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[Intervention Review]

Beta2-agonists for acute cough or a clinical diagnosis of acute bronchitis

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ABSTRACT

Background

The diagnosis of acute bronchitis is made on clinical grounds and a variety of clinical definitions have been used. There are no clearly effective treatments for the cough of acute bronchitis. Beta2-agonists are often prescribed, perhaps because clinicians suspect many patients also have reversible airflow restriction (as seen in asthma or chronic obstructive pulmonary disease (COPD)) contributing to the symptoms.

Objectives

To determine whether beta2-agonists improve acute bronchitis symptoms in people with no underlying pulmonary disease (such as asthma, COPD or pulmonary fibrosis).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2015, Issue 5, MEDLINE (January 1966 to May 2015), EMBASE (1974 to May 2015), Web of Science (2011 to May 2015) and LILACS (1982 to May 2015).

Selection criteria

Randomised controlled trials (RCTs) which allocated people (adults, or children over two years of age) with acute bronchitis or acute cough and without known pulmonary disease to beta2-agonist versus placebo, no treatment or alternative treatment.

Data collection and analysis

Three review authors independently selected outcomes and extracted data while blinded to study results. Two review authors independently assessed each trial for risk of bias. We analysed trials in children and adults separately.

Main results

Two trials of moderate quality in children (n = 134) with no evidence of airflow restriction did not find any benefits from oral beta2-agonists. Five trials in adults (n = 418) had mixed results but overall summary statistics did not reveal any significant benefits from oral (three trials) nor from inhaled (two trials) beta2-agonists. Three studies with low-quality evidence demonstrated no significant differences in daily cough scores, nor in the percentage of adults still coughing after seven days (control group 71%; risk ratio (RR) 0.86, 95% confidence interval (CI) 0.63 to 1.18; 220 participants). In one trial, subgroups with evidence of airflow limitation had lower symptom scores if given beta2-agonists. The trials that noted quicker resolution of cough with beta2-agonists were those with a higher proportion of people wheezing at baseline.

Low-quality evidence suggests that adults given beta2-agonists were more likely to report tremor, shakiness or nervousness (RR 7.94, 95% CI 1.17 to 53.94; 211 participants; number needed to treat for an additional harmful outcome (NNTH) 2).

Authors' conclusions

There is no evidence to support the use of beta2-agonists in children with acute cough who do not have evidence of airflow restriction. There is also little evidence that the routine use of beta2-agonists is helpful for adults with acute cough. These agents may reduce symptoms, including cough, in people with evidence of airflow restriction. However, this potential benefit is not well supported by the available data and must be weighed against the adverse effects associated with their use.

PLAIN LANGUAGE SUMMARY

Beta2-agonist drugs for treating cough or a clinical diagnosis of acute bronchitis

Background

Acute bronchitis is a chest infection, with cough and sometimes sputum production, chest pain and fever. People affected feel unwell and for those who do not have asthma or chronic lung disease there is no clear treatment. Viruses cause most cases of bronchitis, so antibiotics usually do not help. Beta2-agonists (such as albuterol or salbutamol) are drugs that relieve asthma by relaxing muscles that cause narrowing in the passages to the lungs. They are sometimes used to relieve the cough in acute bronchitis, even in people who do not have asthma.

Review question

What are the benefits and harms of beta2-agonist drugs for children or adults with a cough from acute bronchitis, and with no other lung disease?

Study characteristics

Our searches are current to May 2015. We found no new trials. In previous searches, we found seven randomised controlled trials that used beta2-agonist drugs for people with acute bronchitis. Two trials studied children aged one to 10 years (134 participants) and five were conducted in adults (418 participants). None of the studies reported receiving grants from drug-making companies to conduct the study, but people who work for a drug maker were listed as authors on reports from two trials and study drugs were supplied free of charge by the company in three trials.

Key results

Daily cough scores were no different between children given oral beta2-agonists and children in the placebo control groups. Daily cough scores, or the number of people still coughing after seven days, did not change in the adult trials either.

However, the results were mixed. Some trials show a benefit and some show no benefit. This may be because some participants also had wheezing or other signs of narrowed airways, in which case beta2-agonists may be helpful only for them. More of the adults taking beta2-agonists had tremor, shakiness or nervousness.

Quality of the evidence

We rated this as low or moderate. There were few trials, with small numbers of people with acute bronchitis or cough. The trials were of short duration (three to seven days) and only two used inhaled beta2-agonists, which is now the usual way the drug is taken by adults and older children. Some important information about how the trial was done was not mentioned in the papers giving results for many of the trials.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Beta-2 agonists versus placebo for acute bronchitis

Beta-2 agonists versus placebo for acute bronchitis

Patient or population: people with acute cough or a clinical diagnosis of acute bronchitis
Settings: primary care
Intervention: beta-2 agonists
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Beta-2 agonists				
Children: cough score after one day cough score Follow-up: mean 1 day		The mean children: cough score after 1 day in the intervention groups was **0.35 standard deviations higher** (0.05 lower to 0.76 higher)[1]		96 (2 studies)	⊕⊕⊕⊖ **moderate** 2,3,4,5	Higher score indicates more coughing
Children: cough score after three days cough score Follow-up: mean 3 days		The mean children: cough score after 3 days in the intervention groups was **0.36 standard deviations higher** (0.05 lower to 0.77 higher)[6]		95 (2 studies)	⊕⊕⊕⊖ **moderate** 2,3,4,5	Higher score indicates more coughing
Children: cough after seven days daily phone call Follow-up: 7 days	**414 per 1000** [7]	**368 per 1000** (194 to 695)	**RR 0.89** (0.47 to 1.68)[8]	59 (1 study)	⊕⊕⊕⊖ **moderate** [2,4,5]	Dichotomous outcome: presence of cough
Children: shaking or tremor recorded/reported by parents Follow-up: 3-7 days[9]		[10]	**RR 6.76** (0.86 to 53.18)[11]	108 (2 studies)	⊕⊕⊕⊖ **moderate** 2,3,4,12	Dichotomous outcome: presence of these side effects
Adults: cough after seven days diary Follow-up: 7 days	**709 per 1000** [7]	**610 per 1000** (447 to 837)	**RR 0.86** (0.63 to 1.18)[13]	220 (3 studies)	⊕⊕⊖⊖ **low** [12,14,15,16]	Dichotomous outcome: presence of cough

Adults: night cough after seven days diary Follow-up: 7 days	**290 per 1000** [7]	**243 per 1000** (156 to 385)	**RR 0.84** (0.54 to 1.33)[17]	210 (3 studies)	⊕⊕⊕⊖ **moderate** 3,12,14,16	Dichotomous outcome: presence of cough
Adults: shaking, tremor or nervousness diary Follow-up: 7 days	**113 per 1000** [7]	**899 per 1000** (132 to 1000)	**RR 7.94** (1.17 to 53.94)[18]	211 (3 studies)	⊕⊕⊖⊖ **low** 5,14,15,16	Dichotomous outcome: presence of these side effects

*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;

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]see Analysis 1.2
[2]both studies had low risk of bias on 3 out of 5 items, and unknown risk of bias on 2 additional items
[3]large overlap between confidence intervals and I^2 is small
[4]both studies included children with cough and normal lung exam
[5]95% confidence interval of pooled effect includes relevant effect sizes
[6]see Analysis 1.4
[7]event rate in control group
[8]see Analysis 1.1
[9] Bernard 1999 7 days follow-up; Korppi 1991 3 days follow-up
[10]not calculated because of absence of these adverse events in control group
[11]see Analysis 1.9
[12]small number of events and confidence interval large, including important effect
[13]see Analysis 2.1
[14]if reported, most items scored low risk of bias
[15]considerable heterogeneity (I^2 = 63%)
[16]participants with cough and no abnormal findings
[17]see Analysis 2.3
[18]see Analysis 2.12

BACKGROUND

Description of the condition

Acute bronchitis is a clinical syndrome characterised by cough in association with, or preceded by, other symptoms of upper respiratory infection. Affected individuals may also have sputum production, dyspnoea, chest pain and fever. Acute bronchitis is a common illness and leads to about 10 ambulatory care visits per 1000 people per year (Armstrong 1999). Although acute bronchitis is a self-limiting condition, most patients feel ill and many do not perform their usual activities. Unfortunately, in those who do not have underlying pulmonary disease there is no clear optimal treatment for this common condition. Clinicians often prescribe antibiotics in spite of the fact that most cases of bronchitis are believed to be caused by viral infections (Gonzales 1997; Mainous 1996; Meza 1994; Oeffinger 1998). A Cochrane review has determined that antibiotics are of little overall benefit (Smith 2014). It is important, therefore, to examine the possible effectiveness of alternative therapeutic approaches to treat symptoms.

Description of the intervention

One potentially effective treatment may be beta2-agonists, which can be administered either orally or via metered dose inhaler, and are used to relieve bronchoconstriction in people with asthma and chronic obstructive pulmonary disease (COPD).

How the intervention might work

Indirect evidence to support the use of beta2-agonists in acute bronchitis comes from two camps. First, people have been shown to have impaired airflow from bronchial reactivity when infected with pathogens (such as viruses and the bacteria *Mycoplasma pneumoniae* (*M. pneumoniae*) and *Chlamydia pneumonia* (*C. pneumonia*)) known to cause acute bronchitis (Hahn 1991; Melbye 1994). In one study, 41% of people diagnosed with acute bronchitis had less than 80% of the predicted forced expiratory volume in one second (FEV-1) (Williamson 1987). Second, cough is the primary symptom in some people who have asthma (Johnson 1991) and a majority of such people may have total resolution of symptoms with beta2-agonist therapy (Ellul-Micallef 1983). It is therefore possible that bronchial reactivity may lead not only to the dyspnoea of which some people with acute bronchitis complain, but to the cough, which is also the hallmark of the illness. These symptoms may both respond well to beta2-agonists. These agents have been shown to be effective in reducing cough due to other acute causes such as bronchoscopy (Vesco 1988) and intravenous fentanyl (Lui 1996).

Why it is important to do this review

If beta2-agonists are effective for acute bronchitis then they should be more widely used. Surveys of US family physicians reported that only a small minority routinely prescribe beta2-agonists for this condition (Mainous 1996; Oeffinger 1998). However, these agents can cause adverse effects, such as skeletal muscle tremor, tachycardia, or other cardiac arrhythmias, and should clearly not be used if there is no good evidence for their effectiveness.

OBJECTIVES

To determine whether beta2-agonists improve acute bronchitis symptoms in people with no underlying pulmonary disease (such as asthma, COPD or pulmonary fibrosis).

Specifically, we:

1. Compared people who received beta2-agonists with those who did not receive beta2-agonists regarding the duration of symptoms of acute bronchitis;
2. Attempted to determine which subgroups of recipients were most likely to benefit from beta2-agonists; and
3. Compared adverse effects between those who received beta2-agonists and those who did not receive beta2-agonists.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of participants with acute cough or a diagnosis of acute bronchitis, allocated either to a beta2-agonist group or to a no-beta2-agonist group.

Although the pathophysiological definition of acute bronchitis seems clear (an inflammation of the tracheobronchial tree in association with a generalised respiratory infection), the clinical definition of acute bronchitis is not standardised. The third edition of the International Classification of Health Problems in Primary Care (ICHPPC-2 1983) defines acute bronchitis as cough with scattered or generalised abnormal chest signs (wheeze, coarse or moist sounds). However, textbooks describe a variety of clinical presentations. Some texts state that abnormal chest signs (for example, wheezing, rhonchi, rales or coarse breath sounds) should be heard (Stern 1996), and other texts state that abnormal signs may be heard (Gwaltney 1995; Marrie 1998) but that examination of the chest may also be normal (Weller 1996). There are similar conflicting statements regarding whether sputum must be present and what the character of the sputum, if present, should be. Studies (chart reviews and surveys) of clinicians have also revealed a variety of clinical definitions of acute bronchitis (Dunlay 1984; Oeffinger 1997; Verheij 1990; Vinson 1991). Although cough is universally described, there is wide variation regarding the need for abnormal chest findings or sputum to make this diagnosis. In this meta-analysis we therefore included studies that enrolled participants who received a clinical diagnosis of acute bronchitis or acute cough, unless the cough was felt to be clearly due to another aetiology, such as pneumonia or sinusitis. We realise that some of these participants may have had an upper respiratory infection (that is to say, the common cold) and not inflammation of the tracheobronchial tree. However, many clinicians do indeed call this condition acute bronchitis. Through subgroup analyses, we attempted to determine whether such participants might respond differently to beta2-agonist treatment from those who have other signs which more clearly suggest lower respiratory tract involvement.

