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ORIGINAL RESEARCH

Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis

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Background: Aclidinium bromide is a new long-acting muscarinic antagonist (LAMA) indicated for maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD). The efficacy of aclidinium was compared with tiotropium and glycopyrronium, using a network meta-analysis (NMA) of randomized controlled trials (RCTs) in moderate-to-severe COPD patients.

Methods: A systematic review was performed to identify RCTs evaluating aclidinium 400 µg twice daily (BID), glycopyrronium 50 µg once daily (OD), tiotropium 18 µg OD, or tiotropium 5 µg OD in adults with moderate-to-severe COPD. The outcomes of interest were: trough forced expiratory volume in 1 second (FEV_1); St George's Respiratory Questionnaire (SGRQ) total score and proportion of patients achieving ≥4 unit change; Transition Dyspnea Index (TDI) focal score and proportion of patients achieving ≥1 point change. The results were synthesized by means of a Bayesian NMA.

Results: Twenty-one studies (22,542 patients) were included: aclidinium 400 µg BID (three studies); tiotropium 5 µg OD (three studies); tiotropium 18 µg OD (13 studies); and glycopyrronium 50 µg OD (two studies). Regarding trough FEV_1 at 24 weeks, aclidinium demonstrated comparable efficacy to tiotropium 5 µg (difference in change from baseline [CFB]), (0.02 L [95% credible interval CrI –0.05, 0.09]); tiotropium 18 µg (0.02 L [95% CrI –0.05, 0.08]); and glycopyrronium (0.00 L [95% CrI –0.07, 0.07]). Aclidinium resulted in higher improvement in SGRQ score at 24 weeks, compared to tiotropium 5 µg (difference in CFB, –2.44 [95% CrI –4.82, –0.05]); and comparable results to tiotropium 18 µg (–1.80 [95% CrI –4.52, 0.14]) and glycopyrronium (–1.52 [95% CrI –4.08, 1.03]). Improvements in TDI score were comparable for all treatments.

Conclusion: Maintenance treatment with aclidinium 400 µg BID is expected to produce similar improvements in lung function, health-related quality of life, and dyspnea compared to tiotropium 5 µg OD; tiotropium 18 µg OD; and glycopyrronium 50 µg OD.

Keywords: COPD, aclidinium, tiotropium, glycopyrronium, systematic review, network meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) treatments aim to prevent and control symptoms, reduce exacerbations, and improve health status. Current Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] and the National Institute for Health

and Care Excellence (NICE) guidelines[2] recommend the use of long-acting bronchodilators, including long-acting muscarinic antagonists (LAMA), as they are more effective at producing maintained symptom relief than short-acting bronchodilators.

Until 2012, the only LAMA marketed for the treatment of COPD was tiotropium bromide. Tiotropium bromide is a once-daily (OD) LAMA and a widely prescribed medication for COPD. Inhaled tiotropium is available as a powder and in solution as a mist. The dose of the powder formulation is 18 μg and 5 μg for the mist.[3,4]

Aclidinium bromide is a new LAMA that was recently approved in Europe and the United States as a maintenance bronchodilator treatment in adult patients with COPD.[5,6] The recommended dose is one inhalation of aclidinium 400 μg bromide twice-daily (BID), equivalent to 322 μg of active treatment. Aclidinium bromide is administered by inhalation through a multidose dry powder inhaler device.[7] Glycopyrronium bromide was recently approved in Europe for maintenance bronchodilator treatment of COPD.[8] The recommended dose is one inhalation of 50 μg once daily, equivalent to glycopyrronium 44 μg.

The recent availability of aclidinium bromide poses the question of what its long-term relative efficacy would be in comparison to other LAMA treatment options. Only short-term (<12 weeks), randomized controlled trials (RCTs) comparing aclidinium to tiotropium are available,[9,10] which have shown comparability of the two treatments. There are no head-to-head RCTs comparing aclidinium to glycopyrronium.

To address the need for treatment comparisons, a systematic literature review was undertaken to identify long-term RCTs (≥12 weeks) while the data were synthesized by means of a network meta-analysis (NMA). A NMA allows for indirect comparisons in the absence of trials involving a direct comparison of interventions, and it can provide useful evidence of the relative treatment effects between competing interventions.

The relative efficacy of aclidinium 400 μg BID, tiotropium 5 μg OD, tiotropium 18 μg OD, and glycopyrronium 50 μg OD as maintenance bronchodilator treatment to relieve symptoms in patients with moderate-to-severe COPD was assessed in terms of lung function, health status, and dyspnea.

Materials and methods

Study identification and selection

Using a predefined strategy (Table S1), MEDLINE, MEDLINE in Process, EMBASE (using OVID), and Cochrane Controlled Trials Registry databases were searched for the period of July 1989 to October 2012. To capture advance online publications ahead of print that are not yet available on EMBASE or MEDLINE, a PubMed search was performed restricted to 2012 and excluding articles indexed for MEDLINE or PubMed In Process. Search terms included a combination of free text and thesaurus terms relevant to COPD, aclidinium bromide, tiotropium bromide, glycopyrronium bromide, and RCTs. Additional targeted searches were performed in clinicaltrials.gov database (Table S1). Conference abstracts dating back 2 years were included in the screening process. Abstracts and full-text articles in a language other than English were excluded.

The inclusion criteria for population, intervention, comparators, outcomes, and study design (PICOS) are described below.

- Population of interest: Adults with COPD, as defined by GOLD guidelines.[1] Studies with high proportions (>30%) of mild and/or very severe patients were excluded.
- Interventions: aclidinium 400 μg BID, glycopyrronium 50 μg OD, tiotropium 18 μg OD, or tiotropium 5 μg OD, administered using any inhalation device.
- Comparators: Studies that compare any of the interventions against each other or placebo.
- Outcomes: Outcomes of interest included the following: trough Forced Expiratory Volume in 1 second (FEV_1) at 12 weeks and 24 weeks; St George's Respiratory Questionnaire (SGRQ) total score at 12 weeks and 24 weeks; the proportion of patients within each group achieving a clinically meaningful change (at least four units) in SGRQ total score at 12 weeks and 24 weeks; Transition Dyspnea Index (TDI) total score at 12 weeks and 24 weeks; the proportion of patients within each group achieving a clinically meaningful change (at least one unit) in TDI focal score at 12 weeks and 24 weeks. Studies reporting outcomes within 2 weeks of the time point of interest, ie, between 10–14 weeks and 22–26 weeks, were included, and the outcomes were grouped as 12 and 24 weeks, respectively.
- Study design: RCTs with study duration ≥10 weeks.

Data collection and validity assessment

Two reviewers were involved in a three-step approach for data collection. All three steps were performed independently and in duplicate. First, titles and abstracts of the identified citations were assessed, according to the research question and PICOS criteria. In a second screening step, potentially

relevant articles were screened as full texts, using the same PICOS criteria. As a third step, for identified trials that met the selection criteria, the reviewers conducted extraction of data relating to study design, population characteristics, interventions, and the outcomes of interest, using a standardized prepiloted form. Any disagreement was resolved by consensus.

The following study characteristics were extracted: author; publication year; drug dose and administration; inhalation device; number of patients randomized and intention-to-treat (ITT) population; trial design; inclusion criteria; background treatments; trial location; and duration. Additionally, the following patient characteristics were extracted in order to evaluate the comparability of the patients: proportion of males; mean age; mean FEV_1; FEV_1 percentage predicted; mean forced vital capacity (FVC); mean FEV_1/FVC percentage; proportion of current smokers; mean duration of COPD; mean smoking history in pack-years; concomitant use of long-acting β-agonist (LABA); percentage of patients with concomitant use of inhaled corticosteroids (ICS); number of exacerbations in previous year; percentage reversibility; and race/ethnicity.

For the continuous outcomes (trough FEV_1, SGRQ total score, TDI focal score), the mean difference in change from baseline (CFB) versus placebo (or difference at follow-up, adjusted for baseline characteristics) and its standard error (SE) were extracted, where available. If not available, difference in CFB were calculated based on the CFB (or the CFB adjusted for baseline characteristics) per treatment arm. The SE, if not reported, was estimated based on the uncertainty or variation reported (eg, confidence intervals). For the dichotomous outcomes (% of SGRQ and TDI responders), the number of responders was extracted, if reported, or calculated, based on the reported percentage and the ITT population. If the necessary data were not reported in the text or the tables of the publication but in graphs, these were digitalized, and then the software DigitizeIt version 1.5 (Digitize It, Braunschweig, Germany) was used to extract them.

