Pharmacologic treatments for chronic obstructive pulmonary disease: a mixed-treatment comparison meta-analysis

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CRD summary
This generally well-conducted review found that combination regimens of inhaled corticosteroids and long-acting β₂-agonists were associated with fewer symptom exacerbations and with mortality benefits for patients with chronic obstructive pulmonary disease. The authors' conclusions are based on the evidence and are likely to be reliable.

Authors' objectives
To evaluate the efficacy of pharmacological agents for the maintenance treatment of chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and Web of Science were searched to October 2007 for relevant studies; search terms were reported. Reference lists of included trials, previous meta-analyses and review articles were searched for additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated frequencies of COPD exacerbations or mortality in patients with COPD who were treated with one or more of inhaled corticosteroids, tiotropium and long-acting β₂-agonists or combination therapy were eligible for inclusion. Interventions needed to be compared with placebo or active control.

Patients in included trials had moderate to severe COPD with mean one-second forced expiratory volumes (FEV₁) that ranged between 32.6% and 86.9%. Medications given included fluticasone, salmeterol, budesonide, triamcinolone, tiotropium and formoterol. Primary study end points were the effects of various drug classes on COPD exacerbations and mortality (classified as all-cause mortality). The effect of different COPD medications on withdrawals of patients from studies was evaluated. Definitions of COPD exacerbations varied between studies.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality of studies was assessed by two reviewers using the Jadad scale of appropriateness of randomisation, allocation concealment, double blinding and attrition rates in the groups. The authors evaluated use of intention-to-treat analyses in included trials.

Data extraction
Data were extracted to permit calculation of odds ratios (OR) and 95% confidence intervals (CI). Where there were incomplete or unclear data, relevant study authors, drug manufacturers or regulatory websites were contacted or searched to obtain additional data.

Three reviewers performed data extraction independently using a standardised data extraction form.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using a DerSimonian and Laird random-effects model. Q-statistic was used to evaluate statistical heterogeneity across studies. Reviewers conducted a mixed-treatment comparison (MTC) meta-analysis using a Bayesian Markov Chain Monte Carlo method to calculate odds ratios and 95% credible intervals (CrI) of experiencing a COPD exacerbation, mortality or withdrawal from a study for all treatments relative to control or placebo treatment.
Subgroup and sensitivity analyses were undertaken to examine effects of: longer follow-up periods; severity of COPD defined by hospitalisation of FEV; studies that used intention-to-treat analyses; and studies that attained a Jadad quality score of more than 3 out of 5.

**Results of the review**

Forty-three trials (n=31,020) were included in the review. Medications assessed were long-acting \( \beta_2 \)-agonists (23 trials), inhaled corticosteroids (13 trials), tiotropium (16 trials) and combination inhaled corticosteroid/long-acting \( \beta_2 \)-agonists (11 trials). Placebo treatment was the sole comparator in 29 trials. Forty-one studies scored 3 or more on the 5-item Jadad scale, which indicated good to high quality studies. Thirty-five trials used intention-to-treat analyses. Study durations ranged from four to 160 weeks.

**Exacerbations (39 trials, n=28,232):**

Traditional meta-analysis showed that compared to placebo the odds of having an exacerbation of COPD were significantly decreased: by 17% with use of long-acting \( \beta_2 \)-agonists (OR 0.83, 95% CI 0.76 to 0.90); by 28% with tiotropium (OR 0.72, 95% CI 0.65 to 0.80); and by 22% with combination regimens of inhaled corticosteroids and long-acting \( \beta_2 \)-agonists (OR 0.78, 95% CI 0.70 to 0.87).

Results from MTC analysis were similar, but additional decreases in the odds of an exacerbation were observed: by 15% when inhaled corticosteroids were compared to placebo (OR 0.85, 95% CrI 0.75 to 0.97); by 18% when tiotropium was compared to long-acting \( \beta_2 \)-agonists (OR 0.82, 95% CrI 0.72 to 0.93); and by 19% when compared to inhaled corticosteroids (OR 0.81, 95% CrI 0.69 to 0.94).

**Mortality (28 trials, n=26,112):**

In the traditional meta-analysis, mortality decreased by 21% with use of combination therapy of inhaled corticosteroids and long-acting \( \beta_2 \)-agonists compared to placebo (OR 0.79, 95% CI 0.65 to 0.96) and by 24% with use of combination regimens compared to use of inhaled corticosteroids alone (OR 0.76, 95% CI 0.63 to 0.93).

In the MTC analyses, statistically significant increases in mortality were found with tiotropium treatment compared to combination therapy of inhaled corticosteroids and long-acting \( \beta_2 \)-agonists (OR 1.84, 95% CI 1.07 to 3.17). Other comparisons of medications to placebo or to each other did not result in statistically significant reductions in mortality.

**Withdrawals from trials (29 trials, n=22,487):**

Patient withdrawals were significantly reduced with: all active treatments compared to placebo; tiotropium and combination therapies compared to monotherapy with long-acting \( \beta_2 \)-agonists; and combination therapy compared to inhaled corticosteroids. Similar trends were observed in the MTC analysis.

Statistical heterogeneity was reported for comparisons of exacerbations with inhaled corticosteroids with placebo (Q=15.9, p=0.04), combination therapy of inhaled corticosteroids and long-acting \( \beta_2 \)-agonists (Q=17.3, p=0.008) and patient withdrawals from trials when long-acting \( \beta_2 \)-agonists were compared to placebo treatments (p=0.04).

No significant variations from the results of the MTC meta-analyses were observed in: sensitivity or subgroup analyses conducted on the basis of follow-up periods; severity of COPD; studies that used intention-to-treat analyses; and studies that attained a Jadad quality score of 3 or more out of 5.

**Authors' conclusions**

Combination therapeutic regimens of inhaled corticosteroid with long-acting \( \beta_2 \)-agonist therapy were associated with the greatest positive effect on outcomes in patients with COPD and provided a significant benefit in mortality. Of the monotherapies under investigation, tiotropium monotherapy was associated with the lowest odds of both having a COPD exacerbation and the need to withdraw from a study.

**CRD commentary**
The review question was clear and supported by appropriate inclusion criteria with respect to study design, participants, treatments and outcomes. The search included appropriate electronic databases. The risk of language bias was unclear as the authors did not report whether language restrictions were applied. Steps were taken to minimise reviewer bias and errors for assessment of methodological quality and data extraction; no such steps were reported for study selection. The authors used appropriate methods to statistically combine studies. Potential causes of statistical heterogeneity were explored with subgroup and sensitivity analyses. This was generally a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that although treatment guidelines had not previously stated a preference for a particular type of bronchodilator for patients with moderate COPD, the results of this review suggested that tiotropium could be the preferred agent (compared with long-acting β2-agonists).

Research: The authors stated that additional large trials that compared tiotropium and long acting β2-agonists were required to confirm the results found in the review pertaining to greater reductions in exacerbations and fewer withdrawals observed with tiotropium treatment.

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