Effect of long-acting beta2 agonists on exacerbation rates of asthma in children

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CRD summary
This review assessed long-acting beta2-adrenoreceptor agonists (LABAs) in children with asthma. The author concluded that there was a lack of evidence supporting the regular use of LABAs as add-on treatment. The author’s conclusions are likely to be reliable.

Authors’ objectives
To compare the effects of long-acting beta2-adrenoreceptor agonists (LABAs) plus inhaled corticosteroids (ICS) with either placebo or short-acting beta2 agonists (SABAs) plus ICS in children with asthma.

Searching
MEDLINE, EMBASE and Current Contents were searched from 1985 to 2003 for studies published in English. In addition, the results from a non-systematic review of the literature up to 2003 were added. Studies were only included if they were published in full in peer-reviewed publications.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Crossover and parallel group double-blind RCTs were included.

Specific interventions included in the review
Studies that directly compared LABAs plus ICS with either placebo or SABAs plus ICS were eligible for inclusion. Studies of LABAs as monotherapy were excluded. The included studies compared LABAs (4.5 to 24 microg formoterol, or 25 to 100 microg salmeterol) with placebo. Some of these studies included a proportion of patients on concomitant ICS (52 to 100%, where stated). The included studies also compared LABAs plus ICS combinations (budesonide/formoterol or salmeterol plus budesonide or beclomethasone). In some studies the LABA was added to regular ICS maintenance treatment. The studies lasted from 6 weeks to 12 months.

Participants included in the review
Studies of children with asthma were eligible for inclusion, while those that included both children and adults were excluded. The children in the included studies were aged from 4 to 17 years and had mild to severe asthma.

Outcomes assessed in the review
Studies that reported asthma exacerbation rates or hospitalisation rates for asthma were eligible for inclusion. The studies used different definitions for asthma exacerbation: some defined exacerbation as a deterioration in asthma requiring a change in medication, while other studies provided no definition.

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

Assessment of study quality
The author did not state that they assessed validity.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included sample size, definition of asthma exacerbation, study duration, treatments
compared, and the number and percentage of patients with an event in each treatment group.

For each study, the relative risks (RRs) and 95% confidence intervals (CIs) of asthma exacerbation and asthma-related hospitalisation were calculated. The RR was not defined for studies in which none of the children had an exacerbation.

**Methods of synthesis**

How were the studies combined?
The RRs and 95% CIs of asthma exacerbation were plotted on a forest plot in order of the increasing percentage of children on regular ICS. The relative weight of each study, assuming a fixed-effect model, was also presented. The data were not pooled. The range of RRs across studies was reported.

How were differences between studies investigated?
The author referred to differences between the studies and details of such differences were tabulated.

**Results of the review**

Eight RCTs (2,401 children) were included.

Asthma exacerbation.

None of the 8 RCTs reported a statistically significant reduction in asthma exacerbation with LABAs compared with placebo, SABAs, or SABAs plus ICS. The RR of asthma exacerbations for LABA against comparator ranged from 0.95 to 1.86.

Hospitalisation for asthma (3 RCTs).

The studies found that 3 to 9% of children treated with LABAs were hospitalised, compared with no children hospitalised when on comparator treatment. The RR of hospitalisation for asthma in children treated with LABAs ranged from 3.3 to 21.6. In one of the RCTs the increase in RR was statistically significant.

**Authors' conclusions**

There was a lack of evidence supporting the regular use of LABAs as add-on treatment.

**CRD commentary**

The review question was clear in terms of the study design, intervention, participants and outcomes. The inclusion criteria for participants were not adhered to, as not all of the participants in all studies took ICS. The review actually compared the effects of LABAs with or without ICS with placebo and SABAs with or without ICS. Full details of the search strategy were not given: the search terms were not reported and there were no details of the sources searched in the non-systematic search of the literature. In addition, no attempts were made to limit language and publication bias. The methods used to select the studies and extract the data were not described, thus it is not known whether efforts were made to reduce errors and bias. Validity was not systematically assessed, although some aspects of validity were briefly mentioned in the discussion.

Given the differences among the studies, the graphical presentation of results appears appropriate. The proportion of children receiving concomitant steroids in each treatment group was not reported and this, as the author stated, might have influenced the results. The author’s conclusions appear reliable, but it must be remembered that a lack of evidence does not mean a lack of effect.

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

Practice: The author stated that there is a need to reconsider the standard recommendation that LABAs be routinely used as add-on treatment in children with asthma.
Research: The author stated that studies are required to assess the effects of using LABAs as add-on treatment in children with asthma. In addition, future studies should assess the effects of using LABAs in conjunction with ICS.

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