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[Intervention Review]

# Anticholinergic therapy for chronic asthma in children over two years of age

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## ABSTRACT

### Background

In the intrinsic system of controlling airway calibre, the cholinergic (muscarinic) sympathetic nervous system has an important role. Anticholinergic, anti muscarinic bronchodilators such as ipratropium bromide are frequently used in the management of childhood airway disease. In asthma, ipratropium is a less potent bronchodilator than beta-2 adrenergic agents but it is known to be a useful adjunct to other therapies, particularly in status asthmaticus. What remains unclear is the role of anticholinergic drugs in the maintenance treatment of chronic asthma.

### Objectives

To determine the effectiveness of anticholinergic drugs in chronic asthma in children over the age of 2 years.

### Search methods

The Cochrane Airways Group Specialised Register and reference lists of articles were searched. The most recent search was carried out in February 2010.

### Selection criteria

Randomised controlled trials in which anticholinergic drugs were given for chronic asthma in children over 2 years of age were included. Studies including comparison of: anticholinergics with placebo, and anticholinergics with any other drug were included.

### Data collection and analysis

Eligibility for inclusion and quality of trials were assessed independently by two reviewers.

### Main results

Eight studies met the inclusion criteria. Three papers compared the effects of anticholinergic drugs with placebo, and a meta-analysis of these results demonstrated no statistically significant benefit of the use of anticholinergic drugs over placebo in any of the outcome measures used. The results of one of these trials could not be included in the meta-analysis but the authors did report significantly lower symptom scores with inhaled anticholinergics compared with placebo. However, there was no significant difference between ipratropium bromide and placebo in the percentage of symptom-free nights or days. Two trials studied the effects of anticholinergics on bronchial hyper responsiveness to histamine, by measuring the provocation dose of histamine needed to cause a fall of 20 % in FEV<sub>1</sub> (PD 20). One study (comparing anticholinergics with placebo) reported a statistically significant increase in PD 20 but this was not found in another study (comparing anticholinergics with a beta-2 agonist). Both trials also examined the effect of anticholinergic drugs on diurnal variation in peak

expiratory flow rate (PEFR) and reported no significant effect. Two studies compared the addition of an anticholinergic drug to a beta-2 agonist with the beta-2 agonist alone. Both trials failed to show any significant benefit from the long term use of combined anticholinergics with beta-2 agonists compared with beta-2 agonists alone. One trial compared the effects of oral and inhaled anticholinergic drugs with placebo. No statistically significant differences were found in any of the outcome measures except for a higher FEV1 / VC ratio and RV / TLC ratio with oral anticholinergic therapy when compared with placebo.

### **Authors' conclusions**

The present review summarises the best evidence available to date. Although there were some small beneficial findings in favour of anticholinergic therapy, there is insufficient data to support the use of anticholinergic drugs in the maintenance treatment of chronic asthma in children.

## **PLAIN LANGUAGE SUMMARY**

### **Anticholinergic drugs versus either placebo or other medications for children over two years of age with asthma**

Anticholinergic drugs are widely used in the management of both acute and chronic asthma in children. Their effect is achieved through relief of narrowing of the airways that occurs in asthma. Current guidelines for the management of chronic asthma advise that anticholinergic drugs may be used if children are already on high dose inhaled steroids. This study undertook a comprehensive search of the literature unrestricted by country of publication or language. Unfortunately small numbers of relevant trials were found and these were of variable quality. This review found that although anticholinergic drugs are well tolerated, in children over two years of age, there is not enough data to be sure if they are better than placebo in terms of effects on lung function or symptoms.

## BACKGROUND

The cholinergic (muscarinic) sympathetic nervous system plays an important role in the intrinsic system of controlling airway calibre. Anticholinergic, anti muscarinic bronchodilators such as ipratropium bromide are frequently used in the management of childhood airway disease. In asthma, ipratropium is a less potent bronchodilator than beta-2 adrenergic agents but it is known to be a useful adjunct to other therapies, particularly in status asthmaticus. What remains to be proved is the role of anticholinergic drugs in chronic asthma.

The medicinal benefits of atropine and other naturally occurring anticholinergic alkaloids have been known for many centuries. Atropine, an alkaloid extract of belladonna, is extracted from the *Datura stramonium* plant. These agents were first used in western medicine in the early 1800s after British colonists learned of their uses in India. By the middle of the 19th century, belladonna agents were widely used and were the sole bronchodilating agents available. In the 1920s, epinephrine was discovered, followed by the methylxanthines, replacing belladonna alkaloids as bronchodilating agents (Gross 1988). Part of this declining use was due to the side effects of atropine. However, the development of synthetic analogues of atropine, which retained good anticholinergic activity with minimal side effects, resulted in a resurgence of interest. The most studied, and now most widely used of these agents is Ipratropium Bromide (Atrovent, formerly known as Sch 1000) (Goodman 1996).

Ipratropium bromide (IB) is an anticholinergic bronchodilator. It acts at muscarinic receptors, competitively inhibiting the effects of acetylcholine. Acetylcholine acts by causing smooth muscle constriction, which provides broncho motor tone. By antagonising the effects of acetylcholine, cholinergic broncho motor tone is inhibited and the vagal reflexes that mediate bronchoconstriction are blocked.

Since the introduction of inhaled anticholinergic agents, their clinical uses have been explored in many diseases. It is now becoming apparent that these drugs are regarded as first-line broncho dilatory agents in the treatment of chronic obstructive pulmonary disease (COPD). There is no equivalent in childhood disease. COPD generally occurs after years of smoking and is characterised by chronic mucus secretion, airway infection and variable airway hyper responsiveness (Rubin 1996; Chapman 1996).

In children, anticholinergic agents are used in the management of several diseases, including broncho-pulmonary dysplasia (BPD), bronchiolitis, viral induced wheeze and asthma.

Many definitions of asthma exist and the term itself is controversial (Keeley 1999). Asthma may be defined as "reversible airways obstruction associated with bronchial hyper reactivity, allergic inflammation of the airways and a response to treatment with bronchodilators with regular prophylactic inhaled anti-inflammatory agents" (Silverman 1997). More simply, it may be defined as "episodic cough and / or wheeze in a clinical setting, where asthma is likely and other rarer conditions have been excluded" (Doull 1997).

The initial management of acute severe asthma in the paediatric setting involves rapid relief of bronchospasm with inhaled or nebulised bronchodilators. Children who do not fully respond

require corticosteroids in addition. Beta-2 agonists provide a rapid bronchodilating effect and are the most widely used bronchodilators in acute severe asthma (Rubin 1996). However, many studies have examined the effects of adding anticholinergic agents to beta-2 agonists (Qureshi 1997; Brophy 1998; Craven 2001). Although anticholinergics have a slower onset of action and a weaker bronchodilating effect than beta-2 agonists, they work through different mechanisms and specifically reduce cholinergic broncho motor tone. A systematic review by the Cochrane Airways Group (Plotnick 2000) reviewed the evidence for a beneficial effect of treating children during acute severe asthma with an anticholinergic agent or both beta-2 agonist and anticholinergic drugs. They concluded that "a single dose of an anticholinergic agent is not effective in the treatment of mild and moderate exacerbations and is insufficient for acute exacerbations. Adding multiple doses of anticholinergics to beta-2 agonists appears safe, improves lung function and would avoid admission in one of eleven such treated patients".

Ipratropium bromide has been used for many years in the treatment of asthma. Use of anticholinergic drugs declined with the development of beta-2 agonists, but interest renewed with the realisation that parasympathetic pathways are important in bronchospasm in some asthmatics. The bronchodilatation produced by ipratropium is slower and less intense than with beta-2 agonists, but effects can last for up to 6 hours. There appears to be variability in the response of asthmatics to ipratropium. This may be related to the amount of parasympathetic tone and to the degree to which reflex activation of cholinergic pathways participate in generating symptoms in individual patients. Therefore, the effects of ipratropium should be monitored on an individual basis.

The British Thoracic Society guidelines (BTS 1997; BTS 1993; BTS 1997a) recommended that the management of asthma should be a stepwise approach. Ipratropium was recommended for regular maintenance bronchodilator therapy in schoolchildren who are already on high dose inhaled steroids (Step 4). It was not included in the management of asthma in children under the age of 5 years in these guidelines. The British Thoracic Society guidelines have been recently revised (BTS 2003) and no longer recommend the use of anticholinergic treatment in chronic asthma in children.

## OBJECTIVES

To determine the efficacy of anticholinergic drugs in chronic asthma in children over the age of 2 years.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised controlled clinical trials in which anticholinergic drugs were given for chronic asthma in children over 2 years of age were included.

#### Types of participants

Children aged 2 years (24 months) or over with chronic asthma in all settings (emergency department, inpatient or outpatient, general practice and the home). Asthma must have been physician diagnosed or have been diagnosed using internationally

established criteria. Treatment in both the inpatient and outpatient setting was included.

Studies involving children under the age of 2 years were excluded since different pathophysiologies may occur in babies and young infants. The effectiveness of anticholinergic agents in children less than 2 years has recently been reviewed elsewhere (Everard 2005).

Studies in which the effects of anticholinergic drugs on exercise-induced asthma (EIA) were examined were also excluded.

### Types of interventions

Inhaled anticholinergic drugs, delivered by any means; nebulised or by metered dose inhaler (MDI); with or without a holding chamber +/- a mask. All doses and dosing regimes were included. As this review was examining the effectiveness of anticholinergic therapy on chronic asthma, patients were required to have received the study drug for the duration of at least one week.

Studies including comparison of: anticholinergics with placebo, and anticholinergics with any other drug were included.

### Types of outcome measures

Primary outcome measures:  
 days without wheeze or asthma

Secondary outcome measures:  
 changes in lung function  
 changes in symptomatology  
 indicators of exacerbations (for example, increased use of bronchodilators, use of oral steroids, hospital admission or physician attendance).  
 patient and / or parent assessment  
 physician's assessment  
 number of withdrawals from study

### Search methods for identification of studies

#### Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials which is derived from systematic searching of electronic databases including CENTRAL, MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts (please see the [Airways Group Module](#) for further details). Additional searches of CENTRAL were also carried out. The general structure of the original electronic search strategy was (anticholinergics OR synonyms) AND (children OR synonyms).

All records in the Specialised Register coded as 'asthma' were searched with the following terms:

Anticholinergic\* or cholinergic\* or antagonist\* or muscarinic\* or "ipratropium bromide" or atropin\* or atrovent\* or oxitropium or Sch1000

The following search terms were used in CENTRAL:

(Anticholinergic\$.tw. OR cholinergic antagonist\$.tw. OR muscarinic antagonist\$.tw. OR ipratropium bromide.tw. OR ipratropium.tw. OR atropine.tx. OR atrovent.tw. OR oxitropium bromide.tx. OR sch1000.tx OR EXP ANTICHOLINERGIC\$/ OR EXP CHOLINERGIC ANTAGONIST/ OR EXP MUSCARINIC ANTAGONIST/ OR EXP IPRATROPIUM BROMIDE/ OR EXP IPRATROPIUM/ OR EXP

ATROPINE/ OR EXP ATROVENT/ OR EXP OXITROPIUM BROMIDE/ OR EXP SCH1000/)

### Searching other resources

- Handsearching of medical journals through the Cochrane Collaboration.
- The reference lists in primary sources were searched.
- Personal communication with authors and experts in the field was made in order to trace other unpublished sources.
- The pharmaceutical company, Boehringer Ingelheim, was contacted to obtain additional trials and information.

