FINAL REPORT

Comparative safety and effectiveness of long-acting muscarinic antagonists for chronic obstructive pulmonary disease (COPD): A rapid review and network meta-analysis

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Executive Summary

Summary

This rapid review and network meta- analysis was conducted to determine the comparative safety and efficacy of inhaled corticosteroids (ICS) and long- acting muscarinic antagonists (LAMA) in patients with chronic obstructive pulmonary disease (COPD). The results of a network meta-analysis (NMA) restricted to patients with moderate COPD found that tiotropium+formoterol had the highest probability of reducing the risk of exacerbations.

Glycopyrronium and aclidinium had the lowest risk of all-cause mortality while glycopyrronium and glycopyrronium+ indacaterol had the greatest probability of being safest for cardiovascular-related mortality in patients with all severities of COPD. Glycopyrronium and tiotropium had the greatest probability of being safest for pneumonia in patients with all severities of COPD. There were no significant differences in risk of arrhythmia across all treatment comparisons.

Implications

Tiotropium+formoterol is likely effective in preventing exacerbations in patients with moderate COPD. Glycopyrronium and aclidinium are likely to have the least risk for all-cause mortality while glycopyrronium and glycopyrronium+ indacaterol likely have the least risk for cardiovascular-related mortality for patients with all severities of COPD. Glycopyrronium and tiotropium are less likely to cause pneumonia in patients with all severities of COPD. These inhalers likely don't increase the risk of cardiac arrhythmia. As this is a rapid review, our results should be interpreted with caution.

What is the current practice in treating COPD with long-acting inhaled agents?

- Evidence suggests that therapy with long-acting muscarinic antagonists (LAMA) for patients with chronic obstructive pulmonary disease (COPD) is promising
- However, it is not clear which combinations of therapies are safest and most effective for these patients

Objective

- To determine the comparative safety and efficacy of LAMA for patients with COPD through a rapid review of the literature

How was the study conducted?

- The protocol for the review was developed and revised with input from researchers, clinicians, industry stakeholders, and the Ontario Ministry of Health and Long Term Care

- Three electronic databases and unpublished literature were searched for randomized controlled trials (RCTs) of long-acting inhaled agents in adults with COPD
- The primary outcome of interest was the proportion of patients with moderate COPD experiencing exacerbations and secondary outcomes included mortality, pneumonia, arrhythmia, and cardiovascular related mortality
- Screening of literature search results was conducted independently by two reviewers, data abstraction was completed by one reviewer and independently verified by a second, and risk of bias assessment was independently assessed by one reviewer
- Random-effects NMA was conducted based on the availability of evidence

What did the study find?

- 186 published articles reporting on 190 RCTs were identified for inclusion in the review
- Tiotropium+formoterol and GSK961081 (not commercially available) had the greatest probability of decreasing the risk of exacerbation in patients with moderate COPD (68 RCTs)
- Glycopyrronium and aclidinium had the greatest probability of decreasing the risk of mortality for patients with all severities of COPD (79 RCTs)
- Glycopyrronium and tiotropium had the greatest probability of being safest for pneumonia for patients with all severities of COPD (33 RCTs)
- Glycopyrronium and glycopyrronium+indacaterol had the greatest probability of being safest for cardiovascular-related mortality (32 RCTs)
- There were no significant differences in risk of arrhythmia across the compared agents (17 RCTs)

Rationale

Evidence from previous systematic reviews and network meta-analyses suggests that therapy with inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and long-acting muscarinic antagonists (LAMA) for patients with chronic obstructive pulmonary disease (COPD) is promising (1-9). However, to date, it is not clear which combinations of therapies are safest and most effective for these patients. This rapid review and network meta-analysis was completed to address this, and specifically to determine the comparative safety and efficacy of long-acting inhaled agents (ICS, LABA, LAMA) for patients with COPD. This report focuses on the comparative safety and effectiveness of LAMA compared with ICS, LABA (in any combination) or placebo.

Methods

Our rapid review protocol was drafted using guidance from the Preferred Reporting Items for Systematic reviews and Meta-analyses for Protocols (PRISMA-P) (10). The protocol was revised based on feedback from various stakeholders, including policy makers from the Ontario Ministry of Health and Long-term care, industry partners, patients, researchers with the ODPRN, and health care professionals. The protocol was registered with the international prospective systematic review register (PROSPERO 2013: CRD42013006725).

Eligibility criteria

We included parallel-group randomised clinical trials (RCTs) examining inhaled LAMA, LABA, ICS, and combinations of these agents. Studies examining these agents in any combination compared with each other, combinations of each other, or placebo in adults diagnosed with COPD were included. Concomitant COPD medications were included if both groups received the same interventions (e.g., rescue medication with a short-acting beta-agonist). A full list of included agents can be found in Appendix 1. We excluded studies that did not examine long-acting formulations or inhaler formulations. A full list of the excluded medications can be found in Appendix 2.

The proportion of patients with exacerbations overall (e.g., worsening of COPD symptoms that may require treatment with oral steroids and/or antibiotics) was the primary outcome of interest. Additional outcomes were selected based on feedback from patients with COPD and other stakeholders, including researchers, healthcare providers, and industry partners. We surveyed 19 patients with COPD and asked them to rate the importance of 24 efficacy and safety outcomes that were reported in RCTs of COPD therapies, as outlined in Appendix 3. Further details on the survey methodology are outlined in the qualitative analysis section. Patients identified quality of life, functional status and shortness of breath to be important patient-related efficacy outcomes, as outlined in Appendix 4. The patients also indicated that cardiac events and fractures were important patient-related adverse events associated with therapy. We considered patient’s preferences along with input from other stakeholder groups (such as researchers, healthcare providers, industry partners) and came to a consensus regarding the final outcomes that were chosen.

Studies were included regardless of duration of follow-up, date of dissemination, and publication status. Due to the numerous studies identified, this report focuses on data from published studies. Due to feasibility constraints, we limited inclusion to English language articles; this has not been shown to bias meta-analysis estimates in the past (11).

Information sources and literature search

Comprehensive literature searches were conducted by an experienced librarian in consultation with our research team. We searched MEDLINE, EMBASE, and Cochrane Library electronic databases from inception to mid-November 2013. The MEDLINE search is presented in Appendix 5. The main (MEDLINE) search was peer reviewed by another experienced librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist (12). After this exercise, the MEDLINE search was modified and the other databases were searched in a similar manner. Literature saturation was ensured by searching the reference lists of included studies and reference lists of relevant reviews (1-8, 13, 14). The results from the literature search were uploaded to online screening software (Synthesi.SR) (15).

Study selection process

To ensure reliability, a training exercise was conducted prior to commencing screening. Using the inclusion and exclusion criteria, a random sample of 25 titles and abstracts from the literature search was screened by all team members. Inter-rater agreement for study inclusion was calculated using percent agreement and we proceeded to the next stage of study selection when it was >90% across the team. This level of agreement occurred after 1 round of screening for level 1 (screening of titles and abstract) and 2 rounds of screening for level 2 (screening of full-text articles). Subsequently, two reviewers screened citations for inclusion, independently for level 1 screening and the same process was followed for level 2 screening. Conflicts were resolved by discussion or the involvement of a third reviewer (ACT and SES).

Data items and data abstraction process

We abstracted data on study characteristics (e.g., year of conduct, sample size, setting [e.g., multi-center, single center], country of study conduct, duration of treatment, duration of follow-up, intervention and comparator dosage, monotherapy, combination therapy), participant characteristics (e.g., number of patients, age mean and standard deviation, severity of COPD, diagnosis of COPD), and the definitions of outcomes (e.g., exacerbations [e.g., number of patients with at least 1 exacerbation],, arrhythmia [e.g., arrhythmia]). We selected 5 outcomes for analysis for this report based on feedback from our stakeholders; COPD exacerbations [main efficacy outcome] and mortality [secondary efficacy outcome] and, pneumonia, arrhythmia, and cardiovascular-related mortality for the safety outcomes. We abstracted the outcome results (e.g. number of patients with exacerbations) for the longest duration of follow-up only, as this is the most conservative approach(16). Prior to data abstraction, we completed a calibration exercise of the data abstraction form on a random sample of 5 articles. Subsequently, all of the included studies were abstracted in duplicate by independent reviewers and the data were verified by another team member.

Risk of bias and methodological quality appraisal process

One reviewer independently assessed each of the included studies using the 7-item Cochrane Risk of Bias Tool (17).

Synthesis of included studies

Study and patient characteristics were summarised descriptively. All outcomes presented here are dichotomous and the odds ratios (OR) were calculated. Clinical, methodological, and statistical heterogeneity were assessed for each pairwise comparison. We assessed statistical heterogeneity using a restricted maximum likelihood (REML) estimator (18) and the I^2 statistic, which measures the percentage of variability that cannot be attributed to random error alone. Since the GOLD criteria have changed over time, a clinician (SES) reviewed all of the included studies to establish the average COPD severity of the patients included in each trial using the most recent GOLD guidelines. Meta-analysis was analyzed in the R statistical software using the *metafor* command (19).

We completed a random effects network meta-analysis to synthesise the available evidence from the network of trials for the five outcomes analyzed. A frequentist approach was used. Treatments were grouped into nodes based on input from clinicians, methodologists, and statisticians on the team.

We assessed network heterogeneity using the I^2 statistic (20). To assess the consistency assumption in certain parts of the network, we used the loop-specific method (also known as the node-splitting method) (21, 22) and the separating indirect and direct evidence method (23). We evaluated whether the network was consistent as a whole using the design-by-treatment interaction model (24). When important inconsistency and/or heterogeneity were observed, we explored the possible sources using sub-network meta-analysis.

One unique advantage of network meta-analysis is that it allows the ranking of interventions. We estimated the ranking probabilities for all treatments and presented this using rankograms. A treatment hierarchy was also obtained using the surface under the cumulative ranking curve (SUCRA) (25). All network meta-analysis was done in Stata using *mvmeta* command (26).

ORs, 95% confidence intervals (CI) and number needed to treat (NNT) or number needed to harm (NNH) for statistically significant results are reported below. NNT and NNH were calculated using the formula:

For OR <1: NNT = (1-[PEER*(1-OR)]) / ([1-PEER]*[PEER]*[1-OR])

For OR >1: NNH = ([PEER*(OR-1)]+1) / [PEER*(OR-1)*(1-PEER)]

where, PEER or Patient Expected Event Rate = SUM (events across all placebo arms) / SUM (sample sizes across all placebo arms) for an outcome.

Due to the numerous treatment comparisons examined (approximately 600 comparisons), we have presented statistically significant results for the network meta-analysis results only. The network meta-analysis results for all outcomes are presented in Table 1.

