-13.6	0.113
COPD history							
Emphysema	352	0.579	413	0.586	0.989 (0.120)	-1.1	0.925
Chronic bronchitis ± emphysema	817	0.486	847	0.659	0.738 (0.068)	-26.2	0.001
Chronic bronchitis ± emphysema with concomitant ICS	492	0.608	493	0.871	0.698 (0.077)	-30.2	0.001
Chronic bronchitis ± emphysema: no ICS	325	0.391	354	0.462	0.845 (0.140)	-15.5	0.310
Cough score at Week 0							
≥ 1 (average/day)	896	0.560	939	0.708	0.791 (0.067)	-20.9	0.006
< 1 (average/day)	395	0.523	385	0.508	1.030 (0.142)	3.0	0.830
Sputum score at Week 0							
≥ 1 (average/day)	829	0.576	862	0.700	0.822 (0.074)	-17.8	0.030
< 1 (average/day)	458	0.512	460	0.549	0.933 (0.113)	-6.7	0.565
Study completion status							
Completers	894	0.453	1011	0.573	0.790 (0.064)	-21	0.004
Non-completers	433	1.126	348	1.155	0.975 (0.113)	-2.5	0.826

Rates (per patient/year), Rate ratio and two-sided p-values (significance level 5%) are based on a Poisson regression model with the following factors and covariates: treatment, age, sex, smoking status, baseline post-bronchodilator FEV_1 (% predicted), study, concomitant treatment with ICS and country pool (only for the overall population).

was not associated with an increase in adverse events in the subgroups that experienced a greater reduction in exacerbations with roflumilast compared with placebo (Table 3; and see Additional file 1, Appendix 3). Concomitant ICS did not affect the adverse event profile of roflumilast.

Discussion

PDE4 inhibitors have demonstrated an anti-inflammatory effect in animal models and patients with COPD [6,7]. In two previous 12-month studies, in patients with severe-to-very-severe COPD, roflumilast improved lung function, although neither study demonstrated a significant effect on exacerbations [10]. Given the pleiotropic effects of PDE4 inhibition [16], we hypothesized that a roflumilast effect could be present in specific subgroups of patients with COPD. In addition, exacerbation rates in the individual trials were lower than expected. Combining the datasets of the two studies improved statistical power and allowed definition of the patients more likely to respond to roflumilast. In the combined dataset, a significant effect of roflumilast was observed for the entire population but, importantly, the subgroup analysis showed a preferential effect in patients with chronic

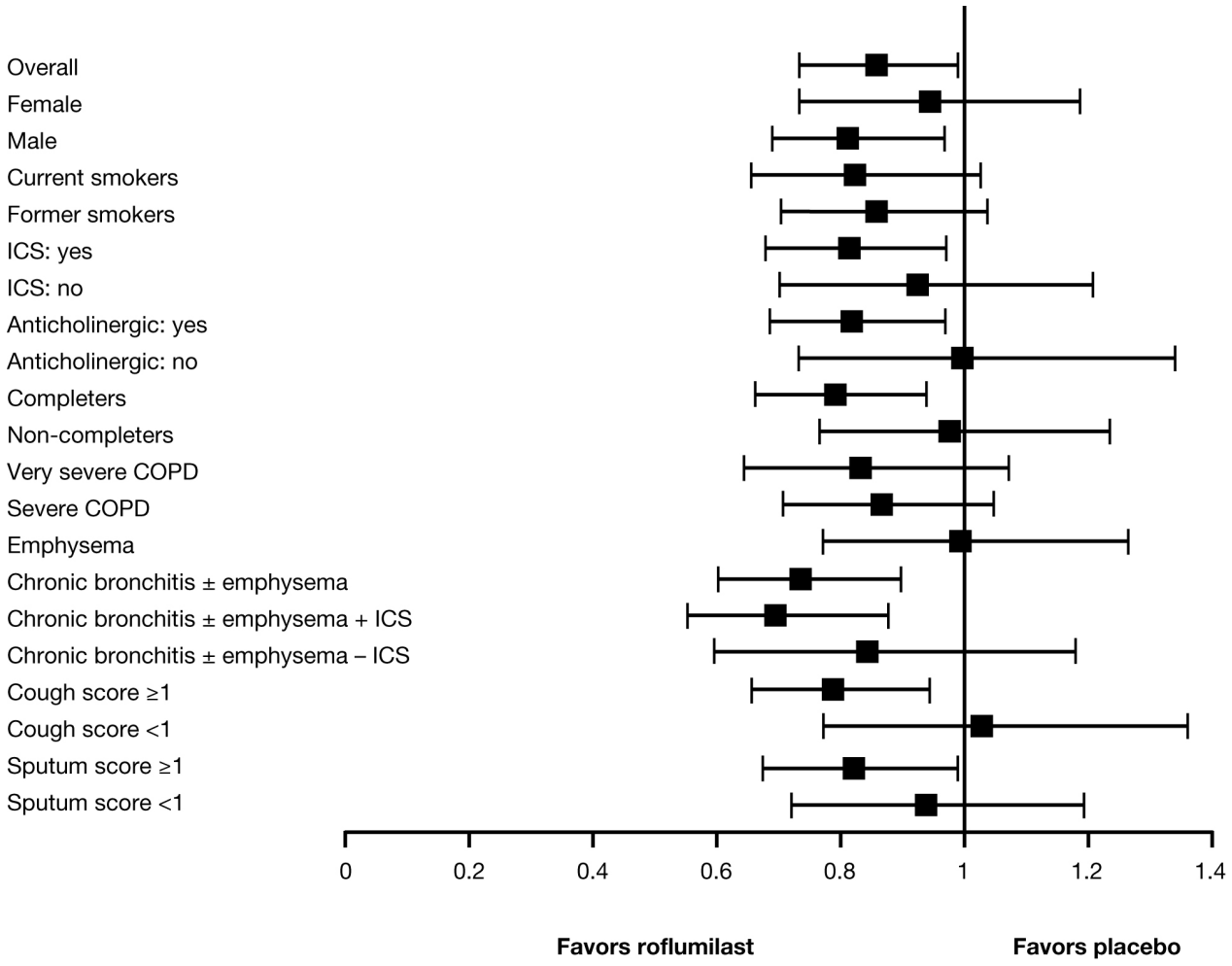

Figure 2 Rate ratios and 95% CIs for reduction in COPD exacerbations with roflumilast by patient subgroup. Error bars represent 95% CIs.

bronchitis or with high cough or sputum scores in the week prior to randomization, and in patients taking concomitant ICS or anticholinergics. These results suggested that it is possible to identify a subset of patients that is more likely to benefit from roflumilast with regard to reduced exacerbations.

