Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital (Review)

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[Intervention Review]

Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

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Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 7, 2014.
Review content assessed as up-to-date: 17 December 2013.

Citation: Vézina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No.: CD010283. DOI: 10.1002/14651858.CD010283.pub2.

ABSTRACT

Background

Inhaled anticholinergics given in addition to β_2-agonists are effective in reducing hospital admissions in children presenting to the emergency department with a moderate to severe asthma exacerbation. It seems logical to assume a similar beneficial effect in children hospitalised for an acute asthma exacerbation.

Objectives

To assess the efficacy and safety of anticholinergics added to β_2-agonists as inhaled or nebulised therapy in children hospitalised for an acute asthma exacerbation. To investigate the characteristics of patients or therapy, if any, that would influence the magnitude of response attributable to the addition of anticholinergics.

Search methods

We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO and through handsearching of respiratory journals and meeting abstracts. The search is current to November 2013.

Selection criteria

Randomised trials comparing the combination of inhaled or nebulised anticholinergics and short-acting β_2-agonists versus short-acting β_2-agonists alone in children one to 18 years of age hospitalised for an acute asthma exacerbation were eligible.

Data collection and analysis

Two review authors independently assessed the methodological quality of trials and extracted data; disagreement was resolved by consensus or with the input of a third review author, when needed. Primary outcomes were duration of hospital stay and serious adverse events. Secondary outcomes included admission and duration of stay in the intensive care unit (ICU), ventilation assistance, time to short-acting β_2-agonists spaced at four hours or longer, supplemental asthma therapy, duration of supplemental oxygen, change from baseline in asthma severity, relapse after discharge, adverse health effects and withdrawals.

Main results

Seven randomised trials were included, four of which reported usable data on 472 children with asthma one to 18 years of age who were admitted to paediatric wards. No trials included patients admitted to the ICU. The anticholinergic used, ipratropium bromide 250 μg, was given every one to eight hours over a period from four hours to the entire length of the hospital stay. Two of four trials (50%) contributing data were deemed of high methodological quality. The addition of anticholinergics to β_2-agonists showed no evidence of effect on the duration of hospital admission (mean difference (MD) -0.28 hours, 95% confidence interval (CI) -5.07 to 4.52, 3 studies, 327 participants, moderate quality evidence) and no serious or non-serious adverse events were reported in any included trials. As a result of the similarity of trials, we could not explore the influence of age, admission site, intensity of anticholinergic treatment and co-interventions on primary outcomes. No statistically significant group difference was noted in other secondary outcomes, including the need for supplemental asthma therapy, time to short-acting β_2-agonists spaced at four hours or longer, asthma clinical scores, lung function and overall withdrawals for any reason.

Authors' conclusions

In children hospitalised for an acute asthma exacerbation, no evidence of benefit for length of hospital stay and other markers of response to therapy was noted when nebulised anticholinergics were added to short-acting β_2-agonists. No adverse health effects were reported, yet the small number of trials combined with inadequate reporting prevent firm reassurance regarding the safety of anticholinergics. In the absence of trials conducted in ICUs, no conclusion can be drawn regarding children with impending respiratory failure. These findings support current national and international recommendations indicating that healthcare practitioners should refrain from using anticholinergics in children hospitalised for acute asthma.

PLAIN LANGUAGE SUMMARY

Are inhaled anticholinergics added to β_2-agonists beneficial in children hospitalised with acute asthma?

Background: Anticholinergics (e.g. ipratropium bromide, atropine sulfate) are inhaled drugs. They relax the airway muscles and decrease secretions. Anticholinergics are sometimes used in addition to beta$_2$-agonists (such as salbutamol and terbutaline), which are potent drugs given to relax smooth muscles in the airways in children with acute asthma. We do not know whether the addition of inhaled anticholinergics to beta$_2$-agonists is beneficial for children hospitalised with acute asthma.

Review question: We wished to examine the efficacy and safety of inhaled or nebulised (mist inhaled into the lungs) anticholinergics added to beta$_2$-agonists compared with beta$_2$-agonists alone in children one to 18 years of age hospitalised for an acute asthma exacerbation.

Study characteristics: In reviewing evidence available until November 2013, we found seven eligible studies of children hospitalised with acute asthma; four of these studies (472 children one to 18 years of age) contributed data to the review. Four studies compared the combination of anticholinergics (ipratropium bromide) and beta$_2$-agonists versus the same dose of beta$_2$-agonists alone. Included studies enrolled both girls and boys, with a gender ratio ranging from 59% to 73% males.

Results: No additional benefit was noted by adding anticholinergics to β_2-agonists in terms of duration of hospital stay in patients compared to those who received beta$_2$-agonists alone. Two of four trials (50%) contributing data were deemed of high methodological quality. No trial reported information on serious adverse events. No statistically significant group difference was noted in other markers of response to therapy, that is, the need for supplemental asthma therapy, time to short-acting beta$_2$-agonists spaced at four hours or longer, asthma clinical scores, lung function and overall withdrawals for any reason.

Conclusion: No apparent benefit is derived from adding anticholinergics to beta$_2$-agonists in children hospitalised for an acute asthma exacerbation, that is, beyond initial treatment in the emergency department. No adverse health effects were reported, yet the small number of trials combined with inadequate reporting prevents firm reassurance regarding the safety of anticholinergics. In the absence of trials conducted in the intensive care unit (ICU), no conclusion can be drawn regarding children with very severe exacerbations who are admitted to the ICU. Our findings support the ongoing recommendations provided by national and international guidelines.

Quality of the results: This review is based on a small number of identified trials conducted in children with acute asthma. All trials contributing to the primary outcome are of high methodological quality, but they are few. As the addition of new trials may change the conclusion, the quality of evidence was downgraded from high to moderate. Additional and larger trials are needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Combination of AC + beta$_2$-agonists versus beta$_2$-agonists alone

Patient or population: children hospitalised with an acute asthma exacerbation
Settings: hospitalised
Intervention: combination of anticholinergic + beta$_2$-agonists
Comparison: beta$_2$-agonists alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Beta$_2$-agonistsalone	Combination of AC + beta$_2$-agonists				
Duration of the hospital stay (hours)	The mean duration of the hospital stay (hours) in the control groups was 44 hours	The mean reduction in duration of hospital stay (hours) was 0.28 hours in the intervention groups Mean 43.8 (39 to 49) hours	**-0.28 hours** (-5.07 to 4.52)	327 (3 studies)	⊕⊕⊕◯ **moderate**[1]	
Time to regular dose of short-acting beta$_2$-agonists (hours)[2] **Follow-up: 4 hours or longer**	The mean time to regular short-acting beta$_2$-agonists in the control groups was 33 hours	The mean reduction in time to regular short-acting beta$_2$-agonists in the intervention groups was 2.17 hours Mean 31 (26 to 36) hours	**-2.17 hours** (-7.01 to 2.66)	269 (2 studies)	⊕⊕⊕◯ **moderate**[1]	
Asthma clinical scores Follow-up: 8 to 36 hours after initial treatment	See comment	See comment	**0.02 SMD** (-0.34 to 0.38)	117 (2 studies)	⊕⊕⊕◯ **moderate**[1]	Scores were measured on different scales.

Admission to the intensive care unit	See comment	See comment	Not estimable	210 (1 study)	⊕⊕⊕○ **moderate**[3]	Single trial reported admission to the intensive care unit. No events were reported
Overall withdrawals	**12 per 100**	**7 per 100** (4 to 15)	**OR 0.59** (0.27 to 1.30)	294 (2 studies)	⊕⊕⊕○ **moderate**[1]	
Adverse health events	See comment	See comment	Not estimable	290 (2 studies)	⊕⊕⊕○ **moderate**[3]	No adverse events were reported in either trial

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded because of wide confidence intervals.
[2]This is the time at which emergency dosing with the trial intervention was replaced with regular 4-hourly treatment with short-acting beta$_2$-agonists.
[3]No events were reported in either arm of the studies.

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory disorder of the airways that is associated with airway hyperresponsiveness (Ortiz-Alvarez 2012). Globally the prevalence of severe asthma symptoms, defined as four or more attacks of wheeze or one or more night per week of sleep disturbance from wheeze or wheeze affecting speech in the past 12 months ranged from 0% to 20% in children (Asher 2010; Lai 2009). Asthma exacerbation is defined as an acute or subacute worsening of symptoms and lung function from the individual's usual status or, in some cases, the initial presentation of asthma (GINA 2014). One of the main goals in the management of acute asthma exacerbations in children is to achieve a rapid reversal of airflow obstruction (NAEPP 2011). This is achieved by using inhaled or nebulised short-acting β_2-agonists (Camargo 2003; Karpel 1997), which are the most effective bronchodilators because of their rapid onset of action and the magnitude of bronchodilation that they achieve (Sears 1992; Svedmyr 1985). Systemic corticosteroids should be added early in the course of treatment for patients who have moderate or severe exacerbations or for children who fail to respond promptly and completely to bronchodilators (Rechelefsky 2003; Rowe 2004).

Description of the intervention

Anticholinergic agents, such as ipratropium bromide and atropine sulfate, have a slower onset of action and a weaker bronchodilating effect but may specifically relieve cholinergic bronchomotor tone and decrease mucosal edema and secretions (Chapman 1996; Gross 1988; Silverman 1990). Thus, with their slower onset but prolonged duration of action, anticholinergics (AC) can work as complementary therapy to β_2-agonists, thereby enhancing bronchodilation.

Several trials have explored the role of ipratropium bromide in the emergency department setting. One systematic review of randomised controlled trials (RCTs) concluded that multiple doses of inhaled anticholinergic agents added to β_2-agonist therapy in the initial treatment of children with acute asthma exacerbations were safe and efficacious, with most of the effect observed in those with severe asthma exacerbations and no apparent benefit noted in children presenting with mild to moderate asthma exacerbations (Plotnick 2000). An updated Cochrane review suggests that the benefit extends to children with moderate and severe exacerbations (Griffiths 2013). Moreover, multiple doses of inhaled anticholinergic agents added to β_2-agonists have been shown to be cost-effective (Lord 1999).