Results

Literature search

The literature search yielded a total of 2,724 titles and abstracts (Figure 1). Of these, 1,256 articles were potentially relevant and their full-text was reviewed. Subsequently, 186 RCTs plus 58 companion reports fulfilled our eligibility criteria and were included. The list of 186 articles reporting the 190 included RCTs can be found in Appendix 6.

Study and patient characteristics

The year of publication ranged from 1989 to 2013. The majority of the RCTs were multi-center, conducted across numerous countries. Only 31 studies were single center trials. The median number of patients per trial was 280, which ranged from 15 to 17,135. The duration of treatment with long-acting inhaled agents ranged from 9 hours to almost 4 years. The mean age of included patients ranged from 47.1 to 65.8 and the percent female ranged from 0 to 58%.

Risk of bias

The most important internal validity criteria for RCTs are adequacy of generating the random sequence (e.g., through the use of a random numbers table) and ensuring that the allocation sequence is adequately concealed (e.g., through the use of sealed, opaque envelopes). Across the included RCTs, the majority were appraised as having unclear random sequence generation and unclear allocation concealment (Figure 2). Furthermore, the majority had a high risk of bias or unclear risk of bias in selective outcome reporting, as the outcomes reported in the registered trial protocols differed from those reported in the final publication. Finally, many of the RCTs had a high or unclear risk of bias due to other bias, mainly due to the potential for funding bias because many studies were funded by a pharmaceutical company and included authors on the trial who were employed by the drug manufacturer.

Primary efficacy outcome

Exacerbations for all severities of COPD

Ninety-two RCTs reported on exacerbations overall including 64,341 patients with all severities of COPD. This was comprised of 68 trials including patients with moderate COPD, 4 trials including patients with mild to moderate COPD, 5 trials including patients with severe COPD, and 15 trials including patients with mild to severe COPD. A network meta-analysis was done for all severities but inconsistency was present statistically and therefore, we have only reported the statistically significant results from direct comparison meta-analysis in Table 2. Specifically, 48 meta-analyses were conducted. Seventeen of these were statistically significant, of which 15 looked at relevant treatment comparisons included in this report.

Exacerbations for moderate COPD

Although we were unable to do a network meta-analysis for all severities of COPD, we were able to conduct such an analysis for patients with moderate COPD. Sixty-eight RCTs reported on exacerbations in 53,412 people with moderate COPD and contributed data to 210 treatment comparisons in a network meta-analysis. The included RCTs assessed LAMA agents (aclidinium, glycopyrronium, tiotropium), LABA/LAMA agents (formoterol+tiotropium, salmeterol+tiotropium, indacaterol+tiotropium, indacaterol+glycopyrronium, GSK 961081), ICS/LABA/LAMA agents (fluticasone+salmaterol+tiotropium), ICS agents (budesonide, fluticasone, mometasone), LABA agents (formoterol, indacaterol, salmeterol, vilanterol), ICS/LABA agents (budesonide+formoterol [BFC], fluticasone+vilanterol [FVC], fluticasone+salmeterol [FSC], mometasone+formoterol [MFC]) or placebo. No trials examining LAMA/LABA agent unmeclidinium+vilanterol reported data for this outcome.

A total of 40 meta-analyses were conducted; 12 of these were statistically significant, all of which looked at relevant treatment comparisons and are reported in Table 3. There was no significant statistical inconsistency between direct and indirect meta-analysis as well as no statistically significant heterogeneity in the network as a whole. As such, the focus is on the statistically significant network meta-analysis results.

LAMA vs. placebo

Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with glycopyrronium (NNT 15) or tiotropium (NNT 15) (Table 3).

LAMA vs. LAMA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LABA

Tiotropium decreased the risk of exacerbation compared with indacaterol (NNT 21).

LAMA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison. This might be due to a lack of power to detect a true difference between the agents; indeed, only two trials including 756 patients provided data on this treatment comparison.

LAMA vs. ICS+LABA

Glycopyrronium increased the risk of exacerbation compared with BFC (NNH 9) and MFC (NNH 10). Similarly, tiotropium increased the risk of exacerbation compared with BFC (NNH 10) and MFC (NNH 10).

LAMA+LABA vs. placebo

Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with tiotropium+formoterol NNT 6) and tiotropium+indacaterol (NNT 9).

LAMA+LABA vs. LABA

Tiotropium+formoterol decreased the risk of exacerbation compared with indacaterol alone (NNT 6) or salmeterol alone (NNT 7). Tiotropium+indacaterol decreased the risk of exacerbation compared with indacaterol alone (NNT 11).

LAMA+LABA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison. However, only one trial with 293 patients was included for this analysis, and therefore these results should be interpreted with caution.

LAMA+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison. However only one trial with 422 patients (fluticasone plus salmeterol vs. indacaterol plus glycopyrronium) was used for this comparison, and therefore these results should be interpreted with caution.

LAMA+ICS+LABA vs. placebo

Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with tiotropium+fluticasone+salmeterol (NNT 10).

LAMA+ICS+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

ICS+LABA vs. placebo

Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with budesonide+formoterol (NNT 6), fluticasone+salmeterol (NNT 17), or mometasone+formoterol (NNT 7).

ICS+LABA vs. LABA

When compared with indacaterol, treatment with BFC (NNT 7) or MFC (NNT 7) led to decreased risk of exacerbation. Decreased risk of exacerbation was also seen with BFC (NNT 8) or MFC (NNT 8) when compared to treatment with salmeterol. When compared with vilanterol, treatment with BFC (NNT 7), FVC (NNT 16), or MFC (NNT 8) led to decreased risk of exacerbation.

ICS+LABA vs. ICS+LABA

Compared with FSC, BFC NNT 8) or MFC (NNT 10) decreased risk of exacerbation.

LABA vs. placebo

Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with formoterol (NNT 9) or salmeterol (NNT 24).

LABA vs. LABA

Formoterol given alone decreased risk of exacerbation compared with indacaterol (NNT 11) or salmeterol (NNT 14) alone.

Results of our ranking analysis

Of all the drugs compared, BFC, tiotropium+formoterol, MFC, GSK961081 and formoterol alone had the largest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD with a probability of 86%, 85%, 83%, 79% and 67%, respectively.

Exacerbations for severe COPD

Five RCTs reported on 5,469 patients with severe COPD. There was insufficient data to complete a network meta-analysis or meta-analysis. Based on data from a single RCT, only 3 statistically significant results were observed; FSC led to a statistically significant decreased risk of COPD exacerbation when compared to treatment with salmeterol alone, and tiotropium led to a statistically significant decreased risk of COPD exacerbation when compared to placebo and compared to indacaterol.

Secondary efficacy outcome

Mortality

One hundred one RCTs reported on mortality overall and 79 RCTs including 140,849 patients contributed data on 378 treatment comparisons in a network meta-analysis. Twenty-two studies were excluded because they had zero events in all arms and do not contribute data to the network meta-analysis. The included RCTs assessed LAMA agents (aclidinium, glycopyrronium, tiotropium Handihaler, tiotropium Respimat, unmeclidinium), LABA/LAMA agents (formoterol+tiotropium, salmeterol+tiotropium, indacaterol+tiotropium, indacaterol+glycopyrronium, vilanterol+unmeclidinium), ICS/LABA/LAMA agents (fluticasone+salmaterol+tiotropium, budesonide+formoterol+tiotropium), ICS/LAMA agents (fluticasone+tiotropium), ICS agents (budesonide, fluticasone, mometasone, triamcinolone), LABA agents (AZD3199, formoterol, indacaterol, salmeterol, vilanterol), ICS/LABA agents (beclomethasone+formoterol, budesonide+formoterol [BFC], fluticasone+vilanterol [FVC], fluticasone+salmeterol [FSC], mometasone+formoterol [MFC]) or placebo.

There was no statistically significant heterogeneity or inconsistency in the network as a whole. The results focus on the statistically significant network meta-analysis results, and the statistically significant results from the direct meta-analysis are presented in Table 4. Specifically, a total of 58 meta-analyses were conducted; 3 of these were statistically significant, of which 2 looked at relevant treatment comparisons (Table 4).

LAMA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

ICS+LABA vs. placebo

Compared with placebo, there was a significant decrease in risk of death for those patients treated with FSC (NNT 99) (Table 4).

ICS+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

ICS+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

Results of our ranking analysis

Out of all the drugs compared, FSC, glycopyrronium, AZD3199, MFC and aclidinium had the largest probability of being the most effective for decreasing risk of mortality with a probability of 73%, 71%, 70%, 68% and 68%, respectively.

Secondary safety outcomes

Pneumonia

Thirty-seven RCTs reported on pneumonia and 33 RCTs including 47,628 patients contributed data on 153 treatment comparisons in a network meta-analysis. Four studies were excluded because they had zero events in all arms and do not contribute data to the network meta-analysis. The included RCTs assessed LAMA agents (glycopyrronium bromide, tiotropium), LABA/LAMA combined agents (indaceterol+glycopyrronium), or ICS/LABA/LAMA combined agents (tiotropium+salmeterol+fluticasone, tiotropium+budesonide+formoterol). Comparators included placebo, LABA agents (formoterol, indacaterol, salmeterol, vilanterol), ICS/LABA combined agents (beclomethasone+formoterol, BFC, FSC, FVC, MFC) or ICS agents (budesonide, fluticasone, mometasone). A total of 35 meta-analyses were conducted; 6 of these were statistically significant, of which 4 looked at relevant treatment comparisons and are reported in Table 5. The statistically significant network meta-analysis results are presented below and in Table 5.

LAMA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. ICS+LABA

Glycopyrronium significantly decreased risk of pneumonia compared with FVC (NNT 19) and FSC (NNT 21) (Table 5). Similarly, patients who received tiotropium experienced significantly less pneumonia than those receiving FVC (NNT 21) and FSC (NNT 26).

LAMA+LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. LAMA+ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

ICS+LABA vs. placebo

Statistically significantly more patients receiving FVC (NNH 10) and FSC (NNH 16) experienced pneumonia versus patients who received the placebo (Table 5).

ICS+LABA vs. LABA

Statistically significantly more patients taking FVC experienced pneumonia compared with formoterol (NNH 7) and vilanterol (NNH 17). Statistically significantly more patients receiving FSC experienced pneumonia versus those who received formoterol (NNH 10), indacaterol (NNH 15), and salmeterol (NNH 19).

ICS+LABA vs. ICS+LABA

Significantly more patients taking FSC experienced pneumonia versus BFC (NNH 19).

LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

Results of our ranking analysis

The probabilities for being the safest regarding pneumonia were 76% for formoterol, 76% for glycopyrronium, 63% for tiotropium, 62% for MFC, and 58% for indacaterol.

