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[Intervention Review]

Anticholinergic agents for chronic asthma in adults

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ABSTRACT

Background

Anticholinergic agents such as ipratropium bromide are sometimes used in the treatment of chronic asthma. They effect bronchodilation and have also been used in combination with ß2 -agonists in the management of chronic asthma.

Objectives

To examine the effectiveness of anticholinergic agents versus placebo and in comparison with ß2 -agonists or as adjunctive therapy to ß2 -agonists.

Search methods

The Cochrane Airways Group asthma and wheeze database was searched with a pre-defined search strategy. Searches were current as of August 2008. Reference lists of articles were also examined.

Selection criteria

Randomised trials or quasi-randomised trials were considered for inclusion. Studies assessing an anticholinergic agent versus placebo or in combination/comparison with ß2 -agonists were included. In practice, all ß2 -agonists were short acting. Short-term (less than 24 hours duration) were not considered for this review.

Data collection and analysis

Two reviewers independently assessed abstracts for retrieval of full text articles. Papers were then assessed for suitability for inclusion in the review. Data from included studies were extracted by two reviewers and entered into the software package (RevMan 4.2). We contacted authors for missing data and some responded. Adverse effect data were analysed if reported in the included studies.

Main results

The studies analysed were in two groups: those comparing anticholinergics with placebo and those comparing the combination of anticholinergics with short acting ß2 -agonists versus short acting ß2 -agonists alone. The former group had 13 studies involving 205 participants included in this review, and the latter 9 studies involving 440 patients. Generally methodological quality was poorly reported, and there were some reservations with respect to the quality of the studies. Despite the limited number of studies that could be combined, anticholinergic agents in comparison with placebo resulted in more favourable symptom scores particularly in respect of daytime dyspnoea (WMD -0.09 (95%CI -0.14, -0.04, 3 studies, 59 patients). Daily peak flow measurements also showed a statistically significant improvement for the anticholinergic (e.g. morning PEF: WMD =14.38 litres/min (95%CI 7.69, 21.08; 3 studies, 59 patients). However the

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clinical significance is small and in terms of peak flow measurements equates to approximately a 7% increase over placebo. The more clinically relevant comparison of a combination of anticholinergic plus short acting ß2 -agonist versus short acting ß2 -agonist alone gave no evidence in respect of symptom scores or peak flow rates of any significant differences between the two regimes. Again there are reservations with respect to the quality of the information from which these conclusions are drawn. An update search in August 2004 did not identify any new studies.

Authors' conclusions

Overall this review provides no justification for routinely introducing anticholinergics as part of add-on treatment for patients whose asthma is not well controlled on standard therapies. This does not exclude the possibility that there may be a sub-group of patients who derive some benefit and a trial of treatment in individual patients may still be justified. The role of long term anticholinergics such as tiotropium bromide has yet to be established in patients with asthma and any future trials might draw on the messages derived from this review.

PLAIN LANGUAGE SUMMARY

Anticholinergic agents for chronic asthma in adults

Anticholinergic agents such as Atrovent are sometimes used to treat people with asthma as a bronchodilator that opens up the airways in the lungs. This review found that although this treatment was better than placebo, the size of the effect was rather small. When the drug was used in combination with more widely used bronchodilators (beta-agonists such as fenoterol), it did not appear to add much benefit. However, there are concerns about the quality of the studies that have been analysed. It could be that there are some adults with chronic asthma who respond to treatment with anticholinergic drugs, but the review has not been able to identify their common characteristics.

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BACKGROUND

Asthma is the commonest chronic disease affecting all age groups in developed countries (Harrison 1998), and has been recognised and treated in the East for centuries (Gross 1984). The anticholinergic agent, atropine was probably the first treatment used for asthma and was introduced in the West in the early 1800s (Gross 1984). Atropine acts as a bronchodilator, but has adverse effects, even at doses close to those used for bronchodilation (Gross 1988), and, as a result, fell from favour following the commercial development of ephedrine and adrenaline - beta-agonists - in the 1920s and, later, the methylxanthines. However, in the 1970s a quaternary ammonium synthetic analogue of atropine, ipratropium bromide, was developed, which gave few systemic side effects and revived interest in the anticholinergics (Gross 1988). A recent study in the USA (Taylor 1999) showed that anticholinergics were prescribed for asthma in 7 of 85 cases (8%) - age range 18-54 years, with a range of disease severities. Data from a UK general practice database on new use bronchodilators in severe asthma showed that, of 14657 patients, 20% received ipratropium bromide (Meier 1997).

Anticholinergic agents act as bronchodilators. The rationale for using them in asthma is based on the assumption that activation of the parasympathetic (cholinergic) nerve pathway is an important mechanism for producing airway obstruction. Anticholinergics work by competing with acetylcholine for receptor sites at the vagus nerve-nerve or nerve-muscle junctions. This prevents transmission of reflexes induced by asthma stimuli (Gross 1997, Beakes 1997).

Until the early 1980s, the treatment for asthma was regular bronchodilator agents (especially short-acting selective ß2 -agonists - the successors to adrenaline and ephedrine) and other agents were added only when symptoms reached an unacceptable level of frequency or severity (O'Connor 1998). Treatment was based around relieving the symptoms (airway constriction) and patients were often encouraged to tolerate continuing symptoms, treating them when necessary with repeated doses of ß2 -agonists. However, in the mid 1980s, opinions on asthma changed rather strikingly, because asthma was recognised as a chronic inflammatory disease (Barnes 1996). The therapeutic emphasis in chronic asthma in adults changed to embrace agents that suppress the underlying inflammation, notably inhaled corticosteroids (BTS 1993, Bousquet 2000).

Asthma guidelines have been available since the late 1980s and are updated regularly (Harrison 1998, Kemp 2000, Creer 1999). Initially they were arrived at by consensus, based on discussion and state-of-the-art literature reviews. More recent guidelines such as the BTS/SIGN guidelines (BTS/SIGN 2004) have adhered to systematic electronic searching and standardised guideline methodology. The grades of recommendation are derived from levels of evidence. According to current guidelines, the early introduction of anti-inflammatory treatment in the form of inhaled steroids is indicated for all but the mildest forms of asthma. Bronchodilators are adjuvant treatments used in one of two ways. Firstly, short-acting bronchodilators in the form of ß2 -agonists are used as-needed to relieve episodic symptoms. Secondly, in patients whose asthma is inadequately controlled despite regular inhaled steroids, the addition of long-acting ß2 -agonists has been shown to improve lung function and symptoms, and to decrease exacerbations (Ni Chroinin 2005). A small proportion of patients have asthma which is not adequately controlled despite moderate doses of inhaled steroid and a long-acting ß2 -agonist. There are few clinical trials in this specific patient group and possible options include an increase in the dose of inhaled steroid or additional treatment, which might include leukotriene receptor antagonists, theophyllines or anticholinergics.

It is a widely held view that anticholinergics are less effective than ß2 -agonists in the symptomatic treatment of chronic asthma (Cazzola 1998), although there is considerable variation in treatment effect amongst patients. Attempts to identify subgroups that respond better to anticholinergics have not been very successful. In general, though, anticholinergics may be better in the following: older patients - the ß2 -agonist responsiveness apparently declines with age (Cazzola 1998, Connolly 1993); patients intolerant to ß2 -agonists (Boulet 1999); patients with nocturnal asthma (Beakes 1997); patients with chronic asthma and concurrent fixed airway obstruction (Cazzola 1998), patients with intrinsic asthma and those with longer duration of asthma (Partridge 1981). Patients with high serum immunoglobulin-E levels may be better treated with anticholinergic agents (Cazzola 1998), although earlier studies show that atopic patients respond less well to anticholinergics than those with non-atopic disease (Jolobe 1984).

The possible differences in responsiveness to anticholinergics between different patient groups illustrates the heterogeneous nature of asthma. This is further compounded when taking into account the overlap of asthma and COPD. At one end of the spectrum are patients whose airflow limitation shows marked spontaneous fluctuations and improves considerably with treatment (asthma). At the other end of the spectrum are patients whose disease fluctuates to a very limited extent and is "irreversible". Whilst an improvement of greater than 15% after inhaling a short-acting ß2 -agonist indicates a degree of reversibility, any such figure is inevitably arbitrary when there is a spectrum of airway disease ranging from "reversible" to "irreversible". Clinical features such as age, nature of symptoms, atopic status and smoking history are important factors in terms of diagnosis. This blurring of the boundaries becomes important when considering anticholinergics since it is generally regarded that they may have a small but proportionately greater effect than ß2 -agonists in patients with COPD.

The other factor that needs to be taken into consideration is the relative safety of ß2 -agonists and anticholinergics - the former can cause an increased heart rate and have also been associated with increased bronchial activity and increased mortality (Emilien 1998, Spitzer 1992). In comparison, the anticholinergics have relatively few side effects. Finally, anticholinergics are also used in combination with ß2 -agonists (Gross 1984). In severe asthma, the main treatment is based on inhaled steroids, but the benefit : harm ratio of inhaled steroids appears to be reduced once the total daily dose exceeds 1000 mg (O'Connor 1998), with adverse effects leading to increased risk of osteoporosis, skin thinning and adrenal problems (van Schayck 1995). As an alternative to high doses of inhaled steroid, moderate levels of inhaled steroid have been used in conjunction with oral steroids, leukotriene-receptor antagonists, steroid sparing alternatives, theophylline, anticholinergics or long-acting ß2 -agonists (O'Connor 1998). Oral steroids and some of the alternatives, including long-acting beta-agonists, have adverse

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effects too (Barnes 1997, Hougardy 2000), which might indicate a place for the relatively safe anticholinergics.