The methodological and reporting quality of the trials included were assessed by means of the Jadad checklist for RCTs.[11] The risk of bias at the study level was assessed, based on the adequacy of the following factors: randomization; allocation concealment; blinding of patients and investigators; and complete and nonselective results reporting. The risk of bias at the outcome level was assessed, based on the adequacy of the following factors: application of the ITT principle; blinding of the outcome assessor; statistical evaluation; and complete and nonselective results reporting.

Publication bias of primary outcomes, trough FEV_1, SGRQ total score, and TDI focal score was evaluated by visual inspection of funnel plots.

Data synthesis

The relative efficacy of the study drugs was evaluated using a NMA within a Bayesian framework.[12–15] For all continuous outcomes, a generalized linear model with identity link and a normal likelihood distribution was used,[16,17] while a logit link with binomial likelihood distribution was used for dichotomous outcomes.

For each outcome, fixed and random effects models were evaluated. The goodness of fit of each model to the data was assessed using the Deviance Information Criterion (DIC),[16] and the model with the lower DIC value was selected.

Vague (flat) priors were used for all calculations. A normal distribution with zero mean and variance equal to 10^4 was used for treatment effects and a uniform distribution with range zero to 5 for the between-trial standard deviation.

The posterior densities for the unknown parameters were estimated using Markov chain Monte Carlo (MCMC) simulations for each model. All results are based on 80,000 iterations on three chains, with a burn-in of 20,000 iterations. Convergence assessment was based on visual inspection of trace and autocorrelation plots and on the Gelman–Rubin–Brooks diagnostic ($R < 1.2$). The accuracy of the posterior estimates was assessed, using the Monte Carlo error for each parameter (Monte Carlo error $<5\%$ of the posterior standard deviation).

Differences in study design and patient characteristics across trials that could affect the relative treatment effect introduce bias to the analysis. Based on clinical experience and the results of published systematic reviews,[18,19] the percentage of current smokers, the severity level (% severe–% very severe patients), the FEV_1 percentage predicted at baseline, the percentage of patients with concomitant use of ICS, and the concomitant use of LABA were identified as potential factors that could modify the treatment effect. To address this risk, adjustment by treatment-by-covariate meta-regression models,[20] when feasible, was used for the former four while a sensitivity analysis, excluding LABA-allowing studies, was used to address the latter. For all analyses, WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) was used,[21] while the regression models were based on those reported by Dias et al.[17]

The results of the NMA are presented as differences in CFB and odds ratios (OR). Point estimates of both were derived from the median of the posterior distribution while their 95% credible intervals (CrI) were estimated from the 2.5th and 97.5th percentiles of the posterior distribution. When adjusted for covariates, the treatment effects obtained were estimated at the mean covariate value. At each endpoint, the probability that aclidinium is the better treatment is presented.

Results

Study selection

An overview of the study selection process is presented in Figure 1. The search in MEDLINE, MEDLINE In-Process, EMBASE, and Cochrane Controlled Trials Registry databases identified 1,088 potentially relevant abstracts. After removing duplicates, abstracts not in English and conference proceedings predating 2009, a total of 668 abstracts were screened using PICOS criteria. The abstract and title

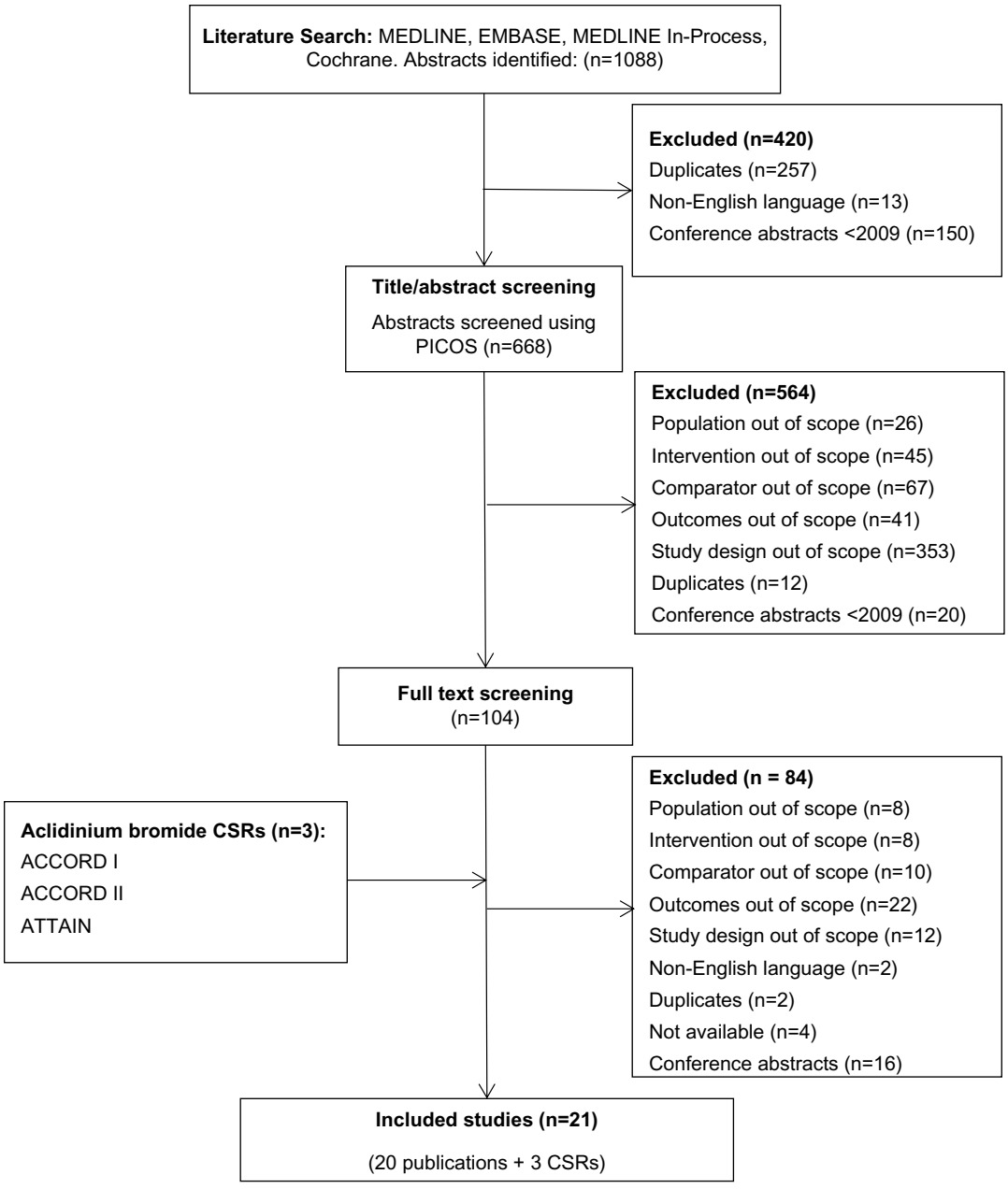

Figure 1 Flow diagram of study selection process.
Note: Both a publication and CSR were available for the ATTAIN and ACCORD I study.
Abbreviations: PICOS, population, intervention, comparators, outcomes, and study design; CSRs, clinical study reports; ACCORD, AClidinium in Chronic Obstructive Respiratory Disease COPD; ATTAIN, Aclidinium To Treat Airway obstruction IN COPD patients.

screening excluded 564 abstracts due to trial design (63%), or because the comparators (12%), interventions (8%), outcomes (7%), or population were out of scope (5%). An additional 20 conference proceedings were found to predate 2009, and twelve abstracts were identified as duplicates and removed from the database. For the remaining 104 abstracts, full-text publications were obtained and screened. An additional 84 publications were excluded due to outcomes (26%), study design (14%), comparators (12%), population (10%), or interventions not of interest (10%), language (2), duplicates (2), and not available (4). Furthermore, 16 conference abstracts were excluded as they were superseded by full-text articles, and no additional data were reported.

Three relevant Clinical Study Reports (CSR) were provided by Almirall and Forest on aclidinium ([AClidinium in Chronic Obstructive Respiratory Disease COPD], ACCORD I,[22,23] ACCORD II,[24] and [Aclidinium To Treat Airway obstruction In COPD patieNts] ATTAIN[25,26]). Ultimately, 20 publications[27–44] and three clinical study reports,[22,24,25] comprising 21 different trials, were identified from the systematic literature review and were included in the NMA.