In subjects with chronic bronchitis, this post-hoc, pooled analysis suggested a benefit of roflumilast on health status as measured by the SGRQ. The difference, compared with placebo, of -1.073 units did not achieve the conventional minimum important difference of 4 units, but was statistically significant and similar to differences seen between therapy in other 1-year trials [17]. This is consistent with the benefit in SGRQ resulting from the reduction in exacerbations.

Interestingly, roflumilast demonstrated a consistent effect on airflow, assessed as both pre- and post-bronchodilator FEV_1 across all subgroups. There are several possibilities why the effect on exacerbations may be limited to a subset of patients. First, the subsets may identify those individuals at greater risk for exacerbations. A therapeutic benefit can be observed only if the individuals are at risk. Alternatively, as roflumilast can affect many aspects of the inflammatory response, it is possible that an anti-inflammatory effect, such as reduction in airway edema, may account for the improved airflow and a different mechanism accounts for the reduced exacerbations.

The effects seen with roflumilast in symptomatic patients and in patients with chronic bronchitis are comparable with those obtained by ICS/long-acting bronchodilator combination therapy [18-20]. The enhanced benefit of roflumilast in patients with chronic bronchitis is particularly interesting as this phenotype has been shown to be associated with serum markers indicative of increased systemic inflammation [21]. These patients are also at higher risk for mortality at a younger age [21]. The trend for a greater benefit in

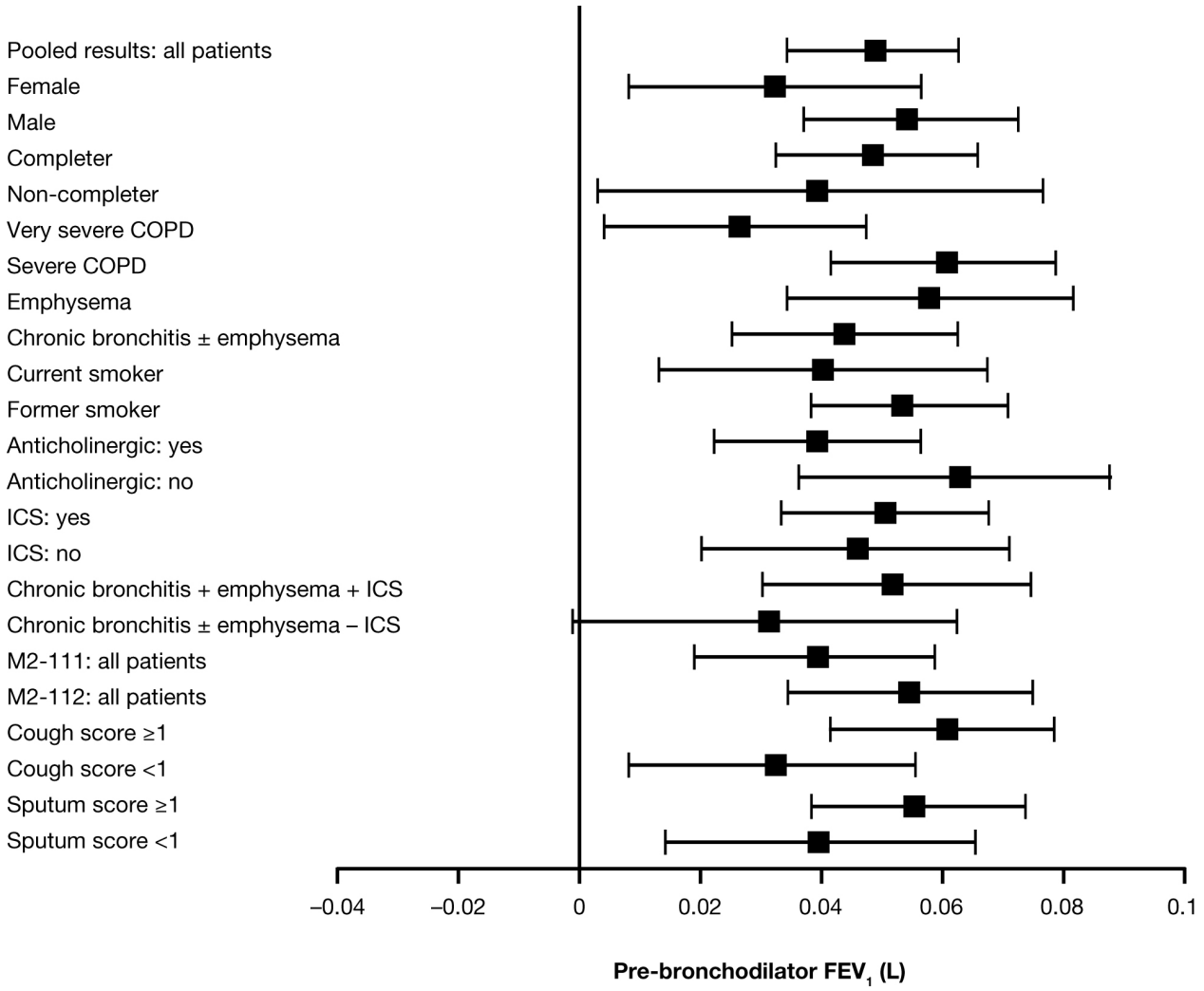

Figure 3 Differences and 95% CIs between roflumilast and placebo for increase in pre-bronchodilator FEV_1 (L) by patient subgroup. Error bars represent 95% CIs.

patients receiving concomitant ICS may be a marker of disease severity. This patient subgroup is at higher risk for exacerbations, indicated by the higher exacerbation rate in the placebo group in ICS-treated patients vs non ICS-treated patients (0.886 vs 0.460). That these individuals had been identified by their clinicians for treatment with ICS suggests that they were recognized as being at risk clinically and that further reductions in exacerbations and improved airflow were observed with roflumilast in this group suggests that a PDE4 inhibitor may add incremental value to ICS therapy.