How the intervention might work

To our knowledge, two trials have assessed the efficacy of ipratropium bromide added to β_2-agonists after the emergency department treatment period, that is, in children hospitalised for an acute asthma exacerbation (Craven 2001; Goggin 2001). Both trials independently demonstrated no benefit conferred by the addition of anticholinergics. Consequently, national and international asthma guidelines currently recommend that inhaled anticholinergics should not be used in hospitalised children with acute asthma (GINA 2014; NAEPP 2011). Yet, in several institutions, anticholinergics are used for a specified period of time after children are admitted, particularly, but not only, those admitted to the intensive care unit (ICU).

Why it is important to do this review

The difference in practice between institutions, termed practice variation, underlines a gap between recommended and observed care, or a care gap. In the absence of an identified systematic review, we believe that a Cochrane review would clarify the evidence accumulated to date regarding the role of anticholinergics in the treatment of children hospitalised for an acute asthma exacerbation.

OBJECTIVES

To assess the efficacy and safety of anticholinergics added to β_2-agonists as inhaled or nebulised therapy in children hospitalised for an acute asthma exacerbation. To investigate the characteristics of patients or therapy, if any, that would influence the magnitude of response attributable to the addition of anticholinergics.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs.

Types of participants

We included children one to 18 years of age who were hospitalised for an acute asthma exacerbation.

Types of interventions

Intervention: nebulised or inhaled anticholinergics with short-acting β_2-agonists.
Comparison: nebulised or inhaled short-acting β_2-agonists alone.
Co-interventions: Systemic corticosteroids were anticipated and permitted, provided they were similar in the two groups.

Types of outcome measures

Primary outcomes

1. Duration of hospital stay.
2. Serious adverse events.

Secondary outcomes

1. Duration of stay in the ICU (for those admitted to the ICU).
2. Admission to the ICU (for those admitted on the wards).
3. Ventilation assistance.
4. Need for supplemental asthma therapy (e.g. aminophylline).
5. Duration of need for supplemental oxygen.
6. Time to short-acting β_2-agonists spaced at four hours or longer.
7. Change from baseline in asthma severity measured as lung function, symptoms or clinical scores.
8. Relapse within 72 hours of discharge from hospital.
9. Adverse health events.
10. Withdrawals, namely, overall withdrawals, withdrawals due to poor control of symptoms or deterioration and withdrawals due to adverse effects.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and through handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR coded as "asthma," using the strategy provided in Appendix 2. The literature search covered all years from inception until November 2013.
No restriction on type or language of publication was applied.

Searching other resources

We checked the reference lists of all identified RCTs to identify potentially relevant citations. We checked the websites of international headquarters of pharmaceutical companies producing anticholinergics for reports of relevant completed trials. We also explored the ClinicalTrials.gov website for relevant clinical trials.

Data collection and analysis

Two review authors (KV and BFC) independently extracted data, and disagreement was resolved by consensus or through the input of a third review author (FMD). When necessary, we contacted authors of included studies to request missing data.

Selection of studies

One review author (KV) independently reviewed each abstract and annotated each as (1) RCT; (2) clearly not an RCT; or (3) unclear. The full-text publications of citations identified as included RCTs or unclear were reviewed by two review authors independently.

Data extraction and management

Two review authors (KV and BFC) independently extracted data, and disagreement was resolved by consensus or with the input of a third review author (FMD), when needed.

Assessment of risk of bias in included studies

We assessed the methodological quality of included trials by using the 'Risk of bias' tool of The Cochrane Collaboration, which is based on:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

Quality assessment was performed independently by two review authors. We resolved disagreement by consensus or with the input of a third review author. The study was deemed to have high methodological quality if reported randomisation procedures and blinding were adequate and there was a low and balanced group attrition, supporting a low risk of bias.

Measures of treatment effect

We calculated treatment effects for dichotomous variables as risk ratio (RR) or risk difference (RD), or both, with 95% confidence intervals (CIs). We assumed equivalence if the RR estimate and its 95% CI fell between 0.9 and 1.1. For continuous outcomes, such as lung function tests, we calculated pooled statistics as mean

difference (MD) or standardised mean difference (SMD) with 95% CI.

Unit of analysis issues

The unit of analysis was the participant. If a trial had more than one intervention or control group, we considered additional comparisons, when appropriate.

Dealing with missing data

When possible, we contacted investigators or study sponsors to obtain missing numerical outcome data or data in the required format to allow aggregation in the review. We did not impute missing data.

Assessment of heterogeneity

Homogeneity between included studies for which results were pooled will be tested with the DerSimonian and Laird method, and I^2 > 40% was to be used as the cutoff level for significance. In cases of statistically significant heterogeneity, a random-effects model was applied to the summary estimates. Unless specified otherwise, the fixed-effect model was used.

Assessment of reporting biases

If missing or incomplete outcome data were identified, we attempted to contact study authors to obtain the missing data.

Data synthesis

Summary estimates were reported with their 95% CIs. We performed meta-analysis using RevMan 5.2.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to explore possible reasons for heterogeneity of study results for primary outcomes. A priori defined subgroups were based on:

1. age (preschool children vs school-aged children);
2. admission site (hospital ward vs intensive care unit);
3. intensity of anticholinergic treatment; and
4. co-intervention with systemic corticosteroids (yes or no).

Sensitivity analysis

For the primary outcomes, we planned to perform sensitivity analyses for publication status by removing the unpublished data, and for methodological quality by removing trials that did not meet the following criteria: random sequence generation, double-blinding and low and balanced attrition in both groups.

Summary of findings table

We created a 'Summary of findings' table using the primary and secondary outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies contributing data to the meta-analyses for prespecified outcomes. We used methods and recommendations as described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and GRADE pro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes and made comments to aid readers' understanding of the review, when necessary.

RESULTS

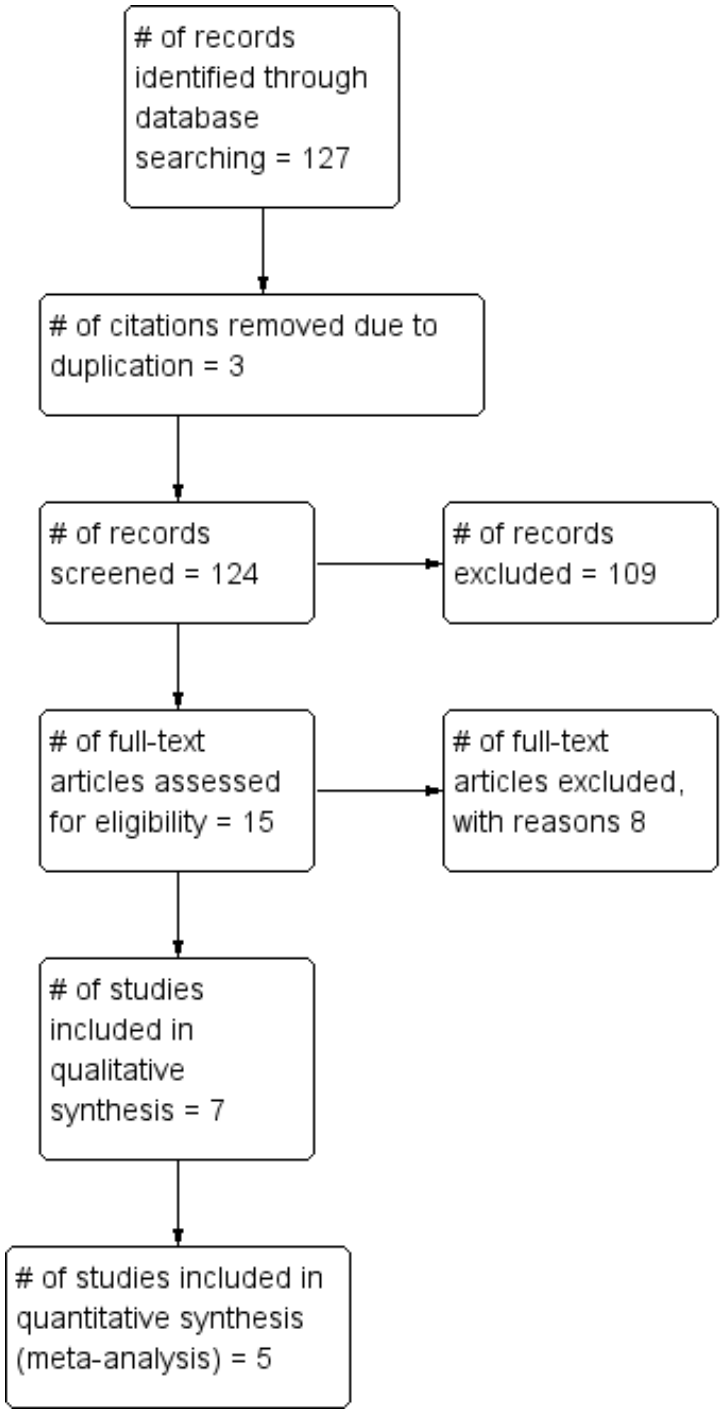
Description of studies

See Characteristics of included studies; Characteristics of excluded studies and Characteristics of ongoing studies

Results of the search

The search, conducted until November 2013, yielded a total of 127 citations (Figure 1). Of these, 120 citations were excluded for the following non-mutually exclusive reasons: (1) duplicate references (N = 3), (2) ongoing trials (N = 1), (3) studies not randomised trials (N = 8), (4) participants not asthmatic (N = 7), (5) participants not exclusively children (N = 38), (6) participants not hospitalised for an acute asthma exacerbation or not receiving treatment beyond initial treatment in the emergency department (N = 48), (7) intervention not a combination of anticholinergics and β_2-agonists (N = 11) and (8) control intervention not β_2-agonist alone (N = 4).

Figure 1. Study flow diagram.