Study characteristics

Tables 1 and 2 present an overview of the study design and patient characteristics of the selected studies. Overall, the 21 studies included had randomized 22,542 patients to either one of the interventions or placebo. Three studies compared aclidinium 400 µg with placebo; three studies compared tiotropium 5 µg with placebo; 13 studies compared tiotropium 18 µg with placebo; one study compared glycopyrronium 50 µg to placebo; and one study compared glycopyrronium 50 µg, tiotropium 18 µg, and placebo.

The results of the methodological quality assessment for the included studies, by means of Jadad score, are presented in Table 1. All studies scored at least 3 out of 5, indicating good-quality RCTs.

All studies included were parallel-group, placebo controlled, and randomized. Eighteen studies were double-blind; three studies were open-label.[35,41,44] All studies were multicenter in design. The average sample size was 1,242, ranging from 100[40] to 5,993[38] patients. Patients were permitted to use short-acting bronchodilators for symptom relief. The use of ICSs was permitted in most trials, although Brusasco in 2003[29] did not report on ICS use. Differences were observed in the concomitant use of LABAs during the trial period: six trials allowed LABA use;[28,32,33,36–38] two trials did not report on the use of LABAs;[29,31] and the remaining trials forbade the use of LABAs.

Enrolled patients were adults with a diagnosis of COPD, and average disease duration of 8.7 years. Patients were predominantly male (between 49% and 99% of patients), and mean age ranged from 60–68 years. All patients were current or exsmokers, with most studies including patients with a smoking history of at least 10 pack-years. Most trials included patients with an FEV_1/FVC of ≤70%, and an FEV_1% predicted that ranged from <80% to <50%. Baseline FEV_1 ranged from 0.96 L–1.51 L. Spirometry measurements for mean FEV_1%, predicted at baseline, ranged from 38%–40% in tiotropium 5 µg; 36%–54% in tiotropium 18 µg; 44%–51% in aclidinium studies; and it was not reported in both glycopyrronium studies. The proportion of patients taking concomitant-inhaled corticosteroids ranged from 36%–66% in tiotropium 18 µg, 39%–51% in aclidinium, and 55%–56% in glycopyrronium studies. The use of meta-regression models can reduce the impact of bias due to inconsistencies and between-study heterogeneity.[20] For this reason, the results of the NMA were adjusted for the baseline FEV_1% predicted and the ICS use by means of treatment-by-covariate meta-regression.

Despite some differences identified across the studies in terms of study design, patient characteristics or outcome definitions, 20 studies are considered to be broadly comparable and, therefore, were included in the base case analysis. One study, ACCORD II,[24] was excluded from the base case analysis due to a chance imbalance in patients' baseline characteristics in favor of the placebo group – despite randomization. The impact of this study on the indirect treatment comparison results was accessed by including it in a scenario analysis.

A visual inspection of the funnel plots of FEV_1, SGRQ total score, and TDI focal score did not reveal any profound asymmetries, suggesting the absence of publication bias. Given the low number of studies per outcome and time point, this assessment should be interpreted with caution.

Network meta-analysis

Figure 2 presents the network diagram based on the 21 studies identified in the review that were included in the NMA, showing a total of 26 connections between the comparators. There is one closed loop, providing indirect evidence. As all studies were placebo-controlled, placebo is used as the reference treatment. The individual study results reported in the 21 trials included in the NMA are presented in Table 3. Mean and standard error, as extracted or estimated, are presented for the continuous outcomes, while percentages of responders for placebo and active treatment arms are presented for the dichotomous outcomes.

Table 1 Characteristics of included studies

Source	Trial design	Treatment	Number of patients	Location	Inclusion/exclusion criteria	Background treatment	Study duration	Jadad score
Bateman[27]	RCT, PC, DB, MC	Tiotropium, 5 μg, OD; Tiotropium, 10 μg, OD; Placebo	670 667 653	South Africa, Europe, Canada	≥40 years age; $FEV_1 \leq 60\%$; $FEV_1 \leq 70\%$ of FVC; ≥10 pack-years; diagnosis of COPD and stable, moderate-to-severe airway obstruction	Allowed: oral and inhaled corticosteroids, theophylline, mucolytic agents and antileukotrienes, salbutamol. Patients on long-acting β-adrenergics and inhaled corticosteroids were switched to a monoproduct inhaled corticosteroid prior to run-in	48 weeks	3
Bateman[28]	RCT, PC, DB, PG, MC	Tiotropium, 5 μg, OD; Placebo	1 952 1 965	336 centers; 31 countries	$FEV_1 \leq 60\%$ prebronchodilator; $FEV_1/FVC \leq 70\%$ prebronchodilator; ≥40 years age; ≥10 pack-years	Allowed: salbutamol pMDI; all respiratory medications were permitted Not allowed: inhaled anticholinergics	48 weeks + 1 week run-in	5
Voshaar[42]	RCT, PC, DB, MC	Tiotropium, 5 μg, OD; Tiotropium, 10 μg, OD; Ipratropium, 36 μg, OD; Placebo	180 180 178 181	64 centers; Europe, South Africa, USA, Canada	$FEV_1 \leq 60\%$ prebronchodilator; $FEV_1/FVC \leq 70\%$; ≥10 pack-years	Allowed: salbutamol, oral corticosteroids, orally inhaled corticosteroids, theophyllines, and mucolytics Not allowed: anticholinergics, inhaled β-adrenergics other than salbutamol, fixed combination inhalers	12 weeks	3
Brusasco[29]	RCT, PC, DB, MC, DD	Tiotropium, 18 μg, OD; Salmeterol, 50 μg, BID; Placebo	402 405 400	18 countries	$FEV_1 \leq 65\%$; $FEV_1/FVC \leq 70\%$; > 40 years of age; > 10 pack-years	NR	24 weeks	4
Casaburi[30]	RCT, PC, DB, MC	Tiotropium, 18 μg, OD; Placebo	279 191	25 centers; USA	$FEV_1 \leq 65\%$; $FEV_1/FVC \leq 70\%$; ≥40 years of age; diagnosis of COPD defined by ATS; smoking history of >10 pack-years	Allowed: stable doses of theophylline, ICS, oral prednisone Not allowed: other inhaled or oral bronchodilators	13 weeks	3
Casaburi[31]	2 RCTs, PC, DB, MC	Tiotropium; 18 μg; OD; Placebo	550 371	50 centers	$FEV_1 \leq 65\%$; $FEV_1/FVC \leq 70\%$	Allowed: stable doses of theophylline, ICS, oral prednisone	56 weeks	3
Chan[32]	RCT, PC, DB, MC	Tiotropium, 18 μg, OD; Placebo	608 305	101 centers; Canada	$FEV_1 \leq 65\%$; $FEV_1/FVC \leq 70\%$; ≥1 exacerbation previous year but not 6 weeks prior to randomization	Allowed: stable dose oral corticosteroids, ICS, theophylline preparations, mucolytic preparations (not containing bronchodilators), LABAs	48 weeks	4
Covelli[33]	RCT, PC, DB, MC	Tiotropium, 18 μg, OD; Placebo	100 96	12 centers; USA	$FEV_1 \leq 60\%$; $FEV_1/FVC \leq 70\%$ excluded if exacerbation in prior 6 weeks	Allowed: ICS, LABAs and theophyllines Not allowed: cromones, leukotriene antagonists, and inhaled anticholinergics	12 weeks	4
Donohue[34]	RCT, PC, DB, MC, DD	Tiotropium, 18 μg, OD; Salmeterol, 50 μg, BID; Placebo	209 213 201	39 countries; 12 countries	$FEV_1 \leq 60\%$; $FEV_1/FVC \leq 70\%$; ≥40 years of age; smoking history of >10 pack-years	Allowed: usual ICS and oral steroids Not allowed: Inhaled anticholinergic LABAs	24 weeks	4

