Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma

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CRD summary
This review concluded that the addition of salmeterol to moderate doses of inhaled corticosteroids (ICS) in symptomatic adults with asthma is significantly more beneficial than at least doubling the dose of ICS. There were limitations to this review but, overall, the conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of adding salmeterol compared with at least a doubling of the dose of inhaled corticosteroids (ICS) in adults with asthma who are symptomatic on moderate doses of ICS.

Searching
MEDLINE (1966 to August 2003), EMBASE (1980 to August 2003) and the Cochrane Controlled Trials Register were searched using the reported search terms. The manufacturer of salmeterol was contacted and reference lists of relevant studies were screened.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) of at least 12 weeks' duration were eligible for inclusion. The duration of most of the included studies was 12 weeks; in other studies the duration was 24 or 26 weeks.

Specific interventions included in the review
Studies that compared the addition of salmeterol with at least a two-fold higher dose of ICS (at least 400 microg fluticasone propionate or equivalent) taken twice daily were eligible for inclusion. The included studies evaluated the addition of 100 microg/day salbutamol to the following daily ICS regimens: beclometasone dipropionate (BDP) 400 microg versus BDP 800 or 1,000 microg; and fluticasone 200 microg versus fluticasone 400 or 500 microg or budesonide 800 microg. The drugs were delivered using different devices (including, where reported, metered dose inhaler, diskhaler and diskus); some studies used combination salmeterol-fluticasone inhalers.

Participants included in the review
Studies of adolescents (aged 12 years or older) or adults with asthma who were symptomatic on moderate doses of ICS (fluticasone propionate 200 microg/day or equivalent) were eligible for inclusion. Studies of patients who were dependent on oral steroids or involved in oral steroid reduction regimens were excluded. The included studies involved patients with moderate to severe asthma: mean forced expiratory volume in one second (FEV1) 61 to 84% of predicted value.

Outcomes assessed in the review
Studies that reported measures of clinical efficacy were eligible for inclusion. The primary review outcomes were the number of participants withdrawn due to asthma and the number with at least one moderate or severe exacerbation of asthma. The secondary review outcomes included morning and evening peak expiratory flow rate (PEF), FEV1, night-time awakenings, and day and night-time beta-agonist use. The included studies defined moderate or severe exacerbations as any event requiring treatment with oral or parenteral corticosteroids, and/or emergency hospital treatment, and/or use of any asthma mediation excluded as concurrent treatment during the study.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion in the review.
Assessment of study quality
Study validity was assessed using the 5-point Jadad scale. This scale considers the reporting and handling of randomisation, blinding and withdrawals. The authors did not state how the validity assessment was performed. [A: Two reviewers independently assessed validity and resolved any disagreements by consensus.]

Data extraction
[A: Two reviewers independently extracted data and resolved any disagreements by consensus.] Means, measures of variance and the number of participants with the outcome of interest were extracted primarily from the original publications. Data not in a standardised format were obtained from the MIASMA publication (see Other Publications of Related Interest) or from GlaxoSmithKline. Two reviewers compared data obtained from different sources and where discrepancies were found, the data were preferentially selected from the original publication, followed by MIASMA, followed by data from GlaxoSmithKline.

Methods of synthesis
How were the studies combined?
The results from the individual studies were combined initially using a fixed-effect meta-analysis (weighted by the inverse of the variance). Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous data and pooled weighted mean differences with 95% CIs for continuous data. A continuity correction was used for studies reporting zero events.

How were differences between studies investigated?
Statistical heterogeneity was assessed using inconsistency measures. Where significant statistical heterogeneity was found, the meta-analyses were repeated using random-effects models.

Results of the review
Twelve RCTs (n=4,576) were included in the review.

All of the included studies were of a high quality (Jadad score of at least 4).

Primary outcomes. There was a significant reduction in the number of patients withdrawing due to asthma in the salmeterol-ICS group compared with the high-dose ICS group: 59 out of 2,036 versus 86 out of 1,992. The OR was 1.58 (95% CI: 1.12, 2.24; 10 studies).

There was a significant reduction in the number of patients with one or more moderate or severe exacerbations in the salmeterol-ICS group compared with the high-dose ICS group: 184 out of 2,312 versus 243 out of 2,264. The OR was 1.35 (95% CI: 1.10, 1.66; 12 studies).

Secondary outcomes. Significant heterogeneity was found for morning PEF, FEV1, daytime beta-agonist use and night-time beta-agonist use. Morning and evening PEF were significantly greater and daytime use of beta-agonist was significantly less for patients taking salmeterol-ICS than for those taking high-dose ICS.

FEV1 (using a random-effects model) was barely statistically significantly increased for patients taking salmeterol-ICS compared with high-dose ICS. There was no significant difference between treatments in night-time awakenings and night-time beta-agonist use.

Authors' conclusions
Adding salmeterol to moderate doses of ICS in symptomatic patients with asthma is significantly more beneficial than at least doubling the dose of ICS.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, interventions and study design; inclusion criteria for the outcomes were broad but the primary review outcomes were reported clearly. Several relevant sources were searched and attempts were made to locate unpublished studies, thus minimising the possibility of publication bias. Methods were used to minimise reviewer errors and bias in the study selection, validity assessment and data extraction processes. Only double-blind RCTs were included and validity was assessed using an established checklist.

There was adequate information about the included studies. The use of strict inclusion criteria meant that studies were similar and the pooling of statistically homogeneous studies appeared appropriate. Where significant statistical heterogeneity was found, potential reasons were neither investigated nor discussed. There were limitations to this review but, overall, the authors' conclusions are likely to be reliable.

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

Practice: The authors stated that the review findings should help clinicians decide the dose of ICS at which they should consider adding salbutamol.

Research: The authors did not state any implications for further research.

**Bibliographic details**

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