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Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma (Review)

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TABLE OF CONTENTS

[Intervention Review]

Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma

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ABSTRACT

Background

Inhaled short-acting anticholinergics (SAAC) and short-acting beta$_2$-agonists (SABA) are effective therapies for adult patients with acute asthma who present to the emergency department (ED). It is unclear, however, whether the combination of SAAC and SABA treatment is more effective in reducing hospitalisations compared to treatment with SABA alone.

Objectives

To conduct an up-to-date systematic search and meta-analysis on the effectiveness of combined inhaled therapy (SAAC + SABA agents) vs. SABA alone to reduce hospitalisations in adult patients presenting to the ED with an exacerbation of asthma.

Search methods

We searched MEDLINE, Embase, CINAHL, SCOPUS, LILACS, ProQuest Dissertations & Theses Global and evidence-based medicine (EBM) databases using controlled vocabulary, natural language terms, and a variety of specific and general terms for inhaled SAAC and SABA drugs. The search spanned from 1946 to July 2015. The Cochrane Airways Group provided search results from the Cochrane Airways Group Register of Trials which was most recently conducted in July 2016. An extensive search of the grey literature was completed to identify any other potentially relevant studies.

Selection criteria

Included studies were randomised or controlled clinical trials comparing the effectiveness of combined inhaled therapy (SAAC and SABA) to SABA treatment alone to prevent hospitalisations in adults with acute asthma in the emergency department. Two independent review authors assessed studies for inclusion using pre-determined criteria.

Data collection and analysis

For dichotomous outcomes, we calculated individual and pooled statistics as risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI) using a random-effects model and reporting heterogeneity (I^2). For continuous outcomes, we reported individual trial results using mean differences (MD) and pooled results as weighted mean differences (WMD) or standardised mean differences (SMD) with 95% CIs using a random-effects model.

Main results

We included 23 studies that involved a total of 2724 enrolled participants. Most studies were rated at unclear or high risk of bias.

Overall, participants receiving combination inhaled therapy were less likely to be hospitalised (RR 0.72, 95% CI 0.59 to 0.87; participants = 2120; studies = 16; I^2 = 12%; moderate quality of evidence). An estimated 65 fewer patients per 1000 would require hospitalisation after receiving combination therapy (95% 30 to 95), compared to 231 per 1000 patients receiving SABA alone. Although combination inhaled therapy was more effective than SABA treatment alone in reducing hospitalisation in participants with severe asthma exacerbations, this was not found for participants with mild or moderate exacerbations (test for difference between subgroups P = 0.02).

Participants receiving combination therapy were more likely to experience improved forced expiratory volume in one second (FEV_1) (MD 0.25 L, 95% CI 0.02 to 0.48; participants = 687; studies = 6; I^2 = 70%; low quality of evidence), peak expiratory flow (PEF) (MD 36.58 L/min, 95% CI 23.07 to 50.09; participants = 1056; studies = 12; I^2 = 25%; very low quality of evidence), increased percent change in PEF from baseline (MD 24.88, 95% CI 14.83 to 34.93; participants = 551; studies = 7; I^2 = 23%; moderate quality of evidence), and were less likely to return to the ED for additional care (RR 0.80, 95% CI 0.66 to 0.98; participants = 1180; studies = 5; I^2 = 0%; moderate quality of evidence) than participants receiving SABA alone.

Participants receiving combination inhaled therapy were more likely to experience adverse events than those treated with SABA agents alone (OR 2.03, 95% CI 1.28 to 3.20; participants = 1392; studies = 11; I^2 = 14%; moderate quality of evidence). Among patients receiving combination therapy, 103 per 1000 were likely to report adverse events (95% 31 to 195 more) compared to 131 per 1000 patients receiving SABA alone.

Authors' conclusions

Overall, combination inhaled therapy with SAAC and SABA reduced hospitalisation and improved pulmonary function in adults presenting to the ED with acute asthma. In particular, combination inhaled therapy was more effective in preventing hospitalisation in adults with severe asthma exacerbations who are at increased risk of hospitalisation, compared to those with mild-moderate exacerbations, who were at a lower risk to be hospitalised. A single dose of combination therapy and multiple doses both showed reductions in the risk of hospitalisation among adults with acute asthma. However, adults receiving combination therapy were more likely to experience adverse events, such as tremor, agitation, and palpitations, compared to patients receiving SABA alone.

PLAIN LANGUAGE SUMMARY

Combined beta-agonists and anticholinergics compared to beta-agonists alone for adults with asthma treated in emergency departments

Review question

We looked at if combined treatment of short-acting beta-agonists and anticholinergics were more effective to improve outcomes in adults with asthma who were treated in emergency departments compared to treatment with beta-agonists alone.

Background

Asthma attacks result from airway passages to the lungs becoming constricted due to inflammation, resulting in wheezing, coughing, and difficulty breathing. People experiencing asthma attacks often go to emergency departments, and are usually treated using short-acting inhaled beta-agonists, although some patients may be treated with short-acting inhaled anticholinergics.

Some research looks at whether treating people with asthma in emergency departments with a combination of beta-agonists and anticholinergics is more effective than beta-agonists alone.

Search date

The search was current to July 2016.

Study characteristics

We included 23 studies that compared the effectiveness of combined treatment with beta-agonists and anticholinergics versus treatment with beta-agonists alone. A total of 2724 adult participants were enrolled in the studies. Salbutamol (also called albuterol) was the most common beta-agonist investigated and ipratropium bromide was the most common anticholinergic assessed.

Study fundin g sources

We found that most studies did not report sources of funding (14 studies); one study was supported by a hospital; another received support from a pharmaceutical company, but indicated that there was no involvement from the company in conducting or reporting research. Two studies were part-funded and four were funded by pharmaceutical companies.

Key results

Patients with severe asthma who received combined treatment of beta-agonists and anticholinergics were less likely to be admitted to hospital. An estimated 65 fewer patients per 1000 would require hospital admission after receiving combined inhaled therapy in the

emergency department. Among patients with mild -to-moderate asthma, combined inhaled therapy was less effective in preventing admission to hospital compared with people with severe asthma. Patients receiving combined treatment were less likely to return to the emergency department with worsening asthma symptoms and had better outcomes in most lung function tests. On the other hand, 103 more participants per 1000 who receive combined inhaled therapy would experience side effects compared to people who receive beta-agonists alone.

Quality of the evidence

Quality of the evidence that combination inhaled therapy can improve health outcomes compared to treatment with beta-agonists alone ranged from very low to moderate. Our confidence about the effects of combination inhaled therapy on hospital admissions, peak expiratory flow, percent change in peak expiratory flow from baseline, and relapse was moderate because of the overall risk of bias among included studies. Factors associated with inconsistency and imprecision were additional aspects that reduced the quality of the evidence for forced expiratory volume in one second, and percent predicted peak expiratory flow.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Combination inhaled therapy compared with SABA alone for acute asthma

Combination inhaled therapy compared with SABA alone for acute asthma

Patient or population: Adults with acute asthma

Intervention: Combined inhaled therapy (SAAC + SABA)

Comparison: SABA alone

Settings: Emergency Department

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with SABA alone	Risk difference with combination therapy			
Hospitalisation	231 per 1000	65 fewer per 1000 (from 30 fewer to 95 fewer)	**RR 0.72** (0.59 to 0.86)	2120 (16 studies)	⊕⊕⊕⊖ **moderate** [1]
Total adverse events	131 per 1000	103 more per 1000 (from 31 more to 195 more)	**OR 2.03** (1.28 to 3.20)	1392 (11 studies)	⊕⊕⊕⊖ **moderate** [2]
FEV_1	Control group range 1.36 to 2.4 Litres	MD 0.25 higher (0.02 to 0.48 higher)		687 (6 studies)	⊕⊕⊖⊖ **low** [1,3]
Percent change FEV_1(%)	Control group range 32 to 106%	MD 21.28 higher (5.62 lower to 48.18 higher)		578 (5 studies)	⊕⊖⊖⊖ **very low** [1,3,4]
Peak expiratory flow (PEF)	Control group range 190 to 313 litres/min	MD 36.58 higher (23.07 to 50.09 higher)		1056 (12 studies)	⊕⊕⊕⊖ **moderate** [1]
Percent change from baseline PEF (%)	Control group range 32 to 82%	MD 24.88 higher (14.83 to 34.93 higher)		551 (7 studies)	⊕⊕⊕⊖ **moderate** [1]
Relapse rates	250 per 1000	50 fewer per 1000 (from 5 fewer to 85 fewer)	**RR 0.8** (0.66 to 0.98)	1180 (5 studies)	⊕⊕⊕⊖ **moderate** [1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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; **RR:** Risk Ratio; **OR:** Odds Ratio; **MD**: Mean Difference

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] Most studies had an overall unclear of high risk of bias. Methods of randomisation or blinding were frequently unclear.
[2] Potential selective reporting bias. Several studies did not report adverse events that enabled inclusion in the meta-analysis.
[3] Inconsistency. Large differences in effects between studies.
[4] Imprecision around the pooled effect including both benefit, harm, and no effect.

BACKGROUND

Description of the condition

Acute asthma is a common cause for visits to the emergency department (ED). Although most people with acute asthma are safely discharged home, some require admission to hospital for continued care. Of those presenting to an ED for acute asthma, approximately 11% (Hasegawa 2013) to 13% (Rowe 2010) were hospitalised in Japan and Canada respectively. The percentage of people who reported being hospitalised for asthma in the previous year ranged from 7% in Europe (Rabe 2000), 9% in the United States (Adams 2002), 15% in the Asia-Pacific region (Lai 2003) and 22% in Latin America (Neffen 2005). The direct costs (including prescriptions, hospitalisations, clinic and ED visits) for asthma in the United States are approximately USD 5.1 billion (Smith 1997), while in Canada, direct costs were approximately CAD 306 million (Krahn 1996). In Europe the estimated total costs of asthma are approximately EUR 17.7 billion (Braman 2006).

Description of the intervention

Generally, adults presenting to the ED with acute asthma are treated with inhaled bronchodilators. There are two inhaled bronchodilators which have been proven to be particularly effective in reducing airway bronchospasm: short-acting anticholinergics (SAAC; Aaron 2001) and short-acting beta$_2$ -agonists (SABA; Price 1989). While SABA agents have become the first-line treatment for people with acute asthma, some researchers have examined if there could be a synergistic effect in combining SAAC with SABA to improve important outcomes, such as improvements in pulmonary function, reduced hospitalisations, and improved quality of life.

How the intervention might work

The combination of inhaled SAAC and SABA agents potentially improves pulmonary function because each has a different mechanism of action designed to reduce airway bronchospasm. While SABA agents are known for their strong bronchodilating effect through their effect on airway smooth muscle and quick onset of action, SAAC agents act through different receptors, reduce airway secretions, and are weaker bronchodilators. Although SAAC agents have a slower onset of action, they are longer-acting (Lanes 1998; Rebuck 1987). The combination of inhaled SAAC and SABA agents may provide prolonged and enhanced bronchodilation, and reduce need for hospitalisation compared to traditional treatment with SABA agents alone. Indeed, Rebuck 1987, found that one-second forced expiratory volume (FEV_1) was significantly improved among patients receiving combined inhaled therapy of SAAC and SABA agents than those receiving either SAAC or SABA agents alone. Additional studies suggest that combination inhaled therapy may provide greater improvements in pulmonary function than treatment with SABA agents alone (Garrett 1997; Lin 1998; Nakano 2000; Rodrigo 2000).

Why it is important to do this review

Although some evidence supports the use of combination inhaled therapy, some studies found no significant difference between combination inhaled therapy or SABA alone in changes to pulmonary function or hospitalisation (Cydulka 2010; FitzGerald 1997; Salo 2006; Weber 1999). Accordingly, some reviews have attempted to pool and summarise the available evidence. A Cochrane review that considered children with acute asthma found combination inhaled therapy reduced the risk of hospitalisation, improved pulmonary function, and reduced the risk of adverse events (Griffiths 2013). With regard to adults with acute asthma, a pooled analysis of three studies reported a small benefit from combination inhaled therapy to improve pulmonary function and reduce risk of hospitalisation (Lanes 1998). Similarily, a systematic review of 16 studies found that combination inhaled therapy reduced hospitalisation and improved pulmonary function in adults with asthma (Rodrigo 2005). However, it is important to note that Rodrigo 2005 included studies that assessed patients either in the ED or hospital, as well as studies that provided patients with either long-acting anticholinergics (LAAC) or SAAC agents as part of the combination inhaled therapy.

Since 2005, there have been several studies (Cydulka 2010; Hossain 2013; Salo 2006) which may impact the results of earlier systematic reviews. We found sufficient new evidence on the use of combination inhaled therapy (SAAC + SABA agents) vs. SABA alone for the treatment of acute asthma to indicate that a Cochrane review was necessary. The aim of this Cochrane review was to provide patients and healthcare professionals with current evidence to inform updating asthma guidelines on the use of combination inhaled therapy for adults in the ED.

OBJECTIVES

To conduct an up-to-date systematic search and meta-analysis on the effectiveness of combined inhaled therapy (SAAC + SABA agents) vs. SABA alone to reduce hospitalisations in adult patients presenting to the ED with an exacerbation of asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Only prospective randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing the effectiveness of combined inhaled therapy of short-acting anticholinergics (SAAC) and short-acting beta$_2$-agonists (SABA) vs. treatment with SABA alone in the emergency department (ED) were eligible for inclusion.

Types of participants

Studies including adult (aged ≥ 16 years) participants presenting to an ED or other equivalent acute care setting with an uncomplicated exacerbation of asthma were considered for inclusion in this review. The asthma diagnosis needed to have been made using international or national clinical criteria or spirometric assessment results or both. Studies involving children or patients already admitted to hospital were excluded. Studies that enrolled participants with either chronic obstructive pulmonary disease (COPD) or asthma were included only if COPD participants made up fewer than 20% of the total participant population, or if outcome data from the asthma only participants could be extracted for analysis. Outcomes that included more than 20% of COPD participants were not extracted for this review.

Types of interventions

Participants received either single or repeated doses of inhaled or nebulised SAAC agents either alongside or combined with SABA agents. Control group participants received SABA agents with or

without placebo. Studies examining long-acting anticholinergic (LAAC) agents, such as tiotropium, glycopyrrolate, or aclidinium bromide, were excluded. There were no limitations on co-interventions participants with acute asthma could receive while being managed in the ED or at discharge, including additional treatments such as beta$_2$-agonists, corticosteroids, theophylline compounds, and antihistamines. There were no limitations on inclusion based on types of interventions patients could have received before presenting to the ED. Co-interventions provided are reported in Characteristics of included studies tables..

Types of outcome measures

Primary outcomes

The primary dichotomous outcome included:

- the proportion of participants requiring hospitalisation.

Hospitalisation was defined as a decision by the treating physician to continue to provide continuing asthma care in an inpatient setting. Asthma severity, receiving corticosteroids as co-interventions, and single or multiple doses of combination inhaled therapy were considered for subgroup analysis. We performed as reported and worst-case scenario intention-to-treat (ITT) analyses. For worst-case scenario ITT, withdrawals from the study by the participant or attending physician due to a lack of improvement after receiving treatment were considered to have been hospitalised.

Secondary outcomes

We assessed the following secondary outcomes for this review:

- ED length of stay;
- adverse events;
- continuous data from pulmonary function testing (including: percent change of forced expiratory volume in one second (FEV_1), and percent predicted FEV_1, peak expiratory flow (PEF), percent change from baseline PEF, percent predicted PEF);
- symptom scores;
- quality of life;
- number of additional bronchodilator treatments required; and
- relapse proportions.

Search methods for identification of studies

Electronic searches

We conducted a systematic search of bibliographic databases: MEDLINE (Appendix 1), Embase (Appendix 2), CINAHL (Appendix 3), SCOPUS (Appendix 4), LILACS (Appendix 5), ProQuest Dissertations and Theses Global (Appendix 6) and evidence-based medicine (EBM) reviews sources (Appendix 7). These included: Cochrane Database of Systematic Reviews (2005 to July 2015), ACP Journal Club (1991 to July 2015), Database of Abstracts of Reviews of Effects (DARE) (second quarter 2015), Cochrane Central Register of Controlled Trials (CENTRAL) (June 2015), Cochrane Methodology Register (third quarter 2012), Health Technology Assessment (second quarter 2015), and NHS Economic Evaluation Database (second quarter 2015). This search spanned from 1946 to July 2015. We also searched the Cochrane Airways Group register of trials which was most recently conducted on July 2016 (Appendix 8).

Search terms were adapted for each database using controlled vocabulary (e.g. MESH, EMTREE, etc.) and natural language terms and a variety of specific and general terms for beta$_2$-agonists and short-acting anticholinergic drugs. Searches in MEDLINE and Embase were restricted to adult populations. No other limits were applied including year of publication or language. Articles published in languages other than English and unpublished articles were included. We sought translation of studies by fluent bilingual speakers, but if this could not occur, articles were translated using Google Translate.

Searching other resources

The search of the grey literature for additional studies included:

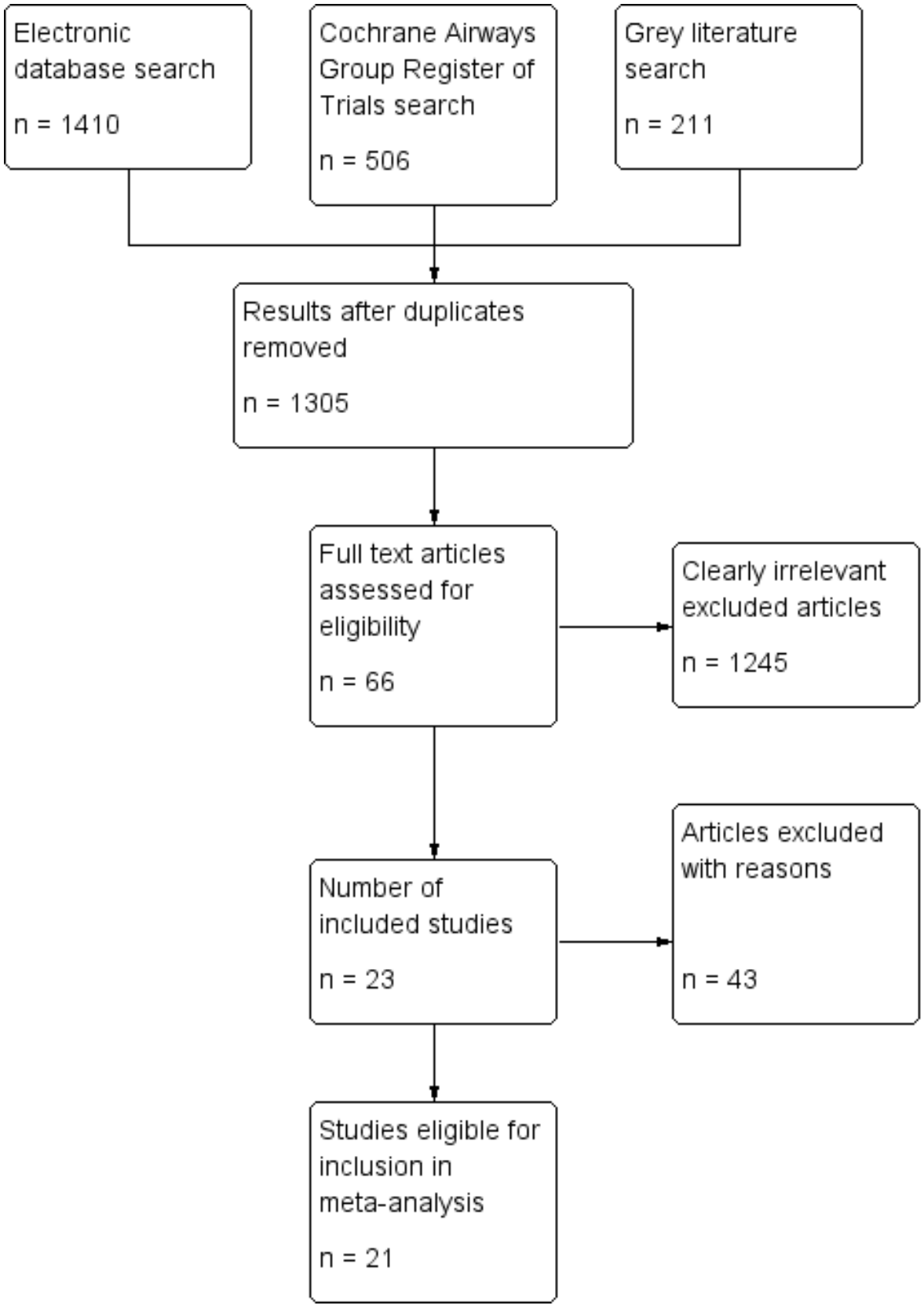
- clinical trial registries (Cochrane Central Register of Controlled Trials, controlled-trials.com and ClinicalTrials.gov);
- Google Scholar;
- reference lists of included studies and reviews;
- SCOPUS forward search of a sentinel paper (Rebuck 1987); and
- Hand-searches of the most recent emergency medicine conference abstracts associated with Canadian (Canadian Association of Emergency Physicians; *Canadian Journal of Emergency Medicine, 2008 to 2016)*, US (American College of Emergency Physicians; *Annals of Emergency Medicine, 2008 to 2015*) and international (Society for Academic Emergency Medicine; *Academic Emergency Medicine, 2008 to 2016*) emergency medicine research meetings.

Data collection and analysis

Selection of studies

At least two independent review authors (CV, AD, BV, RC, TN, SWK) identified potentially relevant studies of citations by assessing titles, abstracts and MESH terms. Once identified, the full text of potentially relevant studies were assessed using pre-defined inclusion and exclusion criteria by at least two independent review authors (TN, AD, RC, BV, SWK). Disagreements were resolved and discussed using third party adjudication (BHR) to achieve consensus. (Figure 1).

Figure 1. Study flow diagram



Data extraction and management

Data were extracted independently by at least two review authors (TN, AD, RC, BV, SWK) into a standardised form to collate information about participants, methods, interventions, outcomes, and adverse events provided in the articles. Data were verified (SWK) to ensure accuracy of the extraction process. Discrepancies were resolved by discussion and confirmation of the results from the text of the articles. Attempts were made to contact all primary authors for clarification of any missing or unclear data and to inquire if they could provide original study data.

Assessment of risk of bias in included studies

Quality assessment of included studies was completed using Cochrane's risk of bias (RoB) assessment tool (Higgins 2011). Two independent review authors (SWK, CV, BV) assessed seven different categories of bias including:

1. Sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessors;
5. Incorporation of outcome data (attrition and exclusions);
6. Selective reporting; and
7. Other potential sources of bias.

Disagreements were resolved and discussed by third party adjudication (BHR) to achieve consensus.

Measures of treatment effect

For dichotomous variables, individual and pooled statistics were calculated as risk ratios (RR) with 95% confidence intervals (CI) using a random-effects model. For clinically rare dichotomous events, such as adverse events, odds ratios (OR) were calculated with 95% CI using a random-effects model. A random-effects model was chosen over fixed-effect because it was assumed that the intervention effect would vary among included studies due to factors other than the intervention due to heterogeneity in study methodology, participant characteristics, co-interventions and interventions received. For continuous outcomes, individual trial results were reported using mean differences (MD) and pooled results as weighted mean differences (WMD) or standardised mean differences (SMD) with 95% CIs using a random-effects model. The weights given to each study in the pooled analysis were based on the inverse variance method.

Unit of analysis issues

The unit of analysis was the participants in the included studies.

Dealing with missing data

We attempted to contact study authors to obtain missing or unclear data. If a study did not provide values for standard deviation, and attempts to retrieve the original data from study authors were unsuccessful, imputation was employed or standard deviation estimated from figures using GraphClick software (Version 3.0; Arizona Software, San Francisco, United States).