OBJECTIVES

The objectives of this review, as defined in the original protocol ("Anticholinergic agents for chronic asthma in adults"), were to investigate the efficacy and safety of the various anticholinergic agents in chronic asthma in adults in two modes of treatment:

1. Anticholinergics for symptom relief (as-needed use), either alone or in combination with ß2 -agonists, in comparison with ß2 -agonists or placebo. This included both acute (short-term) bronchodilating effects and the longer-term effectiveness of bronchodilators for symptom relief.
2. Anticholinergics as regular, longer-term treatment, including their use as adjuncts to inhaled steroids, in comparison with ß2 -agonists (long- or short- acting) or placebo.

Protocol splitting
It was decided to split the original review in line with the two objectives because there was so much data, in an attempt to make the reviews more comprehensible. In practice there were no prn (as-needed) studies in the longer term, so that the two reviews focussed on (A) short-term bronchodilator effects (up to 24 hours) and (B) longer-term regular treatment (for periods from 2 days to 3 years). The latter focus is reported in this review and the former in the review, "Anticholinergic agents for chronic asthma in adults short term".

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials and quasi-randomised trials (e.g. allocation to treatment by alternation or date of birth) were analysed in the review. If a study did not report allocation details, but the allocation could have been randomised or quasi-randomised, further information was sought from the authors and the study was included if randomisation could be confirmed. Included studies reported the measurement of at least one of the outcome variables.

Types of participants

Adult patients with stable asthma: stability was defined as an absence of exacerbations, and stable medication prior to the study. Asthma therapy used during the study was also required to be stable.

The studies were required to report that the patients had asthma - preferably this was defined according to reliable criteria, such as those of the ATS, but less exactly, the patients had to display a reversibility in their lung function of at least 15% following administration of a short term ß2 -agonist (reversibility shown using anticholinergics was considered confounded and such studies were excluded).

Studies of patients with serious, non-respiratory diseases (e.g. cancer, heart disease) were excluded, as were those of patients with cystic fibrosis or irreversible airways disease. Studies involving a mixed group of patients having either asthma or COPD were included if separate results were given (or could be obtained from trialists) for the patients with asthma.

Types of interventions

Studies were included if they used anticholinergic agents (including ipratropium bromide, oxitropium bromide, tiotropium bromide, atropine methonitrate and glycopyrrolate) used as a bronchodilator, in comparison with a ß2 -agonist or placebo. Delivery systems included nebulisers, metered dose inhalers and powder inhalers, with and without a spacer device.

Studies were included that compared:

1. Anticholinergics versus ß2 -agonist
2. Anticholinergics versus placebo
3. The combination of ß2 -agonist and anticholinergic versus ß2 -agonist alone
4. Different doses of anticholinergics
5. One anticholinergic versus another

Analysis was carried out only for comparisons 2 and 3 for the longer-term studies.

It was decided not to analyse trials that had atropine sulphate as the sole anticholinergic agent, because this has a different mode of action to the quaternary salts of atropine, has adverse effects and is therefore not routinely used as a bronchodilator in chronic asthma. Similarly, studies using non-selective ß-agonists such as isoprenaline were included, but not analysed.

Types of outcome measures

All possible outcome measures were considered, but the main focus was as follows:

1. Daytime and night-time asthma symptom scores (primary outcome)
2. Bronchodilator use for symptom relief (i.e. 'rescue medication')
3. Daily peak flow (PEF; morning and evening)
4. Patient preference
5. Quality of life score
6. Asthma exacerbation rates/ hospital admissions - number of patients, not exacerbations
7. Adverse events and effects, e.g. tachycardia

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 searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms:

Anticholinergic* OR cholinergic* OR ipratropium OR Muscarinic* OR ipratropium OR N-isopropylatropine OR oxitropium OR tiotropium OR atropine OR glycopyrrolate OR Atrovent OR Sch1000 OR Oxivent

The most recent search was conducted in August 2008.

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Other sources

Bibliographies from retrieved trials, meta-analyses and narrative reviews were checked to identify relevant cross-references. Attempts were made to obtain additional data from the authors and from the drug company, Boehringer Ingelheim (Bracknell UK); largely these were fruitless because many of the studies were about 20 years old and the data not available or we were unable to contact the authors.

Data collection and analysis

Step I. Trials that appeared potentially relevant were identified independently by two reviewers (MW and MB) from the search citation abstracts.

Step II. Using the full text of each study, two reviewers (MB and MW) independently selected trials for inclusion in the review. Agreement was measured using simple agreement and differences were resolved by discussion.

Step III. After a preliminary review of all studies to confirm the basic requirements, two reviewers independently assessed the methodological quality of the included trials with particular emphasis on the concealment of allocation, which was ranked using Cochrane criteria (grade A: adequate concealment; grade B: uncertain; grade C: clearly inadequate concealment). Any differences were resolved by discussion. The Jadad scale (Jadad 1996), described in the protocol, was not used for additional analysis because it and other scales are no longer thought to be the best approach to quality assessment (Clarke 2003).

Step IV. Two reviewers (MB and MW) independently extracted data from the included trials and one reviewer (MW) entered results into the Cochrane Collaboration software program (Review Manager, version 4.2). These data were checked by MB. A pilot for the data extraction form was carried out on a small sample of studies and was revised appropriately. In practice this led to the use of two forms, the first stage involving details of participants, the interventions, the type of outcomes and whether variability measures (e.g. standard errors, p-values) were reported. The second form contained results if available (e.g. mean and standard deviations for continuous outcomes). In some cases, information regarding outcomes was estimated from graphs; this was performed independently by the two reviewers.

Data extraction included the following items:

- Participants: age, gender, smoking status, type of asthma (intrinsic, extrinsic), allergic status (atopic, non-atopic), presence of co-existing COPD, severity of asthma (rated by MB based on baseline lung function, maintenance therapy and descriptions of the authors), history of asthma, symptom status at trial entry (symptomatic/asymptomatic)
- Intervention: anticholinergic agent, dose, schedule, spacer device, concurrent ß2 -agonist
- Control: ß2 -agonist, placebo
- Outcomes: self-rated daily symptom score/symptoms - daytime and night-time, pulmonary function measures (baseline and daily peak flow rates), bronchodilator use for symptom relief, hospital admissions/rate of acute exacerbations, quality-of-life instruments, adverse events and effects.
- Design: method of randomisation, allocation concealment, blinding, presence and type of run-in period, study design (parallel, cross-over), concurrent background therapy, duration of study and, for crossover studies, the duration of any washout period and/or the time between successive crossover arms
- Funding and multi-centre trials

STATISTICAL CONSIDERATIONS

- The results for particular outcomes for each trial were combined using RevMan (Version 4.2). An intention-to-treat analysis was completed where possible. Most of the studies in this review had a crossover design, that is, the patients were given each intervention in a random order. This means that there are within-patient correlations, which, ideally, should be treated using a paired analysis (Elbourne 2002). Where possible, this was carried out for continuous outcomes according to the guidance given by Elbourne 2002. The standard error for the difference of means was calculated, either from individual patient data or from p-values, and the between-period correlation parameter, ρ, was calculated. For some studies the standard error was imputed using the lowest value of ρ from the other studies. For parallel studies the standard error was calculated as the square root of the sum of the variances for each arm. All similar parallel and crossover studies with sufficient data were pooled using the fixed effects generic inverse variance method in RevMan Version 4.2 to give a weighted mean difference and 95% confidence intervals.
- In the absence of paired data the trials were analysed by the conventional approach of treating the two arms of the crossover as if they were from a parallel trial with separate groups (i.e. setting ρ=0). If this was the case, parallel and crossover trials were analysed separately.
- For non-paired data and continuous variables, a fixed effects weighted mean difference (WMD) or standardised mean difference (SMD) and 95% confidence interval (CI) were calculated for each study. All similar studies were pooled using fixed effects WMD/SMD and 95% CIs.
- For dichotomous variables, a fixed effects odds ratio (OR) with 95% confidence intervals (95% CI) was calculated for individual studies. All similar studies were pooled using fixed effects OR and 95% CIs.
- For pooled effects, heterogeneity was tested using the Breslow-Day test; $p < 0.1$ was considered statistically significant. The statistical term I^2 (which is a measure of the inconsistency among results) was also used to monitor the variability among studies.
- Funnel plots were not constructed because of the paucity of included studies.

SUB-GROUP/SENSITIVITY ANALYSES:

If there had been sufficient studies sub-group analyses would have been carried out. *A-priori* defined subgroups were:

1. Concurrent therapy with inhaled corticosteroid or not
2. Asthma severity (mild, moderate or severe)
3. Concurrent COPD or not
4. Smoking status
5. Age (<40; 40-69; 70+)
6. Symptom status at trial entry (symptomatic/asymptomatic)

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7. Asthma type (intrinsic, extrinsic)
8. Allergic status (atopic, non-atopic)
9. Duration of asthma
10. Dose, duration and delivery method of therapy
11. Type of anticholinergic agent

Sensitivity analyses had been proposed using the following domains:

1. Methodological quality
2. Random effects versus fixed effects modelling

However, there was insufficient data to examine these.