Although the incidence of adverse events was comparable between treatment groups, there were more discontinuations due to adverse events with roflumilast compared with placebo. The majority of adverse events in both groups lasted less than 4 weeks and resolved with continued treatment. The incidence of treatment-related adverse events was low and similar to those reported previously [9,18]. These treatment-related events included diarrhea, nausea, and headache, which are all adverse events known to be associated with PDE4 inhibitors [22]. Weight loss was more frequent with roflumilast treatment. Several serious adverse events and deaths occurred, as would be expected in this patient population. The number of deaths was higher in the placebo group and most fatal events were related to COPD. A slightly higher incidence of adverse events and serious adverse events was seen in patients receiving ICS; this was seen in both the roflumilast and placebo groups. Oropharyngeal adverse events typically associated with ICS treatment, such as oral candidiasis, dysphonia, and pharyngitis, as well as pneumonia, were more frequently reported in patients treated with ICS, but there was no indication that roflumilast increased

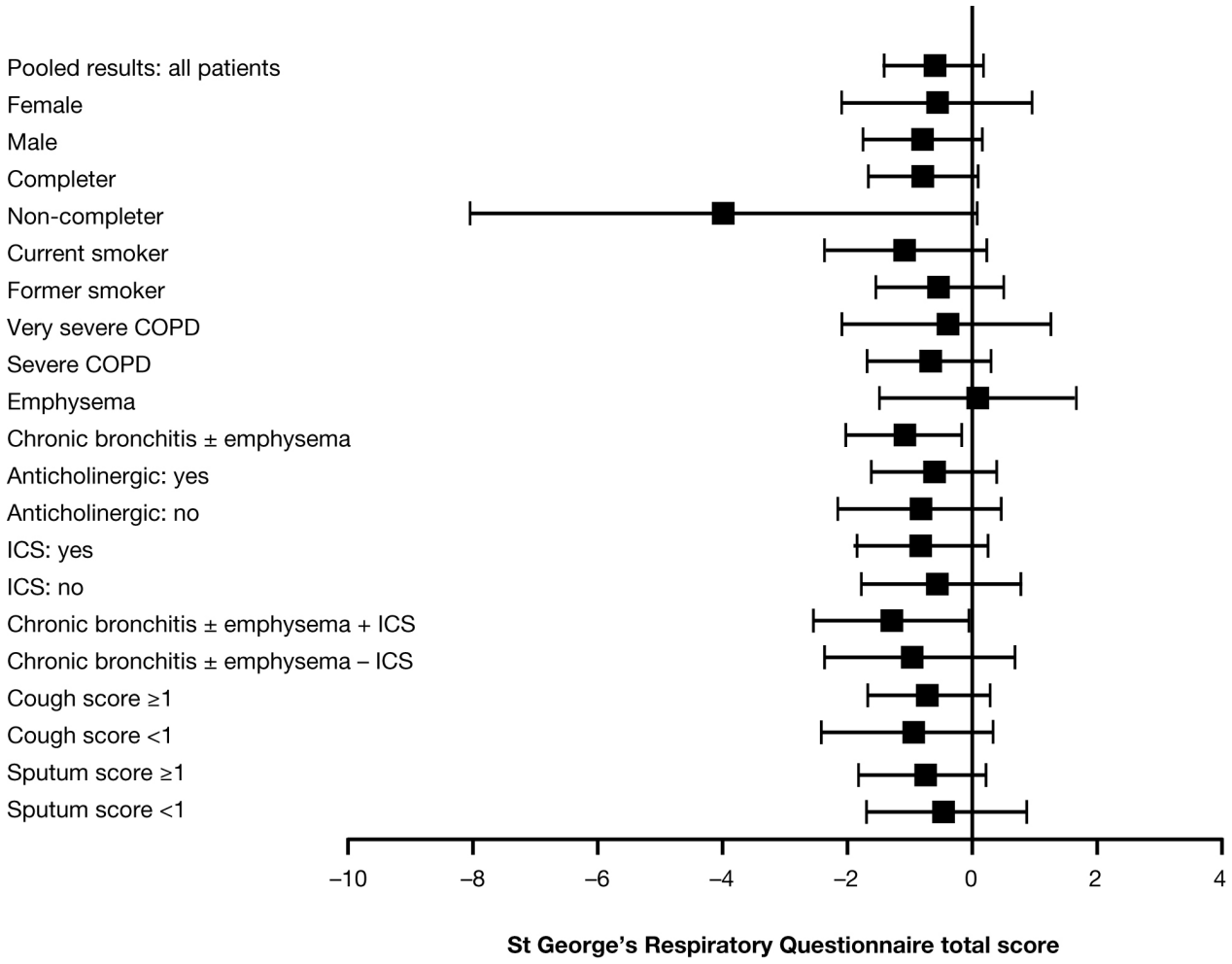

Figure 4 Differences and 95% confidence intervals between roflumilast and placebo for changes in St George's Respiratory Questionnaire (SGRQ) total score by patient subgroup. Error bars represent 95% CIs.

ICS-associated adverse events. Importantly, subjects with chronic bronchitis who were more likely to benefit from roflumilast did not experience an increased incidence of adverse events. On the contrary, there was a trend for these individuals to have fewer of the adverse events (nausea, diarrhea, and weight loss) that are associated with PDE4 inhibitors.

There are limitations to the pooled analysis presented in this manuscript, which includes both fully published and previously unpublished results. The post-hoc nature of the comparisons, particularly those in various subsets, must be interpreted with caution and serve principally as hypothesis generating. However, these results were used to design two additional randomized trials that specifically evaluated patients with severe COPD associated with chronic bronchitis, a group expected to be more likely to experience reductions in exacerbations with roflumilast. In this defined population, a significant beneficial effect of roflumilast compared with placebo in both lung function and exacerbation rate was observed in both studies [15]. In this context, the sequence of studies is crucial. Following a phase 2 trial that showed promising results [9], two 'conventional' 12-month phase 2 trials (Study M2-111, reported here for the first time, and M2-112 [10]) were conducted, both of which showed improvements in FEV_1 but demonstrated only a trend toward exacerbation reduction. The pooled analysis presented here demonstrated that a subset of the COPD population appeared to account for all the benefit with regard to exacerbations. This 'hypothesis' formed the basis of two subsequent trials [15] which demonstrated the efficacy of roflumilast for exacerbation reduction in this subset.

Novel therapies for COPD are urgently needed [11]. The current manuscript describes the successful use of a strategy for identification of a responding subset from