Donohue[35]	RCT, PC, DB,** MC, DD	Indacaterol, 150 μg, OD; Indacaterol, 300 μg, OD; Tiotropium, 18 μg, OD; Placebo	420 418 420 425	USA, Europe	FEV_1 30%–80% postbronchodilator; FEV_1/FVC < 70%; ≥40 years age; ≥20 pack-years; diagnosis of moderate-to-severe COPD (GOLD criteria)	ICS monotherapy, albuterol, treatment with anticholinergic bronchodilators or β2-agonists was discontinued with appropriate washout; patients receiving fixed-combination β2-agonist/ICS were switched to ICS monotherapy at an equivalent dose	26 weeks	4
Moita[36]	RCT, PC, DB, MC	Tiotropium, 18 μg, OD; Placebo	147 164	31 centers; Portugal	FEV_1 ≤ 70%; FEV_1/FVC ≤ 70%, excluded if ≥3 exacerbations previous year or exacerbation in 6 weeks prior	Allowed: LABAs, theophylline, mucolytics, ICS, stable doses oral corticosteroids. Temporary increases in theophylline or oral steroids for exacerbations; Not allowed: theophylline 24-hour preparations	12 weeks	4
Niewoehner[37]	RCT, PC, DB, MC	Tiotropium, 18 μg, OD; Placebo	914 915	26 centers; USA	FEV_1 ≤ 60%; FEV_1/FVC ≤ 70% excluded if not recovered from exacerbation ≥30 days prior	Allowed: all other respiratory medications (including ICS and LABAs) Not allowed: open-label anticholinergic bronchodilator	24 weeks	4
Tashkin (UPLIFT)[38]	RCT, PC, DB, MC	Tiotropium, 18 μg, OD; Placebo	2 987 3 006	490 centers; 37 countries	FEV_1 ≤ 70%; FEV_1/FVC ≤ 70%; excluded if exacerbation 4 weeks prior	Allowed: all respiratory medications, except other inhaled anticholinergic drugs	4 years	5
Tonnel (TIPHON)[39]	RCT, PC, DB, MC	Tiotropium, 18 μg, OD; Placebo	266 288	123 centers; France	FEV_1 20%–70%; FEV_1/SVC ≤ 70%	Allowed: stable doses of theophylline preparations (excluding 24-hour preparations), mucolytics, ICS, and oral steroids	36 weeks	5
Verkindre[40]	RCT, PC, DB, MC	Tiotropium; 18 μg, OD; Placebo	46 54	10 centers; France	FEV_1 ≤ 50%; FEV_1/FVC ≤ 70%; residual volume ≥125%; excluded if unstable doses oral corticosteroid 6 weeks prior	Allowed: stable doses oral corticosteroids, ICS, theophylline preparations, mucolytic agents Not allowed: use of SABAs, oral ß2-agonists, or LABAs	12 weeks	3
Vogelmeier[41]	RCT, PC, DB,* MC	Formoterol, 12 mcg BID + Tiotropium, 18 mcg, OD; Formoterol, 12 μg, BID; Tiotropium, 18 μg, OD; Placebo	 207 210 221 209	86 centers; 8 countries Europe	FEV_1 < 70%; FEV_1/FVC < 70%; stable COPD; aged 40 years at COPD onset; ≥10 pack-years	Allowed: salbutamol, ICS monotherapy	24 weeks	3
CSR ACCORD I[22]	RCT, MC, PC, DB	Aclidinium, 200 μg, BID; Aclidinium, 400 μg, BID; Placebo	185 190 187	106 centers; USA, Canada	≥40 years of age, ≥10 pack-years; stable, moderate-to-severe COPD as defined by criteria of GOLD; FEV_1 30%–80% postsalbutamol; FEV_1/FVC < 70% Excluded: patients with asthma; respiratory tract infection or COPD exacerbation in the 6 weeks before visit 1	ICS allowed; LABA discontinued	12 weeks	4

(*Continued*)

Table 1 (*Continued*)

Source	Trial design	Treatment	Number of patients	Location	Inclusion/exclusion criteria	Background treatment	Study duration	Jadad score
CSR ACCORD II[24]	RCT, MC, PC, DB	Aclidinium, 200 μg, BID; Aclidinium, 400 μg, BID; Placebo	184 178 182	103 centers; USA, Canada	≥40 years of age, ≥10 pack-years; stable, moderate-to-severe COPD as defined by criteria of GOLD; FEV_1 30%–80% postsalbutamol; $FEV_1/FVC < 70\%$ Excluded: patients with asthma; respiratory tract infection or COPD exacerbation in the 6 weeks before visit 1	ICS allowed; LABA discontinued	12 weeks	4
CSR ATTAIN[25]	RCT, MC, PC, DB	Aclidinium, 200 μg, BID; Aclidinium, 400 μg, BID; Placebo	277 269 273	103; Europe, South America, Russia, South Africa	≥10 pack-years; FEV_1 30%–80% postsalbutamol; $FEV_1/FVC < 70\%$	NR	24 weeks	4
GLOW 1[43]	RCT, DB, PC, MC	Glycopyrronium, 50 mcg, OD; Placebo	552 270	128; US, Europe, Australia, SE Asia, South America	postbronchodilator $FEV_1 \geq 30\%$ and $< 80\%$; postbronchodilator $FEV_1/FVC < 0.7$; ≥10 pack-years	Allowed: ICS monotherapy, short acting β2-agonists as required Not allowed: LABAs, LAMAs, theophylline	26 weeks	3
GLOW 2[44]	RCT, MC, PC, DB**	Glycopyrronium, 50 μg, OD; Tiotropium, 18 μg, OD; Placebo	529 268 269	NR	Men and woman aged ≥40 years, smoking history ≥10 pack-years, moderate-to-severe stable COPD (2008 GOLD guidelines), postbronchodilator $FEV_1 \geq 30\%$ and $< 80\%$ of the predicted normal, and postbronchodilator $FEV_1/FVC < 0.70$ were enrolled	Allowed: concomitant medications (inhaled or intranasal corticosteroids and H1 antagonists) and salbutamol/albuterol inhaler to be used as rescue medication during the study Not allowed: LABA, LAMA	52 weeks	3

Notes: *Tiotropium versus placebo is not DB; **open label for tiotropium arm. + indicates that the first two lines of this cell (Formoterol and Tiotropium) were administered simultaneously.

Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; CSR, clinical study report; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium; TIPHON, Tiotropium: Influence sur la Perception de l`amelioration des activites Habituelles Objectivee par une echelle Numerique; ACCORD, AClidinium in Chronic Obstructive Respiratory Disease COPD; ATTAIN, Aclidinium To Treat Airway obstruction IN COPD patients; GLOW, GLycopyrronium bromide in COPD airways clinical study 1; DB, double blind; DD, double dummy; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long acting β-agonist; LAMA, long-acting muscarinic antagonist; MC, multicenter; NR, not reported; OD, once daily; OL, open label; PC, placebo controlled; RCT, randomized controlled trial; S, south; SE, southeast; USA, United States of America; pMDI, pressurized metered-dose inhaler; ATS, American Thoracic Society.

Table 2 Patient characteristics at baseline for the included studies (only arms of interest)

Author	Treatment	Male (%)	Mean age (years)	Current smokers (%)	Patients in severe or very severe COPD states (%)	Patients with concomitant ICS use (%)	Mean pack-years	Mean FEV_1% pred
Bateman[27]	Tiotropium, 5 μg, OD;	73	65	38	NR	49	NR	38
	Placebo	75	65	36	NR	55	NR	38
Bateman[28]	Tiotropium, 5 μg, OD;	78	65	36	NR	56	46	40
	Placebo	77	65	36	NR	56	45	40
Voshaar[42]	Tiotropium, 5 μg, OD;	69	64	37	59	48	52	40
	Placebo	69	63	43	47	52	51	42
Brusasco[29]	Tiotropium, 18 μg, OD;	77	64	NR	82	NR	44	39
	Placebo	76	65	NR	82	NR	42	39
Casaburi[30]	Tiotropium, 18 μg, OD;	67	65	NR	NR	NR	65	39
	Placebo	63	65	NR	NR	NR	61	38
Casaburi[31]	Tiotropium, 18 μg, OD;	67	65	NR	NR	43	63	39
	Placebo	63	65	NR	NR	40	59	38
Chan[32]	Tiotropium, 18 μg, OD;	59	67	32	NR	66	50	39
	Placebo	61	67	30	NR	71	51	39
Covelli[33]	Tiotropium, 18 μg, OD;	66	66	40	NR	54	66	40
	Placebo	49	63	37	NR	58	65	39
Donohue[34]	Tiotropium, 18 μg, OD;	74	65	42	59	66	47	41
	Placebo	75	66	42	60	66	46	41
Donohue[35]	Tiotropium, 18 μg, OD;	65	64	NR	NR	35	50	54
	Placebo	61	63	NR	NR	40	50	56
Moita[36]	Tiotropium, 18 μg, OD;	NR	NR	28	NR	NR	Per	Per
	Placebo	NR	NR	25	NR	NR	subgroup	subgroup
Niewoehner[37]	Tiotropium, 18 μg, OD;	98	68	29	NR	61	67	36
	Placebo	99	68	30	NR	58	69	36
Tashkin (UPLIFT)[38]	Tiotropium, 18 μg, OD;	75	65	29	52	62	49	40
	Placebo	74	65	30	53	62	48	39
Tonnel (TIPHON)[39]	Tiotropium, 18 μg, OD;	87	65	24	57	38	44	47
	Placebo	85	64	30	62	36	43	46
Verkindre[40]	Tiotropium, 18 μg, OD;	94	61	24	NR	NR	46	35
	Placebo	94	60	33	NR	NR	42	36
Vogelmeier[41]	Tiotropium, 18 μg, OD;	79	63	NR	44	NR	39	52
	Placebo	78	62	NR	46	NR	40	51
CSR ACCORD I[22]	Aclidinium, 400 μg, BID;	53	65	42	36	47	57	48
	Placebo	52	65	47	37	45	53	48
CSR ACCORD II[24]	Aclidinium, 400 μg, BID;	50	63	50	54	39	54	44
	Placebo	55	62	56	37	42	53	49
CSR ATTAIN[25]	Aclidinium, 400 μg, BID;	68	63	55	31	51	42	51
	Placebo	69	62	53	34	58	39	52
GLOW 1[43]	Glycopyrronium, 50 μg, OD;	83	64	33	40	55	45	NR
	Placebo	81	64	34	38	51	45	NR
GLOW 2[44]	Glycopyrronium, 50 μg, OD;	65	64	45	37	56	49	NR
	Tiotropium, 18 μg, OD;	63	64	44	35	52	50	NR
	Placebo	65	64	46	35	51	48	NR

Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; CSR, clinical study report; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium; TIPHON, Tiotropium: Influence sur la Perception de l`amelioration des activites Habituelles Objectivee par une echelle Numerique; ACCORD, AClidinium in Chronic Obstructive Respiratory Disease COPD; ATTAIN, Aclidinium To Treat Airway obstruction IN COPD patients; GLOW, GLycopyrronium bromide in COPD airways clinical study; FEV_1% pred, forced expiratory volume in 1 second percentage predicted at baseline; ICS, inhaled corticosteroids; OD, once daily; NR, not reported.

The data were synthesized in three series of NMAs. The base case analysis is based on 20 trials, excluding the ACCORD II study.[24] In a sensitivity analysis, all studies reporting concomitant use of LABA treatment[28,32,33,36–38] were excluded (Scenario 1). In a second scenario analysis, results including ACCORD II are presented (Scenario 2). Furthermore, a covariates analysis was performed by adjusting the results for ICS concomitant use and the FEV_1% predicted at baseline.

The results of the NMA, as differences in CFB or OR with the corresponding 95% CrI for base case for all treatments

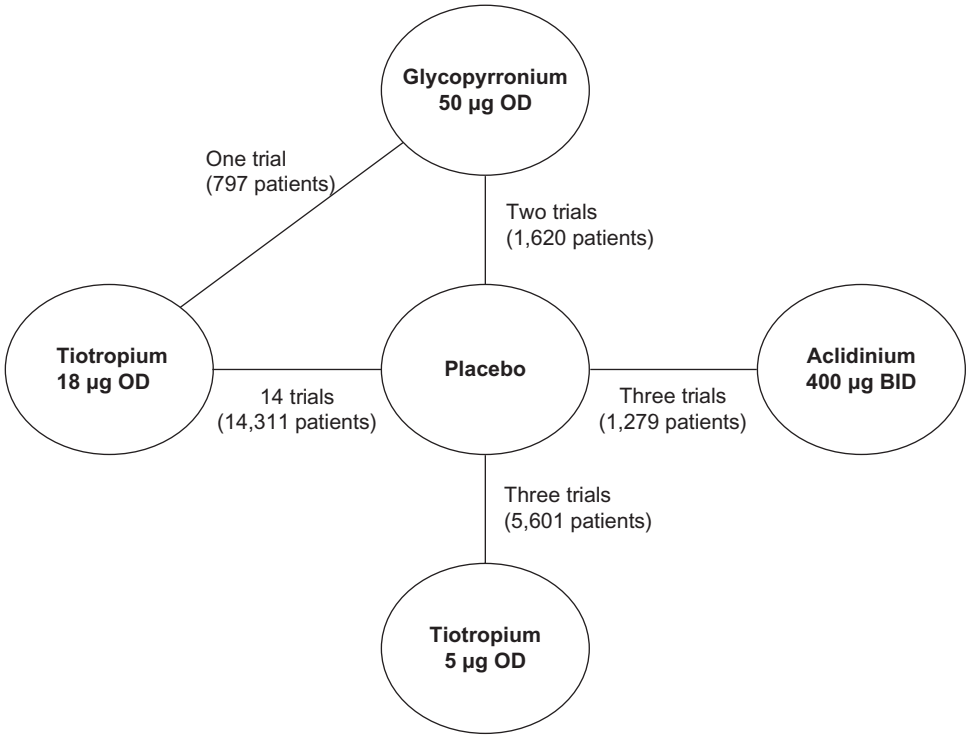

Figure 2 Network formed by interventions and their direct comparisons included in the analyses.
Note: The GLOW2 trial compares glycopyrronium to tiotropium 18 µg and placebo and is therefore included three times in this figure.
Abbreviations: GLOW, GLycopyrronium bromide in COPD airways clinical study; OD, once daily; BID, twice a day.

versus placebo (reference treatment of the NMA) are summarized in Table 4. The comparative efficacy of aclidinium versus placebo and alternative active treatments is presented for the base case in Figure 3. Base case results, adjusted for percentage of ICS use and FEV_1%-predicted covariates – together with the results of Scenarios 1 and 2 – are presented in Table 5.

Adjustment of the base case results for percentage of current smokers (results not presented in this paper) suggested that they are not likely to be affected, in line with the published results of similar studies.[18] Similarly, a scenario analysis excluding studies with a gender imbalance, ie, GLycopyrronium bromide in COPD airWays clinical study 1 (GLOW1), ATTAIN, and Covelli,[33] showed minor effects in the NMA results; eg, <0.01 L in CFB difference for trough FEV_1 at 12 weeks, and are not presented in this paper. The proportion of patients with severe or very severe COPD was not reported in ten out of 16 studies (Table 2). Therefore, the authors decided not to address this source of inhomogeneity (eg, by imputing data or excluding the nonreporting studies).

Lung function

Data on lung function measured by means of trough FEV_1 were reported by 19 studies[22,24,25,27–40,42,44] (including 21,558 patients). All treatments were more efficacious than placebo, with a point estimate above the Minimal Clinically Important Difference (MCID) of 100 mL (Table 4).

In the base case, after 12 weeks, aclidinium demonstrated comparable results versus tiotropium 5 µg (difference in CFB −0.01 L [95% CrI −0.06, 0.05]) and no difference versus tiotropium 18 µg (difference in CFB 0.00 L [95% CrI −0.03, 0.03]) and glycopyrronium (difference in CFB 0.00 L [95% CrI −0.03, 0.04]) (Figure 3). The corresponding probabilities of aclidinium being a better treatment range from 41%–59% (Figure 3). After 24 weeks, aclidinium showed a numerically higher difference in terms of trough FEV_1 versus tiotropium 5 µg (difference in CFB 0.02 L [95% CrI −0.05, 0.09]) and tiotropium 18 µg (difference in CFB 0.02 L [95% CrI −0.05, 0.08]) with the probabilities of aclidinium being a better treatment at 69% and 72%, respectively. At the same time point, there was no difference versus glycopyrronium (difference in CFB 0.00 L [95% CrI −0.07, 0.07]), and the probability of aclidinium being a better treatment was at 48%.