Types of participants

We included trials that enrolled people who had a clinical diagnosis of acute bronchitis or acute cough unless they were:

1. Less than 24 months of age (a meta-analysis of the effectiveness of beta2-agonists for wheezing and or bronchiolitis, or both, in this age group has already been conducted (Gadomski 2014));
2. Known to have pre-existing pulmonary disease, such as asthma, chronic obstructive pulmonary disease (emphysema or chronic bronchitis, or both) or cystic fibrosis;
3. Known to have another acute respiratory illness, such as sinusitis, pertussis or pneumonia.

Types of interventions

We included RCTs that assigned participants to a beta2-agonist (oral or inhaled) treatment or to no beta2-agonist (no treatment, placebo or alternative treatment). We limited the primary analyses to trials that compared beta2-agonists with placebo or no additional treatment. We first examined separately, and then included in a sensitivity analysis, those trials that compared beta2-agonists with other active treatments, namely antibiotics, because of the potential for confounding. We included trials that provided both the beta2-agonist group and the alternative group with additional therapies as long as both groups had the same likelihood of receiving the co-interventions.

Types of outcome measures

The primary outcome measures are symptoms that we believe would be important to patients.

Our methodology for including the specific outcomes was as follows: after we selected the studies that would be included in our review, one review author listed all of the outcomes reported in the various studies. The other three review authors, who were blinded to the results for each outcome in each of the studies, then determined which outcomes we would include in the review based on the criteria mentioned above. We used this approach to minimise selective reporting bias in our choice of outcomes.

The studies reported a variety of outcomes, most of which were not reported in every study we included. Our decision to include an outcome was not determined by the number of studies that reported that outcome, because we believe that important outcomes should be included in our review even if they are not reported in all or even most of the studies.

Outcomes that we selected related to the persistence and severity of cough; specific characteristics of cough; work and activity limitations; general well-being; use of adjunctive medications; number of unplanned return visits; and adverse effects.

Primary outcomes

Most studies reported three outcomes.

1. Daily cough scores;
2. The number of participants who were still coughing at the end of the trial;
3. Adverse effects.

Choosing daily cough scores and persistence of cough at the end of the trial also allowed us to examine short-term and intermediate-term effects, respectively.

Secondary outcomes

1. Specific characteristics of cough such as night cough and productive cough;
2. Limitations in the ability to work or perform other activities;
3. General well-being.

Search methods for identification of studies

Electronic searches

For this 2015 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 5 May 2015, part of the Cochrane Library, www.thecochranelibrary.com (accessed 26 May 2015) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (February 2011 to May 2015), EMBASE (February 2011 to May 2015), Web of Science (2011 to May 2015) and LILACS (1982 to May 2015). See Appendix 1 for details of original search and previous updates.

We used the search strategy described in Appendix 2 to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in Medline: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted these search terms for Embase (Appendix 3), Web of Science (Appendix 4) and LILACS (Appendix 5).

There were no language or publication restrictions in our search.

Searching other resources

For this 2015 update we searched the trials registers WHO ICTRP and clinicaltrials.gov (latest search 13 October 2014).

Previously we searched for trials in conference proceedings databases Inside Conferences (1993 to 1999); Conference Papers Index (1973 to 1999); in the reference lists of retrieved articles, review articles and textbooks; and in the Science Citation Index (1990 to 2000) using the key studies we retrieved for the first publication of this review (Smucny 2001). We wrote to all US manufacturers of currently approved brand-name beta2-agonists. We did not repeat these searches for the current update or for previous updates of this review (Smucny 2004; Smucny 2006) .

Data collection and analysis

Selection of studies

Two review authors (CF, JS) independently reviewed all the retrieved titles and abstracts to determine which studies appeared to meet the inclusion criteria for the initial review (Smucny 2001). This initial screen was sensitive; we selected studies for potential inclusion unless a study clearly did not meet our inclusion criteria. We retrieved selected studies identified by either author in their entirety. Two review authors (RG, JS) reviewed the results of the first updated search that was conducted in July 2003 (Smucny 2004). Three review authors (LB, RG, JS) assessed the results of the second updated search that was conducted in November 2005 (Smucny 2006). Two review authors used the identical process for all of the titles and abstracts identified in the searches conducted in 2011 (Becker 2011) and in 2015.

Data extraction and management

The review authors of the initial version of this review extracted the data. We did not repeat the data extraction or analyses as we identified no additional studies for this update. One of the review authors (JS) deleted the journal of publication, title, author(s), affiliation(s) and results sections of each study; and compiled a list of the outcomes measured in each study for the initial version of this review. The other three review authors (LB, CF, RG) determined which outcomes would be included in our review, first independently and then through discussion. The same three review authors then reviewed all of the articles that had passed the initial study selection screen and excluded any article that all three review authors agreed did not meet our inclusion criteria. We then distributed the remaining articles in their entirety to all review authors, each of whom independently extracted the data from each study for every selected outcome. Again, we resolved any disagreements by discussion and consensus.

Assessment of risk of bias in included studies

In the initial version of the review, we assessed risk of bias using the Jadad scale (Jadad 1996). For the 2011 update, we reassessed the methodological quality of included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). We used one article to discuss issues and standardise our approach (Bernard 1999). Each of the four review authors of this update independently assessed the article. We then discussed each item and arrived at a consensus for each item. Two review authors (either LB and MK or JW and JH) independently assessed each of the remaining studies using a standardised form that included a section for each of the risk of bias domains and explicitly addressed co-interventions, compliance, timing of outcome assessments and trial sponsorship by a manufacturer as 'Other' sources of bias (Appendix 6). The same two review authors then compared their results for each item and resolved disagreements by consensus.

Measures of treatment effect

We calculated summary statistics with Review Manager 5 (RevMan 2014) software. We reported risk ratios (RR), absolute risk differences (RD), and numbers needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH) for dichotomous outcomes (such as the presence or absence of a symptom at the time of follow-up). In calculating RRs, RevMan adds 0.5 to cells with zero values. We reported mean differences (MD) for continuous linear outcomes, such as duration of symptoms in days; and standardised mean differences (SMD) for continuous ordinal outcomes, such as cough symptom scores. We considered a level of P less than 0.05 as being statistically significant.

Dealing with missing data

We attempted to contact trial authors to obtain any missing data in preparing the initial version of the review. Two review authors (RG, JS) reviewed the results of the first updated search that was conducted in July 2003 (Smucny 2004). Three review authors (LB, RG, JS) reviewed the results of the second updated search that was conducted in November 2005 (Smucny 2006). Two review authors (LB, JH) used the identical process for all of the titles and abstracts identified in the searches conducted in 2011 (Becker 2011) and in 2015.

Assessment of heterogeneity

We did not compare outcomes between participants assigned to beta2-agonists versus those assigned to control as a whole, because there was considerable clinical heterogeneity among trials (see Description of studies). Instead, we considered the trials in children separately from those in adults and in the trials of adults we initially analysed, the trials comparing beta2-agonists with placebo (or no additional treatment) separately from the trials comparing beta2-agonists with antibiotics. We then combined these in a sensitivity analysis.

Assessment of reporting biases

We did not feel that analysis of funnel plots would be helpful in assessing publication bias, because of the small numbers of trials identified. We also searched conference proceedings and contacted manufacturers to attempt to identify additional studies in addition to our search of electronic databases.

Data synthesis

We used fixed-effect models for outcomes without statistically significant heterogeneity (P value less than 0.10) and random-effects models for outcomes with significant heterogeneity.

Subgroup analysis and investigation of heterogeneity

We were unable to do quantitative summary subgroup analyses based on other clinical characteristics, because of the lack of explicit data from individual trials.

RESULTS

Description of studies

Results of the search

For this 2015 update we retrieved 381 records from the searches of the electronic databases after duplicates were removed. We found no new trials for inclusion but have added two trials to our list of excluded studies. For the 2011 update of this review we retrieved a total of 871 search results after duplicates were removed.

Included studies

Seven trials (with a total of 552 participants) met our inclusion criteria in our original search (see Characteristics of included studies). We identified no additional trials in the updated searches (Becker 2011; Smucny 2001; Smucny 2004; Smucny 2006) or for this 2015 update. Four studies were performed in the United States, two in Finland and one in Norway. Six RCTs compared beta2-agonists with placebo (Bernard 1999; Hueston 1994; Korppi 1991; Littenberg 1996; Melbye 1991; Tukiainen 1986) and one RCT compared a beta2-agonist (oral albuterol) with an antibiotic (erythromycin) (Hueston 1991). The beta2-agonists used in the randomised placebo-controlled trials were oral albuterol (or salbutamol) (Bernard 1999; Korppi 1991; Littenberg 1996; Tukiainen 1986), inhaled albuterol (Hueston 1994) and inhaled fenoterol (Melbye 1991). Two of the randomised placebo-controlled trials had three groups: salbutamol plus dextromethorphan, dextromethorphan only and placebo (Korppi 1991; Tukiainen 1986). We limited our analyses of these studies to only the salbutamol plus dextromethorphan group versus the dextromethorphan only group. Hueston 1994 had a factorial design with four groups: albuterol inhaler plus erythromycin, albuterol inhaler plus placebo, placebo plus

erythromycin and placebo plus placebo. The published paper from this trial reported only the combined data for the two groups given albuterol versus the two groups not given albuterol. The trial author stated that there was no statistical interaction between albuterol and erythromycin, so we believe that it is valid to use the combined data in this review.

Regarding other co-interventions, three trials prohibited other antitussives (Bernard 1999; Korppi 1991; Tukiainen 1986); two trials allowed them and recorded their use as an outcome (Hueston 1994; Littenberg 1996); one allowed them, but did not record this use (Hueston 1991); and the last did not mention co-interventions (Melbye 1991). Only one trial prohibited the use of antibiotics (Tukiainen 1986); all other trials comparing beta2-agonists with placebo or dextromethorphan allowed the use of antibiotics at the discretion of the clinician (except as noted above for Hueston 1994).

Two trials were limited to children (age range one to 10 years, means 3.3 and 3.8 years); and the rest enrolled only adults. One of the studies in children excluded those with abnormal lung examinations (Bernard 1999) and the other excluded those with bronchial obstruction requiring bronchodilating medication (Korppi 1991). None of the adult trials excluded people with wheezing and the percentage of participants with this finding ranged from 20% to 44% in the four trials that mentioned it (see Table 1). All adult trials included both smokers and non-smokers. The duration of illness was less than four weeks in all trials. All trials enrolled participants who initially presented to primary care settings.

The duration of treatment was seven days in five trials, four days in one and three days in the last. Participants or their parents kept daily diaries of symptoms and other items. In three trials, participants were re-evaluated after seven days of treatment.

The only trial that mentioned how well participants adhered to study medications reported more than 95% compliance for both groups (Hueston 1991).

None of the studies reported receiving grants from pharmaceutical manufacturers to conduct the study, but the medications were reported to be supplied free of charge from manufacturers in three studies (Bernard 1999; Melbye 1991; Tukiainen 1986).

Studies had participants report outcomes in daily diaries (Hueston 1991; Hueston 1994; Korppi 1991; Littenberg 1996; Melbye 1991; Tukiainen 1986) or by daily telephone contact (Bernard 1999). Studies reported data in a variety of ways: as average duration of symptoms; presence or absence of symptoms daily or after a specified time period, or both; or as symptom scores. Studies that used symptom scores each had unique scoring systems that incorporated subjective measures of the frequency or severity of the symptoms, or both. Higher scores indicated more frequent or severe symptoms, or both.