Searches were current as of February 2010.

### Data collection and analysis

#### Selection of studies

The abstract list obtained from the Airways Group search strategy was reviewed by two researchers to identify all potential studies for inclusion. If the study was thought to potentially meet the inclusion criteria, or if further details were needed to assess the study, then the full text of the publication was obtained for further information. Studies were next assessed independently as included or excluded by two reviewers (NM and AB). Disagreement between the two reviewers was resolved by consensus. A list of excluded studies was also made by the two reviewers (NM and AB) with reasons for their exclusion documented (see Table of Excluded Studies). The following questions were asked of each study:

- 1) Was the study an RCT?
- 2) Was the study carried out in adults or children? Where the study population included both adults and children, the mean age of the population was noted, and authors contacted for the children only data. If no additional data were obtained, and the mean age was between two and eighteen years of age, then the study was included.
- 3) Was the study in acute or chronic asthma?
- 4) Was the research in exercise-induced asthma?
- 5) Was the research a single-dose study?

#### Data extraction and management

Data for trials were independently extracted by both reviewers (NM and AB). Data were entered into the Cochrane Collaboration software program Review Manager, version 5, by the two reviewers (NM and AB).

#### Assessment of risk of bias in included studies

Studies to be included underwent quality assessment performed independently by both reviewers (NM and AB), using two methods. The first involved using the Cochrane approach to assessment of allocation of concealment. Trials were scored using the following principles:

- Grade A: Adequate concealment
- Grade B: Unclear concealment
- Grade C: Clearly inadequate concealment

Secondly, each study was also assessed using a 1 to 5 scale described by [Jadad 1995](#) and summarised as follows:

- Was the study described as randomised? (1=yes; 0=no)
- Was the study described as double blind? (1=yes; 0=no)

Was there a description of withdrawals and dropouts? (1=yes; 0=no)

Was the method of randomisation clearly described and appropriate? (1=yes; 0=no)

Was the method of double blinding well described and appropriate? (1=yes; 0=no)

One point was deducted if the methods for randomisation or blinding were inappropriate.

Any disagreement between the two reviewers regarding the quality scoring was resolved by consensus.

### Data synthesis

Following the integration of generic inverse variance (GIV) in RevMan 5, we have opted to re-analyse the trial data from crossover studies with this method which analyses studies of that design appropriately. Included trials were combined where possible using Review Manager. For dichotomous variables, individual and pooled statistics were calculated as Odds Ratios with 95% Confidence Intervals. For continuous outcomes, individual and pooled statistics was calculated as Weighted Mean Differences or Standard Mean Differences, as indicated, with 95% Confidence Intervals. A fixed effects model was used to pool the data.

Heterogeneity of effect size across pooled studies was calculated, with  $p < 0.05$  used as the cut-off level for significance. The results from parallel studies were not pooled with those from cross-over studies.

It was anticipated that measures of bronchial hyper-responsiveness (BHR) such as the provocation dose of a challenge substance (e.g. histamine) required to produce a 20% fall in FEV1 (PD 20) would often be reported as geometric means. Presentation of results in this way indicate that the data has been logarithmically transformed prior to analysis by investigators to take account of skewed distribution. Data from such outcomes could only therefore be pooled across studies if the mean and standard deviation of logged values (from which the geometric means are derived) could be calculated.

### Subgroup analysis and investigation of heterogeneity

If we had found sufficient data, we could have performed subgroup analysis on

Females versus males.

Age (e.g. comparing children aged 2 -5 years versus 5 - 18 years).

Co-interventions with corticosteroids versus none.

Different doses of anticholinergics - low dose (up to and including 200 mcg/day) versus high dose (over 200 mcg/day).

Duration of anticholinergic administration - Less than 6 weeks versus greater than 6 weeks administration.

#### Assessment of clinical heterogeneity

The influence of trial characteristics that may have influenced the observed treatment effect were examined. If sufficient numbers of trials and the necessary data had been available, clinical heterogeneity would have been investigated according to:

Treatment setting

Asthma severity

### Sensitivity analysis

Sensitivity analyses provide an approach for testing how robust the results of a review are relative to key decisions and assumptions that have been made in the process of conducting the review.

Two factors would have been investigated if sufficient numbers of included studies had been found.

Publication bias - the existence of publication bias would have been examined using a funnel plot.

Trial quality - the effects of overall trial quality on the pooled result would have been examined using both the Cochrane approach and that of [Jadad 1995](#).

## RESULTS

### Description of studies

Eight studies met the inclusion criteria (194 participants). For details of each included study, see 'Characteristics of included studies'. An updated search conducted in February 2010 identified 12 references, none of which met the inclusion criteria. For details of previous searches see [Table 1](#).

The patients included in these studies were between the ages of 4 and 18 years. A total of 194 patients were included with 97 males and 46 females reported. One study ([Vazquez 1984](#) - 49 patients) did not report the numbers of males and females. All participants were studied in the home and outpatient setting.

The studies used a variety of delivery systems (metered dose inhalers with holding chambers and masks, nebulisers and tablets), doses and dosing regimes. Ipratropium bromide, atropine, beta-2 agonists, disodium cromoglycate and placebo were utilised. With one exception, ([Hutchison 1980](#)) ipratropium bromide was the anticholinergic agent.

Asthma severity varied between studies. All patients had chronic asthma, either physician diagnosed or diagnosed according to ATS definitions. In two studies, asthma was described as moderate to severe asthma requiring daily medication ([Bratteby 1986](#); [Mann 1982](#)). [Freeman 1989](#) included patients with moderate asthma with the majority on daily medication. [Sly 1987](#) did not specifically state the asthma severity of the trial patients but all were on daily maintenance treatment. [Hutchison 1980](#) included patients with severe chronic asthma which was inadequately controlled despite maximal daily medication. [Zimmermann 1984](#) selected children with mild, moderate and severe asthma. [Raes 1989](#) included those with mild chronic symptomatic asthma and [Vazquez 1984](#) studied those with asymptomatic asthma.

Maintenance treatment included regular inhaled sympathomimetic drugs, disodium cromoglycate, inhaled steroids, oral theophyllines and oral steroids.

Study periods varied from 2 weeks to 4 months. In studies using a cross-over design, a washout period was only described in one study ([Sly 1987](#) - washout period 4 weeks). In another cross-over study ([Bratteby 1986](#)), data were analysed only from days 5-14 (out of a trial of 2 x 2 weeks) to provide a wash-out period.

Symptom diaries were recorded in all eight studies. A variety of symptoms were recorded on a daily basis including nocturnal wheeze and cough, daytime wheeze and cough, exercise tolerance,



days of school missed and the need for additional medications (e.g. the need for additional courses of oral steroids). In seven studies, daily PEFs were also recorded; before and after treatment twice daily. Several of the studies attempted to examine the effects of anticholinergic drugs on the diurnal variation in airway calibre seen in children with asthma.

None of the studies reported the validity of their symptom diaries. In addition, at certain time points in each study, each patient underwent lung function tests. These were performed in the hospital setting.

### Risk of bias in included studies

All studies were described as randomised and double-blind. Five out of eight studies were cross-over studies ([Bratteby 1986](#); [Freeman 1989](#); [Hutchison 1980](#); [Mann 1982](#); [Sly 1987](#)). The three remaining studies were parallel studies ([Raes 1989](#); [Vazquez 1984](#); [Zimmermann 1984](#)).

#### [Bratteby 1986](#)

Jadad score 4

Allocation concealment B - Unclear

This study was described as a randomised, double-blind, cross-over study. The method of blinding was described in the text but the method of randomisation was not stated. The study was in two parts with the second part of the study being relevant to this review. The first part of this trial was a single dose study over two days and was not included in the review.

No withdrawals or dropouts were reported.

#### [Freeman 1989](#)

Jadad score 2

Allocation concealment B - Unclear

This study was described as a randomised, double-blind, cross-over study. The methods of randomisation and blinding were not stated. The study was in two parts. The second part of the study was relevant to this review. The first part of this trial studied hospitalised children with an acute asthma attack, in the last two days of their admission and this was not included in the review.

Withdrawals or dropouts were not described.

#### [Hutchison 1980](#)

Jadad score 3

Allocation concealment B - Unclear

This study was described as a randomised, double-blind, cross-over study. The method of randomisation was not stated. The method of blinding was described in the text.

No withdrawals or dropouts were reported.

#### [Mann 1982](#)

Jadad score 3

Allocation concealment A - Adequate

This study was described as a randomised, double-blind, cross-over study. The method of randomisation was not stated. The method of allocation concealment was described in the text.

Two patients (out of 20) were withdrawn from the study for failing to complete adequate records.

#### [Raes 1989](#)

Jadad score 3

Allocation concealment B - Unclear

This study was described as a randomised, double-blind, parallel study. The method of randomisation and blinding was described in the text.

Three patients (out of 20) were withdrawn or dropped out of the study.

#### [Sly 1987](#)

Jadad score 3

Allocation concealment B - Unclear

This study was described as a randomised, double-blind, cross-over study. The method of randomisation was not stated. The method of blinding was described in the text.

No withdrawals or dropouts were reported.

#### [Vazquez 1984](#)

Jadad score 2

Allocation concealment B - Unclear

This study was described as a randomised, double-blind, parallel study. The method of randomisation and blinding was not stated. The study was in two parts. The second part of the study was relevant to this review. The first part of this trial was a single dose study over two days.

Data from 32 out of 49 patients were obtained for the second part of the study. We are unable to report the reasons for this due to poor result reporting in the paper.

#### [Zimmermann 1984](#)

Jadad score 2

Allocation concealment B - Unclear

This study was described as a randomised, double-blind, parallel study. The method of randomisation and blinding was not stated.

No withdrawals or dropouts were reported.

### Effects of interventions

Five comparison groups were identified within the studies:

- 1) Inhaled anticholinergics versus placebo
- 2) Inhaled anticholinergics versus beta-2 agonist
- 3) Inhaled anticholinergics + beta-2 agonist versus beta-2 agonist
- 4) Inhaled anticholinergics versus beta-2 agonist + inhaled anticholinergics
- 5) Inhaled anticholinergics versus oral anticholinergics

Ipratropium bromide was the most common anticholinergic drug used but in one trial atropine (inhaled and oral) was used. These results have been analysed separately in two subgroups as it is well recognised that ipratropium bromide is associated with fewer side effects than atropine.

No data could be entered for our primary outcome measure - "days without wheeze or asthma" as none of the studies specifically used this measure, although in some studies it was incorporated into symptom diaries.

#### 1) INHALED ANTICHOLINERGICS versus PLACEBO

Three studies could be included within this comparison group. All three studies were cross-over studies. [Mann 1982](#) and [Sly 1987](#) both used IB as the anticholinergic agent. Combining the results of the



studies by [Mann 1982](#) and [Sly 1987](#) produced a total of 49 patients. [Hutchison 1980](#) used inhaled atropine as the anticholinergic agent and 12 patients were included in their study. All three studies could be combined in a meta-analysis only for PEFr (am) and PEFr (pm). Two studies could be combined for the outcomes of hospitalisation rates and the need for additional oral steroids. The other results presented are from a single study only.

