Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma: a systematic review
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CRD summary
This well-conducted review found that long-acting beta agonists remained the preferred add-on therapy to inhaled corticosteroids for asthma patients whose disease could not be controlled adequately by inhaled corticosteroids alone, and that long-acting beta agonists could not be prescribed as monotherapy. These conclusions are likely to be reliable.

Authors’ objectives
To evaluate the safety of regular use of long-acting beta agonists compared with placebo, or long-acting beta agonist added to inhaled corticosteroids compared with inhaled corticosteroids for the treatment of persistent asthma.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to September 2008. Search terms were reported. Relevant files from drug companies, the US Food and Drug Agency and clinical trials databases were searched. No language restrictions were applied. Trials published only as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that compared inhaled long-acting beta agonists (delivered via metered dose or dry powder inhalers) versus placebo, or long-acting beta agonist added to inhaled corticosteroids versus inhaled corticosteroids, for the treatment of adults and children with asthma were eligible for inclusion. Eligible trials had to included patients with a clinical diagnosis of asthma for at least six months prior to trial entry and include at least four weeks follow-up.

The primary review outcomes were asthma exacerbations requiring systemic corticosteroids or hospitalisation, life threatening exacerbations, and asthma-related deaths. Secondary outcomes were withdrawals due to adverse events.

Included trials compared salmeterol (21mcg to 50mcg twice a day) or formoterol (4.5mcg to 24mcg twice a day) versus placebo, or they compared salmeterol or formoterol plus corticosteroids (fluticasone, budesonide, beclomethasone) versus corticosteroids alone. Trials either compared the same dose of inhaled corticosteroids in both treatment arms or compared long-acting beta agonists plus corticosteroids with a higher dose of inhaled corticosteroids, or both. Some of the placebo controlled trials reported concomitant use of inhaled corticosteroids. Trials that combined long-acting beta agonists with inhaled corticosteroids administered the doses in the same or separate inhaler devices. The mean age of participants ranged from eight to 49 years; the proportion of males ranged from 30 to 73%. Almost all trials were sponsored by pharmaceutical companies.

Two reviewers independently assessed studies for inclusion; disagreements were resolved through consensus.

Assessment of study quality
Trial quality was assessed using the Jadad scale which assessed randomisation, blinding and withdrawals. Trials were assigned a score out 5 based on the number of items fulfilled.

The authors did not state how many reviewers assessed study quality.

Data extraction
Data were extracted to estimate relative risks (RR) together with 95% confidence intervals (CI).

The authors did not state how many reviewers extracted the data.
Methods of synthesis
Summary relative risks, with 95% confidence intervals were estimated. In the absence of heterogeneity, a fixed-effect model was used; otherwise a random-effects model was used. For significant comparisons, the summary number needed to treat (NNT) or number needed to harm (NNH) was calculated. Heterogeneity was quantified using the I² statistic.

Sensitivity analyses were conducted to examine the influence of age, type of long-acting beta agonist, concomitant use of inhaled corticosteroids, inhaled corticosteroid dose, asthma severity, single or separate devices to deliver the long-acting beta agonist/inhaled corticosteroid combination, quality score, and trial duration. Subgroup estimates were compared using the interaction test.

Publication bias was assessed using funnel plots and the Egger test.

Results of the review
Ninety-two RCTs were included in the review (n>74,000 patients). Summary trial quality scores ranged from 3 to 5 out of 5 points; all trials were reported to be double blinded. Details on individual items fulfilled were not reported. Trial duration ranged from four to 56 weeks.

Long-acting beta agonist versus placebo (40 RCTs, n>40 000 patients): Long-acting beta agonists resulted in a significant decrease in asthma exacerbations requiring systemic corticosteroids (RR 0.80, 95% CI 0.73 to 0.88; NNT 24 patients, 95% CI 17 to 39; 24 RCTs) and withdrawals related to asthma exacerbations (RR 0.68, 95% CI 0.61 to 0.76; NNT 68 patients, 95% CI 53 to 93; 24 RCTs) compared with placebo. There was no significant difference between treatment groups for the incidence of acute exacerbations requiring hospitalisation (17 RCTs), or incidence of life threatening exacerbations (nine RCTs). However, there was an increased risk of asthma related deaths among patients receiving long-acting beta agonists (RR 3.83, 95% CI 1.21 to 12.14; NNH 1,226 patients, 95% CI 703 to 10,585; two RCTs). There was no evidence of heterogeneity for any of these analyses. Some outcomes showed evidence of publication bias.

Long-acting beta agonist plus inhaled corticosteroids versus inhaled corticosteroids: (57 RCTs, n=34 747 patients)
Compared with inhaled corticosteroids, long-acting beta agonists plus inhaled corticosteroids resulted in a significant decrease in asthma exacerbations requiring systemic corticosteroids (RR 0.73, 95% CI 0.67 to 0.79; NNT 20 patients, 95% CI 16 to 26; 30 RCTs), asthma exacerbations requiring hospitalisation (RR 0.58, 95% CI 0.45 to 0.74; NNT 135 patients, 95% CI 90 to 282; 25 RCTs), and withdrawals related to asthma exacerbations (RR 0.64, 95% CI 0.52 to 0.78; NNT 91 patients, 95% CI 54 to 310; 25 RCTs). There was no significant difference between treatment groups for incidence of life threatening exacerbations (11 RCTs) or asthma related deaths (three RCTs). There was no evidence of heterogeneity for any of these analyses. There was evidence of publication bias for withdrawals due to acute exacerbations, but not for other outcomes.

Most subgroup analyses showed similar results across groups.

Authors' conclusions
Long-acting beta agonist remained the preferred add-on therapy to inhaled corticosteroids for asthma patients whose disease could not be controlled adequately by inhaled corticosteroids alone. Long-acting beta agonists could not be prescribed as monotherapy. Asthmatic children using salmeterol showed an increased risk of non-fatal serious adverse events.

CRD commentary
The review addressed a defined question supported by clearly stated inclusion criteria. The literature search was appropriate and included some attempts to locate unpublished studies although it was unclear whether unpublished studies were eligible. Publication bias was assessed in the review and generally found to be absent. Appropriate steps were taken to minimise bias and errors when selecting studies for inclusion, but it was unclear whether such steps were also taken for data extraction and quality assessment.
Trial quality was assessed using the Jadad criteria; allocation concealment was not considered. Appropriate trial details were presented in tables. Methods used to synthesise results were appropriate and clearly reported.

The authors conclusions were supported by the data (a large number of reasonable quality trials) and are likely to be reliable.

All authors disclosed financial links with several pharmaceutical companies, including the manufacturers of the drugs evaluated in this review.

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

**Practice:** The authors stated that the results of this review support the international recommendations that long-acting beta agonist remain the preferred add-on therapy to inhaled corticosteroids for patients whose disease cannot be controlled adequately by inhaled corticosteroids alone, and that long acting beta agonists cannot be prescribed as monotherapy.

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

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