Included studies

Seven trials met the inclusion criteria for this review. Of these, three eligible clinical trials did not contribute data to the review because reports were incomplete (Lew 1990; Mirkinson 2000; Ozdemir 2003). The data presented hereafter pertain to only four eligible trials, representing a total of 472 children hospitalised for an acute asthma exacerbation that contributed data to this meta-analysis (Craven 2001; Goggin 2001; Rayner 1987; Storr 1986). All four trials were published in full text. We describe below the characteristics of trials that contributed data for analysis for this review.

Design

All included trials had a parallel-group design (Craven 2001; Goggin 2001; Rayner 1987; Storr 1986), and the data on lung function as presented in one trial (Lew 1990) could not be aggregated because of its cross-over design.

Participants

All four trials involved children one to 18 years of age (Craven 2001; Goggin 2001; Rayner 1987; Storr 1986). The mean (or median) age of children in three studies was five years or younger (Craven 2001; Goggin 2001; Storr 1986) and 6.5 years in Rayner 1987. Most trials described a gender ratio ranging from 59% to 73% males. One study (Goggin 2001) enrolled children with moderate to severe asthma symptoms at baseline, defined as requiring inhaled β_2-agonists at a minimum of every two hours, having forced expiratory volume in one second (FEV_1) of 25% to 80% of predicted value or having a clinical asthma score of three to nine on a scale of zero to 10 (higher indicating worse). The other trials did not report asthma severity at baseline (Craven 2001; Rayner 1987; Storr 1986), and no trials provided data that were stratified according to the severity of baseline airway obstruction.

Intervention drugs

Important variability must be noted in the proportion of participants who had received anticholinergics before randomisation. Indeed, in Goggin 2001, children had received intensive ipratropium bromide before randomisation, with a mean of 5.9 doses in the control group and 6.0 doses in the treatment group, but in Craven 2001, only three of 210 participants (all in the treatment group) had received anticholinergics in the emergency department before randomisation. The number of participants who received anticholinergics before enrolment was not reported in the remaining three studies (Lew 1990; Rayner 1987; Storr 1986)

The intervention drug and frequency (Table 1) were as follows: 250 μg ipratropium bromide every four hours, every six hours afterwards and then every eight hours, depending on the asthma care algorithm phase (Craven 2001); 250 μg ipratropium bromide every 30 to 60 minutes initially, progressing to every two hours and then to every four hours as the participant improved clinically (Goggin 2001); 250 μg ipratropium bromide every eight hours (Rayner 1987); or 250 μg ipratropium bromide given within set limits at the discretion of the nursing staff (Storr 1986).

Co-intervention

The use of systemic corticosteroids was variable. All children in two trials received corticosteroids delivered intravenously or orally (Craven 2001; Goggin 2001). However, only 78% of participants in the control group and 74% of those in the treatment group were given oral corticosteroids in one study (Rayner 1987), and fewer participants received systemic steroids (26% and 28% in control and treatment groups, respectively) in the remaining study (Storr 1986). Intravenous aminophylline was used as a rescue therapy in two older studies (Rayner 1987; Storr 1986). If the clinical condition of a child was deteriorating in Craven 2001, subcutaneous epinephrine (0.01 mg/kg, maximum 0.5 mg) was added as part of the rescue therapy.

Outcomes

The primary efficacy outcome, that is, duration of hospital stay, was documented in three trials (Craven 2001; Goggin 2001; Rayner 1987) in a total of 327 children. None of these trials reported the primary safety outcome for our review, that is, serious adverse events. Other reported outcomes included admission to the ICU, need for supplemental asthma therapy, time to short-acting β_2-agonists spaced at four hours or longer, relapse within 72 hours of discharge from the hospital and change from baseline in asthma severity measured as lung function, symptoms or clinical scores, adverse health effects and withdrawals.

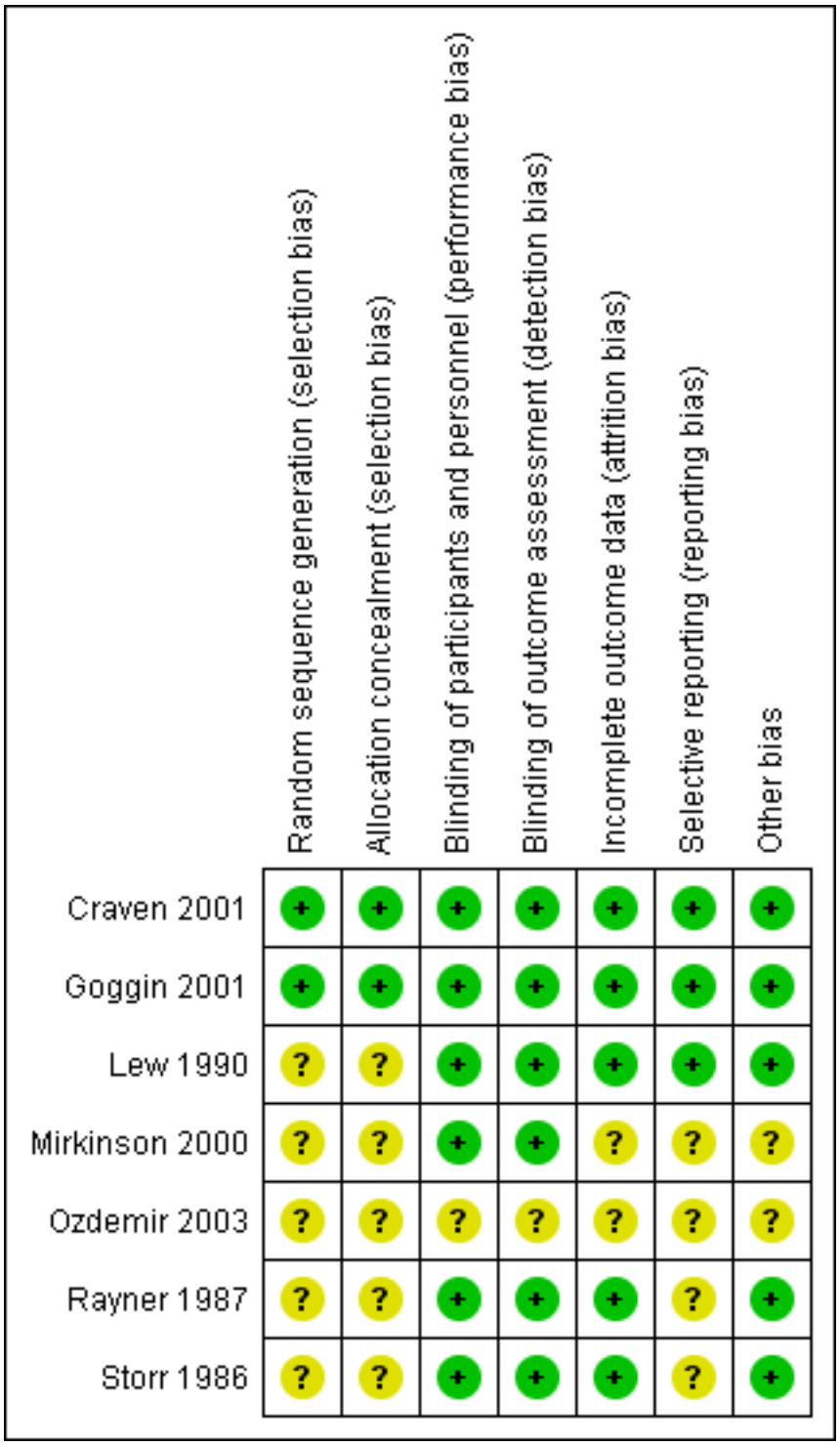
Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

Full details of risk of bias for all seven eligible trials are listed in the Characteristics of included studies table, and a graphical summary is presented in Figure 2. However, the following information pertains only to the four trials contributing data to the review.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



All four trials reported the method of randomisation in sufficient detail to confirm adequacy.

Allocation

Two of four trials contributing data reported details on allocation concealment, and both convincingly reported a valid allocation concealment (Craven 2001; Goggin 2001). Therefore, we judged these two trials to be at low risk of bias and the remaining trials to be at unclear risk of bias (Rayner 1987; Storr 1986).

Blinding

All trials reported double-blinding, with convincing details indicating low risk of bias.

Incomplete outcome data

All four trials contributing data (Craven 2001; Goggin 2001; Rayner 1987; Storr 1986) reported on missing data; the proportion of withdrawals or missing values was balanced in numbers across intervention groups with similar reasons for missing data across groups, or no missing data were noted at all; thus all four trials were considered at low risk of bias on this criterion.

Selective reporting

Two trials (Craven 2001; Goggin 2001) clearly specified primary and secondary outcomes and reported all outcomes and thus were considered at low risk of bias on this criterion.

Other potential sources of bias

We encountered no other significant sources of bias in the included trials contributing data to the review.

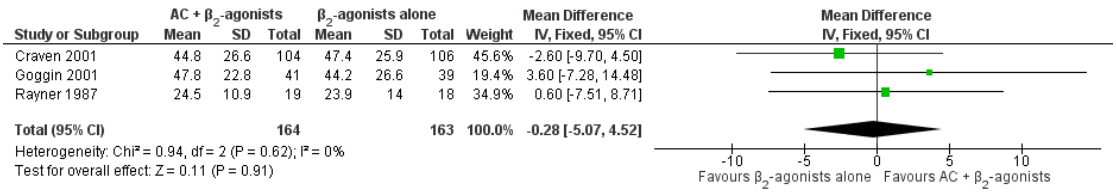
Effects of interventions

See: **Summary of findings for the main comparison** Combination of anticholinergics + beta$_2$-agonists versus beta$_2$-agonists alone

Primary efficacy outcome: duration of hospital stay

Three trials (Craven 2001; Goggin 2001; Rayner 1987) representing 327 children hospitalised with acute asthma contributed to the primary endpoint, that is, duration of hospital stay. The difference in hours of length of hospitalisation between participants treated with the combination of anticholinergics and short-acting β_2-agonists versus β_2-agonists alone was not statistically significant, with an MD of -0.28 hours (95% CI -5.07 to 4.52; Analysis 1.1; Figure 3) and no apparent heterogeneity (I^2 = 0%). Because of the similarity of trials contributing to the primary outcome with regards to the age of enrolled children, the absence of any trial conducted in the ICU, the use of similar doses of anticholinergics and co-intervention with systemic corticosteroids in all participants in two trials (Craven 2001; Goggin 2001) and three-quarters of participants in the remaining trial (Rayner 1987), we could not perform any of the a priori planned subgroup analyses on the primary efficacy outcome.

