The safety of long-acting beta-agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis

CRD summary
The review concluded that long-acting β-agonists did not increase the risk of asthma-related hospitalisations in patients with asthma who used inhaled corticosteroids. The authors' conclusions reflected the evidence presented and appear likely to be reliable.

Authors' objectives
To examine the safety of long-acting β-agonists (both formoterol and salmeterol) when taken regularly by patients with asthma who were also taking inhaled corticosteroids.

Searching
MEDLINE, EMBASE, ACP Journal Club and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to April 2008; search terms were reported. Reference lists of relevant articles were screened. Manufacturers were contacted and their websites searched for further studies.

Study selection
Parallel randomised controlled trials (RCTs) that compared a long-acting β-agonist plus inhaled corticosteroids versus inhaled corticosteroids alone in patients (>12 years) with asthma were eligible. Studies had to provide treatment for at least 12 weeks. Patients and care-givers had to be blinded. Control groups could not receive another type of asthma medication. Details of acceptable follow-up drop-out rates were provided. Primary outcomes were death from all causes and asthma-related death, non-fatal intubation and ventilation, non-fatal hospitalisation and non-fatal serious adverse events.

Mean age of included participants varied and all were 50 years or less. Doses of 4.5µg, 9µg and 12µg of formoterol and 42µg and 50µg of salmeterol were frequently used. Salmeterol was the most commonly studied drug. In half of the the studies the dose of corticosteroids in the corticosteroids-only group was higher than in the long-acting β-agonists group.

Two reviewers screened studies for inclusion.

Assessment of study quality
Criteria used to assess study quality were allocation concealment, blinded assessment and classification of outcomes, blinding of patients and care-givers and funding source. Authors of the primary studies were contacted to clarify details.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted to calculate odds ratios (OR) with 95% confidence intervals. Authors, sponsors and manufacturers were contacted for data where necessary.

Two reviewers independently extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Where there were six or more events, meta-analyses were performed to calculate pooled odds ratios using a random-effects model. Meta-regressions were performed to investigate a number of pre-specified factors. Heterogeneity was assessed with I².
Results of the review
Sixty-two studies (n=29,401 participants) were included. All studies used an intention-to-treat analysis, were double-blind (with blinded outcome assessors) and had allocation concealment.

There were no statistically significant differences between groups for asthma-related hospitalisations (OR 0.74, 95% CI 0.53 to 1.03, \(^{2}=0\%\); 34 RCTs), asthma-related serious adverse events (OR 0.75, 95% CI 0.54 to 1.03) or total mortality (OR 1.26, 95% CI 0.58 to 2.74, \(^{2}=0\%\); 13 RCTs). Results were similar for studies in which all patients received a similar dose of corticosteroids. Subgroup analyses suggested that formoterol may have shown fewer adverse effects than salmeterol, but these results were not statistically significant at \(p\leq0.05\).

Authors' conclusions
Long-acting \(\beta\)-agonists did not increase the risk of asthma-related hospitalisations in patients with asthma using inhaled corticosteroids. There were very few asthma-related deaths and intubations and events were too infrequent to establish the relative effect of long-acting \(\beta\)-agonists on these outcomes.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies were undertaken by searching electronic databases and checking references. It was unclear whether there were language restrictions. The authors contacted manufacturers in order to identify further relevant studies. Suitable methods were employed to reduce risks of reviewer error and bias during data extraction and study selection; whether such methods were used to assess study quality was not reported. Comprehensive details of the primary studies were provided via an online supplement. Study quality was assessed and used in interpreting the results of the review. Appropriate methods were used to pool data and assess heterogeneity.

The authors provided a conflict of interest statement related to support from several pharmaceutical companies.

The authors' conclusions reflected the evidence presented and appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that among patients with asthma that was not well controlled with low doses of corticosteroids, those concerned about the remaining uncertainty (and their physicians) may well prefer increasing the dose of corticosteroids instead of adding long-acting \(\beta\)-agonists.

Research: The authors stated that direct comparisons of formoterol and salmeterol were needed to establish whether there were real differences in safety.

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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.