Rationale for the presentation of studies in the review

The original review had a very large number of included studies, separated into two modes of treatment (short-term bronchodilation and longer-term regular treatment). To manage the data we used a Microsoft Access database and prioritised the comparisons to be studied. This prioritisation took place before data extraction. For the longer-term studies, the clinical question of particular interest was whether a combination of anticholinergic with ß2 -agonist would give additional symptom relief compared to that obtained with ß2 -agonist alone, so this was the main focus. It was decided to set aside the comparison anticholinergic versus ß2 -agonist because it was of little practical interest, and to look at the comparison anticholinergic versus placebo only if no difference was found between the combination and the ß2 -agonist. This would clarify whether the anticholinergic had any effect (relative to placebo) alone. In reality, two types of comparison were analysed for the longer term studies:

1. Anticholinergic versus placebo
2. Anticholinergic plus ß2 -agonist versus ß2 -agonist alone.

It was felt appropriate to separate the studies according to duration and the following definitions were provided by MB prior to data extraction: short (2 days to 2 weeks), medium (more than 2 weeks to 2 months) and long (more than 2 months).

RESULTS

Description of studies

Results of the search

From electronic searches conducted for the original review, a total of 623 references were identified. From the abstracts of the study reports, 210 references were marked for further scrutiny, and the remaining 413 were excluded because they clearly did not meet the inclusion criteria (for example, the patients were children or were treated for acute asthma). A further 103 possible studies were identified from other sources (e.g. references in included studies and reviews). This gave 302 possible references for which the full papers were obtained where possible. 26 reports were in non-English languages, of which 19 were translated. 239 studies were included in the original review. Of these, 45 studies had only longer-term data, 187 had only short-term data and 7 had both. The longer-term studies were all concerned with the regular addition of anticholinergics and there were no studies of longer-term as-needed use. For details of the studies that were excluded and the studies included in the short term review see the Table of Excluded Studies. Two longer-term studies were later excluded and deserve particular mention: Tarlo 1982, which is a crossover comparison of anticholinergic and placebo over 90 days was excluded because the patients were instructed to reduce gradually their dose of bronchodilators - thus their concurrent medication was not stable, which we considered to be confounding. Secondly, Brand 1992 (and its 7 accompanying papers) was a large parallel 3 year comparison of the combination of ipratropium bromide and terbutaline versus terbutaline alone. Unfortunately the study did not report separate results for asthma, although these were recorded, and contact with the authors has failed to produce any data. Four other studies did not state if the patients were randomised to treatments, and no further information was obtained from the authors. This left 39 reports of randomised or quasi randomised trials. Of these 39 longer-term study reports, 9 were additional reports of trials already reported, leaving 30 trials.

The 30 longer-term trials sometimes included more than two randomised interventions, giving rise to more than one comparison per trial; thus 23 trials had one comparison, 6 two comparisons and 1 trial had 3 comparisons. The number of trials reporting the different comparisons was:

1. Anticholinergic versus placebo in 13 trials (analysed in this review)
2. Anticholinergic plus ß2 -agonist versus ß2 -agonist alone in 9 trials (analysed in this review)
3. Anticholinergic versus ß2 -agonist compared in 12 trials (not analysed)
4. Anticholinergic dose comparison in 4 trials (not analysed)
5. Different anticholinergics were compared in 0 trials (not analysed).

Thus, 22 trials were included for the two types of comparison prioritised here. The flow of studies is shown in figure 1 (Figure 1).

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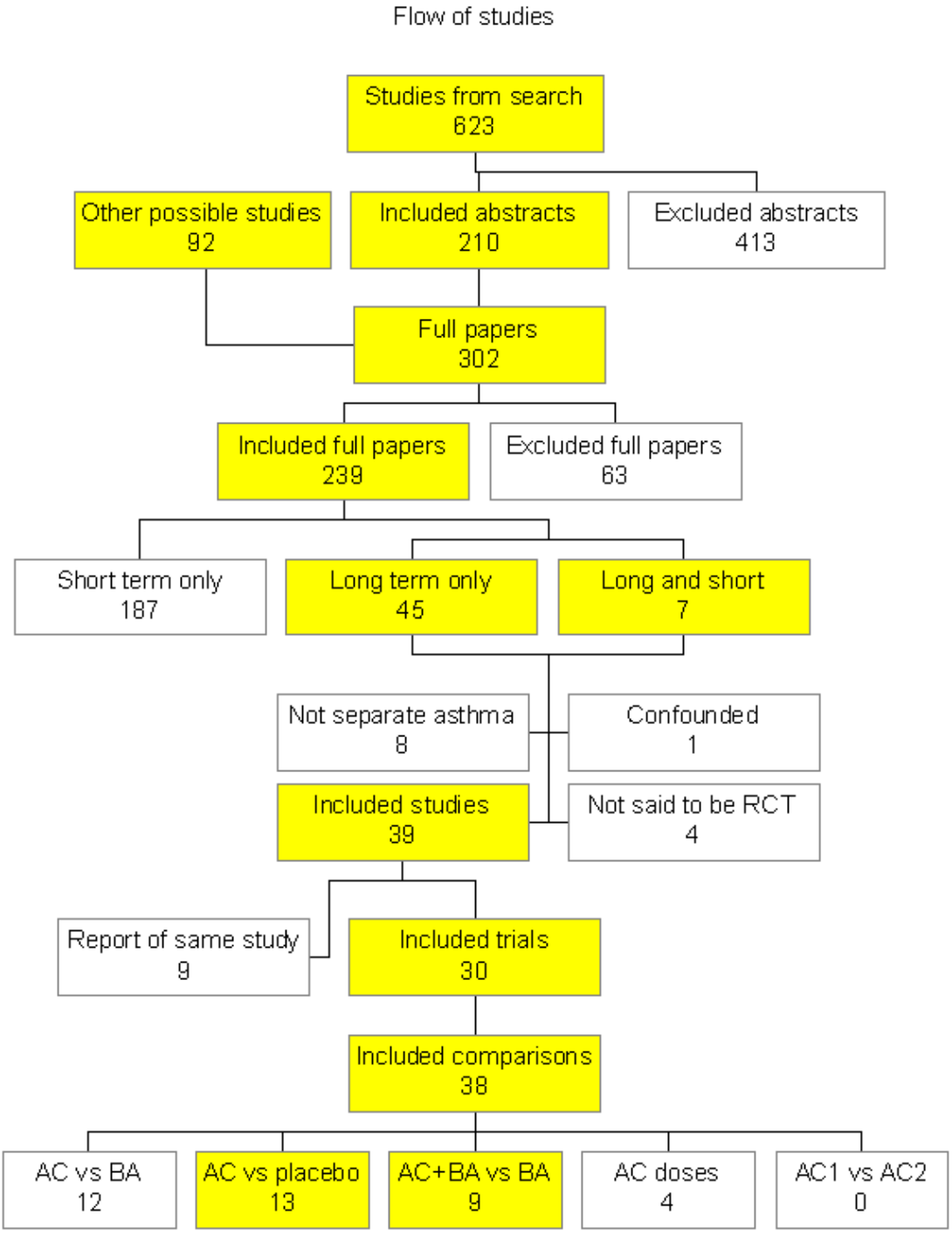
Figure 1. Fig 1 Study flow.



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Update searches to August 2008 identified two studies which we excluded as they were in children (Dutt 1990; Li 2003).

Included studies

Study size

In the placebo comparison the study size of the crossover studies ranged from 6 to 39 patients and all but two studies (Vaughan 1988, Wheeler 1987) had fewer than 20 patients with asthma. In the combination comparison there were two parallel trials each with over 100 patients and the remaining crossover trials had a study size ranging from 12 to 28, with only two studies having more than 20 participants (Rebuck 1983, Tammivaara 1993).

Design

In the placebo comparison all the trials had a crossover design; for the combination versus ß2 -agonist comparison there were 2 parallel trials and 7 with a crossover design. For the placebo comparison, 1 trial had a quasi-randomised design (Light 1977), but all other included trials reported randomisation.

Duration

In the placebo comparison the duration ranged from 4 days to 1 month per phase; for the combination versus ß2 -agonist comparison the parallel trials had durations ranging from 8 -12 weeks, and the crossover trials' phases ranged from 2 weeks to 3 months.

Participants

In the anticholinergic-placebo comparison, one study (Taytard 1984) had patients with perennial asthma that became worse in spring and summer and improved over the course of the study. The authors found an order effect and for this reason only first period results were used for this study, and the individual patient data analysed as a parallel trial.

One study did not give any details about concurrent medication (Ruffin 1990), one was unclear but had no oral steroids (Coe 1986), two had no concurrent medication (Ahonen 1978, Taytard 1984), one had sodium cromoglycate only (Bellia 1988), three had inhaled steroids only (Pavia 1989, Tormey 1995, Wheeler 1987), one had unspecified steroids (Kreisman 1981) and the others had oral and inhaled steroids (Light 1977, Salorinne 1988, Taylor 1986, Vaughan 1988).