Data from these three studies produced the following results (see Comparisons and Data):

No statistically significant effect of inhaled anticholinergic therapy compared to placebo was observed for the following outcome measures:

Peak expiratory flow rate (am) - SMD (95%CI) = 0.05 (-0.31, 0.40)

Peak expiratory flow rate (pm) - SMD (95% CI) = 0.02 (-0.33, 0.38)

Hospital admissions - Odds Ratio (95 % CI) = 0.14 ( 0.02, 1.25)

Need for additional oral steroids - Odds Ratio (95% CI) = 0.79 (0.21, 3.03)

Symptom scores from [Mann 1982](#) could not be included in the meta-analysis because data were not available for entry into Review Manager. In this study, daily records were kept of day and night cough and wheeze, scoring zero for no symptoms, one for occasional wheeze and/or cough, two for troublesome wheeze and/or cough, and three for very ill with severe wheeze and /or cough.

The authors reported that symptom scores were significantly lower with IB compared to placebo for both night symptom scores (IB 47.8 % compared with placebo 42.9% with score 1; 15.1% IB compared to 21.8% placebo with score 2; 1% IB compared with 3.1% placebo with score 3) and day symptom scores (51.4% IB compared to 48.8% placebo at score 1; 10.2% IB compared with 16.6% placebo at score 2 and 1.4% IB compared with 3.9% placebo at score 3). No standard deviations were given with these results but a p value of < 0.005 was obtained.

However, there was no significant difference between IB and placebo in the percentage of symptom-free nights or days.

[Sly 1987](#) examined the effect of IB on diurnal variation in airway calibre and also on bronchodilator responsiveness. [Sly 1987](#) postulated that the nocturnal exacerbation of asthma might be due to an exaggeration in the diurnal variation in airway calibre and an increase in airway sensitivity. He postulated that by treating this, a reduction in the effects of nocturnal asthma might be obtained. To study this, PEFrs were recorded twice daily. In addition, the diurnal variation in bronchodilator responsiveness was assessed by examining the increase in PEFr after salbutamol.

[Sly 1987](#) found that 74% of his subjects recorded significant diurnal variation in PEFr during the baseline period of this study. Treatment with IB did not have an effect on this diurnal variation. 21 out of the 31 patients inhaled three times daily salbutamol. The study initially proposed that all trial patients should take regular salbutamol. However, the reasons for 10 patients not taking salbutamol were not given. An increase in morning PEFrs was observed in 12 out of 21 patients (i.e. 57%) but this increase was not affected by treatment with IB compared to placebo.

The study period in this trial was four periods each lasting four weeks (a baseline period and two treatment periods separated by a washout period). At the end of each study period histamine challenges were performed. Subjects did not use salbutamol or treatment aerosols for between 8 and 12 hours before the challenge test. The provocation dose of histamine needed to cause a fall of 20% in FEV1 (PD 20) was recorded. It was found that treatment with IB was associated with significantly higher mean PD 20 values (geometric mean 0.78 versus 0.49 mg/ml,  $P < 0.01$ ).

The trial by [Hutchison 1980](#) was the only trial within this comparison group where the effects of anticholinergic drugs were compared to placebo by using formal lung function testing. Vital capacity (VC), forced expiratory volume in one second (FEV1), FEV1/VC, and average forced expiratory flow from 25% to 75% of the vital capacity (FEF 25-75%) were calculated. In addition, residual volume (RV) and total lung capacity (TLC) were calculated. Results were expressed as percentages of predicted values for FEV1, FEV1/VC, FEF 25-75% and RV.

As mentioned above, inhaled atropine did not have an effect on lung function testing. However, the use of oral atropine resulted in significantly higher results ( $p < 0.05$ ) for FEV1/VC and a significant reduction ( $p < 0.05$ ) in RV/VC (see below).

However, there were no differences between oral atropine, inhaled atropine or placebo for the number of days of school missed, night time waking, the need for additional oral steroids, or morning and evening PEFrs. (see also Comparison of Inhaled anticholinergics versus oral anticholinergics).

## 2) INHALED ANTICHOLINERGICS versus BETA-2 AGONIST

[Raes 1989](#) compared the effects of IB with the beta-2 agonist, fenoterol, on bronchial hyper responsiveness (BHR) to histamine. Their study group was in children with mild stable asthma. Daily diary cards were kept and lung function was assessed formally at monthly intervals through the study. The authors reported no statistically significant differences between the treatment groups in terms of:

- symptom scores of cough, wheeze, number of asthma attacks
- PEFr diurnal variation
- FEV1
- PD 20 values

In the IB group, three of the 12 patients were withdrawn. The exact timing of this withdrawal is not documented by the authors. Two of these patients had an increase in asthma symptoms in the weeks prior to entering the study and the third patient's symptoms worsened during the study (in all patients in the trial, medications apart from trial drugs had been stopped one week before the start of the study).

## 3) INHALED ANTICHOLINERGICS PLUS BETA-2 AGONISTS versus BETA-2 AGONISTS

Two trials compared the effects of inhaled anticholinergic drugs combined with a beta-2 agonist with a beta-2 agonist alone ([Bratteby 1986](#); [Freeman 1989](#)). Unfortunately data could not be combined in a meta-analysis due to data presentation in the [Freeman 1989](#) study. Both trials were cross-over studies.

[Bratteby 1986](#) studied 13 children in a two-part study, the second part being relevant to this review. The authors reported

that there was no statistically significant difference in symptom scores (recording daytime breathlessness, cough, physical activity, tremor, palpitations and sleep) between the two comparison groups except for a slightly higher score for disturbed sleep during the IB period ( $p < 0.05$ ). The number of additional doses of salbutamol used were not significantly different between the two groups. The authors also reported that there was no statistically significant difference in the changes in PEFrs or in FEV1 between the two comparison groups.

Freeman 1989 studied 10 children in a two-part study, the second part being relevant to this review. Once again, the authors reported no statistically significant differences in symptom scores (recording nocturnal wheeze and cough, daytime wheeze, daytime activity and sputum production) between the two study groups. In addition, there were no statistically significant differences in PEFrs, which were recorded twice daily. The authors did not examine the effect of trial drugs on diurnal variation. At three time points in the study, lung function tests were performed and results compared to those found at the baseline point in the study. No statistically different changes in lung function (as measured by FEV1, FVC, FEF 25-75% and heart rate) were found between the two study groups.

In summary, both trials failed to show any significant benefit from the long term use of combined anticholinergics with beta-2 agonists compared with beta-2 agonists alone.

#### 4) INHALED ANTICHOLINERGICS PLUS BETA-2 AGONISTS versus INHALED ANTICHOLINERGICS

The trial by Zimmermann 1984 involved 39 children over a two week study period in a parallel trial. Children were either given fenoterol plus IB or IB alone. However, the dose of IB in the IB alone arm of the study was 5 times that of the dose in the combination arm, making data comparison difficult.

Results were reported by using means but no standard deviations were given. Data could therefore not be entered into the RevMan statistical software package. No tests for significance were calculated by the authors and the baseline data of the two groups were different. Therefore the results from this study will not be reported further. Despite diary cards for symptom scores being recorded by the patients, the results of these were not given in the text.

#### 5) INHALED ANTICHOLINERGICS versus ORAL ANTICHOLINERGICS

The trial by Hutchison 1980 has already been discussed in the comparison above, "Inhaled anticholinergics versus placebo". This trial compared the effects of both inhaled and oral anticholinergics with placebo on chronic asthma in 12 children. The authors reported no statistically significant differences between any of the three study groups in terms of the number of days missed from school, night time waking, the subjective assessment of adequate asthma control or the need for additional doses of oral steroids. In addition, no significant difference in morning and evening PEFrs between the three groups was noted. The effects on diurnal variation were not examined in the trial. The authors reported a significantly higher FEV1 / VC ratio ( $p < 0.05$ ) while subjects were taking oral atropine. In addition, the residual volume expressed as a percentage of total lung capacity (RV / TLC) was significantly reduced with oral atropine. Inhaled atropine was not found to be significantly different to placebo.

The trial by Vazquez 1984, has not been included in the results section above. The trial was a two-part parallel study, the second part of which was relevant to this review. The first part examined and compared the effects of disodium cromoglycate, salbutamol and IB on exercise-induced bronchospasm in 49 patients. 32 patients were then given the trial medications for one month and then reassessed. Outcome measures included symptom diaries, PEFrs and formal lung function (including FEV1) testing at the end of the trial. The study was published in Spanish but a translation was obtained. Unfortunately, the results section of the paper concentrated on reporting the results from the initial phase of the study. No results were given for symptom diaries, PEFrs or FEV1. In addition, the authors did not explain why only 32 of the original 49 patients continued into the second phase of the trial. The study authors have been contacted to obtain more information and their response is awaited.

#### Heterogeneity

Data were merged from the trials by Hutchison 1980; Mann 1982 and Sly 1987 so these were examined for heterogeneity for treatment setting and asthma severity. In all three studies, the trial settings were similar in that all patients were assessed in both the home and in the outpatient clinic. The three studies were then examined for heterogeneity in asthma severity. In Hutchinson, patients were included with severe chronic asthma. Patients were all said to be inadequately controlled despite maximal daily medication, including regular inhaled sympathomimetics, oral theophylline and inhaled and oral steroids. Mann enrolled patients with chronic asthma who were all on regular daily medication, although none were on oral steroids. Sly did not specifically state the asthma severity of their trial group but all children were on salbutamol, oral theophyllines and inhaled steroids, suggesting at least moderate asthma. The PEFr data analysed in the meta-analysis from these three studies showed no evidence of heterogeneity (chi square = 0.23,  $p = 0.89$ ), and was therefore not explored further.

The existence of publication bias would have been assessed by using a funnel plot. However, as only three studies could be merged these data were considered insufficient to examine for this. However, in future updates of this review, if more data can be merged then the presence of publication bias will be sought.

Mann was graded A by the Cochrane assessment of allocation of concealment, whereas the other seven trials scored B. Where data from three trials were compared (Mann 1982; Hutchison 1980; Sly 1987), similar results were found. So, although a formal sensitivity analysis could not be performed due to the low numbers, it was encouraging that similar data were found when trials of different allocation concealment were compared.

Secondly, each study was also assessed using a 1 to 5 scale described by Jadad 1995 as discussed above. One trial obtained a Jadad score of 4 (Bratteby 1986); four trials obtained a score of 3 (Mann 1982; Sly 1987; Hutchison 1980) and three studies a score of 2 (Freeman 1989; Vazquez 1984; Zimmermann 1984). However, despite the variation in trial quality, once again when data were compared between studies, findings were similar, suggesting that trial quality did not affect the findings of the review.

#### ADVERSE EVENTS AND EFFECTS

Very few adverse events or side effects were reported in any of the trials. Mann reported no apparent side effects but one child disliked the taste of IB. Sly did not discuss or monitor side effects. Hutchison 1980 reported no side effects for either inhaled or oral atropine. They did report however, that if they increased the dose of oral atropine, a small increase in their selected dose caused dry mouth and mydriasis. Bratteby 1986 reported mild tremor and palpitations in both their treatment groups (i.e. IB plus beta-2 agonists and beta-2 agonists alone). Zimmermann 1984 reported cough occurring in seven children in both treatment groups. Raes 1989; Freeman 1989; Vazquez 1984 reported no side effects during their study period.

