Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis
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CRD summary
This review compared the effectiveness of inhaled anticholinergics plus beta-2 agonists with beta-2 agonists alone for acute asthma exacerbations in the emergency department. The authors concluded that combined treatment significantly reduced hospital admissions and increased spirometry measures for children, adolescents and adults. While individual aspects of study quality were generally not reported, the overall conclusions are likely to be reliable.

Authors' objectives
To update the evidence on the effectiveness of a combination of inhaled beta-2 agonists and anticholinergics compared with beta-2 agonists alone for the treatment of children and adults with acute asthma in the emergency department.

Searching
MEDLINE (from 1966), EMBASE (from 1974) and CINAHL (from 1982) were searched to April 2005; the search terms were reported. The Cochrane Controlled Trials Register, reference lists of included studies and journals in the field were also searched. The drug manufacturer was also contacted for other published and unpublished trials. Trials published only as abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Single or repeated doses of inhaled beta-2 agonists combined with anticholinergics, compared with inhaled beta-2 agonists alone, were eligible interventions. Studies involving atropine were excluded. The included beta-2 agonists were salbutamol, fenoterol and terbutaline, while in most studies the anticholinergic agent was ipratropium bromide (others were oxtropium bromide and glycopyrrolate). Single and multiple doses were used and the doses varied between studies. In most studies, the drugs were administered by nebuliser and concomitant systematic corticosteroids were given.

Participants included in the review
Eligible participants were children aged 5 months to 17 years and adults aged 18 or older with acute asthma exacerbations, who presented to an emergency department or equivalent care setting. In most studies the patients had moderate to severe asthma; some studies reported the results stratified by asthma severity.

Outcomes assessed in the review
The inclusion criteria specified admission to hospital and spirometric testing (final values or change from baseline after the last combined inhalation) as primary outcomes. The secondary outcomes were clinical score, duration of emergency department treatment, respiratory rate, oxygen saturation, heart rate and side-effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for relevance. Any disagreements were resolved by consensus.

Assessment of study quality
Validity was assessed using the Jadad scale. This assesses randomisation, blinding, and the handling of withdrawals and drop-outs and assigns a score of 0 to 5. The authors did not state how the validity assessment was performed.
**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The relative risk (RR) was calculated for binary outcomes, and mean differences or standardised mean differences (SMDs) for continuous outcomes depending on whether the outcomes were measured using the same or different units.

**Methods of synthesis**

*How were the studies combined?*

The studies were combined in a random-effects meta-analysis. Pooled weighted mean differences (WMDs), SMDs and RRs were calculated together with their 95% confidence intervals (CIs). The number-needed-to-treat (NNT) was also calculated. Publication bias was assessed using Egger's regression method.

*How were differences between studies investigated?*

Heterogeneity was assessed using the Q statistic and the I-squared statistic. For the I-squared statistic, values of 25%, 50% and 75% were classed as low, moderate and high heterogeneity, respectively. Subgroup analyses were performed for the following groups: intensity of anticholinergic protocol (single or multiple doses), baseline asthma severity (moderate or severe), co-therapy with concomitant systematic corticosteroids, and study methodological quality.

**Results of the review**

Thirty-two RCTs (n=4,045) were included: 16 trials (n=1,998) of children and adolescents and 16 trials (n=2,047) of adults.

Twenty-six studies were double-blinded. The Jadad scores ranged from 1 to 5 out of a possible 5.

Hospital admissions.

The combination of inhaled anticholinergic and beta-2 agonist treatment was associated with statistically significant reductions in the risk of hospital admission for children and adolescents (RR 0.73, 95% CI: 0.63, 0.85; based on 10 studies; NNT 13, 95% CI: 9, 28) and for adults (RR 0.68, 95% CI: 0.53, 0.86; based on 9 studies; NNT 14, 95% CI: 9, 30), compared with beta-2 agonists alone. There was no evidence of publication bias or heterogeneity (I-squared 0% for the analysis of children and 13.8% for adults). Subgroup analyses suggested that the greatest effect was seen in children and adults with the most severe asthma attacks treated with multiple doses of anticholinergics.

Spirometric testing.

Combined treatment was also associated with statistically significant increases in spirometric parameters 1 to 2 hours after the last treatment (either the percentage change in forced expiratory volume, peak expiratory flow rate, or respiratory resistance) for children and adolescents (SMD -0.54, 95% CI: -0.81, -0.28; based on 9 studies) and for adults (SMD -0.36, 95% CI: -0.49, -0.23; based on 16 studies). There was significant heterogeneity for both groups (I-squared 57.3% for children and 41.3% for adults). There was no evidence of publication bias. It appeared that combined treatment was most effective in those receiving more than two doses of anticholinergics.

Other outcomes.

Three studies of children found a significant reduction in clinical score after combined treatment (SMD -0.29, 95% CI: -0.51, -0.07). There was no evidence of a difference in side-effects, such as tremor, amongst patients treated with single or multiple doses. There was also no evidence that the combined treatment affected heart rate amongst adults.

**Authors’ conclusions**
The review suggested that the addition of multiple doses of inhaled anticholinergic agents to beta-2 agonists was indicated as the standard treatment in children, adolescents and adults with moderate to severe asthma exacerbations in the emergency setting.
CRD commentary
This was a generally well-conducted review. The aims and inclusion criteria were clearly stated. Several sources were searched (including journal handsearches and contact with a drug manufacturer) without any apparent language restrictions, and two independent reviewers screened studies. It was unclear whether two reviewers conducted the data extraction and validity assessment. The methods of analysis were appropriate, heterogeneity was assessed, and subgroup analyses were used to explore reasons for heterogeneity. However, study validity was only reported as a total score, making it difficult for review users to assess study validity for themselves. The authors stated that the exclusion of trials of lower methodological quality did not affect the conclusions, but they did not report these results or define how they used the quality score to define 'low' quality. Apart from the lack of clarity about study quality, the conclusions of this review are likely to be reliable.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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