Arrhythmia

Forty RCTs reported on arrhythmia and 17 RCTs including 16,761 patients contributed data on 171 treatment comparisons in a network meta-analysis. The other 23 studies were excluded because they had zero events in all arms and do not contribute data to the network meta-analysis. The included RCTs assessed LAMA agents (glycopyrronium, tiotropium), and combined LABA/LAMA agents (indacaterol+tiotropium, indaceterol+glycopyrronium, umeclidinium+vilanterol). Comparators include placebo, LABA agents (AZD3199, formoterol, indacaterol, salmeterol, vilanterol), ICS/LABA combinations (beclomethasone+formoterol, BFC, FSC, FVC, MFC), and ICS agents (budesonide, fluticasone, mometasone). No statistically significant differences were observed across any of the agents compared with each other or placebo in the network meta-analysis. A total of 20 meta-analyses were conducted. There were no statistically significant differences between any of the agents regarding arrhythmia across all of the pair-wise comparisons from head-to-head trials.

LAMA vs. any other comparator

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. any other comparator

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. any other comparator

No statistically significant differences were observed for this treatment comparison.

ICS+LABA vs. any other comparator

No statistically significant differences were observed for this treatment comparison.

LABA vs. any other comparator

No statistically significant differences were observed for this treatment comparison.

Results of our ranking analysis

Given that the results were not statistically significant, we did not rank the agents in terms of their arrhythmia safety.

Cardiovascular-related mortality

Thirty two RCTs including 76,710 patients contributed data on 190 treatment comparisons in a network meta-analysis, after excluding studies with zero events in all arms. The included RCTs assessed LAMA agents (aclidinium, glycopyrronium, tiotropium Handihaler, tiotropium Respimat, unmeclidinium), LABA/LAMA agents (indacaterol+tiotropium, indacaterol+glycopyrronium, vilanterol+unmeclidinium), ICS agents (budesonide, fluticasone, triamcinolone), LABA agents (AZD3199, formoterol, indacaterol, salmeterol, vilanterol), or ICS/LABA agents (budesonide+formoterol [BFC], fluticasone+vilanterol [FVC], fluticasone+salmeterol [FSC]). A total of 35 meta-analyses were conducted, of which one of was statistically significant (Table 6). The statistically significant network meta-analysis results are presented below and in Table 6.

LAMA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LABA

There was a significant increase in risk of cardiovascular-related death for patients treated with tiotropium delivered via Handihaler (NNH 76) or tiotropium delivered via Respimat (NNH 59) when compared with salmeterol (Table 6).

LAMA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA vs. LAMA+ICS+LABA

No available data for this treatment comparison (no trials examining a LAMA+ICS+LABA reported data for this outcome).

LAMA vs. ICS+LABA

There was a significant increase in risk of cardiovascular-related death for patients treated with tiotropium delivered via Handihaler (NNH 131) or tiotropium delivered via Respimat (NNH 94) when compared with FSC (Table 6).

LAMA+LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LAMA+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+LABA vs. LAMA+ICS+LABA

No available data for this treatment comparison (no trials examining a LAMA+ICS+LABA reported data for this outcome).

LAMA+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LAMA+ICS+LABA vs. placebo

No available data for this treatment comparison (no trials examining a LAMA+ICS+LABA reported data for this outcome).

LAMA+ICS+LABA vs. LABA

No available data for this treatment comparison (no trials examining a LAMA+ICS+LABA reported data for this outcome).

LAMA+ICS+LABA vs. LAMA+ICS+LABA

No available data for this treatment comparison (no trials examining a LAMA+ICS+LABA reported data for this outcome).

LAMA+ICS+LABA vs. ICS+LABA

No available data for this treatment comparison (no trials examining a LAMA+ICS+LABA reported data for this outcome).

ICS+LABA vs. placebo

No statistically significant differences were observed for this treatment comparison.

ICS+LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

ICS+LABA vs. ICS+LABA

No statistically significant differences were observed for this treatment comparison.

LABA vs. placebo

Compared with placebo, there was a significant decrease in risk of cardiovascular-related death for those patients treated with salmeterol alone (NNT 211) (Table 6).

LABA vs. LABA

No statistically significant differences were observed for this treatment comparison.

Results of our ranking analysis

The probabilities for being the safest regarding cardiovascular-related mortality were 84% for glycopyrronium, 76% for glycopyrronium+indacaterol, 75% for salmeterol, 69% for AZD3199, and 63% for FSC.

Discussion

For risk of COPD exacerbation, we could not complete a network meta-analysis for all COPD severities because the data were inconsistent. However, we were able to conduct a network meta-analysis for patients with moderate COPD. We found that BFC (ICS+LABA), tiotropium+formoterol (LAMA+LABA), MFC (ICS+LABA), GSK961081 (a bi-functional molecule with both muscarinic antagonism and β2-agonism (MABA) properties; LAMA+LABA) and formoterol (LABA) had the largest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD. Although the network meta-analysis was consistent and didn't show evidence of statistical inconsistency between direct and indirect evidence overall, there were some direct meta-analysis estimates that were statistically significant that were no longer significant in network meta-analysis. This specifically refers to the results for tiotroprium versus salmeterol and MFC versus formoterol (although the upper bound of the 95% CI is very close to the null hypothesis at 0.99). In general, network meta-analysis estimates include more data so have more power to show a difference if a true difference exists. Treatment comparisons with statistically significant results from direct meta-analysis that were no longer statistically significant in our network meta-analysis should be interpreted with caution. These treatment comparisons need to be further explored by analyzing potential effect modifiers. A network meta-analysis could not be done for studies that focused on patients with severe COPD because of insufficient data.

A previously published network meta-analysis funded by private industry (Merck, Dhome, and Nycomed) concluded that combination therapy is likely superior to single therapy regarding exacerbations (9). The authors included 26 RCTs after searching the literature until 2010. A second network meta-analysis of inhaled drugs for COPD concluded that ICS/LABA combination therapy reduced exacerbations only in patients with low forced expiratory volume (8). The review included 35 RCTs with 26,786 patients.

We also analyzed all-cause mortality in a network meta-analysis and found that FSC significantly reduced this outcome compared to placebo (NNT 99) although the confidence interval is close to 1. Although the network meta-analysis was consistent and didn't show evidence of statistical inconsistency between direct and indirect evidence overall, FSC caused significantly less mortality when compared with tiotropum HandiHaler in direct meta-analysis, yet this was no longer statistically significant in our network meta-analysis. As such, this result should be interpreted with caution and will need to be further explored by analyzing potential effect modifiers.

A previously published network meta-analysis examined mortality overall in 42 trials (52,516 patients) of tiotropium Soft Mist Inhaler, tiotropium HandiHaler, ICS+LABA, LABA, ICS or placebo (32). In the random effects model, tiotropium Soft Mist Inhaler increased risk of all-cause mortality compared with placebo, tiotropium HandiHaler, ICS+LABA combination, and LABA alone. Overall, tiotropium Soft Mist Inhaler had the largest probability of being the least effective regarding mortality with a probability of 95%.

A recent Cochrane review and network meta-analysis compared four classes of long acting inhalers for COPD (ICS, LABA, ICS/LABA combination, and LAMA) for 2 efficacy outcomes: mean trough forced expiratory volume in one second (FEV1) and mean total score on the St George's Respiratory Questionnaire (SGRQ) (27). Seventy-one RCTs with 73,062 patients were included. FEV1 data were available for 46 studies (47,409 patients) with 120 treatment nodes across the networks, which provided data after 6 and 12 months of follow-up. Compared with placebo, ICS/LABA combination was the highest ranked class in terms of improved mean FEV1 at 6 and at 12 months. LAMAs and LABAs had a similar effect overall, and ICS ranked fourth. For SGRQ, data were available in 42 studies (54,613 patients) with 118 treatment nodes across the networks, which provided data after 6 and 12 months of follow-up. Similar to lung function, ICS/LABA ranked highest and patients receiving ICS/LABA combination had higher quality of life compared with placebo. LAMAs, LABAs, and ICS ranked second, third, and fourth, respectively, and were all better than placebo in terms of improved quality of life in patients with COPD. As this recent Cochrane review and network meta-analysis did not examine efficacy outcomes exacerbations or mortality, there is no overlap in results with our review.

In our rapid review presented here, the network meta-analysis suggested that the following agents were likely the safest regarding pneumonia: formoterol (LABA), glycopyrronium (LAMA), tiotropium (LAMA), MFC (ICS+LABA), and indacaterol (LABA). Since treatment effects were different within treatment classes, we chose not to conduct a class analysis. The results between direct and indirect evidence were consistent statistically and evidence of statistical inconsistency was not observed in the network overall. Furthermore, all of the meta-analysis results that were statistically significant were also significant in our network meta-analysis.

Our results for pneumonia are consistent with a recent Cochrane review on ICS, LABA and ICS/LABA combination which looked at pneumonia in patients with COPD (28). The study authors found an increased risk of pneumonia for fluticasone versus placebo and for fluticasone/LABA combination versus LABA alone.

We found no differences in risks of arrhythmia across any of the compared agents in our rapid review.

Regarding cardiovascular-related mortality, patients administered tiotropium using the HandiHaler or Respimat experienced significantly more cardiovascular-related deaths than those receiving salmeterol and FSC (NNH ranging from 59 to 131). As well, patients receiving salmeterol experienced significantly less cardiovascular-related mortality than those receiving placebo (NNT 211). The results between direct and indirect evidence were consistent statistically and evidence of statistical inconsistency was not observed in the network overall. Furthermore, all of the meta-analysis results that were statistically significant were also significant in our network meta-analysis.

In a previously published random effects network meta-analysis of 31 trials, tiotropium Soft Mist Inhaler increased risk of cardiovascular-related death compared with ICS+LABA, and had the largest probability of being the least safe for this outcome with a probability of 89% (32).

The results of our rapid review must be interpreted with caution for several reasons. First, because of the tight timelines, we were only able to include published literature. This is a very common practice when conducting a rapid review. As such, the results for treatments with many trials included in the network will likely be more stable than those for treatments with fewer studies, which is usually the case for newer drugs. Second, many of the included RCTs were at a high risk of bias for many of the Cochrane risk-of-bias criteria, especially for important items such as random sequence generation and allocation concealment, which are imperative for the internal validity of a RCT. As this is a rapid review, we were unable to conduct meta-regression analyses to determine the impact of risk of bias on our results. Third, we were unable to explore other important effect modifiers, such as duration of treatment administration, gender, definition of outcomes. Fourth, given the inconsistency across the data, we could not complete a network meta-analysis for risk of exacerbation for patients with all COPD severities. Finally, the COPD criteria for severity have changed over time and this has led to heterogeneity across the studies.