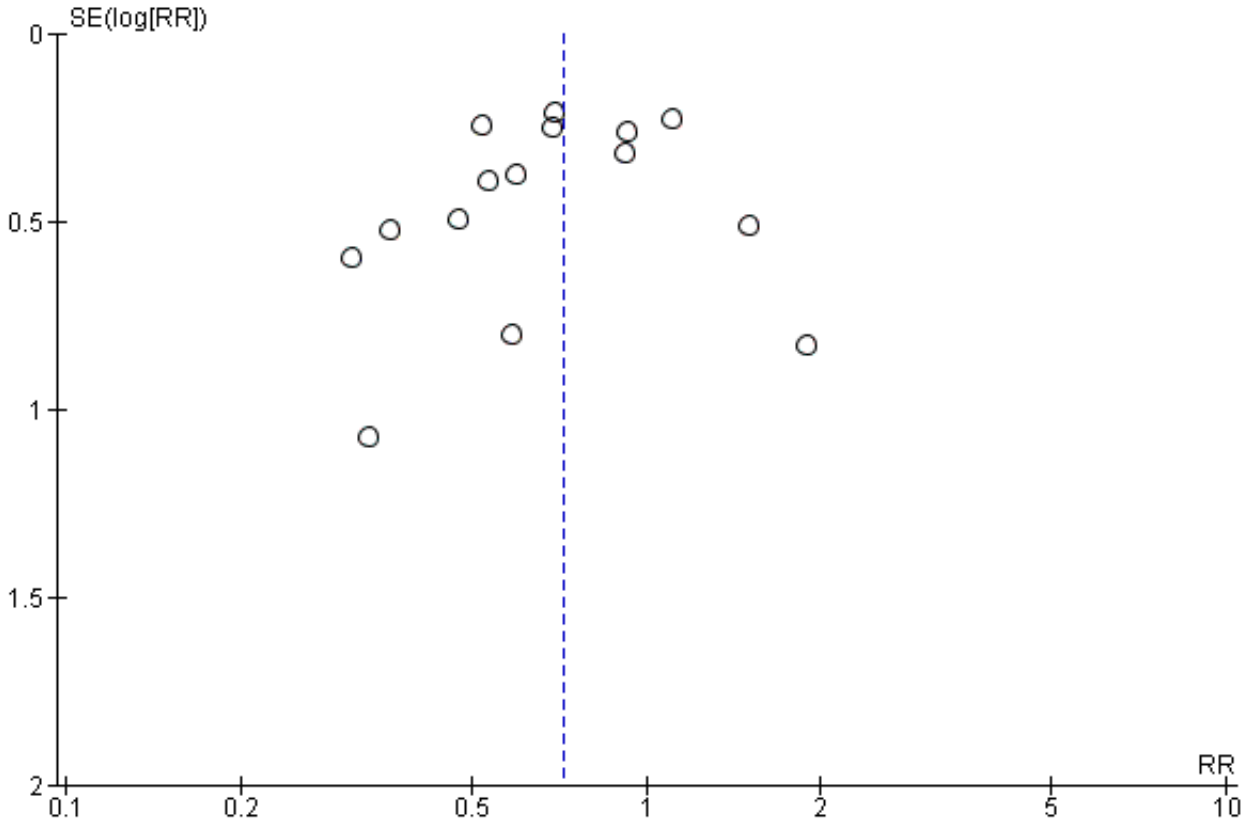
Assessment of heterogeneity

Heterogeneity was assessed visually, methodologically, and statistically (using Chi^2 and I^2 statistics). The I^2 values of 25%, 50% and 75% were assessed to represent low, moderate, and high degrees of heterogeneity, respectively (Higgins 2011). Heterogeneity was assessed using I^2 in RevMan (RevMan 2014).

Assessment of reporting biases

A funnel plot of the primary outcome was created to assess publication bias using RevMan 2014 (Figure 2).

Figure 2. Funnel plot of comparison: 1 Hosptialisation rates, outcome: 1.1 Hospitalisation rates



Data synthesis

Data were extracted by review authors (TN, AD, RC, BV) and checked for reliability (SWK). Studies were pooled only if they represented similar populations, outcomes, and designs, and the review authors judged that clinical heterogeneity was sufficiently low. The PRISMA checklist was used to ensure that standard outcomes were reported (Moher 2009). Statistical analyses were performed using RevMan 2014. We compiled a summary of findings table for outcomes including hospitalisations, adverse events, PEF, percent change from baseline PEF (%), FEV_1, percent change FEV_1 (%), and relapse using GRADEpro (GRADEpro 2014) (Summary of findings for the main comparison). The quality of the primary outcome and important secondary outcomes were assessed using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) based on the criteria developed by the GRADE Working Group (GRADE Working Group 2004). The quality of the evidence was either upgraded or downgraded based on the following criteria:

- Limitations in study design or execution (risk of bias);
- Inconsistency of results;
- Indirectness of evidence;
- Imprecision; and
- Publication bias.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analysis was established a priori to examine the effects of single vs. multiple doses of combination inhaled therapy, exacerbation severity (mild, moderate, severe), co-interventions with corticosteroids (received/did not receive corticosteroids in the ED), and type of SAAC used (ipratropium bromide vs. other SAAC) on heterogeneity.

Sensitivity analysis

Planned sensitivity testing included study quality (studies with an overall low vs. unclear vs. high risk of bias) and use of random-effects vs. fixed-effect models.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The literature search identified a total of 2127 records (see Figure 1). There were 1305 records following removal of duplicates. Following assessment based on titles and abstracts, we identified 66 potentially relevant studies that were obtained in full-text. Following assessment we excluded 43 studies. We included 23 studies in this review. Two included studies were available only as abstracts, and did not include data that could be extracted for meta-analysis (Canete 1991; Rahman 2006). Attempts to retrieve original data were unsuccessful, and as a result, the review included outcome data from 21 studies. Five included studies were exclusive to the search of the Cochrane Airways Group's Register of Trials

(Canete 1991; Hossain 2013; Kohistani 2007; Rahman 2006; Rashid 2010). Solarte 2004 was identified from a search of the grey literature. Two articles were translated from Spanish (Canete 1991; Rodrigo 1995). A funnel plot based on the primary hospitalisation outcome did not show obvious publication bias (Figure 2).

Included studies

Design

Most included studies (n = 19) were published as journal articles; four were available only as abstracts (Canete 1991; Rahman 2006; Rashid 2010; Solarte 2004). All included studies reported prospective RCTs or CCTs.

Participants

The included studies enrolled a total of 2724 adult participants with acute asthma presenting to the ED. Five included studies were conducted in South Asia: India (Aggarwal 2002), Bangladesh (Hossain 2013; Rahman 2006; Rashid 2010), and Pakistan (Kohistani 2007). The remaining studies were conducted in Australia (Summers 1990), Canada (FitzGerald 1997; Rebuck 1987), Colombia (Solarte 2004), Japan (Kamei 1999; Nakano 2000), New Zealand (Garrett 1997), Spain (Canete 1991), United Kingdom (O'Driscoll 1989), United States (Cydulka 2010; Diaz 1997; Karpel 1996; Lin 1998; Owens 1991; Salo 2006; Weber 1999) and Uruguay (Rodrigo 1995; Rodrigo 2000). Two studies (O'Driscoll 1989; Rebuck 1987) included both asthma and COPD patients. Although people with the COPD made up more than 20% of the total patient population both O'Driscoll 1989 and Rebuck 1987 reported data on pulmonary function for only adult patients. The occurrence of other outcomes, such as hospitalisation and adverse events, was not provided. Attempts to contact the study authors to obtain additional data for the asthma population were unsuccessful, and as a result, only results for pulmonary function could be included in the meta-analysis.

Only three studies classified the severity of asthma exacerbations among participants (Cydulka 2010; Nakano 2000; Rodrigo 1995). An attempt was made to estimate and categorise exacerbation severity among the included studies based on the pulmonary function eligibility criteria established by the study, in addition to the percentage of patients hospitalised in the SABA alone group, as developed and reported in a previous review (Rowe 2000a; Rowe 2000b). If studies reported forced expiatory volume in one second (FEV_1) or peak expiratory flow (PEF) of less than 50% predicted, the overall severity of acute asthma among participants was considered to be severe (Cydulka 2010; Nakano 2000; Rodrigo 2000). Studies reporting FEV_1 or PEF of less than 70%, or a peak expiratory flow rate (PEFR) of less than 200 L/minute, were estimated to have an overall exacerbation severity of mild, moderate, or severe based on the proportion of participants who were hospitalised. A percentage of hospitalisations of less than 10%, between 10% and 30%, and over 30% in the comparison groups were used to estimate the overall exacerbation severity of participants as mild (Kamei 1999), moderate (Diaz 1997; FitzGerald 1997; Garrett 1997; Karpel 1996; Owens 1991; Salo 2006; Solarte 2004), or severe (Kohistani 2007; Lin 1998; Rodrigo 1995; Weber 1999) (Table 1). If studies did not report an eligibility criterion based on pulmonary function, then the overall estimate of acute asthma severity was based on the proportions of participants hospitalised in the SABA alone group and classified as either mild (Aggarwal 2002) or moderate (Diaz 1997; Solarte 2004).

Interventions

All included studies compared combined inhaled therapy of SAAC with SABA vs. SABA treatment alone provided in the ED. Most included studies (n = 19) provided participants with ipratropium bromide as the SAAC agent (Aggarwal 2002; Canete 1991; Cydulka 2010; FitzGerald 1997; Garrett 1997; Hossain 2013; Karpel 1996; Kohistani 2007; Lin 1998; O'Driscoll 1989; Rahman 2006; Rashid 2010; Rebuck 1987; Rodrigo 1995; Rodrigo 2000; Salo 2006; Solarte 2004; Summers 1990; Weber 1999). Four studies used either atropine sulphate (Diaz 1997; Owens 1991) or oxitropium bromide (Kamei 1999; Nakano 2000).

Salbutamol (albuterol) was the most commonly-used SABA agent (Aggarwal 2002; Canete 1991; Diaz 1997; FitzGerald 1997; Garrett 1997; Hossain 2013; Karpel 1996; Kohistani 2007; Lin 1998; Nakano 2000; O'Driscoll 1989; Rahman 2006; Rashid 2010; Rodrigo 1995; Rodrigo 2000; Salo 2006; Solarte 2004; Summers 1990; Weber 1999). Other SABA agents used were levabuterol (Cydulka 2010), fenoterol (Kamei 1999; Rebuck 1987), and metaproterenol (Owens 1991). Most studies administered the interventions via nebulisers; seven studies used a metered-dose inhaler (MDI) and spacer devices (Canete 1991; Kamei 1999; Nakano 2000; Rahman 2006; Rashid 2010; Rodrigo 1995; Rodrigo 2000).

We included 12 studies that administered multiple doses of the drugs, including five puffs (Kamei 1999) four puffs (Nakano 2000; Rahman 2006; Rashid 2010; Rodrigo 1995; Rodrigo 2000), three puffs (Cydulka 2010; Hossain 2013; Solarte 2004), or two puffs (Diaz 1997; Karpel 1996). Canete 1991 did not specify the total number of puffs participants received.

There were 12 studies that administered a single dose of combined inhaled therapy (Aggarwal 2002; Diaz 1997; FitzGerald 1997; Garrett 1997; Kohistani 2007; Lin 1998; O'Driscoll 1989; Owens 1991; Rebuck 1987; Salo 2006; Summers 1990; Weber 1999). Diaz 1997 compared the effectiveness of single vs. multiple doses of combination inhaled therapy to SABA monotherapy. Two studies provided a single continuous dose of combined inhaled therapy or SABA agents alone for a two (Salo 2006) or three (Weber 1999) hour period.

Outcomes

Hospitalisation was assessed in 15 of the 23 included studies (Aggarwal 2002; Cydulka 2010; Diaz 1997; FitzGerald 1997; Garrett 1997; Kamei 1999; Karpel 1996; Kohistani 2007; Lin 1998; Nakano 2000; Owens 1991; Rodrigo 2000; Salo 2006; Solarte 2004; Weber 1999). Criteria for hospitalisation were defined in only five studies (Diaz 1997; Kohistani 2007; Lin 1998; Nakano 2000; Weber 1999) (Table 2).

The total number of participants reporting adverse events was commonly reported, although several studies reported non-significant differences in the occurrence of adverse events between groups and did not include any data which could be extracted. The frequency of particular adverse events including dry mouth, tremor, anxiety, palpitations, nausea, headache, blurred vision, agitation, and chest retractions, were inconsistently reported across studies, resulting in limited analysis of specific adverse events.

Meaningful analysis of proposed secondary outcomes including ED length of stay, symptom scores, and quality of life could not

be completed as planned due to a lack of available data. Only one study reported on ED length of stay (Weber 1999). No studies reported symptoms scores or quality of life. Pulmonary function results were reported in most studies; however, the measures used to assess pulmonary function (PEF, FEV_1) differed. The final assessment of pulmonary function after the administration of study medications in all included studies was used in the meta-analysis. Only studies that reported percent change in PEF from baseline to the last PEF value taken after treatment were extracted and included in the analysis.

Relapse and need for additional bronchodilator treatment in the ED were assessed in five (Cydulka 2010; FitzGerald 1997; Garrett 1997; Karpel 1996; Weber 1999) and four (Aggarwal 2002; Karpel 1996; Nakano 2000; Owens 1991) studies, respectively. Two studies reported relapse as a return to a healthcare provider within 24 hours after discharge (Karpel 1996; Weber 1999); two other studies assessed relapse within two weeks after discharge (Cydulka 2010; FitzGerald 1997).

No studies reported any participant deaths.

Supplemental information for Rashid 2010, was retrieved from another abstract that presented the same data (Rashid 2012). Supplemental data on relapse and hospitalisations for three studies (FitzGerald 1997; Garrett 1997; Karpel 1996) were retrieved from a previously published pooled analysis (Lanes 1998), and the proportion of patients who were hospitalised in Rodrigo 1995 was retrieved from a later systematic review (Rodrigo 2005). In several cases, standard deviation was estimated from standard error or confidence intervals (FitzGerald 1997; Garrett 1997; Kamei 1999; Owens 1991; Rodrigo 2000; Summers 1990; Weber 1999) or from a figure (O'Driscoll 1989). In two cases, pulmonary function data were not provided in the text, and were estimated from figures using GraphClick software (Kamei 1999; Nakano 2000).

Co-interventions

Most studies provided participants with additional treatments during their stay in the ED (see Characteristics of included studies). Five studies did not state whether participants were provided with co-interventions in the ED (Kohistani 2007; Owens 1991; Rahman 2006; Rashid 2010; Solarte 2004). Co-interventions varied, but frequently included oxygen and intravenous (IV) aminophylline. No studies reported on whether patients received long-acting anticholinergics or beta-agonists as a co-intervention in the ED or at discharge. Oral (Cydulka 2010; Lin 1998; Salo 2006; Weber 1999), intramuscular (Hossain 2013), and IV (Aggarwal 2002; FitzGerald 1997; Garrett 1997; Kamei 1999; Nakano 2000; Rebuck 1987; Rodrigo 1995; Summers 1990) corticosteroids were administered in 13 studies. The route of corticosteroid administration was unclear in two studies (Canete 1991; Diaz 1997). Several studies stated that all participants received corticosteroids as a co-intervention along with combination inhaled therapy or SABA alone (Cydulka 2010; FitzGerald 1997; Garrett 1997; Nakano 2000; Rodrigo 1995; Salo 2006; Weber 1999) and some studies left the decision to provide corticosteroids to the discretion of attending physicians (Aggarwal 2002; Canete 1991; Diaz 1997; Kamei 1999; Lin 1998; O'Driscoll 1989; Rebuck 1987; Summers 1990). Diaz 1997 did not provide corticosteroids until after the participant's discharge disposition had been made, and Kamei 1999 only provided participants with IV corticosteroids if inhalation therapy was found to be ineffective.

Excluded studies

We excluded 43 studies following full-text assessment. Reasons for exclusion were: studies did not report not a prospective RCTs or CCTs; did not include participants with acute asthma; settings were not EDs, or did not compare inhaled SAAC + SABA vs. SABA alone. See Characteristics of excluded studies.

Risk of bias in included studies

Most studies were assessed at high (Diaz 1997; FitzGerald 1997; Garrett 1997; Kamei 1999; Karpel 1996; Lin 1998; Nakano 2000; O'Driscoll 1989; Owens 1991; Rahman 2006; Rashid 2010; Solarte 2004; Summers 1990; Weber 1999) or unclear (Aggarwal 2002; Canete 1991; Hossain 2013; Kohistani 2007; Rebuck 1987; Rodrigo 1995; Rodrigo 2000; Salo 2006) risk of bias (Figure 3; Figure 4). Only one study was assessed at overall low risk of bias (Cydulka 2010).

Figure 3. Risk of bias summary

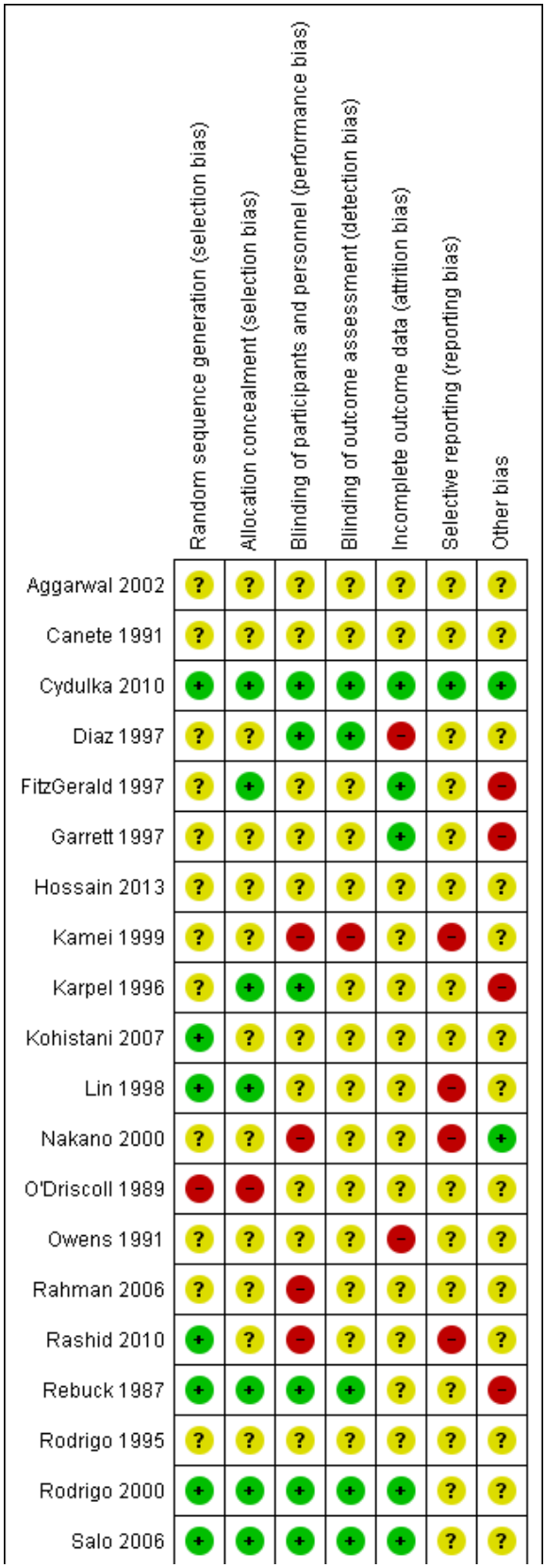


Figure 3. (Continued)

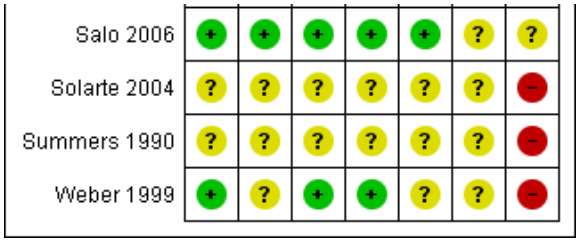
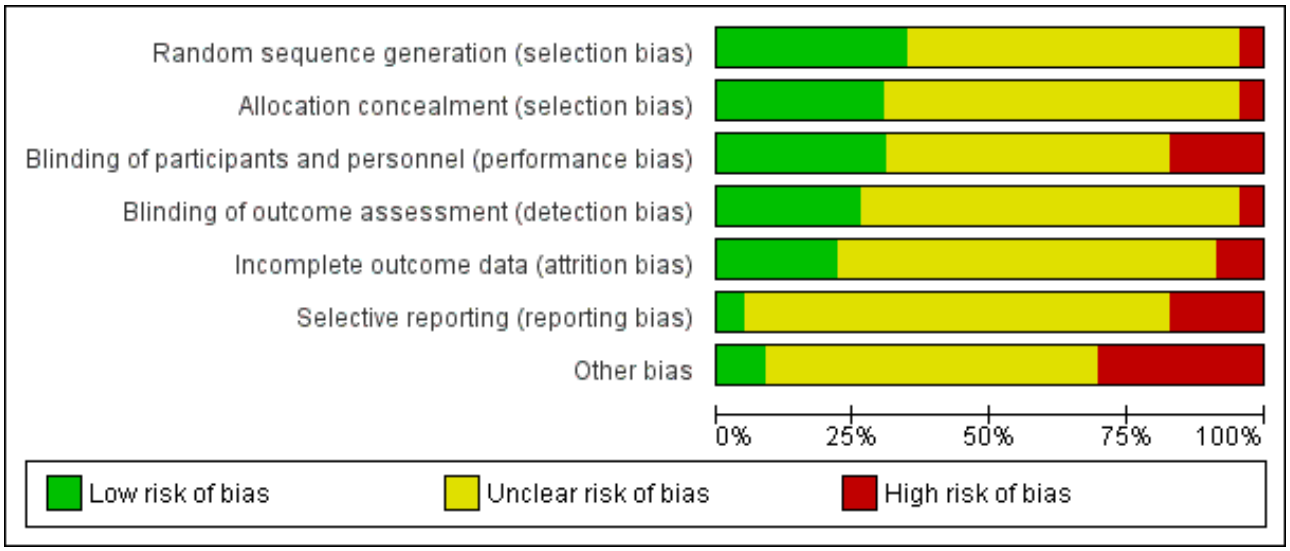


Figure 4. Risk of bias graph



Allocation

Although all studies reported being randomised, fewer than half provided adequate information on randomisation methods to enable assessment of selection bias (Cydulka 2010; Kohistani 2007; Lin 1998; O'Driscoll 1989; Rashid 2010; Rebuck 1987; Rodrigo 2000; Salo 2006; Weber 1999). Most studies provided insufficient information on methods of allocation concealment. Authors of three studies (FitzGerald 1997; Garrett 1997; Kamei 1999) provided additional clarification about methods of allocation concealment.

Blinding

Most studies were reported to be double-blinded, although only seven adequately described methodology to enable assessment of low risk of bias (Cydulka 2010; Garrett 1997; Karpel 1996; Rebuck 1987; Rodrigo 2000; Salo 2006; Weber 1999). The four studies which were assessed at high risk of bias for this domain were self-described as single-blinded (Nakano 2000; Rahman 2006; Rashid 2010) and open-labelled (Kamei 1999) studies. Only six studies were assessed at low risk of detection bias (Cydulka 2010; Garrett 1997; Rebuck 1987; Rodrigo 2000; Salo 2006; Weber 1999).

Incomplete outcome data

Most studies did not provide adequate information about numbers of participants screened for the study, including those who refused or were excluded from the study, to enable clear assessment of bias. Two studies (Diaz 1997; Owens 1991) were assessed at potentially high risk of bias because no information was provided on to which groups excluded participants belonged.

Selective reporting

Most studies were assessed at unclear risk of reporting bias due to a lack of an available protocol. Several studies reported side-effects as an outcome; however, they did not provide data suitable for meta-analysis, resulting in high risk of bias assessment (Kamei 1999; Lin 1998; Nakano 2000; Rashid 2010). Two studies (FitzGerald 1997; Karpel 1996) provided additional outcome data, but were assessed at unclear risk of bias. Cydulka 2010 was the only included study that published a protocol.

Other potential sources of bias

Most studies (n = 14) did not report sources of funding. Of two studies assessed at low risk of bias assessment, one reported receiving funding from a hospital (Nakano 2000), and the other received industry funding, but included a statement that the sponsor did not influence manuscript preparation or outcome reporting (Cydulka 2010). Seven studies reported receiving funding from pharmaceutical companies, but did not provide statements about funders' involvement in manuscript preparation or outcome reporting (FitzGerald 1997; Garrett 1997; Karpel 1996; Rebuck 1987; Solarte 2004; Summers 1990; Weber 1999).

Effects of interventions

See: **Summary of findings for the main comparison** Combination inhaled therapy compared with SABA alone for acute asthma

Hospitalisation

We included 15 studies, involving 2047 participants, that compared hospitalisation proportions in adults receiving combined inhaled therapy vs. SABA alone. Participants receiving combination inhaled therapy were less likely to be hospitalised than participants receiving SABA alone (RR 0.72, 95% CI 0.59 to 0.87; participants = 2120; studies = 16; I^2 = 12%; Analysis 1.1). Similiarily, worst-case intention-to-treat (ITT) analysis found participants receiving combined inhaled therapy in the ED were less likely to be hospitalised (RR 0.76, 95% CI 0.63 to 0.91; participants = 2085; studies = 15; I^2 = 19%; Analysis 1.2) compared to participants receiving SABA only.

Subgroup analyses

Subgroup analysis did not reveal whether single or multiple doses of combination inhaled therapy were more effective in mitigating the risk of hospitalisation (P = 0.29) (Analysis 2.1). Similarily, a subgroup analysis of participants who received or did not receive corticosteroids as a co-intervention was unable to determine whether receiving additional corticosteroids modified the impact of combination therapy on reducing the risk for hospitalisation (P = 0.48) (Analysis 2.2).

