Effect of long-acting beta-agonists on the frequency of COPD exacerbations: a meta-analysis
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CRD summary
This well-conducted review found that long-acting beta-agonists reduced the frequency of moderate and severe exacerbations in patients with stable chronic obstructive pulmonary disease (COPD). Salmeterol, formoterol and indacaterol each significantly reduced COPD exacerbations compared with placebo. The results are likely to be reliable, but the conclusions on severe exacerbations should be considered tentative given potential publication bias.

Authors' objectives
To evaluate the effect of long-acting beta-agonists on the frequency of exacerbations in patients with chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to December 2010. Search terms were reported. No language restrictions were applied. Bibliographies of included studies and reviews were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared a long-acting beta agonist with placebo in patients with stable COPD were eligible for inclusion. Treatment had to last at least 24 weeks. Eligible trials had to include at least 100 patients and report outcome data on exacerbations. The primary outcome was moderate to severe COPD exacerbations using a definition based on symptoms and events. Moderate exacerbations were defined as those that required treatment with antibiotics and/or systemic steroids; severe exacerbations were defined as those that required hospitalisation.

The included trials were all double-blind and multicentre, and lasted from six to 12 months. The mean age of included patients ranged from 60 to 65 years; the proportion of men ranged from 63% to 83% (where reported). Mean forced expiratory volume in one second (FEV₁) ranged from 36% to 56%. Most trials included patients who had been treated with inhaled corticosteroids. Patients in the intervention group received one of salmeterol 50μg twice daily, formoterol 9 to 24μg twice daily, formoterol 9μg twice daily (plus 4.5μg as needed), or indacaterol 150μg to 600μg four times daily.

Two reviewers independently selected trials.

Assessment of study quality
Quality was assessed using the Cochrane risk of bias tool, which rated each trial as adequate, inadequate or unclear based on the following domains: sequence generation, allocation concealment, blinding, addressing incomplete outcome data, free of selective reporting, free of other bias.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted to allow the calculation of odds ratios with 95% confidence intervals. Trial authors were contacted to obtain missing data, where needed.

Two reviewers independently extracted the data; it was not clear how disagreements were resolved.

Methods of synthesis
Data were pooled using fixed-effect meta-analysis where the results appeared to be homogenous, and random-effects meta-analysis in the presence of statistical heterogeneity. Heterogeneity was investigated by using the Q statistic and I². I² values indicated low (<25%), moderate (25% to 75%) and high (>75%) degrees of inconsistency.
Stratified analyses were performed by each long-acting beta-agonist and by exposure to inhaled corticosteroids. Sensitivity analyses to test the robustness of the meta-analyses were conducted by excluding individual trials sequentially.

Funnel plots and Egger's weighted regression test were used to investigate publication bias.

**Results of the review**

Seventeen RCTs (11,871 patients) were included in the review. The overall risk of bias was relatively low in most trials. Two trials were judged to be at high risk of bias for blinding. For allocation concealment and other sources of bias, the risk of bias was unclear for many trials.

Long-acting beta-agonists had a beneficial effect on chronic obstructive pulmonary disease (COPD) exacerbations compared with placebo (OR 0.81, 95% CI 0.75 to 0.88; I²=0%; 18 RCTs). The results for each drug (salmeterol, formoterol and indacaterol) compared with placebo were similar to the overall pooled result.

When results were stratified according to whether patients were treated with inhaled corticosteroids or not, salmeterol was equally effective in those treated and not treated compared with placebo. Formoterol was more beneficial than placebo in trials of patients treated with inhaled corticosteroids, but not better than placebo in trials of patients not treated with inhaled corticosteroids. There were no trials of patients treated with indacaterol but not treated with inhaled corticosteroids.

Long-acting beta-agonists had a beneficial effect on severe COPD exacerbations or withdrawals owing to exacerbations compared with placebo (OR 0.74, 95% CI 0.63 to 0.88; I²=4%; 16 RCTs). When stratified by drug, the effect was evident for salmeterol (OR 0.66, 95% CI 0.49 to 0.89; I²=0%; seven RCTs) and indacaterol (OR 0.42, 95% CI 0.21 to 0.83; I²=23%; two RCTs), but was not statistically significant for formoterol (OR 0.85, 95% CI 0.68 to 1.06; I²=0%; seven RCTs).

For all long-acting beta-agonists compared with placebo, the effect on severe COPD exacerbations or withdrawals owing to exacerbations was evident in patients who used inhaled corticosteroids (OR 0.68, 95% CI 0.52 to 0.89; I²=0%) and those who did not (OR 0.79, 95% CI 0.63 to 0.99; I²=25%). When these analyses were further stratified by drug, the only significant effects were in patients taking indacaterol and inhaled corticosteroids (OR 0.42, 95% CI 0.21 to 0.83; I²=23%) and in those taking salmeterol but not inhaled corticosteroids (OR 0.48, 95% CI 0.29 to 0.81; I²=0%).

Sensitivity analysis showed the meta-analyses was robust to excluding individual studies sequentially.

Funnel plots and Egger's test showed not evidence of publication bias for COPD exacerbations, but there was evidence of publication bias for severe exacerbations or withdrawals owing to exacerbations (Egger's bias value -2.36, 95% CI -2.83 to -0.13).

**Authors' conclusions**

Long-acting beta-agonists reduced the frequency of exacerbations in patients with stable chronic obstructive pulmonary disease (COPD). Salmeterol, formoterol and indacaterol each significantly reduced COPD exacerbations compared with placebo. Salmeterol, but not formoterol, decreased exacerbations in patients who had not been treated with inhaled corticosteroids.

**CRD commentary**

The review question was clear. Participant, intervention, design and outcome criteria were clear and appropriate. The search covered several sources, with no language restrictions. Steps were taken to reduce error and bias during the search and data extraction, but it was not clear whether this was also the case for the quality assessment.

The risk of bias assessment was appropriate, as was the meta-analysis. The authors were careful to ensure relatively homogenous patients were included; the outcomes were also homogenous. For the analyses of severe exacerbations, there was evidence of publication bias. The authors acknowledged that some of the lack of effect seen in the stratified analyses of severe exacerbations could have been due to low statistical power.

The authors' conclusions reflected the evidence presented, but because of potential publication bias, the conclusions
regarding severe exacerbations should be considered tentative.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that more large clinical trials with exacerbations as primary outcomes were required to confirm the effect of Long-acting beta-agonists on exacerbations.

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