Table 3 Adverse events

Subgroup	All patients		COPD history				CB ± emphysema and ICS treatment			
			Emphysema		CB ± emphysema		With ICS		Without ICS	
Treatment (n)	Rof (1327)	Pbo (1359)	Rof (352)	Pbo (413)	Rof (817)	Pbo (847)	Rof (492)	Pbo (493)	Rof (325)	Pbo (354)
Adverse events, n (% of patients)										
All adverse events	1081 (81.5)	1089 (80.1)	309 (87.8)	344 (83.3)	642 (78.6)	673 (79.5)	402 (81.7)	399 (80.9)	240 (73.8)	274 (77.4)
All serious adverse events	263 (19.8)	264 (19.4)	73 (20.7)	81 (19.6)	154 (18.8)	152 (17.9)	112 (22.8)	109 (22.1)	42 (12.9)	43 (12.1)
Adverse events related to study medication	285 (21.5)	113 (8.3)	91 (25.9)	39 (9.4)	134 (16.4)	67 (7.9)	77 (15.7)	35 (7.1)	57 (17.5)	32 (9.0)
Adverse events leading to study discontinuation	235 (17.7)	136 (10.0)	52 (14.8)	40 (9.7)	94 (11.5)	56 (6.6)	65 (13.2)	40 (8.1)	29 (8.9)	16 (4.5)
Most common adverse events (≥ 5% of patients in any treatment group), %										
COPD exacerbation	42.9	48.0	45.5	47.7	43.0	48.5	49.8	54.4	32.6	40.4
Diarrhea	12.1	2.9	18.5	3.4	7.1	3.1	8.3	3.2	5.2	2.8
Nausea	6.0	1.5	8.0	1.9	4.4	1.3	4.7	1.0	4.0	1.7
Weight loss	7.5	2.8	11.9	4.1	6.1	2.5	5.3	1.6	7.4	3.7
Nasopharyngitis	6.8	7.4	7.7	8.2	7.5	7.7	6.5	7.3	8.9	8.2
Pneumonia	2.8	4.0	1.7	2.9	3.5	4.1	4.3	5.7	2.5	2.0
Upper respiratory tract infection	5.4	6.3	7.4	9.2	5.4	5.5	4.5	5.1	6.8	6.2
Headache	6.9	3.0	8.5	5.3	5.6	2.1	6.1	2.2	4.9	2.0
Influenza	4.4	4.0	5.4	5.3	4.4	3.7	4.5	2.2	4.3	5.6

Rof = roflumilast; pbo = placebo.

clinical trial data that was then confirmed in two prospective, randomized, placebo-controlled clinical trials. At present, segmentation of meaningful sub-populations of COPD patients is difficult, although several large observational studies are addressing this question. The current study demonstrates that this goal can also be achieved by post-hoc analysis of responses to a clinical intervention.

Conclusions

This post-hoc, pooled analysis of two large-scale trials in patients with severe and very severe COPD showed a significant reduction in exacerbations with roflumilast treatment and identified a subgroup of patients who are most likely to benefit from treatment with roflumilast, namely those patients with chronic bronchitis. In addition there was a greater effect in those patients taking concomitant ICS. Identification of a subgroup of patients more likely to respond to therapy is consistent with the concept that the COPD population includes multiple phenotypes and is a step towards personalized medicine, matching therapy to phenotype [11,23,24]. Importantly, identification of a responding subset can facilitate drug development by increasing the ability of clinical trials to show a benefit. In this regard, the analysis presented in the current report was used to design subsequent clinical trials that have demonstrated the clinical efficacy of roflumilast in reducing COPD exacerbations. This is the first time such an approach has been used successfully to aid a drug development program in COPD.

Additional material

Additional file 1: Appendices 1-3, Table S1, Table S2, and Figure S1. Appendix 1: Trial design; Appendix 2: IRB approval; Appendix 3: Adverse events; Table S1: Lung function results summary table (change in lung function variable after 52 Weeks compared with baseline); Table S2: St George's Respiratory Questionnaire (SGRQ) total score: change after 52 Weeks compared with baseline; Figure S1: Trial profile of M2-111.

Additional file 2: List of investigators for Studies M2-111 and M2-112. M2-111 investigators; M2-112 investigators.

Abbreviations

ANCOVA: Analysis of covariance; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; PDE4: phosphodiesterase 4; SD: standard deviation; SE: standard error; SGRQ: St George's Respiratory Questionnaire.

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SIR contributed to the conception and design of these studies, the acquisition of study data, and the analysis and interpretation of these data. He was fully involved in the drafting and revision of this manuscript, and provided final approval of its content ahead of submission. PMAC contributed to the conception and design of these studies, the acquisition of study data, and the analysis and interpretation of these data. He was fully involved in the drafting and revision of this manuscript, and provided final approval of its content ahead of submission. U-MG contributed to the conception and design of these studies, the acquisition of study data, and the analysis and interpretation of these data. He was fully involved in the drafting and revision of this manuscript, and provided final approval of its content ahead of submission. He had full access to all of the data in the study and he takes full responsibility for the integrity of all of the data and the accuracy of the data analysis, including and especially any adverse effects. DB contributed to the conception and design of these studies, the acquisition of study data, and the analysis and interpretation of these data. He was fully involved in the drafting and revision of this manuscript, and provided final approval of its content ahead of submission. FJM contributed to the conception and design of these studies, as well as the analysis and interpretation of these data. He was fully involved in the drafting and revision of this manuscript, and provided final approval of its content ahead of submission.

Competing interests
SIR has served on advisory boards and as a consultant for Almirall Prodesfarma, Aradigm Corporation; AstraZeneca, Boehringer Ingelheim, Defined Health, Eaton Associates, GlaxoSmithKline, MEDACorp, Mpex Pharmaceuticals, Novartis, Nycomed, Otsuka Pharmaceutical, Pfizer, Pulmatrix, Theravance, United BioSource Corporation, Uptake Medical, and VantagePoint. He has served as a speaker or a member of a speaker's bureau for: AstraZeneca, Novartis, Network for Continuing Education, Pfizer, and SOMA. He has also received research funding from AstraZeneca, BioMarck, Centocor, Novartis, and Nycomed.
PMAC has served on advisory boards for AstraZeneca, GlaxoSmithKline, Nycomed, and Novartis. He has received research funding from GlaxoSmithKline, Nycomed, and Boehringer Ingelheim, and has spoken at meetings supported by AstraZeneca, GlaxoSmithKline, and Nycomed.
FJM has been a member of advisory boards for GlaxoSmithKline, Schering Plough, Novartis, Nycomed, Genzyme, Forest/Almirall, MedImmune, AstraZeneca, Potomac, Bayer, Elan, Talecris, and Roche. He has been on the speaker's bureau for Boehringer Ingelheim, GlaxoSmithKline, France Foundation, MedEd, NACE, and AstraZeneca. He has also been a member of steering committees for studies supported by Altana/Nycomed, GlaxoSmithKline, Gilead, Actelion, Johnson/Johnson, Mpex, UCB, and the National Institutes of Health. He has been an investigator in trials supported by Boehringer Ingelheim and Actelion.
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ORIGINAL RESEARCH

Long-term azithromycin therapy in patients with severe COPD and repeated exacerbations

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Background: The aim of this study was to determine whether long-term intermittent azithromycin therapy reduces the frequency of exacerbation in severe chronic obstructive pulmonary disease (COPD).