## DISCUSSION

Anticholinergic agents are widely used in the treatment of acute asthma and in infants with airways obstruction with associated wheeze. A systematic review by the Cochrane Collaboration (Plotnick 2000) concluded that using multiple doses of anticholinergic in addition to beta-2 agonists was beneficial in the management of acute asthma in children. It is also well recognised that a single dose of anticholinergic has bronchodilating effects although the effect may be slightly less and slower in onset of action than with beta-2 agonists. However, the effectiveness of anticholinergics as part of the regular maintenance treatment in chronic asthma remains unclear, resulting in the need for this review.

Despite an extensive and thorough literature search in which hundreds of papers examining anticholinergic drugs were found, only eight met the inclusion criteria of this review. Three papers compared the effects of anticholinergic drugs with placebo, and a meta-analysis of these results demonstrated no statistically significant benefit of the use of anticholinergic drugs over placebo in any of the outcome measures (including symptom scores, PEFs and formal lung function testing). The results of one trial could not be included in the meta-analysis but the authors did report significantly lower symptom scores with inhaled anticholinergics compared with placebo. However, there was no significant difference between IB and placebo in the percentage of symptom-free nights or days.

Two trials studied the effects of anticholinergics on bronchial hyperresponsiveness to histamine, by measuring the provocation dose of histamine needed to cause a fall of 20% in FEV1 (PD 20). One study (comparing anticholinergics with placebo) reported a statistically significant increase in PD 20 but this was not found in another study (comparing anticholinergics with beta-2 agonist). A meta-analysis could not be performed to view the overall effect as the comparison groups were different.

Both of these trials also examined the effect of anticholinergic drugs on diurnal variation in PEF and both reported no effect.

Two studies compared the addition of an anticholinergic drug to a beta-2 agonist with a beta-2 agonist alone. Although the results could not be combined in a meta-analysis, both trials failed to show any significant benefit from the long term use of combined anticholinergics with beta-2 agonists compared with beta-2 agonists alone (symptom scores, PEFs and lung function tests were used as outcome measures).

One trial compared the effects of oral and inhaled anticholinergic drugs with placebo. No statistically significant differences were found in any of the outcome measures except for a higher FEV1 / VC ratio and RV / TLC ratio (i.e. reduced "gas-trapping") with oral anticholinergic therapy when compared with placebo.

Two non-English language trials were included in our review. Unfortunately, data reporting in these papers was poor so conclusions are difficult to draw from these trials. In addition, the IB doses in the two arms of the Zimmermann 1984 study were different and therefore, comparison could not be made.

It was noted that three out of the five cross-over studies did not incorporate a formal wash-out period. However, we think that this is unlikely to have affected the study results as inhaled anticholinergic drugs are known to have a relatively short duration of action.

The present review summarises the best evidence available to date. Although there were some small beneficial findings in favour of anticholinergic therapy as detailed above, the results presented here do not support the use of anticholinergic drugs in the maintenance treatment of chronic asthma in children. Further work is required to clarify their exact role if any.

The British Thoracic Society guidelines (BTS 1993; BTS 1997; BTS 1997a) recommended the use of IB as regular maintenance therapy in schoolchildren who are already on high dose inhaled steroids (Step 4). They were not recommended for use in the management of chronic asthma in children under the age of 5 years. The new BTS/SIGN guidelines have recently been published (BTS 2003). From this review, it seems that there is little evidence to support their use for the maintenance treatment of chronic asthma in children, and this is reflected in the new guidelines that withdrawn the previous recommendation.

## METHODOLOGICAL LIMITATIONS

### Systematic bias

Bias related to missed trials: a large volume of literature was searched for relevant studies. Despite a comprehensive search strategy it is possible that relevant studies were missed.

### Power

A significant proportion of outcome data from individual trials could not be included in the meta-analysis because either standard deviation values for mean effect sizes were not presented in the original citation or no numerical data were presented at all. These missing data will diminish the power of the meta-analysis.

### Generalisability

The studies included in this review included children with a spectrum of asthma severity being treated with a range of drug doses delivered by various means (nebuliser, MDI, MDI plus spacer) over a range of treatment periods. These factors should be taken into account when considering the findings of this review.

## AUTHORS' CONCLUSIONS

### Implications for practice

In children with chronic asthma (ranging in severity from mild to severe), there is not enough data to assess the efficacy of adding long term anticholinergic therapy to maintenance treatment.

It does however appear that anticholinergic agents are safe and well tolerated.

### Implications for research

Future trials could improve on several aspects: interventions, choice of outcomes, and stratified reporting of results by asthma severity level.

Several of the trials that were included in this review discussed the uncertainty about selecting appropriate doses and delivery methods of anticholinergic drugs. A variety of doses were therefore selected and drugs were delivered by a variety of delivery systems. In some of the trials, it was unclear how the drug had been delivered and if by inhaler +/- holding chamber, whether the inhaler technique had been checked.

It is clearly difficult to monitor the effects of the trial drug on a child's quality of life and asthma control over a long period of time when the child is at home. Completing symptom and PEF diaries is time consuming and results are difficult to validate. Future

trials should include more sensitive and reliable endpoints and should perhaps consider the use of researchers in the community environment to monitor outcome measures. When children are assessed in the hospital environment for formal lung function testing, a wider and more consistent choice of outcome measures would help to compare results from a number of studies.

Finally, the small number of trials found during this review meant that results could not be separated meaningfully with regard to asthma severity. This may be important and should be considered if further trials are planned.

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\* Indicates the major publication for the study

**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies [ordered by study ID]**
**Bratteby 1986**

Methods	Design: randomised, double-blind, cross-over study. Method of randomisation: not stated. Concealment of randomisation: unclear (B) Blinding: double-blind, using identical aerosols for trial drug and placebo. Description of withdrawals or dropouts: no. Jadad's score: 4
Participants	Number enrolled into trial: 13 Number in treatment group: 13 Number in control group: 13 Number of withdrawals or dropouts (treatment/control): 0 Number completing trial (treatment / control): 13. Age (range): 9.3-16.7 yrs Age (mean): 11.9 yrs Sex: 8 males, 5 females. Asthma diagnosis: Physician diagnosed. Severity of asthma: Chronic bronchial asthma on daily medication. Inclusion criteria: (1) Moderate to severe asthma in a stable state, and (2) Reversibility of bronchial obstruction with >15% improvement in FEV1 after inhaling nebulised salbutamol (0.1 mg/kg of body weight).
Interventions	Setting: Home / outpatient clinic. Types: Ipratropium bromide 40mcg (2 puffs) via metered aerosol QDS - each dose preceded by an inhalation of salbutamol as a metered aerosol (0.1mg per inhalation). Duration: Total 4 weeks (2 X 2 weeks)
Outcomes	Outcomes: Diary card recording: -Symptoms (scores graded 0-3: 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms) -Additional medications taken -PEFRs 4 times daily Adverse events: side effects recorded in daily diary, specifically palpitations and tremor.  Only results from days 5-14 used in analysis (to provide wash-out period).
Notes	Study in two parts, second part relevant to this review.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear



**Freeman 1989**

Methods	Design: randomised, double-blind, cross-over study. Method of randomisation: not stated. Concealment of randomisation: unclear (B) Blinding: double-blind Description of withdrawals or dropouts: no. Jadad's score: 2.
Participants	Number enrolled into trial: 10 Number in treatment group: 10 Number in control group: 10. Age (range): 6-14 yrs Age (mean): 9 yrs Sex: 6 males, 4 females. Asthma diagnosis: Physician diagnosed. Severity of asthma: Moderate asthma, all except one patient on oral theophyllines, 4 pts on sodium cromoglycate (SCG), 3 on inhaled steroids. Inclusion criteria: Chronic asthma. Exclusion criteria: known hypersensitivity to ipratropium bromide +/- sympathomimetic drugs or if known cardiac disease / thyrotoxicosis or other major illnesses. Source of participants: hospital outpatient clinic.
Interventions	Setting: Home / outpatient clinic. Types: Ipratropium bromide nebulised (125 - 250mcg according to age) plus nebulised fenoterol (0.2-0.4mg according to age) vs placebo plus fenoterol., each given three times daily. Duration: Total 8 weeks (2 X 4 weeks). Additional notes: No washout period stated.
Outcomes	Outcome: Diary cards recording nocturnal wheeze and cough, daytime wheeze, daytime activity, sputum production and PEFs (am and pm) Lung function testes were performed at each of three visits (before starting trial, after the 1st month and after the 2nd month). Adverse events: Daily diary
Notes	Study in two parts, second part relevant to this review.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Hutchison 1980**

Methods	Design: randomised, double-blind, cross-over study. Method of randomisation: not stated. Concealment of randomisation: unclear (B). Blinding: double-blind - placebo tablets or inhalations. Description of withdrawals or dropouts: not stated. Jadad's score: 3
Participants	Number enrolled into trial: 12 Number in treatment group : 12 Number in control group : 12 Number of withdrawals or dropouts : None stated. Age (range): 7-17 yrs Sex: 11 males, 1 females.

**Anticholinergic therapy for chronic asthma in children over two years of age (Review)**



### Hutchison 1980 (Continued)

Asthma diagnosis: Physician diagnosed.  
Severity of asthma: Severe chronic asthma.  
Inclusion criteria: Inadequate control despite maximum therapy with regular inhaled sympathomimetics, oral theophylline, inhaled and oral steroids.  
Source of participants: Not stated.

**Interventions**                      Setting: Home / outpatient clinic.  
Types: (1) Inhaled atropine and oral placebo; (2) Oral atropine and inhaled placebo; (3) Double placebo.  
Duration: Total 3 months (3 X 4 weeks of each treatment).  
Additional notes: Medications given TDS, and all regular medication continued.  
Atropine (inhaled) dose: 20mcg/kg inhalation (i.e. 60mcg/kg/24 hrs)  
Atropine (oral) dose: 20mcg/kg TDS.  
No washout period stated.

**Outcomes**                              Outcomes: Weekly diary card recording symptoms, days of school missed, night time waking and amount of medications, particularly use of oral steroids.  
PEFRs measured daily before morning and evening treatment.  
Lung function tests performed at end of each study period. VC, FEV1, FEV1/VC and FEF25-75% were calculated.  
Adverse events: side effects recorded in daily diary (with particular reference to blurred vision and dry mouth).

Notes

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

### Mann 1982

**Methods**                                  Design: randomised, double-blind, cross-over study.  
Method of randomisation: not stated.  
Concealment of randomisation: adequate (A) - inhalers coded by manufacturers, code broken after trial completion.  
Blinding: double-blind.  
Description of withdrawals or dropouts: yes.  
Jadad's score: 3

**Participants**                              Number enrolled into trial: 20  
Number in treatment group: 20  
Number in control group: 20  
Number of withdrawals or dropouts (treatment/control): 2 (failed to keep adequate records).  
Number completing trial (treatment / control): 18.  
Age (range): 6-14 yrs  
Age (mean): 9.2 yrs  
Sex: 9 males, 11 females.  
Asthma diagnosis: Physician diagnosed.  
Severity of asthma: Chronic bronchial asthma on daily medication - 8 pts on regular SCG or inhaled steroids. None on oral steroids.  
Inclusion criteria: Pts selected from those attending paediatric asthma clinic for > 6 months.  
Source of participants: Outpatient clinic.