Key messages:

- For patients with moderate COPD, BFC (ICS+LABA), tiotropium+formoterol (LAMA+LABA), MFC (ICS+LABA), GSK961081 (LABA+LAMA) and formoterol (LABA) had the greatest probability of decreasing the risk of exacerbation.
- For patients with all severities of COPD, FSC (ICS+LABA), glycopyrronium (LAMA), AZD3199 (LABA), MFC (ICS+LABA) and aclidinium (LAMA) had the greatest probability of decreasing the risk of mortality.
- For patients with all severities of COPD, formoterol (LABA), glycopyrronium (LAMA), tiotropium (LAMA), MFC (ICS+LABA), and indacaterol (LABA) had the greatest probability of

being the safest for pneumonia.

- There were no significant differences in risk of arrhythmia across the compared agents.
- For patients with all severities of COPD, glycopyrronium (LAMA), glycopyrronium+indacaterol (LAMA+LABA), salmeterol (LABA), AZD3199 (LABA) and FSC (ICS+LABA) had the greatest probability of being the safest for cardiovascular-related mortality.

Our results should be interpreted with caution, as our review was conducted in a very short period of time.

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Figure 1: Study flow

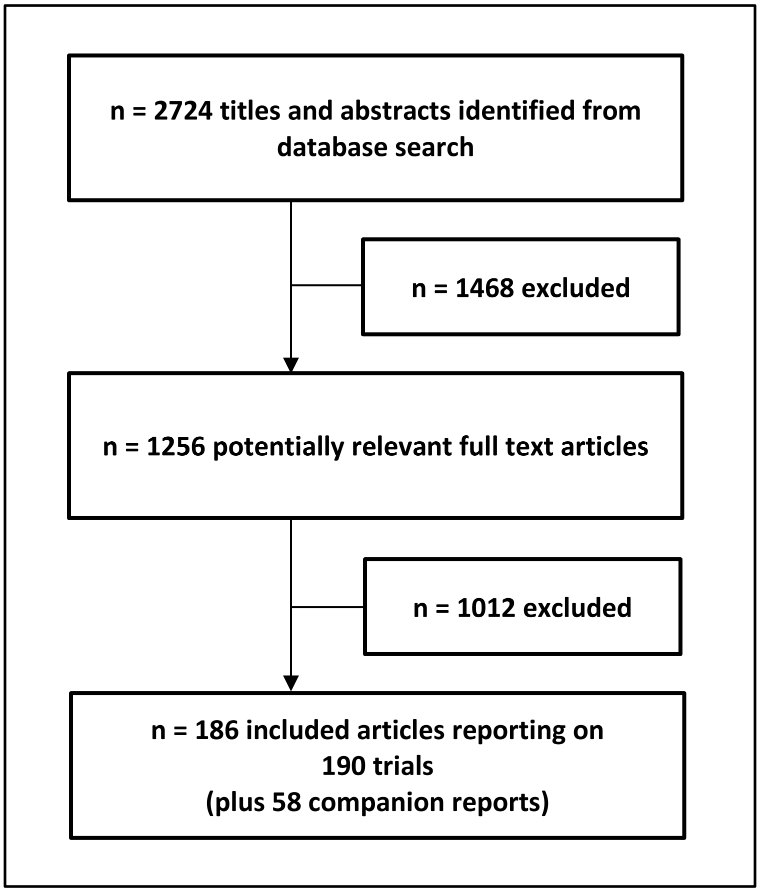

Figure 2: Risk of bias

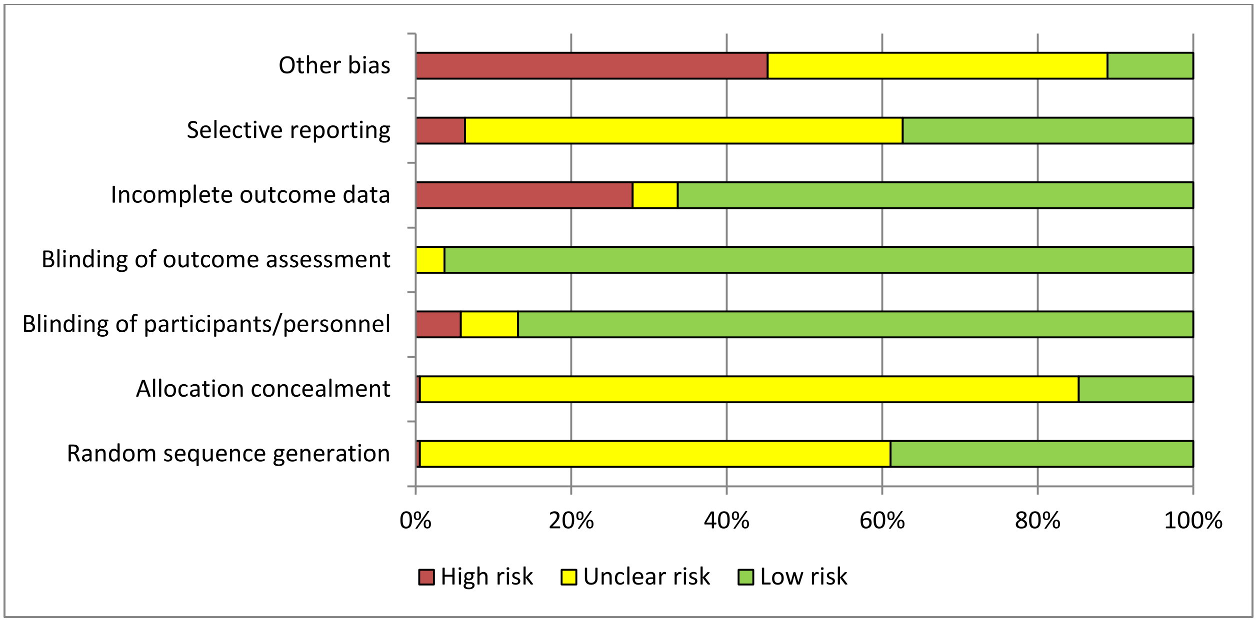

Table 1: Results of network meta-analysis by outcome

Treatment comparison	Exacerbations for moderate COPD	Mortality	Pneumonia	Arrhythmia	Cardiovascular-related mortality
LAMA vs. placebo	Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with glycopyrronium (NNT 15) or tiotropium (NNT 15).	NS	NS	NS	NS
LAMA vs. LAMA	NS	NS	NS	NS	NS
LAMA vs. LABA	Tiotropium decreased the risk of exacerbation compared with indacaterol (NNT 21).	NS	NS	NS	There was a significant increase in risk of cardiovascular-related death for patients treated with tiotropium Handihaler (NNH 76) or tiotropium Respimat (NNH 59) when compared with salmeterol.
LAMA vs. LAMA+LABA	NS	NS	NS	NS	NS
LAMA vs. LAMA+ICS+LABA	NS	NS	NS	NS	No data available

Treatment comparison	Exacerbations for moderate COPD	Mortality	Pneumonia	Arrhythmia	Cardiovascular-related mortality
LAMA vs. ICS+LABA	Glycopyrronium increased the risk of exacerbation compared with BFC (NNH 9) and MFC (NNH 10). Similarly, tiotropium increased the risk of exacerbation compared with BFC (NNH 10) and MFC (NNH 10).	NS	Glycopyrronium significantly decreased risk of pneumonia compared with FVC NNT 19) and FSC (NNT 21). Similarly, patients who received tiotropium experienced significantly less pneumonia than those receiving FVC (NNT 21) and FSC (NNT 26).	NS	There was a significant increase in risk of cardiovascular-related death for patients treated with tiotropium delivered via Handihaler (NNH 131) or tiotropium delivered via Respimat (NNH 94) when compared with FSC.
LAMA+LABA vs. placebo	Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with tiotropium+formoterol (NNT 6) and tiotropium+ indacaterol (NNT 9).	NS	NS	NS	NS

Treatment comparison	Exacerbations for moderate COPD	Mortality	Pneumonia	Arrhythmia	Cardiovascular-related mortality
LAMA+LABA vs. LABA	Tiotropium+formoterol decreased the risk of exacerbation compared with indacaterol alone (NNT 6) or salmeterol alone (NNT 7). Tiotropium+indacaterol decreased the risk of exacerbation compared with indacaterol alone (NNT 11).	NS	NS	NS	NS
LAMA+LABA vs. LAMA+LABA	NS	NS	NS	NS	NS
LAMA+LABA vs. LAMA+ICS+LABA	NS	NS	NS	NS	No data available
LAMA+LABA vs. ICS+LABA	NS	NS	NS	NS	NS
LAMA+ICS+LABA vs. placebo	Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with tiotropium+fluticasone+ salmeterol (NNT 10).	NS	NS	NS	No data available
LAMA+ICS+LABA vs. LABA	NS	NS	NS	NS	No data available
LAMA+ICS+LABA vs. LAMA+ICS+LABA	NS	NS	NS	NS	No data available
LAMA+ICS+LABA vs. ICS+LABA	NS	NS	NS	NS	No data available

Treatment comparison	Exacerbations for moderate COPD	Mortality	Pneumonia	Arrhythmia	Cardiovascular-related mortality
ICS+LABA vs. placebo	Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with budesonide+formoterol (NNT 6), fluticasone+ salmeterol (NNT 17), or mometasone+formoterol NNT 7).	Compared with placebo, there was a significant decrease in risk of death for those patients treated with FSC (NNT 99).			
	Statistically significantly more patients receiving FVC (NNH 10) and FSC (NNH 16) experienced pneumonia versus patients who received the placebo.	NS	NS		

Treatment comparison	Exacerbations for moderate COPD	Mortality	Pneumonia	Arrhythmia	Cardiovascular-related mortality
ICS+LABA vs. LABA	Compared with indacaterol, treatment with BFC (NNT 7) or MFC (NNT 7) led to decreased risk of exacerbation. Decreased risk of exacerbation was also seen with BFC (NNT 8) or MFC (NNT 8) when compared to treatment with salmeterol. When compared with vilanterol, treatment with BFC (NNT 7), FVC (NNT 16), or MFC (NNT 8) led to decreased risk of exacerbation.	NS	Statistically significantly more patients taking FVC experienced pneumonia compared with formoterol (NNH 7) and vilanterol (NNH 17). Statistically significantly more patients receiving FSC experienced pneumonia versus those who received formoterol (NNH 10), indacaterol (NNH 15), and salmeterol (NNH 19).	NS	NS
LABA vs. placebo	Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with formoterol (NNT 9) or salmeterol (NNT 24).	NS	NS	NS	Compared with placebo, there was a significant decrease in risk of cardiovascular-related death for those patients treated with salmeterol alone (NNT 211).