Methods: We retrospectively investigated the clinical benefits of long-term azithromycin (500 mg orally three times per week) over 12 months in patients with severe COPD and a minimum of four acute exacerbations (AECOPD) per year or chronic bronchial colonization by *Pseudomonas aeruginosa*, comparing the number of AECOPD, hospitalizations due to respiratory disease, days of hospital stay, and bacterial infections during azithromycin treatment and in the year prior to this therapy.

Results: Twenty patients who completed the 12-month treatment period were analyzed. No clinically significant adverse events were observed during azithromycin treatment. Compared with baseline data, azithromycin therapy significantly reduced the number of AECOPD (2.8 ± 2.5 versus 6.8 ± 2.8, $P < 0.001$), hospitalizations (1.4 ± 1.5 versus 3.6 ± 1.4, $P < 0.001$), and cumulative annual days of hospital stay (25 ± 32.2 versus 43.7 ± 21.4, $P = 0.01$). The improvement was particularly significant in patients with exacerbations caused by common potentially pathogenic microorganisms, who had 70% fewer AECOPD and hospitalizations. Patients colonized by *P. aeruginosa* had reductions of 43% in AECOPD and 47% in hospitalizations.

Conclusion: Long-term azithromycin is well tolerated and associated with significant reductions in AECOPD, hospitalizations, and length of hospital stay in patients with severe COPD.

Keywords: azithromycin, chronic obstructive pulmonary disease, exacerbation, macrolides

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a frequent event during evolution of the disease,[1] and the mortality risk increases with its frequency, especially when patients require hospitalization.[2,3] Previous studies using protected specimen brushing have shown that bacterial infection could be the etiology in approximately 50% of acute exacerbations of COPD (AECOPD).[4] However, it is sometimes difficult to distinguish colonization from infection when organisms are found in sputum cultures from COPD patients.

Recently, interest in the use of prophylactic antibiotics to prevent AECOPD has increased,[5] and macrolides in this setting have the advantage of having both antibacterial and anti-inflammatory properties. Long-term macrolide therapy is routinely used in two diseases, ie, diffuse panbronchiolitis and cystic fibrosis, both of which involve chronic airway inflammation. Erythromycin is the most commonly used macrolide in diffuse panbronchiolitis, and obtains notable improvements in symptoms and survival.[6]

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Studies in cystic fibrosis have mostly used azithromycin and have found improvement in lung function and a reduced exacerbation frequency.[7,8] These effects are probably due to modulation of the inflammatory response and its ability to impede formation of biofilm.[9] Azithromycin has also been shown to be useful in the treatment of patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*.[10,11]

Given the importance of inflammation[12] and bacterial infection in the pathogenesis of COPD, it has been proposed that macrolides may offer unique advantages as disease-modifying agents. Only two studies to date have analyzed the effectiveness and safety of long-term erythromycin in COPD over a 12-month period, reporting a significant reduction in moderate to severe AECOPD.[13,14] It remains to be established whether the therapeutic effect of erythromycin reflects antimicrobial activity, an immunomodulatory effect, or both. Preliminary data have recently been reported for the MACRO study, a randomized controlled trial evaluating the utility of long-term azithromycin therapy to reduce AECOPD, with promising results.[15] Compared with erythromycin, the prototypical 15 member-ring macrolide, azithromycin, appears to have a better safety profile in long-term use, as well as improved bacteriological activity.[16]

In this study, we investigated: the usefulness of long-term intermittent azithromycin therapy in reducing exacerbation frequency in severe COPD patients at a high risk of AECOPD despite conventional maximum treatment; its impact on the bacteriology of bronchial secretions, examining baseline and follow-up colonization by *P. aeruginosa* or other potentially pathogenic microorganisms; and its impact on the development of resistance to macrolides.

Materials and methods

Subjects

We identified a cohort of 203 patients with severe COPD, with a postbronchodilator forced expiratory volume in one second (FEV_1) <50% of predicted and routinely controlled at the respiratory day care unit of the Sabadell Hospital in Barcelona, Spain, between March 2007 and August 2009. Patients with chronic bronchitis who had repeated AECOPD (at least four exacerbations in the previous year) or chronic bronchial colonization by *P. aeruginosa* treated with long-term azithromycin therapy were recruited for this study. Patients with asthma, significant bronchiectasis, malignancy, unstable heart disease, or liver disease were excluded. Ethical permission for the study was obtained from the Sabadell Hospital ethics committee.

Study design

Retrospective analysis of data for the year before initiation of long-term azithromycin therapy (for 12 months) in patients with severe COPD was undertaken in order to assess the clinical benefits of this treatment to reduce AECOPD frequency. Azithromycin (one 500 mg tablet) was administered three times per week (Monday, Wednesday, Friday), in accordance with standard practice in patients with bronchiectasis associated with cystic fibrosis and chronic bronchial colonization by *P. aeruginosa*.[17]

Patients were classified into three groups according to the potentially pathogenic microorganisms isolated from their sputum samples during AECOPD in the year prior to azithromycin therapy, ie: Group 1, patients with at least two positive cultures for common potentially pathogenic microorganisms (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*); Group 2, patients with chronic bronchial colonization by *P. aeruginosa* (at least three consecutive sputum cultures for potentially pathogenic microorganisms during a 6-month period of stability);[18] and Group 3, patients whose cultures alternated between being positive for common potentially pathogenic microorganisms and *P. aeruginosa* during exacerbations but without chronic bronchial colonization by this bacteria.

We compared the following parameters overall and by group before and after the 12-month azithromycin treatment period: number of registered AECOPD; number of hospitalizations due to respiratory disease; and length of hospital stay. We also traced the evolution of positive cultures for potentially pathogenic microorganisms during AECOPD in each group and the development of resistance to azithromycin before and after long-term therapy.

All patients underwent the same scheduled clinical assessments at the respiratory day care unit[19] by the same team of pulmonologists before and after starting long-term azithromycin therapy. At baseline, pulmonary function tests and use of home oxygen therapy were recorded. A high-resolution computed tomography of the chest was performed in all patients in a stable state to assess and quantify possible bronchiectasis. Monitoring visits were conducted every 3 months during the 2 years of study.

Number of registered AECOPD, hospitalizations due to respiratory disease, length of hospital stays, and microbiological isolates in the previous 12 months were recorded just before the initiation of azithromycin therapy and 1 year later. A sputum sample was routinely collected during each AECOPD. All patients received regular treatment with

long-acting beta-agonists, long-acting anticholinergics, and inhaled corticosteroids during the 2 years of study.

When used in patients with chronic *P. aeruginosa* colonization, inhaled colimycin therapy was maintained during the full length of the study and recorded. During follow-up, an electrocardiogram, liver and renal function test, and complete blood count measurements were performed before and after initiation of azithromycin treatment. The appearance of possible adverse events was assessed at each monitoring visit.