Subgroup analysis of exacerbation severity did reveal a significant subgroup difference on the effects of combination inhaled therapy on mild, moderate and severe exacerbations (test for subgroup differences: P = 0.02). Although combination inhaled therapy was more effective than SABA alone in reducing hospitalisation in participants with severe exacerbations (RR 0.56, 95% CI 0.43 to 0.72; participants = 599; studies = 7; I^2 = 0%), no significant differences between combination inhaled therapy and SABA alone were found for participants with mild (RR 1.88, 95% CI 0.37 to 9.54; participants = 112; studies = 2; I^2 = 0%), or moderate (RR 0.88, 95% CI 0.69 to 1.11; participants = 1409; studies = 7; I^2 = 0%) exacerbations (Analysis 2.3). An analysis of exacerbation severity using risk difference revealed similar results, in which combination inhaled therapy was more effective in preventing hospitalisation among participants with severe acute asthma (RD -0.18, 95% CI -0.25 to -0.11; participants = 599; studies = 7; I^2 = 0%) compared to those with mild (RD 0.01, 95% CI -0.05 to 0.08; participants = 112; studies = 2; I^2 = 0%) or moderate (RD -0.03, 95% CI -0.07 to 0.01; participants = 1409; studies = 7; I^2 = 0%) acute asthma.

No subgroup differences were found in regard to the type of SAAC therapy provided to participants (P = 0.62) (Analysis 2.4).

Sensitivity analyses

Sensitivity analysis found that despite the removal of high risk of bias studies, participants receiving combination inhaled therapy were less likely to be hospitalised compared with participants receiving SABA alone (RR 0.63, 95% CI 0.44 to 0.90; participants = 513; studies = 6; I^2 = 22%; Analysis 3.1). Similar results were very similar using random-effects (RR 0.72, 95% CI 0.59 to 0.87; participants = 2120; studies = 16; I^2 = 12%) and fixed-effect models (RR 0.72, 95% CI 0.60 to 0.85; participants = 2120; studies = 16; I^2 = 12%; Analysis 3.2).

Adverse events

There were 11 studies involving 1392 participants that compared the frequency of adverse events after treatment with combination inhaled therapy vs. SABA alone. Participants who received combination inhaled therapy were more likely to experience adverse events than those who received SABA agents alone (OR 2.03, 95% CI 1.28 to 3.20; participants = 1392; studies = 11; I^2 = 14%; Analysis 1.3). Only a few studies reported the frequency of specific side effects related to inhaled SAAC or SABA use, such as tremor or dry mouth.

Additional analysis did not reveal differences in the frequency of specific adverse events including dry mouth (OR 2.08, 95% CI 0.84 to 5.12; participants = 447; studies = 5; I^2 = 54%; Analysis 1.4), tremor (OR 1.33, 95% CI 0.88 to 2.01; participants = 804; studies = 5; I^2 = 0%; Analysis 1.5), anxiety (OR 0.82, 95% CI 0.31 to 2.17; participants = 564; studies = 2; I^2 = 0%; Analysis 1.6), palpitations (OR 1.03, 95% CI 0.17 to 6.06; participants = 809; studies = 5; I^2 = 79%; Analysis 1.7), nausea (OR 0.65, 95% CI 0.19 to 2.17; participants = 245; studies = 3; I^2 = 0%; Analysis 1.8), headache (OR 1.46, 95% CI 0.31 to 6.78; participants = 247; studies = 2; I^2 = 13%; Analysis 1.9), blurred vision (OR 0.73, 95% CI 0.12 to 4.50; participants = 141; studies = 1; I^2 = 100%; Analysis 1.10), or agitation (OR 2.90, 95% CI 0.11 to 74.10; participants = 62; studies = 1; I^2 = 0%; Analysis 1.11) between participants receiving combined inhaled therapy vs. SABA treatment alone.

Pulmonary function

We assessed six studies that compared changes in FEV_1 between combination inhaled therapy and SABA alone. Participants who received combination inhaled therapy were more likely to exhibit improved FEV_1 by the end of the study period (MD 0.25 L, 95% CI 0.02 to 0.48; participants = 687; studies = 6); however, heterogeneity was high (I^2 = 70%; Analysis 1.12). In contrast, no significant differences were found in percent change in FEV_1 between participants who received combination inhaled therapy or SABA alone (MD 21.28% predicted, 95% CI -5.62 to 48.18; participants = 578; studies = 5), although heterogeneity was very high (I^2 = 84%; Analysis 1.13).

There were 12 studies that assessed lung functions using PEF. Participants who received combined inhaled therapy demonstrated improved PEF compared to those who received SABA only (MD 36.58 L/min, 95% CI 23.07 to 50.09; participants = 1056; studies = 12; I^2 = 25%; Analysis 1.14).

Six studies compared the effects of combined inhaled treatment vs. SABA alone on percent change in PEF from baseline to the final PEF assessed after treatment. Participants who received combined inhaled therapy were more likely to have higher percent improvement in PEF compared to those who received SABA treatment alone (MD 24.88% improvement, 95% CI 14.83 to 34.93; participants = 551; studies = 7; I^2 = 23%; Analysis 1.15). Only two studies reported the percent predicted PEF, which was found to be higher among participants who received combination inhaled therapy compared to those who received SABA only (MD 13.67% predicted, 95% CI 3.88 to 23.46; participants = 102; studies = 2; I^2 = 50%; Analysis 1.16).

Additional care

The need for additional treatments in the ED were examined in four studies. Only Nakano 2000 defined what was provided to

participants as part of the additional ED treatments: these included IV aminophylline, inhaled bronchodilators, or both. Participants who received combined inhaled therapy did not show a difference in the need for additional treatment in the ED compared with participants who received SABA alone (RR 0.85, 95% CI 0.64 to 1.13; participants = 543; studies = 4); heterogeneity was moderate (I^2 = 27%; Analysis 1.17).

Relapse

Five studies assessed whether participants needed to return to the ED after discharge due to a lack of improvement or worsening of symptoms. Participants who received combined inhaled therapy were less likely to return to the ED with worsening symptoms after discharge compared with those who received SABA treatment alone (RR 0.80, 95% CI 0.66 to 0.98; participants = 1180; studies = 5; I^2 = 0%; Analysis 1.18).

DISCUSSION

Summary of main results

By using a comprehensive search strategy, and techniques to mitigate selection and publication bias, we identified 23 studies that included 2724 adult participants which compared combination inhaled treatment with inhaled short-acting anticholinergics (SAAC) and short-acting beta$_2$-agonists (SABA) to treatment with inhaled SABA alone for the management of adults with acute asthma in the emergency department (ED). Only RCTs, CCTs and trials involving direct comparisons were eligible for inclusion. However, a lack of available data in two studies meant that 21 studies were included in the meta-analysis for the primary outcome; even fewer studies could be meta-analysed for the secondary outcomes.

The overall quality of the included studies was moderate to low; most were assessed at unclear risk of bias, and some at high risk of bias.

We identified several important findings regarding the effectiveness of combination therapy to mitigate hospitalisations.

First, combination inhaled therapy was shown to be more effective in reducing hospitalisations compared to treatment with inhaled SABA alone, particularly in participants with severe exacerbations who are at high risk for hospitalisation. Caution is warranted in the interpretation of this subgroup analysis due to the heterogeneity in assessing asthma severity employed across the studies.

Second, the benefit combination inhaled therapy does not appear to be related to whether or not participants were administered systemic corticosteroids. It is important to note, however, that co-interventions were inconsistently reported across the studies, so it is possible that more studies could have provided corticosteroids in the ED, but did not report it.

Third, combination inhaled therapy appears to be effective regardless of whether or not ipratropium bromide or other SAACs were provided.

Finally, there was inconclusive evidence regarding the effectiveness of single versus multiple doses of combined inhaled therapy to prevent hospitalisation. Additional studies assessing direct comparisons between single and multiple doses of combination inhaled therapy are needed to directly compare these approaches. Overall, the effectiveness of combined inhaled therapy to prevent hospitalisations were robust in the face of sensitivity analyses which included random-effects vs. fixed-effect results and study quality.

Participants who received combination inhaled therapy were more likely to experience improvements in pulmonary function testing representing higher forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), and higher percent improvement in PEF. Standard recommendations for the minimally clinically important difference in most guidelines are 12% (Global Initiative for Asthma 2016); however, data from asthma trials suggest minimally clinically important difference change from baseline percentages for FEV (10%) and PEF (6%) may be even lower (Santanello 1999). In addition, participants receiving the combination inhaled treatment experienced less relapses after discharge. No significant differences were noted between participants receiving combination inhaled therapy or SABA alone with regard to percent improved FEV_1 and the need for additional bronchodilators in the ED. Although it is unclear why no significant improvement in percent improved FEV_1 was found, despite an improvement in FEV_1, results showed considerable inconsistency and imprecision. Furthermore, although the effect was moderate, caution is warranted in the interpretation of these results due to the heterogeneity in assessing and reporting airway obstruction employed across the studies.

Participants who received combination inhaled therapy were more likely to report adverse events compared to those treated with SABA agents alone. Despite this finding representing a picture of the overall symptoms experienced by participants, studies frequently failed to report in sufficient detail on the frequency of individual adverse events, such as dry mouth, termor, palpitations, and headache. As such, although results from this review suggest that participants who received combination inhaled therapy were more likely to report adverse events, we were unable to report on which particular adverse event participants could experience.

These findings provide important outcomes that should assist clinicians in informing patients and balancing treatment benefit with risk. It is important to note that most adverse events would not be considered serious and many would be self-limiting.

Overall completeness and applicability of evidence

Overall, we believe the completeness and applicability of the evidence to be high. This is a moderately-sized review with 23 studies including 2724 participants. The studies were conducted in EDs in the Americas, Europe, Asia, and Pacific regions.

Most included studies enrolled adult participants with a minimum age of 18 years. There were two studies which set the minimum age for enrolment as 13 years and 15 years (Aggarwal 2002; Canete 1991), respectively. After consideration, it was decided that these studies would be included in the review because the stated median ages were frequently between 30 and 42, suggesting that most included participants were adults aged over 16 years.

We included only studies in which participants presented to the ED with acute asthma. Studies that included participants with either asthma or other airway diseases, such as chronic obstructive pulmonary disease (COP, were excluded unless data were available

for only asthma participants, or if the sample of asthma participants made up at least 80% of the study population.

Most included studies assessed hospitalisation as a primary outcome. As a result, we believe the review results are applicable to adults presenting to the ED with acute asthma. Unfortunately, some proposed secondary outcomes, such as quality of life, symptoms scores, and ED length of stay, were not reported widely and could not be included in the meta-analysis as planned. In addition, pulmonary function measures and adverse events were inconsistently reported, and in some cases, were reported incompletely in the text, and could not be extracted for meta-analysis. Our attempts to contact study authors to provide clarification of their data were successful in some cases (Cydulka 2010; Garrett 1997; Salo 2006), particularly with regard to frequency of adverse events.

Quality of the evidence

The quality of the included studies was generally considered to be low or unclear. We assessed 14 studies at high risk of bias due to lack of double blinding, incomplete reporting of adverse events, and receiving industry funding with no clarification of the role that company had on outcome reporting or manuscript preparation (Diaz 1997; FitzGerald 1997; Garrett 1997; Kamei 1999; Karpel 1996; Lin 1998; Nakano 2000; O'Driscoll 1989; Owens 1991; Rahman 2006; Rashid 2010; Solarte 2004; Summers 1990; Weber 1999). Only Cydulka 2010 was assessed as being a high quality study.

On GRADE assessment, the overall quality of outcomes reported ranged from very low to moderate. The primary outcome, hospitalisation, was reduced to moderate quality because most studies were assessed at unclear or high risk of bias, frequently due to inadequate (or no) reporting of randomisation, allocation concealment or blinding. The quality of the evidence for adverse events was considered moderate due to the high risk bias relating to selective reporting.

Despite that the quality of the evidence for PEF, percent change PEF from baseline, and relapse were considered moderate (due to overall unclear and high risk of biases found in the studies), the quality of the evidence regarding FEV_1 and percent change in FEV_1, was found to be low and very low respectively due to inconsistency and imprecision of the results.

A limitation of this review is that the included studies tended to be small, and despite the low-moderate statistical heterogeneity identified across the outcomes of this review, clinical heterogeneity, including participant characteristics, treatment dosing, and settings (in regard to different healthcare systems) exists.

Differences in admission criteria may have influenced the results of this review, because studies may have applied more liberal or conservative admission criteria. Only five of the included studies provided defined admission criteria, and it is unclear what criteria the remaining studies used to decide whether or not participants should be hospitalised. Moreover, the influence of funding, such as payment models for admission, and hybrid models of care, such as short-stay units and observation units, on these results could not be determined from the available data.

Potential biases in the review process

As with all reviews, there was a risk of potential screening and study selection bias, although strategies were applied to minimise this risk. Extensive searches of electronic databases, grey literature, and the Cochrane Airways Group register of trials were conducted with no limits on language, publication type or year of publication. Several articles published in languages other than English were identified, and were included or excluded based on the information translated from the text. Where information provided in studies did not inform a clear inclusion or exclusion decision, attempts were made to contact the authors to clarify information provided in the text. Screening and study selection was completed independently by several trained review authors in an effort to limit the possibility of bias. Despite this, it is recognised that some articles may have been missed. The funnel plot (Figure 2) was not indicative of potential publication bias for the primary outcome.

Agreements and disagreements with other studies or reviews

Our results align with previous systematic reviews which found combination inhaled therapy to be more effective in reducing hospitalisation and improving pulmonary function measures than treatment with SABA alone in adults (Rodrigo 1999; Rodrigo 2005; Stoodly 1999) and children (Griffiths 2013; Rodrigo 2005) with acute asthma. Lanes 1998, a pooled analysis of three studies (FitzGerald 1997; Garrett 1997; Karpel 1996) also reported a significant reduction in hospitalisation and improvement in FEV_1 among participants who received combination therapy.

There were several disagreements between findings of this review and previous reviews. Rodrigo 1999 and Rodrigo 2005 reported a similar rate of adverse events, such as tremor, between participants who received combination inhaled therapy and SABA alone, whereas we found more side effects with combination therapy. The reason for this difference is likely due to the increased number of studies included in this review, as well as additional information which was received from study authors regarding the occurrence of adverse events. In addition, we reported similar effectiveness of single and multi-dose combination inhaled therapy to mitigate hospitalisation, which appears to differ from other reviews. For example, Rodrigo 2005 reported a "trend" toward reduced risk of hospitalisation in adults receiving multi-dose combination therapy; however, unlike this review, the authors did not conduct a statistical subgroup comparison of the trials using multiple or single doses of combination inhaled therapy. Furthermore, we identified more studies for inclusion than Rodrigo 2005, and featured a more up-to-date and extensive search of the electronic and grey literature, which is likely to be the greatest contributor to reported differences in results.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, combination inhaled therapy appears to be effective in reducing the risk of hospitalisation among adult patients at high risk for hospitalisation presenting to the emergency department (ED) with acute asthma.

In particular, combination inhaled therapy is more effective at preventing hospitalisation in adult patients with severe exacerbations who are at increased risk for hospitalisation,

compared to those patients with mild-moderate exacerbations who are at a lower risk of hospitalisation.

It is unclear whether there is a difference between single or multiple doses of combination inhaled therapy in mitigating hospitalisation.

The beneficial effects of combination inhaled therapy appear to be independent of co-treatment with corticosteroids in the ED.

While effective at mitigating the risk for hospitalisations, patients who received combination inhaled therapy were at increased risk for adverse events.

Implications for research

Additional research comparing the effectiveness of combination inhaled therapy for mild, moderate, and severe exacerbations of asthma is needed to better understand how to optimise care. Researchers need to improve on reporting of the severity of acute asthma among study participants.

Additional research conducting direct comparisons between the effectiveness of multiple vs. single doses of combination inhaled therapy is needed.

Additional research needs to examine the effects of combination inhaled therapy on ED length of stay, quality of life, and symptom scores. Further standardisation of techniques to assess pulmonary function are required.

Additional research is needed to better understand the relationship of combination inhaled therapy and relapse proportions.

We included several studies which reported no differences in the frequency of adverse events; however, these studies provided no data for inclusion in the text of the study. This prohibited several studies from being included in the meta-analysis. It is very important for studies examining interventions to provide results for important outcomes such as adverse events. Around half of the included studies did not report data on the overall occurrence of adverse events, and even fewer provided details on the specific adverse events experienced. Despite the lack of reporting, a significant difference in the frequency of adverse events was found. Consistent reporting of the frequency of adverse events in future research is needed.

Future researchers need to clearly report methods of randomisation, allocation concealment, blinding, participant attrition rates during study recruitment, and sources of funding. Several included studies were funded by the pharmaceutical industry with no statements indicating companies' influence on the study or the content of the manuscript.

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CHARACTERISTICS OF STUDIES

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

Aggarwal 2002

Methods	- Prospective RCT. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Randomisation accomplished via random numbers tables. - No information on allocation concealment provided.
Participants	- Adult participants who presented to the ED in with acute bronchial asthma during working hours and had a previous diagnosis or treatment of bronchial asthma. - Set in India. - Ages: 15 to 30 years. - Asthma exacerbation severity of presenting patients estimated as mild.

Aggarwal 2002 *(Continued)*

Interventions	- Single dose of combination inhaled therapy provided. Study interventions provided via ultrasonic nebuliser. - Group one received salbutamol (5 mg) over a period of five minutes at 0 and 60 minutes. - Group two received ipratropium bromide (500 µg) over a period of five minutes at 0 and 60 minutes. - Group three received a single dose of combined ipratropium bromide (500 µg) and salbutamol (5 mg) over a period of 5 minutes, followed by placebo nebulisation 60 minutes later. For the purposes of this review, group two was not included in the analysis. - Additional co-interventions provided in the ED included IV hydrocortisone, and supplemental oxygen.
Outcomes	- Outcome measurements include hospitalisation, ED length of stay, vital signs, adverse events, and additional bronchodilator treatments. - Only the outcomes of groups one and three were extracted. - Outcomes measurements were performed at baseline, as well as 15, 60, 75, and 120 minutes after treatment.
Notes	- Author was contacted to retrieve the original database for subgroup comparisons but the author stated that he no longer had access to the original data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random numbers drawn from random numbers table. Quote (p. 354): "For randomisation of the patients into three groups, random numbers were drawn from the random number table to decide allocation group of patients well in advance".
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided on whether participants or personnel were blinded were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided on number of patients excluded during the screening process.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Canete 1991

Methods	- Prospective RCT.

Canete 1991 *(Continued)*

	- Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Method of randomisation unclear. - No information on allocation concealment provided.
Participants	- Patients presenting to the ED for exacerbation of asthma. - Set in Spain. - Ages: 13 to 85 years. - Asthma exacerbation severity of patients presenting unclear. Insufficient information provided.
Interventions	- Mutliple doses of combined inhaled therapy. Study interventions provided via nebuliser. Abstract states that patients received study interventions every two hours, but it is unclear how many doses patients received. - Group one received ipratropium bromide (0.1 mg) and salbutamol (2.5 mg) every two hours. - Group two received salbutamol (5.0 mg) alone every two hours. - Additional co-interventions provided in the ED included IV corticosteroids, IV aminophylline and supplemental oxygen according to need.
Outcomes	- Outcome measurements included adverse events, and vital signs. - Not enough information provided to extract data on pulmonary function or adverse events. - Outcome measurements were performed at baseline and at two hours after the start of treatment.
Notes	- Contacted primary author to clarify their methodology and results but they stated that they no longer had access to the original data. - No full-text, only an abstract available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on method of randomisation. Quote (p. 32): "Aleatoriamente se distribuyeron en dos grupos de tratamiento." *(Translation: "They were randomised into two treatment groups.")*
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided on blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inadequate information provided.

Canete 1991 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Cydulka 2010

Methods	- Prospective, double-blinded RCT. - Comparison of ipratropium bromide and levabuterol vs. levabuterol alone. - Randomisation was accomplished using computer-generated block random numbers table (blocks of 15 by site). - Allocation concealment was reported and discussed as pharmacy controlled.
Participants	- Patients who presented to the ED with an exacerbation of acute asthma. - Set in United States. - FEV on presentation to the ED was < 50% of predicted (In compliance with National Asthma Education and Prevention Program definition of severe asthma exacerbation). - Age: 18 to 45 years. - Asthma exacerbation severity of presenting patients was severe. Estimates of asthma severity based on control hospitalisation rates were estimated as moderate.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via nebuliser. - Group one received three doses of levabuterol (1.25 mg) combined with ipratropium bromide (0.5 mg). - Group two received three doses of levabuterol alone (1.25 mg). - Additional co-interventions provided in the ED include a single dose of oral prednisone (60 mg); discharged patients received an additional two day supply. - Interventions provided only at discharge included SABA and inhaled corticosteroids if patient had a history of chronic persistent asthma.
Outcomes	- Primary outcome was the change in FEV percent predicted over time. - Additional outcomes included hospitalisation, ED discharge, adverse events and pulmonary testing. - Outcome measurements were performed at baseline, 30 and 60 minutes after treatment.
Notes	- Author was contacted and provided additional data on adverse events.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients randomised via computer-generated numbers table. Quote (p. 1095): "Patients were randomised to treatment group using a computer-generated, block random numbers table (blocks of 15 by site)."

Cydulka 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	Centrally allocated, pharmacy controlled. Quote (p. 1095): "The medication for both treatment groups was premixed in three vials by the pharmacy in a total of 3 mL normal saline solution. The pharmacist packed the treatments in brown numbered envelopes for the ED. The sequence assignment sheet was stored in a locked cabinet in the hospital pharmacy and concealed from the research nurses enrolling patients and assessing participants."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinding. Nurses, physicians, and patients were blind to the contents of the envelopes. Quote (p. 1095): "The research nurses were required to use the brown envelope containing medications in pre numbered sequence and record the sequence number on the data collection form. The brown envelopes contained all medications to use during the study. All vials contained in the envelope looked identical to one another. Physicians were asked to assess the patients before and between scheduled treatments. Blinding to group assignment was maintained throughout the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors (research nurses) blinded. Quote (p. 1096): "At all times, the research nurses, patients, and treating physicians were blinded to group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Detailed information on study attrition provided in flow diagram provided (p. 1095).
Selective reporting (reporting bias)	Low risk	Protocol available from ClinicalTrials.gov (NCT00583778). All proposed outcomes, including FEV, hospitalisations, relapse, and side effects were reported. The authors were contacted to provide additional data on adverse events to enable meta-analysis.
Other bias	Low risk	Quote (p. 1099): "The study was supported by a grant from Sepracor (*authors note: Sepracor is now known as Sunovion*). The authors alone are responsible for the content and writing of the paper." Sunovion is a pharmaceutical manufacturer offering products to treat respiratory conditions.

Diaz 1997

Methods	- Prospective, randomised, double-blinded, placebo-controlled study. - Comparison of atropine sulphate (multidose) and albuterol vs. atropine sulphate (single dose) and albuterol vs. albuterol alone. - Method of randomisation unclear. - Allocation concealment was reported and discussed as pharmacy controlled.
Participants	- Patients who presented to the ED with an exacerbation of asthma and had a history of asthma. - Set in United States. - History of recurrent, episodic exacerbations of reversible bronchospasms were considered to have asthma.

Diaz 1997 *(Continued)*

	- Age: 18 to 70 years. - Asthma exacerbation severity of presenting patients estimated as moderate.
Interventions	- Study assessed single and multiple doses of combination inhaled therapy. Study interventions provided via nebuliser. - All groups received albuterol (2.5 mg) every 30 minutes for 3 doses (0, 30, 60 minutes). - Group one received two additional doses of 2 mg of atropine sulphate at time 0, as well as an additional 2 mg at 60 minutes (multidose). - Group two received one additional dose of 2 mg of atropine sulphate at time 0 only (single dose). - Group three received only albuterol in the doses stated above. - No additional co-interventions in the ED provided. Systematic steroids, additional beta agonists, and IV therapy given only at discharge or upon admittance to hospital.
Outcomes	- Outcomes included hospitalisations, pulmonary testing, ED length of stay, and presence of adverse events. - Outcome measurements were performed at baseline, as well as 30, 60 and 90 minutes after treatment.
Notes	- Unable to contact authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation unclear, not enough information provided. Quote (p. 108): "A block-design randomization scheme was devised prior to patient enrolment."
Allocation concealment (selection bias)	Unclear risk	No information provided on where the separate confidential location was located. Unclear if centrally allocated. Quote (p. 102): "The study agent (2 mg of atropine sulfate or an equal volume of normal saline) was prepared in advance and coded. All patients had a coded syringe added to the first and third nebulizers (time 0 and 60 minutes). The contents of the syringe were unknown to the treating physician, nurse, and patient. The code key was kept in a separate confidential location."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study. Study medications kept in coded identical syringes. Contents of syringe were unknown to the treating physician, nurse and patient. Quote (p. 102): "The contents of the syringe were unknown to the treating physician, nurse, and patient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study. Study medications kept in coded identical syringes. Contents of syringe were unknown to the treating physician, nurse and patient. Quote (p. 102): "The contents of the syringe were unknown to the treating physician, nurse, and patient."
Incomplete outcome data (attrition bias) All outcomes	High risk	Reported several patients were withdrawn or excluded after inclusion into the study. Did not specify from which groups patients were excluded or withdrew.