Although the point estimates showed minimal changes, the results were not sensitive to scenario and covariate analyses (Table 5). In all cases, the point estimate of the differences

Table 3 Individual studies results included in the network meta-analysis

	AB 400				TIO 5				TIO 18				GLYCO 50				Placebo	
	Diff CFB (SE)	FEV_1 trough (Liters)	Diff CFB (SE)	SGRQ Total score	Diff CFB (SE)	FEV_1 trough (Liters)	Diff CFB (SE)	SGRQ Total score	Diff CFB (SE)	FEV_1 trough (Liters)	Diff CFB (SE)	SGRQ Total score	Diff CFB (SE)	FEV_1 trough (Liters)	Diff CFB (SE)	SGRQ Total score	%	SGRQ Responders
	%	TDI Responders	%	SGRQ Responders	%	TDI Responders	%	SGRQ Responders	%	TDI Responders	%	SGRQ Responders	%	TDI Responders	%	SGRQ Responders	%	TDI Responders
12 weeks																		
Voshaar[42]					0.12 (0.02)													
Covelli[33]									0.18 (0.04)									
Casaburi[30]									0.15[×] (0.02)[×]									
Casaburi[31]									0.11[*] (0.02)[†]		0.95[×] (0.18)[×]							
Chan[32]									0.10 (0.02)									
Donohue[35]									0.14 (0.02)[†]		−1.10 (0.87)[†]		0.75 (0.22)[†]				42	
Moita[36]									0.10 (0.03)[†]									
Niewoehner[37]									0.10 (0.01)[†]									
Tonnel (TIPHON)[39]											−3.51[*] (1.30)[*]	58					45	
Verkindre[40]											−6.50 (2.90)	59	1.28 (0.89)				35	
CSR ACCORD I[22]	0.12 (0.02)[†]	−2.54 (1.10)[†]	44		1.00 (0.31)[†]		48										36	33

(*Continued*)

Table 3 (*Continued*)

	AB 400				TIO 5				TIO 18				GLYCO 50				Placebo			
	FEV_1 trough				FEV_1 trough				FEV_1 trough				FEV_1 trough							
	Diff CFB (SE)	Total score	Responders		Diff CFB (SE)	Total score	Responders		Diff CFB (SE)	Total score	Responders		Diff CFB (SE)	Total score	Responders					
	(Liters)	SGRQ	%	TDI	(Liters)	SGRQ	%	TDI	(Liters)	SGRQ	%	TDI	(Liters)	SGRQ	%	TDI	SGRQ	TDI	SGRQ	TDI
				Responders				Responders				Responders				Responders	Responders		Responders	
		Diff CFB (SE)		Total score		Diff CFB (SE)		Total score		Diff CFB (SE)		Total score		Diff CFB (SE)		Total score				
				TDI				TDI				SGRQ				TDI				
CSR ATTAIN[25]	0.11 (0.02)†	−4.10 (1.00)†	57	0.88 (0.27)†													40	42		
CSR ACCORD II[24]	0.07 (0.02)†	−1.09 (1.37)†	45	1.00 (0.40)†													39	35		
GLOW 1[43]													0.11 (0.02)							
GLOW 2[44]									0.08 (0.02)	−2.84 (0.97)			0.10 (0.02)	−3.17 (0.84)		0.60 (0.27)				
24 weeks																				
Bateman[27]					0.12× (0.01)×															
Bateman[28]					0.10 (0.01)†	−2.20 (0.46)†	51										42			
Brusasco[29]									0.12 (0.02)	−2.70× (0.99)×	49	1.10 (0.30)					39	30		
Casaburi[31]									0.12* (0.02)†	−3.08× (1.37)×		0.84× (0.17)×								
Donohue[34]									0.14 (0.02)	−2.71× (1.20)†	51	1.02 (0.36)†	0.11 (0.02)		42		42	26		
Donohue[35]									0.14 (0.02)†	−1.00 (0.92)†		0.87 (0.23)†	0.10 (0.02)		58			47		
Niewoehner[37]									0.10 (0.01)†											

Tashkin (UPLIFT)[38]							0.09* (0.01)*	−2.86* (0.82)*										
Tonnel (TIPHON)[39]								−3.51* (1.29)*	58								47	
Vogelmeier[41]								−2.09* (1.20)*										
CSR ATTAIN[25]	0.13 (0.02)†	−4.63 (1.13)†	57	1.00 (0.29)†	57												41	46
GLOW 1[43]										0.11 (0.02)	−2.81 (0.96)	57	1.04 (0.24)	61	46	48		
GLOW 2[44]							0.08 (0.02)	−2.52 (1.11)	0.94 (0.30)	53	0.13 (0.02)	−3.38 (0.97)		0.81 (0.26)	55		44	

Notes: *Extracted from figure; ˣcalculated based on baseline and follow up data; †calculated based on *P*-value, SD, or 95% CI. The SE for SGRQ total score in Vogelmeier 2008, Tonnel 2008, Tashkin 2008, and the SE for FEV_1 for Tashkin 2008 are calculated based on the 95% CI extracted from a graph.

Abbreviations: AB400, aclidinium 400 μg bromide twice daily; CFB, change from baseline; CI, confidence interval; CSR, clinical study report; UPLIFT, ?; TIPHON, ?; ACCORD, AClidinium in Chronic Obstructive Respiratory Disease COPD; ATTAIN, Aclidinium To Treat Airway obstruction IN COPD patients; GLOW, GLycopyrronium bromide in COPD airways clinical study; FEV_1, forced expiratory volume in 1 second; GLYCO, glycopyrronium 50 μg bromide once daily; SD, standard deviation; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO 5, tiotropium 5 μg bromide once daily; TIO 18, tiotropium 18 μg bromide once daily.

Table 4 Base case: results of the NMA for all treatments versus placebo

	Trough FEV_1		SGRQ total score		SGRQ % responders		TDI focal score		TDI % responders	
	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks
	Diff CFB (95% CrI)	Diff CFB (95% CrI)	Diff CFB (95% CrI)	Diff CFB (95% CrI)	Odds ratio	Odds ratio	Diff CFB (95% CrI)	Diff CFB (95% CrI)	Odds ratio	Odds ratio
TIO 5	0.12 (0.07, 0.16)	0.11 (0.08, 0.15)		−2.20 (−3.10, −1.30)		1.44 (1.27, 1.63)				
TIO 18	0.11 (0.10, 0.12)	0.11 (0.09, 0.13)	−2.37 (−3.48, −1.25)	−2.45 (−3.18, −1.71)	1.82 (1.32, 2.53)	1.50 (1.24, 1.83)	0.77 (0.53, 1.02)	0.92 (0.71, 1.13)	1.69 (1.29, 2.23)	1.67 (1.42, 1.97)
GLYCO	0.11 (0.08, 0.13)	0.13 (0.09, 0.17)	−2.99 (−4.53, −1.45)	−3.11 (−4.38, −1.84)		1.56 (1.16, 2.09)	0.80 (0.32, 1.27)	0.92 (0.59, 1.25)		1.69 (1.38, 2.07)
AB 400	0.11 (0.08, 0.14)	0.13 (0.07, 0.19)	−3.38 (−4.82, −1.95)	−4.63 (−6.85, −2.42)	1.75 (1.34, 2.27)	1.94 (1.38, 2.73)	0.93 (0.53, 1.33)	1.00 (0.43, 1.57)	1.99 (1.53, 2.60)	1.58 (1.13, 2.33)

Abbreviations: AB 400, aclidinium 400 μg bromide twice daily; CFB, change from baseline; CrI, credible interval; FEV_1, forced expiratory volume in 1 second; GLYCO, glycopyrronium 50 μg bromide once daily; NMA, network meta-analysis; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO 5, tiotropium 5 μg bromide once daily; TIO 18, tiotropium 18 μg bromide once daily.