Assessment of bronchiectasis

Bronchiectasis in the high-resolution computed tomography scan was scored in each lobe by consensus, using the grading system proposed by Smith et al[20] as follows: 0 if no bronchiectasis was present, 1 if <25% of bronchi were bronchiectatic, 2 if 2%–49% bronchi were bronchiectatic, 3 if 50%–74% bronchi were bronchiectatic, and 4 if ≥75% of the bronchi were bronchiectatic. The lingula was graded as a separate lobe, resulting in a maximum score of 24 per patient. Patients with a score ≤1 were considered normal.

Definition and treatment of exacerbations

AECOPD was defined as a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, of acute onset, and requiring a change in regular treatment (oral corticosteroids and/or antibiotics and/or hospital admission) in a patient with underlying COPD.[21]

A chest radiography was performed for each AECOPD to exclude acute pneumonia. AECOPD were attended from Monday to Friday (8 am to 5 pm) at the respiratory day care unit, always by the same team of pulmonologists.[19] Outside these hours, AECOPD were attended at the emergency department and registered by reviewing the emergency reports.

Antibiotics were prescribed during AECOPD according to Anthonisen's criteria and were adjusted by antibiogram, maintaining azithromycin at the same dose.[22] Indications of hospital admission were made according to clinical practice guidelines.[23]

Bacteriological assessments

Sputum samples were collected from all patients for each AECOPD and were processed locally for Gram stain and bacteriological culture. Identification and antibiogram were performed on all bacterial isolates following standardized microbiological protocols.[24] Positive cultures for *P. aeruginosa* during AECOPD were followed by performing additional sputum cultures at every follow-up visit to identify chronic colonization, diagnosed when three or more consecutive sputum cultures for this potentially pathogenic microorganism were found over a period of 6 months in clinically stable patients, in samples separated by at least 1 month.[18]

Statistical analysis

All the information was entered into a database and analyzed using SPSS version 17 (SPSS Inc, Chicago, IL). Quantitative variables are expressed as mean ± standard deviation, and categorical variables as absolute and relative frequencies. The frequency and length of exacerbations and the microbiology of the sputum cultures before and after azithromycin treatment were compared. Statistical analysis was performed using the Student's *t*-test for paired data and Chi-square tests as required. All statistical tests were performed with a confidence level of 95%.

Results

Twenty-four eligible patients with severe COPD and frequent AECOPD from the cohort of 203 patients controlled at the respiratory day care unit agreed to participate in this study. Baseline variables for the long-term azithromycin treatment group are shown in Table 1. Ten of 24 patients (41.6%) had no detectable bronchiectasis on high-resolution

Table 1 Baseline variables of the first year of follow-up for the long-term azithromycin therapy group

Baseline variables (year 1 of follow-up)	Mean (SD)
Age (years)	70.9 (7.4)
FEV_1, L	0.9 (0.2)
FEV_1, %predicted	32.2 (9.3)
FVC (L)	2.4 (0.5)
FEV_1/FVC (%)	39.6 (9.6)
Number of AECOPD/previous year	7.0 (3.0)
Number of hospitalization/previous year	3.3 (2.0)
Days of hospital stay/previous year	43.0 (26.2)
	n (%)
Very severe COPD (GOLD IV)	11 (46)
Chronic bronchitis	24 (100)
Current smoker	0 (0)
Male	24 (100)
Chronic oxygen therapy	5 (20.8)
Pseudomonas aeruginosa colonization	9 (37.5)

Abbreviations: COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SD, standard deviation.

computed tomography. The median ± standard deviation of total bronchiectasis score[20] was 3.3 ± 3.5 (range 0–9).

After initiation of azithromycin, four patients did not complete the scheduled 12-month antibiotic treatment period. One was withdrawn for mild dyspepsia, one because of a diagnosis of malignancy during follow-up, and the other two discontinued the treatment prematurely as a personal decision in the absence of reported side effects. No significant adverse events were observed among the 20 patients who completed the 12-month treatment period. One patient died in hospital as a result of an AECOPD during the last month of follow-up. These 20 patients comprised the sample for the comparative study.

In the 12 months prior to the start of azithromycin, the 20 study participants had a total of 136 AECOPD, of which 72 (52.9%) were severe and required hospitalization. Long-term azithromycin therapy achieved statistically significant reductions in AECOPD from 136 to 57 (a 58.9% decrease) and hospitalizations from 72 to 28 (a 61.2% decrease) and a reduction of 18.7 days in yearly mean hospital stay due to respiratory disease (see Table 2).

On the basis of potentially pathogenic microorganisms isolated in sputum samples during the year prior to starting azithromycin, seven patients with common potentially pathogenic microorganisms were included in Group 1, nine patients with chronic bronchial colonization by *P. aeruginosa* in Group 2 (of whom five [55.5%] were receiving inhaled colimycin therapy), and four patients with exacerbations due to common microorganisms and *P. aeruginosa* in Group 3. Long-term azithromycin therapy reduced the number of AECOPD, hospitalizations, and days of hospital stay in all groups. This reduction was particularly significant in Group 1 (common potentially pathogenic microorganisms) with a 70% reduction in AECOPD and hospitalizations, and a mean reduction of 25 days in mean hospital stay. In the group colonized by *P. aeruginosa*, a statistically significant reduction in AECOPD of 43.5% was observed, the number of hospitalizations fell by 47.1%, and their hospital stays by 32.5%, although these differences did not reach statistical significance. The group alternating between common potentially pathogenic microorganisms and *P. aeruginosa* during exacerbations showed improvements in all parameters studied, but no statistical comparisons were performed because of their small sample size (see Table 2 and Figure 1). AECOPD with sputum cultures isolating only common potentially pathogenic microorganisms fell from 31 of an overall 136 (22.7%) to five of 57 (8.7%) during long-term azithromycin therapy ($P < 0.05$).