Excluded studies

We excluded one study because it selected participants with recurrent rather than acute cough (Chang 1998). The median duration of cough symptoms was eight weeks at entry into this trial. We excluded two studies because the intervention groups received co-interventions that were not received by the control group (Ovchinnikov 2014; Zanasi 2014).

Risk of bias in included studies

We presented results for the assessment of these trials using the Cochrane 'Risk of bias' tool in Characteristics of included studies and summarised in Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

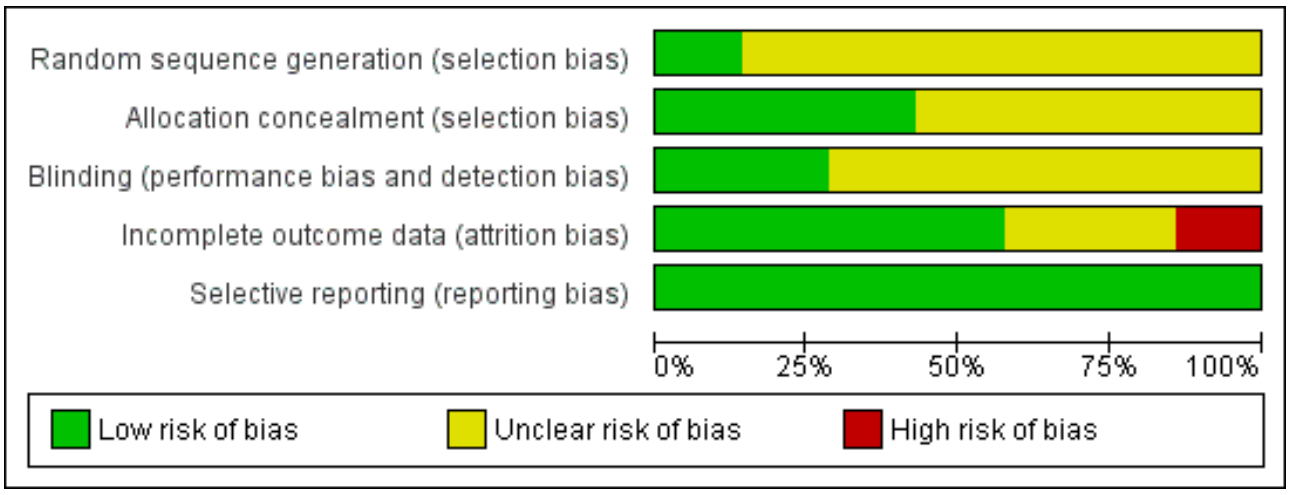
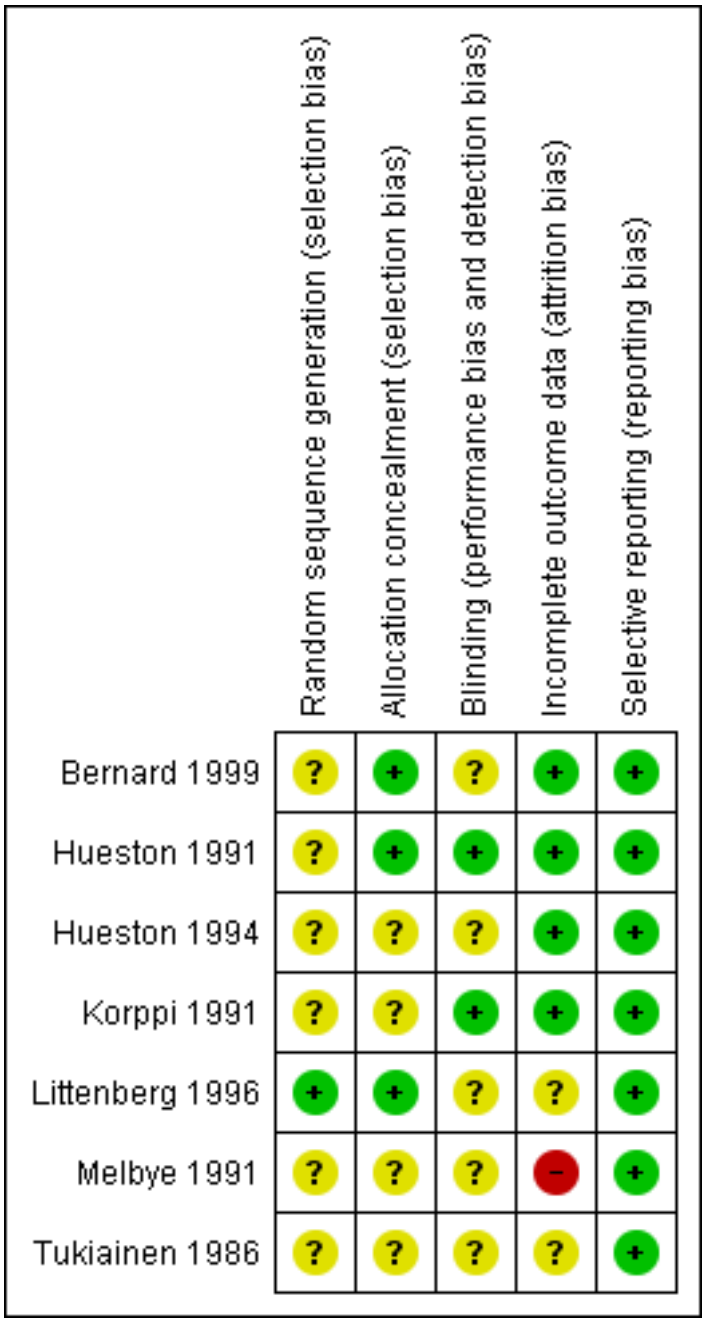


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Only three of the trials explicitly documented allocation concealment; two used central allocation by the pharmacy and the third explicitly noted that all investigators were blinded throughout the study (Bernard 1999; Hueston 1991; Littenberg 1996). However, it is likely that the double-blind methods used in the other four trials also resulted in adequate concealment of allocation. Although all the trials were described as randomised, only one trial described the method used (computer-generated random numbers) (Littenberg 1996).

Blinding

All trials were described as double-blind, but one trial report provided inadequate detail about the methods used (Tukiainen 1986). In several of the trials, participants allocated to the active treatment had higher side-effect rates, leading us to suspect that some participants may have been able to guess their assignment group despite the blinding. The one trial that surveyed participants to see if they knew into which group they were randomised found that 84% guessed correctly (Littenberg 1996). All trials included self reporting of symptoms by participants or their parents, so any lack of blinding may have biased the results reported.

Incomplete outcome data

Only three trials adequately discussed withdrawals (Hueston 1991; Hueston 1994; Melbye 1991). Dropout rates varied widely between trials (from 0% to 27%). None of the trials reported results of an intention-to-treat (ITT) analysis, although one reported that such an analysis had been performed (Bernard 1999).

Selective reporting

The trials appeared to be free of significant selective reporting bias. Only one had a protocol but the others either reported results for all of the key outcomes mentioned in the Methods section, or reported that none of their outcome measures showed statistically significant differences.

Other potential sources of bias

Three of the trial reports documented support for the study that did not include commercial sources (Hueston 1991; Hueston 1994; Littenberg 1996). Employees of pharmaceutical companies were listed authors on two papers (Korppi 1991; Tukiainen 1986). A pharmaceutical company supplied medication for three studies (Bernard 1999; Melbye 1991; Tukiainen 1986).

Only two of the trials reported on participant compliance (Hueston 1991; Hueston 1994).

Antibiotic prescribing was allowed at the physician's discretion in three trials and may have occurred at different rates in the intervention and control groups (Bernard 1999; Korppi 1991; Melbye 1991). Use of over-the-counter (OTC) antitussive or other medication was also allowed in two of these trials.

Effects of interventions

See: **Summary of findings for the main comparison** Beta-2 agonists versus placebo for acute bronchitis

The trials have such clinical heterogeneity that examining them as a single group did not seem appropriate. We therefore examined the trials in the following groups.

1. Trials in children.
2. Trials in adults:
   a. beta2-agonist versus placebo (including the trial in which both groups received dextromethorphan);
   b. beta2-agonist versus erythromycin.

Trials in children

Neither trial involving children demonstrated any benefits from albuterol. In Bernard 1999, there was no difference in daily cough impact scores, daily proportion of children with cough or in median duration of cough (three days) between the albuterol and placebo groups. In Korppi 1991, albuterol plus dextromethorphan was compared with dextromethorphan alone. There was a significant difference in favour of dextromethorphan alone on day one (lower cough score reflects less coughing), but otherwise no significant differences were apparent in daily cough symptom scores on other days, in daily general condition or in overall symptom relief after three days, between the albuterol plus dextromethorphan group and the dextromethorphan-only group. Combining the daily cough scores for days one to three for these two trials (96 participants) revealed no statistically significant difference in the scores for the group receiving albuterol versus the comparison group (Analysis 1.2; Analysis 1.3; Analysis 1.4). In both the albuterol and control groups, there was a steady decrease in cough scores from day one through to day three. Regarding adverse effects, there was a non-significant trend towards shaking or tremor in children given albuterol versus those given placebo or dextromethorphan only (RR 6.76, 95% confidence interval (CI) 0.86 to 53.18) (Analysis 1.9, two trials, 108 participants). There were no differences for other adverse effects.

Trials in adults comparing beta2-agonists with placebo or non-antibiotic comparator

The results of the placebo-controlled trials in adults were mixed. In Littenberg 1996, there were no differences between the albuterol and placebo groups for daily severity of cough, average daily activity level, mean nights of sleep interrupted by cough, mean days using additional medications or mean additional health visits. In Melbye 1991, the fenoterol group had more of a decrease in sputum production than the placebo group by the seventh day of the trial, but the decreases in day cough, night cough, dyspnoea and overall symptom score were not significantly different on any day. In Tukiainen 1986, the mean severity of night cough was less in the albuterol plus dextromethorphan group than in the dextromethorphan-only group on days three and four, but there were no differences in the severity or frequency of day cough, ease of expectoration or sputum production on any day. Hueston 1994 reported that participants given albuterol were less likely to be coughing after seven days, and to have returned to work after four days, than those given placebo, but there were no differences in the persistence of night cough or productive cough, time until improvement in general well-being, or in the use of OTC medications between groups.

When the data from Melbye 1991, Hueston 1994, and Littenberg 1996 were combined, there was no significant difference in the percentage of participants with cough (control group 71%; RR 0.86, 95% CI 0.63 to 1.18) (Analysis 2.1, three trials, 220 participants) or night cough (control group 29%; RR 0.84, 95% CI 0.54 to 1.33) (Analysis 2.3, three trials, 210 participants) after seven days of therapy. The combined data from Melbye 1991 and Hueston 1994 did not show a difference for the percentage of the group with a productive cough after seven days (control group 52%; RR 0.76, 95% CI 0.32 to 1.84) (Analysis 2.2, two trials, 119 participants); and the combined data from Hueston 1994 and Littenberg 1996 did not show a difference in whether participants were working or not after seven days (control group 31%; RR 0.82, 95% CI 0.28 to 2.34) (Analysis 2.11, two trials, 149 participants).

Trial in adults comparing beta2-agonist with erythromycin

In Hueston 1991, participants given albuterol were less likely to have a cough or a productive cough after seven days than those given erythromycin but there were no differences in the presence of night cough after seven days or in mean days until improvement in cough, well-being, or return to work or normal activities.

When the data from Hueston 1991 were combined in a sensitivity analysis with the data from the other adult trials, there were no significant differences for percentage with cough after seven days (control group 73%; RR 0.77, 95% CI 0.54 to 1.09) (four trials, 254 participants), productive cough (control group 58%; RR 0.66, 95% CI 0.35 to 1.25) (three trials, 150 participants) or night cough

(control group 32%; RR 0.85, 95% CI 0.57 to 1.26) (four trials, 232 participants).

