Use of long-acting beta-agonists and inhaled steroids in asthma: meta-analysis of observational studies
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CRD summary
This review found that patients in clinical practice treated with single inhalers containing inhaled corticosteroids plus long-acting beta-agonists experienced fewer exacerbations of their condition than patients treated with inhaled corticosteroids alone. The unknown quality of the included observational studies and potential for bias and confounding in the results mean that the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To assess the safety of the concurrent use of long-acting beta-agonists (LABAs) and inhaled corticosteroids in patients with asthma.

Searching
MEDLINE and EMBASE were searched to identify relevant studies to August 2008; search terms were reported. TrialTrove, SearchLight conference abstracts database and GlaxoSmithKline registry database were searched for abstracts and additional studies. Reference lists of the included studies were checked. There were no restrictions on publication type. It was unclear whether there were any language restrictions.

Study selection
Observational cohort or case-control studies of adults with asthma that evaluated treatment with LABAs with inhaled corticosteroids compared to treatment with inhaled corticosteroids alone were eligible for inclusion. Outcomes were asthma-related emergency room visits, hospitalisations, intubations, intensive care unit admissions and mortality.

The included studies were conducted between 1998 and 2005. The source for the data were from health insurance claims in USA. Patients ranged in age from six years to 65 years. The presence of asthma was determined by claims for asthma and asthma treatment, recent hospitalisation for asthma and diagnosis of mild persistent asthma. The medication regimens were fixed-dose inhalers with inhaled corticosteroids plus LABAs (salmeterol) and single-inhaler inhaled corticosteroids plus LABAs in a separate device. The included inhaled corticosteroids were beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone and ciclesonide. Follow-up durations ranged from two to 12 months.

Two reviewers independently performed the study selection with consultation from other review team members and clinical experts when a study was not selected for inclusion.

Assessment of study quality
The authors did not state that they assessed methodological quality.

Data extraction
Data were extracted to calculate odds ratios (OR) and 95% confidence intervals (CI). Where hazard ratios were reported, these estimates were used as a proxy for the odds ratio. Where more than two corticosteroid arms were included, fluticasone propionate was chosen as the comparator corticosteroid where possible. The reviewers contacted individual study authors for clarification of key information when required.

Data were extracted by one reviewer and checked by a second reviewer. Any disagreements were resolved through discussion with a third reviewer.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using a random-effects model. Statistical heterogeneity was evaluated using the Cochran \(X^2\) test. Subgroup analyses were used to examine potential sources of heterogeneity. Sensitivity analyses were conducted to determine the role of individual studies in observed heterogeneity across the studies.
Potential for publication bias was assessed by visual appraisal of funnel plots.

**Results of the review**

Seven retrospective cohort studies (89,196 participants, range 733 to 58,270) were included in the review: three published studies and four unpublished reports.

Statistically significant benefits were observed with treatment with inhaled corticosteroids plus LABAs. There were reductions in asthma-related emergency room admissions (OR 0.84, 95% CI 0.76 to 0.94; four studies, 82,996 participants) and asthma-related hospitalisation (OR 0.85, 95% CI 0.74 to 0.97; four studies, 82,996 participants) compared to when inhaled corticosteroids were used alone. There was no evidence of statistically significant heterogeneity across the results for these outcomes. Similar results were found in subgroup and sensitivity analyses.

Significant reductions were observed in asthma exacerbations (OR 0.82, 95% CI 0.72 to 0.94; seven studies, 89,196 participants, $\chi^2=18.03, p=0.006$). Sensitivity analyses conducted on the basis of asthma severity and the exclusion of one particular study from the analysis did not affect the overall findings.

**Authors’ conclusions**

The results from this review indicated that patients in clinical practice treated with a single inhaler containing inhaled corticosteroids plus long-acting beta-agonists experienced fewer asthma exacerbations than similar patients treated with inhaled corticosteroids alone.

**CRD commentary**

The review addressed a clear question. Criteria for inclusion of studies were defined. Appropriate databases were searched for relevant studies. Attempts were made to identify unpublished studies. The authors used validated methods to examine the likelihood of publication bias. Steps were taken by the reviewers to minimise errors and bias for study selection and data extraction. There was no assessment of methodological quality, so the reliability of the results was unclear. Observational studies are vulnerable to a number of biases and confounding, so the results should be interpreted with caution. The authors correctly acknowledged some of the limitations of the review for potential for confounding and heterogeneity among the effect measures and severity of asthma across the included studies.

One author was an employee of GlaxoSmithKline and three were employees of RTI Health Solutions.

The authors' conclusions reflected the evidence presented, but the lack of information on study quality and use of information from uncontrolled observational studies mean that the results should be interpreted with caution.

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

**Practice:** The authors stated that the findings of the review were consistent with asthma treatment and control guidelines which recommend use of inhaled corticosteroids with LABAs for the long-term control and prevention of symptoms in patients with asthma aged 12 years and over

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

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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.