**Interventions**                              Setting: Home / outpatient clinic.

**Mann 1982** (Continued)

Types: Ipratropium bromide 40mcg (2 puffs inhaled via metered dose inhaler) TDS for 4 weeks vs placebo inhalers TDS for 4 weeks.  
Duration: Total 8 weeks (2 X 4 weeks).  
Additional notes: No washout period stated

**Outcomes**

Outcomes: Diary card recording:  
-Symptoms of day and night cough and wheeze (scoring 0 for no symptoms, 1 for occasional wheeze and/or cough, 2 for troublesome wheeze and/or cough, and 3 for very ill with severe wheeze and/or cough).  
-PEFRs measured am and pm before treatment.  
-Need for additional bronchodilators  
-Need for any other drugs e.g. steroids.  
Adverse events: side effects recorded in daily diary.

**Notes**

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**Raes 1989**

**Methods**

Design: randomised, double-blind, parallel study.  
Method of randomisation: allocation to group by study sponsor.  
Concealment of randomisation: unclear (B).  
Blinding: double-blind - pharmaceutical company provided each patient with coded boxes containing drug..  
Description of withdrawals or dropouts: yes.  
Jadad's score: 3

**Participants**

Number enrolled into trial: 20  
Number in treatment group (ipratropium bromide): 12  
Number in control group (salbutamol): 8  
Number of withdrawals or dropouts (treatment group): 3.  
Number completing trial (treatment / control): 17.  
Age (range): 7-15 yrs  
Sex: 14 males, 6 females.  
Asthma diagnosis: Physician diagnosed.  
Severity of asthma: Mild chronic symptomatic asthma  
Inclusion criteria: (1) PD20 of <150mcg, (2) FEV1 and FVC > 80% of predicted, (3) FEV1/FVC >70% of predicted, (4) <20% increase in baseline FEV1 after 0.4mg of inhaled fenoterol.  
Source of participants: Outpatient clinic.  
Additional notes: Study performed between February and July (European study).

**Interventions**

Setting: Home / outpatient clinic.  
Types: Ipratropium bromide 40mcg (2 puffs inhaled via metered dose inhaler) TDS vs fenoterol 0.2mg via inhaler TDS.  
Duration: Total 4 months.

**Outcomes**

Outcomes: Diary card recording:  
-Symptoms of cough, wheeze and frequency of asthma attacks (score severity between 0 to 3 for each item).  
-PEFRs measured am and pm before treatment.  
-Need for additional bronchodilators

**Raes 1989** (Continued)

-Need for any other drugs e.g. steroids.  
 At clinic (monthly assessments): PD20 and FEV1.  
 Adverse events: side effects recorded in daily diary.

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Sly 1987**

Methods	Design: randomised, double-blind, cross-over study. Method of randomisation: not stated. Concealment of randomisation: unclear (B). Blinding: double-blind - identically labelled aerosols labelled A or B. Description of withdrawals or dropouts: no. Jadad's score: 3	
Participants	Number enrolled into trial: 31 Number in treatment group : 31 Number in control group : 31 Number of withdrawals or dropouts : None stated. Age (range): 8-18 yrs Age (mean): 12.0 yrs Sex: 21 males, 10 females. Asthma diagnosis: Physician diagnosed. Severity of asthma: Not stated. All children on salbutamol (via nebuliser or inhaler), theophylline (oral) and inhaled steroids as maintenance therapy. Inclusion criteria: Nil stated. Source of participants: Not stated.	
Interventions	Setting: Home / outpatient clinic. Types: Ipratropium bromide 40mcg (2 puffs inhaled via metered dose inhaler) TDS for 4 weeks vs placebo inhalers TDS for 4 weeks. At end of each group each patient had histamine challenge. Duration: Total 8 weeks (2 X 4 weeks). Additional notes: Washout period of 4 weeks between trial drugs.	
Outcomes	Outcomes: Daily diary card recording: -Symptoms of amount of wheeze during the night; amount of cough during the night; amount of wheeze during the day and limitation of activity during the day (score between 0 to 3 for each of the above). Symptom scores were added daily to give a daily total. -PEFRs measured on waking, at 1600 hrs and at bedtime. -Medications taken. Histamine challenges performed at completion of each study period. Adverse events: side effects recorded in daily diary.	
Notes		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

**Sly 1987** (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
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**Vazquez 1984**

Methods	Design: randomised, double-blind parallel study. Method of randomisation: not stated. Concealment of randomisation: unclear (B). Blinding: double-blind. Description of withdrawals or dropouts: not stated. Jadad's score: 2.
Participants	Number enrolled into trial: 49 Number in treatment groups: Group A (salbutamol)=13 Group B (disodium cromoglycate)=12 Group C (ipratropium bromide)=12 Group D (placebo)=12 Number of withdrawals or dropouts : 17 but reason unclear. Age (mean): 9.4 yrs (SD=2.05) Sex: not stated. Asthma diagnosis: Diagnosed according to ATS definition. Severity of asthma: Asymptomatic asthma. Inclusion criteria: All showed exercise-induced asthma, all except 2 had atopic asthma. Source of participants: Allergy or respiratory consultations.
Interventions	Types: Group A = salbutamol 200mcg; Group B = disodium cromoglycate 20mg; Group C = ipratropium bromide 40 mcg; Group D = placebo. All medications were by inhaler at a dose of two puffs administered three times a day. Duration: 1 month.
Outcomes	Outcomes: Diary records, spirometry (FEV1, PEFr), exercise test. Spirometry measured pre-exercise and immediately post-exercise, followed by at 5, 10, 15 and 20 minutes post exercise.
Notes	Study in two parts, second part relevant to this review. Data from 32 patients only were obtained for the second part of the study (17 did not return). We are unable to report the reasons for this due to limited translation of the paper. In addition, we suspect that there was a typing error in the paper. In the second part of the study, doses were quoted in 'mg' where we suspect 'mcg' was meant instead.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Zimmermann 1984**

Methods	Design: randomised, double-blind parallel study. Method of randomisation: not stated. Concealment of randomisation: unclear (B). Blinding: double-blind.
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**Zimmermann 1984** (Continued)

Description of withdrawals or dropouts: not stated.  
 Jadad's score: 2.

Participants	Number enrolled into trial: 39 Group A (ipratropium bromide + fenoterol) = 20. Group B (ipratropium bromide)=19. Number of withdrawals or dropouts : None stated. Age (mean): 4 to 14 years and 9 months. Sex: 30 males, 9 females. Asthma diagnosis: Physician diagnosed. Severity of asthma: Six had severe asthma, 27 had moderate asthma, and six had mild asthma. Inclusion criteria: Asthma for greater than one year. Source of participants: Paediatric outpatient clinic.
Interventions	Types: Group A = 0.1mg fenoterol + 0.04mg ipratropium bromide. Group B = 0.2mg ipratropium bromide. All medications were by inhaler at a dose of two to three puffs administered three times a day. Duration: 2 weeks.
Outcomes	Outcomes: FEV1, symptom scores, concomitant medication usage, subjective effectiveness, safety and tolerability, total airway resistance, specific airway resistance.
Notes	Limited data obtained because of translation.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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

Study	Reason for exclusion
<a href="#">Agostini 1983</a>	Exercise-induced asthma
<a href="#">Agostini 1983b</a>	Exercise-induced asthma (study same trial as above, published in different journal)
<a href="#">Alanko 1973</a>	Study group - adults only.
<a href="#">Allen 1985</a>	Study involved 11 patients but ages were not specified. Abstract only obtained so far, authors have been written to requesting more information. Their response is awaited.
<a href="#">Bach-Mortensen 1987</a>	Exercise-induced asthma.
<a href="#">Bandouvakis 1981</a>	Study group -adults only.
<a href="#">Beck 1985</a>	Study on acute asthma only.
<a href="#">BenitoFernandez 2000</a>	Study in acute asthma only.

Study	Reason for exclusion
<a href="#">Bonner 1984</a>	Exercise-induced asthma.
<a href="#">Bonner 1987</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Bonner 1987b</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Borut 1977</a>	Exercise-induced asthma.
<a href="#">Caubet 1988</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Chen 1981</a>	Exercise-induced asthma.
<a href="#">Chervinsky 1977</a>	Study group - adults only.
<a href="#">Clarke 1982</a>	Study group of 12 patients. Three patients were aged 13, 17 and 18 years. The author was written to and a response was received. Unfortunately Dr Clarke died a few years ago and so no further information could be obtained.
<a href="#">Cook 1985</a>	Study in acute asthma only.
<a href="#">Coulthard 1985</a>	Published data obtained is in abstract form only. The authors have been contacted for more information. Their response is awaited.
<a href="#">Craven 2001</a>	Study in acute asthma only.
<a href="#">Crimi 1986</a>	Study in acute asthma only.
<a href="#">Crimi 1992</a>	Study group - adults only.
<a href="#">Cropp 1975</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Davis 1984</a>	Study on chronic asthma but a single-dose study only.
<a href="#">DeStefano 1990</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Ducharme 1998</a>	Study in acute asthma only.
<a href="#">Dutt 1990</a>	Acute study conducted over 300 minutes
<a href="#">Filiz 1994</a>	Study group - adults only.
<a href="#">Friberg 1989</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Godfrey 1975</a>	Exercise-induced asthma.
<a href="#">Godfrey 1976</a>	Exercise-induced asthma, sama data as in Godfrey, 1975 but published in different journal.
<a href="#">Greenough 1993</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Groggins 1981</a>	Study on chronic asthma but a single-dose study only.
<a href="#">Groot 1994</a>	Study group - adults only.
<a href="#">Gross 1975</a>	Study group - adults only.



Study	Reason for exclusion
Guill 1987	Study on acute asthma only.
Hemstreet 1980	Unclear if study was an RCT. Published data unclear so authors have been contacted. Their response is awaited.
Henry 1989	Study excluded as comparison of preservative-free IB versus preservative containing IB. Study did therefore not meet inclusion criteria.
Hodges 1981	Study in "acute wheeze" only. Also unclear if study an RCT.
Jedrys 1994	Unclear if study a RCT. Authors have been contacted. Their response is awaited.
Kishida 1992	Study excluded as did not involve an anticholinergic drug.
Krasnowska 1994	Study less than 7 days duration
Krasnowska 2004	Study conducted in adults
Kreisman 1984	Study in acute asthma only.
Larsson 1987	Study group - adults only.
Lefcoe 1982	Study group - adults only.
Lenney 1986	Study on chronic asthma but a single-dose study only. Unclear if study an RCT.
Lew 1990	Study in acute asthma only.
Li 2003	Study conducted in acute setting.
Lightbody 1978	Study in adults only.
Lin 1978	Not an RCT - maintenance phase of trial was "open".
Lines 1983	Published data obtained in abstract form only. The authors were contacted for more information. A response was received from Professor Lines but no more data was obtained.
Mannino 1996	Study group - adults only.
Mazzei 1986	Study group - adults only.
McNeill 1966	Exercise-induced asthma.
Miraglia 1983	Study not explicitly described as randomised.
Muranyi 1974	Study not an RCT. Study used parenteral atropine only.
Neijens 1981	Exercise-induced asthma.
Neild 1985	Study group - adults only.
Pasterkamp 1985	Exercise-induced asthma.
Pauwels 1995	Study less than 7 days duration.