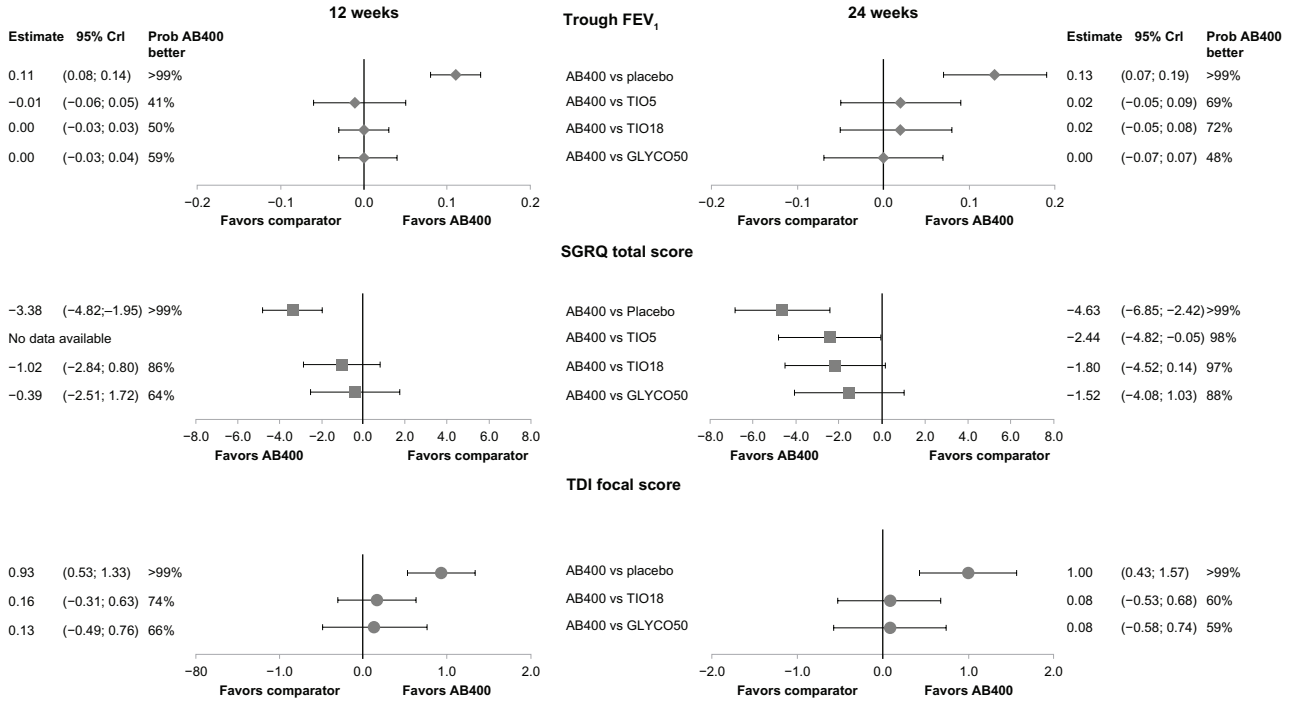

Figure 3 Forest plot of base case network meta-analysis results for aclidinium.
Note: Difference in change from baseline (CFB), 95% credible intervals (95% CrI) and probability that aclidinium is better than the comparator at 12 weeks and 24 weeks.
Abbreviations: AB400, aclidinium 400 μg twice daily; TI05, tiotropium 5 μg bromide once daily; TI018, tiotropium 18 μg bromide once daily; GLYC050, glycopyrronium 50 μg once daily; FEV, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

in CFB between the regimens was in the range of –0.02 L to 0.02 L (Figure 3; Table 5).

Health status

In total, 14 studies[22,24,25,28,29,31,34,35,38–41,43,44] (including 17,140 patients) reported on health status using SGRQ as the assessment tool. All active treatments improved CFB of SGRQ total score versus placebo (a lower SGRQ score represents improvement) at both time points (Table 4). Aclidinium demonstrated an improvement of 4.63 units (95% CrI –6.85, –2.42) after 24 weeks as compared to placebo, for which the point estimate is above the clinically significant improvement of four units (Figure 3).

In the base case, aclidinium resulted in comparable results at 12 weeks versus tiotropium 18 μg (difference in CFB –1.02 [95% CrI –2.84, 0.8]) and glycopyrronium (difference in CFB –0.39 [95% CrI –2.51; 1.72]), with the probabilities of aclidinium being a better treatment at 86% and 64%, respectively (Figure 3). At 24 weeks, aclidinium is expected to improve health-related quality of life more than tiotropium 5 μg (difference in CFB –2.44 [95% CrI –4.82, –0.05]) and demonstrate a trend toward lower (better) SGRQ scores compared to tiotropium 18 μg (difference in CFB –1.80 [95% CrI –4.52, 0.14]) and glycopyrronium (difference in CFB –1.52 [95% CrI –4.08, 1.03]). The probabilities of aclidinium being a better treatment are reflecting these results, ranging from 88%–98% (Figure 3). The results for both scenarios and for the covariate analyses were consistent with the base case (Table 5). No studies allowing LABA use reported SGRQ data at 12 weeks. At 24 weeks, in the scenario where studies that allowed LABA concomitant treatment were excluded, aclidinium showed improved SGRQ total scores over tiotropium 18 μg as well.

The proportion of patients achieving the MCID in SGRQ total score of >4 units was reported in nine studies[22,24,25,28,29,34,39,40,43] (including 7,886 patients). In line with the NMA results for the CFB of total SGRQ score, a greater proportion of patients achieved the MCID in SGRQ total score with active treatments than with placebo (Table 4). For aclidinium, the OR versus placebo was 1.75 (95% CrI 1.34, 2.27) after 12 weeks and 1.94 (95% CrI 1.38, 2.73) after 24 weeks.

Dyspnea

Relief from dyspnea, assessed by the Transitional Dyspnea Index (TDI), was reported in ten studies[22,24,25,29,31,34,35,40,43,44] (including 6,248 patients). All treatments improved dyspnea versus placebo (a higher TDI score represents improvement) with a difference in CFB for TDI focal score close to the

Table 5 Results of the network meta-analysis for AB400 versus all other treatments

	Trough FEV_1				SGRQ				TDI			
	12 weeks		24 weeks		12 weeks		24 weeks		12 weeks		24 weeks	
	Diff CFB (95% CrI)	Probability AB400 better	Diff CFB (95% CrI)	Probability AB400 better	Diff CFB (95% CrI)	Probability AB400 better	Diff CFB (95% CrI)	Probability AB400 better	Diff CFB (95% CrI)	Probability AB400 better	Diff CFB (95% CrI)	Probability AB400 better
Scenario I: excluding LABA allowing studies												
TIO 5	−0.01 (−0.06, 0.05)	41%	0.00 (−0.05, 0.06)	57%								
TIO 18	−0.01 (−0.04, 0.02)	32%	0.00 (−0.04, 0.05)	58%			−2.29 (−4.66, 0.07)	97%				
GLYCO	0.00 (−0.03, 0.04)	55%	0.00 (−0.05, 0.05)	46%			−1.55 (−4.12, 1.00)	88%				
Scenario II: including ACCORD II												
TIO 5	−0.02 (−0.09, 0.05)	28%										
TIO 18	−0.02 (−0.05, 0.02)	19%			−0.50 (−2.20, 1.18)	72%			0.17 (−0.26, 0.60)	78%		
GLYCO	−0.01 (−0.06, 0.04)	33%			0.12 (−1.89, 2.11)	45%			0.15 (−0.45, 0.74)	69%		
Base case: adjusted for ICS												
TIO 5	−0.01 (−0.06, 0.05)	40%	0.02 (−0.03, 0.06)	75%			−2.53 (−4.94, −0.12)	98%				
TIO 18	0.00 (−0.04, 0.03)	38%	0.02 (−0.03, 0.06)	78%	−0.47 (−2.45, 1.51)	68%	−2.15 (−4.49, 0.17)	97%	0.34 (−0.20, 0.89)	89%	0.02 (−0.60, 0.65)	53%
GLYCO	0.00 (−0.04, 0.04)	49%	0.00 (−0.05, 0.05)	47%	−0.44 (−2.55, 1.68)	66%	−1.54 (−4.10, 1.01)	88%	0.14 (−0.48, 0.76)	67%	0.08 (−0.58, 0.74)	59%
Base case: adjusted for FEV_1% predicted												
TIO 5	0.00 (−0.08, 0.08)	45%	0.00 (−0.08, 0.07)	44%			−3.47 (−6.21, −0.74)	>99%				
TIO 18	0.00 (−0.05, 0.05)	46%	0.01 (−0.07, 0.07)	51%	−1.12 (−3.95, 0.70)	89%	−2.83 (−5.30, −0.37)	99%	0.20 (−0.29, 0.69)	79%	0.10 (−0.56, 0.76)	62%
GLYCO	0.00 (−0.06, 0.06)	53%	0.00 (−0.09, 0.06)	30%	−1.05 (−3.30, 1.20)	82%	−2.30 (−5.03, 0.43)	95%	0.19 (−0.46, 0.84)	71%	0.11 (−0.61, 0.82)	61%

Abbreviations: AB400, aclidinium 400 μg bromide twice daily; CFB, change from baseline; CrI, credible interval; FEV_1, forced expiratory volume in 1 second; FEV_1% pred, FEV_1 percentage predicted at baseline; GLYCO, glycopyrronium 50 μg bromide once daily; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; ACCORD, AClidinium in Chronic Obstructive Respiratory Disease COPD; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO 5, tiotropium 5 μg bromide once daily; TIO 18, tiotropium 18 μg bromide once daily.