Diaz 1997 *(Continued)*

		Quote (p. 110): "A total of 153 patients satisfied enrolment criteria and 148 were randomised into 1 of the 3 treatment groups (5 patients were excluded due to previous entry into the study population). Another 4 patients were withdrawn from the study because they quickly decompensated during treatment and needed additional therapy. An additional 3 patients were excluded from analyses due to insufficient essential data (i.e. pulmonary function tests at > 1 time point). A total of 141 patients were analyzed with the intention to treat."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

FitzGerald 1997

Methods	- Multicentre, double-blind randomised, active-controlled trial. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Method of randomisation unclear. - Allocation concealment achieved via central allocation, telephone; drugs were kept in pharmacy.
Participants	- Patients who presented to the ED with an exacerbation of asthma and had a diagnosis of asthma consistent with ATS guidelines. - Set in Canada. - Could perform reproducible spirometry. - Initial FEV < 70% of predicted normal value. - Age: 18 to 55 years. - Asthma exacerbation severity of presenting participants estimated as moderate.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser. - Group one received ipratropium bromide (0.5 mg) and salbutamol (3.0 mg). - Group two received salbutamol alone (3.0 mg). - Additional co-interventions provided in the ED included 125 mg of IV methylprednisolone within 15 minutes of nebulisation, as well as supplemental oxygen given continuously.
Outcomes	- Outcomes measured included hospitalisations, ED discharge, pulmonary testing and relapse. - Outcome measurements were performed at baseline, as well as 45, and 90 minutes. Relapse and hospitalisation assessed for two weeks after discharge from the ED.
Notes	- Study authors contacted and provided clarification of some methodology and study results including relapse rates.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on method of randomisation.

FitzGerald 1997 *(Continued)*

		Quote (p. 312): "Following enrolment and measurement of baseline FEV_1 patients were randomised to receive in double-blind fashion either a fixed-dose combination of ipratropium bromide and salbutamol sulfate (0.5 mg and 3.0 mg, respectively) or salbutamol sulfate alone (3.0 mg)".
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled central allocation. Information retrieved from personnel communication with authors. Personal communication: "Randomisation was centralised for NZ and Canadian Study and probably using similar software as this was by BI and Nebulisers were maintained in pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study reported as double-blinded but no information provided on methods to ensure double-blinding. Quote (p. 312): "Following enrolment and measurement of baseline FEV_1 patients were randomised to receive in double-blind fashion"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Extensive information provided on study attrition. Patient withdrawals evenly balanced between groups. Quote (p. 312): "Of 952 patients screened against inclusion or exclusion criteria for this study, 606 were found to be ineligible. Patients were excluded for the following reasons: smoking history greater than 10 pack-years, 155; in extremis or with severe obstruction, 43; ATS definition of chronic obstructive lung disease, 10; previously recruited into the study, 19; receiving treatment for or suspected of having glaucoma, three; uncontrolled hypertension, three; known allergy or contraindications to study drugs or their excipients, 12; known or suspected to be pregnant or nursing, 17; suspected to have pneumonia, pneumothorax, or pneumomediastinum, 26; history of chest surgery, 13; other respiratory conditions, 13; required treatment of asthma attack other than study treatment regimen, 18; had been in other clinical trials within 3 months previously, 18; had an acute myocardial infarction, pulmonary edema, or other life-threatening disease, six; or had obvious or previously diagnosed serious hepatic or renal impairment or bladder neck obstruction, six.Patients failing to meet the inclusion criteria were as follows: no diagnosis of asthma according to ATS criteria, outside the age range, nine; unable to perform spirometry, 60; FEVX > 70% of predicted normal, 259; and unwilling or unable to sign witnessed informed consent form, 156. The remaining 342 patients were randomised into the study with 171 patients in each treatment group. Of 342 patients randomised, two patients received no study drugs. Of the 342 patients randomised, 17 patients in the combination therapy group and 16 patients in the salbutamol alone group were either withdrawn by the study physician or requested to be withdrawn early."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Funding provided by Boehringer Ingelheim. No statement provided on influence of funding on preparation of the manuscript. Quote (p. 311): "Supported in part by a research grant from Boehringer Ingelheim (Canada) Ltd."

Garrett 1997

Methods	- Prospective, randomised, double-blind parallel-group study. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Method of randomisation unclear. - Allocation concealment achieved via central allocation by telephone.
Participants	- Participants who presented to the ED with an exacerbation of asthma, capable of performing a forced respiratory maneuver. - Set in New Zealand. - Patients who had received a nebulised bronchodilator within 6 hours of presentation were not excluded. - Asthma exacerbation was defined as a FEV < 70% predicted. - Ages: 18 to 55 years. - Asthma exacerbation severity of presenting patients reported as severe. Estimates of asthma severity based on control hospitalisation rates were estimated as moderate.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser mask. - Group one received ipratropium bromide (0.5 mg) and salbutamol (2.5 mg). - Group two received salbutamol alone (2.5 mg). - Co-interventions provided in the ED included IV hydrocortisone (200 mg). Isotonic IV fluid was only given if needed.
Outcomes	- Primary outcomes included absolute change in FEV_1 at 90 minutes. - Additional outcomes included pulmonary function, adverse events, vital signs, hospitalisation, ED discharge, and relapse rates. - Outcome measurements were performed at baseline, as well as 45, and 90 minutes after treatment. Unclear from original text when relapse was assessed but supplemental information from Lanes 1998 suggests relapse was assessed at 48 hours after discharge.
Notes	- Study authors contacted who provided clarification of some methodology, as well as frequency of adverse events and relapse rates.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on how patients were randomised. Quote (p. 165): "Two New Zealand EDs participated in a double-blind, randomised, active-controlled, parallel-group study comparing the bronchodilating effect of a fixed combination of nebulized ipratropium (0.5 rag) and salbutamol (2.5 rag) (Combivent) with nebulized salbutamol (2.5 mg) alone in patients with acute severe asthma."
Allocation concealment (selection bias)	Unclear risk	Central allocation. Information retrieved from personnel communication with authors. Personal communication: "Randomisation was centralised for NZ and Canadian Study and probably using similar software as this was by BI and Nebulisers were maintained in pharmacy".

Garrett 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blinded. Study medications were kept in indistinguishable vials. Quote (p. 166): "Indistinguishable unit dose vials of 2.5 ml were developed for the Combivent and salbutamol solutions."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Extensive information provided on study attrition. Patient withdrawals evenly balanced between groups. Quote (p. 167): "Fifty-nine of 338 patients recruited into the study were withdrawn before the primary outcome measurement of FEV_1 at 90 minutes (ΔFEV_1 90) was obtained; 13 requested early withdrawal, (9 receiving Combivent and 4 receiving salbutamol), 45 were withdrawn early by the ED doctor because of a lack of satisfactory improvement (18 receiving Combivent and 27 receiving salbutamol), and one was withdrawn before treatment was administered because he was unable to provide blood samples."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Funding provided by Boehringer Ingelheim. No statement provided on influence of funding on preparation of the manuscript. Quote (p. 165): "Supported by Boehringer Ingelheim Ltd."

Hossain 2013

Methods	- Prospective, randomised, single-centre study. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Method of randomisation unclear. - No information on allocation concealment provided.
Participants	- Patients who presented to the ED with an exacerbation of asthma. - Set in Bangladesh. - Asthma exacerbation was defined as PEF < 50% predicted. - Ages: 18 to 65 years. - Asthma exacerbation severity of presenting patients reported as severe. Unable to assess estimates of asthma severity based on control hospitalisation rates due to lack of information.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via nebuliser. - Group one received three doses of salbutamol alone (2.5 mg diluted in 2 mL of normal saline) every 20 minutes. - Group two received three doses of ipratropium bromide (250 µg in 2 mL solution) and salbutamol (2.5 mg diluted in 2 mL of normal saline) every 20 minutes. - Additional co-interventions provided in the ED included supplemental oxygen and injection hydrocortisone.

Hossain 2013 *(Continued)*

Outcomes	- The primary outcome was pulmonary function at 30 and 60 minutes after nebulisation. - Outcome measurements were performed as baseline, as well as 30 and 60 minutes after treatment.
Notes	- Study authors contacted and provided clarification of some methodology and study results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on how patients were randomised. Quote (p. 347): A total of 80 patients were randomly assigned to two treatment groups,..."
Allocation concealment (selection bias)	Unclear risk	Study did not address allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study did not address blinding of participants or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study did not address blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement. Quote (p. 347): "A total 80 patients were randomly assigned to two treatment groups. Forty (40) received Salbutamol alone (Group A) and 40 received combination Ipratropium Bromide and Salbutomol (group B)..."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Kamei 1999

Methods	- Prospective, multicenter, randomised open trial. - Comparison of oxitropium bromide and fenoterol vs. fenoterol alone. - Method of randomisation unclear. - No information on allocation concealment provided.
Participants	- Patients who present to the ED with an exacerbation of asthma and a previous diagnosis of asthma according to ATS guidelines. - Patients capable of performing spirometry test. - Asthma exacerbation defined as a PEF ≤ 70% of predicted value. - Ages: 18 to 65 years. - Asthma exacerbation severity in presenting participants estimated as moderate.

Kamei 1999 *(Continued)*

Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via MDI with a spacer device. - Group one received fenoterol alone (200 µg/puff), taking one puff/minute for five minutes for a total of five puffs. - Group two received oxitropium bromide (200 µg/puff) and fenoterol (200 µg/puff), taking one puff/minute each for five minutes for a total of five puffs. - Additional co-interventions provided in the ED included successive IV glucocorticoids and IV aminophylline if inhalation therapy was not effective.
Outcomes	- Outcomes included pulmonary function, hospitalisations, ED discharge, and adverse events. - Outcome measurements were performed at baseline, as well as 1, 15, 30, 60 minutes after treatment.
Notes	- Unable to contact authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on how patients were randomised. Quote (p. 68): "This study was a multicenter, randomised, open trial conducted at seven academic and nonacademic centers."
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial study. Quotes: "This study was a multicenter, randomised, open trial conducted at seven academic and nonacademic centers." (p. 68) "Because we used an MDI with an InspirEase device, it was impossible to perform this study in a double-blinded fashion." (p. 74)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial study. Quote (p. 68): "This study was a multicenter, randomised, open trial conducted at seven academic and nonacademic centers."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Excluded patients balanced between groups. No information provided on number of patients screened. Quote (p. 69): "Thirty-five patients were entered in the combination group and 34 patients were entered in the fenoterol-only group. On the basis of chart review, 5 of the 69 patients were found to be ineligible. Before the study, four patients used inhalation therapy of oxitropium bromide on their own, and one patient received intravenous aminophylline, which was considered to be a physician's protocol violation. Therefore, 33 patients were evaluated in the combination group and 31 patient were evaluated in the fenoterol-only group."
Selective reporting (reporting bias)	High risk	No protocol available. The frequency of side effects were incompletely reported. Quote (p. 70): "There was no significant difference in the number of adverse reactions between the groups (data not shown)."

Kamei 1999 *(Continued)*

Other bias	Unclear risk	No source of funding provided.

Karpel 1996

Methods	- Prospective, randomised, double blind controlled study with a parallel group design. - Comparison of ipratropium bromide and albuterol vs. albuterol alone. - Randomisation was accomplished using computer-generated random numbers via software however method of randomisation was unclear. - Allocation concealment was done via central allocation, telephone. Medication was kept in pharmacy.
Participants	- Patients who presented to the ED with an exacerbation of asthma. - Set in the United States. - Had to be capable of performing a forced expiratory maneuver. - Asthma exacerbation was defined as FEV ≤ 60% of predicted value with a 12% adjustment for persons of African-American heritage based on the equations of Morris 1988. - Ages: 18 to 55 years. - Asthma exacerbation severity of presenting patients estimated as moderate.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via updraft nebuliser. - Group one received two doses of albuterol (0.5 mL of 0.5% solution) mixed with saline solution (2.5 mL). The second dose was provided 45 minutes after the first dose. - Group two received two doses of ipratropium bromide (2.5 mL of 0.02% solution) and albuterol (0.5 mL of 0.5% solution). The second dose was provided 45 minutes after the first dose. - Additional co-interventions provided in the ED included supplemental oxygen delivered at 3 L/min at all times throughout the course of the study.
Outcomes	- Outcomes included pulmonary function, hospitalisation, vital signs, ED discharge, ICU admission, adverse events and relapse. - Outcome measurements were performed at baseline, as well as 45 and 90 minutes after the first dose. Relapse was assessed 24 hours after discharge from the ED.
Notes	- Study authors contacted who provided clarification of some methodology and study results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation via site specific randomisation schedule using software, but no information available on method of randomisation. Quote (p. 612): "Patients were assigned to receive one of the two treatment regimens according to a center-specific randomization schedule using software (ADLS-11 software; Almedica Corp; Waldwick, NJ).
Allocation concealment (selection bias)	Low risk	Central allocation. Information retrieved from personnel communication with authors.

Karpel 1996 *(Continued)*

		Personal communication (May 7, 2014): "I think we called them & was assigned # over phone."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded study. Study medications provided in identical, previously coded vials. Quote (p. 612): "The albuterol was obtained from unblinded multidose bottles. The blinded solution (either normal saline solution or Atrovent) was provided in identical, previously coded unit dose vials."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if staff were followed up with patients to assess relapse were blinded. Quote (p. 612): "Patients discharged from the ED were followed up for 24 h to assess the need for repeated ED visits."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Excluded patients balanced between groups. No information provided on number of patients screened. Quote (p. 612): "Three hundred eighty-four patients were randomised into the trial and 380 completed it. Two patients withdrew consent during the study: one withdrew due to worsening asthma, and one was withdrawn due an administrative problem."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Funding provided by Boehringer Ingelheim. No statement provided on influence of funding on preparation of the manuscript. Quote (p. 611): "Supported by a grant from Boerhinger Ingelheim Pharmaceuticals, Inc."

Kohistani 2007

Methods	- Prospective, comparative study. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Randomisation was accomplished using a random numbers table. - Allocation concealment unclear, treatment designation placed in envelopes, unclear if opaque or sealed. Held by uninvolved staff.
Participants	- Patients who presented to the ED with an exacerbation of asthma and had a history or diagnosis of asthma. - Set in Pakistan. - Asthma was defined as being physician diagnosed, having a bronchodilator prescribed by a physician, or having prior episodes of wheezing that improved with beta agonist inhalers. - Ages: 18 to 45 years. - Asthma exacerbation severity of presenting patients estimated as severe.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via continuous nebuliser. - Group one received a single dose ipratropium bromide (0.5 mg) and salbutamol (5.0 mg). Patients then received salbutamol alone at 30 and 60 minutes after the initial treatment with combination therapy.

Kohistani 2007 *(Continued)*

	- Group two received salbutamol (5.0 mg) alone. Patients received an additional dose of salbutamol alone at 30 and 60 minutes after the initial treatment with salbutamol alone. - No additional co-interventions in the ED stated.
Outcomes	- Primary outcomes measured included pulmonary function. - Secondary outcomes included hospitalisation and vital signs. - Outcome measurements were performed at baseline, as well as 30, 60, and 90 minutes after start of the study protocol.
Notes	- Unable to contact primary author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table. Quote (p. 587): "Randomization was performed on the basis of a random assignment list generated using the random table."
Allocation concealment (selection bias)	Unclear risk	Treatment designation placed in envelopes and held by uninvolved ED staff, however unclear if envelopes were opaque or sealed. Quote (p. 587): "Each treatment designation was placed in a closed envelop the uninvolved E.D. staff used to administer treatment according to the treatment designation to which the patient would to do and the staff would not communicate the details of the treatment to the study physician who happened to be the resident physician on duty in the E.D."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study medications provided by uninvolved ED staff who did not inform staff the identity of the medications provided. No details provided on how patients were blinded. Quote (p. 587): "Each treatment designation was placed in a closed envelop the uninvolved E.D. staff used to administer treatment according to the treatment designation to which the patient would to do and the staff would not communicate the details of the treatment to the study physician who happened to be the resident physician on duty in the E.D."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided on patient attrition during screening process.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Lin 1998

Methods	- Prospective, double-blind, placebo-controlled trial.

Lin 1998 *(Continued)*

	- Comparison of ipratropium bromide and albuterol vs. albuterol alone. - Randomisation was accomplished via random assignment list generated by computer. - Allocation concealment was reported, sealed envelopes stored in a locked cabinet were used.
Participants	- Patients presenting to the ED with an exacerbation of asthma and had prior episodes of wheezing that improved with beta-agonist inhalers. - Set in the United States. - Asthma exacerbation defined as PEF < 200 L/min. - Patients had to be capable of performing PEF. - Ages: 18 years or older. - Asthma exacerbation severity in presenting patients estimated as severe.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via acorn nebuliser. - Group one received a single dose of ipratropium bromide (3.5 mL) and albuterol (2.5 mg), followed by albuterol (2.5 mg) alone every 20 minutes for a total of two doses. - Group two received a dose of albuterol (2.5 mg/3 doses) alone every 20 minutes for a total of three doses. - Additional co-interventions provided in the ED included supplemental oxygen and oral methylprednisolone if treatment given was believed to be inadequate.
Outcomes	- Primary outcome assessed changes in pulmonary function. - Additional outcomes included hospitalisation, vital signs, and adverse events. - Outcome measurements were performed at baseline, as well as 20, 40 and 60 minutes after the start of treatment.
Notes	- Contacted authors to clarify missing data but was informed they no longer had access to the original data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers. Quote (p. 209): "Randomization was performed on the basis of a random assignment list generated by computer."
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes stored in a locked cabinet. Quote (p. 209): "Each treatment designation was placed in sealed, opaque envelopes stored in a locked cabinet."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded study. Study medications prepared by uninvolved ED staff without any communication of its contents to the ED staff. No details provided on how patients were blinded. Quote (p. 209): "The initial nebulized mixture was prepared and placed into a nebulizer by an uninvolved ED staff member without any communication of its contents to the study physician. A double-blind study design was thus employed on a convenience sample of patients selected as described above."

Lin 1998 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions between groups were balanced. No details provided on patients attrition during the screening process. Quote (p. 210): "Among 60 patients recruited for the study, 4 did not receive the protocol, and a fifth patient was inadvertently studied twice, leaving 55 patients available for analysis."
Selective reporting (reporting bias)	High risk	No protocol available. The frequency of side effects were incompletely reported. Quote (p. 211): "The proportion of patients with tremor, agitation, and accessory muscle use did not significantly differ between the two groups at any time points (data not shown)."
Other bias	Unclear risk	No source of funding provided.

Nakano 2000

Methods	- Prospective, randomised, single-blinded trial. - Comparison of oxitropium bromide and salbutamol vs. salbutamol alone. - Randomisation was accomplished but no details were given. - Allocation concealment was reported as using sealed envelopes but no mention if they were opaque or sequentially numbered.
Participants	- Patients who present to the ED with an exacerbation of asthma who met the criteria for asthma from ATS guidelines. - Set in Japan. - Had PEF ≤ 50% normal predicted value. - Ages: 18 to 55 years. - Asthma exacerbation severity of presenting patients was severe. Estimates of asthma severity based on control hospitalisation rates were estimated as moderate.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via MDI with a spacer device. - Group one received a combination of oxitropium bromide (100 µg/puff) and salbutamol (100 µg/puff) at 4 puffs each at 0, 20, and 40 minutes. - Group two received salbutamol alone (100 µg/puff) with placebo propellant gas at 4 puffs each at 0, 20, and 40 minutes. - Additional co-interventions provided in the ED included a single dose of IV betamethasone (8 mg) given to all patients in addition to supplemental oxygen. After 120 minutes, patients who showed no improvements received additional inhaled bronchodilators and IV aminophylline.
Outcomes	- Primary outcome was pulmonary function. - Additional outcomes included hospitalisation, adverse events, the need for additional ED treatment, and frequency of intubation.

Nakano 2000 *(Continued)*

	- Outcome measurements were performed at baseline, as well as 20, 40, 60, and 120 minutes after treatment.
Notes	- Unable to contact authors to clarify missing data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no information provided. Quote (p. 473): "Patients who agreed to participate in the study were randomly assigned to one of two treatments by means of sealed envelopes."
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used but no mention if they were opaque or sequentially numbered. Quote (p. 473): "Patients who agreed to participate in the study were randomly assigned to one of two treatments by means of sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blinded study. Quote (p. 472): "Methods: A randomised, single-blind, placebo-controlled study was performed in 74 patients between 18 and 55 years old presenting to the emergency department (ED) for treatment of acute asthma with a peak expiratory flow (PEF) of 50% or less than the normal predicted value."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions between groups were balanced. No details provided on patients attrition during the screening process. Quote (p. 473): "Of the 80 patients who were enrolled and randomised, 6 patients (2 receiving combination therapy and 4 receiving salbutamol alone) requested early withdrawal and were excluded. The remaining 74 patients were analyzed."
Selective reporting (reporting bias)	High risk	No protocol available. The frequency of side effects were incompletely reported. Quote (p. 475): "There was no statistically significant difference in incidence of tremor, palpitations, cough, dry mouth, or bad taste between the groups."
Other bias	Low risk	Funding provided by grant from the Hammamatsu Rosai Hospital. Quote (p. 472): "Supported by a department grant of Hamamatsu Rosai Hospital, Hamamatsu, Japan."

O'Driscoll 1989

Methods	- Prospective, double-blind trial. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Patients randomised into groups via year of birth (odd vs. even).

O'Driscoll 1989 *(Continued)*

Participants	- Patients who presented to the ED with an acute airflow obstruction. - Set in the United Kingdom. - Patients were classified has having either asthma or COPD according to the criteria of the ATS guidelines. - Ages: 17 years and older. - Asthma exacerbation severity of presenting patients was unclear. Not enough information provided to estimate asthma severity based on hospitalisations.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser with oxygen. - Group one received a single dose of ipratropium bromide (0.5 mg) and salbutamol (10 mg). - Group two received a single dose of salbutamol alone (10 mg) with additional 2 ml saline solution. - Additional co-interventions included supplemental oxygen. Intravaneous hydrocortisone and IV aminophylline was provided only if physicians determine further treatment was necessary.
Outcomes	- Outcomes included pulmonary function, admission to the ICU, need for mechanical ventilation, and adverse events. - Outcome measurements were performed at baseline and one hour after treatment.
Notes	- Contacted authors to clarify results but no response received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation generated by odd/even days of birth. Quote (p. 1418): "The solutions were coded and treatment was determined by the patient's year of birth (odd or even numbers)."
Allocation concealment (selection bias)	High risk	No allocation concealment, patients grouped based on date of birth. Quote (p. 1418): "The solutions were coded and treatment was determined by the patient's year of birth (odd or even numbers)."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported staff were blinded to treatments but no details provided on whether participants were blinded. Quote (p. 1418): "The staff were blind to the treatment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Excluded patients were equally balanced between groups. No information provided on attrition during the screening process prior to enrolment. Quote (p. 1419): "125 consecutive patients were entered in the study. 2 patients wished to go home within 60 min of starting nebulised treatment and a further 20 patients were transferred to a hospital ward within this period, either because accident and emergency beds were needed for other patients or because the patient was assigned to another hospital. No patient needed urgent admission to the intensive care unit or mechanical ventilation. The 22 pa-

O'Driscoll 1989 *(Continued)*

		tients who did not complete the trial were equally divided between the treatment groups."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Owens 1991

Methods	- Prospective, randomised, double-blind study. - Comparison of atropine sulphate and metaproterenol vs. metaproterenol alone. - Methods of randomisation unclear. - No information on allocation concealment provided.
Participants	- Patients who presented to the ED with an exacerbation of asthma and had a history of asthma as defined by the ATS guidelines. - Set in the United States. - Asthma exacerbation was defined as having an FEV < 2 L prior to beginning the study. - Ages: 18 to 65 years. - Asthma exacerbation severity of presenting patients estimated as moderate.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser. - Group one received a single dose of atropine sulphate (2.5 mg) and metaproterenol (0.3 mL, 5% solution). - Group two received a single dose of metaproterenol alone (0.3 mL, 5% solution). - No additional ED co-interventions stated.
Outcomes	- Outcomes included pulmonary function, hospitalisation, adverse events, and additional treatment in the ED. - Outcome measurements were performed at baseline, as well as 30, 60, and 120 minutes after treatment.
Notes	- Unable to contact authors to clarify original data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no information provided. Quote (p. 1084): "Patients who meet the admission criteria were randomised in a double-blinded fashion to receive either one dose of nebulized metaproterenol (5 percent solution, 0.3 ml) alone or combined with atropine sulfate (2.5 mg) in 3 ml normal saline solution."
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.