Long-term azithromycin therapy rendered sputum cultures negative during AECOPD in nine of 20 patients during follow-up, including four from the common potentially pathogenic microorganism group, four from the *P. aeruginosa* colonization group (without any significant association with the presence of mucoid forms or inhaled colimycin therapy, data not shown), and one from the common potentially pathogenic *P. aeruginosa* group. Table 3 shows the microbiological evolution of patients

Table 2 Number of AECOPD, hospitalizations due to respiratory disease, and days of hospitalization with and without azithromycin, overall and according to the group of potentially pathogenic microorganisms isolated from sputum samples before initiation of azithromycin

Variable Overall (n = 20)	0–12 months without azithromycin		12–24 months with azithromycin		% Red	*P*
	Total	Mean ± SD	Total	Mean ± SD		
Exacerbations (n)	136	6.8 ± 2.8	57	2.8 ± 2.5	58.9	0.000
Hospitalizations (n)	72	3.6 ± 1.9	28	1.4 ± 1.5	61.2	0.001
Hospital stay (days)	874	43.7 ± 21.4	500	25.0 ± 32.2	42.8	0.013
Common PPM group (n = 7)						
Exacerbations (n)	63	9.0 ± 2.3	19	2.7 ± 2.2	70	0.00
Hospitalizations (n)	29	4.1 ± 2.6	9	1.2 ± 1.4	70.8	0.04
Hospital stay (days)	309	44.1 ± 17.5	133	19 ± 25	57	0.05
Pseudomonas aeruginosa group (n = 9)						
Exacerbations (n)	42	4.6 ± 2.2	24	2.6 ± 2.0	43.5	0.04
Hospitalizations (n)	31	3.4 ± 1.6	17	1.8 ± 1.7	47.1	0.08
Hospital stay (days)	454	50.4 ± 23.9	306	34.0 ± 38.5	32.5	0.23

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PPM, potentially pathogenic microorganisms; SD, standard deviation; % Red, percentage reduction.

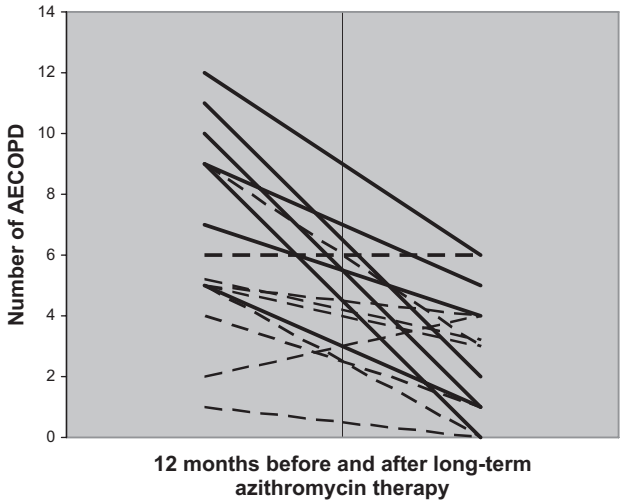

Figure 1 Number of AECOPD per patient before and after long-term azithromycin therapy. The continuous line represents Group 1 patients with potentially pathogenic microorganisms and the discontinuous line represents Group 2 patients with chronic bronchial colonization by *Pseudomonas aeruginosa*.
Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

during azithromycin treatment in relation to sputum cultures obtained during the first year.

Table 4 shows the sensitivity of common potentially pathogenic microorganisms to macrolides before and after long-term azithromycin therapy. Interestingly, all strains of *H. influenzae* isolated were resistant to erythromycin and 30% to clarithromycin, while none were resistant to azithromycin prior to treatment. The macrolide-resistant *S. pneumoniae* strains were also resistant to clindamycin, representing a highly resistant phenotype.

On assessment of the bactericidal effect of long-term azithromycin therapy on common potentially pathogenic microorganisms and the development of bacterial resistance, we found no isolates of *M. catarrhalis* with azithromycin resistance during follow-up, a single isolate of *H. influenzae* with resistance to the antibiotic, and four isolates of *S. pneumoniae,* all resistant to azithromycin. The prevalence of resistance did not show statistically significant differences from the figures found in the first year of the study.

Discussion

This is the first study to examine long-term intermittent azithromycin therapy over a 12-month period in patients with severe COPD and repeated AECOPD, or chronically colonized by *P. aeruginosa*, assessing its usefulness in reducing exacerbation frequency and its bactericidal effect, and comparing the results of sputum cultures at exacerbation with the prevalence of bacteria-related exacerbation before the treatment. Our results show that long-term intermittent dosing of azithromycin as addon therapy to conventional maximum triple therapy (long-acting anticholinergics, long-term beta-agonists, and inhaled corticosteroids) reduces the number of AECOPD and hospitalizations by more than a half, and also the days of hospital stay. The treatment was well tolerated over the 12-month period, and was stopped by only one patient due to dyspepsia.

Few studies focusing on the prophylactic use of antibiotics in COPD to prevent AECOPD have been published thus far, most of them examining long-term use of fluoroquinolones or macrolides. Sethi et al demonstrated that a 12-month regime with pulsed moxifloxacin 400 mg once a day for 5 days every 8 weeks achieved a 25% reduction in AECOPD, and a larger reduction (45%) in patients who reported mucopurulent sputum at baseline. The authors concluded that pulsed moxifloxacin might be indicated in COPD patients with a high frequency of AECOPD, but excluded patients colonized by *P. aeruginosa*, one of the specific subgroups discussed in our study, because of the risk of development of resistant strains.[25] Long-term macrolide therapy in COPD was also advocated in two published studies which analyzed erythromycin over a period of 12 months, with a significant reduction in the number and severity of AECOPD.[13,14] In the first, Suzuki et al reported the results of a prospective randomized trial of erythromycin therapy 200–400 mg/day versus nonactive treatment for 12 months in 109 COPD patients

Table 3 Microbiological evolution during long-term azithromycin therapy according to baseline groups and sputum culture isolates during AECOPD

Year 1 no azithromycin	n	Year 2 azithromycin therapy			
		No AECOPD	AECOPD with negative cultures	≥1 AECOPD for common PPMs	≥1 AECOPD for *P. aeruginosa*
Common PPM	7	1	3	2	1
P. aeruginosa colonization	9	2	2	0	5
Alternating PPM	4	1	0	0	3
Total (patients)	20	4	5	2	9

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PPM, potentially pathogenic microorganisms; *P. aeruginosa*, *Pseudomonas aeruginosa*.

Table 4 Common microorganisms isolated in sputum culture during exacerbations before and after starting azithromycin and its antibiogram to macrolides

Year 1 no AZT	Isolates pre-AZT	Erythromycin			Clarithromycin			Azithromycin		
		Sen	Int	Res	Sen	Int	Res	Sen	Int	Res
H. influenzae	10 (31.3%)	0	0	10	7	2	1	10	0	0
S. pneumoniae	6 (18.8%)	3	0	3	3	0	3	3	0	3
M. catarrhalis	15 (50%)	14	1	1	15	0	1	15	0	0
Year 2 AZT therapy	**Isolates post AZT**									
H. influenzae	1 (20%)	0	0	1	0	0	1	0	0	1
S. pneumoniae	4 (80%)	0	0	4	0	0	4	0	0	4
M. catarrhalis	0	0	0	0	0	0	0	0	0	0

Abbreviations: AZT, azithromycin; *H. influenzae*, *Haemophilus influenzae*; *S. pneumoniae*, *Streptococcus pneumoniae*; *M. catarrhalis*, *Moraxella catarrhalis*; SEN, sensitive; INT, intermediate; RES, resistant.