MCID of one unit (Table 4). No tiotropium 5 µg studies reported this outcome. Aclidinium demonstrated favorable results versus tiotropium 18 µg and glycopyrronium, with the probabilities of aclidinium being a better treatment ranging from 59%–74% (Figure 3). When adjusting for covariates, differences tended to become more pronounced in favor of aclidinium (Table 5). In all analyses performed, the drugs showed comparable efficacy in improving TDI focal score (all credible intervals include zero), although aclidinium showed a numerically higher mean effect. None of the studies reporting this outcome allowed for LABA concomitant treatment.

The proportion of patients achieving the MCID in TDI focal score of >1 unit than placebo was examined in eight studies[22,24,25,29,34,35,43,44] (including 5,224 patients); the NMA showed that all active drugs produced a greater improvement of the TDI focal score than placebo (Table 4). The OR for aclidinium versus placebo was 1.99 (95% CrI 1.53, 2.60) after 12 weeks and 1.58 (95% CrI 1.13, 2.23) after 24 weeks.

Discussion

The aim of this study was to assess the relative effectiveness of aclidinium 400 µg bromide BID compared to tiotropium 18 µg OD, tiotropium 5 µg OD, and glycopyrronium 50 µg OD in patients with moderate-to-severe COPD in terms of lung function, health-related quality of life, and dyspnea.

This NMA suggests that aclidinium is expected to be comparable to all active treatments and better than placebo with respect to all outcomes assessed at 12 and 24 weeks. The meta-regression adjustment for percentage of concomitant use of ICS, and FEV_1% predicted at baseline did not change the main findings. This was also the case for two scenario analyses undertaken, ie, including ACCORD II – excluding LABA-allowing studies.

The outcomes assessed in this study are of key importance in maintenance treatments for COPD. FEV_1 was the primary endpoint in all of the studies, as spirometry reflects an important prognostic factor that is used to define severity for COPD. Although spirometry is clinically important, patient-centered outcomes, such as health status and dyspnea, may better reflect the effectiveness of a particular pharmacotherapy.[45] SGRQ represents a key patient-reported outcome that provides direct insight into the overall health status of patients, while dyspnea is a common and troublesome manifestation of COPD, and relief from dyspnea is an important goal of pharmacotherapy.

Other meta-analyses assessing the efficacy and safety of tiotropium have previously been published.[18,46,47] The results of these studies are consistent with the current NMA with respect to the comparison of tiotropium 18 µg, aclidinium 400 µg, and placebo. The current NMA extends those findings by including other LAMAs in the analysis. To our knowledge, there are no systematic literature reviews published on the relative efficacy of LAMAs.

Limitations

As with any systematic review, the quality of the trials included present a limitation of the current study. Overall, the RCTs were of high quality. A potential limitation of the evidence base is the perceived imbalance in patient severity between the treatments compared in the ACCORD II aclidinium study. For this reason, the study was excluded from the base case and was included only as a scenario analysis. Although in the scenario analysis the results for all outcomes were slightly less favorable for aclidinium, it did not change the conclusion of the current study that the active treatments are comparable. Another potential limitation of the evidence base is the open-label evaluation of tiotropium in three studies,[35,41,44] although there is no evidence that the treatment effect is different.[35] Furthermore, our review was limited to studies published in the English language.

In many cases, the data required for the analysis (eg, standard error) were not reported, and an estimation based on the available data (eg, confidence interval) was performed, thus restricting the accuracy. Furthermore, when not reported in the text or tables, values were estimated from figures which could also limit the accuracy.

Another inherent limitation of systematic reviews is the presence of heterogeneity. The degree of heterogeneity between studies included in the NMA was evaluated during the validity assessment step of the current study. Differences were identified in terms of the proportion of ICS use and FEV_1% predicted at baseline, and adjustment of the analyses for these differences using a constant treatment-by-covariate interaction led to consistent interpretation. Results adjusted for differences identified in the study design or patient characteristics had only a marginal impact on the effect estimates (by changing the estimated mean difference in change from baseline or the odds ratio or by increasing the uncertainty) and are, therefore, not believed to be a likely source of bias in the unadjusted analysis.

Although the meta-regression analysis suggests that the results of the NMA are not likely to be greatly affected by similarity and consistency violations, it was not possible to

evaluate or adjust for all potential effect modifiers. In some cases, there was insufficient information reported across the studies to fully evaluate the study or patient characteristics. For example, the concomitant treatments permitted during the study were not always clearly reported, and the proportion of patients receiving alternative concomitant treatments was inconsistently reported across the studies. Similarly, the proportion of patients with severe or very severe COPD was not always reported. In the case of ethnicity, it was assumed that this factor was not a treatment effect modifier, although limited information regarding the breakdown of this information was available.

Conclusion

Based on a NMA of the available RCTs reporting on efficacy outcomes in terms of bronchodilator (trough FEV_1), health status (as assessed by SGRQ total score and proportion of responders with at least four-point improvement), and dyspnea (as assessed by TDI focal score and proportion of responders with at least one point improvement), aclidinium 400 µg bromide BID is expected to be at least comparable to tiotropium 18 µg OD, tiotropium 5 µg OD, and glycopyrronium 50 µg OD at 12 and 24 weeks. Compared to tiotropium 5 µg, at 24 weeks, aclidinium is expected to be more efficacious in the SGRQ total score in all scenarios.

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Disclosure

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Supplementary table

Table S1 Search strategy

Databases: Embase, MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations
Search engine: Ovid
Time period: 1989 to October 2012
Search date: October 26th, 2012

1. Tiotropium bromide/or aclidinium bromide/or glycopyrronium bromide/(6235)
2. (Tiotropium or spiriva or aclidinium bromide or Eklira or Glycopyrronium or NVA-237 or NVA237 or (NVA adj "237") or glycopyrronium bromide or glycopyrrolate).ti,ab. (3378)
3. (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema).ab. or (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema).ti. (112741)
4. Exp Pulmonary Disease, Chronic Obstructive/or exp Chronic obstructive lung disease/(74383)
5. (Randomised or randomized or randomly or placebo or trial).ab. or (randomised or randomized or randomly or placebo or trial).ti. (1503026)
6. Exp RANDOMIZED CONTROLLED TRIAL/(654235)
7. Exp controlled clinical trial/(530101)
8. (1 or 2) and (3 or 4) and (5 or 6 or 7) (1004)
9. (Animals not humans).sh. (3705463)
10. 8 not 9 (1004)
11. 10 (1004)
12. Limit 11 to English language (944)
13. Limit 12 to yr = "1989-Current" (944)
14. Remove duplicates from 13 (632)

Database: Cochrane
Search date: October 26th, 2012

1. MeSH descriptor Pulmonary Disease, Chronic Obstructive explode all trees (1834)
2. (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema) (9973)
3. Tiotropium or spiriva or aclidinium bromide or Eklira or Glycopyrronium or NVA-237 or NVA237 or (NVA adj "237") or glycopyrronium bromide or glycopyrrolate (953)
4. ((#1 OR #2) AND #3) (520)
5. (#4), from 1989 to 2012 limit to trials (446)

Database: clinicaltrials.gov
Search date: October 26th, 2012
NVA-237 or NVA237 or (NVA adj "237") or glycopyrronium bromide or glycopyrrolate [INTERVENTION]
AND copd [CONDITION]
AND ("Phase II" OR "Phase III" OR "Phase IV") [PHASE]
Database: Pubmed
Search date: October 26th, 2012

1. Search tiotropium OR spiriva OR aclidinium bromide OR Eklira OR Glycopyrronium OR NVA-237 OR NVA237 OR glycopyrronium bromide OR glycopyrrolate [Title/Abstract] (1782)
2. Search COPD OR chronic obstructive pulmonary disease OR COAD OR chronic obstructive airway disease OR chronic obstructive lung disease OR chronic bronchitis OR emphysema [Title/Abstract] (65084)
3. Search randomised OR randomized OR randomly OR placebo OR trial [Title/Abstract] (846800)
4. Search ((#3) AND #2) AND #1 (366)
5. Search (("Glycopyrrolate" [Mesh]) OR "tiotropium" [Supplementary Concept]) OR "(3R)-3-((hydroxy(di-2-thienyl)acetyl)oxy)-1-(3-phenoxypropyl)-1-azoniabicyclo(2.2.2)octane bromide" [Supplementary Concept] Filters: Publication date from 2012/01/01 to 2013/12/31 (55)
6. Search (#4) NOT #5 Filters: Publication date from 2012/01/01 to 2013/12/31 (32)