Figure 3. Forest plot: Combination of anticholinergics + β2-agonists versus β2-agonists alone, outcome: duration of the hospital stay (hours).



As all trials contributing data on the primary outcome were of high methodological quality and were published as full text, we did not perform sensitivity analyses on quality and publication status.

Primary safety outcome: serious adverse events

No trials reported information on serious adverse events.

Secondary outcomes

Duration of stay in ICU

No studies reported on this outcome.

Admission to the ICU

No admission to the ICU was described by the one study reporting on this outcome (Analysis 1.2).

Ventilation assistance

No studies reported on this outcome.

Need for supplemental asthma therapy

Four trials (Craven 2001; Goggin 2001; Rayner 1987; Storr 1986) representing 465 children contributed data on this outcome. No statistically significant impact of therapy on the need for supplemental therapy was described (RR 0.77, 95% CI 0.41 to 1.42; Analysis 1.3). The supplemental asthma therapy was intravenous aminophylline in two studies (Rayner 1987; Storr 1986), intravenous aminophylline or oral theophylline in one study (Goggin 2001) and an "intensification regimen," consisting of subcutaneous epinephrine (0.01 mg/kg, maximum 0.5 mg) and a one-time 500-μg dose of ipratropium bromide nebulised in combination with higher-dose albuterol (5.0 mg) in another study (Craven 2001).

Time to short-acting β_2-agonists spaced at four hours or longer

Two trials (Craven 2001; Goggin 2001) representing 290 participants contributed to this outcome. No statistically significant group difference (MD -2.17, 95% CI -7.01 to 2.66; Analysis 1.4) was reported.

Change from baseline in asthma severity measured as lung function, symptoms or clinical scores

Two trials reported on the change from baseline in the asthma clinical score eight to 36 hours after initial treatment (higher is worse). No statistically significant group difference was described (SMD 0.02, 95% CI -0.34 to 0.38; Analysis 1.5).

Only a single trial reported on peak expiratory flow rate (PEFR) and described no statistically significant group difference in any of these outcomes (Analysis 1.7). No pooling of data was thus possible.

Relapse

No relapse was reported in the one study reporting on these outcomes (Analysis 1.6).

Adverse health effects

Two trials (Craven 2001; Goggin 2001) totaling 290 children reported that no adverse health events were observed (Analysis 1.8).

Withdrawals

Two trials (Craven 2001; Goggin 2001) representing 294 children contributed to this outcome. No statistically significant group difference was noted in overall withdrawals (RR 0.80, 95% CI 0.38 to 1.70; Analysis 1.9) or in the proportion of withdrawals due to deterioration reported by a single trial (Analysis 1.10).

DISCUSSION

Summary of main results

In children hospitalised on hospital wards for an acute asthma exacerbation, the combination of nebulised anticholinergics with short-acting β_2-agonists was associated with no statistically significant reduction in duration of hospital stay. We did not set *a priori* boundary for equivalence, but after reviewing the literature to determine the cut-off for a clinically meaningful reduction in length of hospital stay, we proposed that a group difference of 8 hours be considered the minimally clinically important based on various reported length of hospital stay (Cunningham 2008; Smith 2003; Lim 2000). Indeed, the narrow confidence intervals rule out an effect of eight hours or larger of combination therapy over β_2-agonists alone. Because of the similarity of trial designs and participant characteristics (supported by the absence of significant heterogeneity) and incomplete reporting, it was not possible to explore whether characteristics of participants or therapy, such as age, admission site (ward or ICU) or intensity of anticholinergic treatment or co-interventions, could influence the magnitude of response attributable to the addition of anticholinergics. All trials contributing to the primary outcome were of high methodological quality and were published in full text, thus no bias due to quality or publication status was apparent. Although power was severely limited by the small number of trials, precluding the use of any statistics (Higgins 2011), inspection of the funnel plot did not suggest bias.

This finding was supported by all secondary outcomes, which showed no statistically significant group differences in the need for supplemental asthma therapy, asthma clinical scores, time to short-

acting β_2-agonists spaced at four hours or longer and withdrawals. Although the remaining outcomes could not be pooled because they were reported in only one trial, none showed a statistically significant group difference or effect.

Our findings contrast with those of a prior systematic review of RCTs, which concluded on the efficacy of multiple doses of inhaled anticholinergics in combination with β_2-agonist therapy versus β_2-agonist alone in the emergency management of severe asthma exacerbations (Plotnick 2000) and, more recently, on the treatment of children with moderate and severe exacerbations (Griffiths 2013). Recognising that the onset of action of oral corticosteroids is within three to four hours (Rowe 2001), we hypothesise that the beneficial effect of anticholinergics is best observed before the onset of action of systemic corticosteroids, at which point the effect of the latter surpasses that of the former. As hospital admission typically occurs at least three to four hours after oral corticosteroids are administered in the emergency department, perhaps the relative beneficial effect of anticholinergics becomes negligible when compared with systemic corticosteroids.

Only two trials (Craven 2001; Goggin 2001) examined adverse health effects; in both trials, no adverse health effects were observed in either intervention group. In the absence of adverse events in 145 intervention participants in these two trials, the upper limit around this null estimate is 2%. No trial reported any serious adverse health event-our primary safety outcome-possibly because of the absence of events, although we cannot rule out sub-optimal documentation or reporting. The paucity of data prevents any firm conclusions on the safety of either treatment strategy based on the proportion of adverse health effects or withdrawals, but the proportions would appear to be low. However, use of anticholinergics in the emergency department was not associated with an increase in serious adverse events or adverse events (Griffiths 2013; Plotnick 2000).

Overall completeness and applicability of evidence

The results of this review apply to children one to 18 years old, with a good representation of preschoolers and school-aged children, as three studies (Craven 2001; Goggin 2001; Storr 1986) included children with a mean or median age younger than five years and one trial (Rayner 1987) included predominantly school-aged children. Concomitant use of aminophylline and withholding of systemic corticosteroids in participants with acute asthma was noted in two older studies (Rayner 1987; Storr 1986); these approaches contrast to the current standard practice in which systemic corticosteroids was used systematically in all enrolled participants in the two recent studies (Craven 2001; Goggin 2001). Of note, one cannot extrapolate these data to children with impending respiratory failure admitted to the ICU, as the trial was conducted in the ICU.

Quality of the evidence

A very modest number of studies contributed data to the review. Trials contributing most of the data were of high methodological quality. Yet the four studies contributing data totaled only 472 children hospitalised for acute asthma. Clearly the large confidence intervals observed for all outcomes suggest that additional trials could change the conclusion. In addition, the paucity of trials prevented identification of subgroups (e.g. age, intensity of treatment, admission site) for whom the treatment may provide more or less effect. Finally, evidence regarding the safety profile of nebulised anticholinergics is insufficient.

Potential biases in the review process

No evidence of bias due to publication or methodological quality was shown by funnel plot. We recognise that, in view of the small number of studies, our power to identify bias was limited.

Agreements and disagreements with other studies or reviews

On the basis of efficacy, available results support the recommendation of current national and international guidelines (GINA 2014; NAEPP 2011) that anticholinergics should not be used in children hospitalised for an acute asthma exacerbation beyond initial treatment in the emergency department.

AUTHORS' CONCLUSIONS

Implications for practice

Among children hospitalised for an acute asthma exacerbation, no evidence suggests that nebulised anticholinergics added to β_2-agonists are effective in reducing length of hospital stay, need for supplemental asthma therapy or time to short-acting β_2-agonists spaced at four hours or longer, or that this combination improves clinical scores compared with those of β_2-agonists alone. Data are insufficient to reveal whether specific subgroups of patients are more likely to benefit, or if certain characteristics of therapy may influence the magnitude of response attributable to the addition of anticholinergics.

Because of the absence of identified studies conducted in the ICU, no evidence elucidates the possible role of anticholinergics in children with impending respiratory failure.

No adverse health effects were reported; yet the small number of trials combined with inadequate reporting prevented firm reassurance regarding the safety of anticholinergics.

Results support the recommendation of current guidelines that anticholinergics are not indicated in children hospitalised for an acute asthma exacerbation, beyond initial treatment in the emergency department.

Implications for research

Additional efficacy studies are needed to increase the precision of summary estimates and, urgently, to explore the efficacy of ipratropium bromide in children with impending respiratory failure.

Trials of high methodological quality with adequate documentation of adverse health effects associated with anticholinergics are needed to provide a fair comparison of the safety of these treatment options.

Future trials should aim to incorporate the following design characteristics.

1. Inclusion of double-blinding and adequate randomisation with details provided on allocation concealment and complete reporting of withdrawals and dropouts on intention-to-treat analysis.

2. Comparison of different intensities of anticholinergic therapy.

3. Subgroup data on patients stratified by age group (preschool children vs school-aged children) and severity of asthma on admission (mild, moderate or severe).

4. Continuous data provided as means with standard deviations.

5. Report of changes from baseline (at the time of randomisation) in asthma severity.

6. Systematic documentation of serious, overall and specific adverse health effects.

7. Systematic documentation of reasons for withdrawals.

ACKNOWLEDGEMENTS

We wish to thank the following individuals, who graciously provided additional data, namely, Dr Daniel Craven from Rainbow Babies and Children's Hospital, USA, and Dr Norma Goggin from the Department of Paediatrics, University of Toronto Faculty of Medicine, Canada.

We are indebted to the Cochrane Airways Review Group, namely, Dr Chris Cates, Dr Emma Welsh and Elizabeth Stovold, for performance of the literature search, their ongoing support and their constructive comments.