Adverse effects in adult trials

Participants given beta2-agonists were more likely to report tremor, shaking or nervousness in the four trials in adults that mentioned specific side effects. The overall percentage of participants having these side effects in the three trials (211 participants) with explicit data ranged from 35% to 67% (versus a summary control rate of 11%; RR 7.94, 95% CI 1.17 to 53.94; NNTH 2 (Analysis 2.12). These side effects were seen in the trials using inhaled fenoterol as well as in those using oral albuterol or salbutamol. However, in Hueston 1994 only 9% of the participants given inhaled albuterol reported any side effects (the specific side effects were not mentioned in the paper and the data were not available from the trial author). There were no significant differences regarding other adverse effects between the beta2-agonist groups and control groups as a whole, but the trial comparing albuterol with erythromycin noted more gastrointestinal side effects in the erythromycin group (RD 0.35, 95% CI 0.12 to 0.59; NNTH 3, 95% CI 2 to 8) Hueston 1991 (6 of 17 in the erythromycin group versus 0 of 17 in the albuterol group).

Subgroup analyses

Four trials conducted subgroup analyses. In Melbye 1991, we analysed a subgroup of participants (35 of the 73 participants) with any one or more of the following: wheezing on initial examination, FEV-1 of less than 80% predicted, or a positive response to a methacholine challenge test. Those who were given fenoterol had significantly lower symptom scores, beginning at day two, than those in this subgroup who were given placebo. This was also true for a smaller subgroup of 15 participants who just had wheezing, but no difference was noted for participants with a normal lung examination. Hueston 1994, in a similar subgroup analysis, did not find differential responses based on the initial lung examination

Melbye 1991 also found that fenoterol-treated subgroups of participants who smoked or who had been treated with antibiotics had better overall symptom scores on day seven than those in these subgroups who were given placebo. Smokers did not have different responses from non-smokers in two other trials (Hueston 1991; Hueston 1994). Hueston 1994 reported that the differences between the groups given albuterol versus those not given albuterol persisted after stratification by erythromycin use.

DISCUSSION

Summary of main results

See Summary of findings for the main comparison

The findings from this review do not support the routine use of beta2-agonists for people who do not have underlying pulmonary disease and who present with an acute cough or a clinical diagnosis of acute bronchitis. However, these generally negative results must be interpreted in light of the participants who were enrolled in the trials. The two trials in children excluded those who were either wheezing or who had evidence of airflow restriction for which bronchodilator therapy was clinically indicated. There were therefore no data in children who had clinical signs of airflow restriction at the initial examination. The utility of beta2-agonists is unknown in children over the age of two and who have evidence of airflow restriction. A meta-analysis of the effectiveness of beta2-agonists in bronchiolitis (defined as an acute lower respiratory tract infection with wheezing) in children less than two years old showed that these agents do produce modest short-term improvements in clinical scores in this younger population (Gadomski 2014).

Overall completeness and applicability of evidence

The discordant results seen in the trials of adults may reflect different patient populations. More participants were wheezing on initial examination in Hueston 1994 and Hueston 1991 than in Littenberg 1996 or Melbye 1991. The latter's subgroup analysis demonstrated that people with evidence of airflow restriction (wheezing, bronchial hyper responsiveness or decreased FEV-1 values) had lower average symptom scores when treated with beta2-agonists than placebo, but that there was no difference in participants without these characteristics. Wheezing in unforced expiration is a sign of airflow restriction (Holleman 1995); therefore, more participants in Hueston's trials were likely to have had airflow restriction than in the other trials.

In the Melbye 1991 subgroup analysis of participants with evidence of airflow restriction, all components of the symptom score (including both cough and dyspnoea) were improved in the beta2-agonist group compared with the placebo group. Beta2-agonists have been shown to improve symptoms of cough in people with asthma (both in typical asthma as well as in the minority with cough-variant asthma). This improvement is not believed to be due to a direct effect on the cough reflex (Karlsson 1999) but is perhaps due to increased mucociliary clearance or other non-smooth muscle effects. Interestingly, the trials that noted improvements in cough with beta2-agonists were also the trials that enrolled more participants with a productive cough. It may be that these participant characteristics (wheezing or a productive cough, or both) can be used to identify a subgroup of people with acute cough who might benefit from beta2-agonists.

Quality of the evidence

There are limitations to this review. The number of studies and total number of participants included (especially children) are small. The review therefore has limited power to detect differences between those who were given beta2-agonists and those who were not. In the combined data of trials in adults, there was a trend towards improvements regarding cough, productive cough and night cough as well as in daily cough severity scores in participants randomised to the beta2-agonists. While these differences did not reach statistical significance, the confidence intervals were quite broad and include the possibility of clinically significant beneficial effects. For example, the possibility of up to a 46% reduction in cough after seven days for adults cannot be excluded, given the low power of the combined results.

The studies were also all of a short duration (three to seven days). There is therefore no information as to whether treatment with beta2-agonists would alter outcomes beyond this time. This is an important omission because many participants in these studies were still bothered by symptoms at the end of the trials.

We were able to find only two studies that evaluated inhaled beta2-agonists, which would currently be the most likely formulation used in adults and older children. Neither of these studies used spacing devices and therefore the delivery of the medicine may have been suboptimal.

Overall, the quality of evidence was low or moderate for individual interventions (see Summary of findings for the main comparison). However, there may have been additional biases because most of the trials had unequal distribution of co-interventions and did not record compliance with study medications.

We were able to include data on our outcomes from the majority of the studies. The summary statistics therefore do reflect the available evidence (including unpublished data from three trials (Bernard 1999; Littenberg 1996; Melbye 1991)).

Potential biases in the review process

We may have missed relevant studies, either because these were unpublished or because they were not published in journals covered by the databases we searched. All the studies we found stem from the previous century, when registration of new trials was not mandatory. However, as we also searched conference proceedings and contacted manufacturers, we think the chance of having missed studies is low.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that beta2-agonists are useful in healthy children who have an acute cough, particularly if their lung examination is normal. These children are more likely to have adverse effects than to derive any clinical benefit. Overall, there does not seem to be a clear benefit to adults either, although there is a trend toward some improvement in cough, especially in people who have evidence of airflow restriction. This benefit, however, is not well supported by the available evidence and must be weighed against the adverse effects of these medications, such as shaking, tremor and nervousness. These conclusions for both children and adults are based on a relatively small number of trials, and the confidence intervals in our analyses could not completely rule out the possibility of clinically significant beneficial effects of beta2-agonists.

Implications for research

There is a need for additional study of the utility of beta2-agonists in the treatment of acute bronchitis in people without underlying pulmonary disease. There is a particular need for identifying clinical characteristics that can predict who might benefit. For example, data are lacking in children older than two years who have signs of airflow restriction. More evidence is also necessary on the risk-benefit ratio of beta2-agonists in adults with clinical signs of airflow limitation. This should include further examination of other indicators of illness, such as generally feeling ill, as well as cough. Additional areas of useful research would be the evaluation of long-acting beta2-agonists (because of ease of adherence), evaluating the benefits of inhaled beta2-agonists with spacing devices, and comparing beta2-agonists with other symptomatic treatments. Because of the reported adverse effects seen in the trials thus far, studies of short-acting beta2-agonists should use inhaled albuterol (salbutamol) or another inhaled agent with a low incidence of adverse effects instead of oral albuterol or inhaled fenoterol.

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CHARACTERISTICS OF STUDIES

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

Bernard 1999

Methods	RCT, 13/59 withdrawals
Participants	USA: 59 children, aged 1 to 10 years, with cough 1 to 14 days (median 4 days), respiratory rate less than 35 and normal lung exam
Interventions	Albuterol syrup (0.1 mg/kg to max dose of 2 mg every 8 hours) (N = 30); versus placebo syrup (N = 29) for 7 days
Outcomes	Daily cough impact score, number with complete resolution of cough at trial end; number with daily cough; number with hyperactivity or shaking
Notes	Prohibited codeine, dextromethorphan, antihistamines, OTC cough preparations; 27% of albuterol group and 38% of placebo group treated with antibiotics for co-existing otitis media Study medication was provided by a pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were described as "randomized in blocks of 4" but no details were provided about the method of sequence generation
Allocation concealment (selection bias)	Low risk	"Investigators ... were blinded to group assignment until the trial was completed"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and personnel were described as blinded, but no details were provided about the methods used. Children receiving the active treatment were more likely to develop shaking (a known side effect of the intervention), so it is possible that study personnel, parents, or care providers may have become aware of the treatment assignment in some cases. Outcome assessment was done with a telephone interview asking parents to assess symptoms
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates were provided and an ITT analysis was carried out
Selective reporting (reporting bias)	Low risk	No positive outcomes were reported

Hueston 1991

Methods	RCT, 8/42 withdrawals

Hueston 1991 *(Continued)*

Participants	USA: 42 adults with productive cough for less than 30 days (mean 5 days); temp less than 39.5 C and no clinical or radiographic evidence of pneumonia; 47% in albuterol group and 41% in placebo group had wheezing on initial exam
Interventions	Albuterol syrup (2 mg every 6 hours) (N = 20) versus erythromycin ethylsuccinate syrup (400 mg every 6 hours) (N = 22) for 7 days
Outcomes	Days until improvement in cough or well-being, night cough resolved, return to work or normal activity; after 7 days, number with cough, productive cough, night cough, purulent sputum; improvement in well-being after 7 days; number with tremulousness, nervousness, or GI side effects
Notes	No prohibitions regarding adjunctive treatments, and use of adjunctive treatments not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, but there is no information about the sequence generation method
Allocation concealment (selection bias)	Low risk	Central allocation by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Number coded, tinted vials
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates were small and comparable between groups. No ITT analysis was performed
Selective reporting (reporting bias)	Low risk	No primary outcome was specified, but all planned outcomes appear to have been reported

Hueston 1994

Methods	RCT, 0/46 withdrawals
Participants	USA: 46 adults with productive cough for less than 30 days (mean 9 days) and no clinical or radiographic evidence of pneumonia (52% in albuterol group and 30% in placebo group with wheezing on initial exam)
Interventions	Albuterol inhaler (N = 23) versus placebo inhaler (N = 23) for 7 days; participants in each group were also randomised to receive erythromycin or placebo capsule
Outcomes	Daily presence of cough, night cough, ability to perform normal work and general level of well-being; number using OTC medications, having side effects during trial; after 7 days, number with cough, productive cough, night cough; and days until improvement in well-being
Notes	No prohibitions regarding adjunctive treatments, but proportion using OTC medications was recorded as an outcome measure

Risk of bias

Bias	Authors' judgement	Support for judgement

Hueston 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, but there is no information about the sequence generation method
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of masking information on active and placebo inhaler canisters to blind participants was described, but no details were given re blinding of care providers or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All initially enrolled participants completed the trial
Selective reporting (reporting bias)	Low risk	All planned outcomes appear to have been reported

Korppi 1991

Methods	RCT, 3/75 withdrawals
Participants	Finland: 75 children, aged 1 to 10 years, with respiratory infection associated with cough and no bronchial obstruction requiring bronchodilators
Interventions	3 groups: 1 - Dextromethorphan (7.5 mg every 8 hours if less than 7 years old, 15 mg every 8 hours if older) plus Salbutamol (1 mg every 8 hours if less than 7 years old, 2 mg every 8 hours if older) (N = 25); 2 - Dextromethorphan alone at the same dose (N = 24):3 - placebo syrup (N = 26). All treatments were given for for 3 days. Only groups 1 and 2 were used for the analyses in this review.
Outcomes	Daily cough symptom scores, daily general condition scores, number with relief at end of trial, number reporting side effects
Notes	Prohibited expectorants, other antitussives, antihistamines and other bronchodilators; antibiotics allowed, but not recorded A pharmaceutical company employee was listed as an author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, but there is no information about the sequence generation method
Allocation concealment (selection bias)	Unclear risk	There is no information about the method of allocation used
Blinding (performance bias and detection bias) All outcomes	Low risk	The study is described as double-blind. The authors stated: "The placebo mixture was identical to base mixtures used in active medicaments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data were available for 72/75 children who all completed the study. This study was not analysed as ITT, but the percentage of dropouts is very small

Korppi 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods were reported as not statistically significant