Treatment comparison	Exacerbations for moderate COPD	Mortality	Pneumonia	Arrhythmia	Cardiovascular-related mortality
LABA vs. LABA	Formoterol given alone decreased risk of exacerbation compared with indacaterol (NNT 11) or salmeterol (NNT 14) alone.	NS	NS	NS	NS

Table 2: Results of meta-analysis for risk of exacerbation with all severities of COPD*

Intervention	Comparison	NNT
LAMA vs. placebo		
Glycopyrronium	Placebo	14
Tiotropium	Placebo	14
LAMA vs. LABA		
Tiotropium	Indacaterol	22
Tiotropium	Salmeterol	25
LAMA+LABA vs. placebo		
Tiotropium + formoterol	Placebo	6
LAMA+ICS+LABA vs. LAMA		
Tiotropium + budesonide + formoterol	Tiotropium	5
ICS+LABA vs. placebo		
Fluticasone + Salmeterol	Placebo	5
Mometasone + Formoterol	Placebo	8
ICS+LABA vs. LABA		
Budesonide + Formoterol	Formoterol	20
Mometasone + Formoterol	Formoterol	12
Fluticasone + Salmeterol	Salmeterol	20
Fluticasone + Vilanterol	Vilanterol	16
LABA vs. placebo		
Formoterol	Placebo	11
Salmeterol	Placebo	16
LABA vs. LABA		
Indacaterol	Formoterol	5

*Note: network meta-analysis results not conducted

Table 3: Results of meta-analysis and network meta-analysis for risk of exacerbation with moderate COPD*

Intervention	Comparison	NNT
LAMA vs. placebo		
Glycopyrronium	Placebo	15
Tiotropium	Placebo	15
LAMA vs. LABA		
Tiotropium	Indacaterol	21
Tiotropium	Salmeterol	25
LAMA vs. ICS+LABA		
Glycopyrronium	Budesonide + formoterol	9 (NNH)
Glycopyrronium	Mometasone + formoterol	10 (NNH)
Tiotropium	Budesonide + formoterol	10 (NNH)
Tiotropium	Mometasone + formoterol	10 (NNH)
LAMA+LABA vs. placebo		
Tiotropium + formoterol	Placebo	6
Tiotropium + indacaterol	Placebo	9
LAMA+LABA vs. LABA		
Tiotropium + formoterol	Indacaterol	6
Tiotropium + indacaterol	Indacaterol	11
Tiotropium + formoterol	Salmeterol	7
LAMA+ICS+LABA vs. placebo		
Tiotropium + fluticatone + salmeterol	Placebo	10
ICS+LABA vs. placebo		
Budesonide + formoterol	Placebo	6
Fluticasone + salmeterol	Placebo	17
Mometasone + formoterol	Placebo	7

Intervention	Comparison	NNT
ICS+LABA vs. LABA		
Mometasone + formoterol	Formoterol	12
Budesonide + formoterol	Indacaterol	7
Mometasone + formoterol	Indacaterol	7
Budesonide + formoterol	Salmeterol	8
Mometasone + formoterol	Salmeterol	8
Budesonide + formoterol	Vilanterol	7
Mometasone + formoterol	Vilanterol	8
Fluticasone + vilanterol	Vilanterol	16
ICS+LABA vs. ICS+LABA		
Budesonide + formoterol	Fluticasone + salmeterol	8
Mometasone + Formoterol	Fluticasone + salmeterol	10
LABA vs. placebo		
Formoterol	Placebo	9
Salmeterol	Placebo	24
LABA vs. LABA		
Formoterol	Indacaterol	11
Formoterol	Salmeterol	14

Note: NNT calculated using the odds ratio from the meta-analysis whenever network meta-analysis was not statistically significant.

Table 4: Results of meta-analysis and network meta-analysis for mortality overall

Intervention	Comparison	NNT
LAMA vs. ICS+LABA		
Tiotropium Handihaler	Fluticasone + salmeterol	30 (NNH)
ICS+LABA vs. placebo		
Fluticasone + salmeterol	Placebo	99

Note: NNT calculated using the odds ratio from the meta-analysis whenever network meta-analysis was not statistically significant.

Table 5: Results of Meta-analysis and Network Meta-analysis for pneumonia

Intervention	Comparison	NNH
LAMA vs. ICS+LABA		
Glycopyrronium	Fluticasone + vilanterol	19 (NNT)
Glycopyrronium	Fluticasone + salmeterol	21 (NNT)
Tiotropium	Fluticasone + vilanterol	21 (NNT)
Tiotropium	Fluticasone + salmeterol	26 (NNT)
ICS+LABA vs. placebo		
Fluticasone + vilanterol	Placebo	10
Fluticasone + salmeterol	Placebo	16
ICS+LABA vs. ICS+LABA		
Fluticasone + salmeterol	Budesonide + formoterol	19
ICS+LABA vs. LABA alone		
Fluticasone + vilanterol	Formoterol	7
Fluticasone + salmeterol	Formoterol	10
Fluticasone + vilanterol	Vilanterol	17
Fluticasone + salmeterol	Indacaterol	15
Fluticasone + salmeterol	Salmeterol	19

Note: NNT calculated using the odds ratio from the meta-analysis whenever network meta-analysis was not statistically significant.

Table 6: Results of Meta-analysis and Network Meta-analysis for cardiovascular mortality

Intervention	Comparison	NNH
LAMA vs. LABA		
Tiotropium Handihaler	Salmeterol	76
Tiotropium Respimat	Salmeterol	59
LAMA vs. ICS+LABA		
Tiotropium Handihaler	Fluticasone + salmeterol	131
Tiotropium Respimat	Fluticasone + salmeterol	94
LABA vs. placebo		
Salmeterol	Placebo	211 (NNT)

Appendices

Appendix 1: Medications included in the rapid review

Generic name(s)*	Trade name(s)*
Inhaled long-acting beta$_2$-agonists (LABA)	
formoterol or eformoterol	Foradil, Oxeze, Oxis
Indacaterol	Arcapta
Salmeterol	Serevent, SereventDiskus
olodaterol	Striverdi
vilanterol or GW642444	
Inhaled long-acting muscarinic anticholinergics (LAMA)	
aclidinium bromide	Tudorza Genuair
glycopyrronium bromide	Seebri Breezhaler
tiotropium bromide	Spiriva
umeclidinium bromide or GSK573719	Incruse Ellipta
Inhaled corticosteroids (ICS)	
beclomethasone	QVAR, Clenil
budesonide	Pulmicort
fluticasone or GW685698	Flovent, FloventDiskus, Flixotide
mometasone	Asmanex Twisthaler
Combo LABA plus ICS in one inhaler**	
formoterol/budesonide	Symbicort
formoterol/mometasone	Zenhale
salmeterol/fluticasone	Advair, AdvairDiskus, Seretide
vilanterol/fluticasone	BreoEllipta
Combo LAMA plus ICS in one inhaler**	
Combo LAMA plus LABA in one inhaler**	
vilanterol/umeclidinium	AnoroEllipta
indacaterol/glycopyrronium	QVA149, Ultibro
Combo LAMA plus LABA in one inhaler (MABA)	
GSK961081 (formerly TD5959)	

Note: *This is not an exhausitve list. **Combination therapy could also be given in multiple inhalers.

Appendix 2: Medications excluded in the rapid review

Generic name(s)*	Trade name(s)*
We will exclude the following formulations:	
Long-acting beta$_2$-agonists (LABA) in nebulizer and transdermal form	
formoterol (when in nebulizer form)	
arformoterol	
tulobuterol	
Inhaled corticosteroids (ICS) in nebulizer form	
beclomethasone (when in nebulizer form)	
budesonide (when in nebulizer form)	
We will exclude ALL of the following agents:	
Short-acting beta2-agonists (SABA) (inhaled, nebulizer, oral, injection)	
fenoterol	
levosalbutamol or levalbuterol	Xopenex
salbutamol or albuterol	Ventolin
terbutaline	Bricanyl
Short-acting muscarinic anticholinergics (SAMA) (inhaler, nebulizer)	
ipratropium bromide	Combivent, Atrovent
oxitropium bromide	
Combo SABA plus anticholinergic in one inhaler (inhaler, nebulizer)	
fenoterol/ipratropium	
salbutamol/ipratropium	
Methylxanthines (oral, injection)	
aminophylline	
theophylline	
Systemic corticosteroids (oral)	
prednisone	
methyl-prednisolone	
Phosphodiesterase-4 (PDE4) inhibitors (oral)	
roflumilast	

Note: *This is not an exhausitve list.

Appendix 3: All efficacy and safety outcomes considered

Efficacy outcomes:

1. Proportion of patients with exacerbations (primary outcome of interest)
2. Number of hospitalizations (overall and due to exacerbations)
3. Number of emergency room visits (overall and due to exacerbations)
4. Function (e.g., 6 minute walk test, paced shuttle walk test)
5. Forced expiratory volume (FEV)
6. Quality of life
7. Mortality

Safety outcomes:

1. All harms
2. Serious harms
3. Withdrawals due to lack of efficacy
4. Treatment-related withdrawals
5. Cardiovascular-related mortality
6. Bone mineral density
7. Dyspnea
8. Ischemic heart disease
9. Heart failure
10. Arrhythmia
11. Pneumonia
12. Cataracts
13. Oral thrush
14. Palpitations
15. Headache
16. Constipation
17. Dry mouth

Appendix 4: Patient ratings of relevant outcomes

TOP 3 - MOST important efficacy outcomes:

1. Quality of Life (10/19 rated this outcome in their top 4)

2. Shortness of Breath (9/19 rated this in their top 4)

3. Functional Abilities (8/19 rated this in their top 4)

TOP 3 - LEAST important efficacy outcomes:

1. Mortality (7/19 rated this in their bottom 4)

2. Emergency Room Visits (6/19 rated in bottom 4)

3. Hospitalizations/Exacerbations/FEV (5/19 people rated this in their bottom 4)

TOP 3 - MOST important safety/side effects:

1. & 2. Heart Attack & Heart Failure (12/19 rated this in top 5)

3. Bone Fractures (8/19 rated this in top 5)

TOP 3 - LEAST important safety/side effects:

1. Dry Mouth (13/19 rated this in bottom 5)

2. Headache (9/19 rated this in bottom 5)

3. Constipation & Cataracts (7/19 rated this in bottom 5)

Appendix 5: Final MEDLINE Search

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1 exp Pulmonary Disease, Chronic Obstructive/

2 exp Emphysema/ or exp Pulmonary Emphysema/

3 ((chronic adj2 obstructi*) and (pulmonary or airway* or air way* or lung$1 or airflow* or air flow*)).tw.

4 (COPD or COAD).tw.

5 (chronic adj2 bronchitis).tw.

6 emphysema*.tw.

7 or/1-6

8 Formoterol*.tw,rn.

9 (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.

10 (eformoterol or Foradil).tw.

11 73573-87-2.rn.)

12 Indacaterol.tw,rn.

13 (Arcapta or Onbrez or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.

14 312753-06-3.rn.

15 Salmeterol*.tw,rn.

16 (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or SN408D or UNII-2I4BC502BT).tw.

17 89365-50-4.rn.

