The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials

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Authors' objectives
To determine whether long-term inhaled corticosteroids improve clinically important outcomes (such as exacerbation or death) for patients with stable chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE (1966 to 2000), EMBASE (1980 to 2001), CINAHL (1982 to 2000), SIGLE (1980 to 2000) and the Cochrane Controlled Trial Register were searched; the search terms were listed. No language restrictions were applied. In addition, the reference lists of retrieved studies were checked and topic experts were consulted.

Study selection
Study designs of evaluations included in the review
Placebo-controlled randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared inhaled corticosteroids with placebo for a duration of at least 6 months were eligible for inclusion. The included studies compared budenoside (dose: 800 to 1,600 microg/day; duration: 6 to 36 months), fluticasone (dose 1,000 microg/day; duration: 6 to 36 months), triamcinolone (dose 1,200 microg/day; duration: 40 months) and beclomethasone (dose: 1,500 to 2,000 microg/day; duration 24 months) with placebo. In all of the included studies, the control group received usual care.

Participants included in the review
Studies that included patients with stable COPD were eligible for inclusion. Trials that included patients with COPD and patients with asthma were only included if the results for COPD patients were reported separately. The patients in the included studies were aged from 18 to 70 years (mean age: 52 to 66), and most were from out-patient or community settings. Seven included studies were carried out in Europe, and two in North America.

Outcomes assessed in the review
The primary outcome was the frequency of respiratory exacerbations. In trials that did not define exacerbation, the authors assumed that an exacerbation was a hospitalisation for a respiratory condition. However, only one included study defined exacerbation this way. Other definitions of exacerbation in the included studies were: more cough and phlegm than usual; the use of oral steroids or antibiotics for worsening of symptoms; and worsening of symptoms. Three studies did not provide a definition. The secondary outcomes were the rate of decline in forced expiratory volume in 1 second (FEV1) and all-cause mortality. Adverse effects were also reported.

How were decisions on the relevance of primary studies made?
Three authors independently reviewed studies for relevance.

Assessment of study quality
Trial quality was assessed using the Jadad scale, which uses three criteria (randomisation, blinding and handling of missing participants) to produce a maximum score of five. Two authors independently assessed validity.

Data extraction
The data were extracted using a standardised extraction form, with any discrepancies resolved by iteration and consensus. The authors did not state how many reviewers extracted the data. The authors calculated the total COPD
exacerbation rate by assuming that the frequency of COPD exacerbations followed a Poisson distribution, and then calculated the frequency of COPD exacerbations per patient-month of treatment. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for COPD exacerbations and all-cause mortality.

**Methods of synthesis**

How were the studies combined?
Pooled RRs and 95% CIs were calculated for COPD exacerbations and all-cause mortality using the random-effects model of DerSimonian and Laird. Data on FEV1 could not be combined across studies, so summary data from each trial were noted.

How were differences between studies investigated?
P-values for heterogeneity tests were reported in the 'Results' section, but the authors did not state which heterogeneity test they performed. Sensitivity analyses were carried out to investigate the effects of dosage of inhaled cortical steroids. Subgroup analyses of studies with and without a run-in phase were performed.

**Results of the review**

Nine RCTs (n=3,976) were included in the review.

The results of the validity assessment were not reported for each trial, but it was stated that 5 of the 6 trials that reported COPD exacerbation rates scored the maximum of five on the Jadad scale; the other study scored three points.

**COPD exacerbations (6 RCTs).**

The use of inhaled corticosteroids was associated with a 30% reduction in exacerbations (RR 0.70, 95% CI: 0.58, 0.84). The authors stated that the benefits were similar in patients receiving or not receiving systemic corticosteroids during the run-in phase, and in patients suffering one or more exacerbations. However, in the subgroup of studies in which patients received systemic steroids during the run-in phase, the difference between the groups was not significant (RR 0.77, 95% CI: 0.56, 1.09).

The test for heterogeneity was significant (P=0.03). This was thought to be due to one study which defined exacerbation differently from the others. When this study was omitted from the analysis, heterogeneity was no longer present (P=0.79) and the result was similar (RR 0.67, 95% CI: 0.63, 0.71). Sensitivity analysis revealed no dose-response effect.

**All-cause mortality (5 RCTs).**

There was no significant difference between groups (RR 0.84, 95% CI: 0.60, 1.18) and no significant heterogeneity (P=0.99).

**FEV1 (9 RCTs).**

The results were variable. Only 2 of the 9 trials found a statistically significant difference between the groups.

**Adverse effects.**

The authors reported that the frequencies of oropharyngeal candidiasis (RR 2.1, 95% CI: 1.5, 3.1) and skin bruising (RR 2.1, 95% CI: 1.6, 2.8) were increased in patients treated with corticosteroids but it was unclear how many trials reported on these effects. Effects on bone mineral density and cortisol concentrations were reported to be variable, while no differences in the rate of cataract or fracture were found.

**Authors' conclusions**

Inhaled corticosteroids have a beneficial effect in reducing the rates of COPD exacerbation.
CRD commentary
The review had clear inclusion criteria and undertook a comprehensive literature search to find relevant studies. No language restrictions were applied and attempts were made to identify unpublished studies. The selection, validity assessment and data extraction processes all seemed to have been carried out by more than one author, which reduces the potential for bias in the review process. The decision to combine the studies and the methods used seemed appropriate, although the test used for statistical heterogeneity was not reported. The authors’ conclusions are reasonable given the data presented in the review.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that additional studies are needed to clarify the effects of inhaled corticosteroids on mortality, and to define the long-term effects and the risk-to-benefit ratio of inhaled corticosteroids for patients with COPD.

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