Littenberg 1996

Methods	RCT; 38/142 withdrawals
Participants	USA: 142 adults with nonspecific bronchitis or acute cough less than 4 weeks duration (mean 10 days), and no findings of consolidation on exam or radiograph; 36% in albuterol group and 19% in placebo group had wheezing on forced expiration
Interventions	Albuterol sulphate pills (4 mg every 8 hours) (N = 71) versus placebo pills (N=71) for 7 days
Outcomes	Daily and overall severity of cough, overall activity score, days using cough suppressants, days of sleepless nights, days of side effects
Notes	Prohibited corticosteroids and antibiotics other than erythromycin; allowed erythromycin (61% in albuterol group versus 74% in placebo group), dextromethorphan (57% in albuterol group versus 52% in placebo group), and codeine (43% in albuterol group versus 28% in placebo group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central allocation by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study is described as double-blind. Participants were given “identical-looking pills.” However, 84% of participants correctly guessed which group they had been assigned to
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The dropout rate was relatively high (27%). There is no description of the reason for withdrawals. Participants who did not complete the study seem to have a more serious condition. No ITT analysis was performed
Selective reporting (reporting bias)	Low risk	All outcomes listed in the Methods were reported

Melbye 1991

Methods	RCT, 7/80 withdrawals
Participants	Norway: 80 adults with acute respiratory infection with more than 1 week of cough (95%) and/or dyspnoea (71%); mean duration of illness 24 days, no evidence of pneumonia, tonsillitis or sinusitis (without wheezing or dyspnoea); temp less than 38 C; baseline FEV-1 more than 60%; 22% in fenoterol group and 19% in placebo group had wheezing on initial exam
Interventions	Fenoterol aerosol (0.2 mg every 6 hours) (N = 40) versus placebo aerosol (N = 40) for 7 days

Melbye 1991 *(Continued)*

Outcomes	Per cent change from baseline for day cough, night cough, sputum production, dyspnoea, chest pain, clamminess, fatigue; number with tremor or palpitations
Notes	Antibiotics allowed if begun more than 3 days prior to enrolment (40% in fenoterol group versus 28% in placebo group); other adjunctive treatments not mentioned Study medication was provided by a pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, but there is no information about the sequence generation method
Allocation concealment (selection bias)	Unclear risk	There is no information about the method of allocation used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Details about blinding of participants, care providers, or outcome assessors were not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	73 participants completed the trial (80 enrolled); information was available for only 6 of the 7 dropouts. No ITT analysis
Selective reporting (reporting bias)	Low risk	All planned outcomes appear to have been reported

Tukiainen 1986

Methods	RCT. Withdrawals not mentioned
Participants	Finland: 108 adults with acute respiratory infection with cough (mean duration 9 days); per cent with wheezing on initial exam not mentioned
Interventions	Oral salbutamol (2 mg every 8 hours) + dextromethorphan (N=38) versus dextromethorphan only (N = 36) versus placebo (N = 34) for 4 days. Only groups 1 and 2 were used for the analyses in this review
Outcomes	Daily symptom scores for day cough frequency and severity, night cough severity, and breathlessness; and number with side effects
Notes	Prohibited other antitussives, expectorants, mucolytics, and antibiotics Study medication was provided by a pharmaceutical company and a pharmaceutical company employee was listed as an author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, but there is no information about the sequence generation process. Also, the groups had different number of participants (38, 36, and 34) and some of the participants characteristics were not similar between groups

Tukiainen 1986 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	The study is described as randomised, but there is no information about the method of allocation used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The methods used for blinding were not described. The group receiving beta agonists had significantly more tremor, so participants and providers may have become aware of their assignment group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data were provided on the number or characteristics of dropouts, or ways in which dropouts were handled
Selective reporting (reporting bias)	Low risk	Results included data on all outcomes except breathlessness

exam: examination
FEV-1: forced expiratory volume in 1 second
GI: gastro intestinal
ITT: intention-to-treat
OTC: over-the-counter
RCT: randomised controlled trial

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

Study	Reason for exclusion
Chang 1998	All enrollees had a history of recurrent cough and the median duration of the present cough was 8 weeks
Ovchinnikov 2014	The intervention group received salbutamol, bromhexine and guaifenesin in a single tablet. The control group did not receive bromhexine or guaiphenesin
Zanasi 2014	The intervention group received a combination of salbutamol and ipratropium bromide. The control group received a placebo but no ipratropium

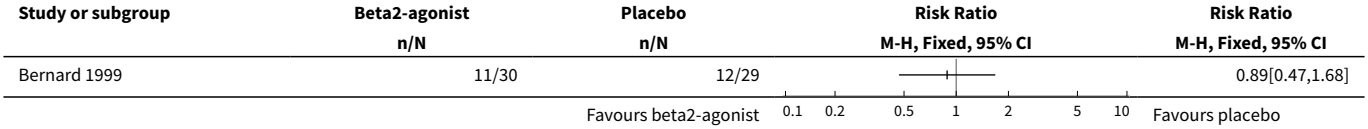
DATA AND ANALYSES

Comparison 1. Beta2-agonists versus placebo in children

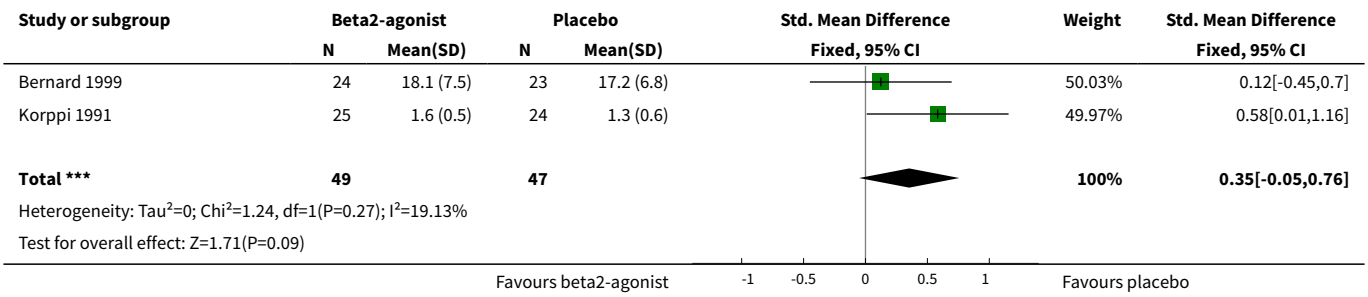
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough after seven days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mean cough score after one day	2	96	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [-0.05, 0.76]
3 Mean cough score after two days	2	96	Std. Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.21, 0.59]
4 Mean cough score after three days	2	95	Std. Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.05, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Mean cough score after four days	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Mean cough score after five days	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Mean cough score after six days	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Mean cough score after seven days	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Shaking or tremor	2	108	Risk Ratio (M-H, Fixed, 95% CI)	6.76 [0.86, 53.18]
10 Other side effects	2	108	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.41, 2.41]

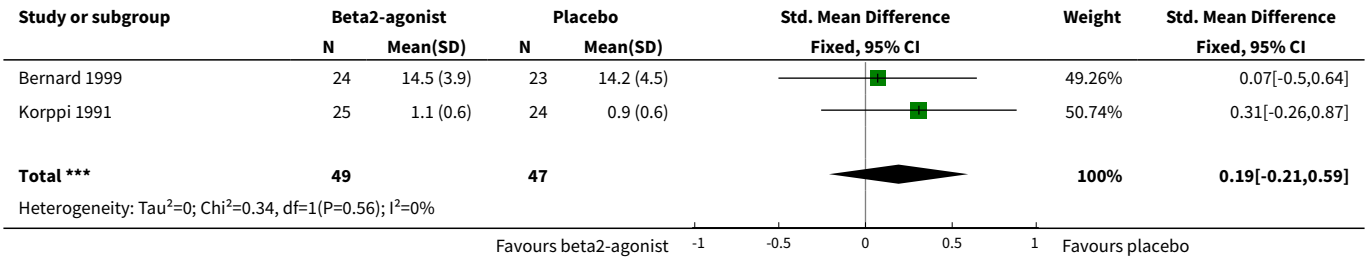
Analysis 1.1. Comparison 1 Beta2-agonists versus placebo in children, Outcome 1 Cough after seven days.

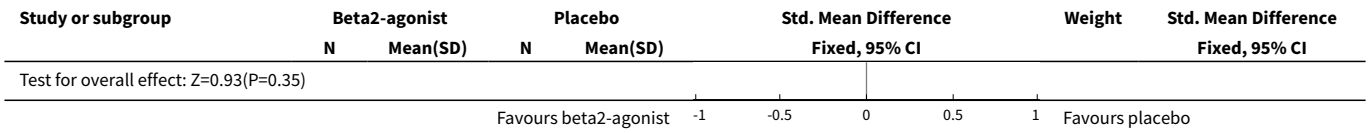


Analysis 1.2. Comparison 1 Beta2-agonists versus placebo in children, Outcome 2 Mean cough score after one day.

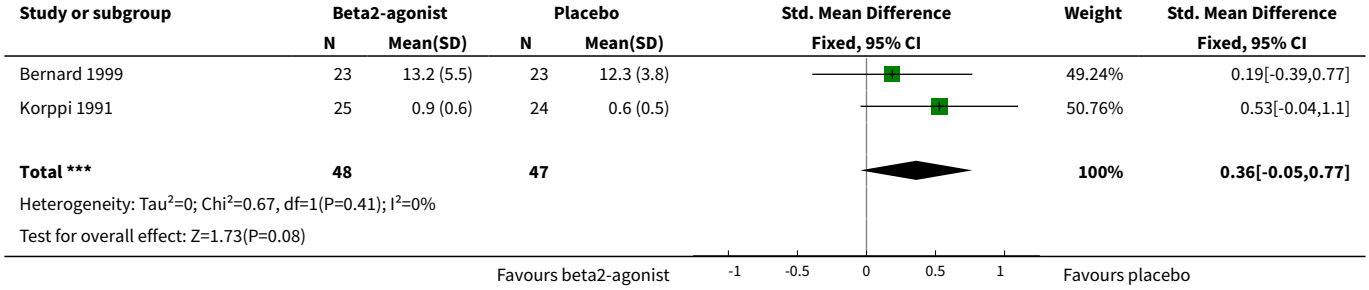


Analysis 1.3. Comparison 1 Beta2-agonists versus placebo in children, Outcome 3 Mean cough score after two days.

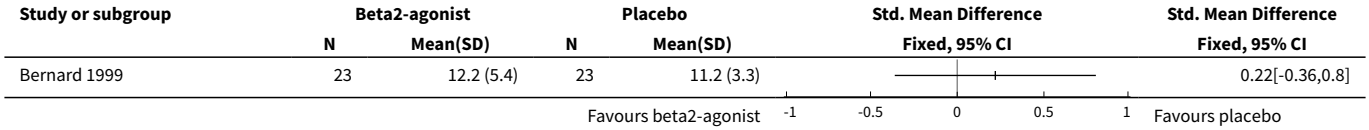




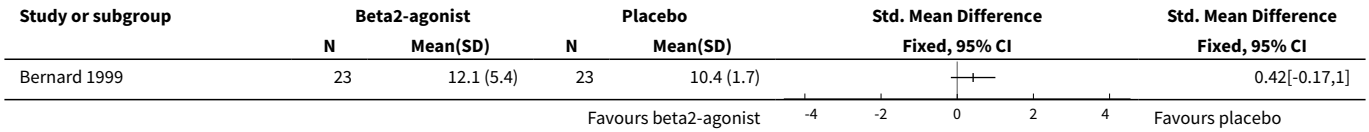
Analysis 1.4. Comparison 1 Beta2-agonists versus placebo in children, Outcome 4 Mean cough score after three days.