18 Salmeterolxinafoate.tw,rn.

19 (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.

20 94749-08-3.rn.

21 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-agonist* or betaagonist* or beta-adrenergic* or adrenergic beta-receptor* or beta-receptor agonist* or beta-adrenoceptor agonist*)).tw.

22 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-2-agonist* or beta-2agonist* or beta-2-adrenergic* or adrenergic beta-2-receptor* or beta-2-receptor agonist* or beta-2-adrenoceptor agonist*)).tw.

23 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta2-agonist* or beta2agonist* or beta2-adrenergic* or adrenergic beta2-receptor* or beta2-receptor agonist* or beta2- adrenoceptor agonist*)).tw.

24 ((longacting or long-acting) and ("beta(2)-agonist*" or "beta(2)agonist*" or "beta(2)-adrenergic*" or "adrenergic beta(2)-receptor*" or "beta(2)-receptor agonist*" or "beta(2)-adrenoceptor agonist*")).tw.

25 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B2-agonist* or B2-adrenergic* or adrenergic B2-receptor* or B2-receptor agonist* or B2-adrenoceptor agonist*)).tw.

26 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B-2-agonist* or B-2-adrenergic* or adrenergic B-2-receptor* or B-2-receptor agonist* or B-2-adrenoceptor agonist*)).tw.

27 (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.

28 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*).tw.

29 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (betamimetic* or beta-mimetic*)).tw.

30 exp Adrenergic beta-Agonists/ or Bronchodilator Agents/

31 (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting).tw.

32 30 and 31

33 or/21-29,32

34 Administration, Inhalation/

35 exp Aerosols/

36 (inhal* or aerosol*).tw.

37 or/34-36

38 33 and 37

39 or/8-20,38)

40 Beclomethasone/

41 (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.

42 (Beclamet or Beclazone or BecloAsma or Beclo AZU or Beclocort or Becloforte or Beclomet or Beclometason* or Beclomethasone or Beclorhinol or Becloturmant or Beclovent or Becodisk* or Beconase or Becotide or BemedrexEasyhaler or Bronchocort).tw.

43 (Ecobec or Filair or Junik or Nasobec Aqueous or Prolair or Propaderm or Qvar or Respocort or Sanasthmax or Sanasthmyl or Vancenase or Vanceril or Ventolair or Viarin).tw.

44 (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.

45 4419-39-0.rn.

46 Budesonide/

47 (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.

48 51333-22-3.rn.

49 Fluticasone.tw,rn.

50 (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.

51 Glucocorticoids/

52 glucocorticoid*.tw.

53 Adrenal Cortex Hormones/

54 (corticoid* or corticosteroid* or cortico-steroid*).tw.

55 ((adrenal cortex or adrenal cortical) adj3 hormon*).tw.

56 ((adrenal cortex or adrenal cortical) adj3 steroid*).tw.

57 or/51-56

58 57 and 37

59 or/40-50,58

60 (Fluticasone adj3 salmeterol).tw,rn.

61 (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.

62 (formoterol adj3 mometasone).tw,rn.

63 (Zenhale or Dulera).tw.

64 (formoterol adj3 budesonide).tw,rn.

65 (Rilast or Symbicord or Symbicort or Vannair).tw.

66 (vilanterol adj3 fluticasone).tw,rn.

67 Breo Ellipta.tw.

68 or/60-67

69 tiotropium.tw,rn.

70 (BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.

71 aclidiniumbromide.tw,rn.

72 (LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.

73 glycoyrroniumbromide.tw,rn.

74 (erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.

75 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (anticholinergic* or anti-cholinergic* or cholinolytic* or cholinergic-blocking or antimuscarinic* or anti-muscarinic* or ((cholinergic or acetylcholine or muscarinic) adj3 antagonist*))).tw.

76 (LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.

77 Muscarinic Antagonists/ or Cholinergic Antagonists/

78 77 and 31

79 75 or 76 or 78

80 79 and 37

81 or/69-74,80

82 39 or 59 or 68 or 81

83 7 and 82

84 randomized controlled trial.pt.

85 controlled clinical trial.pt.

86 randomized.ab.

87 placebo.ab.

88 clinical trials as topic/

89 randomly.ab.

90 trial.ti.

91 or/84-90

92 83 and 91

93 exp Animals/ not (exp Animals/ and Humans/)

94 92 not 93

95 (interview or news).pt.

96 94 not 95

97 96 use mesz

98 96 use prem

99 97 or 98

100 chronic obstructive lung disease/

101 lung emphysema/ or emphysema/

102 ((chronic adj2 obstructi*) and (pulmonary or airway* or air way* or lung$1 or airflow* or air flow*)).tw.

103 (COPD or COAD).tw.

104 (chronic adj2 bronchitis).tw.

105 emphysema*.tw.

106 or/100-105

107 formoterol/ or formoterolfumarate/

108 (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.

109 (eformoterol or Foradil or formoterol).tw.

110 (73573-87-2 or 183814-30-4).rn.

111 indacaterol/

112 (Arcapta or Onbrez or indacaterol or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.

113 312753-06-3.rn.

114 salmeterol/

115 (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or Salmeterol or SN408D or UNII-2I4BC502BT).tw.

116 89365-50-4.rn.

117 salmeterolxinafoate/

118 (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Salmeterolxinafoate or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.

119 94749-08-3.rn.

120 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-agonist* or betaagonist* or beta-adrenergic* or adrenergic beta-receptor* or beta-receptor agonist* or beta-adrenoceptor agonist*)).tw.

121 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-2-agonist* or beta-2agonist* or beta-2-adrenergic* or adrenergic beta-2-receptor* or beta-2-receptor agonist* or beta-2-adrenoceptor agonist*)).tw.

122 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta2-agonist* or beta2agonist* or beta2-adrenergic* or adrenergic beta2-receptor* or beta2-receptor agonist* or beta2- adrenoceptor agonist*)).tw.

123 ((longacting or long-acting) and ("beta(2)-agonist*" or "beta(2)-agonist*" or "beta(2)-adrenergic*" or "adrenergic beta(2)-receptor*" or "beta(2)-receptor agonist*" or "beta(2)-adrenoceptor agonist*")).tw.

124 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B2-agonist* or B2-adrenergic* or adrenergic B2-receptor* or B2-receptor agonist* or B2-

adrenoceptor agonist*)).tw.

125 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B-2-agonist* or B-2-adrenergic* or adrenergic B-2-receptor* or B-2-receptor agonist* or B-2-adrenoceptor agonist*)).tw.

126 (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.

127 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*).tw.

128 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (betamimetic* or beta-mimetic*)).tw.

129 exp beta adrenergic receptor stimulating agent/ or brochodilating agent/

130 (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting).tw.

131 129 and 130

132 or/120-128,131

133 inhalational drug administration/

134 aerosol/

135 (inhal* or aerosol*).tw.

136 or/133-135

137 132 and 136

138 or/107-119,137

139 beclometasone/

140 (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.

141 (Beclamet or Beclazone or BecloAsma or Beclo AZU or Beclocort or Becloforte or Beclomet or Beclometason* or Beclomethasone or Beclorhinol or Becloturmant or Beclovent or Becodisk* or Beconase or Becotide or BemedrexEasyhaler or Bronchocort).tw.

142 (Ecobec or Filair or Junik or Nasobec Aqueous or Prolair or Propaderm or Qvar or Respocort or Sanasthmax or Sanasthmyl or Vancenase or Vanceril or Ventolair or Viarin).tw.

143 (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.

144 4419-39-0.rn.

145 budesonide/

146 (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.

147 51333-22-3.rn.

148 fluticasone/ or fluticasone propionate/

149 (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.

150 (90566-53-3 or 80474-14-2).rn.

151 glucocorticoid/

152 glucocorticoid*.tw.

153 corticosteroid/

154 (corticoid* or corticosteroid* or cortico-steroid*).tw.

155 ((adrenal cortex or adrenal cortical) adj3 (hormon* or steroid*)).tw.

156 or/151-155

157 156 and 136

158 or/139-150,157

159 fluticasone propionate plus salmeterol/

160 (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.

161 (fluticasone adj3 salmeterol).tw.

162 136112-01-1.rn.

163 formoterolfumarate plus mometasonefuroate/

164 (formoterol adj3 mometasone).tw.

165 (Zenhale or Dulera).tw.

166 budesonide plus formoterol/

167 (formoterol adj3 budesonide).tw.

168 (Rilast or Symbicord or Symbicort or Vannair).tw.

169 150693-37-1.rn.

170 fluticasone furoate plus vilanterol/

171 (vilanterol adj3 fluticasone).tw.

172 Breo Ellipta.tw.

173 or/159-172

174 tiotropium bromide/

175 (BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.

176 (186691-13-4 or 136310-93-5).rn.

177 aclidinium bromide/

178 (LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.

179 320345-99-1.rn.

180 glycoyrronium bromide.tw.

181 (erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.

182 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (anticholinergic* or anti-cholinergic* or cholinolytic* or cholinergic-blocking or antimuscarinic* or anti-muscarinic* or ((cholinergic or acetylcholine or muscarinic) adj3 antagonist*))).tw.

183 (LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.

184 muscarinic receptor blocking agent/

185 cholinergic receptor blocking agent/

186 (184 or 185) and 130

187 182 or 183 or 186

188 187 and 136

189 or/174-181,188

190 138 or 158 or 173 or 189

191 106 and 190

192 randomized controlled trial/

193 controlled clinical trial/

194 randomized.ab.

195 placebo.ab.

196 "clinical trial (topic)"/

197 randomly.ab.

198 trial.ti.