Owens 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Drug medications prepared in packages in advance and coded. Selected at random by treating physician and neither physician or the patient knew which medications were administered. Unclear whether medication packaging were identical. Quote (p. 1084): "To ensure double-blind treatment packages were prepared in advance and coded. These were then selected randomly by the treating physician, but neither this physician nor the patient knew which medications were administered."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Patient attrition unbalanced between groups. The only three patients excluded from the intervention study for being too sick. No information on patient attrition during the screening process. Quote (p. 1085): "Forty patients satisfied all entry criteria and were randomised to one of the two treatment groups. Three of these patients were withdrawn from the study during the 2-hour observation period because they were too ill and needed additional therapy."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Rahman 2006

Methods	- Prospective, single blind, randomised study. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Method of randomisation unclear. - No information provided on allocation concealment.
Participants	- Adult patients with acute asthma presenting to the ED. - Set in Bangladesh. - Ages: Adults (exact ages of participants not provided). - Asthma exacerbation of presenting patients unclear. Insufficient information provided, unable to estimate severity of asthma based on hospitalisation.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via MDI. - Group one received four puffs of ipratropium bromide (20 µg/puff) and salbutamol (100 µg/puff) over 10 minutes. - Group two received four puffs of salbutamol (100 µg/puff) alone over 10 minutes. - No additional ED co-interventions stated.
Outcomes	- Outcomes included pulmonary function and vital signs.

Rahman 2006 *(Continued)*

	- Outcome measurements were performed at baseline, as well as 30, 60, and 90 minutes after treatment.
Notes	- The study author was contacted to obtain missing data. No response was received. - No full-text, only an abstract available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methodology of randomisation not stated. Quote (p.): "Single-blind, randomised, prospective study..."
Allocation concealment (selection bias)	Unclear risk	No details provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blinded study. Quote (p.): "Single-blind, randomised, prospective study..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many patients were screened or how many patients refused or were excluded.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Rashid 2010

Methods	- Prospective, randomised, single-blind controlled study. - A comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Randomisation was accomplished using a random number table. - No information on allocation concealment provided.
Participants	- Patients who presented to the ED with an exacerbation of asthma and had an FEV of 30% to 50% predicted. - Set in Bangledesh. - Ages: 18 years or older. - Asthma exacerbation severity of presenting patients was unclear. Not enough information provided.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via volumetric spacer. - Group one received four puffs of ipratropium bromide (20 µg/puff) and salbutamol (100 µg/puff) over 1.5 hours.

Rashid 2010 *(Continued)*

	- Group two received four puffs of salbutamol (100 µg/puff) over 1.5 hours. - No additional ED co-interventions stated.
Outcomes	- Outcomes included pulmonary function. - Presence of side effects reported, but no details given. - Outcome measurements were performed at baseline, as well as 30, 60, and 90 minutes after treatment.
Notes	- The study author was contacted to retrieve missing data. No response was received. - No full-text, only an abstract available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table. Quote (p. 56): "... and were divided into two groups randomly using a random number table."
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blinded study. Quote (p. 56): "This single-blinded, randomised, controlled study..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided on the number of patients screened, refused, or excluded.
Selective reporting (reporting bias)	High risk	No protocol available. The frequency of side effects were incompletely reported. Quote (p. 56): "Side effect profiles were minimal in both groups"
Other bias	Unclear risk	No source of funding provided.

Rebuck 1987

Methods	- Prospective, randomised, double-blind study. - Comparison of ipratropium bromide and fenoterol vs. fenoterol alone. - Randomisation was accomplished using centre specific computer-generated randomised schedule. - No information on allocation concealment provided.
Participants	- Patients who presented to the ED with an exacerbation of asthma or COPD, with an FEV ≤ 70% of the predicted value.

Rebuck 1987 *(Continued)*

	- Set in Canada. - Participants who were able to perform a forced expiratory manoeuvre. - Ages: 18 years or older. - Asthma exacerbation severity of presenting patients was unclear. Not enough information provided.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser mask. - Group one received a single dose of ipratropium bromide (0.5 mg) and fenoterol (1.25 mg). - Group two received a single dose of fenoterol alone (1.25 mg). - Additional co-interventions provided in the ED included IV aminophylline or IV hydrocortisone at the discretion of the attending physician. All patients received supplemental oxygen.
Outcomes	- Outcomes included pulmonary function and adverse events. - Outcome measurements were performed at baseline, as well as 45 and 90 minutes after treatment.
Notes	- Study authors contacted to clarify data, but they no longer had access to the original database.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centre specified computer-generated randomised schedule. Quote (p. 60): "Center specific computer-generated randomised schedule..."
Allocation concealment (selection bias)	Low risk	Study medications identical in appearance and coded. Quote (p. 60): "Unit-dose vials containing these drugs were coded but identical in appearance."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded study. Study medications identical in appearance and coded. Quote (p. 60): "Each studied 50 patients in double-blind, randomised fashion." "Unit-dose vials containing these drugs were coded but identical in appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded. Outcome assessors blinded. Data accumulated centrally for analysis. Uncoded results were not revealed to investigates until all studies were completed. Quote (p. 60): "An identical protocol was adhered to by all investigators, and data were accumulated centrally for subsequent analysis. Although uncoded results were not revealed to Investigators until all studies were completed, an interim independent review of results was performed to ensure that no regimen was hazardous."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided on the number of patients screened, refused, or excluded.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Funded by Boehringer Ingelheim. No statement provided on influence of funding on preparation of the manuscript.

Rebuck 1987 *(Continued)*

	Quote (p. 59): "This work was supported by a research grant from Boehringer Ingelheim (Canada) Ltd."

Rodrigo 1995

Methods	- Prospective, randomised, double-blind study. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Method of randomisation unclear. - No information on allocation concealment provided.
Participants	- Patients presenting to the ED with an exacerbation of asthma with an FEV and PEF ≤ 50% of predicted value. - Set in Uruguay. - Ages: 18 to 50 years. - Asthma exacerbation severity of presenting patients was unclear. Insufficient information presented.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via MDI spacer. - Group one received four puffs of ipratropium bromide (20 µg/puff) and salbutamol (100 µg/puff) every 10 minutes for 3 hours. - Group two received four puffs of salbutamol (100 µg/puff) along with placebo (propellant) every 10 minutes for 3 hours. - Additional co-interventions provided in the ED included IV hydrocortisone (500 mg) after upon completion of initial treatment for all patients.
Outcomes	- Outcomes included pulmonary function and adverse events. - Outcome measurements were performed at baseline, as well as 30, 60, 90, 120, 150, and 180 minutes after the start of treatment.
Notes	- Contacted authors for additional information but no response received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no information provided. Quote (p. 177): "Los sujetos fueron asignados aleatoriamente a uno de dos grupos de tratamiento." (*T ranslation: "Subjects were randomly assigned to one of two treatment groups").*
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blinded but no information was provided. Quote (p. 177): "Se utilizaron procedimiento de tipo doble ciego." *(Translation: "We used double-blind procedures.")*

Rodrigo 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many patients were screened, refused or excluded.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Rodrigo 2000

Methods	- Prospective, randomised, double-blind trial. - Comparison of ipratropium bromide and albuterol vs. albuterol alone. - Randomisation was accomplished using a random number table. - Allocation concealment reported and discussed, hospital pharmacy prepared the drugs and sealed drugs in opaque envelope.
Participants	- Patients who presented to the ED with an exacerbation of asthma, who met the diagnosis criteria of asthma. - Set in Uruguay. - Exacerbation of asthma was defined as having an FEV < 50% predicted value. - Ages: 18 to 50 years. - Asthma exacerbation severity of presenting patients estimated as severe.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via MDI. - Group one received four puffs of ipratropium bromide (21 µg/puff) and albuterol (120 µg/puff) at 10 minutes intervals over 3 hours. - Group two received four puffs of albuterol (120 µg/puff) alone at 10 minutes intervals over 3 hours. - Additional co-interventions provided in the ED included supplemental oxygen if the patients oxygen saturation decreased to < 92%, however the study reveals this did not occur.
Outcomes	- Primary outcomes included pulmonary function and hospitalisation. - Additional outcomes included frequency of adverse events. - Outcome measurements were performed at baseline, as well as 30, 60, 90, 120, 150, and 180 minutes after the start of treatment.
Notes	- Contacted authors for additional information but no response received.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Rodrigo 2000 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random numbers table. Quote (p. 1863): "The hospital pharmacy prepared the IB and control treatments in random sequence, using a random number table,..."
Allocation concealment (selection bias)	Low risk	Central allocation. Hospital pharmacy prepared the study medications. Stored in opaque envelopes. Quote (p. 1863): "The hospital pharmacy prepared the IB and control treatments in random sequence, using a random number table, in identical canisters, which were then numbered consecutively. For each study patient, the treatment nurse selected the next numbered canister from an opaque envelope,..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. Study medications kept in identical, consecutively numbered canisters. Study nurse selected the canisters from an opaque envelope. Quote (p. 1863): "The hospital pharmacy prepared the IB and control treatments in random sequence, using a random number table, in identical canisters, which were then numbered consecutively. For each study patient, the treatment nurse selected the next numbered canister from an opaque envelope,..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded. All outcome measures made by investigators unaware of the patients group assignment. Quote (p. 1863): "... and all measures were made by investigators unaware of the patients' group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information on patient attrition provided and balanced between groups. Quote (p. 1863): "One hundred ninety-five patients were assessed in the ED. Of these, 15 (eight in the control group and seven in the IB group) did not fit the inclusion criteria for the study because they did not meet the age requirement (seven patients), or the FEV_1 requirement (five patients), or had cardiac disease (three patients). Of the remaining 180 patients, mean age ± SD, 34.4 ± 10.5 years), 88 were randomly assigned to the IB group and 92 to the control group. Analyses were by intention-to-treat, although no withdrawals occurred."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding provided.

Salo 2006

Methods	- Prospective, randomised, double-blind, controlled clinical trial. - Comparison of ipratropium bromide and albuterol vs. albuterol alone. - Randomisation was using a computerised random numbers table. - Allocation concealment was reported and discussed as using identical drug containers, with medication being kept in locked room.
Participants	- Patients presenting to the ED with an exacerbation of asthma and had a history of prior episodes of asthma. - Set in the United States.

Salo 2006 *(Continued)*

	- Exacerbation of asthma defined as having a PEF < 70% of the predicted value. - Age: 18 years and older. - Asthma exacerbation severity of presenting patients estimated as moderate.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser. - Group one received ipratropium bromide (2 mg) and albuterol (15 mg) taken continuously over a 2 hour period. - Group two received albuterol (15 mg) alone taken continuously over a 2 hour period. - Additional co-interventions provided in the ED included 1 mg/kg of oral prednisone (maximum 60 mg) at time of enrolment. At discharge from the ED, patients received a prescription for oral corticosteroids for 5 days (1 mg/kg up to 60 mg per day).
Outcomes	- Outcomes included pulmonary function and hospitalisation. Additional data on adverse events was retrieved from the study authors. - Outcome measurements were performed at baseline, as well as 60 and 120 minutes after the start of treatment.
Notes	- Contacted authors for additional information on the study. Study authors provided additional clarification on results for adverse events and pulmonary function.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers tables. Quote (p. 372): "Randomization into study groups was done using a computerized random numbers table."
Allocation concealment (selection bias)	Low risk	Sequentially numbered medications which were identical in appearance. An ED nurse not involved in the direct care of administration of the study medications to the patients, prepared the medications in a separate locked medication room. Medications were prepared in separate locked medication room. Quotes (p. 372): "Patients who verbally consented during this brief assessment phase were then asked to review and provide full informed written consent while a previously inserviced ED nurse, not involved in direct care or administration of study medication to the patient (usually the charge nurse), prepared the study medication in a separate locked medication room. Before study startup, all study medications, a B&B Hope Nebulizer (B&B Medical Technologies Inc., Orangevale, CA), sterile saline, and instructions on how to mix medications were placed into sealed, sequentially marked bags, which were kept secured in the locked medication room."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study. ED staff not involved with the patient or administration of the study medications prepared the study medications for the research staff and instructed to not inform anyone involved in the study the contents of the mixtures. Medications were sequentially numbered and identical in appearance. Quote (pp. 372-3): "The nurse preparing the medication selected the next numerically marked bag, recorded the patient's name, medical record and bag number on a data enrolment form and was instructed not to divulge to anyone involved in the study the contents of the Hope Nebulizer. Both study mixtures were clear, colorless solutions."

Salo 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors in the ED were not informed of the study medications by the ED nurse preparing the study medications. Quote (pp. 372-3): "The nurse preparing the medication selected the next numerically marked bag, recorded the patient's name, medical record and bag number on a data enrolment form and was instructed not to divulge to anyone involved in the study the contents of the Hope Nebulizer."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information on patient attrition provided and balanced between groups with a flow diagram provided. See p. 373.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	No source of funding stated.

Solarte 2004

Methods	- Prospective RCT. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Method of randomisation unclear. - No information on allocation concealment provided.
Participants	- Adults presenting to the ED with an exacerbation of asthma. - Set in Columbia. - Ages: 18 to 65 years. - Asthma exacerbation severity of presenting patients was estimated as moderate.
Interventions	- Multiple doses of combination inhaled therapy. Study interventions provided via nebuliser. - Group one received one dose of ipratropium bromide (500 mg) and salbutamol (2.5 mg) every 20 minutes for one hour, for a total of three doses. - Group two received one dose of salbutamol (2.5 mg) alone every 20 minutes for one hour, for a total of three doses. - No co-interventions stated.
Outcomes	- The primary outcome was change in FEV_1. - Secondary outcomes included peak flow, clinical signs and symptoms, adverse events, and hospitalisation. - Outcome measurements were performed at baseline and 120 minutes after the start of treatment.
Notes	- Contacted authors for missing data but no response received. - No full-text, only an abstract available.

Risk of bias

Bias	Authors' judgement	Support for judgement

Solarte 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomised but no information provided. Quote (p. 1): "Consecutive adult patients (18-65) consulting to emergency room, with clinical and functional AAE were randomly assigned to receive..."
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on patient attrition provided.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Funded by AstraZeneca. No statement provided on influence of funding on preparation of the manuscript. Quote (p. 1): "Supported by an educational grant from AstraZeneca."

Summers 1990

Methods	- Prospective, randomised, double-blind study. - Comparison of ipratropium bromide and salbutamol vs. salbutamol alone. - Methods of randomisation unclear. - No information on allocation concealment provided.
Participants	- Patients presenting to the ED with an exacerbation of acute asthma. - Set in Australia. - Patients must be able to perform PEF. - Ages: 16 to 70 years. - Asthma exacerbation severity of presenting patients was unclear. Insufficient information provided to estimate asthma severity based on hospitalisations.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser. - Group one received a single dose of salbutamol (5 mg) alone, followed by a single dose of Ipratropium bromide (0.5 mg) one hour later. - Group two received a single dose of ipratropium bromide (0.5 mg) alone, followed by a single dose of salbutamol (5 mg) one hour later.

Summers 1990 *(Continued)*

	- Group three received a single dose of ipratropium bromide (0.5 mg) and salbutamol (5 mg), followed by placebo one hour later. - Additional co-interventions provided in the ED included IV hydrocortisone and IV aminophylline if deemed necessary by the attending physician.
Outcomes	- Outcomes included pulmonary function. - Outcome measurements were performed at baseline, as well as 15 minutes, 60, 75, and 120 minutes after treatment. Only pulmonary function data measured 15 minutes after treatment exposure in groups one and three were extracted. Pulmonary data measured at 60, 75 and 120 minutes after treatment was not extracted because group one received Ipratropium bromide one hour after receiving salbutamol.
Notes	- Unable to contact authors for additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no information provided. Quote (p. 426): "The study was double-blind and randomised, and there were three treatment groups as follow:..."
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blinded but no information provided. Quote (p. 426): "The study was double-blind..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many patients were screened, refused or excluded.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Funding provided by GlaxoSmithKline. No statement provided on influence of funding on preparation of the manuscript. Quote (p. 429): "... and Glaxo Australia for financial support."

Weber 1999

Methods	- Prospective, randomised, double-blind, placebo-controlled study. - Comparison of ipratropium bromide and albuterol vs. albuterol alone. - Randomisation was accomplished using a random numbers table. - Allocation concealment was reported and discussed as pharmacy controlled.

Weber 1999 *(Continued)*

Participants	- Patients presenting to the ED with an exacerbation of asthma, who had a PEF < 70% of the predicted value. - Set in the United States. - Ages: 18 years or older. - Asthma exacerbation severity of presenting patients estimated as severe.
Interventions	- Single dose of combination inhaled therapy. Study interventions provided via nebuliser. - First group received ipratropium bromide (1.0 mg/hour) and albuterol (10 mg/hour) taken continuously over a three hour period. - Second group received albuterol (10 mg/hour) alone taken continuously over a three hour period. - Additional co-interventions provided in the ED included oral prednisone and albuterol (2.5 mg) provided to all patients upon presentation to the ED. Supplemental oxygen was given if patients $S0_2$ was < 90%.
Outcomes	- Primary outcomes included pulmonary function, hospitalisation and ED length of stay. - Seconary outcomes included vital signs, symptom scores, and adverse events. - Outcome measurements were performed at baseline, as well as one, two, and three hours after the start of treatment.
Notes	- Contacted primary author who stated that they no longer had access to the original data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers tables. Quote (p. 938): "The combination and control treatments were prepared by the hospital pharmacy in random sequence using a random number table..."
Allocation concealment (selection bias)	Unclear risk	Central allocation, pharmacy-controlled. Quote (p. 938): "The combination and control treatments were prepared by the hospital pharmacy..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. Study medications placed in consecutively numbered identical brown-tinted bottles. Treating physicians, respiratory therapist, patients and investigators were blind to treatment. Quotes (pp. 938-9): "The combination and control treatments were prepared by the hospital pharmacy in random sequence using a random number table and were placed in identical 4-oz brown-tinted bottles, which were then numbered consecutively." "The RT, treating physician, and patient were blinded to treatment, and the code for drug assignment was not known to the investigators until data for all patients had been entered into the study database."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians, and respiratory therapists were blinded to treatment. Code for drug assignment were unknown to the study investigators until all of the patients data have been entered into the study database. Quote (p. 939): "The RT, treating physician, and patient were blinded to treatment, and the code for drug assignment was not known to the investigators until data for all patients had been entered into the study database."

Weber 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided on why most screened patients were not enrolled into the study. Quote (p. 939): "There were 465 patients who presented to the ED with acute bronchospasm during the study period but were not enrolled in the study."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Ipratropium bromide and pharmacy costs provided by Boehringer Ingelheim. No statement provided on influence of funding on preparation of the manuscript. Quote (p. 937): "Ipratropium bromide and pharmacy costs were provided by Boehringer Ingelheim.

Abbreviations:
ATS - American Thoracic Society
COPD - chronic obstructive pulmonary disease
ED - emergency department
FEV - forced expiratory volume
ICU - intensive care unit
IV - intravenous
MDI - metered-dose inhaler
PEF - peak expiratory flow
RCT - randomised controlled trial

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

Study	Reason for exclusion
Anonymous 1994	Not a prospective RCT or CCT
Barrett 2014	Not a prospective RCT or CCT
Beck 1985	Included children
Bonsignore 1986	Not treated for acute asthma, not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs. SABA alone
Bourcereau 1988	Not treated for acute asthma, no comparison of SAAC + SABA vs. SABA alone
Brenner 1988	Included children, not treated for acute asthma, not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs. SABA alone
Britton 1988	Not treated for acute asthma, not recruited in ED or acute care settings
Bryant 1985	Not recruited in ED or acute care settings
Bryant 1990	Not treated for acute asthma, not recruited in ED or acute care settings
Chen 1989	Not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs. SABA alone
Chhabra 2002	Not treated for acute asthma, not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs. SABA alone

Study	Reason for exclusion
Cydulka 1994	No comparison of inhaled SAAC + SABA vs. SABA alone
Garcia 2012	Not a prospective RCT or CCT
Gaur 2008	No comparison of inhaled SAAC + SABA vs. SABA alone
Gilman 1990	No comparison of inhaled SAAC + SABA vs. SABA alone
Higgins 1988	Not recruited in ED or acute care settings
Hunt 1983	Not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs SABA alone
Janson 1988	No comparison of inhaled SAAC + SABA vs. SABA alone
Kaik 1980	Not treated for acute asthma, not recruited in ED or acute care settings
Karpel 1986	No comparison of inhaled SAAC + SABA vs. SABA alone
Kerstjens 2011	Not treated for acute asthma, not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs SABA alone
Koumbourlis 2015	Not a prospective RCT or CCT
Lanes 1998	Not a prospective RCT or CCT
Leahy 1983	Not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs SABA alone
Lin 1999	No comparison of inhaled SAAC + SABA vs. SABA alone
Lin 2004	No comparison of inhaled SAAC + SABA vs. SABA alone
Louw 1990	Not recruited in ED or acute care settings
Maesen 1997	Not treated for acute asthma, not recruited in ED or acute care settings
Mazzei 1986	Not treated for acute asthma, not recruited in ED or acute care settings
Nana 1995	Unable to confirm with study authors if patients were recruited in ED or acute care settings, or the age range of included participants
Patrick 1990	Not treated for acute asthma, not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs. SABA alone
Rodrigo 1999	Not a prospective RCT or CCT
Roeseler 1987	Not treated for acute asthma
Salome 1988	Not treated for acute asthma, not recruited in ED or acute care settings
Schlueter 1978	Not treated for acute asthma, not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs. SABA alone
Schneider 2012	No comparison of inhaled SAAC + SABA vs. SABA alone
Stoodly 1999	Not a prospective RCT or CCT

Study	Reason for exclusion
Tamura 2014	Not a prospective RCT or CCT, no comparison of inhaled SAAC + SABA vs SABA alone
Toda 1992	Unable to confirm study design, if participants were recruited in ED or acute care settings, or the age range of included participants
Vogt 1974	Not treated for acute asthma, no comparison of inhaled SAAC + SABA vs. SABA alone
Ward 1981	Not recruited in ED or acute care settings, no comparison of inhaled SAAC + SABA vs. SABA alone
Youngchaiyud 1989	Not treated for acute asthma, not recruited in ED or acute care settings
Zaritsky 1999	Not a prospective RCT or CCT

Abbreviations:
CCT - clinical controlled trial
ED - emergency department
RCT - randomised controlled trial
SAAC - short-acting anticholinergics
SABA - short-acting beta$_2$-agonists

DATA AND ANALYSES

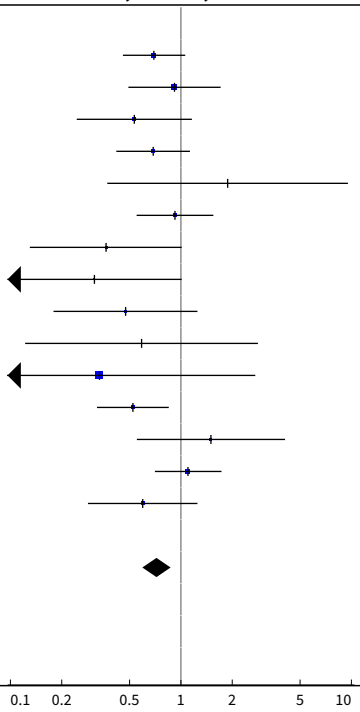
Comparison 1. Combination inhaled therapy versus SABA alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospitalisation	16	2120	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.59, 0.87]
2 Hosptialisation worst-case scenario	15	2085	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.63, 0.91]
3 Total adverse events	11	1392	Odds Ratio (M-H, Random, 95% CI)	2.03 [1.28, 3.20]
4 Adverse events: Dry mouth	5	447	Odds Ratio (M-H, Random, 95% CI)	2.08 [0.84, 5.12]
5 Adverse events: Tremor	5	804	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.88, 2.01]
6 Adverse events: Anxiety	2	564	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.31, 2.17]
7 Adverse events: Palpitations	5	809	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.17, 6.06]
8 Adverse events: Nausea	3	245	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.19, 2.17]
9 Adverse events: Headache	2	247	Odds Ratio (M-H, Random, 95% CI)	1.46 [0.31, 6.78]
10 Adverse events: Blurred vision	1	141	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.12, 4.50]
11 Adverse events: Agitation	1	62	Odds Ratio (M-H, Random, 95% CI)	2.90 [0.11, 74.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 FEV_1	6	687	Mean Difference (IV, Random, 95% CI)	0.25 [0.02, 0.48]
13 Percent change in FEV_1 (%)	5	578	Mean Difference (IV, Random, 95% CI)	21.28 [-5.62, 48.18]
14 Peak expiratory flow (PEF)	12	1056	Mean Difference (IV, Random, 95% CI)	36.58 [23.07, 50.09]
15 Percent change from baseline PEF (%)	7	551	Mean Difference (IV, Random, 95% CI)	24.88 [14.83, 34.93]
16 Percent predicted PEF (%)	2	102	Mean Difference (IV, Random, 95% CI)	13.67 [3.88, 23.46]
17 Additional treatment required in the ED	4	543	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.13]
18 Relapse rates	5	1180	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.66, 0.98]

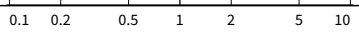
Analysis 1.1. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 1 Hospitalisation.

