Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA)

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Authors’ objectives
To examine the benefits of adding salmeterol compared with increasing dose of inhaled corticosteroids in symptomatic asthma.

Searching
The authors searched MEDLINE and EMBASE and the Glaxo-Wellcome internal clinical study registers for studies published between 1985 and 1999 (search terms not described). There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind controlled trials (RCTs) which lasted twelve weeks or longer. Treatment duration was 12 weeks in two studies and six months (24-26 weeks) in the other studies.

Specific interventions included in the review
Salmeterol (dose not stated) with inhaled corticosteroids 200 to 1000 micrograms/day (baseline) compared with an increasing dose (at least double, 400 to 2000 micrograms/day) of inhaled corticosteroids (beclometasone dipropionate or fluticasone).

Participants included in the review
Patients twelve years and older with symptomatic asthma in primary or secondary care settings.

Outcomes assessed in the review
Efficacy (defined as mean difference in lung function) and exacerbation of asthma (defined as severe - requiring oral steroids or admission to hospital; moderate - requiring an increase in inhaled steroid medication; and mild - requiring an increase in use of rescue medication).

How were decisions on the relevance of primary studies made?
One author selected the studies.

Assessment of study quality
The authors do not report a formal method for assessing the validity of the included studies. However, there is a description in the review of the randomisation and blinding procedures used in the included studies.

Data extraction
Two independent reviewers extracted data from study reports and manuscripts and their results were compared. Discrepancies were resolved by consensus.

Data were extracted, and reported in two tables, for the categories of: study identification, age of participants, country of study, number of participants, run-in (weeks), duration (weeks), definition of ITT, type of steroid, dosage of inhaled steroid (micrograms/day), comparison dose (micrograms/day), PEF/FEV1 reversibility (%), diurnal/period PEFR variation (%), absolute lung function as % predicted, symptoms or score, rescue therapy used, oral steroid use, exacerbation.

Methods of synthesis
How were the studies combined?
Pooled weighted mean differences were calculated with 95% confidence intervals (CIs) using both fixed-effect and random-effects models. Studies were weighted according to inverse study variance.

A funnel plot was used to test for publication bias.

How were differences between studies investigated?
Heterogeneity was formally tested and p-values reported.

Results of the review
Nine RCTs were included in the review with 3,685 participants.

The number needed to treat (NNT) was approximately 40.

Compared with response to increased steroids, in patients receiving salmeterol, morning peak expiratory flow was greater at three months (difference 22.4 (95% CI: 15.0, 30.0) litre/min, P < 0.001) and six months (27.7 (95% CI: 19.0, 36.4) litre/min, P < 0.001). There was no statistically significant heterogeneity.

Forced expiratory volume in one second (FEV1) was also increased at three months (0.10 (95% CI: 0.04, 0.16) litres, P < 0.001) and six months (0.08 (95% CI: 0.020, 014) litres, P < 0.01). There was no statistically significant heterogeneity.

Mean percentage of days and nights without symptoms (three months: days, 12% (95% CI: 9%, 15%), nights, 5% (95% CI: 3%, 7%); six months: days, 15% (95% CI: 12%, 18%), nights, 5% (95% CI: 3%, 7%); all P < 0.001. There was no statistically significant heterogeneity.

Mean percentage of days and nights without need for rescue treatment (three months: days, 17% (95% CI: 14%, 20%), nights, 9% (95% CI: 7%,11%); six months: days, 20% (95% CI: 17%, 23%), nights, 8% (95% CI: 6%, 11%); all P < 0.001.

Fewer patients experienced any exacerbation with salmeterol (difference 2.73% (95% CI: 0.43%, 5.04%), P = 0.02), and the proportion of patients with moderate or severe exacerbations was also lower (2.42% (95% CI: 0.24%, 4.60%), P = 0.03).

Authors' conclusions
The authors state that addition of salmeterol in symptomatic patients, aged 12 years and over, on low to moderate doses of inhaled steroid gives improved lung function and increased number of days and nights without symptoms or need for rescue treatment with no increase in exacerbations of any severity.

CRD commentary
This review was well reported. The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search was reasonably thorough with no language restrictions, although searches for unpublished and grey literature were not mentioned.

The quality of the included studies was not formally assessed but the authors did state that the included studies met the company-wide minimum quality standards. The authors have reported how the articles were selected, and who performed the selection, although this was done by only one person. The validity assessment was managed by one of the authors, while the data extraction was done by two of the researchers and checked by a third.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a statistical analysis, however, the authors state that the results of the analysis may not be generalisable in clinical practice because of limitations in the way study participants were chosen for the individual studies. Six studies used a requirement for entry of a demonstrable, clinically relevant, response to beta-agonist. In the other three studies airway
liability was not a prerequisite.

It should also be noted that this study was funded by a company who manufacture salmeterol and who employs or provides financial support for the authors of the review.

The scope of the review was large and very little detail of the results of each study and overall assessment of the outcome are reported. Although the quality of the review is good, the authors state that the individual studies have limitations which lead the authors to recommend that the results of the review should be viewed with caution.

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

Practice: The authors state that the results of this review should reassure prescribers undecided about which option to pursue at step 3 of the British Guidelines for Asthma Management and help them when deciding on the appropriate treatment choice.

Research: The authors do not state any implications for research.

**Bibliographic details**

Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA) BMJ 2000; 320: 1368-1373

**PubMedID**

10818025

**Original Paper URL**

http://bmj.com/cgi/content/full/320/7246/1368

**Other publications of related interest**

These additional published commentaries may also be of interest. Meta-analysis of increased inhaled steroid or addition of salmeterol in asthma. [series of letters]. BMJ 2000;321:1016-1018. Cicutto L. Review: addition of salmeterol leads to improved lung function and fewer exacerbations in symptomatic asthma. Evid Based Nurs 2001;4:15.

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adrenergic beta-Agonists /therapeutic use; Albuterol /analogs & derivatives /therapeutic use; Asthma /drug therapy /physiopathology; Beclomethasone /administration & dosage; Drug Administration Schedule; Drug Therapy, Combination; Forced Expiratory Volume /drug effects; Glucocorticoids /administration & dosage; Humans; Peak Expiratory Flow Rate /drug effects; Randomized Controlled Trials as Topic; Salmeterol Xinafoate; Treatment Outcome

**AccessionNumber**

12000008284

**Date bibliographic record published**

31/05/2001

**Date abstract record published**

31/05/2001

**Record Status**

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the reliability of the review and the conclusions drawn.