Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis

Sin D D, Man J, Sharpe H, Gan W Q, Man S F

CRD summary
This review assessed the long-term effects of therapies in adults with chronic asthma. The authors concluded that inhaled corticosteroids were the most effective single treatment, followed by leukotriene modifiers/receptor antagonists as second choice. If symptoms were not controlled with low-dose corticosteroids, long-acting beta2 agonists may be added. The authors' conclusions are likely to be reliable.

Authors' objectives
To assess the long-term effects of inhaled corticosteroids, long-acting beta2 agonists, leukotriene pathway modifiers/receptor antagonists, and anti-immunoglobulin-E (anti-IgE) therapies on adults with chronic asthma.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched for studies published in English between January 1980 and April 2004. The bibliographies in retrieved studies were checked and experts were contacted. Studies published as abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible if they scored three or more on the Jadad scale, had complete or near complete follow-up, and the treatment groups were comparable at baseline. Crossover studies were excluded.

Specific interventions included in the review
Eligible for inclusion were studies of inhaled corticosteroids, long-acting beta2 agonists, leukotriene pathway modifiers/receptor antagonists, a combination of inhaled corticosteroids plus long-acting beta2 agonists, and anti-IgE therapies. Higher dose inhaled corticosteroids were defined as doses of greater than 500mg/day of beclomethasone equivalent and at least twice that of the inhaled steroid dose in the comparator treatment.

Participants included in the review
Studies of adults (older than 19 years) with asthma were included. Studies using anti-IgE were only conducted in patients with asthma who had allergy skin tests that were positive for at least one or two perennial allergens, and had high anti-IgE levels.

Outcomes assessed in the review
The studies had to assess asthma exacerbations after at least 3 months' follow-up. Studies were excluded if they defined exacerbations only as episodes requiring increased short-acting beta2 agonists without requiring systemic steroids, emergency visits or hospitalisations, or reported exacerbations only as part of withdrawal data. Most of the included studies defined exacerbations as an episode requiring oral or parenteral corticosteroids, emergency visits or hospitalisation, or a decrease in the morning peak flow measurements of greater than 25 to 30% on two consecutive days. The review also assessed forced expiratory volume in 1 second (FEV1).

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
Studies were assessed using the Jadad scale, which considers randomisation, blinding and withdrawals. The authors did not state who performed the validity assessment.

Data extraction
Two reviewers independently extracted the data using a standardised form. Any disagreements were resolved through consensus. The extracted data included the mean age of the participants and FEV1, as a percentage of the predicted or absolute volume (in litres), for each treatment comparison. For each study, the relative risks (RRs) and 95% confidence intervals (CIs) of asthma exacerbations were extracted, and absolute FEV1 values were converted into standardised effect sizes.

**Methods of synthesis**

**How were the studies combined?**

The studies were combined using a random-effects model (DerSimonian and Laird) for the meta-analysis when significant statistical heterogeneity was found and a fixed-effect model in its absence (P>0.10). Pooled RRs and 95% CIs for asthma exacerbations were calculated for inhaled corticosteroids versus placebo, higher verses lower doses of inhaled corticosteroids, LABA versus placebo, and inhaled corticosteroids plus LABA versus higher dose inhaled corticosteroids.

**How were differences between studies investigated?**

Statistical heterogeneity was assessed using the Cochran Q test. Pooled weighted mean differences between treatments were also calculated. Subgroup analyses were conducted for studies comparing inhaled corticosteroids with placebo to examine the influence of treatment duration, sample size and disease severity at baseline (according to FEV1). Disease severity was investigated through the comparison of higher and lower dose trials.

**Results of the review**

The number of studies reported in this commentary were those used in the meta-analyses of asthma exacerbation rates. Eleven RCTs (9,418 patients) compared inhaled corticosteroids with placebo. Seven RCTs (1,884 patients) compared higher dose with lower dose corticosteroids. Nine RCTs (2,854 patients) compared long-acting beta2 agonists with placebo. Ten RCTs (5,680 patients) compared combination treatment with inhaled corticosteroids plus long-acting beta2 agonists with higher dose corticosteroid therapy. Seven RCTs (4,375 patients) compared leukotriene pathway modifiers/receptor antagonists with placebo; five RCTs (2,368 patients) compared leukotriene pathway modifiers/receptor antagonists with inhaled corticosteroids. The number of patients in the four referenced studies of IgE therapy was not reported in the paper. Nineteen RCTs (3,271 patients) were used to assess the effect of treatment on FEV1.

