Combination therapy with the single inhaler salmeterol/fluticasone propionate versus increased doses of inhaled corticosteroids in patients with asthma
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CRD summary
The authors concluded that combination therapy with a single salmeterol and fluticasone inhaler improved lung function and symptoms in patients with asthma, compared to increased doses of inhaled corticosteroids. It did not significantly reduce the risk of exacerbation. Although few details were reported about trial quality, the review was otherwise well conducted and these conclusions appear likely to be reliable.

Authors' objectives
To assess the effectiveness and safety of salmeterol and fluticasone combined in a single inhaler versus increased doses of inhaled corticosteroids for adults and adolescents with asthma.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and GlaxoSmithKline Clinical Study Register were searched from 1977 to December 2005. Search terms were reported. The reference lists of relevant articles were checked. The search was limited to articles in English. There was no restriction by publication status.

Study selection
Randomised controlled trials (RCTs) that compared the clinical efficacy or safety of salmeterol and fluticasone propionate in a single inhaler (fluticasone propionate/salmeterol) versus increased doses of inhaled corticosteroids, administered once or twice daily, in adults or adolescents (aged at least 12 years) with asthma, were eligible for inclusion. Included trials were required to be double blind and parallel group RCTs with a duration of at least 12 weeks.

The primary outcomes were changes in lung function variables. Secondary outcomes included asthma exacerbation (defined as clinical deterioration or decrease in peak expiratory flows below a set threshold), use of rescue medication, symptom-free 24 hours, and overall or drug-related adverse events and discontinuation.

Most trials in the review were open to both adults and adolescents. The age range of included participants was 12 to 80 years and asthma severity varied. One trial specifically selected participants with a smoking history. The intervention group received 100 to 500 micrograms (µg) of fluticasone propionate combined with 50 to 100 µg of salmeterol daily. The control group received 200 to 1000 µg of fluticasone propionate or 400 to1600 µg of budesonide daily, in most cases administered in two doses by dry powder inhaler (Diskus or Turbuhaler) or metered dose inhaler. All the included trials permitted short-acting β-antagonist to be used as a rescue medication. Symptom-scoring methods used in the primary trials were heterogeneous. Trial duration was usually 12 weeks (range 12 to 52 weeks).

The authors did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality
Study validity was assessed with the 5 point Jadad scale (5 points indicating highest quality), which measured reported adequacy of randomisation, blinding, and management of withdrawals and drop-outs.

The authors did not state how the assessment was performed.

Data extraction
Odds ratios and 95% confidence intervals were calculated for binary outcomes. Mean differences with associated standard deviations or standard errors were calculated for continuous outcomes. These were based on adjusted data reported in the primary trials (e.g. for baseline values). Intention-to-treat analysis was used in the review. Data for 12
week follow-up were utilised where there were multiple assessment times.

Two reviewers independently extracted the data, with disagreements resolved by discussion. Authors were contacted for additional data as required. Where there were discrepancies, the published article was preferred over other data sources.

**Methods of synthesis**

Data were combined in meta-analysis to obtain pooled odds ratios and mean differences using fixed-effect models. Statistical heterogeneity appears to have been assessed by a comparison of the random-effects and fixed-effect models and with another assessment which was not described. A continuity correction was used in analysis to compensate for data sets with zero cell counts. A funnel plot and Egger's linear regression test were used to assess publication bias. Sensitivity analyses were performed to evaluate the effect of removing influential trials from analysis.

**Results of the review**

Twelve randomised controlled trials (RCTs) were included (n=5,218 participants); seven were published (in full or as abstracts) and five were unpublished. The published trials used computer-generated randomisation. All trials scored at least 2 out of 5 on the Jadad scale.

**Lung function changes**: At 12 weeks lung function variables were significantly improved in the intervention group receiving the combination inhaler: morning peak expiratory flow improved by 17.86 litres per minute (L/min) (95% confidence interval (CI): 14.75 to 20.98; p<0.001, 10 RCTs); evening peak expiratory flow improved by 15.57 L/min (95% CI: 12.50 to 18.64; p<0.001, nine RCTs); clinic forced expiratory volume improved by 0.09 litre (95% CI: 0.06 to 0.11; p<0.001, six RCTs).

**Secondary outcomes**: There was a significant difference favouring the intervention group in the overall rate of adverse events (odds ratio 0.85, 95% CI: 0.76 to 0.96; p=0.008, 11 RCTs) and in the rate of symptom-free 24 hours (odds ratio 3.80%, 95% CI: 1.31 to 6.28; p=0.003, four RCTs). There was no significant difference between the groups for other outcomes.

No significant heterogeneity or obvious publication bias was found for any of the analyses. Sensitivity analyses did not materially affect the results.

**Authors' conclusions**

Combination therapy with salmeterol and fluticasone, via a single inhaler, improved lung function and symptoms in patients with asthma compared to increased doses of inhaled corticosteroids, but did not significantly reduce the risk of exacerbation.

**CRD commentary**

The review objectives and inclusion criteria were clear. Relevant sources were searched for studies, although the restriction to articles in English may have created language bias. Steps were taken to minimise the risk of bias and error by having more than one reviewer independently extract data, but it is unclear whether this also applied to study selection and validity assessment. It was difficult to assess the reliability of the evidence presented as no details were reported about important aspects of trial quality (e.g. losses to follow-up, type of blinding used). The statistical methods used to pool trials and to assess for heterogeneity and publication bias appeared appropriate. The limitations of the evidence were well addressed in the text; these included clinical heterogeneity among the primary trials, the short-term duration of follow-up in most trials, and the questionable clinical significance of statistically significant findings. Although few details were reported about trial quality, the review was, in most other respects, well conducted and the authors' conclusions appear likely to be reliable.

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

**Practice**: The authors stated that first line treatment for suboptimal asthma control in a patient on a low dose of inhaled corticosteroids should be an increase to a moderate dose of inhaled corticosteroids. Combination products could be considered if the patient remains symptomatic and high inhaled corticosteroids doses are required.
Research: The authors stated that large studies with duration of at least one year are needed to compare the effectiveness, safety and cost-effectiveness of higher doses of inhaled corticosteroids versus combination products.

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