Chris Cates was the Editor for this review and commented critically on the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Craven 2001

Methods	Design: double-blind, randomised, placebo-controlled trial Confirmation of methodology: not obtained
Participants	Symptomatic participants Randomly assigned: N = 210 1. Combination placebo + β_2-agonists: 106 2. Combination AC + β_2-agonists: 104 Withdrawals: reported Age: median years (interquartile range): 1. Combination placebo + β_2-agonists: 4.5 (1.0-17.3) 2. Combination AC + β_2-agonists: 4.2 (0.9-17.3) Gender: male (%) 1. Combination placebo + β_2-agonists: 72.6 2. Combination AC + β_2-agonists: 67.3 Participants who received systemic corticosteroids before study enrolment (%): 1. Combination placebo + β_2-agonists : 95.3 2. Combination AC + β_2-agonists: 91.3 Doses of β_2-agonists before study enrolment: median number (interquartile range) 1. Combination placebo + β_2-agonists : 6 (0-8) 2. Combination AC + β_2-agonists: 5 (0-7) Participants who received AC before study enrolment: number (total N) 1. Combination placebo + β_2-agonists: 0 (106) 2. Combination AC + β_2-agonists: 3 (104) Participants who required supplemental oxygen before study enrolment (%) 1. Combination placebo + β_2-agonists: 27.4 2. Combination AC + β_2-agonists: 26.9 Time from first treatment in the emergency department to enrolment in hours (mean ± SD): not reported Eligibility criteria: 1. Age: 1-18 years 2. Children hospitalised for an acute asthma exacerbation at Rainbow Babies and Children's Hospital Exclusion criteria: 1. Need for supplemental oxygen at home 2. Diagnosis of cystic fibrosis, cyanotic congenital heart disease, chronic neonatal lung disease or pulmonary hypertension 3. Anticholinergic therapy at home 4. History of hypersensitivity to anticholinergic agents 5. Need for initial treatment in the intensive care unit
Interventions	Protocol Duration 1. 40-Week study period from December 15, 1996, to September 21, 1999 Test group: combination AC + β_2-agonists

	1. 250 μg (1.25 cc) of ipratropium bromide with 2.5 mg albuterol by jet nebulisation Control group: combination placebo + β_2-agonists 1. 1.25 cc of sterile preservative-free isotonic saline solution with 2.5 mg albuterol by jet nebulisation Treatment (combination AC + β_2-agonists or combination placebo + β_2-agonists) is given every 4 hours during phase I, every 6 hours during phase II and every 8 hours during phase III of the Asthma Care Algorithm (ACA) Utilisation of the ACA, which consists of 4 stepwise phases of chest assessment performed at prescribed intervals: every 2 hours in phase I, every 3 hours in phase II, every 4 hours in phase III and every 6 hours in phase IV Chest assessment consists of measurement of: 1. Respiratory rate and heart rate 2. Arterial oxyhaemoglobin saturation by pulse oximetry 3. Rating of accessory muscle use, wheezing severity and air entry according to defined criteria Advancement to the next phase: 1. "Good" ratings are reached for all chest assessment items while oxyhaemoglobin saturation of at least 94% is maintained on the current level of inspiratory oxygen 2. Assessment ratings have not deteriorated after 12 hours at a particular phase, even without a rating of "good" on all assessment criteria Nebulised albuterol (2.5 mg in 2 cc isotonic saline solution, driven by oxygen at 6 L/min) is administered after an assessment only if the child fails to meet advancement criteria If a child's rating deteriorates, then she or he reverts to ACA phase I after receiving the "intensification regimen," which consists of subcutaneous epinephrine (0.01 mg/kg, maximum 0.5 mg) and a 1-time 500-μg dose of ipratropium bromide nebulised in combination with higher-dose albuterol (5.0 mg) Children complete the ACA when they require albuterol no more often than every 6 hours for a minimum of 12 hours All children receive systemic corticosteroids (1-2 mg/kg/d, maximum dose 60 mg) Crteria for withdrawal from study: reported
Outcomes	Analysis: ITT Outcomes: 1. Duration of hospital stay 2. Serious adverse events: not reported 3. Admission to ICU: mentioned 4. Need for supplemental oxygen: mentioned 5. Need for supplemental asthma therapy: mentioned 6. Time to short-acting β_2-agonists spaced at 6 hours (ACA-P): mentioned 7. Change from baseline in asthma severity measured as lung function, symptoms or clinical scores: not reported 8. Relapse within 72 hours of discharge from hospital: mentioned 9. Adverse health effects: mentioned 10. Withdrawals: mentioned
Notes	Full paper (2001) Funding information not available "Intensification regimen" consisted of subcutaneous epinephrine (0.01 mg/kg, maximum

Craven 2001 (*Continued*)

	0.5 mg) and a 1-time 500-μg dose of IB nebulised in combination with higher-dose albuterol (5.0 mg)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A table of random numbers was used to assign children by simple randomisations in blocks of 10
Allocation concealment (selection bias)	Low risk	Centralised supply of unit dose-coded vials containing study drug or placebo solutions with identical aroma and appearance in both liquid and nebulised states
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in quantity across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were specified and all results were presented
Other bias	Low risk	No apparent bias was observed

Goggin 2001

Methods	Design: double-blind, randomised, placebo-controlled trial Confirmation of methodology: not obtained
Participants	Symptomatic participants Randomly assigned: N = 84 1. Combination placebo + β_2-agonists: 42 2. Combination AC + β_2-agonists: 42 Withdrawals: reported Age: median years (interquartile range): 1. Combination placebo + β_2-agonists: 3.7 (2.3-6.1) 2. Combination AC + β_2-agonists: 2.9 (1.8-5.8) Gender: N (male %) 1. Combination placebo + β_2-agonists: 23 (59)

	2. Combination AC + β_2-agonists: 26 (63) Number of participants who received systemic corticosteroids before study enrolment: not reported Number of doses of β_2-agonists before study enrolment: mean (± SD) 1. Comination placebo + β_2-agonists : 7.9 (± 2.4) 2. Combination AC + β_2-agonists: 8.3 (± 2.7) Number of doses of AC before study enrolment: mean (± SD) 1. Combination placebo + β_2-agonists: 5.9 (± 3.2) 2. Combination AC + β_2-agonists: 6.0 (± 3.2) Number of participants who required supplemental oxygen before study enrolment: not reported Time from first treatment in the emergency department to enrolment in hours: mean (± SD) 1. Combination placebo + β_2-agonists: 7.0 (± 2.6) 2. Combination AC + β_2-agonists: 6.9 (± 2.2) Eligibility criteria: 1. Age: 1-18 years 2. Known history of asthma (defined as at least 1 previous episode of wheezing or a history of chronic cough that required treatment with bronchodilators or anti-inflammatory agents) 3. Moderate to severe asthma symptoms at admission to the inpatient unit (defined as requiring inhaled β_2-agonists a minimum of every 2 hours, having a forced expiratory volume in 1 second [FEV_1] of 25%-80% of predicted volume or having a clinical asthma score of 3-9) Exclusion criteria: 1. Co-existent cardiac, neurological, immunosuppressive or other chronic pulmonary disease 2. Known hypersensitivity to study drugs 3. Preexisting ocular abnormalities 4. Need for airway intervention or admission to the critical care unit 5. Severe asthma symptoms at admission to the inpatient unit (clinical asthma score of 10) 6. Undue delay (defined as time longer than 12 hours from first treatment in the emergency department to admission to the inpatient unit)
Interventions	Test group: Combination AC + β_2-agonists 1. Nebulised ipratropium bromide inhalation solution 1.0 mL (250 μg) with nebulised albuterol inhalation solution 0,15 mg/kg per dose (maximum 5 mg per dose) Control group: combination placebo + β_2-agonists 1. Nebulised isotonic sodium chloride solution 1.0 mL with nebulised albuterol inhalation solution 0,15 mg/kg per dose (maximum 5 mg per dose) The combination AC + β_2-agonists or the combination placebo + β_2-agonists was given every half an hour to 1 hour at the beginning, progressing to 2 hours and then to 4 hours as the participant improves clinically Device: face mask and nebuliser All children were treated with corticosteroids using intravenous hydrocortisone 4 to 6 mg/kg every 6 hours or oral prednisone 1 mg/kg once daily. The total duration of corticosteroid therapy was a minimum of 5 days Use of supplemental oxygen therapy and other concurrent therapy (e.g. aminophylline)

Goggin 2001 (*Continued*)

	was at the discretion of the attending staff and was recorded Crteria for withdrawal from study: reported
Outcomes	Analysis: ITT Outcomes: 1. Duration of hospital stay 2. Serious adverse events: not reported 3. Admission to ICU: not reported 4. Need for supplemental oxygen: not reported 5. Need for supplemental asthma therapy: mentioned 6. Time to short-acting β_2-agonists spaced at 4 hours: mentioned 7. Asthma severity measured as lung function at baseline and every 6 hours for 36 hours FEV_1 8. Asthma severity measured with a validated clinical asthma score at baseline and every 6 hours for 36 hours for 5 clinical variables (respiratory rate, wheezing, inspiratory-expiratory ratio, indrawing and observed dyspnoea) Each variable is scored 0, 1 or 2 and is summed, with a total possible score of 10 1. Relapse within 72 hours of discharge from hospital: mentioned 2. Adverse health effects: mentioned heart rate and visual symptoms measured every 6 hours 3. Withdrawals: mentioned
Notes	Full paper (2001); contacted the trial author and received additional data Funding information not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was independently performed by a research pharmacist using a table of random numbers. Participants enrolled in the study were stratified at enrolment by 2 criteria (age and number of doses of nebulised ipratropium bromide administered in the emergency department). Children within each stratum were randomly allocated to treatment groups in blocks of 4
Allocation concealment (selection bias)	Low risk	Intervention and placebo solutions were clear, colourless and odourless liquids, and the 2 solutions were indistinguishable from one another in liquid and nebulised states
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured

Goggin 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in quantity across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Primary outcome was specified and all outcomes were reported
Other bias	Low risk	No apparent bias was noted