199 or/192-198

200 191 and 199

201 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/

202 exp humans/ or exp human experimentation/ or exp human experiment/

203 201 not 202

204 200 not 203

205 204 use emcz

206 99 or 205

207 remove duplicates from 206

Appendix 6: List of included studies

1. Aalbers R, Ayres J, Backer V, Decramer M, Lier PA, Magyar P, et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. Eur Respir J. 2002;19(5):936-43.
2. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545-55.
3. Abrahams R, Moroni-Zentgraf P, Ramsdell J, Schmidt H, Joseph E, Karpel J. Safety and efficacy of the once-daily anticholinergic BEA2180 compared with tiotropium in patients with COPD. Respir Med. 2013;107(6):854-62.
4. Ambrosino N, Foglio K, Balzano G, Paggiaro PL, Lessi P, Kesten S, et al. Tiotropium and exercise training in COPD patients: effects on dyspnea and exercise tolerance. Int J Chron Obstruct Pulmon Dis. 2008;3(4):771-80.
5. Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. COPD. 2009;6(5):320-9.
6. Auffarth B, Postma DS, de Monchy JG, van der Mark TW, Boorsma M, Koeter GH. Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease. Thorax. 1991;46(5):372-7.
7. Barnes NC, Qiu YS, Pavord ID, Parker D, Davis PA, Zhu J, et al. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. Am J Respir Crit Care Med. 2006;173(7):736-43.
8. Bateman E, Feldman G, Kilbride S, Brooks J, Mehta R, Harris S, et al. Efficacy and safety of the long-acting muscarinic antagonist GSK233705 delivered once daily in patients with COPD. Clin Respir J. 2012;6(4):248-57.
9. Bateman ED, Tashkin D, Siafakas N, Dahl R, Towse L, Massey D, et al. A one-year trial of tiotropium Respimat plus usual therapy in COPD patients. Respir Med. 2010;104(10):1460-72.
10. Bateman ED, van Dyk M, Sagriotis A. Comparable spirometric efficacy of tiotropium compared with salmeterol plus fluticasone in patients with COPD: a pilot study. Pulm Pharmacol Ther. 2008;21(1):20-5.
11. Baumgartner RA, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, Hanrahan JP. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. Clin Ther. 2007;29(2):261-78.
12. Bedard ME, Brouillard C, Pepin V, Provencher S, Milot J, Lacasse Y, et al. Tiotropium improves walking endurance in COPD. Eur Respir J. 2012;39(2):265-71.
13. Beier J, Chanez P, Martinot JB, Schreurs AJ, Tkacova R, Bao W, et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily beta(2)-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. Pulm Pharmacol Ther. 2007;20(6):740-9.
14. Beier J, Kirsten AM, Mroz R, Segarra R, Chuecos F, Caracta C, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb

study. COPD. 2013;10(4):511-22.

15. Bogdan MA, Aizawa H, Fukuchi Y, Mishima M, Nishimura M, Ichinose M. Efficacy and safety of inhaled formoterol 4.5 and 9 mug twice daily in Japanese and European COPD patients: phase III study results. BMC Pulm Med. 2011;11:51.
16. Bolukbas S, Eberlein M, Eckhoff J, Schirren J. Short-term effects of inhalative tiotropium/formoterol/budenoside versus tiotropium/formoterol in patients with newly diagnosed chronic obstructive pulmonary disease requiring surgery for lung cancer: a prospective randomized trial. Eur J Cardiothorac Surg. 2011;39(6):995-1000.
17. Bourbeau J, Christodoulopoulos P, Maltais F, Yamauchi Y, Olivenstein R, Hamid Q. Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomised controlled trial. Thorax. 2007;62(11):938-43.
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21. Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J. 2011;38(4):797-803.
22. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297-303.
23. Caillaud D, Le Merre C, Martinat Y, Aguilaniu B, Pavia D. A dose-ranging study of tiotropium delivered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(4):559-65.
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25. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.
26. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J. 2003;22(6):912-9.
27. Calverley PM, Kuna P, Monso E, Costantini M, Petruzzelli S, Sergio F, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. Respir Med. 2010;104(12):1858-68.
28. Calverley PM, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax.

2003;58(10):855-60.

29. Calverley PM, Rennard S, Nelson HS, Karpel JP, Abbate EH, Stryszak P, et al. One-year treatment with mometasone furoate in chronic obstructive pulmonary disease. Respir Res. 2008;9:73.
30. Campbell SC, Criner GJ, Levine BE, Simon SJ, Smith JS, Orevillo CJ, et al. Cardiac safety of formoterol 12 microg twice daily in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2007;20(5):571-9.
31. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Jr., Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127(3):809-17.
32. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19(2):217-24.
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37. Chan CK, Maltais F, Sigouin C, Haddon JM, Ford GT, Group SS. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. Can Respir J. 2007;14(8):465-72.
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41. Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha JA, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res. 2007;8:93.

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Appendix 7: Definitions of exacerbations

Study	Definition of Exacerbation	Severity
Aalbers, 2002	wWorsening symptoms of COPD requiring the use of any additional treatment other than rescue albuterol/salbutamol	Mild to very severe
Aaron, 2007	An increase in or the new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid	Moderate to very severe
Abrahams, 2013	Exacerbations not defined	Moderate
Ambrosino, 2008	Exacerbations not defined	Moderate to severe
Anzueto, 2009	A complex of respiratory events (i.e. cough, wheezing, dyspnoea or sputum production) lasting greater than 3 days. These were generally treated with antibiotics and/or oral steroids.	Moderate to severe
Barnes, 2006	Exacerbations not defined	Moderate to severe
Bateman, 2010	A complex of respiratory events or symptoms that lasted greater than or equal to 3 days and required treatment with antibiotics and/or systemic corticosteroids, or prompted the investigator to change the patient's regular respiratory medication	Moderate to severe
Baumgartner, 2007	On-treatment exacerbation, including moderate (acute worsening of COPD requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalisation)	Moderate
Beier, 2007	Exacerbation which was treated with mucolytics	Mild to moderate
Bogdan, 2011	Exacerbations not defined	Moderate to very severe
Bourbeau, 1998	Exacerbations not defined	Moderate to severe
Boyd, 1997	Chronic obstructive airways disease exacerbated	Moderate to severe
Briggs, 2005	Worsening of symptoms required a change in medication	Moderate to very severe
Buhl, 2011	Number of patients with at least one exacerbation, defined as requiring a change in medication and/or hospitalization	Moderate to very severe
Burge, 2000	Exacerbations of COPD, determined on clinical grounds by the local physician	Moderate
Caillaud, 2007	Worsening of COPD symptoms that required any change in normal treatment	Moderate to severe
Calverley, 2010	Need for treatment with oral corticosteroids and/or antibiotics and/or the need to visit or be admitted to a hospital	Severe
Calverley, 2003	Exacerbations not defined	Mild to severe
Calverley, 2008	Exacerbations not defined	Moderate to severe
Campbell, 2007	Exacerbations not defined	Mild to severe

Casaburi, 2002	Acute exacerbations, defined according to the TSANZ COPDX guidelines (worsening symptoms requiring additional treatment with antibiotics or systemic corticosteroids, or both)	Mild to moderate
Celli, 2003	Worsening in symptoms requiring treatment with a course of systemic steroid or hospitalization	Moderate to very severe
Chanez, 2010	Exacerbations not defined	Moderate to very severe
Chapman, 2002	Exacerbations not defined	Mild to severe
Covelli, 2005	Exacerbations not defined	Mild to moderate
Criner, 2008	Exacerbations not defined	Moderate to very severe
D'Urzo, 2011	Symptomatic deterioration requiring the short term use of oral/intravenous steroids, antibiotics, or both, by the physician's discretion	Moderate to very severe
Dahl, 2010	Worsening of COPD that required treatment with a course of oral corticosteroids, hospitalization, or both.	Moderate to very severe
Dahl, 2013	Worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician	Moderate to very severe
Decramer, 2013	Acute infective exacerbations	Moderate to severe
Doherty, 2012	Subjects with ≥1 moderate/severe exacerbation: worsening symptoms requiring treatment with antibiotics, oral corticosteroids, and/or hospitalization	Moderate to very severe
Donohue, 2002	Exacerbations not defined	Moderate to very severe
Dransfield, 2013a	Exacerbations of COPD were diagnosed by the physician and reported as adverse events	Severe
Dransfield, 2013b	Presence, for greater than or equal to 2 days consecutively, of an increase in any two major symptoms (dyspnoea, sputum purulence and sputum volume) or in one major and one minor symptom (wheeze, sore throat, cough and symptoms of a common cold)	Mild to severe
Dusser, 2006	Mild: clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use; ≥12 inhalations/day of SABA/short acting anticholinergic, or ≥2 neubulized treatments/day of 2.5mg SABA/short-acting anticholinergic) on any 2 consecutive days. Moderate: clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease. Severe: deterioration of COPD that resulted in emergency treatment or hospitalization due to COPD.	Mild to very severe
Engel, 1989	Exacerbations not defined	Moderate to very severe
Feldman, 2010	COPD exacerbation met criteria for a severe AE (eg, was life-threatening, required hospitalization or prolonged hospitalization) it was recorded as an AE (AE events ≥2% incidence)	Moderate to very severe

Feldman, 2012	COPD exacerbations, defined as use of systemic antibiotics and/or systemic glucocorticosteroids and/or hospitalization related to COPD	Mild to severe
Freeman, 2007	Exacerbations not defined	Moderate to severe
Fukuchi, 2013	A new onset or worsening of more than one respiratory symptom (i.e., dyspnoea, cough, sputum purulence or volume, or wheeze) present for more than 3 consecutive days plus either a documented change or increase in COPD-related treatment due to worsening symptoms (e.g., steroids/antibiotics/oxygen), or documented COPD-related hospitalizations or emergency room visits.	Moderate to severe
Hanania, 2013	Exacerbations not defined	Moderate to severe
Hattotuwa, 2002	Exacerbations were defined in terms of increased dyspnea, sputum production, and sputum purulence.	Moderate to severe
Johansson, 2008	Worsening of two or more major symptoms (dyspnoea, sputum volume or sputum purulence) for at least 2 consecutive days or worsening of any one major symptom together with any minor symptom (colds, fever without other cause, increased cough, increased wheeze or sore throat) for at least 2 consecutive days	Moderate to severe
Jung, 2012	An exacerbation was defined as symptomatic deterioration requiring the shortterm use of oral/intravenous steroids, antibiotics, or both, by the physician's discretion.	Moderate to severe
Kardos, 2007	As a complex of respiratory events/symptoms with duration of 3 or more days (from patient's diary card) requiring a change in treatment (including patient inititated increases). A complex of respiratory events/symptoms meant ≥2 of the following (increase of symptoms or new onset): shortness of breath, sputum production (volume) cough, wheezing and chest tightness. The change in (or requirement of) treatment included prescription of antibiotics and/or systemic steroids and/or significant change (including increase) of the prescribed respiratory medication (bronchodilators including theophylline).	Mild to very severe
Kerwin, 2012	Severe exacerbation (defined as worsening of COPD leading to treatment with systemic corticosteroids [oral or parenteral] and/or hospitalization/emergency room visits)	Mild to very severe