Study or subgroup	Combination therapy n/N	SABA alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aggarwal 2002	0/23	0/25			Not estimable
Cydulka 2010	22/67	35/74		15.31%	0.69[0.46,1.06]
Diaz 1997	23/98	11/43		8.08%	0.92[0.49,1.71]
FitzGerald 1997	9/154	17/155		5.47%	0.53[0.25,1.16]
Garrett 1997	22/144	30/135		11.74%	0.69[0.42,1.13]
Kamei 1999	4/33	2/31		1.35%	1.88[0.37,9.54]
Karpel 1996	24/192	26/192		11.02%	0.92[0.55,1.55]
Kohistani 2007	4/30	11/30		3.26%	0.36[0.13,1.01]
Lin 1998	3/27	10/28		2.51%	0.31[0.1,1.01]
Nakano 2000	5/38	10/36		3.61%	0.47[0.18,1.25]
Owens 1991	2/17	4/20		1.44%	0.59[0.12,2.83]
Rodrigo 1995	1/11	3/11		0.81%	0.33[0.04,2.73]
Rodrigo 2000	18/88	36/92		12.24%	0.52[0.32,0.85]
Salo 2006	8/32	5/30		3.42%	1.5[0.55,4.08]
Solarte 2004	29/99	26/98		13.75%	1.1[0.7,1.73]
Weber 1999	8/34	13/33		5.98%	0.6[0.29,1.25]
Total (95% CI)	**1087**	**1033**		**100%**	**0.72[0.59,0.87]**
Total events: 182 (Combination therapy), 239 (SABA alone)					
Heterogeneity: Tau^2=0.02; Chi^2=15.87, df=14(P=0.32); I^2=11.77%					
Test for overall effect: Z=3.39(P=0)					



Analysis 1.2. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 2 Hosptialisation worst-case scenario.

Study or subgroup	Combination therapy n/N	SABA alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aggarwal 2002	0/23	0/25			Not estimable
Cydulka 2010	22/67	35/74		13.06%	0.69[0.46,1.06]
FitzGerald 1997	33/171	39/171		13.33%	0.85[0.56,1.28]
Garrett 1997	49/171	61/167		18.91%	0.78[0.58,1.07]
Kamei 1999	4/35	2/34		1.22%	1.94[0.38,9.92]
Karpel 1996	24/192	26/192		9.6%	0.92[0.55,1.55]
Kohistani 2007	4/30	11/30		2.95%	0.36[0.13,1.01]
Lin 1998	3/27	10/28		2.28%	0.31[0.1,1.01]
Nakano 2000	7/40	14/40		4.7%	0.5[0.23,1.11]
Owens 1991	5/20	4/20		2.35%	1.25[0.39,3.99]
Rodrigo 1995	1/11	3/11		0.74%	0.33[0.04,2.73]
Rodrigo 2000	18/88	36/92		10.6%	0.52[0.32,0.85]
Salo 2006	8/32	5/30		3.1%	1.5[0.55,4.08]
Solarte 2004	29/99	26/98		11.82%	1.1[0.7,1.73]
Weber 1999	8/34	13/33		5.34%	0.6[0.29,1.25]
Total (95% CI)	**1040**	**1045**		**100%**	**0.76[0.63,0.91]**
Total events: 215 (Combination therapy), 285 (SABA alone)					
Heterogeneity: Tau^2=0.02; Chi^2=15.98, df=13(P=0.25); I^2=18.65%					
Test for overall effect: Z=2.99(P=0)					



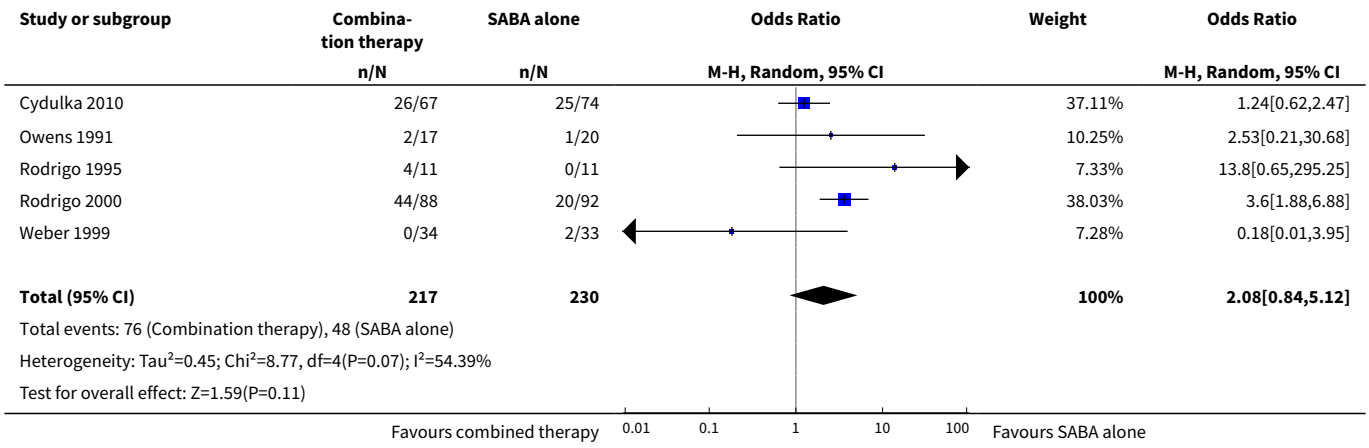
Favors combined therapy — Favors SABA alone

Analysis 1.3. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 3 Total adverse events.

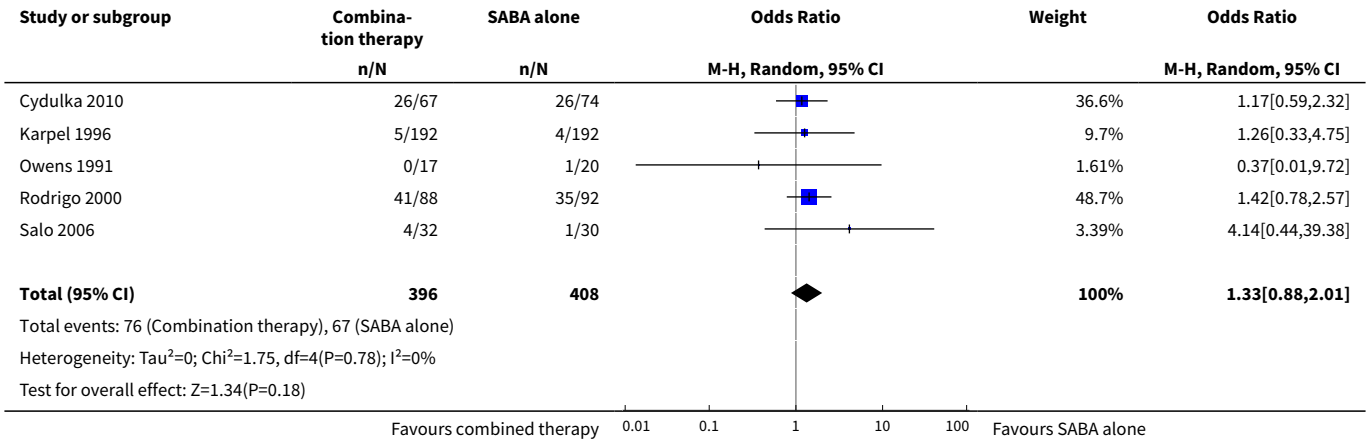
Study or subgroup	Combination therapy n/N	SABA alone n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Aggarwal 2002	0/23	0/25			Not estimable
Cydulka 2010	52/67	38/74		25.93%	3.28[1.58,6.84]
Diaz 1997	9/47	3/22		9.17%	1.5[0.36,6.19]
Garrett 1997	0/144	0/135			Not estimable
Karpel 1996	5/192	4/192		10.25%	1.26[0.33,4.75]
O'Driscoll 1989	5/59	2/44		6.69%	1.94[0.36,10.52]
Owens 1991	4/17	2/20		5.71%	2.77[0.44,17.46]
Rodrigo 1995	4/11	0/11		2.16%	13.8[0.65,295.25]
Rodrigo 2000	44/88	35/92		33.72%	1.63[0.9,2.95]
Salo 2006	5/32	1/30		4.05%	5.37[0.59,48.96]
Weber 1999	0/34	4/33		2.31%	0.1[0,1.84]
Total (95% CI)	**714**	**678**		**100%**	**2.03[1.28,3.2]**
Total events: 128 (Combination therapy), 89 (SABA alone)					
Heterogeneity: Tau^2=0.07; Chi^2=9.34, df=8(P=0.31); I^2=14.38%					
Test for overall effect: Z=3.03(P=0)					

Favours combined therapy — Favours SABA alone

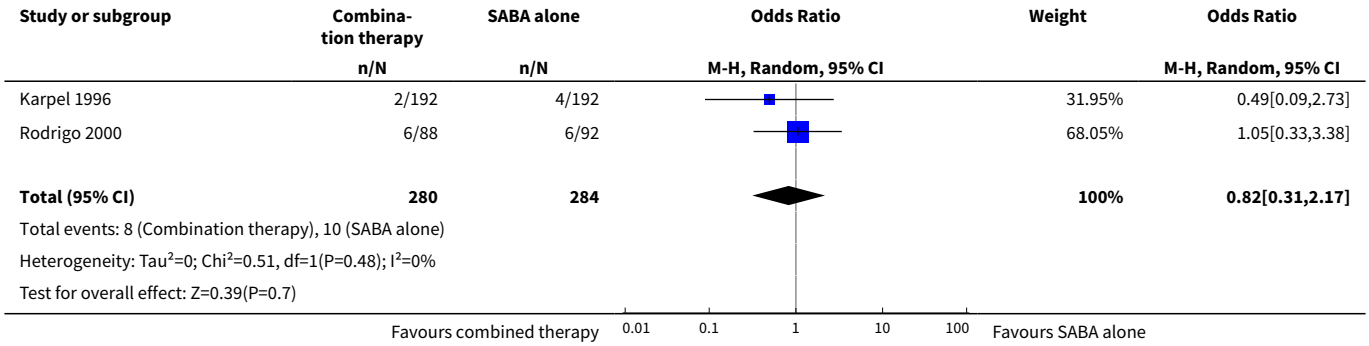
Analysis 1.4. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 4 Adverse events: Dry mouth.



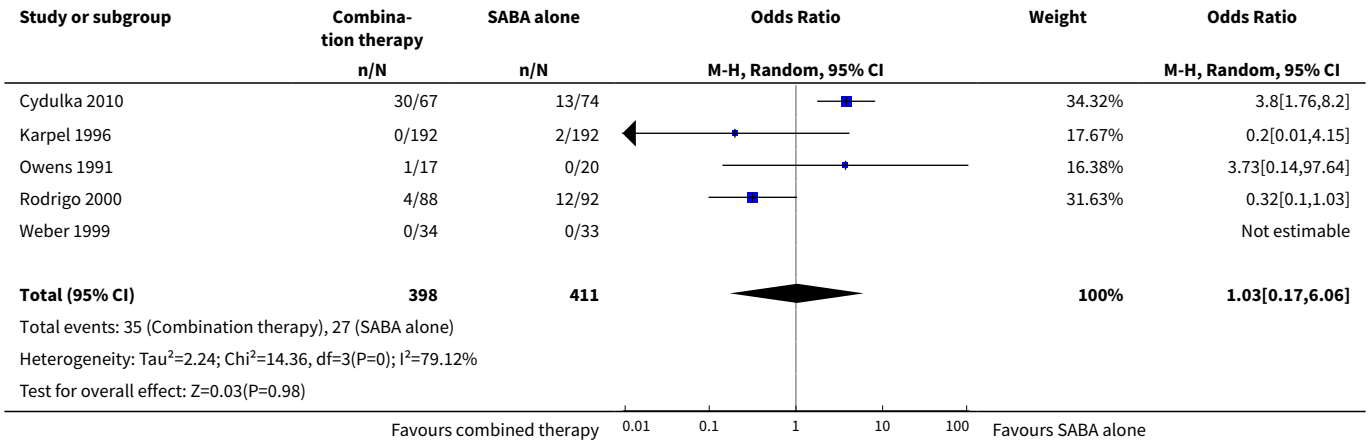
Analysis 1.5. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 5 Adverse events: Tremor.



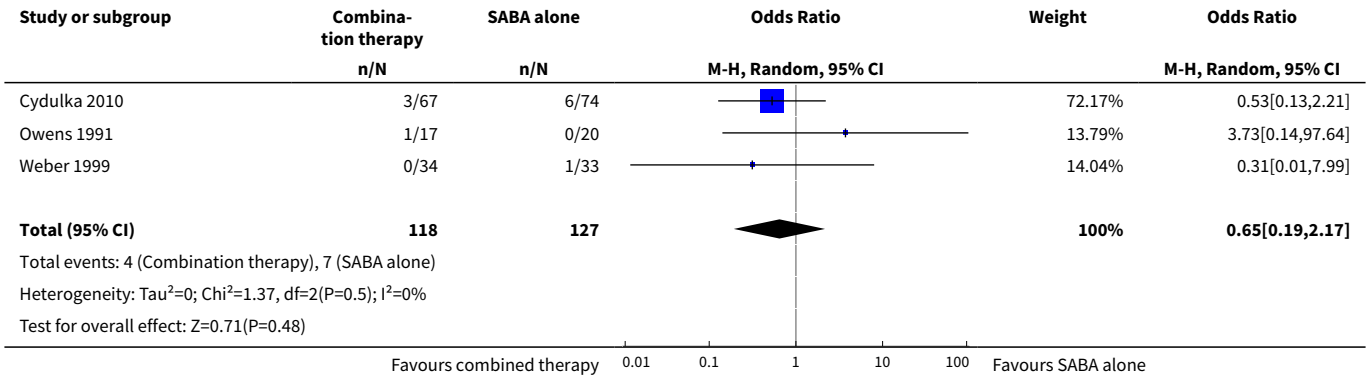
Analysis 1.6. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 6 Adverse events: Anxiety.



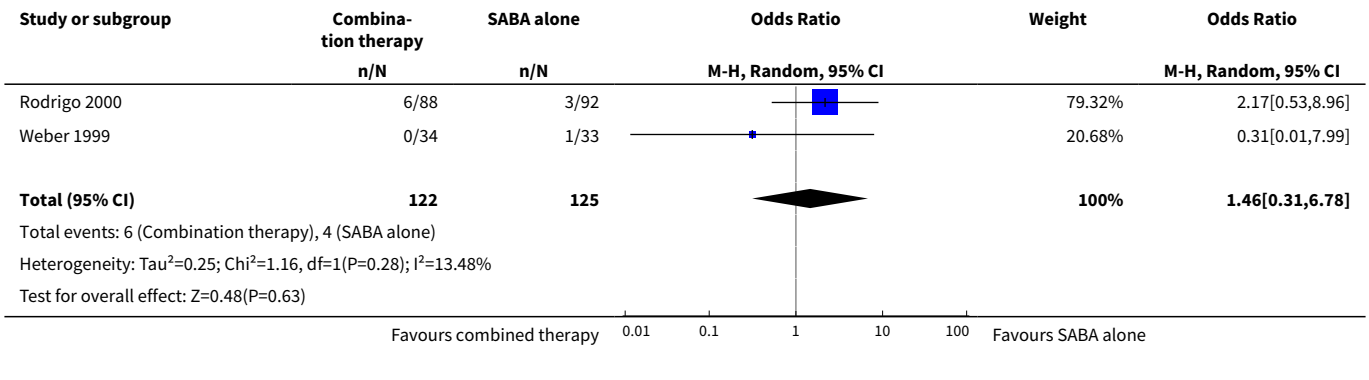
Analysis 1.7. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 7 Adverse events: Palpitations.



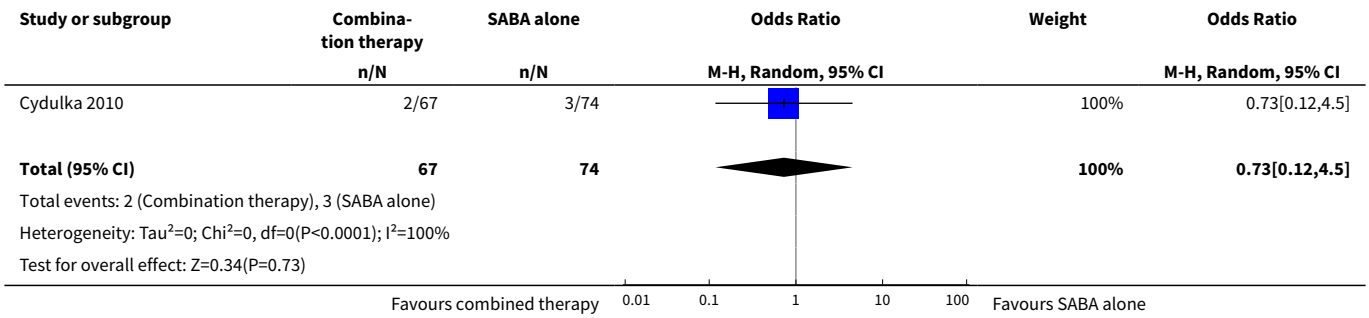
Analysis 1.8. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 8 Adverse events: Nausea.



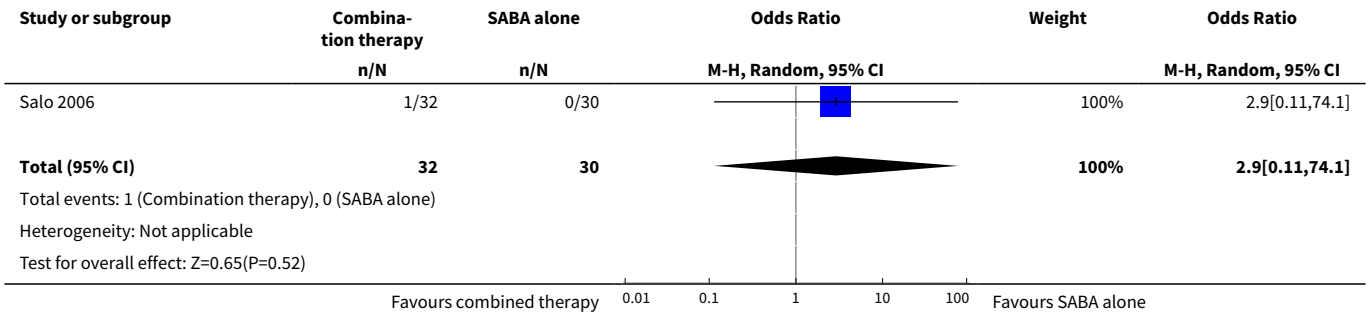
Analysis 1.9. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 9 Adverse events: Headache.



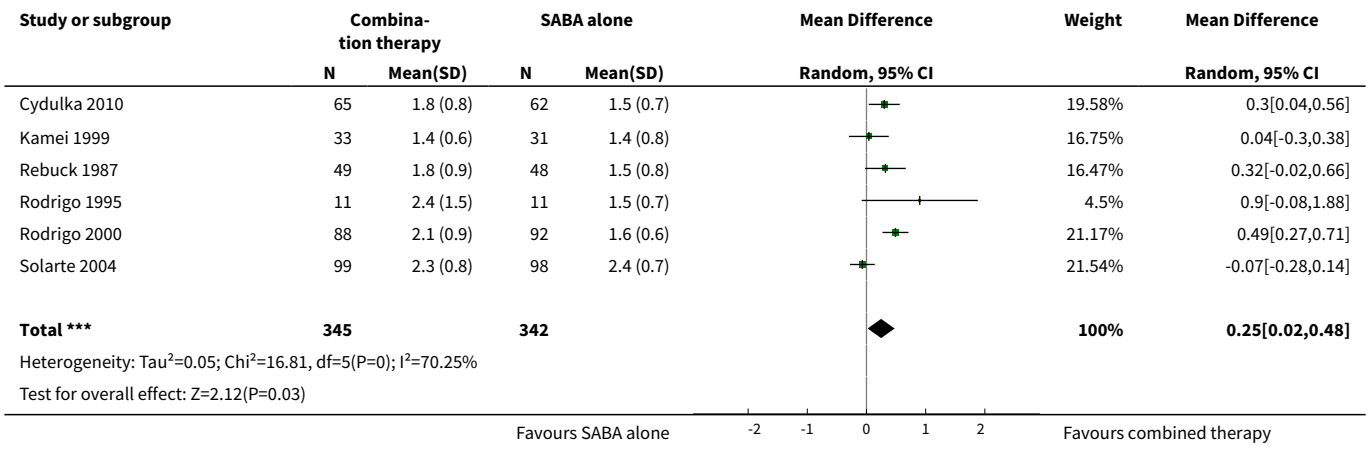
Analysis 1.10. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 10 Adverse events: Blurred vision.



Analysis 1.11. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 11 Adverse events: Agitation.



Analysis 1.12. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 12 FEV_1.



Analysis 1.13. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 13 Percent change in FEV_1 (%).

Study or subgroup	Combination therapy N	Combination therapy Mean(SD)	SABA alone N	SABA alone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kamei 1999	33	81 (57)	31	32 (45)		20.61%	49[23.92,74.08]
Owens 1991	17	57 (54)	20	59 (80)		15.17%	-2[-45.45,41.45]
Rashid 2010	51	80.5 (51.8)	49	62.4 (74.2)		20.58%	18.1[-7.07,43.27]
Rodrigo 2000	88	153.7 (96)	92	105.6 (98.2)		19.63%	48.1[19.73,76.47]
Solarte 2004	99	45 (39)	98	52 (43)		24.01%	-7[-18.47,4.47]
Total ***	**288**		**290**			**100%**	**21.28[-5.62,48.18]**

Heterogeneity: Tau^2=750.17; Chi^2=25.29, df=4(P<0.0001); I^2=84.18%

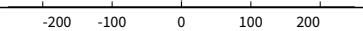
Test for overall effect: Z=1.55(P=0.12)

Analysis 1.14. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 14 Peak expiratory flow (PEF).

Study or subgroup	Combination therapy N	Combination therapy Mean(SD)	SABA alone N	SABA alone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Aggarwal 2002	23	233.3 (118.2)	25	228.4 (120.5)		3.59%	4.9[-62.66,72.46]
Hossain 2013	40	285.3 (55.3)	40	239.8 (46)		17.89%	45.5[23.21,67.79]
Kamei 1999	33	261 (103)	31	210 (95)		6.35%	51[2.49,99.51]
Nakano 2000	38	312 (78)	36	253 (80)		10.02%	59[22.97,95.03]
O'Driscoll 1989	33	222 (118.5)	23	190 (92.5)		5.09%	32[-23.35,87.35]
Rashid 2010	51	186.4 (118.5)	49	146.7 (92.5)		8.11%	39.7[-1.88,81.28]
Rebuck 1987	49	209.7 (121.3)	48	159.3 (106)		7.09%	50.4[5.09,95.71]
Rodrigo 1995	11	365.9 (151.3)	11	249.1 (89.7)		1.61%	116.8[12.86,220.74]
Rodrigo 2000	88	335.9 (100.2)	92	286.1 (89.2)		14.11%	49.8[22.04,77.56]
Salo 2006	32	316.8 (88)	30	313.8 (95.3)		6.98%	3[-42.74,48.74]
Solarte 2004	99	295 (119)	98	295 (98)		12.6%	0[-30.43,30.43]
Summers 1990	40	268 (120.2)	36	244 (90)		6.58%	24[-23.45,71.45]
Total ***	**537**		**519**			**100%**	**36.58[23.07,50.09]**

Heterogeneity: Tau^2=136.14; Chi^2=14.73, df=11(P=0.2); I^2=25.33%

Test for overall effect: Z=5.31(P<0.0001)

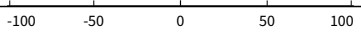


Analysis 1.15. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 15 Percent change from baseline PEF (%).

Study or subgroup	Combination therapy N	Combination therapy Mean(SD)	SABA alone N	SABA alone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hossain 2013	40	94.4 (33.7)	40	62.6 (29.3)		28.98%	31.84[18,45.68]
Kamei 1999	33	81 (57)	31	32 (45)		12.84%	49[23.92,74.08]
Rodrigo 1995	11	105.5 (74.4)	11	79.8 (66.6)		2.77%	25.7[-33.31,84.71]
Rodrigo 2000	88	102 (62.5)	92	81.5 (60.1)		21.11%	20.5[2.57,38.43]
Salo 2006	32	80.9 (69.8)	30	59.9 (50)		9.51%	21[-9.08,51.08]
Summers 1990	40	55 (63.2)	36	49 (48)		12.84%	6[-19.09,31.09]
Weber 1999	34	56 (64)	33	43 (44)		11.95%	13[-13.23,39.23]
Total ***	**278**		**273**			**100%**	**24.88[14.83,34.93]**

Heterogeneity: Tau^2=40.83; Chi^2=7.76, df=6(P=0.26); I^2=22.64%

Test for overall effect: Z=4.85(P<0.0001)



Favours SABA alone — Favours combined therapy

Analysis 1.16. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 16 Percent predicted PEF (%).

Study or subgroup	Combination therapy N	Combination therapy Mean(SD)	SABA alone N	SABA alone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hossain 2013	40	64.8 (7)	40	54.2 (7.8)		72.61%	10.6[7.35,13.85]
Rodrigo 1995	11	69.1 (22.2)	11	47.3 (12.7)		27.39%	21.8[6.69,36.91]
Total ***	**51**		**51**			**100%**	**13.67[3.88,23.46]**

Heterogeneity: Tau^2=31.61; Chi^2=2.02, df=1(P=0.16); I^2=50.4%

Test for overall effect: Z=2.74(P=0.01)

Favours SABA alone — Favours combined therapy

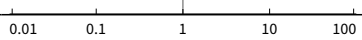
Analysis 1.17. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 17 Additional treatment required in the ED.