Four studies were assessed to have patients with mild asthma (Ahonen 1978, Bellia 1988, Ruffin 1990, Taytard 1984), 5 with moderate asthma (Kreisman 1981, Pavia 1989, Salorinne 1988, Tormey 1995, Vaughan 1988) and 4 with heterogeneous patient populations (Coe 1986, Light 1977, Taylor 1986, Wheeler 1987). No study claimed to have patients with concurrent COPD.

In the combination comparison, one study did not give any details about concurrent medication (Waite 1987), one had aminophylline but did not say if steroids were used (Macaluso 1986), one had no steroids (Tammivaara 1993), one had only inhaled steroids and sodium cromoglycate (Haahtela 1991), two had unspecified steroids (Mazzei 1985, Philip-Joet 1990) and the other three had oral and inhaled steroids (Pierce 1982, Rebuck 1983, Wolstenholme 1989). Most of the studies also used methylxanthines as concurrent medication. Four studies were assessed to have patients with moderate asthma (Haahtela 1991, Pierce 1982, Tammivaara 1993, Wolstenholme 1989), two gave no information on severity (Macaluso 1986, Waite 1987) and three had heterogeneous patient populations (Mazzei 1985, Rebuck 1983, Philip-Joet 1990). One study (Pierce 1982) had patients with concurrent bronchitis.

Interventions

For the anticholinergic-placebo comparisons, there were three main variables with respect to the anticholinergic. The anticholinergic drugs included ipratropium bromide (7 studies), oxitropium bromide (8), nebulised atropine methonitrate (1) and inhaled atropine sulphate (Light 1977). The latter study was not analysed. The dose of ipratropium bromide ranged from 40 µg to 200 µg delivered either by metered dose inhaler or powder inhaler. The frequency of administration ranged from twice daily to five times daily. For further details see table of included studies.

All of the studies comparing a combination of ß2 -agonist plus anticholinergic versus ß2 -agonist alone used ipratropium bromide as the anticholinergic agent at either 40 or 80 µg, three or four times per day. In all studies the ß2 -agonist was short acting. In eight studies fenoterol was combined with ipratropium as Duovent (40 µg ipratropium, 100 µg fenoterol), Berodual (20 µg ipratropium, 50 µg fenoterol) or using two separate inhalers. In the ß2 comparison arm, three studies used fenoterol and the remaining studies used salbutamol. Three further studies used terbutaline as the ß2 -agonist, both in combination and as the comparator. However one of these studies (Tammivaara 1993) used oral controlled-release tablets and this study was analysed separately because of the different pharmacokinetics of the oral formulation. For further details see table of included studies.

Outcome measures

Outcome measures chosen were those generally accepted to reflect the primary outcome of asthma control. Daytime and night time asthma symptom scores were derived from daily diaries. Objective measurements of lung function were daily peak flow measurements, recorded morning and evening, before and after use of inhaler. Additional outcomes were treatment related withdrawal from the study, patient preference, bronchodilator use as rescue medication (number of patients requiring this), number of patients with exacerbations and adverse effects. Clinical and physiological assessments at the beginning and end of each trial period were regarded as being less valuable, given the recognised spontaneous fluctuations which can occur in asthma.

Risk of bias in included studies

The methodological quality was poorly reported in all 22 studies, but the authors provided further details for five studies (Philip-Joet 1990, Pierce 1982, Vaughan 1988, Wheeler 1987, Wolstenholme 1989). All but one of these (Philip-Joet 1990) still did not give an adequate description of allocation concealment, with only partial details provided (for example using sealed envelopes). One additional study (Light 1977) reported an inadequate method of allocation concealment. Generally the reporting of blinding was vague, with all but two being described as double blind or blind (1 study). The Philip-Joet study stated that it did not have a double blind design and the comparison we used for the Salorinne study (inhaled Ipratropium bromide versus powder placebo) could not have been blinded. The Macaluso study, despite stating it was double blinded, was not blinded because the combination arm used three inhalations and the ß2 -agonist four. The Pavia study

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reported that some patients could distinguish by taste oxitropium bromide from placebo, and it is likely that the blinding was broken in some of the other placebo studies too. This may also be true of the combination comparison, because ipratropium bromide and salbutamol, for instance, taste quite different. Nine of the 22 studies had intention to treat analyses carried out and for two other studies it was unclear what was done. Six studies (Haahtela, Philip-Joet, Tammivaara, Wolstenholme, Ruffin and Wheeler) had at least 20% of the patients' results missing for some outcomes, and nearly 40% of the patients were not analysed for the 8-week PEF outcome in the Philip-Joet study.

Effects of interventions

Duration

Although the original intention was to separate the study durations as described in the methods section, in practice there were too few studies to make this feasible, so all durations were considered together.

A) Anticholinergic versus placebo

There were 13 studies comparing anticholinergic with placebo. Of these, one was not included in our analysis because it used atropine sulphate (Light 1977).

Seven studies were also not included in the initial analysis: 6 studies did not record means for the continuous outcomes and 1 other study did not report standard deviations or p-values. The authors of these studies were contacted and Boehringer Ingelheim provided individual patient data for Wheeler 1987; some other authors offered data, but to date these had not arrived. Thus, there were only 4 studies that provided sufficient data for analysis of the continuous outcomes, although 7 studies gave data for the dichotomous outcomes.

Ahonen 1978 compared two doses of anticholinergic and, in order to clarify the main analysis, we decided to choose one dose of ipratropium bromide, based on the head-to-head comparison. It was found that for both symptom scores and peak flow measurements the summary statistics were in favour of the lower dose (40µg), although none was statistically significant (see additional Table 1 and forest plots). Therefore for this study the lower dose was used in comparison with placebo in the main analyses.

The results for various outcomes for the comparison of anticholinergic with placebo are summarised in additional tables 2-5. Where there was more than one similar study, the results were combined and the summary statistics reported in the additional table and shown in a forest plot. Otherwise the results in the table are for single studies.

For some outcomes, the percentage increase or decrease over placebo was calculated. This is an approximation used to give an estimate of the magnitude of the effect in clinical terms. It was done using as denominator the simple average, over the individual studies, of the placebo means; the numerator was the weighted mean difference from the meta-analysis (or single study). It should be noted that the studies involved had a range of asthma severities, so that patients with more severe disease might derive greater benefit than represented by the mean percentage change, but there is insufficient information to look at subgroups, either for peak flows or symptom scores.

1. Symptom scores (Table 2)
The data were analysed by calculating the difference in means and the paired difference standard error and pooling the data, where appropriate, using the generic inverse variance method. The Wheeler study gave individual patient data (IPD) and the Ahonen study reported p-values for the comparison. The scales for the studies were different (Ahonen 1978: 1-4; Wheeler 1987; Salorinne 1988: 0-3 and Taytard 1984 0-13), but the first two scales were linearly equivalent and so could be combined in the analysis. Taytard 1984 was analysed separately because the trialists reported a combined 'clinical score', which was a composite of day-time and night-time symptom scores and drug consumption for symptomatic relief. For this study, only first period results were used (because the authors reported an order effect); the study reported individual patient data and because of large baseline differences, the change scores were used.

The four studies had treatment periods ranging from 4 days to 4 weeks and it was decided to combine these different durations, by calculating the mean symptom score per day.

It should be noted that Wheeler 1987 (which provided individual patient data) had a number of patients who failed to report their scores every day, so we calculated symptom scores based only on the patients who completed their diary cards for more than 20 days (28/30 patients). The study reported symptom scores over the whole period for each patient, so we calculated their daily symptom score (for the number of days they reported), and then took the mean for all patients included. Ahonen 1978 reported placebo values averaged over two placebo arms.

The night-time symptom scores could not be combined because the Ahonen study measured only dyspnoea and the Wheeler study gave an overall measure of cough, breathlessness and wheeze; Salorinne 1988 gave no standard deviations, although it measured cough and dyspnoea separately. Thus there was only one symptom score outcome for which data could be pooled - daytime dyspnoea. In order to use the generic inverse variance method, we calculated the interaction parameter, ρ, for the Wheeler study (ρ=0.817) and used this in the Ahonen study to impute the standard error. Salorinne 1988 gave no standard deviations so for each arm we used the mean of the standard deviations from Ahonen 1978 and Wheeler 1987 and then calculated the standard error for the difference using the Wheeler value of ρ. Although not ideal, we feel that this gives the best representation of the data. This approximation for the Salorinne 1988 was examined by a sensitivity analysis and it was found that the addition of the Salorinne 1988 made little difference to the summary statistics.

The results are summarised in additional Table 2; Table 3; Table 4
Daytime dyspnoea: the summary statistics were: WMD -0.09 (95%CI -0.14, -0.04, 3 studies, 59 patients), i.e. the anticholinergic agent gave more favourable symptom scores than the placebo, and the result was statistically significant. There was little heterogeneity (I^2=0%, p =0.45). This corresponds to a 15% decrease in symptom score over placebo. The other symptom scores could not be pooled and only the Taytard study gave a statistically significant result on its own - which was in favour of the anticholinergic agent. Otherwise the results of single studies indicated that, relative to placebo, the anticholinergic showed some improvement in

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daytime cough and night-time dyspnoea, but some worsening in night-time cough.