Study	Reason for exclusion
Peters 2000	Study group - adults only. Study also in acute asthma although followed for 24 hours after admission to hospital.
Poppius 1973	Exercise-induced asthma; study group - adults only.
Rachelefsky 1978	Exercise-induced asthma.
Rayner 1987	Study in acute asthma only.
Ream 2001	Study in acute asthma only.
Rebuck 1983	Study group - adults only.
Reisman 1988	Study in acute asthma only.
Russo 1986	Exercise-induced asthma. Unclear if trial an RCT.
Sanguinetti 1986	Exercise-induced asthma.
Schlueter 1978	Study group - adults only.
Schuh 1995	Study in acute asthma only.
Sierra Monge 2000	Study in acute asthma only.
Silverman 1981	Study excluded as did not involve an anticholinergic drug.
Simone 1986	Study group - adults only.
Simonsson 1979	This paper was a review of other studies which have been retrieved.
Stokes 1983	This paper was a review of other studies which have been retrieved.
Storms 1975	Study group - adults only.
Storms 1986	Study group - ? if in adults only. The author was contacted and a response was received. However, no further information about this could be found.
Storr 1986	Study in acute asthma only.
Sur 1990	Study group of 11 patients, 3 later excluded. Study group aged 10-31 yrs - 3 patients aged 13, 17 and 18 years. Authors contacted for data on children. Their response is awaited.
Svenonius 1988	Exercise-induced asthma.
Tasche 1997	Study excluded as did not involve an anticholinergic drug.
Tashkin 1977	Exercise-induced asthma.
Taytard 1987	Exercise-induced asthma.
Thomson 1978	Study group - adults only.
Tinkelman 1976	Exercise-induced asthma.

Study	Reason for exclusion
Town 1988	Study group - adults only.
Tullett 1982	Study group - adults only.
Ulrik 1992	Study did not meet inclusion criteria.
Vichyanond 1990	Study on chronic asthma but a single-dose study only.
Walker 1987	Study group - adults only.
Ward 1981	Study group - adults only. Study in acute asthma only.
Ward 1985	Study group - adults only. Study in acute asthma only.
Watson 1988	Study in acute asthma only.
Watson 1994	Study did not assess effects of drugs on asthma.
Wilson 1984	Exercise-induced asthma.
Wilson 1987	Study included 10 patients, aged 9 - 57 years. Authors were contacted for childrens' data, their response is awaited.
Wolkove 1981	Study group - adults only.
Yeung 1980	Exercise-induced asthma.
Yung 1998	Study excluded as did not involve an anticholinergic drug.
Zaritsky 1999	Study in acute asthma only.
Zorc 1999	Study in acute asthma only.

## DATA AND ANALYSES

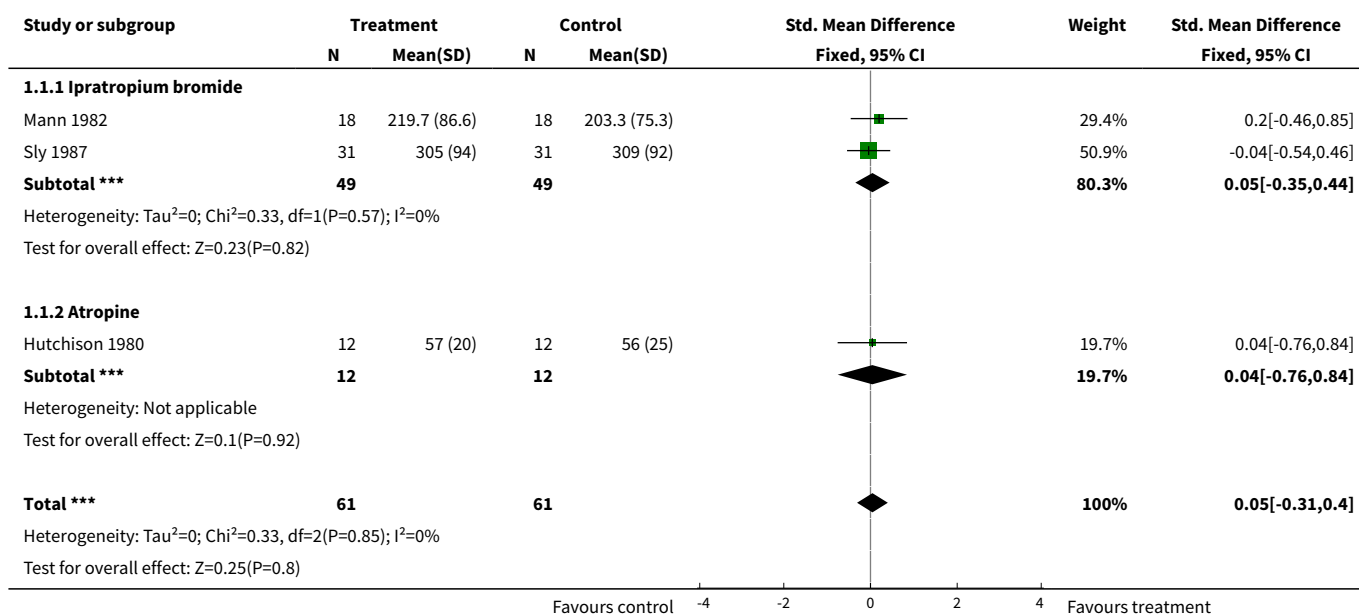
### Comparison 1. Inhaled anticholinergics versus placebo (cross-over studies)

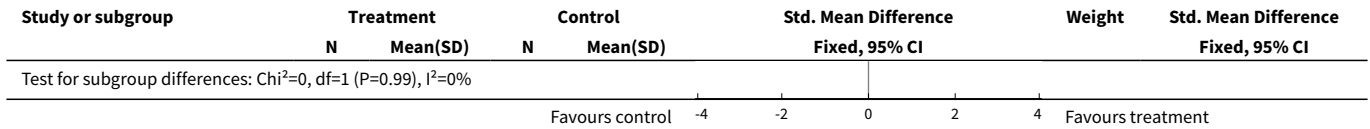
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1 Peak expiratory flow rate (am)</b>	3	122	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.31, 0.40]
1.1 Ipratropium bromide	2	98	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.35, 0.44]
1.2 Atropine	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.76, 0.84]
<b>2 Peak expiratory flow rate (pm)</b>	3	122	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.33, 0.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Ipratropium bromide	2	98	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.34, 0.45]
2.2 Atropine	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.90, 0.70]
<b>3 Number of participants with significant diurnal variation</b>	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Ipratropium bromide	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Atropine	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>4 Amplitude of diurnal variation in PEFs</b>	1		% (Fixed, 95% CI)	Totals not selected
4.1 Ipratropium bromide	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Atropine	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>5 Symptom score</b>	1		Symptoms (Fixed, 95% CI)	Totals not selected
5.1 Ipratropium bromide	1		Symptoms (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Atropine	0		Symptoms (Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>6 FEV1 (% predicted)</b>	1		% (Fixed, 95% CI)	Totals not selected
6.1 Ipratropium bromide	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Atropine	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>7 FEV1/VC (predicted)</b>	1		% (Fixed, 95% CI)	Totals not selected
7.1 Ipratropium bromide	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Atropine	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>8 FEF 25-75% (predicted)</b>	1		% (Fixed, 95% CI)	Totals not selected
8.1 Ipratropium bromide	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Atropine	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>9 RV (predicted)</b>	1		% (Fixed, 95% CI)	Totals not selected
9.1 Ipratropium bromide	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Atropine	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>10 RV/TLC (predicted)</b>	1		% (Fixed, 95% CI)	Totals not selected
10.1 Ipratropium bromide	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]

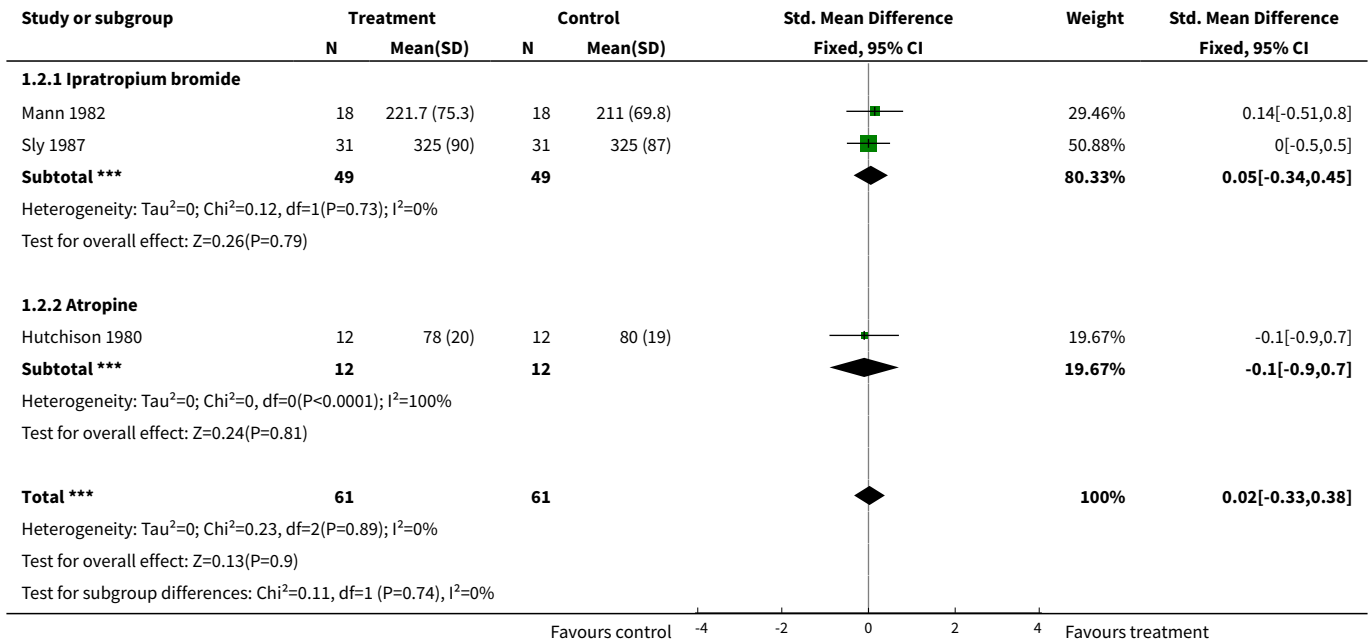
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Atropine	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>11 Hospital admissions</b>	2	64	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.25]
11.1 Ipratropium bromide	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.53]
11.2 Atropine	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 3.90]
<b>12 Need for oral steroids</b>	2	64	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.21, 3.03]
12.1 Ipratropium bromide	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.03, 3.15]
12.2 Atropine	1	24	Odds Ratio (M-H, Fixed, 95% CI)	1.5 [0.25, 8.84]
<b>13 Additional doses of beta-2 agonists</b>	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Ipratropium bromide	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Atropine	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>14 Use of additional medication (physician directed)</b>	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Ipratropium bromide	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Atropine	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