(average FEV_1 1.4 L).[13] They found a statistically significant increase in the relative risk of AECOPD in the control group versus the erythromycin group of 4.71 (95% CI, 1.53–14.5; $P = 0.007$) and more severe AECOPD in the control group than in the erythromycin group ($P = 0.0007$). In the second, a single-center, randomized, controlled trial, Seemungal et al administered erythromycin 250 mg twice daily or placebo for 1 year to 109 patients with moderate to severe COPD (mean FEV_1 50% of predicted).[14] Erythromycin reduced AECOPD in relative terms by 35% and increased the median time to first exacerbation from 89 to 271 days, both differences being statistically significant.

Preliminary data from the prospective, placebo-controlled MACRO study in 1142 COPD patients randomized to receive azithromycin 250 mg or placebo daily for 1 year have been promising.[15] Inclusion criteria were use of supplemental oxygen or treatment with systemic steroids for an AECOPD within the previous year. The frequency of AECOPD for those receiving azithromycin was lower at 1.4 versus 1.8 patients/year ($P = 0.004$).

The microbiology data collected from the MACRO study have not yet been formally published.

Neither study assessed the impact of treatment in patients colonized by *P. aeruginosa*. Seemungal et al included patients with moderate to severe COPD in their series, of whom only 35% had three or more AECOPD during the year prior to inclusion. In the MACRO study, the frequency of AECOPD was also low. Our study enrolled an homogeneous population sample of severe or very severe COPD with very frequent AECOPD and patients with chronic colonization by *P. aeruginosa*.

Azithromycin offers clinical advantages over erythromycin. Its metabolism does not interfere with the metabolic pathway of cytochrome P450, thus avoiding possible metabolic interference with other drugs often used in COPD which share the same pathway, such as steroids and theophylline. It has better gastrointestinal tolerance and less hepatotoxicity, and because it is not associated with long QT syndrome, is better tolerated and has a better safety profile in long-term use.[26] Even though macrolides provide adequate coverage for the most frequent potentially pathogenic microorganisms identified in AECOPD, their activity against *H. influenzae* differs. Azithromycin, the prototypical 15-member ring macrolide, has greater bacteriological and clinical activity than 14-membered ring macrolides, such as erythromycin and clarithromycin.[27] Interestingly, in our study, all strains of *H. influenzae* isolated prior to the initiation of long-term azithromycin were resistant to erythromycin and 30% were resistant to clarithromycin, while none was resistant to azithromycin.

The subanalysis shows that Group 1, despite being the one with the highest number of AECOPD and hospitalizations prior to azithromycin therapy, demonstrated the greatest improvement with long-term azithromycin treatment, with highly significant reductions of around 70% in AECOPD and hospitalizations. The mechanism of improvement may be related to the antibacterial activity of azithromycin, particularly with regard to *H. influenzae* and *M. catarrhalis*. AECOPD with isolates positive for these potentially pathogenic microorganisms fell from 25 pre-azithromycin to just one (for *H. influenzae*) during long-term azithromycin therapy. However, we did not observe this level of bacterial eradication for *S. pneumoniae*, which has a higher prevalence of resistance to azithromycin, independently of the use of this antibiotic in the study.

We cannot exclude the possibility that the improvement observed may be due in part to the anti-inflammatory and immunomodulatory properties of azithromycin.[9] Azithromycin may decrease sputum volume and its viscoelas-

ticity, and increase mucociliary transport.[28] Azithromycin also accumulates in neutrophils, interfering with chemotaxis to the inflammatory focus and promoting neutrophil apoptosis and clearance by macrophages.[29] In their trial with long-term erythromycin, Seemungal et al analyzed inflammatory mediators in sputum (interleukin-6, interleukin-8, myeloperoxidase) and plasma (interleukin-6, interleukin-8, C-reactive protein) as secondary outcomes, but found no statistically significant treatment-related differences.[14] The lack of effect of erythromycin on inflammatory markers suggests that the antimicrobial effects of macrolides in the treatment of COPD patients may be more important.

Patients with advanced COPD, especially those with repeated courses of antibiotic therapy or oral corticosteroids and requiring hospital admissions, have an increased risk of exacerbations caused by *P. aeruginosa*.[30,31] In these patients, antibiotic treatment decisions should consider both the severity of AECOPD and the risk for isolation of *P. aeruginosa*.[23]

The fact that 45% of our patients had chronic bronchial colonization by *P. aeruginosa* (Group 2) reflects the severity of their COPD. In these patients, long-term azithromycin therapy also improved all the outcomes analyzed, achieving a statistically significant reduction of 43% in AECOPD. Hospitalizations and days of hospital stay also fell to 47% and 32%, respectively, in these patients, although these differences did not reach statistical significance.

Macrolides, especially azithromycin, are useful in the treatment of chronic bronchial colonization by *P. aeruginosa* in patients with bronchiectasis, mainly in cases associated with cystic fibrosis.[7,32] Azithromycin interferes with production of virulence factors by *P. aeruginosa*, reduces biofilm formation by inhibiting alginate production, and decreases bacterial adherence.[33] For these reasons, we think that long-term azithromycin is especially indicated in these patients. However, the reductions in hospitalizations and days of mean hospital stay are less evident, possibly because they often require prolonged hospitalizations for parenteral antibiotic treatment, because *P. aeruginosa* is often resistant to oral antibiotics in this clinical situation.

Potential limitations of our study are the small number of patients included and the absence of a control group. However, our findings are very promising, especially for selected patients with severe COPD at high risk of exacerbations despite conventional maximum treatment. This study may help in the design of future, randomized, controlled trials including more patients and assessing the impact of treatment in patients with different degrees of severity, focusing on aspects such as efficacy, safety, development of microbiological resistance, or economic burden.

In conclusion, we have shown that long-term intermittent azithromycin therapy, administered three times a week at a dosage of 500 mg, is well tolerated and associated with significant reductions in AECOPD, number of hospitalizations, and days of hospital stay in patients with severe COPD and repeated AECOPD. This improvement is especially significant in patients with AECOPD associated with common potentially pathogenic microorganisms, possibly due to the antibacterial activity of the drug, and in patients with chronic bronchial colonization by *P. aeruginosa* due to its ability to prevent AECOPD for common potentially pathogenic microorganisms also in these patients. These results suggest that long-term intermittent azithromycin therapy may be useful in the treatment of patients with severe COPD and frequent exacerbations.

Disclosure

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