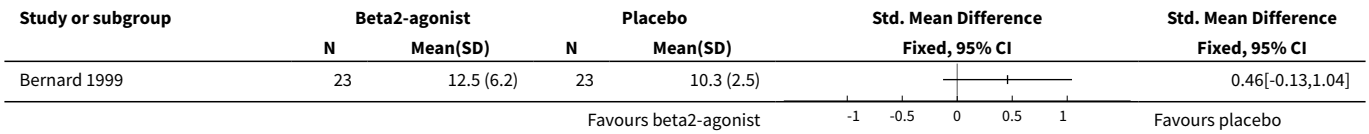
Analysis 1.5. Comparison 1 Beta2-agonists versus placebo in children, Outcome 5 Mean cough score after four days.



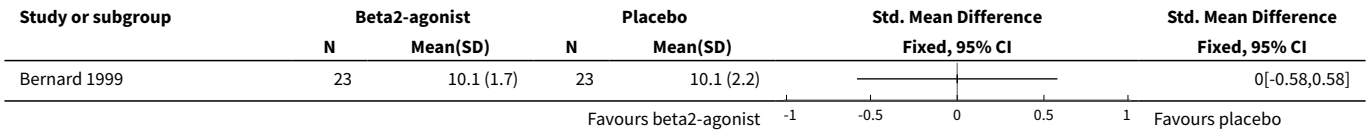
Analysis 1.6. Comparison 1 Beta2-agonists versus placebo in children, Outcome 6 Mean cough score after five days.



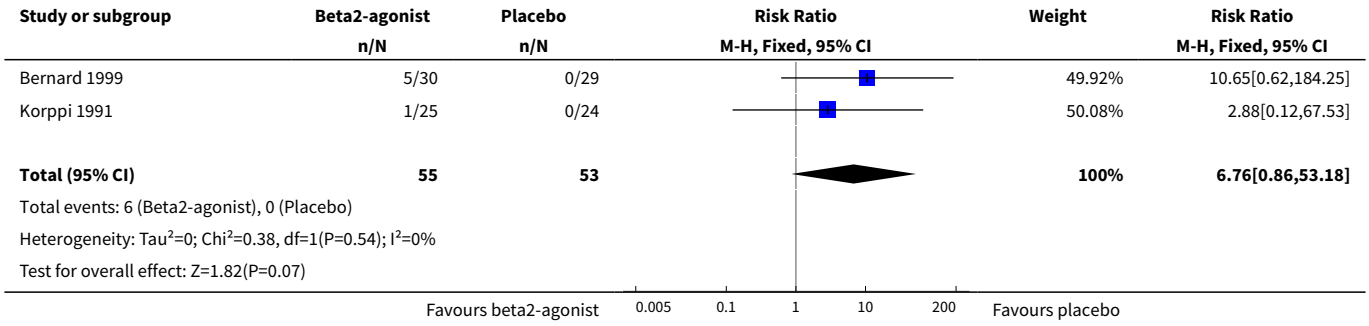
Analysis 1.7. Comparison 1 Beta2-agonists versus placebo in children, Outcome 7 Mean cough score after six days.



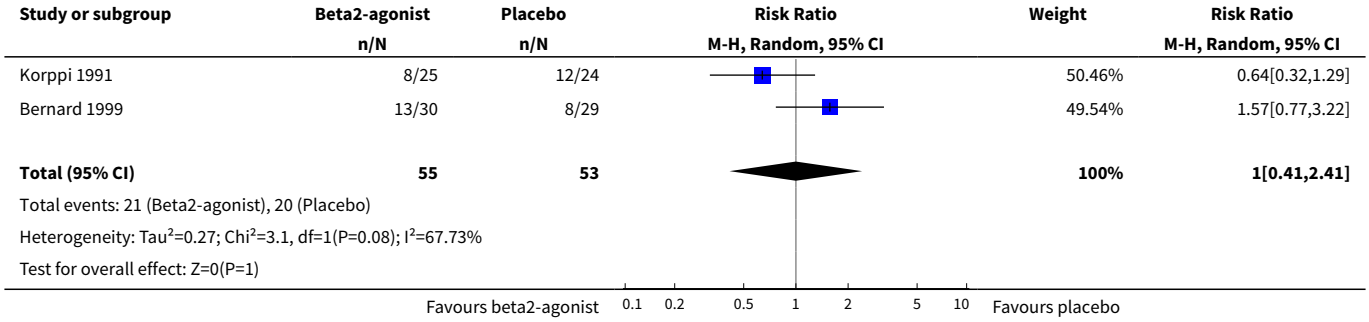
Analysis 1.8. Comparison 1 Beta2-agonists versus placebo in children, Outcome 8 Mean cough score after seven days.



Analysis 1.9. Comparison 1 Beta2-agonists versus placebo in children, Outcome 9 Shaking or tremor.



Analysis 1.10. Comparison 1 Beta2-agonists versus placebo in children, Outcome 10 Other side effects.



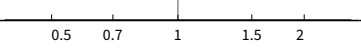
Comparison 2. Beta2-agonists versus placebo in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough after seven days	3	220	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.18]
2 Productive cough after seven days	2	119	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.32, 1.84]
3 Night cough after seven days	3	210	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.33]
4 Mean cough score after one day	3	250	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.47, 0.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Mean cough score after two days	3	251	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.35, 0.15]
6 Mean cough score after three days	3	251	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.42, 0.08]
7 Mean cough score after four days	3	251	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.38, 0.11]
8 Mean cough score after five days	2	176	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.52, 0.07]
9 Mean cough score after six days	2	175	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.49, 0.10]
10 Mean cough score after seven days	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Not working by day seven	2	149	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.28, 2.34]
12 Shaking, tremor or nervousness	3	211	Risk Ratio (M-H, Random, 95% CI)	7.94 [1.17, 53.94]
13 Other side effects	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.42, 1.63]

Analysis 2.1. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 1 Cough after seven days.

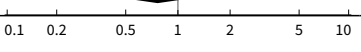
Study or subgroup	Beta2-agonist n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hueston 1994	14/23	21/23		32.3%	0.67[0.47,0.95]
Littenberg 1996	39/50	37/51		42.31%	1.08[0.86,1.35]
Melbye 1991	17/37	20/36		25.39%	0.83[0.52,1.3]
Total (95% CI)	**110**	**110**		**100%**	**0.86[0.63,1.18]**
Total events: 70 (Beta2-agonist), 78 (Placebo)					
Heterogeneity: Tau^2=0.05; Chi^2=5.36, df=2(P=0.07); I^2=62.66%					
Test for overall effect: Z=0.92(P=0.36)					



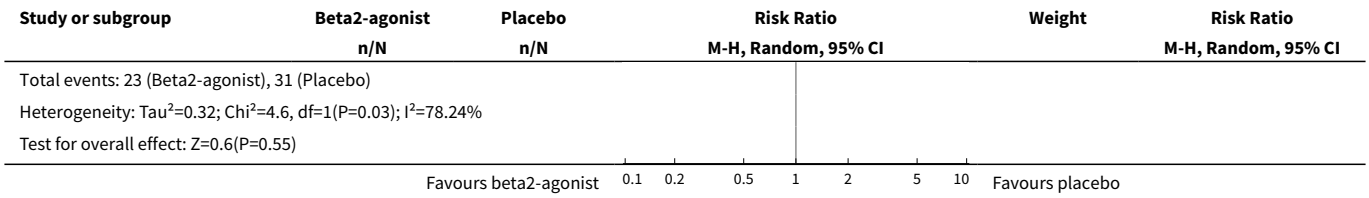
Favours beta2-agonist — Favours placebo

Analysis 2.2. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 2 Productive cough after seven days.

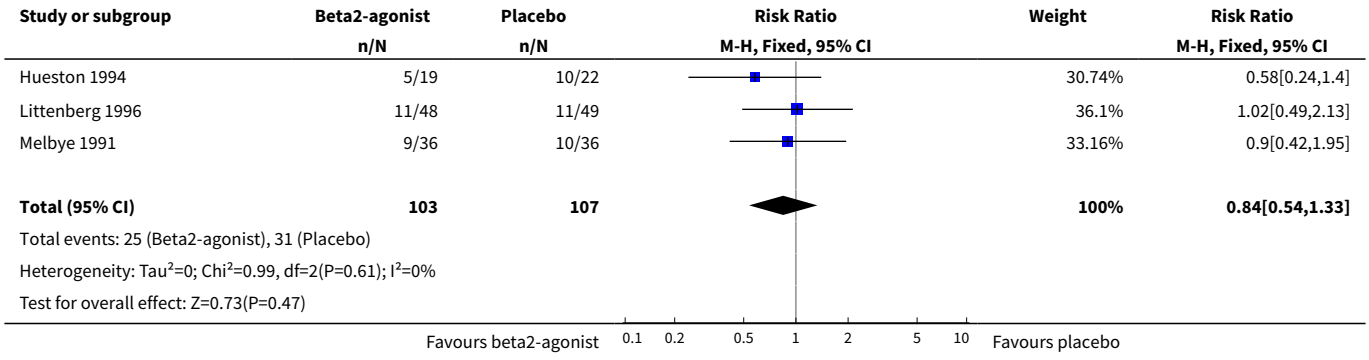
Study or subgroup	Beta2-agonist n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hueston 1994	13/23	11/23		50.88%	1.18[0.68,2.06]
Melbye 1991	10/37	20/36		49.12%	0.49[0.27,0.89]
Total (95% CI)	**60**	**59**		**100%**	**0.76[0.32,1.84]**



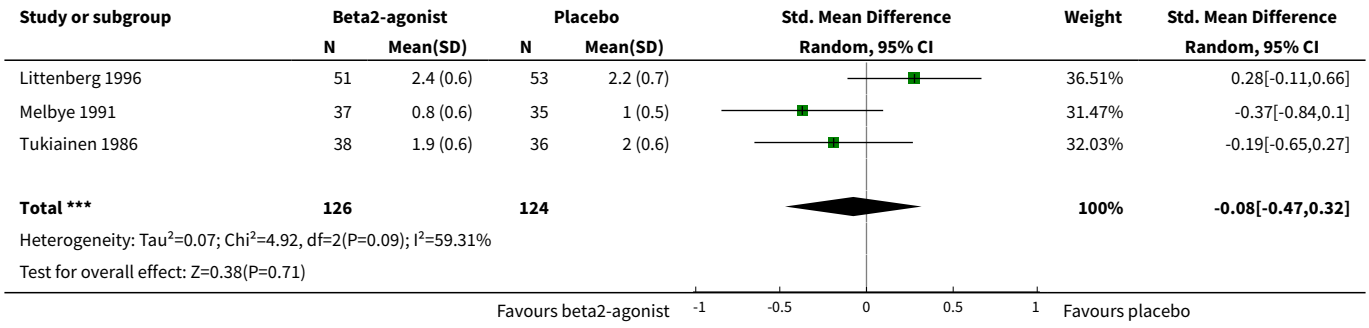
Favours beta2-agonist — Favours placebo



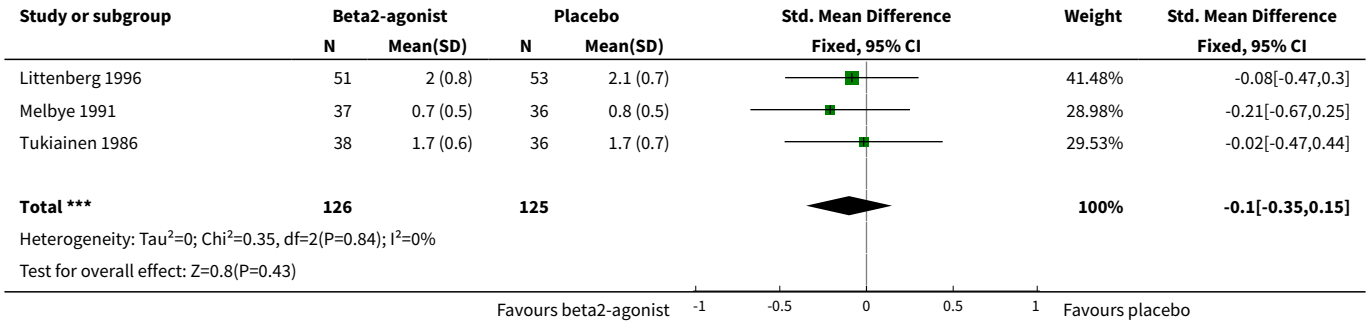
Analysis 2.3. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 3 Night cough after seven days.