In addition, Kreisman 1981 reported that patients coughed more on the ipratropium regimes. Tormey 1995 reported that there were no significant differences in symptom scores (unspecified) between placebo and oxitropium bromide over 28 days; and Vaughan 1988 reported that 'total symptom scores' (cough and wheeze) were no different when using nebulised atropine methonitrate compared with placebo over 2 weeks.

2. PEF measurements (Table 3)
Four studies reported daily peak flow measurements, but one of these gave no p-values or standard deviations; the Ahonen and Salorinne studies reported some p-values, and IPD were given for the Wheeler 1987. ρ values for this study (although not used) were respectively 0.919 and 0.911 for the am and pm peak flows. The outcomes were daily peak flow rates measured before and after the bronchodilator dose.

Summary statistics were calculated using the generic inverse variance method. The Ahonen study gave an upper bound for the p-value for the ipratropium-placebo comparison, which allowed calculation of the standard error for the mean of the difference (AC - placebo). The Salorinne study gave an upper bound for the p-value for the evening PEF, but for the morning value the standard deviation for the Wheeler study was taken and the standard error calculated from this (Ahonen 1978 was not used for this purpose because of a discrepancy between the graph and table values).

The following results were found:
a) Morning PEF
The PEF daily average weighted mean difference (WMD) was:
WMD =14.38 litres/min (95%CI 7.69, 21.08; 3 studies, 59 patients) i.e., statistically significantly higher for the anticholinergic; this showed some heterogeneity (p = 0.22, I^2 = 34%) and corresponds to an increase of about 7% over placebo. We tested the assumptions for Salorinne 1988 using a sensitivity analysis, and found that the heterogeneity was removed (p=0.65, I^2 = 0%), but there was little effect on the WMD (16.26 L/min; 95%CI 9.21, 23.31).
Post-bronchodilator morning PEF measurements were available for 2 studies, and were taken 2 and 3h after the dose. The WMD was 34.91 litres/minute (95%CI 20.13, 49.70, 2 studies, 31 patients), a statistically significant difference, corresponding to an increase of 9% over placebo.

b) Evening PEF
The evening (about 10 pm) PEF daily average WMD was: 23.48 L/m (95%CI 12.32, 34.65, 3 studies, 60 patients) i.e., statistically significantly larger peak flow rate for the anticholinergic, but there was heterogeneity (p=0.01, I^2=78%). The WMD represents an 7% increase over placebo.
Post-bronchodilator evening PEF measurements were available only for Salorinne 1988: WMD 23.94 L/m (95%CI 5.20, 42.68, 1 study, 18 patients), giving a statistically significant increase of 7%.

Vaughan 1988 used nebulised atropine methonitrate over 2 weeks, and reported that the peak flow measurements were not different between placebo and Atropine methonitrate either in the morning or at 5pm.

3. Use of rescue medication (Table 4)
Three studies reported that they recorded the use of rescue medication, but relative numbers of patients were given only in the Wheeler 1987. Taytard 1984 (3 weeks) reported that the 'mean consumption of salbutamol was essentially identical for placebo and oxitropium bromide' and Salorinne 1988 (1 week) reported that 'the number of additional treatments did not differ between the various treatments'. For the Wheeler 1987 (4 weeks) 23 of 30 patients taking oxitropium and 25/30 taking placebo required rescue medication during the day (OR 0.66 ; 95%CI 0.18, 2.36 - not statistically significant) and the corresponding night time ratios were 15/30 and 19/30 (OR 0.58 ;95%CI 0.21, 1.62).

4. Patient preference (Table 4)
The number of patients preferring anticholinergic was compared with the number preferring placebo in two studies (Salorinne 1988 and Wheeler 1987) - in the latter case , some patients did not have a preference. In the former study patients chose between 40 µg, 200 µg (inhaled) and 200 µg powder ipratropium bromide as well as placebo (which was a powder); the odds ratio for patient preference was: OR 1.64 (95%CI 0.68, 3.94) i.e. non-significantly in favour of the anticholinergic, with little heterogeneity.

5. Drug-related withdrawal (Table 4)
Two studies gave data on the number of asthma patients withdrawing while taking one of the study drugs. The pooled odds ratio was 0.70 (95%CI 0.13, 3.72) - non significantly in favour of anticholinergic, with some heterogeneity.

6. Adverse effects (Table 5)
Six studies gave some information on adverse effects, but of these Kreisman 1981 and Bellia 1988 only gave a descriptive account, and Ahonen 1978 and Salorinne 1988 reported the number of effects or symptom scores, rather than the number of patients with those effects. Kreisman 1981 stated that the side effects were equally reported, and Bellia 1988 reported that no significant side effects were recorded for oxitropium bromide. For the studies that gave numerical data, individual side effects (e.g. mouth dryness) gave similar results for anticholinergic and placebo, with no statistically significant differences observed at the lower doses used, and for overall side effects, the pooled odds ratio was OR 1.87 (95%CI 0.51, 6.81) - not statistically significant.

B) Combination of anticholinergic and ß2 -agonist versus ß2 -agonist alone

There were 9 trials comparing the combination of anticholinergic and ß2-agonist with ß2 -agonist alone. One of the studies (Tammivaara 1993) used oral CR terbutaline as the ß2 -agonist and we analysed this study separately because of the different pharmacokinetics. One study could not be analysed because it did not give any results and 2 studies did not report standard deviations or P-values. The authors of these studies were contacted and some offered data, but to date these had not arrived. Additional information, was however provided by Wolstenholme 1989 and Philip-Joet 1990. This left only six studies that provided sufficient data for analysis of the continuous outcomes, and six studies gave data for the dichotomous outcomes. For all studies the final values of the outcome measures were used, rather than adopting change scores.

In Haahtela 1991, the peak flows and symptom scores were reported as a daily average for weeks 1-4 and, separately, 9-12 weeks; we used the mean of 1-4 and 9-12 weeks as a measure of the

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response. Philip-Joet 1990 reported the weekly mean peak flows and standard deviations for weeks 1 to 8. However, many patients dropped out (48/196 overall) and the PEF results showed such a large number of missing patients (e.g., at 8 weeks, 37 of 101 from the combination arm and 40 of 95 from the ß2 -agonist arm) that we decided to include only the results for the first week as being the least confounded (still 11/101 and 12/95 missing).

Unlike the anticholinergic-placebo comparison, these studies differed from one another in various important ways, making pooling questionable. Firstly, there were differences in study duration, but we decided it was reasonable to combine all durations.

Secondly, there was a mixture of study designs, 2 parallel and 7 crossover trials. It was not possible to analyse the crossover studies using the generic inverse variance method because none reported IPD or P-values, and consequently we had to analyse the crossover studies as if they were parallel studies, which meant that the crossover and (true) parallel studies could not be combined in an analysis.

Thirdly, the ß2 -agonist in the two arms differed in both composition and dose. We decided to treat all the ß2 -agonists as having the same equivalence and recorded the difference in doses in a single variable, the ratio of ß2 -agonist in the combination arm to that in the single arm. Two ratios were analysed 1:1 and 1:2 - the latter can be considered as the *substitution* of anticholinergic for some of the ß2 -agonist in the single arm and the former as the *addition* of anticholinergic to the same level of ß2 -agonist. Thus the breakdown of studies is:

- Substitution of anticholinergic for ß2 -agonist (ratio 1:2 combination ß2 -agonist:single ß2 -agonist): Haahtela 1991, two comparisons (Berodual versus 200 µg salbutamol and Duovent versus 400 µg salbutamol) and Philip-Joet 1990
- Addition of anticholinergic to ß2 -agonist (ratio 1:1): Haahtela 1991 (Duovent versus 200 µg salbutamol), all other studies

The differing types of design and interventions meant that, in general, the study data could not be pooled, and the results are shown in additional tables 6-9. Where there was more than one similar study, the results were combined and the summary statistics reported in the additional table and shown in a forest plot. Otherwise the results in the table are for single studies.

1. Symptom scores (Table 6)
Daily symptom scores were measured in six studies and all used a scale of 0-3. Mazzei 1985 only reported symptom scores at a clinic visit, not daily (thus not meeting our criteria). No results were reported for 2 studies and no standard deviations were given for one. Macaluso 1986 reported graphically a distribution of symptom scores, but the exact nature of the representation was unclear; despite these uncertainties, we calculated a mean symptom score and standard deviation from these data. Of the remaining studies, one reported the weekly symptom scores and two reported daily scores: the former values were adjusted to daily scores.
The only possible studies that were sufficiently similar to be combined were Macaluso 1986 and Wolstenholme 1989, but in view of the uncertainties about the Macaluso 1986 symptom score data, we decided to analyse these as single studies.
Generally there is no evidence, from the single studies analysed, for a significant difference in any symptom score between the combination and the single arm, regardless of the trial design, time duration or ratio of ß2 -agonist.
The authors of Haahtela 1991 also stated that, for all symptom score measurements, there were no significant differences among any of the 4 regimens, even when the subgroup of more severe patients was analysed. The authors of Macaluso 1986 stated that there was a statistically significant difference in favour of Duovent for daytime dyspnoea, but our analysis of their available data did not confirm this. The Pierce study stated that 'symptom score cards (measuring daytime and nocturnal dyspnoea, wheeze and cough) failed to reveal any significant differences between the combination and either drug alone'. Waite 1987 stated that 'symptom scores recorded in the morning and evening for wheeze, cough and restrictions in activity showed no significant differences between the two treatments'.

