Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths
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CRD summary
This generally well-conducted review concluded that long-acting beta-agonists increased severe and life-threatening asthma exacerbations, as well as asthma-related deaths. However, the potential for selection bias, and the potential impact of high drop-out rates on the results seen in some studies, should be kept in mind when considering the conclusions of the review.

Authors' objectives
To evaluate the risk for severe, life-threatening or fatal asthma exacerbations associated with long-acting beta-agonists.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane CENTRAL Register were searched from 1966 to December 2005 without any language restrictions; the search terms were reported. Reference lists from identified reviews and files from the U.S. Food and Drug Administration website were also screened.

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

Specific interventions included in the review
Trials of long-acting beta-agonists compared with placebo, of at least 3 months' duration, were eligible for inclusion. The interventions evaluated in the included studies were formoterol, salmeterol or eformoterol. The doses ranged from 4.5 micrograms to 50 micrograms twice daily.

Participants included in the review
There were no inclusion criteria relating to the participants. The mean age of the participants ranged from 8 to 49 years for beta-agonists and from 8 to 48 years for placebo. Where stated, the mean proportion of men ranged from 38.5 to 74.8% for beta-agonists and from 32.1 to 70% for placebo. Where reported, the proportion of patients receiving inhaled corticosteroids varied from 45 to 100% for beta-agonists and from 47 to 100% for placebo.

Outcomes assessed in the review
The review objective addressed severe asthma exacerbations requiring hospitalisation, life-threatening asthma attacks and asthma-related deaths. To be included in the primary analysis of the review, the studies had to report on exacerbations or asthma-related deaths. Studies not reporting exacerbations or asthma-related deaths were eligible for the sensitivity analyses.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed in relation to the randomisation procedure, allocation concealment, blinding of the patients and care providers, the reporting of drop-outs and withdrawals, and the use of an intention-to-treat analysis. Each quality domain scored either 3 points (all criteria met for that domain), 2 points (criteria were partially met), or 1 point (criteria were not met); the maximum obtainable score was 9 points. Two reviewers assessed the quality of each trial.
Data extraction
Two reviewers independently extracted the data, with any disagreements being resolved by consensus. The proportions of patients hospitalised for asthma exacerbations, who had life-threatening asthma exacerbations, or who died from asthma-related causes, were extracted.

Methods of synthesis
How were the studies combined?
Pooled Peto odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a fixed-effect meta-analysis. If more than one event occurred in the same patient, only the first event was used in the meta-analysis. Risk differences (RDs) and 95% CIs were calculated for the difference between two independent binomial proportions, and the results were pooled using a fixed-effect meta-analysis. Trials that reported no events were included in the analysis of RDs. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared test and I-squared statistic. Subgroup analyses were conducted for salmeterol, formoterol, and trials in children (under 12 years) and interaction effects investigated. Sensitivity analyses were conducted to determine the effect of study quality. The 28 studies without relevant outcomes were added to the analysis, assuming no deaths had occurred.

Results of the review
Forty-eight trials met the inclusion criteria. Nineteen trials (n=33,826) were included in the main analysis of the review. The trials ranged from 3 to 12 months in duration. The drop-out rate ranged from 2.9 to 24% for beta-agonists and from 2.9 to 25.7% for placebo. Seventeen trials were funded by pharmaceutical companies. Twenty-eight other trials did not provide information on exacerbations or asthma-related deaths and were only used for sensitivity analyses.

Out of a possible quality score of 9, nine studies scored 9 and ten scored 8.

The authors stated that there was no evidence of publication bias.

Hospitalisation for asthma exacerbations.
There was a statistically significant increase in the incidence of hospitalisation for asthma with beta-agonists compared with placebo (OR 2.6, 95% CI: 1.6, 4.3, P<0.001; 12 studies). There was no statistically significant heterogeneity between the studies. The pooled RD associated with beta-agonists was 0.7% (95% CI: 0.1, 1.3) over 6 months. The results for subgroup analyses were also reported.

Life-threatening asthma exacerbations.
There was a statistically significant increase in the incidence of life-threatening asthma exacerbations with beta-agonists compared with placebo when the results from 7 RCTs were pooled (OR 1.8, 95% CI: 1.1, 2.9, P=0.012). There was no statistically significant heterogeneity between the studies. The pooled RD associated with beta-agonists was 0.12% (95% CI: 0.01, 0.3) over 6 months. The results for subgroup analyses were also reported.

Asthma-related deaths.
Three trials reported deaths: two reported one death in the treatment group and none in the placebo group, while the third trial reported 13 deaths in the treatment group (n=13,174) and 3 in the placebo group (n=13,179). The pooled RD associated with beta-agonists was 0.07% (95% CI: 0.01, 0.1) over 6 months. The results for subgroup analyses were also reported.

Authors’ conclusions
Long-acting beta-agonists increased severe and life-threatening asthma exacerbations, as well as asthma-related deaths.
CRD commentary
The review question was clear, with inclusion criteria relating to the interventions and study design well defined. Published and unpublished trials were sought, and the authors investigated the possibility of publication bias. Language restrictions were not applied during the search, which reduced the risk of language bias. Methods were used to minimise error and bias during the data extraction and quality assessment processes, though it was unclear whether similar methods were used to reduce selection bias. Appropriate measures of effect were calculated, and the lack of statistical heterogeneity added confidence to the pooled results. Clinical heterogeneity was investigated, and the scoring of all trials as high quality negated the need to investigate the impact of study quality. Several trials had high drop-out rates. Although this seemed a generally well-conducted review, the potential for selection bias, and the potential impact of drop-outs on the results, should be kept in mind.

Implications of the review for practice and research
Practice: The authors stated that the results of the review could be used to reassess whether beta-agonists should be withdrawn from the market.

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

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Other publications of related interest

This additional published commentary may also be of interest. Smith BJ, Roy a. Review: long acting beta agonists increase severe asthma exacerbations and asthma related deaths in children and adults. Evid Based Med 2007;12:10.

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic beta-Agonists /administration & dosage /adverse effects; Adult; Albuterol /administration & dosage /adverse effects; Asthma /drug therapy /mortality; Bronchodilator Agents /administration & dosage /adverse effects; Child; Drug Administration Schedule; Ethanolamines /administration & dosage /adverse effects; Female; Formoterol Fumarate; Hospitalization /statistics & numerical data; Humans; Male; Randomized Controlled Trials as Topic; Recurrence; Risk Factors; Salmeterol Xinafoate; Treatment Outcome

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.