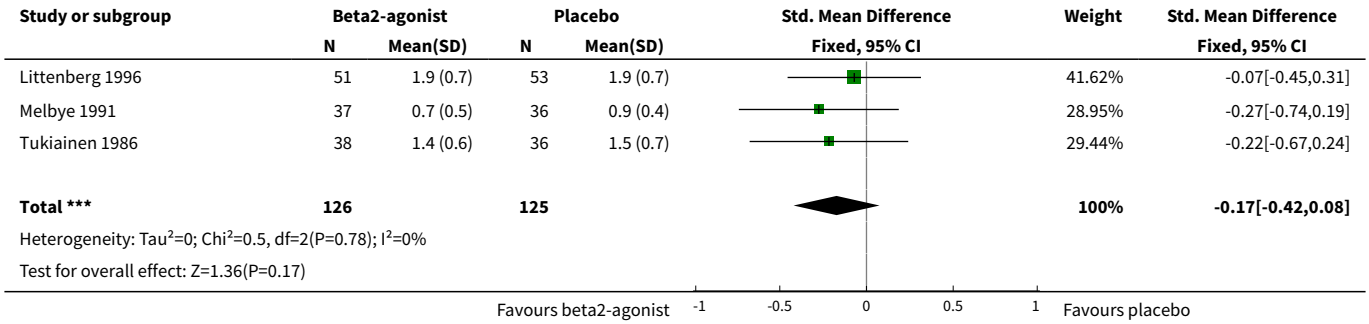
Analysis 2.4. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 4 Mean cough score after one day.



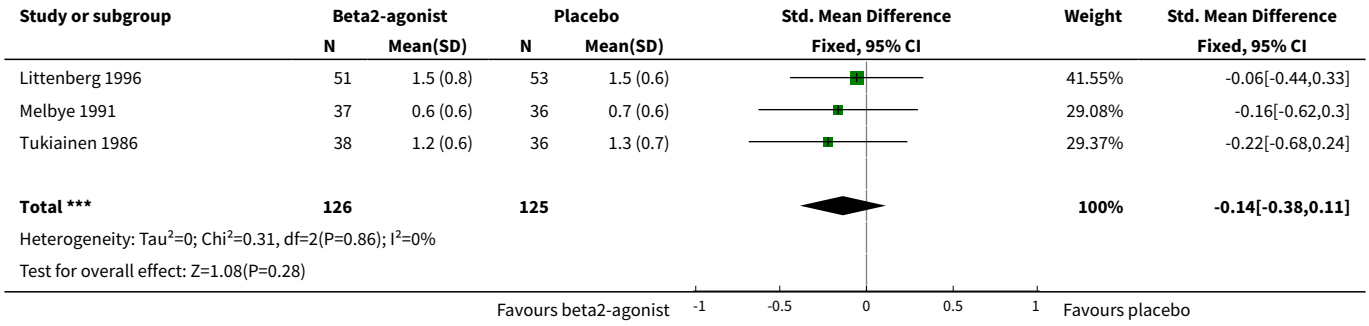
Analysis 2.5. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 5 Mean cough score after two days.



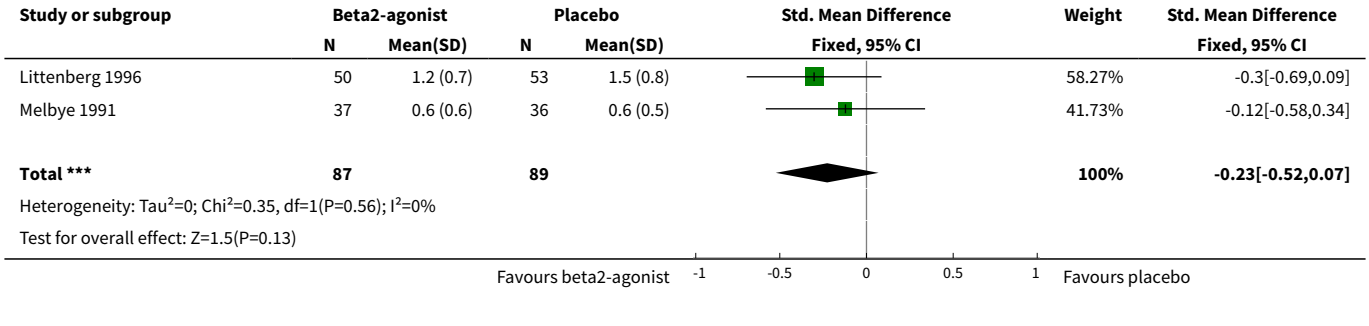
Analysis 2.6. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 6 Mean cough score after three days.



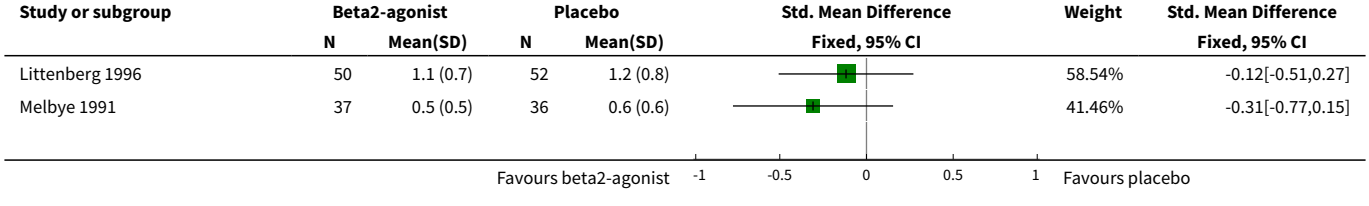
Analysis 2.7. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 7 Mean cough score after four days.

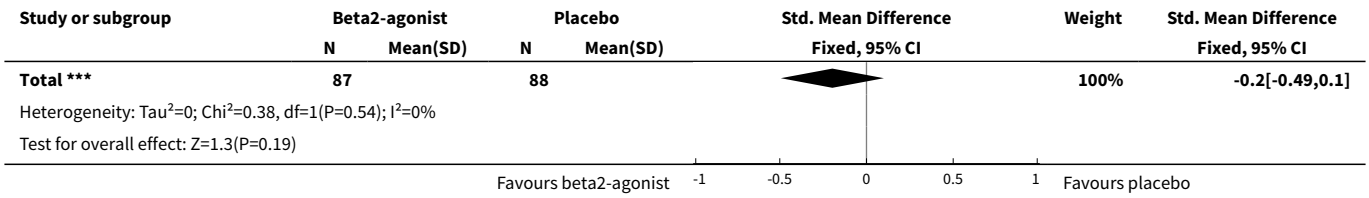


Analysis 2.8. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 8 Mean cough score after five days.

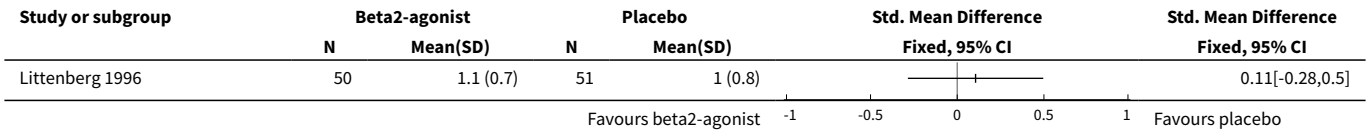


Analysis 2.9. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 9 Mean cough score after six days.

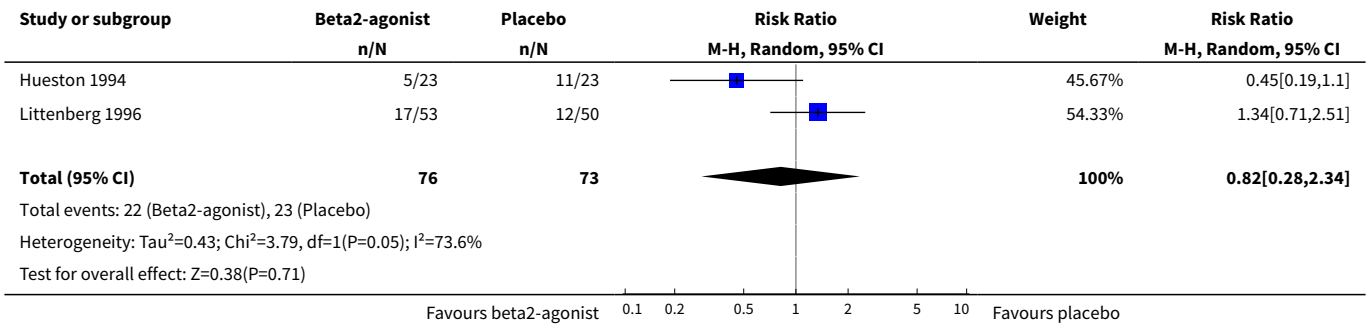




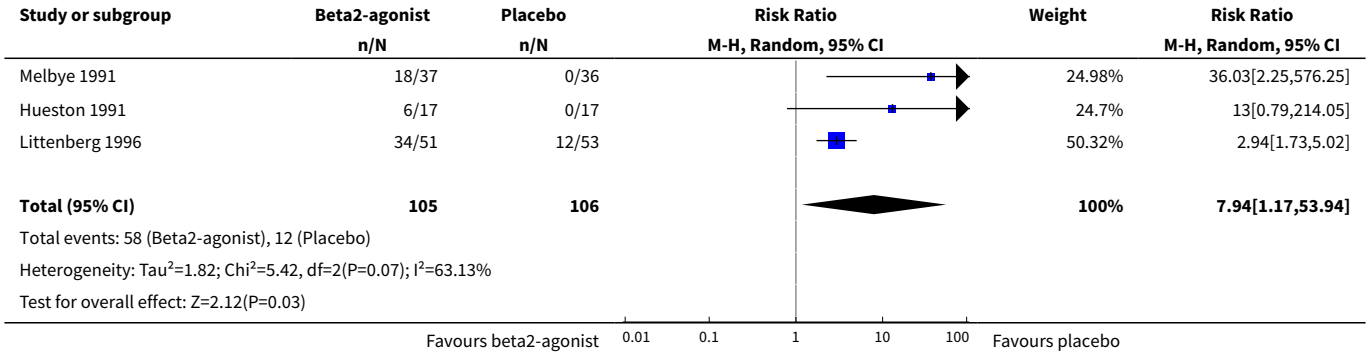
Analysis 2.10. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 10 Mean cough score after seven days.



Analysis 2.11. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 11 Not working by day seven.



Analysis 2.12. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 12 Shaking, tremor or nervousness.



Analysis 2.13. Comparison 2 Beta2-agonists versus placebo in adults, Outcome 13 Other side effects.

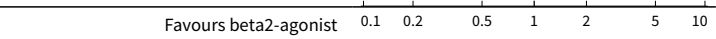
Study or subgroup	Beta2-agonist n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueston 1994	2/23	2/23		13.56%	1[0.15,6.51]
Littenberg 1996	10/51	13/53		86.44%	0.8[0.39,1.66]
Total (95% CI)	**74**	**76**		**100%**	**0.83[0.42,1.63]**
Total events: 12 (Beta2-agonist), 15 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					

Comparison 3. Beta2-agonists versus erythromycin in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough after seven days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Productive cough after seven days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Night cough after seven days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

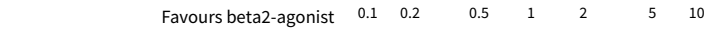
Analysis 3.1. Comparison 3 Beta2-agonists versus erythromycin in adults, Outcome 1 Cough after seven days.

Study or subgroup	Beta2-agonist n/N	Erythromycin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Hueston 1991	7/17	15/17		0.47[0.26,0.85]



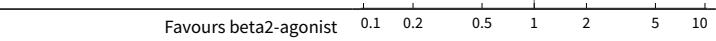
Analysis 3.2. Comparison 3 Beta2-agonists versus erythromycin in adults, Outcome 2 Productive cough after seven days.