Kerwin, 2013	Onset or worsening of more than one respiratory symptom (dyspnoea, cough, sputum purulence or volume or wheeze) for >3 consecutive days (based on diary cards or patients' reports of their health since the previous visit) plus documented proof of intensified treatment (eg, systemic steroids, antibiotics or oxygen) and/or hospitalisation or emergency room visit	Moderate to very severe
Kerwin, 2011a	Exacerbations not defined	Mild to severe
Kerwin, 2011b	Exacerbations of COPD were reported as adverse events. The investigator decided whether worsening of symptoms was severe enough to be considered an exacerbation of COPD as there was no a priori definition.	Moderate to very severe
Kinoshita, 2011	An episode with one or more unscheduled contacts with either a GP or a chest physician due to worsening of respiratory symptoms. Values abstracted for # patients and # events came from adding up the numbers in figure 3.	Mild to severe
Korn, 2011	Exacerbations, defined as moderate (acute worsening of COPD requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalisation), reported as safety outcome	Moderate to very severe
Kornmann, 2011	Exacerbations requiring treatment with antibiotics alone or a course of antibiotics and systemic steroids	Severe to very severe
Kuna, 2013	Deterioration of COPD	Moderate to severe
Littner, 2000	COPD exacerbations requiring additional therapy	Moderate to severe
Llewellyn-Jones, 1996	Reported as the observed number of all moderate plus severe exacerbations [Moderate exacerbations: worsening of chronic obstructive pulmonary disease (COPD) symptoms that required both a change of respiratory medication (increased dose of prescribed drug or addition of new drugs, i.e., antibiotics, mucolytics, systemic steroids, theophylline) and medical assistance. Severe exacerbations: deterioration in COPD resulting in hospitalization or emergency room treatment.]	Severe to very severe
Lomas, 2012	COPD exacerbations were defined as at least two new or increased respiratory symptoms (cough, wheeze, dyspnea, chest congestion, shortness of breath, chest tightness, or sputum production) occurring for at least 3 days and reported as an adverse event.	Moderate to severe
Mahler, 1999	Exacerbations not defined	Moderate to very severe
Mahler, 2012a	Exacerbations not defined	Moderate to severe
Mahler, 2012b	Bronchitis (COPD exacerbation) reported as AE	Moderate to severe

Maltais, 2005	An exacerbation was defined as an increase in symptoms requiring either a course of oral corticosteroids or antibiotics or a hospital admission. This change in medication was at the investigator' s discretion	Mild to moderate
Maltais, 2011	Worsening of COPD symptoms requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids, and other bronchodilator therapy. [Severity: mild, were self managed by the patient at home; moderate exacerbations required treatment by a family physician or as a hospital outpatient; severe exacerbations resulted in hospital admission.]	Mild to severe
Martinez, 2013	COPD exacerbation reported as AE and defined in the protocol as an increase in symptoms leading to any change in baseline medication or additional medical attention (eg, hospitalization, emergency department visit).	Moderate to very severe
Moita, 2008	Worsening for at least two consecutive days of two or more of the major symptoms (dyspnoea, sputum volume, or sputum purulence) or worsening of any one major symptom together with any one minor symptom (sore throat, colds [nasal discharge or nasal congestion], fever without other cause, increased cough, or increased wheeze)	Severe
Niewoehner, 2005	Exacerbations not defined	Moderate to severe
O'Donnell, 2004	A clinically significant worsening of COPD symptoms requiring treatment with antibiotics and/or systemic steroids	Mild to very severe
O'Donnell, 2006	COPD exacerbation: a complex of respiratory symptoms (increase or new-onset) of more than 1 of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics or systemic steroids, hospitalization, or both.	Moderate to very severe
Paggiaro, 1998	Data from AEs; use of oral steroids for exacerbations of COPD	Moderate to very severe
Powrie, 2007	At least 1 exacerbation, defined as chest problems requiring treatment with antibiotics and/or oral corticosteroids, self-reported by patients; [from primary publication: median yearly exacerbation rate (worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics, or both, as judged by the general practitioner; specific symptom criteria were not used)]	Mild to very severe
Rabe, 2008	Exacerbations not defined	Moderate to severe

Reid, 2008	Defined as a complex of lower, respiratory events/symptoms (increased or new onset), related to the underlying COPD, with a duration of 3 days or, more, requiring a change in treatment where a complex of, lower respiratory events/symptoms meant at least two of, the following: Shortness of breath; sputum production, (volume); occurrence of purulent sputum; cough;, wheezing; chest tightness. Captured as AEs.	Moderate to very severe
Rennard, 2001	COPD exacerbations were identified by the investigator and reported as AEs. An exacerbation was defined as symptoms that did not resolve with the use of trial medications (and any established medication) and therefore required additional medical therapy	Moderate to severe
Rossi, 2002	Exacerbations not defined	Moderate
Schermer, 2009	As worsening symptoms of COPD requiring drug therapy in addition to study drug, rescue medication and doses of concomitant COPD medication. Both adverse events that had been flagged by the investigator as an exacerbation and adverse that were described as an exacerbation were included in the analysis	Moderate to very severe
Shaker, 2009	As a worsening of respiratory disease requiring a change in medication and/or hospital care, emergency room care or an unscheduled outpatient visit. Data for number of patients is as an AE.	Mild to very severe
Sharafkhaneh, 2012	Exacerbations were episodes that required medical attention. During an exacerbation, at least two of the following three criteria had to be present: (1) episode with increased (productive) coughing and/or dyspnea and/or wheezing, (2) change in sputum color, or (3) increased use of bronchodilatory drugs	Moderate to severe
Sin, 2008	Exacerbations were defined as a combination of at least 2 of 3 criteria (increased dyspnea - measurement method not reported, increased sputum prodution and change in sputum colour)	Moderate to severe
Stockley, 2005	An exacerbation was defined as the onset of at least one, clinical descriptor (worsening of dyspnoea, cough or sputum, production; appearance of purulent sputum; fever ; appearance of new chest radiograph abnormality) lasting,at least 2 days and requiring a new prescription or an increase in, the dose of b2-agonists, antibiotics, corticosteroids or bronchodilators	Moderate to severe

Tashkin, 2008	Worsening of COPD symptoms leading to hospitalization, a visit to the emergency room, or use of an antimicrobial agent and/or systemic corticosteroids as an outpatient	Moderate to very severe
Tashkin, 2009	An exacerbation was defined by criteria used by Anthonisen and coworkers [ref 41: Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196–204.]	Mild to very severe
Tashkin, 2012	Those that required treatment with oral corticosteroids and/or antibiotics or required hospitalization	Moderate to very severe
Van de Maele, 2010	Episodes (new onset or worsening of at least 2 respiratory symptoms) with a duration of 3 days or more requiring systemic steroids or antibiotics.	Moderate to very severe
van Den Boom, 2001	Exacerbations not defined	Moderate to very severe
van der Valk, 2002	A sustained worsening of the patient's respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD. For the purposes of the trial, we considered that a patient had experienced a new COPD exacerbation if he or she had not been receiving oral steroids and antibiotics for at least 14 days after the previous exacerbation.	Moderate to very severe
van Noord, 2000	An increase in or new onset of more than one symptom of COPD (cough, sputum, wheezing, dyspnea, or chest tightness), with at least one symptom lasting 3 days or more and leading the patient's attending physician to initiate treatment with systemic glucocorticoids, antibiotics, or both (criterion for moderate exacerbation) or to hospitalize the patient (criterion for severe exacerbation).	Moderate to very severe
Vogelmeier, 2010	As a worsening symptoms of COPD requiring a change in drug therapy	Moderate to very severe

Vogelmeier, 2011	If a patient on two or more consecutive days used three or more extra inhalations of salbutamol per 24 hours above their reference rescue value (RRV; mean daily salbutamol use in the run-in period), this was counted as one mild exacerbation. If the patient's condition worsened and a course of oral corticosteroids was indicated based on a clinician's judgment standardised course of prednisolone tablets 30 mg/day for 10 days at the discretion of the physician accompanied by a 10 day course of antibiotics), the exacerbation was defined as moderate. If hospitalisation was required at the discretion of the clinician, the exacerbation was considered severe.	Moderate to severe
Vogelmeier, 2013	Exacerbations not defined	Moderate to severe
Vogelmeier, 2008	Exacerbations not defined	Moderate to severe
Wedzicha, 2008	Exacerbations not defined	Moderate to severe
Welte, 2009	Exacerbations not defined	Moderate to severe
Wielders, 2013	Moderate exacerbations were defined as worsening symptoms of COPD (≥2 consecutive days) necessitating treatment with oral corticosteroids or antibiotics, or both; severe exacerbations were similar events that necessitated hospital admission	Moderate to very severe
Wouters, 2005	Moderate exacerbations were defi ned as worsening symptoms of COPD (≥2 consecutive days) necessitating treatment with oral corticosteroids or antibiotics, or both; severe exacerbations were similar events that necessitated hospital admission	Moderate to very severe

Appendix 8: Definitions of pneumonia

Study	Definition of Pneumonia
Anzueto, 2009	Pneumonia not defined
Bateman, 2010	Pneumonia not defined
Bogdan, 2011	Pneumonia not defined
Calverley, 2010	Pneumonia not defined
Calverley, 2007	Pneumonia not defined
Chapman, 2011	Pneumonia not defined
D'Urzo, 2011	Pneumonia-like AE (includes pneumonia, bacterial pneumonia, and bronchopneumonia)
Dahl, 2013	Pneumonia not defined
Decramer, 2013	Pneumonia AE (includes bacterial pneumonia, pneumonia, lobar pneumonia, bronchopneumonia, staphylococcal pneumonia, pneumonitis)
Doherty, 2012	Pneumonias - AE in ≥5% confirmed by chest x-ray
Dransfield, 2013a	Pneumonia - AEs occurring in >3%
Dransfield, 2013b	Pneumonia - AE (confirmed by chest X-ray)
Ferguson, 2008	Pneumonia - AE (includes pneumonia, pneumonia viral, pneumonia aspiration, and lobar pneumonia)
Fukuchi, 2013	Pneumonia not defined
Hanania, 2013	Pneumonia-related (total) AE (includes pneumonia, bronchopneumonia, pneumococcal pneumonia)
Johansson, 2008	Pneumonia not defined
Jung, 2012	pneumonia - AE with an incidence > 1
Kardos, 2007	Pneumonia not defined
Kerwin, 2013	Pneumonia not defined
Kerwin, 2012	Pneumonia not defined
Kinoshita, 2011	Pneumonia not defined
Martinez, 2013	Pneumonia-related (total) [Pneumonia, Bronchopneumonia, Lobar pneumonia, Pneumonia staphylococcal]
Powrie, 2007	Pneumonia - AE (confirmed by chest X-ray)
Rennard, 2009	Pneumonia not defined
Sharafkhaneh, 2012	Pneumonia not defined
Tashkin, 2012	Pneumonia not defined
Tashkin, 2008a	Pneumonia not defined
Tashkin, 2008b	Pneumonia not defined
Vestbo, 1999	Pneumonia - AE (The diagnosis of pneumonia was based on clinical judgment, with radiologic confirmation not necessarily obtained even in episodes reported as lobar or bronchopneumonia)
Vogelmeier, 2013	Pneumonia (radiologically confirmed)
Vogelmeier, 2011	Pneumonia (events reported as adverse events and those confirmed radiographically)
Wedzicha, 2008	Pneumonia (events reported as adverse events and those confirmed radiographically)
Welte, 2009	Pneumonia not defined