**Analysis 1.1. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 1 Peak expiratory flow rate (am).**

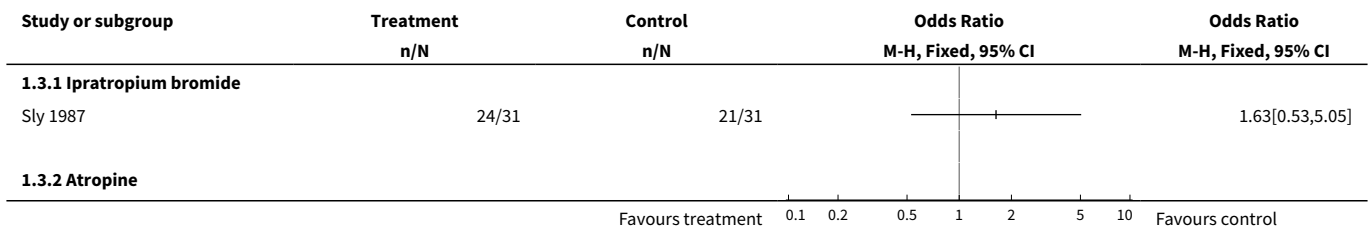




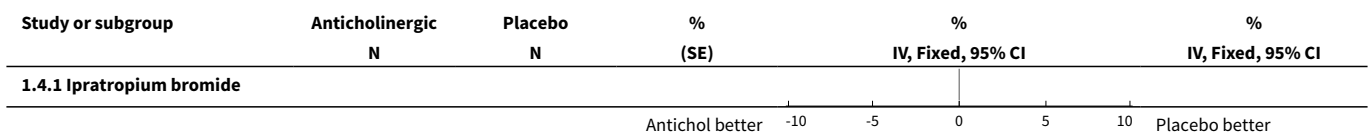
**Analysis 1.2. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 2 Peak expiratory flow rate (pm).**



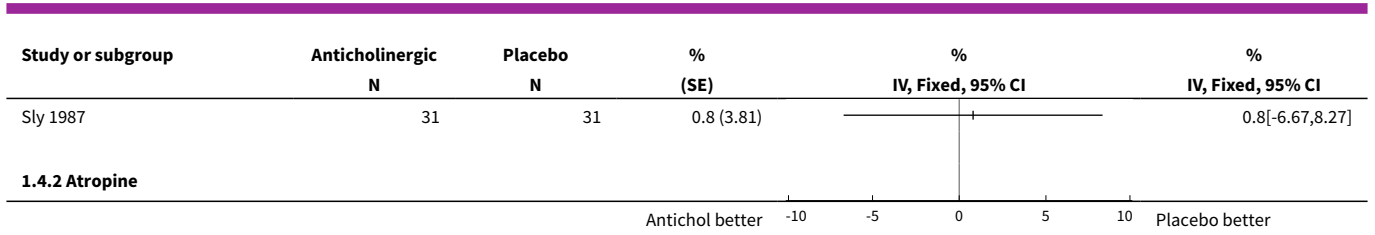
**Analysis 1.3. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 3 Number of participants with significant diurnal variation.**



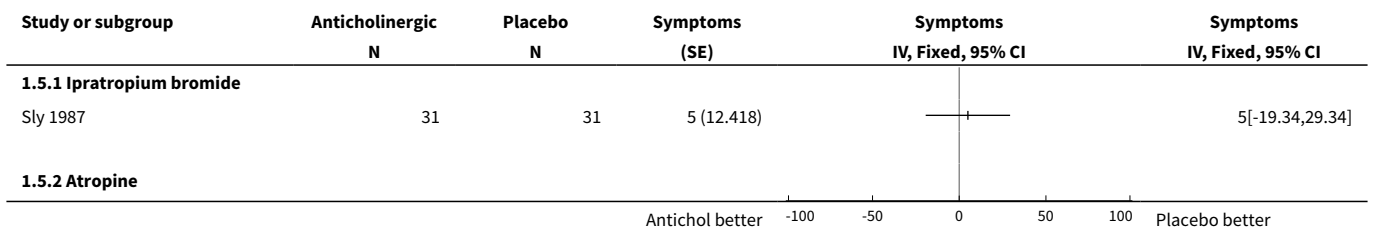
**Analysis 1.4. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 4 Amplitude of diurnal variation in PEFs.**



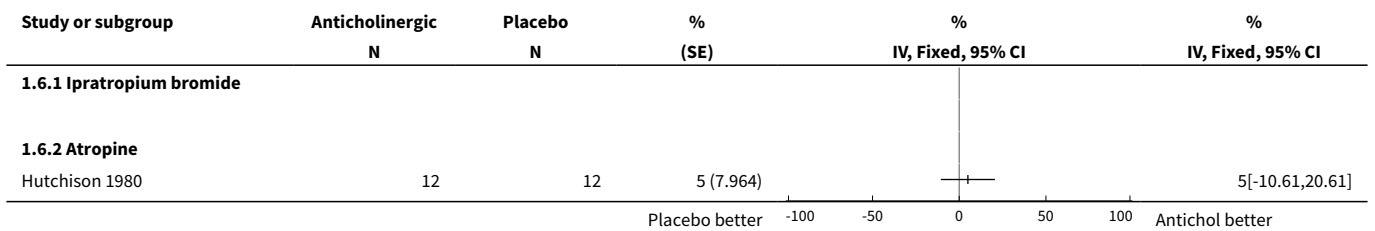




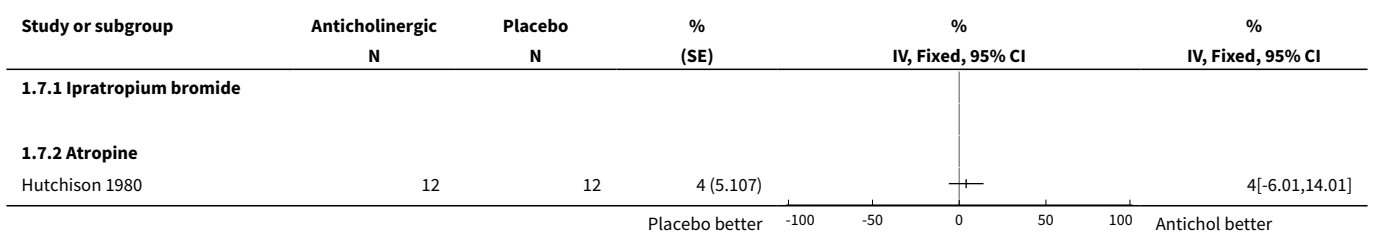
**Analysis 1.5. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 5 Symptom score.**



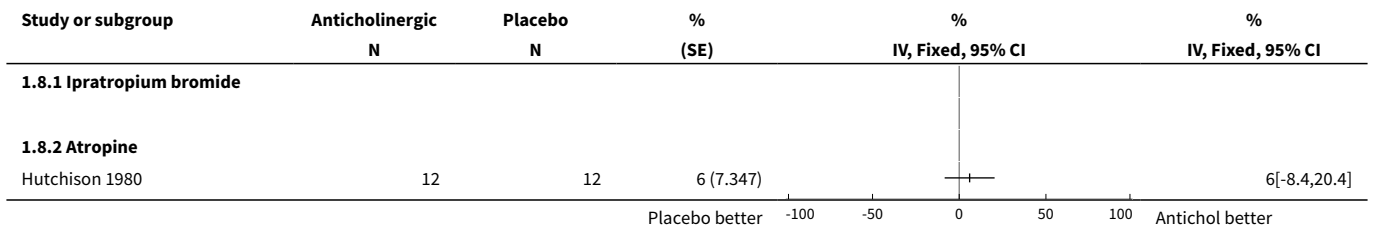
**Analysis 1.6. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 6 FEV1 (% predicted).**



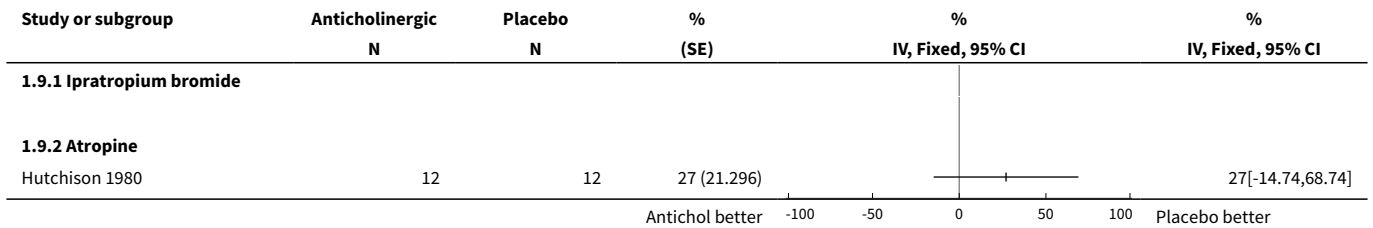
**Analysis 1.7. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 7 FEV1/VC (predicted).**



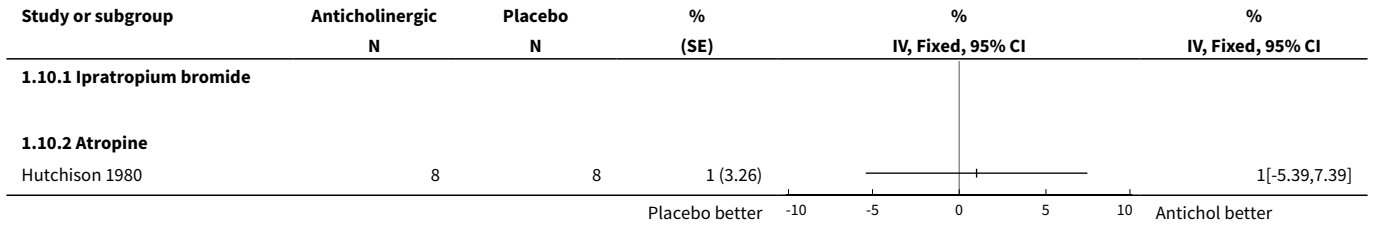
**Analysis 1.8. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 8 FEF 25-75% (predicted).**