Study or subgroup	Beta2-agonist n/N	Erythromycin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Hueston 1991	5/14	13/17		0.47[0.22,0.99]



Analysis 3.3. Comparison 3 Beta2-agonists versus erythromycin in adults, Outcome 3 Night cough after seven days.

Study or subgroup	Beta2-agonist n/N	Erythromycin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Hueston 1991	5/10	7/12		0.86[0.39,1.88]



ADDITIONAL TABLES

Table 1. Participants with wheezing on initial examination

Study	% in intervention group	% in placebo group	Note
Hueston 1991	47	41	
Hueston 1994	52	30	
Littenberg 1996	36	19	on forced expiration
Melbye 1991	22	19	

APPENDICES

Appendix 1. Details of previous searches

For the first publication of this review, we searched the entire Cochrane Library (August 2000), MEDLINE (1966 to 2000) and EMBASE (1974 to 2000) using the keywords "bronchitis" or "cough" (both as MeSH terms and text words), together with the terms "adrenergic beta-agonist (exp)", "bronchodilator agents (exp)", or "sympathomimetic (exp)" (as well as the individual generic names for all approved beta2-agonists: albuterol, salbutamol, bitolterol, isoetharine, metaproterenol, pirbuterol, salmeterol, terbutaline, fenoterol, formoterol and procaterol). Albuterol and salbutamol are the same drug; in North America it is known as albuterol and in many other countries it is known as salbutamol. For MEDLINE and EMBASE searches we used a sensitive strategy for finding controlled trials: "clinical trials (exp)" or "comparative study/ or placebo" or "controlled or clinical or randomised trial (PT)".

We also searched for trials in conference proceedings databases Inside Conferences (1993 to 1999); Conference Papers Index (1973 to 1999); in the reference lists of retrieved articles, review articles and textbooks; and in the Science Citation Index (1990 to 2000) using the key studies we retrieved. Finally, we wrote to all US manufacturers of currently approved brand-name beta2-agonists.

The review was updated in the Cochrane Library, 2002, issue 2, when we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2003, Issue 3), MEDLINE (January 1966 to July 2003), and EMBASE (1974 to July 2003).

When the review was next updated in 2005, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2005, issue 4) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to November 2005) and EMBASE (1974 to November 2005).

The search was updated again in 2011. For the 2011 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 1 which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (November 2005 to February week 1, 2011) and EMBASE (November 2005 to February 2011)

MEDLINE (OVID)
1 exp Bronchitis/
2 bronchitis.mp.
3 exp COUGH/
4 cough.mp.
5 or/1-4
6 exp Adrenergic beta-Agonists/
7 beta2-agonist$.mp.
8 exp Bronchodilator Agents/
9 bronchodilator$.mp.
10 exp SYMPATHOMIMETICS/
11 sympathomimetic$.mp.
12 exp ALBUTEROL/
13 albuterol.mp.
14 salbutamol.mp.

15 bitolterol.mp.
16 exp ISOETHARINE/
17 isoetharine.mp.
18 exp Orciprenaline/
19 metaproterenol.mp.
20 pirbuterol.mp.
21 salmeterol.mp.
22 exp TERBUTALINE/
23 terbutaline.mp.
24 exp FENOTEROL/
25 fenoterol.mp.
26 formoterol.mp.
27 fenoterol.mp.
28 exp PROCATEROL/
29 procaterol.mp.
30 exp Ethanolamines/
31 or/6-30
32 5 and 31
33 RANDOMIZED CONTROLLED TRIAL.pt.
34 CONTROLLED CLINICAL TRIAL.pt.
35 RANDOMIZED CONTROLLED TRIALS.sh.
36 RANDOM ALLOCATION.sh.
37 DOUBLE BLIND METHOD.sh.
38 SINGLE-BLIND METHOD.sh.
39 or/33-38
40 Animals/
41 Humans/
42 40 not 41
43 39 not 42
44 CLINICAL TRIAL.pt.
45 exp Clinical Trials/
46 (clin$ adj25 trial$).ti,ab.
47 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
48 PLACEBOS.sh.
49 placebo$.ti,ab.
50 random$.ti,ab.
51 or/44-50
52 51 not 42
53 43 or 52
54 32 and 53

Appendix 2. MEDLINE (Ovid) search strategy

MEDLINE (OVID)
1 exp Bronchitis/
2 bronchit*.tw.
3 Cough/
4 cough*.tw.
5 or/1-4
6 exp Adrenergic beta-Agonists/
7 beta2-agonist*.tw,nm.
8 exp Bronchodilator Agents/
9 bronchodilator*.tw,nm.
10 exp Sympathomimetics/
11 sympathomimetic*.tw,nm.
12 exp Ethanolamines/
13 ethanolamine*.tw,nm.
14 albuterol.tw,nm.
15 salbutamol.tw,nm.
16 bitolterol.tw,nm.
17 orciprenalin*.tw,nm.
18 metaproterenol.tw,nm.

19 pirbuterol.tw,nm.
20 salmeterol.tw,nm.
21 terbutaline.tw,nm.
22 fenoterol.tw,nm.
23 formoterol.tw,nm.
24 procaterol.tw,nm.
25 Isoetharine/
26 isoetharine*.tw,nm.
27 or/6-26
28 5 and 27

Appendix 3. EMBASE.com search strategy

18. #14 AND #17
17. #15 OR #16
16. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR singl* NEAR/1 blind* OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti
15. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
14. #5 AND #13
13. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
12. albuterol:ab,ti OR salbutamol:ab,ti OR bitolterol:ab,ti OR isoetharine:ab,ti OR orciprenaline:ab,ti OR metaproterenol:ab,ti OR pirbuterol:ab,ti OR salmeterol:ab,ti OR terbutaline:ab,ti OR fenoterol:ab,ti OR formoterol:ab,ti OR procaterol:ab,ti OR ethanolamine*:ab,ti
11. 'salbutamol'/de OR 'bitolterol'/de OR 'isoetarine'/de OR 'orciprenaline'/de OR 'pirbuterol'/de OR 'salmeterol'/de OR 'terbutaline'/de OR 'fenoterol'/d e OR 'formoterol'/de OR 'procaterol'/de OR 'ethanolamine derivative'/exp
10. sympathomimetic*:ab,ti
9. bronchodilator*:ab,ti
8. 'bronchodilating agent'/exp
7. 'beta2-agonist':ab,ti OR 'beta2-agonists':ab,ti
6. 'beta adrenergic receptor stimulating agent'/exp
5. #1 OR #2 OR #3 OR #4
4. cough*
3. 'coughing'/de
2. bronchitis:ab,ti
1. 'bronchitis'/exp

Appendix 4. Web of Science (Thomson Reuters) search strategy

# 6	**46**
# 5	**513**
# 4	**1,340,602**
# 3	**1,388**
# 2	**33,282**
# 1	**36,325**

Appendix 5. LILACS (BIREME) search strategy

(mh:bronchitis OR bronchit* OR bronquit* OR mh:c08.127.446* OR mh:c08.381.495.146* OR mh:c08.730.099* OR mh:cough OR cough* OR tos OR tosse) AND (mh:"Adrenergic beta-Agonists" OR "Agonistas Adrenérgicos beta" OR "Agonistas Adrenérgicos beta" OR "beta-Adrenergic Agonists" OR "beta-Adrenergic Receptor Agonists" OR "Adrenergic beta-Receptor Agonists" OR mh:d27.505.519.625.050.100.200* OR mh:d27.505.696.577.050.100.200* OR "beta-Agonistas Adrenérgicos" OR "Agonistas beta-Adrenérgicos" OR "Agonistas de los Receptores Adrenérgicos beta" OR "Agonistas de los Receptores beta-Adrenérgicos" OR "Agonistas de los beta-Receptores Adrenérgicos" OR "Agonistas dos Receptores Adrenérgicos beta" OR "Agonistas dos Receptores beta-Adrenérgicos" OR "Agonistas dos beta-Receptores Adrenérgicos" OR mh:"Bronchodilator Agents" OR bronchodilator* OR broncodilatador* OR "Dilatadores Bronquiales" OR "Dilatadores Brônquicos" OR "Dilatadores Bronquiais" OR mh:sympathomimetics OR sympathomimetic* OR simpatomiméticos OR simpatomiméticas OR simpatomimético OR mh:ethanolamines OR etanolaminas OR mh:d02.033.100.291* OR mh:d02.033.375.291* OR mh:d02.092.063.291* OR ethanolamine* OR albuterol OR salbutamol OR bitolterol OR orciprenalin* OR metaproterenol OR pirbuterol OR salmeterol OR terbutaline OR fenoterol OR formoterol OR procaterol OR isoetharine OR isoetarina OR mh:isoetharine) AND db:("LILACS") AND type_of_study:("clinical_trials")

Appendix 6. Risk of bias data extraction form

Ref No:	
Authors, year of publication:	
Reviewer:	**Date:**

Assessing risk of bias

Domain/sources of bias	**Judgement based on: (description / quote from text with page number)**	**Review author's judgement of the Risk of Bias**
1. Sequence generation		Was the allocation sequence randomly generated? Low / High / Unclear
2. Allocation concealment		Was allocation adequately concealed? Low / High / Unclear
3. Blinding *(if different for different outcomes, specify by outcome)*		Was knowledge of the allocated interventions adequately prevented during the study? 1. Was the participant blinded to the intervention? Low / High / Unclear 2. Was the care provider blinded to the intervention? Low / High / Unclear 3. Was the outcome assessor blinded to the intervention?

(Continued)

	Low / High / Unclear
4. Incomplete outcome data	Were incomplete outcome data adequately addressed? 1. Was the dropout rate described and acceptable? Low / High / Unclear 2. Were all randomised participants analysed in the group to which they were allocated? (ITT analysis) Low / High / Unclear
5. Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting? Low / High / Unclear
6. Other sources of potential bias:	Were co-interventions avoided or similar? Low / High / Unclear Was the compliance acceptable in all groups? Low / High / Unclear Was the timing of the outcome assessment similar in all groups? Low / High / Unclear Was the trial sponsored by a manufacturer who potentially had an interest in the results? Low / High / Unclear Other? Low / High / Unclear

WHAT'S NEW

Date	Event	Description
26 May 2015	New citation required but conclusions have not changed	Our conclusions remain unchanged.
26 May 2015	New search has been performed	Searches updated. We found no additional trials that fit the inclusion criteria of this review. We excluded two new studies (Ovchinnikov 2014; Zanasi 2014). 'Summary of findings' table added.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 1, 2001

Date	Event	Description
13 October 2014	New citation required but conclusions have not changed	Our conclusions remain unchanged.
16 March 2011	New citation required but conclusions have not changed	Two of the original review authors are not involved in this 2011 update. Three new review authors joined the team to update this review.
14 February 2011	New search has been performed	Searches conducted. No additional trials were found that fit the inclusion criteria of this review.
10 September 2008	Amended	Converted to new review format.
28 November 2005	New search has been performed	Updated
24 July 2003	New search has been performed	Searches conducted.
28 November 2000	New search has been performed	Review first published Issue 1, 2001

CONTRIBUTIONS OF AUTHORS

Drs. Hom and Becker reviewed the search results for this 2011 and 2015 updates of the review. Drs Becker, van der Wouden, Hom and Villasis assessed risk of bias for the included trials. Drs. Becker and van der Wouden revised the text which was approved by Drs Villasis and Hom. Dr van der Wouden prepared the 'Summary of findings' table for the 2015 update.

DECLARATIONS OF INTEREST

Lorne Becker: none known.
Jeffrey Hom: none known.
Miguel Villasis-Keever: none known.
Johannes van der Wouden: none known.

SOURCES OF SUPPORT

Internal sources

- Center for Evidence-Based Practice, Upstate Medical University, Syracuse, NY, USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review now contains 'Risk of bias' tables and a 'Summary of findings' table. Neither of these was present in the initial review or mentioned in the Protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adrenergic beta-2 Receptor Agonists [*therapeutic use]; Airway Obstruction [drug therapy]; Bronchitis [*drug therapy]; Bronchodilator Agents [therapeutic use]; Cough [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Child, Preschool; Humans; Infant