Study or subgroup	Combination therapy n/N	SABA alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aggarwal 2002	11/23	14/25		19.55%	0.85[0.49,1.48]
Karpel 1996	104/192	116/192		60.07%	0.9[0.75,1.07]
Nakano 2000	7/38	15/36		11.32%	0.44[0.2,0.96]
Owens 1991	7/17	6/20		9.06%	1.37[0.57,3.3]
Total (95% CI)	**270**	**273**		**100%**	**0.85[0.64,1.13]**

Total events: 129 (Combination therapy), 151 (SABA alone)

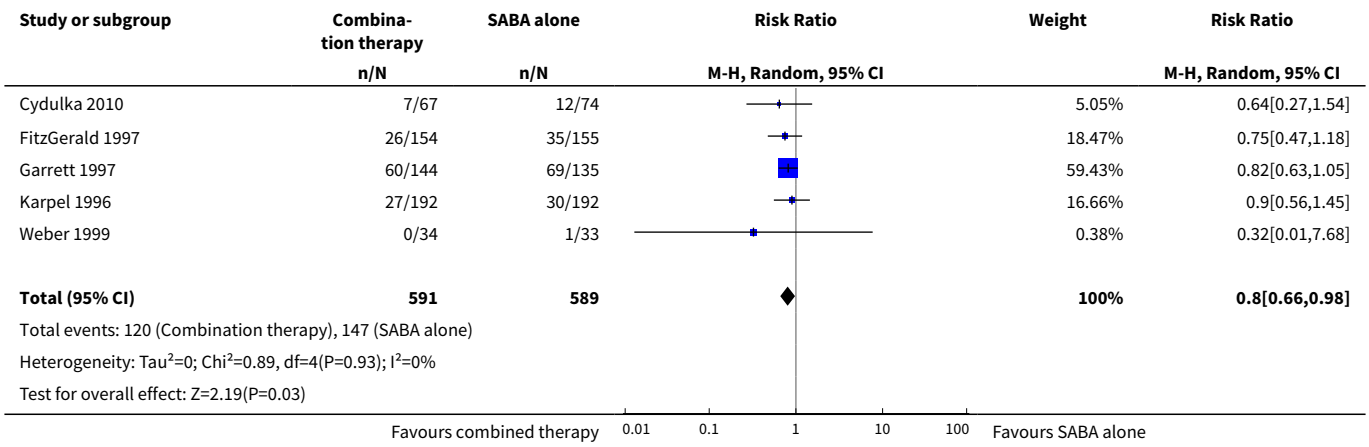
Heterogeneity: Tau^2=0.03; Chi^2=4.13, df=3(P=0.25); I^2=27.44%

Test for overall effect: Z=1.12(P=0.26)



Favours combined therapy — Favours SABA alone

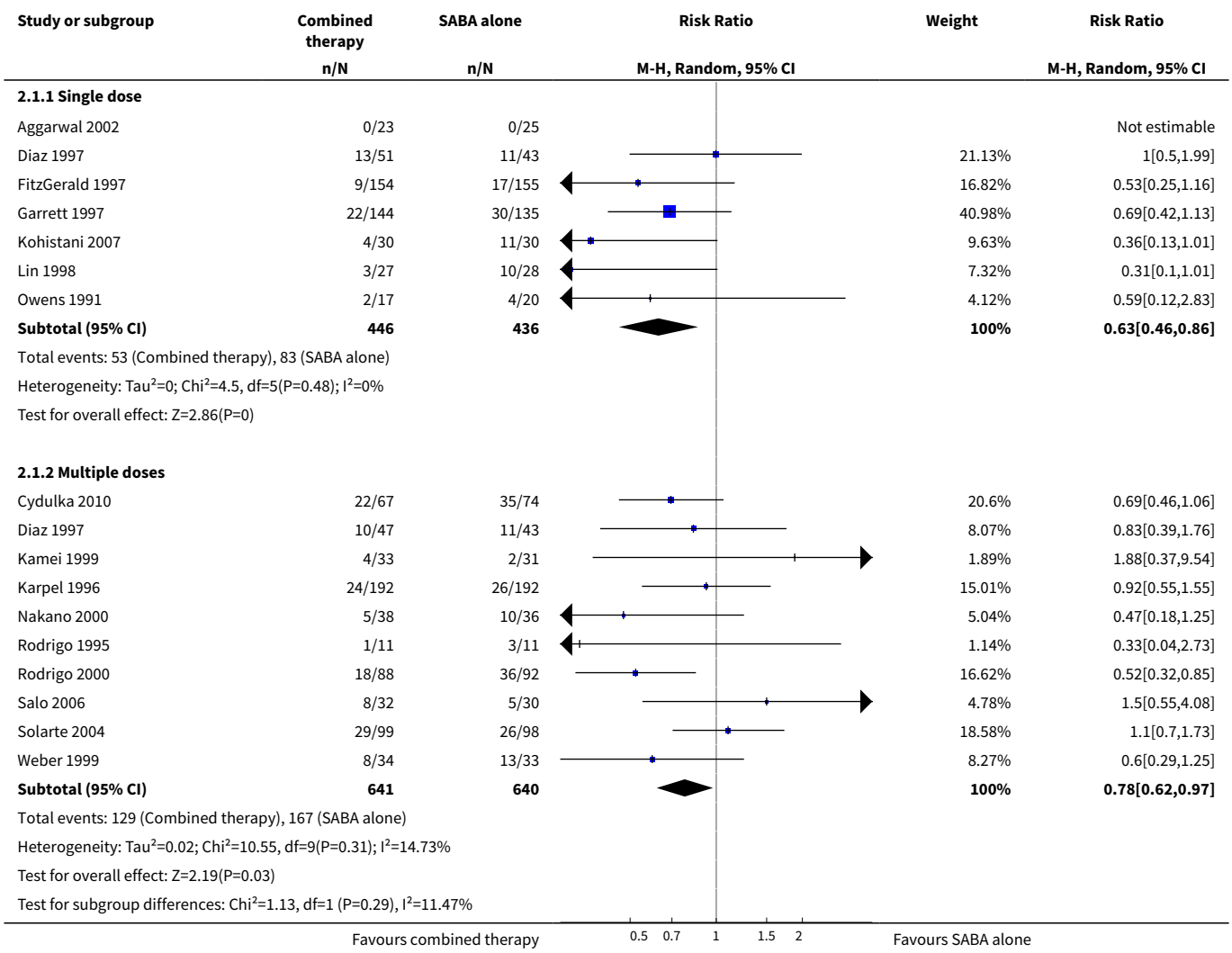
Analysis 1.18. Comparison 1 Combination inhaled therapy versus SABA alone, Outcome 18 Relapse rates.



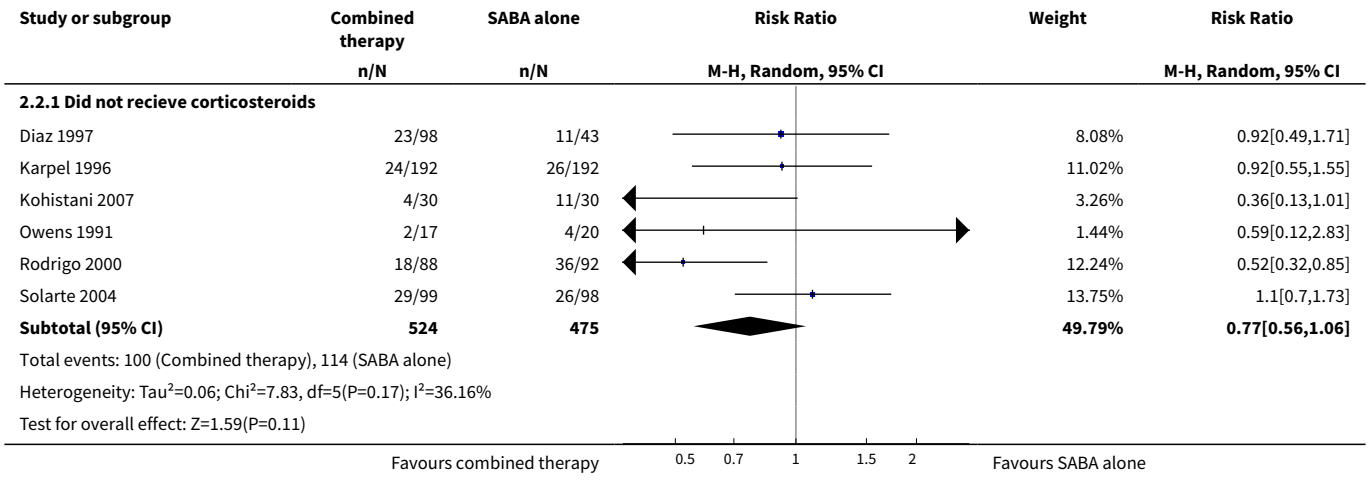
Comparison 2. Hospitalisation subgroup analysis

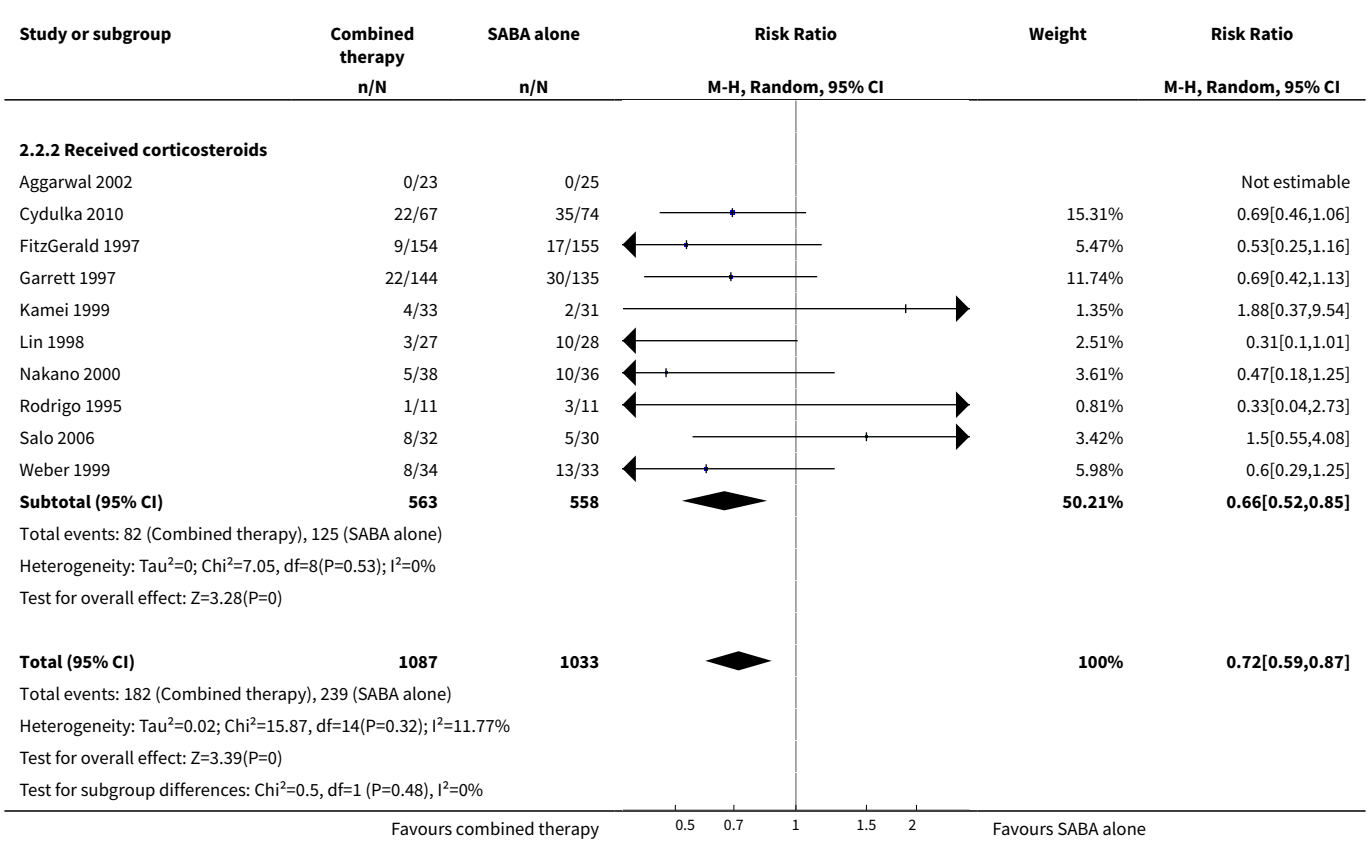
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mulitple versus single dose	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Single dose	7	882	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.46, 0.86]
1.2 Multiple doses	10	1281	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
2 Co-interventions received	16	2120	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.59, 0.87]
2.1 Did not recieve corticosteroids	6	999	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.06]
2.2 Received corticosteroids	10	1121	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.52, 0.85]
3 Exacerbation severity	16	2120	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.59, 0.87]
3.1 Mild exacerbations	2	112	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.37, 9.54]
3.2 Moderate exacerbations	7	1409	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.11]
3.3 Severe exacerbations	7	599	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.43, 0.72]
4 Type of anticholinergic used	16	2120	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.59, 0.87]
4.1 Ipratropium bromide used	12	1804	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.56, 0.88]
4.2 Other SAACs used	4	316	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.50, 1.29]

Analysis 2.1. Comparison 2 Hospitalisation subgroup analysis, Outcome 1 Mulitple versus single dose.

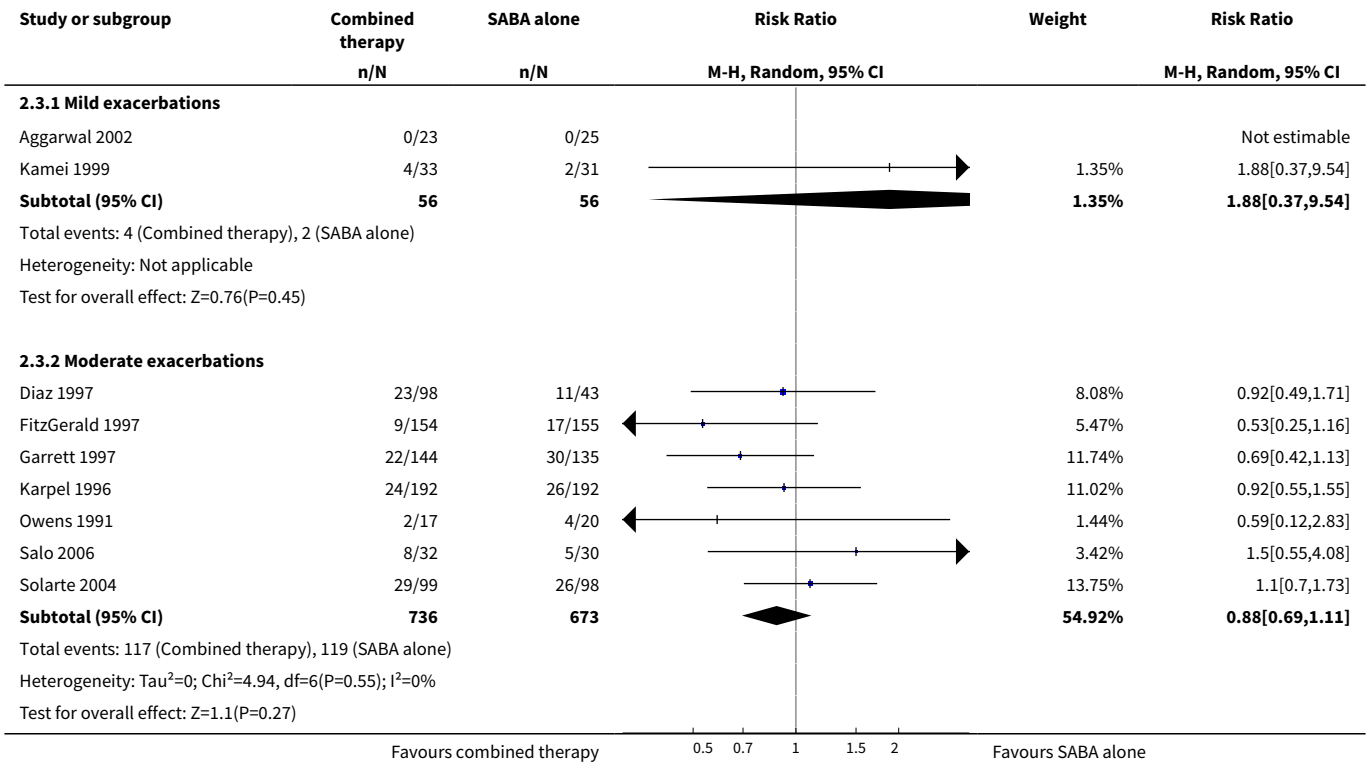


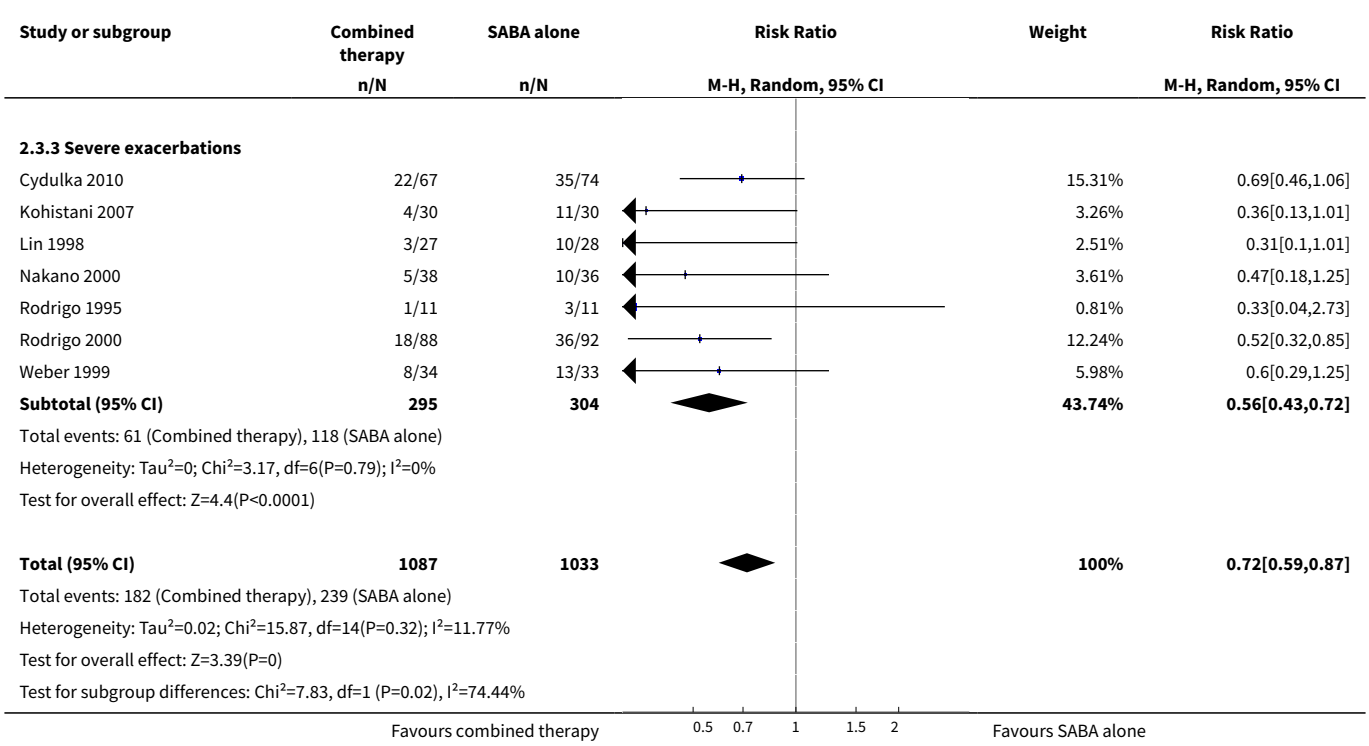
Analysis 2.2. Comparison 2 Hospitalisation subgroup analysis, Outcome 2 Co-interventions received.



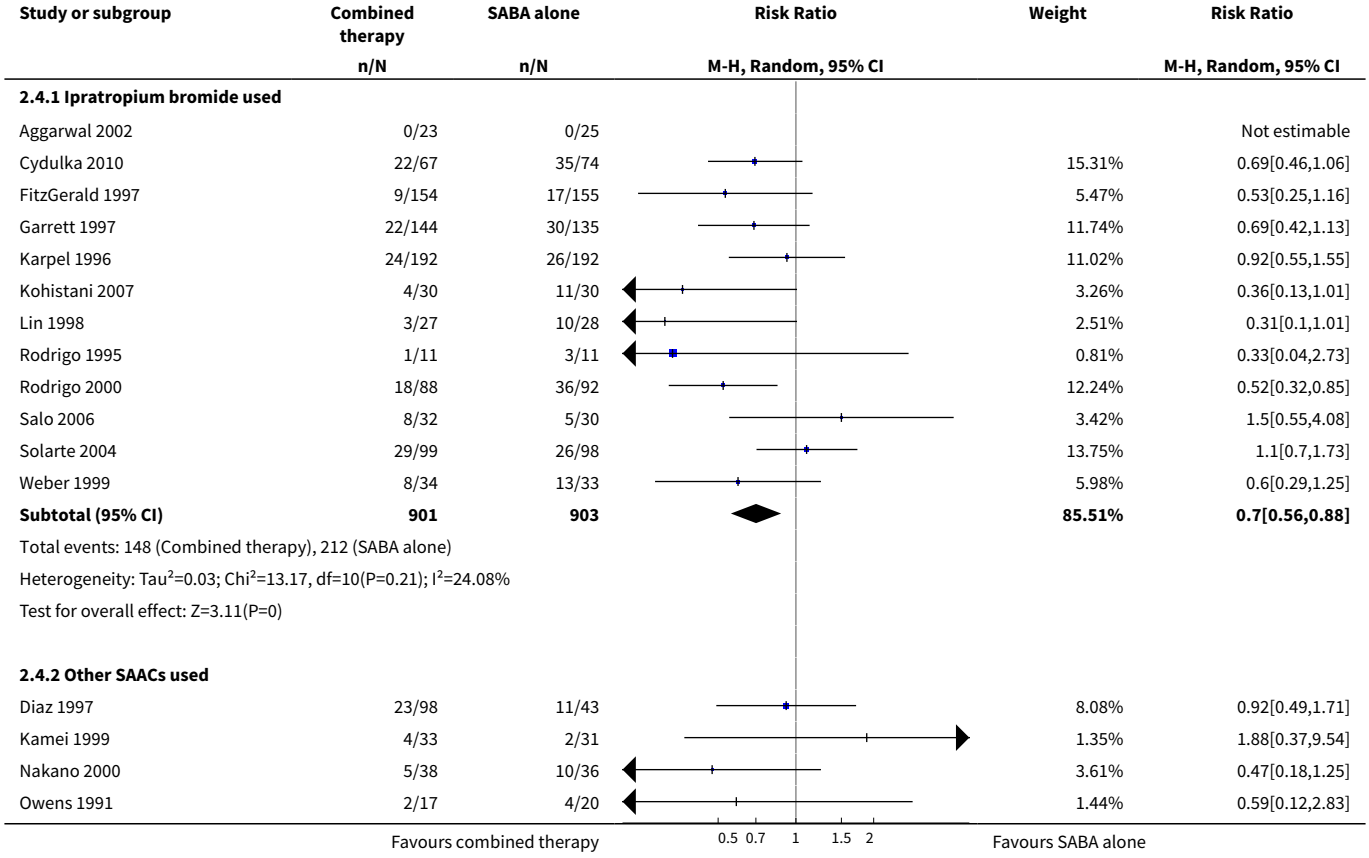


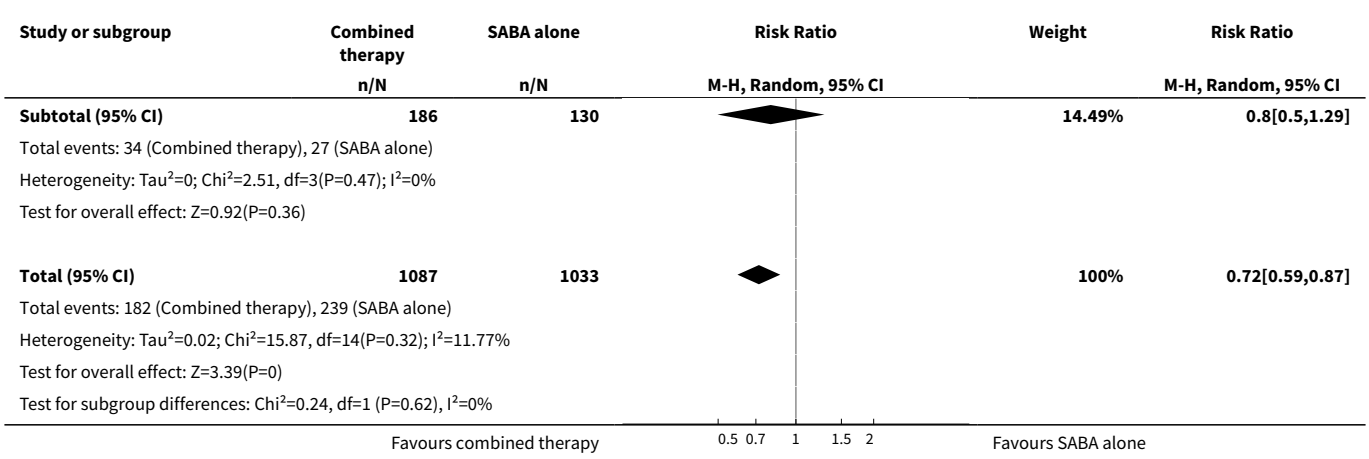
Analysis 2.3. Comparison 2 Hospitalisation subgroup analysis, Outcome 3 Exacerbation severity.