Lew 1990

Methods	Design: double-blind, cross-over, randomised trial Confirmation of methodology: not obtained
Participants	Symptomatic participants Randomly assigned: N = 17 1. β_2-agonists alone: 17 2. Combination AC + β_2-agonists: 17 Withdrawals: not reported Age: mean years (± SD): 1. β_2-agonists alone: 10 (± 2.5) 2. Combination AC + β_2-agonists:10 (± 2.5) Gender: N (male %) 1. β_2-agonists alone: 11 (65) 2. Combination AC + β_2-agonists: 11 (65) Number of participants who received systemic corticosteroids before study enrolment: not reported Number of doses of β_2-agonists before study enrolment: not reported Number of doses of AC before study enrolment: not reported Number of participants who required supplemental oxygen before study enrolment: not reported Time from first treatment in the emergency department to enrolment in hours: not reported Eligibility criteria: 1. Hospitalised children with acute asthma Exclusion criteria: 1. Fever 2. Underlying chronic lung diseases such as cystic fibrosis
Interventions	Participants were randomly assigned in a double-blind cross-over fashion to receive as their first therapy either: 1. An inhalation of both 0.1 % atropine sulfate (0.05 mg/kg up to 2 mg) and a 1% isoetharine solution (0.5 mL) 2. An inhalation of a 1% isoetharine solution (0.5 mL diluted in 2 mL of normal

	saline) Four hours after first inhalation, participants received inhalation of the alternative treatment Device: Nebulised therapy was delivered through a mouthpiece and the nebuliser was attached to tubing with a T-connection to allow intermittent thumb control during 5-second maximal inspiration from functional residual capacity to total lung capacity Participants were entered into the study within 72 hours of hospitalisation Inhaled bronchodilator therapy was withheld from all participants for 4 hours before the beginning of the study All participants received maintenance intravenous fluids, continuous infusion of aminophylline at doses sufficient to maintain serum theophylline concentrations between 10 and 20 μg/mL and 1 mg/kg every 6 hours of intravenous methylprednisolone Participants received oxygen supplement via face mask or nasal cannula as needed Criteria for withdrawal from study: not reported
Outcomes	Analysis: not ITT Outcomes: 1. Duration of hospital stay: not reported 2. Serious adverse events: not reported 3. Admission to ICU: not reported 4. Need for supplemental oxygen: not reported 5. Need for supplemental asthma therapy: mentioned 6. Time to short-acting β_2-agonists spaced at 4 hours: not reported 7. Asthma severity measured as lung function at baseline, at 30 minutes and at 240 minutes after inhalation FVC FEV_1 $FEF_{25-75\%}$ 1. Asthma severity measured with a clinical asthma score at baseline and 30, 60, 120, 180 and 240 minutes after each aerolised treatment 2. Relapse within 72 hours of discharge from hospital: not reported 3. Adverse health effects: mentioned Signs of atropine side effects at baseline and 30, 60, 120, 180 and 240 minutes after each aerolised treatment 1. Withdrawals: not reported
Notes	Full paper (1990) Funding information not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation was provided
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was provided

Lew 1990 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Primary outcome was specified and all outcomes were reported
Other bias	Low risk	No apparent bias was noted

Mirkinson 2000

Methods	Design: randomised, double-blind, placebo-controlled trial Confirmation of methodology: not obtained
Participants	Symptomatic participants Randomly assigned: N = 42 1. β_2-agonists alone: not reported 2. Combination AC + β_2-agonists: not reported Withdrawals: not reported Age: mentioned Gender: not reported Number of participants who received systemic corticosteroids before study enrolment: not reported Number of doses of β_2-agonists before study enrolment: not reported Number of doses of AC before study enrolment: not reported Number of participants who required supplemental oxygen before study enrolment: not reported Time from first treatment in the emergency department to enrolment in hours: not reported Eligibility criteria: 1. Pediatric participants admitted to inpatient service for acute asthma Exclusion criteria: 1. Not mentioned in the abstract
Interventions	Participants were treated with an initial standardised protocol consisting of nebulised albuterol 0.15 mg/kg and nebulised ipratropium bromide 250-500 μg administered together as 3 consecutive doses 20 minutes apart (over 1 hour) All participants continued to receive albuterol at a frequency based on asthma scores and clinical improvement and were then randomly assigned to 2 groups: 1. Half of the participants received Ipratropium bromide every 6 hours 2. Half of the participants received placebo (normal saline) every 6 hours

	All participants additionally received intravenous or oral steroids according to standard practice guidelines and supplemental oxygen and intravenous fluids as needed Clinical status was evaluated at predetermined times, 12 and 24 hours, by assigning asthma scores Criteria for withdrawal from study: not reported in the abstract
Outcomes	Analysis: ITT not mentioned in the abstract Outcomes: 1. Duration of hospital stay: not reported 2. Serious adverse events: not reported 3. Admission to ICU: not reported 4. Need for supplemental oxygen: not reported 5. Need for supplemental asthma therapy: not reported 6. Time to short-acting β_2-agonists spaced at 4 hours: not reported 7. Asthma severity measured as lung function: not reported 8. Asthma severity measured with a clinical asthma score: mentioned in the abstract 9. Relapse within 72 hours of discharge from hospital: not reported 10. Adverse health effects: not reported 11. Withdrawals: not reported
Notes	Abstract only Funding information not mentioned in the abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Ozdemir 2003

Methods	Design: randomised, placebo-controlled trial Confirmation of methodology: not obtained
Participants	Symptomatic participants Randomly assigned: N = 60 1. β_2-agonists alone: not reported 2. Combination AC + β_2-agonists: not reported Withdrawals: not reported Age: not reported Gender: N not reported Number of participants who received systemic corticosteroids before study enrolment: not reported Number of doses of β_2-agonists before study enrolment: not reported Number of doses of AC before study enrolment: not reported Number of participants who required supplemental oxygen before study enrolment: not reported Time from first treatment in the emergency department to enrolment in hours: not reported Eligibility criteria: 1. Children with a diagnosis of moderate and severe acute asthmatic attacks who were admitted to the emergency unit of the studied hospital Exclusion criteria: 1. Not reported
Interventions	Participants were randomly assigned to receive either: 1. Ipratopium in addition to standard therapy (nebulised β_2-agonists and systemic steroid) 2. Placebo (isotonic saline) in addition to standard therapy (nebulised β_2-agonists and systemic steroid) Criteria for withdrawal from study: not reported
Outcomes	Analysis: ITT not mentioned Outcomes: 1. Duration of hospital stay: not reported 2. Serious adverse events: not reported 3. Admission to ICU: not reported 4. Need for supplemental oxygen: not reported 5. Need for supplemental asthma therapy: not reported 6. Time to short-acting β_2-agonists spaced at 4 hours: not reported 7. Asthma severity measured as lung function PEF rates 1. Asthma severity measured with a clinical asthma score 2. Relapse within 72 hours of discharge from hospital: not reported 3. Adverse health effects: mentioned 4. Withdrawals: not reported
Notes	Abstract only Funding information not mentioned in the abstract

Ozdemir 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Rayner 1987

Methods	Design: randomised clinical study Confirmation of methodology: not obtained
Participants	Symptomatic patients Randomly assigned: N = 37 1. β_2-agonists alone: 18 2. Combination AC + β_2-agonists: 19 Withdrawals: not reported Age: mean 6.5 years 1. β_2-agonists alone: not reported 2. Combination AC + β_2-agonists: not reported Gender: not reported Number of participants who received systemic corticosteroids before study enrolment: not reported Number of doses of β_2-agonists before study enrolment: not reported Number of doses of AC before study enrolment: not reported Number of participants who required supplemental oxygen before study enrolment: not reported Time from first treatment in the emergency department to enrolment in hours: not reported Eligibility criteria: 1. Children admitted to the hospital with acute asthma

Rayner 1987 (*Continued*)

	Exclusion criteria: 1. Not reported
Interventions	Test group: nebulised AC 1. Nebulised ipratropium 250 μg in 2 mL physiological saline Control group: nebulised placebo 1. Nebulised placebo in 3 mL physiological saline Nebulisers were given 30 minutes after the first dose of salbutamol and every 8 hours afterwards Both groups received nebulised salbutamol (2.5 mg for children $\leq$ 6 years old and 5 mg for children > 6 years old) on admission and every 4 hours afterwards Steroids were given if good relief was not obtained
Outcomes	Analysis: not ITT Outcomes: 1. Duration of hospital stay: mentioned 2. Serious adverse events: not reported 3. Admission to ICU: not reported 4. Need for supplemental oxygen: not reported 5. Need for supplemental asthma therapy: mentioned 6. Time to short-acting β_2-agonists spaced at 4 hours: not reported 7. Asthma severity measured as lung function at baseline, immediately before and 45 minutes after first administration of trial drug and the next morning (12-24 hours later) Peak expiratory flow rate 1. Asthma severity measured with a clinical asthma score at baseline, immediately before and 45 minutes after first administration of trial drug and the next morning (12-24 hours later) Based on clinical examination, activity and speech (worst possible score = 25) 1. Relapse within 72 hours of discharge from hospital: not reported 2. Adverse health effects: not reported Signs of atropine side effects at baseline and 30, 60,120, 180 and 240 minutes after each aerosolised treatment 1. Withdrawals: not reported
Notes	Full paper (1987) Funding information not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Treatments were randomly allocated, but no information was provided on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was provided

Rayner 1987 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Doule-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	All specified outcomes were reported, but primary and secondary outcomes were not specified
Other bias	Low risk	No apparent bias was observed

Storr 1986

Methods	Design: randomised clinical study Confirmation of methodology: not obtained
Participants	Symptomatic participants Randomly assigned: N = 138 1. β_2-agonists alone: 70 2. Combination AC + β_2-agonists: 68 Withdrawals: not reported Age: mean 5.0 years 1. β_2-agonists alone: not reported 2. Combination AC + β_2-agonists: not reported Gender: 95 boys (69%) 1. β_2-agonists alone: not reported 2. Combination AC + β_2-agonists: not reported Number of participants who received systemic corticosteroids before study enrolment: not reported Number of doses of β_2-agonists before study enrolment: not reported Number of doses of AC before study enrolment: not reported Number of participants who required supplemental oxygen before study enrolment: not reported Time from first treatment in the emergency department to enrolment in hours: not reported Eligibility criteria: 1. All children admitted to Royal Alexandra Hospital for Sick Children (Brighton) between October 1984 and March 1985 because of asthma Exclusion criteria: 1. Not reported