Only the results for asthma exacerbations are reported below (the review also reported results for FEV1).

**Inhaled corticosteroids**: There were statistically significant reduced exacerbations with inhaled corticosteroids compared with placebo (RR 0.46, 95% CI 0.34 to 0.62; 11 trials). Statistically significant heterogeneity was detected (P<0.001). The subgroup analyses showed that risk reduction was influenced by study duration (greatest in short-term studies lasting 12 weeks), but was not influenced by sample size or disease severity at baseline (the results were reported). Higher dose of inhaled corticosteroids statistically significantly reduced exacerbations compared with lower dose therapy (RR 0.77, 95% CI 0.67 to 0.89). No statistically significant heterogeneity was detected (P=0.83).

**Long-acting beta2 agonists**: There were statistically significantly reduced exacerbations with long-acting beta2 agonists compared with placebo (RR 0.75, 95% CI 0.64 to 0.88; nine trials). No statistically significant heterogeneity was detected (P=0.43). The addition of long-acting beta2 agonists to inhaled corticosteroids statistically significantly reduced exacerbations compared with higher dose inhaled corticosteroids (RR 0.86, 95% CI 0.76 to 0.97; 10 trials). No statistically significant heterogeneity was detected (P=0.65).

**Leukotriene pathway modifiers/receptor antagonists**: There were significantly reduced exacerbations with Leukotriene pathway modifiers/receptor antagonists compared with placebo (RR 0.59, 95% CI 0.49 to 0.71; seven trials). No statistically significant heterogeneity was detected (P=0.44). They also significantly increased exacerbations compared with inhaled corticosteroids (RR 1.72, 95% CI 1.28 to 2.31; five trials). No statistically significant heterogeneity was detected (P=0.91).

**Anti-immunoglobulin-E (anti-IgE)**: There were statistically significantly reduced exacerbations over the first 12 to 16 weeks in atopic patients with anti-IgE plus inhaled corticosteroids (see Participants Included in the Review; RR 0.55, 95% CI 0.45 to 0.66; four trials). The review did not state what the comparator treatment was. No statistically
significant heterogeneity was detected (P=0.15).

Authors' conclusions
Inhaled corticosteroids were the most effective single treatment for adults with asthma. Leukotriene modifiers/receptor antagonists may be appropriate for patients unable or unwilling to take corticosteroids. Long-acting beta2 agonists may be added to corticosteroids for patients who were not controlled on low-dose steroid therapy. For young adults with definite allergies and raised serum IgE levels, treatment with adjunctive anti-IgE therapy may be considered.

CRD commentary
The review question was clear for study design, intervention, participants and outcomes. Several relevant sources were searched and the search terms were reported. Some attempts were made to minimise publication bias, but not language bias. The methods used to select the studies and assess validity were not described, so it was not known whether any efforts were made to reduce errors and bias. Two reviewers independently extracted the data, which reduced the potential for bias and errors.

Only RCTs that met specified minimum validity criteria were included; validity was assessed using specified established criteria. The data were appropriately combined in a meta-analysis. Statistical heterogeneity was assessed. Potential causes of the statistically significant heterogeneity found in the meta-analysis of inhaled corticosteroids were explored. The forest plot demonstrated that the direction of effect was consistent among studies in this analysis.

The authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that clinicians should use the review results in conjunction with clinical judgement for the treatment of patients. The authors recommended that inhaled low-dose corticosteroids be used as first-line therapy for patients whose asthma was not controlled by the occasional use of a short-acting beta2 agonist. If symptoms persisted despite the use of a low-dose inhaled corticosteroid, the addition of a long-acting beta2 agonist was reasonable. Increasing the corticosteroid dose was an alternative, but this may be associated with increased side-effects. In relatively young patients with asthma who could not or would not take inhaled corticosteroid, monotherapy with leukotriene pathway modifiers/receptor antagonists may reduce exacerbation rates, although it was not as effective as inhaled corticosteroids. The authors also stated that patients should be educated about factors that influence the systemic absorption of corticosteroids. They stated that, given the limited research evidence, anti-IgE could not be routinely recommended for most patients with asthma. The paper included a proposed guide to asthma treatment.

Research: The authors stated that research was required to evaluate the role of noninvasive markers for monitoring disease.

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