Analysis 2.4. Comparison 2 Hospitalisation subgroup analysis, Outcome 4 Type of anticholinergic used.

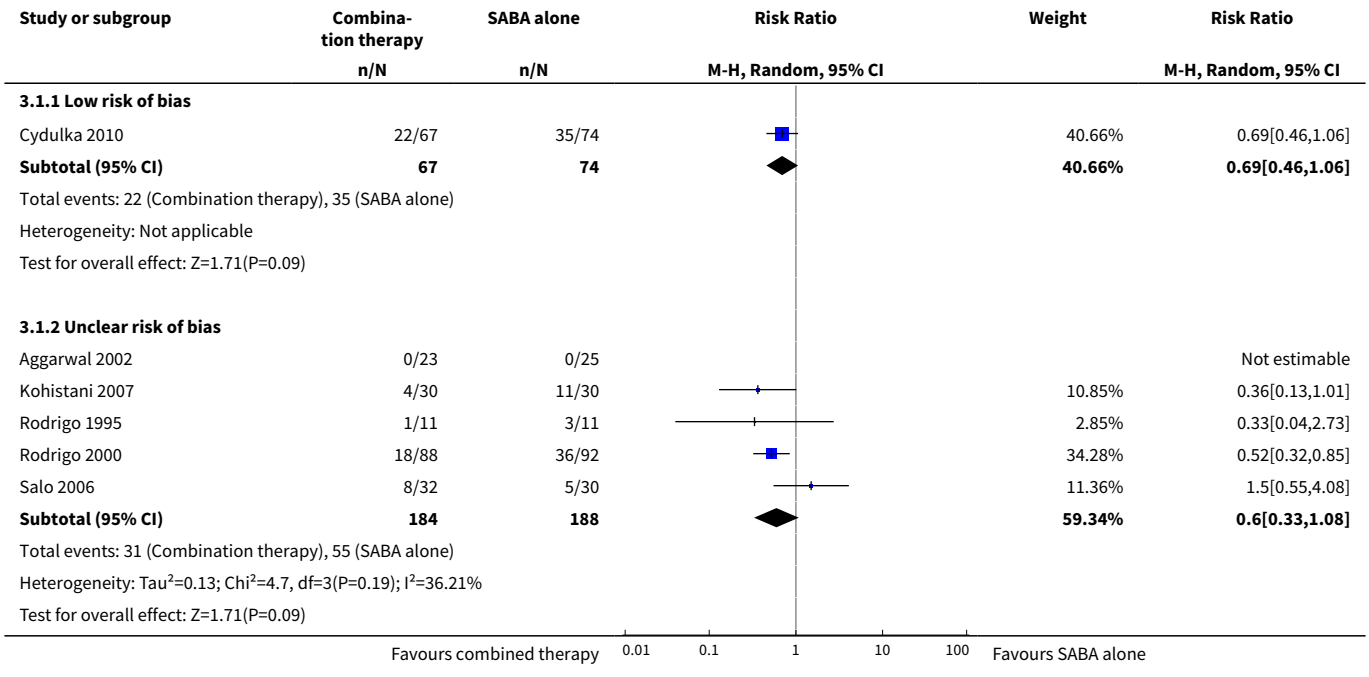


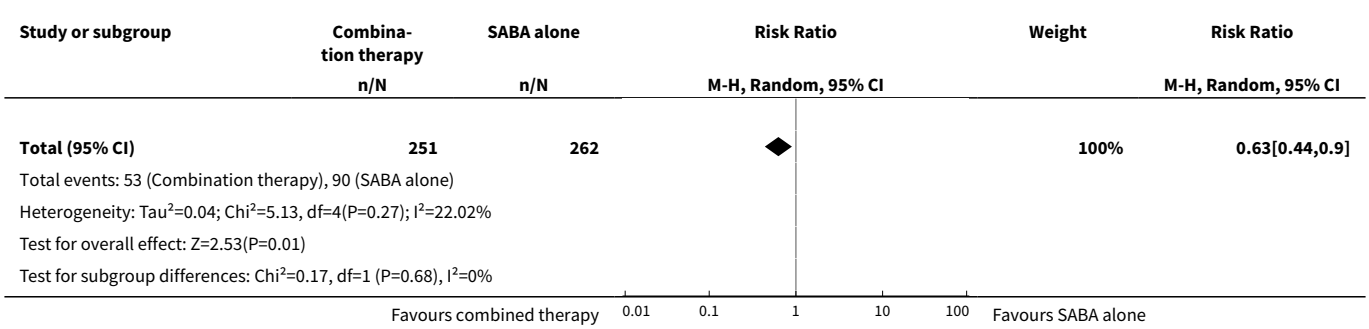


Comparison 3. Hospitalisation sensitivity analysis

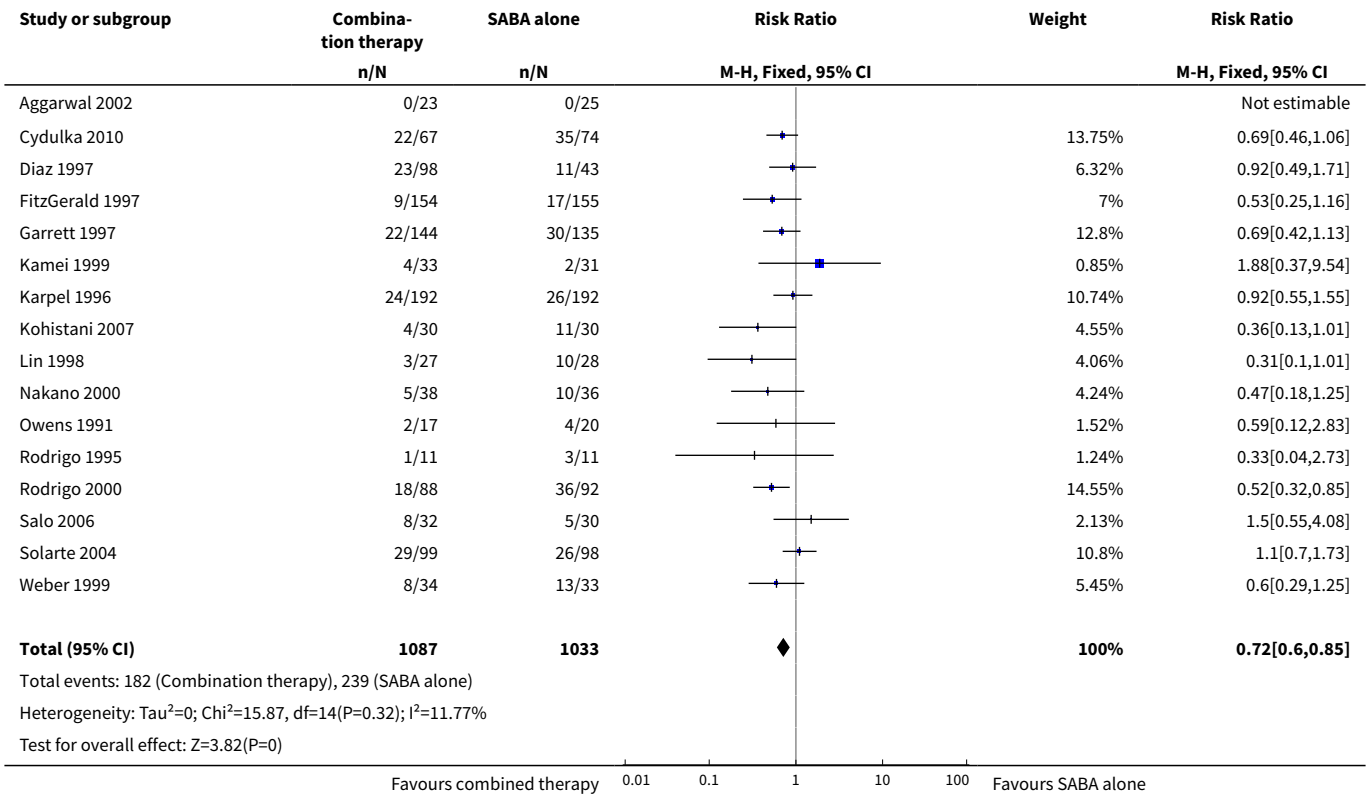
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk of bias	6	513	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.44, 0.90]
1.1 Low risk of bias	1	141	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.06]
1.2 Unclear risk of bias	5	372	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.33, 1.08]
2 Fixed effects	16	2120	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.85]

Analysis 3.1. Comparison 3 Hospitalisation sensitivity analysis, Outcome 1 Risk of bias.





Analysis 3.2. Comparison 3 Hospitalisation sensitivity analysis, Outcome 2 Fixed effects.



ADDITIONAL TABLES

Table 1. Exacerbation severity subgroups to examine the effectiveness of combination therapy to prevent hospitalisation

Studies	Pulmonary function: Eligibility criteria	Placebo group admission rate (%)
Mild subgroup		
Aggarwal 2002	Not defined	0

Table 1. Exacerbation severity subgroups to examine the effectiveness of combination therapy to prevent hospitalisation *(Continued)*

Kamei 1999	FEV_1 < 70% predicted	6
Moderate subgroup		
Diaz 1997	Not defined	26
FitzGerald 1997	FEV_1 < 70% predicted	11
Garrett 1997	FEV_1 < 70% predicted	22
Karpel 1996	FEV_1 < 60% predicted	14
Owens 1991	FEV_1 < 2 L	20
Salo 2006	PEFR < 70% predicted	17
Solarte 2004	Not defined	27
Severe subgroup		
Cydulka 2010*	FEV_1 < 50% predicted	47
Kohistani 2007	PEFR < 200 L per minute	37
Lin 1998	PEFR < 200 L per minute	36
Nakano 2000*	PEF < 50% normal predictive value	28
Rodrigo 1995*	FEV_1 and PEF < 50% predicted	27
Rodrigo 2000	FEV_{11} < 50% predicted	39
Weber 1999	PEFR < 70% predicted after treatment with bronchodilator treatment	39

* Study reported to strictly enrolling patients presenting to the emergency department with severe exacerbations
Abbreviations:
FEV - forced expiratory volume
PEFR -

Table 2. Admission criteria of included studies

Study ID	Admission criteria
Diaz 1997	Considered to by admitted patients if any of the following criteria were met: 1. no subjective improvement 2. inability to achieve baseline PEF if known, or PEF < 250 L/minute in women and < 300 L/minute in men 3. inability to ambulate without dyspnoea
Kohistani 2007	Admission criteria included the presence of any of the following after treatment: 1. accessory muscle use 2. respiratory rate in excess of 24 per minute 3. arterial blood Pco_2 > 44 mm Hg

Table 2. Admission criteria of included studies *(Continued)*

	4. arterial blood Po_2 (on room air) < 70 mm Hg 5. associated diseases such as pneumonia or febrile illness greater than 38.8° C (102° F) 6. failure to show improvement after 5 to 6 hours of observation with associated fatigue and shortness of breath with exertion
Lin 1998	Admission criteria included the presence of any of the following after treatment: 1. respiratory rate in excess of 24 per minute 2. accessory muscle use 3. arterial blood Pco_2 > 44 mm Hg 4. arterial blood Po_2 (on room air) < 70 mm Hg 5. associated diseases such as pneumonia or febrile illness greater than 38.8° C (102° F)
Nakano 2000	Considered eligible for discharge if patients were: 1. asymptomatic and free of accessory muscle use 2. absent or diminished wheezing 3. PEF value of 55% or greater than of the predicted value. Patients not meeting these criteria were given additional treatment with IV aminophylline and/or inhaled bronchodilators. If these patients still did not meet the discharge requirements, they were admitted to hospital
Weber 1999	Decision to admit patients based on the 1991 guidelines in the National Asthma Education Program Expert Panel Report of the National Heart, Lung, and Blood Institute

APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to July 17, 2015
Search strategy:
---
1. exp asthma/
2. asthma*.mp.
3. 1 or 2
4. exp Emergency Service, Hospital/ or (acute or relaps* or exacerbat*).ti,ab.
5. (emergency adj3 (room* or ward or wards or department* or doctor* or nurse* or clincian* or practitioner*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. ("critical care" or "acute care").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. 4 or 5 or 6
8. 3 and 7
9. anticholinergic*.mp.
10. (ipratropium or atrovent or oxitropium or oxivent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. exp Ipratropium/
12. cholinergic.mp. or exp Cholinergic Agents/
13. PARASYMPATHOMIMETICS.mp. or exp Parasympathomimetics/
14. limit 13 to yr="1975 - 1994"
15. 9 or 10 or 11 or 12 or 14
16. 8 and 15
17. salbutamol.mp. or exp Albuterol/
18. ("levalbuterol hydrochloride" or sultanol or albuterol or "2-t-butylamino-1-(4-hydroxy-3-hydroxy-3-hydroxymethyl)phenylethanol" or ventolin or "levosalbutamol hydrochloride" or proventil or "hydrochloride levalbuterol" or "xopenex levalbuterol").mp. [mp=title,

abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19. exp Adrenergic beta-2 Receptor Agonists/
20. 17 or 18 or 19
21. 16 and 20 (336)
22. (combivent or berodual).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
23. 16 and 22
24. 21 or 23
25. limit 24 to "all child (0 to 18 years)"
26. limit 25 to "all adult (19 plus years)"
27. 24 not 25
28. 26 or 27

Appendix 2. Embase search strategy

Database: Embase 1974 to 17 July 2015
Search strategy:
---
1. exp asthma/
2. (asthma* or wheezing or bronchial constriction or bronchial restriction).mp.
3. 1 or 2
4. anticholinergic*.mp.
5. (atropine or ipratropium or atrovent or oxitropium or oxivent).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. cholinergic.mp. or exp Cholinergic Agents/
7. 4 or 5 or 6
8. salbutamol.mp. or exp Albuterol/
9. ("levalbuterol hydrochloride" or sultanol or albuterol or "2-t-butylamino-1-(4-hydroxy-3-hydroxy-3-hydroxymethyl)phenylethanol" or ventolin or "levosalbutamol hydrochloride" or proventil or "hydrochloride levalbuterol" or "xopenex levalbuterol").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10. exp Adrenergic beta-2 Receptor Agonists/
11. beta adrenergic receptor stimulating agent/ or fenoterol/ or exp levalbuterol/ or salbutamol/ or salbutamol sulfate/
12. (salbutamol or levalbuterol or fenoterol or phenoterol or albuterol or metaproterenol).mp.
13. 8 or 9 or 10 or 11 or 12
14. exp ipratropium bromide/
15. exp oxitropium bromide/
16. 7 or 14 or 15
17. 13 and 16
18. combivent.mp. or exp ipratropium bromide plus salbutamol sulfate/
19. berodual.mp. or exp fenoterol plus ipratropium bromide/
20. 17 or 18 or 19
21. exp emergency treatment/
22. emergency physician/
23. emergency nursing/
24. (emergency adj2 (care or service* or medic* or department* or unit or area or ward or physician* or doctor* or nurs*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
25. 21 or 22 or 23 or 24
26. 3 and 20 and 25
27. limit 26 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
28. limit 27 to (adult <18 to 64 years> or aged <65+ years>)
29. 27 not 28
30. 26 not 27
31. 29 or 30

Appendix 3. CINAHL search strategy

1. (MH "Cholinergic Antagonists+")

2. anticholinergic* or atrovent or oxivent

3. "ipratropium bromide" OR (MH "Ipratropium")

4. oxtiropium bromide

5. (MH "Atropine") OR "atropine"

6. (MH "Albuterol") OR "salbuterol"

7. "levalbuterol"

8. "albuterol"

9. "fenoterol"

10. "phenoterol"

11. (MH "Ociprenaline") OR "metaproterenol"

12. "beta n3 agonist"

13. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12

14. (MH "Emergency Service+") OR (MH "Physicians, Emergency") OR (MH "Emergencies+") OR (MH "Emergency Patients") OR "emergency"

15. (MH Asthma+")

16 "wheezing"

17. "bronchial restriction" OR (MH Bronchial Spasm")

18. 15 OR 16 OR 17

19. "combivent"

20. berodual

21. 19 OR 20

22. 1 OR 2 OR 3 OR 4 OR 5

23. 13 AND 22

24. 21 OR 23

25. 14 AND 18 AND 24

Appendix 4. SCOPUS search strategy

1. (salbutamol OR levalbuterol OR fenoterol OR phenoterol OR albuterol OR metaproterenol OR beta w/2 agonist*)

2. (emergency w/2 (care or service* or medic* or department* or unit or area or ward or physician* or doctor* or nurs*))

3. (ematropine OR ipratropium OR atrovent OR oxitropium OR oxivent OR antichol*)

4. (asthma*) OR (bronchial w/1 constrict*) OR (bronchial w/1 restrict*) OR (wheezing*)

5. 1 AND 2 AND 3 AND 4 AND 5

Appendix 5. LILACS search strategy

1. antichol* OR ipratropium OR atrovent OR oxitropium OR oxivent

2. salbutamol OR albuterol OR ventolin

3. (emergen* OR acute OR relapse* OR exacerbat*) AND asthma

4. 1 AND 2 AND 3

Appendix 6. ProQuest Dissertations & Theses Global search strategy

1. (atropine OR ipratropium OR atrovent OR oxitropium OR oxivent OR antichol*)

2. (salbutamol OR levalbuterol OR fenoterol OR phenoterol OR albuterol OR metaproterenol OR beta w/2 agonist*)

3. 1 AND 2

Appendix 7. Evidence-Based Medicine Reviews search strategy

Databases searched for EBM reviews:
Cochrane Database of Systematic Reviews 2005 to June 2015
ACP Journal Club 1991 to July 2015
Database of Abstracts of Reviews of Effects (DARE)Second Quarter 2015 Cochrane Central Register of Controlled Trials (CENTRAL)June 2015
Cochrane Methodology Register third quarter 2012
Health Technology Assessment second quarter 2015
NHS Economic Evaluation Database second quarter 2015.

Search strategy:
---
1. exp asthma/
2. asthma*.mp.
3. 1 or 2
4. exp Emergency Service, Hospital/ or (acute or relaps* or exacerbat*).ti,ab.
5. (emergency adj3 (room* or ward or wards or department* or doctor* or nurse* or clincian* or practitioner*)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
6. ("critical care" or "acute care").mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
7. 4 or 5 or 6
8. 3 and 7
9. anticholinergic*.mp.
10. (ipratropium or atrovent or oxitropium or oxivent).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
11. exp Ipratropium/
12. cholinergic.mp. or exp Cholinergic Agents/
13. PARASYMPATHOMIMETICS.mp. or exp Parasympathomimetics/
14. limit 13 to yr="1975 - 1994" [Limit not valid in DARE; records were retained]
15. 9 or 10 or 11 or 12 or 14
16. 8 and 15
17. salbutamol.mp. or exp Albuterol/
18. ("levalbuterol hydrochloride" or sultanol or albuterol or "2-t-butylamino-1-(4-hydroxy-3-hydroxy-3-hydroxymethyl)phenylethanol" or ventolin or "levosalbutamol hydrochloride" or proventil or "hydrochloride levalbuterol" or "xopenex levalbuterol").mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
19. exp Adrenergic beta-2 Receptor Agonists/
20. 17 or 18 or 19
21. 16 and 20
22. (combivent or berodual).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
23. 16 and 22
24. 21 or 23
25. limit 24 to "all child (0 to 18 years)" [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]
26. limit 25 to "all adult (19 plus years)" [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]
27. 24 not 25
28. 26 or 27
29. from 28 keep 1-240

Appendix 8. Cochrane Airways Group register of trials search strategy

1. AST:MISC1

2. MeSH DESCRIPTOR Asthma Explode All

3. asthma*:ti,ab

4. 1 or 2 or 3

5. MeSH DESCRIPTOR Cholinergic Antagonists Explode All

6. anticholinergic* or anti-cholinergic*

7. ipratropium*

8. MeSH DESCRIPTOR Ipratropium

9. Atrovent

10. MeSH DESCRIPTOR Atropine

11. atropine*

12. oxitropium*

13. Oxivent

14. muscarinic*

15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16. acute* or status* or sever* or emerg* or exacerbat* or hospital* or crisis*

17. 4 and 15 and 16

CONTRIBUTIONS OF AUTHORS

SWK: assisted with protocol development, performed the literature search, selection of studies, quality assessment, data extraction, data analysis and manuscript preparation.

CV: assisted with the selection of studies, quality assessment, and manuscript preparation.

TN: assisted with study selection and manuscript preparation.

BV: assisted with study selection, quality assessment, and manuscript preparation.

SC: developed the search terms and performed the literature search of the systematic literature search and assisted with manuscript preparation.

BHR: initiated the review, assisted with protocol development, selection of studies, risk of bias assessment, data analysis, and manuscript preparation.

DECLARATIONS OF INTEREST

SWK: none known

CV: none known

BV: none known

TN: none known

SC: none known

BHR: Since 2013 Dr Rowe has received funding from GSK for speaking, study enrolment fees from MedImmune and funding for research from GSK.

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  Provided in-kind resources
- Emergency Strategic Clinical Network (SWK), AB, Canada.

External sources

- Canadian Institutes of Health Research (CIHR), Ottawa, ON (BH Rowe), Canada, Canada.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are several differences between the initial protocol and the final review.

- We made changes to the inclusion and exclusion criteria. LAAC agents, such as tiotropium were explicitly excluded from the review as a result of a decision to focus primarily on SAAC agents before searching the electronic databases.
- Studies including participants aged 16 years or older were eligible for inclusion in the review, rather than 18 years or older as stated in the protocol. This change was made to allow for any variations in defining adult populations globally. The included studies enrolled primarily
- participants over the age of 18 years. No studies reported mean ages between 16 years and 17 years.
- In addition to the search provided by the Cochrane Airways Group, the review presents results of searches of seven electronic databases using keywords and subject headings provided by a health librarian.
- In the protocol, the grey literature search consisted solely of handsearching the top 20 respiratory care journals; however, for the review, this was expanded to include: a forward search on SCOPUS of the sentinel paper, Google Scholar, clinical trial registries, reference lists of reviews and included studies, and handsearching the top three evidence-based emergency medicine journals.
- We amended secondary outcomes measures proposed in the protocol, and excluded physiological measures, such as vital signs and SaO_2.
- Because there were few adverse events reported, we calculated OR analyses.
- Risk of bias assessment was completed using the Cochrane Risk of Bias tool, as recommended by Cochrane, rather than the Jadad.
- Changes regarding data analysis included calculating random-effects risk ratios for dichotomous variables for individual studies instead of odds ratios as mentioned in the protocol. Due to the rare occurrence of adverse events, OR analysis were calculated.
- Heterogeneity was assessed using the more widely accepted I^2 statistic with I^2 values of 25, 50, and 75% representing low, moderate, and high degrees of heterogeneity respectively.
- The reported subgroups based on single-dose vs. multiple doses for all of the reported comparisons were not assessed in the final review; however, they were reported for the primary outcome. In addition, sensitivity analysis based on the Jadad score, Cochrane criteria, dosing agents and time of assessment was not assessed in the review.
- The final review included a summary of findings table of the primary outcome and important secondary outcomes, including an assessment of the quality of evidence using GRADE, which was not included in the initial protocol.
- The text of the final review varied considerably from the initial protocol due to a change in the authors involved in the study and its preparation of the final manuscript
- The use of ipratropium bromide vs. other SAAC was added in the final review as a subgroup comparison.
- Based on feedback provided by post peer review comments, the methods of estimating and categorising exacerbation severity was modified to include the pulmonary function eligibility criteria, in addition to the percentage of patients hospitalised in the SABA alone group.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-2 Receptor Agonists [*therapeutic use]; Albuterol [therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Atropine [therapeutic use]; Cholinergic Antagonists [*therapeutic use]; Drug Therapy, Combination; Forced Expiratory Volume [drug effects]; Ipratropium [therapeutic use]; Levalbuterol [therapeutic use]; Metaproterenol [therapeutic use]; Randomized Controlled Trials as Topic; Scopolamine Derivatives [therapeutic use]

MeSH check words

Humans