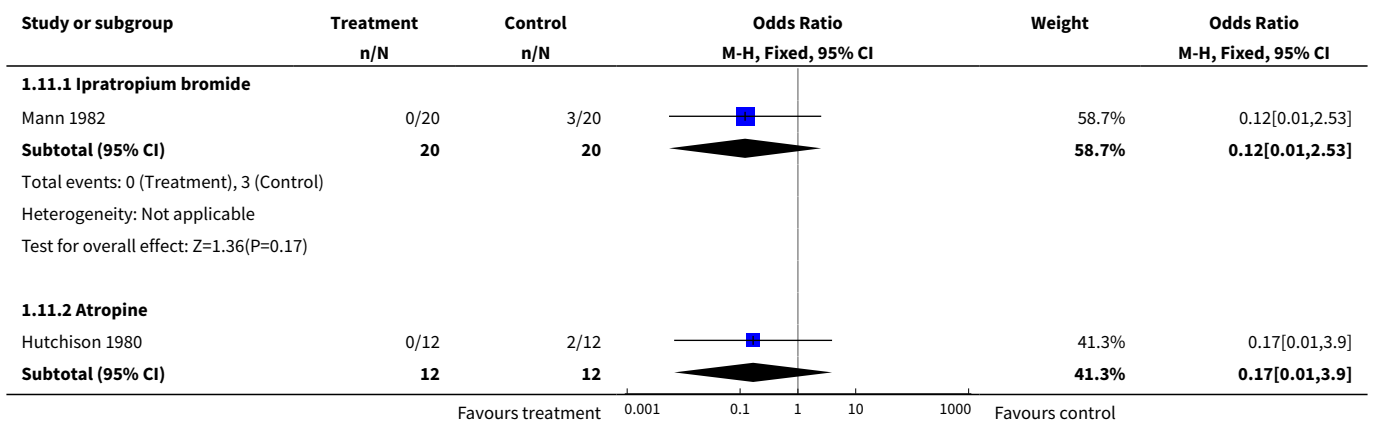
**Analysis 1.9. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 9 RV (predicted).**

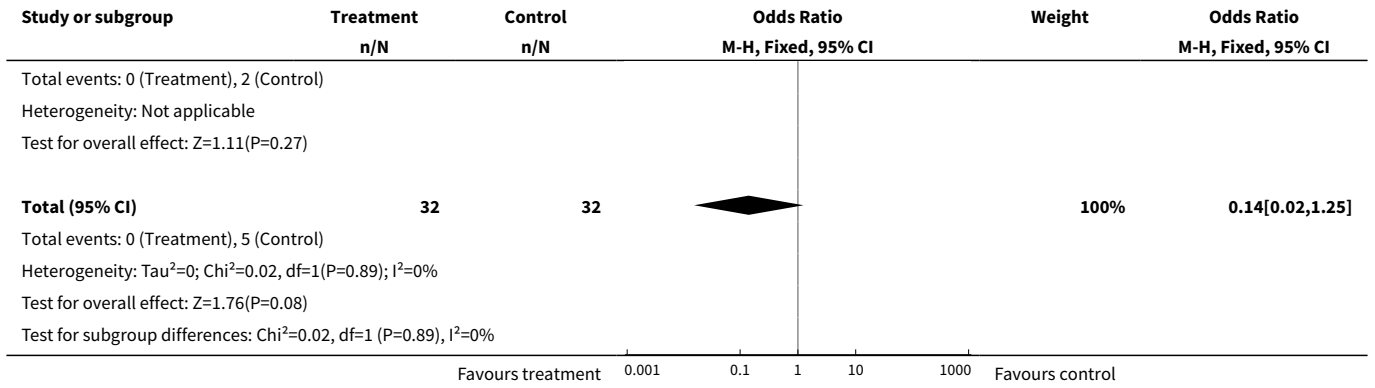


**Analysis 1.10. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 10 RV/TLC (predicted).**

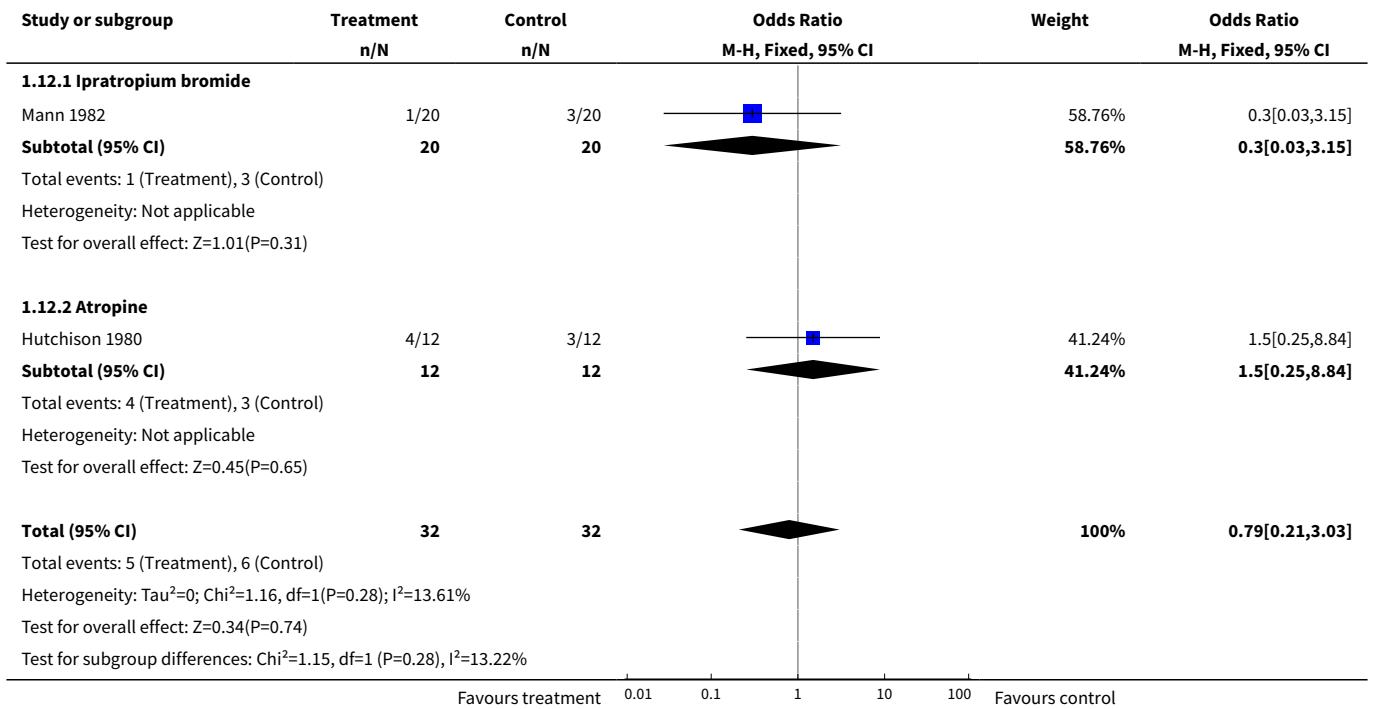


**Analysis 1.11. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 11 Hospital admissions.**

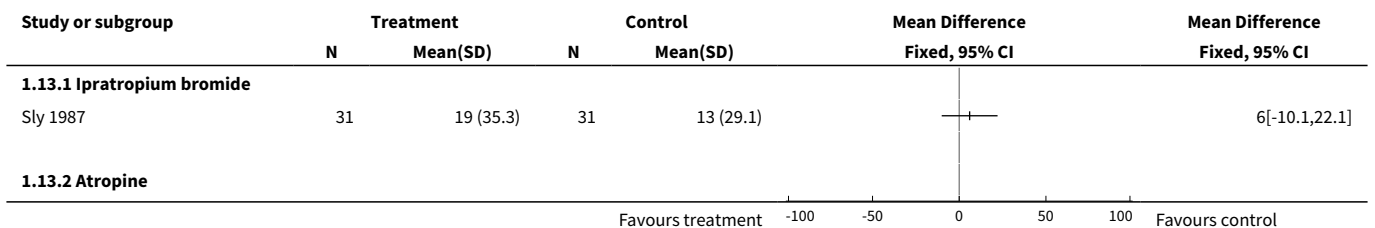




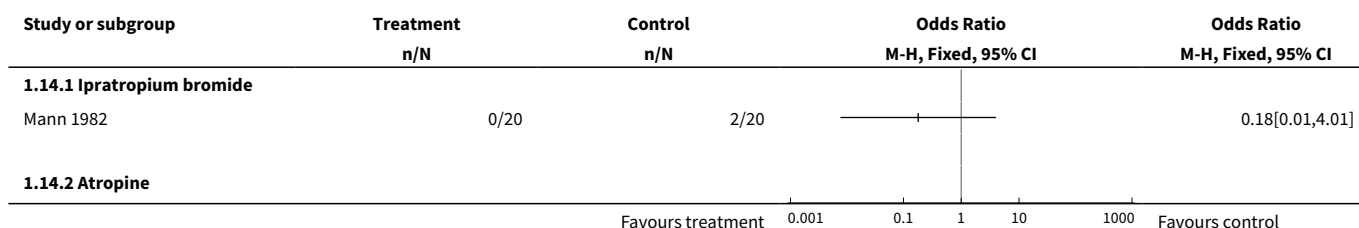
**Analysis 1.12. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 12 Need for oral steroids.**



**Analysis 1.13. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 13 Additional doses of beta-2 agonists.**



**Analysis 1.14. Comparison 1 Inhaled anticholinergics versus placebo (cross-over studies), Outcome 14 Use of additional medication (physician directed).**



**ADDITIONAL TABLES**

**Table 1. Search history**

Years (from/to)	Detail
All years to January 2002	References identified: 438 titles and abstracts Possibly relevant: 107 studies for inclusion. Full text versions of these papers were obtained & assessed independently by NM and AB. Where a query arose about a study's fulfilment of the inclusion criteria, the authors were contacted for further confirmation. If the trial had presented both child and adult data together, authors were asked if they could provide the data for children separately. No further information was provided by study authors. N included: Eight. All study authors contacted to clarify information. N excluded: 99 papers (reasons for exclusion detailed in 'Characteristics of Excluded Studies' .  Nine out of the 107 studies were published in a foreign language (one in French, one in Polish, three in Spanish, two in Italian, one in German, and one in Dutch). No study was excluded on the basis of language of publication. Translations have been obtained for all studies. Two non-English language papers met the inclusion criteria for this review and were included (Vazquez 1984; Zimmermann 1984).
January 2002 to February 2005	References identified: 32 titles and abstracts. Possibly relevant: Six (Dutt 1990; Krasnowska 1994; Krasnowska 2004; Li 2003; Miraglia 1983; Pauwels 1995). N included: 0 N excluded: six
February 2005 to February 2006	References identified: 26 Possibly relevant: 0
February 2006 to February 2007	References identified: 20 Possibly relevant: 0
February 2007 to February 2008	References identified: 14 Possibly relevant: 0
February 2008 to February 2009	References identified: 10 Possibly relevant: 0

## WHAT'S NEW

Date	Event	Description
4 June 2014	Amended	PLS title amended

## HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 3, 2003

Date	Event	Description
16 February 2010	New search has been performed	Literature search re-run; no new studies found.
18 February 2009	New search has been performed	Literature search run: no new studies identified.
7 April 2008	Amended	Converted to new review format.
20 February 2008	Amended	Search re-run; no new eligible trials for inclusion in the review
10 September 2002	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

NM: Protocol initiation, assessed search results, data extraction, data analysis, interpretation

AB: Protocol development, assessed search results, data extraction, data entry

MM: Editorial guidance and support throughout

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- Garfield Weston Foundation, UK.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Anti-Asthmatic Agents [\*therapeutic use]; Asthma [\*drug therapy]; Cholinergic Antagonists [\*therapeutic use]; Chronic Disease; Randomized Controlled Trials as Topic

### MeSH check words

Child; Child, Preschool; Humans