Storr 1986 (*Continued*)

Interventions	Test group: combination AC + β_2-agonists 1. Nebuliser with 0,25 mg ipratropium bromide with 5 mg salbutamol Control group: β_2-agonists alone 1. Nebuliser with 5 mg salbutamol Nebulisers were given within set limits at the discretion of the nursing staff Steroids were given to children not responding satisfactorily to nebulised treatment Intravenous aminophylline was given to children in severe respiratory distress Criteria for withdrawal from study: not reported
Outcomes	Analysis: not ITT Outcomes: 1. Duration of hospital stay: mentioned 2. Serious adverse events: not reported 3. Admission to ICU: not reported 4. Need for supplemental oxygen: not reported 5. Need for supplemental asthma therapy: mentioned 6. Time to short-acting β_2-agonists spaced at 4 hours: not reported 7. Asthma severity measured as lung function Peak expiratory flow rates immediately before and 20 minutes after treatment (except at night) 1. Asthma severity measured with a clinical asthma score: not reported 2. Relapse within 72 hours of discharge from hospital: not reported 3. Adverse health effects: not reported 4. Withdrawals: not reported
Notes	Full paper (1986) Funding information not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Treatments were randomly allocated, but no information was provided on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No adequate information was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data noted

Storr 1986 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	All reported outcomes were presented, but primary and secondary outcomes were not specified
Other bias	Low risk	No apparent bias was observed

AC: anticholinergics; ACA: Asthma Care Algorithm; ACA-P: Asthma Carepath Progression; $FEF_{25-75\%}$: forced expiratory flow 25-75%; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICU: intensive care unit; ITT: intention-to-treat analysis; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmad 2010	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Allen 2005A	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Andrews 2009	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Avital 1992	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Azevedo 1990	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Becker 1999	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Benito Fernandez 2000	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Berger 2006	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Bigham 2010	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Boeree 1998	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN

(*Continued*)

Bogie 2007	ONE OF THE GROUP WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Bradshaw 2008	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Brenner 1988	ONE OF THE GROUP WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Browne 2002	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Camargo 2010	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Chen 2008	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Chen 2012	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Chowdhury 1995	PARTICIPANTS WERE NOT ASTHMATIC
Coulthard 1985	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Cydulka 2010	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Dahlen 2012	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
de Jong 1996	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Douma 1998	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Ducharme 1998	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Dutt 1990	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Freeman 1989A	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Friberg 1989A	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT

(*Continued*)

Garcia 1998	PARTICIPANTS WERE NOT ASTHMATIC
González 1989	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Goodacre 2013	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Gouin 1999	STUDY WAS NOT A RANDOMI SED TRIAL
Gove 1988	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Greenough 1986	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Groot 1994	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Haahtela 1991A	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Hardasmalani 2005	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Hayday 2002E	DUPLICATION OF Goggin 2001
Henry 1989	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Iramain 2011	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Israel 2004	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Jiang 2006	STUDY WAS NOT A RANDOMI SED TRIAL
Kaptein 1993	STUDY WAS NOT A RANDOMI SED TRIAL
Kelso 2011	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Kerstjens 1992	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Kerstjens 1993	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Kerstjens 1994	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Kerstjens 1995	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN

(*Continued*)

Knöpfli 2005	STUDY WAS NOT A RANDOMIS ED TRIAL
Lanes 1998	PARTICIPANTS WERE NOT CHILDREN
Lowry 1994	PARTICIPANTS WERE NOT ASTHMATIC
Macias 2003A	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Mallol 1987a	PARTICIPANTS WERE NOT ASTHMATIC
Mallol 1987bA	PARTICIPANTS WERE NOT ASTHMATIC
Maneechotesuwan 2011	PARTICIPANTS WERE NOT CHILDREN
McDowell 1998	STUDY WAS NOT A RANDOMI SED TRIAL
Meier 1997	STUDY WAS NOT A RANDOMI SED TRIAL
Mitchell 2005A	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Morris 2010	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Morrison 1989	STUDY WAS NOT A RANDOMI SED TRIAL
Nakano 2000	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Newnham 1995A	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Nibhanipudi 2009	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID NO T HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
O'Driscoll 1989B	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Overbeek 1996	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Parkin 1995	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Peters 2000	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Ponce 2009	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT

(*Continued*)

Powell 2012a	DUPLICATION OF Powell 2013
Powell 2013	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Qureshi 1997	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Qureshi 1998	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Qureshi 2001	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Qureshi 2005	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Raes 1989	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Raissy 2006	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Ralston 2005	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Ream 2001	ONE OF THE GROUPS WAS NOT β_2-AGONISTS ALONE
Reisman 1988A	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Richards 1987	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Roberts 2003	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Rodriguez 2008	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Rowe 2007	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN

(*Continued*)

Salmun 1999	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Sano 2000	PARTICIPANTS WERE NOT ASTHMATIC
Schuh 1992	PARTICIPANTS WERE NOT ASTHMATIC
Schuh 1995	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Schuh 1997	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Self 2002	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Sengul 2013	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Sienra Monge 2000	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Silverman 2012	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Singh 2008	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Singhi 2010	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Sly 1987	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Stewart 2012	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Stormon 1999	ONE OF THE GROUPS WAS NOT A COMBINATION OF ANTICHOLINERGICS + β_2-AGONISTS
Sur 1990	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Tasche 1997	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Taytard 1987	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN

(*Continued*)

Timsit 2002	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Ulrik 1992	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
UNKNOWN 2011	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Upham 2011A	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Van Asperen 1988	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
van der Woude 2001A	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Von Berg 2004	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Ward 1981	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Ward 1985	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Watanasomsiri 2006	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Watson 1994	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT
Wilson 1987	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Wolstenholme 1989	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Worth 2012	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Yang 1993	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Young 1991	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN
Youngchaiyud 1989	PARTICIPANTS WERE NOT EXCLUSIVELY CHILDREN

(*Continued*)

Yung 1998	ONE OF THE GROUPS WAS NOT β_2-AGONISTS ALONE
Zaritsky 1999A	DUPLICATION OF Qureshi 1998
Zorc 1999	PARTICIPANTS WERE NOT HOSPITALISED FOR AN ACUTE ASTHMA EXACERBATION OR DID N OT HAVE TREATMENT BEYOND INITIAL TREATMENT IN THE EMERGENCY DEPARTMENT

Characteristics of ongoing studies *[ordered by study ID]*

Powell 2012

Trial name or title	MAGnesium NEbuliser Trial In Children (MAGNETIC)
Methods	Randomised, placebo-controlled, double-blind multi-centre trial
Participants	Children (aged 2-16 years) presenting to hospital emergency departments and acute paediatric inpatient units with severe acute asthma Exclusion criteria will be co-existing respiratory disease such as cystic fibrosis, chronic lung disease of prematurity, severe renal disease, severe liver disease, known to be pregnant
Interventions	Nebulised magnesium sulphate compared with placebo along with standard therapy of nebulised salbutamol and ipratropium bromide
Outcomes	Two principal outcomes: 1. Yung Asthma Severity Score (ASS) 2. Numbers of participants with 'stepping down' therapy at 1 hour after treatment with the study medication Other outcomes: 3. Number and frequency of additional salbutamol 4. Lung function 5. Length of stay in hospital 6. Requirement for intravenous bronchodilator treatment 7. Admission to a paediatric intensive care unit (PICU) 8. Intubation rate A prospective economic evaluation will be conducted alongside the trial
Starting date	December 2007
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. Combination of anticholinergics (AC) + β_2-agonists versus β_2-agonists alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital stay (hours)	3	327	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-5.07, 4.52]
2 Admission to the intensive care unit	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Need for supplemental asthma therapy	4	465	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.42]
4 Time to short-acting β_2-agonists spaced at 4 hours or longer (hours)	2	290	Mean Difference (IV, Fixed, 95% CI)	-2.17 [-7.01, 2.66]
5 Asthma clinical scores 8 to 36 hours after initial treatment	2	117	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.34, 0.38]
6 Relapse within 72 hours of discharge from hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Percentages of predicted PEFR at 8 to 36 hours after initial treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Adverse health effects	2	290	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Overall withdrawals	2	294	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.27, 1.30]
10 Withdrawals due to deterioration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 1 Duration of hospital stay (hours).

Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β 2-agonists versus β 2-agonists alone

Outcome: 1 Duration of hospital stay (hours)

Study or subgroup	AC + β 2-agonists N	Mean(SD)	β 2-agonists alone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Craven 2001	104	44.8 (26.6)	106	47.4 (25.9)		45.6 %	-2.60 [-9.70, 4.50]
Goggin 2001	41	47.8 (22.8)	39	44.2 (26.6)		19.4 %	3.60 [-7.28, 14.48]
Rayner 1987	19	24.5 (10.9)	18	23.9 (14)		34.9 %	0.60 [-7.51, 8.71]
Total (95% CI)	**164**		**163**			**100.0 %**	**-0.28 [-5.07, 4.52]**

Heterogeneity: Chi² = 0.94, df = 2 (P = 0.62); I² =0.0%

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable

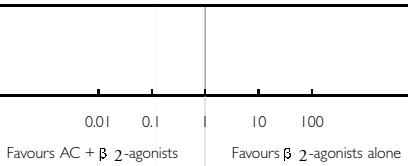
Analysis 1.2. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 2 Admission to the intensive care unit.

Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β 2-agonists versus β 2-agonists alone

Outcome: 2 Admission to the intensive care unit

Study or subgroup	AC + β 2-agonists n/N	β 2-agonists alone n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Craven 2001	0/104	0/106		Not estimable



Analysis 1.3. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 3 Need for supplemental asthma therapy.

Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β_2-agonists versus β_2-agonists alone

Outcome: 3 Need for supplemental asthma therapy

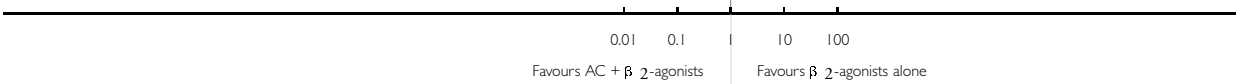
Study or subgroup	AC + β_2-agonists n/N	β_2-agonists alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Craven 2001	12/104	19/106		92.6 %	0.64 [0.33, 1.26]
Goggin 2001	0/41	0/39			Not estimable
Rayner 1987	1/19	0/18		2.5 %	2.85 [0.12, 65.74]
Storr 1986	2/68	1/70		4.9 %	2.06 [0.19, 22.18]
Total (95% CI)	**232**	**233**		**100.0 %**	**0.77 [0.41, 1.42]**

Total events: 15 (AC + β_2-agonists), 20 (β_2-agonists alone)

Heterogeneity: Chi^2 = 1.60, df = 2 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 0.84 (P = 0.40)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 4 Time to short-acting β2-agonists spaced at 4 hours or longer (hours).

Review: Inhaled anticholinergics and short-acting beta2-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β 2-agonists versus β 2-agonists alone

Outcome: 4 Time to short-acting β 2-agonists spaced at 4 hours or longer (hours)

Study or subgroup	AC + β 2-agonists N	Mean(SD)	β 2-agonists alone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Craven 2001	104	31.6 (19.8)	106	34.3 (22.6)		70.8 %	-2.70 [-8.44, 3.04]
Goggin 2001	41	28.2 (16.8)	39	29.1 (23.3)		29.2 %	-0.90 [-9.84, 8.04]
Total (95% CI)	**145**		**145**			**100.0 %**	**-2.17 [-7.01, 2.66]**

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² =0.0%

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 5 Asthma clinical scores 8 to 36 hours after initial treatment.

Review: Inhaled anticholinergics and short-acting beta2-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β 2-agonists versus β 2-agonists alone

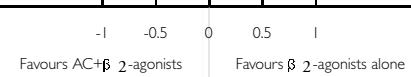
Outcome: 5 Asthma clinical scores 8 to 36 hours after initial treatment

Study or subgroup	AC + β 2-agonists N	Mean(SD)	β 2-agonists alone N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Goggin 2001	41	2.4 (1.9)	39	2.6 (2)		68.6 %	-0.10 [-0.54, 0.34]
Rayner 1987	19	4.6 (3.05)	18	3.9 (1.27)		31.4 %	0.29 [-0.36, 0.94]
Total (95% CI)	**60**		**57**			**100.0 %**	**0.02 [-0.34, 0.38]**

Heterogeneity: Chi² = 0.96, df = 1 (P = 0.33); I² =0.0%

Test for overall effect: Z = 0.12 (P = 0.91)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 6 Relapse within 72 hours of discharge from hospital.

Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β 2-agonists versus β 2-agonists alone

Outcome: 6 Relapse within 72 hours of discharge from hospital

Study or subgroup	AC + β 2-agonists n/N	β 2-agonists alone n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Goggin 2001	0/41	0/39		Not estimable

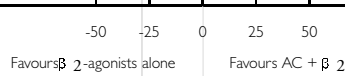
Analysis 1.7. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 7 Percentages of predicted PEFR at 8 to 36 hours after initial treatment.

Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β 2-agonists versus β 2-agonists alone

Outcome: 7 Percentages of predicted PEFR at 8 to 36 hours after initial treatment

Study or subgroup	AC + β 2-agonists N	Mean(SD)	β 2-agonists alone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Rayner 1987	8	70.4 (18.38)	12	72 (15.93)		-1.60 [-17.20, 14.00]



Analysis 1.8. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 8 Adverse health effects.

Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β_2-agonists versus β_2-agonists alone

Outcome: 8 Adverse health effects

Study or subgroup	AC + β_2-agonists n/N	β_2-agonists alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Craven 2001	0/104	0/106			Not estimable
Goggin 2001	0/41	0/39			Not estimable
Total (95% CI)	**145**	**145**			**Not estimable**

Total events: 0 (AC + β_2-agonists), 0 (β_2-agonists alone)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 9 Overall withdrawals.

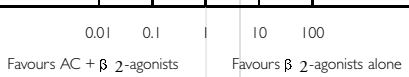
Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β_2-agonists versus β_2-agonists alone

Outcome: 9 Overall withdrawals

Study or subgroup	AC + β_2-agonists n/N	β_2-agonists alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Craven 2001	10/104	15/106		82.1 %	0.65 [0.28, 1.51]
Goggin 2001	1/42	3/42		17.9 %	0.32 [0.03, 3.18]
Total (95% CI)	**146**	**148**		**100.0 %**	**0.59 [0.27, 1.30]**

Total events: 11 (AC + β_2-agonists), 18 (β_2-agonists alone)
Heterogeneity: Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

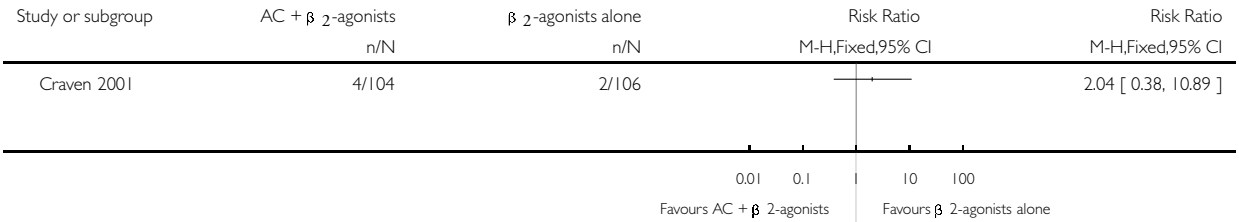


Analysis 1.10. Comparison 1 Combination of anticholinergics (AC) + β2-agonists versus β2-agonists alone, Outcome 10 Withdrawals due to deterioration.

Review: Inhaled anticholinergics and short-acting beta$_2$-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital

Comparison: 1 Combination of anticholinergics (AC) + β 2-agonists versus β 2-agonists alone

Outcome: 10 Withdrawals due to deterioration



ADDITIONAL TABLES

Table 1. Intensity of anticholinergic treatment

Studies	Anticholinergic treatment
Craven 2001	250 μg of ipratropium bromide by jet nebulisation every 4 hours during phase I, every 6 hours during phase II and every 8 hours during phase III of the ACA
Goggin 2001	Nebulised ipratropium bromide inhalation solution 1.0 mL (250 μg) every half an hour to 1 hour at the beginning, progressing to 2 hours and then to 4 hours as the patient improves clinically
Lew 1990	An inhalation of 0.1% atropine sulfate (0.05 mg/kg up to 2 mg in total) at baseline or 4 hours later depending on randomisation
Rayner 1987	Nebulised ipratropium 250 μg 30 minutes after the first dose of salbutamol and every 8 hours afterwards
Storr 1986	Nebuliser with 250 μg ipratropium bromide given within set limits at the discretion of the nursing staff

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy for Cochrane Airways Group Register of trials

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 ipratropium*
#6 MeSH DESCRIPTOR Ipratropium
#7 MeSH DESCRIPTOR Atropine
#8 atropine*
#9 anticholinergic*
#10 anti-cholinergic*
#11 anti* NEXT cholinergic*
#12 MeSH DESCRIPTOR Cholinergic Antagonists Explode All
#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 in-patient* or inpatient or "in patient"

#15 hospital*
#16 #14 or #15
#17 #4 and #13 and #16
#18 MeSH DESCRIPTOR Child Explode All
#19 MeSH DESCRIPTOR Pediatrics Explode All
#20 MeSH DESCRIPTOR Infant
#21 MeSH DESCRIPTOR Adolescent
#22 paediatric* or paediatric* or child* or adolescen* or infant* or young* or preschool* or pre-school* or newborn* or new-born* or neonat* or neo-nat*
#23 #18 or #19 or #20 or #21 or #22
#24 #17 and #23
[Note: MISC1 denotes the field in the Register where the trial report has been coded for condition, i.e. AST=asthma]

CONTRIBUTIONS OF AUTHORS

Kevin Vézina wrote the protocol, screened abstracts, selected and ascertained the methodological quality of and extracted data from included studies, conducted the analysis and wrote the first draft of the review.

Bhupendrasinh Chauhan contributed to development of the protocol, abstract selection and study selection, ascertainment of methodological quality and data extraction and reviewed all drafts of the manuscript, responded to reviewers' comments and approved the final manuscript.

Francine M. Ducharme supervised the overall process, approved the protocol, contacted trial authors, interpreted data and approved the final manuscript.

DECLARATIONS OF INTEREST

Kevin Vézina: none known.

Bhupendrasinh Chuhan received a postdoctoral scholarship through one of Dr Ducharme's grants from the Canadian Institute of Health Research and reports no conflicts of interest.

Francine M Ducharme has received travel support, research funds and fees for speaking from GlaxoSmithKline, Novartis, Nycomed and/or Merck Frosst Inc.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review.

In the protocol, under Methods, Selection of studies, we had planned the involvement of 2 reviewers in the selection of studies, however only one reviewer performed this task.

In the protocol, we has planned to perform a sensitivity analysis to explore the impact of excluding trials with missing outcomes to evaluate the risk of bias. However due to low number of included trials, we did not perform the sensitivity analysis.

In the protocol, we had mentioned: "we will create a summary of findings table using the two primary outcomes and the following secondary outcomes: duration of stay in ICU; admission to the ICU; adverse effects; change from baseline in lung function." However, as no included trial reported data on the one of two primary outcomes (serious adverse events); no trials included patients admitted to the ICU and consequently no data was available for duration of ICU stay; and only one included trial reported lung function (PEFR), we did not include these outcomes in the Summary of findings table. We thus reported on the primary outcome (duration of hospital stay), and other relevant outcomes namely, time to rescue inhaled short-acting ß$_2$-agonists, asthma score and withdrawals.