2. Lung function measurements (Table 7)
Daily peak flow measurements were measured in 5 studies. An additional study, Pierce 1982 measured daily mean flow using an airflowmeter so this study was analysed separately. Rebuck 1983 reported no data (but stated that there was a similar improvement for each arm) and Haahtela 1991 gave no standard deviations for the daily peak flow measurement.

The different characteristics of the studies (parallel/crossover, PEF/flow and oral/inhaled beta-agonist) meant that no studies were sufficiently similar to be combined. However, the general trend is that there is very little difference between interventions with no single study achieving statistical significance. Haahtela 1991 also reported that 'analysis did not reveal any significant differences, even when the subgroup of more severe patients was analysed'.
Post-bronchodilator measurements were made for three studies and were taken after 20m, 30m and 1h. There was little difference between the interventions.

3. Patient preference (Table 8)
Only two crossover studies reported the preference of the patients (Tammivaara 1993; Wolstenholme 1989), but the former used oral beta-agonist. In Tammivaara 1993 the patients preferred the combination, but in Wolstenholme 1989 the reverse was the case; neither study showed statistical significance. Rebuck 1983 reported no significant difference in patient preference. Macaluso 1986 reported that the 'patient's opinion was more favourable with Duovent than salbutamol', but this may have been because the patients received respectively 3 and 4 administrations of the test drug.

4. Drug-related withdrawal (Table 8)
Four studies reported the number of patients withdrawing while taking one of the study drugs, but only 2 studies could be combined. The pooled odds ratio for the parallel study substitutional-anticholinergic was: 1.40 (95%CI 0.69, 2.84, 2, studies, using the Berodual-salbutamol comparison in Haahtela 1991, 161 patients), i.e. in favour of the ß2 -agonist, but not statistically significant and with some heterogeneity (p=0.22, I^2=32%).
Overall, there were fewer withdrawals from the ß2 -agonist arm, regardless of the time duration, ratio of ß2 -agonist levels and trial design, but no result was statistically significant. The exception was the oral beta-agonist crossover study, Tammivaara 1993, which

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showed fewer withdrawals for the combination (not statistically significant).

5. Number of patients with exacerbations (Table 8)
Two studies reported the number of patients with exacerbations (or worsening), Philip-Joet 1990 and Tammivaara 1993, the former shows fewer patients with exacerbations for the ß2 -agonist arm and the latter shows the reverse, neither is statistically significant, and the results have not been combined because of the use of the oral ß2 -agonist in Tammivaara 1993.

6. Adverse effects (Table 9)
Six studies gave some information on adverse effects, but of these Haahtela 1991 and Mazzei 1985 reported the number of effects or symptom scores, rather than the number of patients with those effects and Philip-Joet 1990 had too much missing data to be included without confounding. Two studies gave a descriptive account only: Wolstenholme 1989 stated that there was no difference in side effects reported for the two periods and Macaluso 1986 found that side effects (tremor, palpitations and tachycardia) occurred in negligible percentages for both treatments. The remaining studies were not pooled because they had different ratios of ß2 -agonist and different designs (see additional table 9). Generally, there is little evidence for a difference in adverse effects between the combination and single arm ß2 -agonist, and no result is statistically significant.

DISCUSSION

As a chronic disease, with no known cure, the accepted goals of management in chronic asthma are to minimise the adverse impact of the disease on the patient's physical and mental well-being, to prevent long term damage with fixed airflow obstruction and to reduce mortality. In the majority of patients treatment is therefore directed at improving physiological end-points and patient-perceived physical and mental health. Although anticholinergics are frequently used in patients with more severe forms of asthma, the evidence justifying its use remains limited. Both short-term and long-term anticholinergics are of some benefit in patients with COPD, their role in asthma is less clearly defined. The recent BTS guidelines include anticholinergics as one of the options for short term bronchodilator relief at Step 1, and in the management of acute severe asthma (BTS/SIGN 2004). They receive no mention as regular add-on treatment for use in combination with inhaled steroids and long-acting ß2 -agonists.

The acute bronchodilator effect of an anticholinergic is usually demonstrated by making physiological measurements before and after inhaling the drug. The most commonly used measurements include the FEV1 and vital capacity, although other end-points such as the ability to modify bronchial challenge tests have also been widely studied. It is on this basis that anticholinergics are sometimes used to relieve symptoms although the majority of acute studies do not include symptom scores as part of their evaluation.

This review was specifically directed at examining the role of anticholinergics used on a regular basis, especially when used as an adjunct to a ß2 -agonist. The comparison between a regular anticholinergic and placebo is of limited clinical relevance but was undertaken to determine whether there was a detectable subjective or objective improvement. Despite the limited number of studies, anticholinergic agents resulted in more favourable symptom scores particularly in respect of daytime dyspnoea. Daily peak flow measurements also showed a statistically significant improvement for the anticholinergic. However, the clinical significance is small and in terms of peak flow measurements equates to approximately a 7% increase over placebo. Secondary outcome measures such as use of rescue medication, patient preference and drug-related withdrawals showed no significant differences although these conclusions were based on very limited objective data. The same reservations applied to adverse effects where again there was no evidence for a systematic difference between anticholinergic and placebo.

The second part of the review is more clinically relevant and addresses the question as to whether a combination of anticholinergic plus ß2 -agonist confers significant advantage when compared with ß2 -agonist alone. There was no evidence in respect of primary outcome measures, symptom scores or peak flow rates of any significant differences between the two regimes. Similarly, there were no significant benefits shown in respect of secondary outcome measures. There are however major reservations with respect to the quality of the information from which these conclusions are drawn. The total number of studies suitable for analysis was small and involved limited numbers of patients. A number of studies were excluded from analysis because of methodological flaws, incomplete data or because they included patients with COPD. Even for those studies included, differences in methodology meant that they could not easily be combined. The main differences which might affect analysis have already been identified but merit re-iteration.

Patient characteristics

All the included studies define the patients as having asthma or reversible airflow obstruction. A 15% improvement of FEV1 after an inhaled ß2 -agonist was the most frequently used physiological test although some studies included spontaneous variability. Criteria as defined by the American Thoracic Society were used in a significant number of studies. Patient characteristics varied considerably both between and within studies. There was a wide range of patient age, variable numbers of atopic patients and variable numbers of smokers with symptoms of chronic bronchitis. Despite this heterogeneity, it seems likely that most studies focused on patients at the more reversible end of the spectrum of airway disease.

Severity of the disease

Again there was considerable heterogeneity both between and within studies with patients ranging from having mild to severe asthma. Defining criteria were often not stated. Factors taken into consideration in trying to assess the severity of the disease included patient symptoms, baseline lung function and maintenance treatment. In addition, studies were only included if the asthma was regarded as being "stable". It is theoretically possible that patients with more severe disease might derive greater symptomatic benefit from small improvements in lung function. There were insufficient data to provide sub-group analysis.

Maintenance treatment

Once again there were significant variations both between and within studies. These ranged from low maintenance treatment to patients who were on regular treatment with theophylline, inhaled or oral steroids. Additional ß2 -agonists used as rescue treatment

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were included in a number of studies and used as a secondary outcome measure.

Methodological differences: different drug combinations

There were significant differences between studies with respect to the different drug regimes studied. These included a variety of anticholinergics using different doses. The ß2 -agonist used also varied and in some studies the comparator ß2 -agonist was different from that used in the combination.

Methodological differences: outcome measures

Although diary cards were used in a number of studies, data was often incomplete and the scoring system varied. Studies using regular peak flow measurements were similar although the timing of the measurements with respect to the preceding dose may have influenced the outcome measurement.

The failure to demonstrate any subjective or objective improvement by the addition of anticholinergic to a regular ß2 -agonist may have various explanations which merit further consideration. As indicated, it may simply be that the studies are insufficiently powered to detect what may be small but significant differences. Patient selection is also likely to be critically important. Patients with mild disease will have little potential for further improvement over and above that achieved by inhaled steroids and ß2 -agonists. Conversely, patients with more intractable disease may well have airway obstruction with only limited reversibility. There were insufficient data to permit subgroup analyses, looking specifically at defined patient groups.

None of the studies specifically identified those patients whose asthma was inadequately controlled despite being on regular ß2 -agonists and inhaled steroids. In part this reflects the fact that the studies analysed have been undertaken over the past 20 years and guidelines have evolved during this period.

Overall this review provides no justification for routinely introducing anticholinergics as part of add-on treatment for patients whose asthma is not well controlled on standard therapies. This does not exclude the possibility that there may be a sub-group of patients who derive some benefit and a trial of treatment in individual patients may still be justified. The review does highlight the need for studies of sufficient power using standardised criteria and methodology in order to answer specific questions. It is unlikely that such studies will be undertaken using the currently available short term anticholinergics. The role of long term anticholinergics such as tiotropium bromide has yet to be established in patients with asthma and any future trials might draw on the messages derived from this review.

