Inhaled corticosteroids vs placebo for preventing COPD exacerbations: a systematic review and metaregression of randomized controlled trials

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CRD summary
The review found a modest reduction in risk of exacerbations in patients with severe to very severe chronic obstructive pulmonary disease with use of inhaled corticosteroids that was not related to the level of baseline lung function. The authors suggested that the role of inhaled corticosteroids needed to be further evaluated. Their cautious conclusions are appropriate and reliable.

Authors' objectives
To assess the efficacy of inhaled corticosteroids in reducing chronic obstructive pulmonary disease (COPD) exacerbations in relation to baseline lung function.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for published peer-reviewed studies published in the English language from 1988 to 2008; search terms were reported. Reference lists of retrieved articles and reviews were searched.

Study selection
Studies were eligible if they were randomised controlled trials (RCTs) that compared inhaled corticosteroids alone versus placebo, had participants with confirmed cases of any severity of COPD and follow-up duration of at least one year.

Mean age of participants ranged from 55 to 67.5 years. The proportion of participants who were male ranged from 52% to 81.5%. The proportion who were current smokers ranged from 34.5% to 90.2%. Interventions included budesonide 800ug, fluticasone 1,000ug and beclomethasone 2,000ug, triamcinolone 1,200ug and mometasone 800ug. Some of the studies had a systemic steroid run-in phase of two weeks. The ratio of forced expiratory volume over forced vital capacity at one second (FEV₁) values were less than 50% in most studies. The definition of COPD exacerbation varied among the trials, but was generally equivalent to what is used in daily practice.

Two authors independently selected studies for the review. Disagreements were resolved by discussion.

Assessment of study quality
Validity assessment was undertaken using the Jadad scale with a score of 0 to a maximum of 5 to assess randomisation, blinding and treatment of withdrawals and dropouts. Studies were defined as low quality if the Jadad score was 2 or less and high quality if the Jadad score was 3 or more.

Two authors independently performed the validity assessment. Discrepancies were resolved by consensus.

Data extraction
Data on baseline lung function (FEV₁>50% and FEV₁≤50%) of participants and occurrence of COPD exacerbations were extracted onto a data extraction form in order to calculate relative risks and 95% confidence intervals (CI).

Two authors independently performed data extraction. Discrepancies were resolved by consensus.

Methods of synthesis
Studies were pooled with Mantel-Haenszel fixed-effect and DerSimonian-Laird random-effects models. Relative risks (RR) with 95% CI were calculated. Results were based on the random-effects model. Heterogeneity was assessed by the
I² value (substantial heterogeneity was defined as a value >50%) and the Cochran Q statistic. Publication bias was assessed by inspection of the Begg funnel plot and two statistical tests, the Egger test and the Begg and Mazumdar test. Sensitivity analyses were performed to examine effect sizes according to COPD severity (FEV₁ >50% and FEV₁ ≤50%). Unrestricted maximum likelihood weighted linear random-effects meta-regression was used to estimate the percentage risk reduction in exacerbation predicted at any percentage predicted FEV₁.

**Results of the review**

Eleven prospective double-blind placebo-controlled RCTs (n=8,164) were included in the review. Follow-up ranged from one to four and a half years. The Jadad score was greater than 3 for all studies, which indicated they were of high quality.

Inhaled corticosteroids were associated with a statistically significant 18% risk reduction in the occurrence of exacerbations (RR 0.82, 95% CI 0.73 to 0.92) over a mean follow-up period of 2.1 years. There was significant heterogeneity in the overall risk of exacerbations (I² was 55%, 95% CI 0 to 75.6).

Sensitivity analysis that excluded trials of patients with mild to moderate COPD indicated that the reduction in risk of exacerbations was based mainly on those trials with participants who had severe to very severe COPD (FEV₁ <50% predicted) (RR 0.79, 95% CI 0.69 to 0.89). Heterogeneity in the subgroup of patients with severe COPD was substantial (I²=57.4%).

Metaregression indicated no linear response of FEV₁ on exacerbations reduction by inhaled corticosteroids (coefficient 0.006, standard error 0.008, p=0.36).

There was no evidence of publication bias on any test.

**Authors' conclusions**

There was a modest reduction in the risk of exacerbations in patients with severe to very severe COPD with use of inhaled corticosteroids; this role required reappraisal. Risk of exacerbations was not associated with the level of baseline lung function.

**CRD commentary**

The research question was clearly stated and inclusion criteria were appropriate. Three electronic databases were searched. Attempts were made to find other relevant studies by searching reference lists. Searches were restricted to those in English, so language bias could not be ruled out. No attempts were made to find unpublished studies; publication bias was formally assessed by inspection of a funnel plot and by the use of two statistical tests and no evidence of it was found. Appropriate methods to reduce reviewer bias and error were used for the selection of studies and data extraction. A valid tool was used for validity assessment of included studies. All included studies were defined as high quality (Jadad score >3). Pooling of studies was appropriate, but substantial heterogeneity was reported in both overall summary estimates and the sensitivity analysis restricted to studies of participants with severe COPD. The authors acknowledged that inclusion of only 11 RCTs limited the statistical power of their analysis and the inability to control for length of follow-up of the included studies may have overestimated the pooled effects of inhaled corticosteroids.

This review was well conducted and the authors' cautious conclusions are appropriate and reliable.

**Implications of the review for practice and research**

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

**Research:** The authors stated that an individual patient data meta-analysis that took into account length of follow-up should be undertaken. Future trials should investigate whether the perceived benefits of inhaled corticosteroids were associated with other factors than baseline FEV₁ values.

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