AUTHORS' CONCLUSIONS

Implications for practice

Inhaled anticholinergics have a bronchodilator effect in patients with asthma. In clinical and physiological terms this effect is small. The addition of anticholinergics to regular inhaled bronchodilators has not been shown to confer significant benefits, so the current evidence does not justify their routine use. The study does not exclude the fact that there may be sub-groups of patients who derive some symptomatic benefit.

Implications for research

Future studies need to be sufficiently powered to answer specific questions, which need to be clearly formulated. The role of long term anticholinergics in the management of asthma is a potential case in point. Patient characteristics need to be clearly defined and particular focus directed at those patients with more severe disease that is inadequately controlled on a combination of inhaled steroids and long acting ß2 -agonists. In addition, outcome measures need to be standardised and to include patient-derived symptom scores and quality of life data in addition to physiological measurements.

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* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

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

Ahonen 1978

Methods	Crossover design; each phase 4 days. All patients completed the study correctly. Said to be double blind, but no details. No other concurrent asthma medication.
Participants	Inclusion criteria: patients had asthma - diagnosis according to Ciba Guest symposium criteria; stable asthma medication. Patient details: 13 participants (M/F 7/6); mean age 37; mild asthma (severity homogeneous); 5/8 atopy; no information on concurrent COPD.
Interventions	5 interventions: ipratropium bromide 40 and 80µg, fenoterol 400µg, placebo (twice) by pressurised inhaler; all interventions 5 times per day (01.00, 07.00, 13.00, 19.00, 22.00h).
Outcomes	Daily PEF (measured before dose and at 10am; 7am and 10pm (pre-bronchodilator) and 10am (3h post-bronchodilator) data used in analysis. Daily symptom scores (day and night). Adverse effects.
Notes	Placebo is the mean of 2 periods. The graph recording PEFR did not agree with the table for the SEM - likely that table incorrect (see text).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Ashutosh 1980

Methods	Crossover design, each phase 7 days.
Participants	
Interventions	atropine sulphate and isoprenaline.
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Bellia 1988

Methods	Crossover design; each phase 7 days. All patients completed the study correctly. Said to be double blind, with placebos used, but no other details. Not double blind for dose comparison. Concurrent asthma medication - sodium cromoglycate.

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Bellia 1988 *(Continued)*

Participants	Inclusion criteria: patients had asthma - diagnosis according to ACCP-ATS criteria; stable asthma medication; recent nocturnal asthma. Exclusions: CV, ocular & genito-urinary diseases; history of intolerance to theophylline or anti-muscarinic agents. Patient details: 12 participants; age 18-60; mild asthma; no information on concurrent COPD or atopy.
Interventions	2 interventions: oxitropium bromide 400/600µg, placebo by MDI; all interventions t.i.d. (unclear when).
Outcomes	% change daily PEF(morning/ max PEF; not analysed), symptom scores (night or morning - no numbers); % predicted FEV1 at end of period (not analysed).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Chapman 1983

Methods	See Rebuck 1983
Participants	
Interventions	
Outcomes	
Notes	Same trial as Rebuck 1983

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Coe 1986

Methods	Crossover design; each phase 14 days. All patients completed the study correctly. Said to be double blind (vs placebo), but no details. Concurrent asthma medication unclear, but none had oral steroids or anticholinergics; 200µg salbutamol given each morning and evening as part of test procedure.
Participants	Inclusion criteria: patients had documented nocturnal asthma - difference of >20% in PEFR between evening and morning readings; nocturnal asthma. Patient details: 18 participants (M/F 7/11); age 18-76; mild-severe asthma (heterogeneous severity); 10:8 atopy; no information on concurrent COPD.
Interventions	3 interventions: oxitropium bromide 200 and 400µg, placebo ; all interventions taken once at night.

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Coe 1986 *(Continued)*

Outcomes	Daily PEF, morning and evening (no results or SDs); difference in PEFR (evening-morning) - not analysed; rescue medication - no results; daily symptom scores - no data.
Notes	200µg salbutamol given each morning and evening as part of test procedure.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Dompeling 1992

Methods	See van Schayck 1991a
Participants	
Interventions	
Outcomes	
Notes	This comparison not analysed, so details not extracted

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Dompeling 1993

Methods	See van Schayck 1991a
Participants	
Interventions	
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

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Haahtela 1991

Methods	Parallel design; duration 12 weeks. Overall, 24/120 patients withdrew from study. Said to be double blind, but no details. Concurrent asthma medication: inhaled steroids, cromoglycate, methylxanthines; none had oral steroids; inhaled bronchodilators withdrawn.
Participants	Inclusion criteria: patients had asthma - reversible (>15% increase in FEV1) after beta-agonist. Exclusions: patients taking oral steroids. Patient details: 120 participants, but 96 completed - patient details for 96: M/F 35/61; age 46 (mean); moderate asthma (homogeneous severity); 56:40 atopy; no information on concurrent COPD (but all non-smokers).
Interventions	4 interventions: Berodual, Duovent, Fenoterol 200 and 400µg ; all interventions q.i.d. (07.00 and 19.00h and two other unspecified times).
Outcomes	PEF (daily) for 1-4weeks and 8-12w ; symptom scores ; extra inhaler use (not number of patients); heart rate, side effects score; number of patient withdrawals; no standard deviations/p values for continuous outcomes.
Notes	Large baseline differences for symptom scores.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Kreisman 1981

Methods	Crossover design; each phase 14 days. 3/15 patients withdrew from study. Said to be double blind (vs placebo), but no other details. Concurrent asthma medication: theophylline (study drug), maintenance beta-agonists and steroids kept constant.
Participants	Inclusion criteria: patients had asthma - diagnosis according to ATS criteria; stable asthma medication. Exclusions: no history of chronic bronchitis, cardiac, renal or hepatic disease. Patient details: 15 participants (M/F 7/5); age 21-54 (mean 34); mild-moderate asthma; atopy not stated. No concurrent COPD.
Interventions	4 interventions: ipratropium bromide 40µg and placebo, each with/without theophylline; all interventions q.i.d. (unclear when).
Outcomes	FEV1 at 1 and 2 weeks; symptom scores (wheeze breathlessness, chest tightness, - no numbers); side effects only in words.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Laitinen 1979

Methods	Crossover design; 1st phase 3 weeks, 2nd phase 2 weeks.

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Laitinen 1979 *(Continued)*

Participants	
Interventions	Ipratropium bromide 80µg and salbutamol 400µg; both interventions q.i.d.
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Light 1977

Methods	Crossover design; each phase 2 weeks. All patients completed the study correctly. Said to be double blind (vs placebo), but no other details. Concurrent asthma medication various, some had oral steroids.
Participants	Inclusion criteria: patients had asthma - reversible after isoprenaline and atropine; stable asthma medication; continuous symptoms for 3 months. Patient details: 6 participants; age 28-42 (mean 35); moderate asthma (heterogeneous severity).
Interventions	2 interventions: oral atropine sulphate 5mg and placebo; both interventions q.i.d.
Outcomes	FEV1, side effects.
Notes	Oral atropine - not included in analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Investigators not blinded to randomisation sequence (Cochrane Grade C)

Lightbody 1977

Methods	See Lightbody 1978
Participants	
Interventions	
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Lightbody 1977 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Lightbody 1978

Methods	Crossover design; each phase 3 days.
Participants	
Interventions	2 interventions: Ipratropium bromide 40µg and Salbutamol 200µg, q.i.d.
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Macaluso 1986

Methods	Crossover design; each phase 2 weeks. All patients completed the study. Said to be double blind, but could not be because of different number of doses (Duovent 3; Salbutamol 4 per day). Concurrent asthma medication: all patients received aminophylline (long acting), no further details; no information on withdrawal of bronchodilators.
Participants	Inclusion criteria: patients had "partially reversible chronic bronchospasm". Patient details: 15 participants (M/F 7/8); age 32-65; no information on severity of asthma, atopy or concurrent COPD.
Interventions	2 interventions: Duovent t.i.d. (times not stated), Salbutamol 200µg q.i.d (times not stated).
Outcomes	Daily symptom scores (but unclear what is reported; standard deviation calculated from graph), use of extra aerosol.
Notes	Unblinded study - different number of inhalations; unclear reporting of results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

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Mazzei 1985

Methods	Crossover design; each phase 2 weeks. All patients completed the study. Said to be 'blind', but no details. Concurrent asthma medication: steroids (unspecified), methylxanthines; usual bronchodilators withdrawn.
Participants	Inclusion criteria: patients had asthma - diagnosis according to ATS criteria; exclusions: serious cardiac pathology, arrhymias, hepatic/renal failure, COPD, other pulmonary diseases, neoplasias, pregnancy. Patient details: 20 participants (M/F 7/13); age 16-72 (mean 46); moderate asthma (heterogeneous severity); atopy not stated; no concurrent COPD.
Interventions	2 interventions: Berodual, Salbutamol 200µg; all interventions t.i.d. (every 8h, unclear when).
Outcomes	FEV1, %FEV1/FVC, FVC, symptom scores at 1 and 2 weeks; side effects; patient & physician assessment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

O'Driscoll 1990

Methods	Crossover design; each phase 1 month.
Participants	
Interventions	2 interventions: Ipratropium bromide 500µg (nebuliser) and salbutamol 5mg (neb); q.i.d.
Outcomes	
Notes	This comparison not analysed, so details not extracted. Different trial to O'Driscoll 1992.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

O'Driscoll 1992

Methods	Crossover design; each phase 1 month.
Participants	
Interventions	Ipratropium bromide 500µg (nebuliser) and salbutamol 5mg (neb); q.i.d.
Outcomes	

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O'Driscoll 1992 *(Continued)*

Notes	This comparison not analysed, so details not extracted. Different trial to O'Driscoll 1990.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Pavia 1987

Methods	As Pavia 1989
Participants	
Interventions	
Outcomes	
Notes	Same trial as Pavia 1989

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Pavia 1989

Methods	Crossover design; each phase 28 days. 1/11 asthma patients withdrew from study. Said to be double blind (vs placebo), but some patients could distinguish the OxBr by its taste, no other details. Concurrent asthma medication: no oral steroids; inhaled steroids and oral bronchodilators.
Participants	Inclusion criteria: patients had asthma - reversible (>15% increase in FEV1) after beta-agonist; stable asthma medication. Patient details: 22 participants (11 with asthma(M/F for 10: 4/6), 11 with bronchitis - not separated for most outcomes); age (asthmatics) mean 59; moderate asthma; atopy not stated.
Interventions	2 interventions: oxitropium bromide 200µg and placebo; both interventions t.i.d. (on rising, early pm and on retiring).
Outcomes	PEF (am, early pm, retiring - paired difference +SEM for am); FEV1 at 4 weeks; rescue medication (not for placebo) - all these for mixed asthma/COPD; number of dropouts (asthma only).
Notes	Most outcomes for athma and COPD combined; 1 author worked for Boehringer Ingelheim.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

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Petersen 1979

Methods	Crossover design; each phase 3 days
Participants	
Interventions	2 interventions: ipratropium bromide 125µg (nebuliser) and terbutaline 5mg (neb); q.i.d.
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Philip-Joet 1990

Methods	Parallel design; duration 8 weeks. Overall, 48/196 patients withdrew from study, but 77/196 were not analysed at 8w. "A double blind design was not used"; not stated if outcome assessor blinded. Concurrent asthma medication: steroids (unspecified), methylxanthines; inhaled bronchodilators withdrawn.
Participants	Inclusion criteria: patients had asthma - diagnosis according to ATS criteria and >15% reversibility after beta-agonist; exclusions: pregnancy, respiratory failure, diabetes, contraindications to study drugs. Patient details: 196 participants (M/F group B 56% M; group S 57% M); age: Group B 45 (mean), Group S 48; moderate asthma (fairly heterogeneous severity); atopy not stated; no information on concurrent COPD.
Interventions	2 interventions: Berodual, Salbutamol 200µg; both interventions q.i.d. (times not stated).
Outcomes	PEF (daily) over 7 days (1,2,3,4,5,6,7,8w), symptom scores (not daily), FEV1, PEFR, FVC at 30 and 60 days; adverse effects (but too much data missing); standard deviations.
Notes	Many withdrawals and missing patient data, therefore only used week 1 data for PEFR; concealment: numbered boxes, serially allocated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Investigators blinde to randomisation sequence (Cochrane Grade A)

Pierce 1982

Methods	Crossover design; each phase 4 weeks. 1/10 patients not analysed because of changes in medication. Said to be double blind, with placebo inhalers, but no other details. Concurrent asthma medication: theophylline & steroids (oral/inhaled); withdrawal of inhaled bronchodilators unclear.

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Pierce 1982 *(Continued)*

Participants	Inclusion criteria: patients had asthma - reversibility >25% after beta-agonist. Patient details: 10 participants (all male); age 52-67 (mean 59); moderate asthma; 7/10 atopy; 8/10 concurrent COPD.
Interventions	3 interventions: ipratropium bromide (40µg)+terbutaline (500µg), terbutaline (500µg), ipratropium bromide (40µg); all interventions q.i.d. (times not clear).
Outcomes	Flow - not PEF - (daily) over 4weeks; symptom scores (no results) over 4 weeks; FEV1 at 2 & 4 weeks (mean); adverse effects.
Notes	Partial allocation concealment - opaque sealed envelopes opened after patient enrollment (not serially numbered).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Rebuck 1983

Methods	Crossover design; each phase 30 days. 4/22 patients withdrawn and 17 patients' results were analysed. Said to be double blind, with placebos and the code was not broken until the study was complete. Concurrent asthma medication: steroids (oral and inhaled), cromoglycate, theophylline (study drug in all arms); withdrawal of bronchodilators unclear.
Participants	Inclusion criteria: patients had asthma - diagnosis according to ATS criteria and reversibility >15% after beta-agonist; all patients clinically stable for >1 month. Exclusions: cough and sputum during clinically stable periods, recent respiratory tract infections, cardiac, hepatic, renal, metabolic disease, and others; hypersensitivity to atropinic compounds. Patient details: 22 participants (M/F 9/13); age 17-75 (mean for completers 47); moderate asthma (heterogeneous severity); 13/22 atopy; unclear if concurrent COPD.
Interventions	3 interventions: ipratropium bromide (40µg)+fenoterol (200µg) - may be separate inhalers, fenoterol (200µg), ipratropium bromide (40µg); all interventions q.i.d. (times not clear) and all arms had oral theophylline (200mg) q.i.d.
Outcomes	PEF (daily) over 30d (no results); FEV1 at 30days; patient preference and number of exacerbations (descriptive); adverse effects.
Notes	Authors unable to provide any more data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Ruffin 1990

Methods	Crossover design; phase length unclear - could be 8 weeks. 5/21 patients withdrew from study. Said to be double blind (vs placebo), but no other details. Concurrent medication: not stated.

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Ruffin 1990 *(Continued)*

Participants	Inclusion criteria: patients had asthma - diagnosis reasons not stated. Patient details: 16 remaining participants (M/F 9/7); mean age 56; mild asthma; no information about atopy or concurrent COPD.
Interventions	2 interventions: oxitropium bromide 200µg and placebo; both interventions t.i.d. (not stated when).
Outcomes	PEF (am and pm, probably at end of period); FEV1 at end of period.
Notes	Abstract; funded by Boehringer Ingelheim.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Salorinne 1988

Methods	Crossover design; each phase 7 days. All patients completed the study correctly. Not blinded for the comparison IB (40) vs placebo (powder); no details re outcome assessor. Concurrent medication: 5/18 had oral steroids; 17 had theophylline.
Participants	Inclusion criteria: patients had asthma - improvement in FEV1 of 16-100% (not stated how). Patient details: 18 participants (M/F 10/8); age 22-70 (mean 48); moderate-severe asthma; atopy 5/18, no information on concurrent COPD.
Interventions	4 interventions: ipratropium bromide 40 and 200µg (aerosol) and 200µg powder, and placebo powder ; all interventions q.i.d (08.00, 12.00, 18.00, 22.00h).
Outcomes	PEF (8, 10am, midday, 2, 6, 8, 10pm & midnight); Symptom scores (dyspnoea day and night, cough); rescue medication (words); patient preference.
Notes	Placebo was powder.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Storms 1986

Methods	Parallel design; 90 days.
Participants	
Interventions	2 interventions: ipratropium bromide 40µg and metaproterenol 1500µg; q i.d
Outcomes	
Notes	This comparison not analysed, so details not extracted.

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Storms 1986 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Tammivaara 1993

Methods	Crossover design; each phase 3 weeks. 7/28 patients withdrawn. Said to be double blind and double dummy, but no other details. Concurrent medication: theophylline, none had steroids; patients allowed to use inhaled bronchodilators when needed (NB study drug oral).
Participants	Inclusion criteria: patients had asthma - nocturnal decline in PEFR of at least 20%. Patient details: 28 participants (M/F 10/18); age 18-59 (mean 39); moderate asthma (homogeneous severity); no information on atopy or concurrent COPD.
Interventions	3 interventions: ipratropium bromide 40µg+oral controlled-release terbutaline (10mg), oral CR terbutaline (10mg)+aerosol placebo and 200µg powder, and ipratropium bromide 40µg+oral placebo; aerosols q.i.d (08.00, 12.00, 16.00, 20.00h); oral tablets b.i.d. (08.00 and 20.00h).
Outcomes	PEF (daily), symptom scores over last 2 weeks of treatment period (standard deviations); number of patients with exacerbations, number needing rescue medications (words), patient preference, adverse effects.
Notes	Oral CR terbutaline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Taylor 1986

Methods	Crossover design; each phase 4 weeks. 8/23 (of all patients) failed to complete the study. Double blind (identical inhalers), but no other details. Concurrent asthma medication: mixed asthma/COPD study - medication not distinguished for asthma (3/all patients had oral steroids, 7 had aminophylline).
Participants	Inclusion criteria: patients had asthma - reversibility of >20% with conventional bronchodilators; stable asthma medication implied. Patient details: 23 participants (asthma 7, COPD 8, no details 8) (overall M/F 12/3); asthma & COPD age 27-71 (median 60); mild-severe asthma (severity heterogeneous); no information on concurrent COPD.
Interventions	2 interventions: ipratropium bromide 200µg and placebo; all interventions t.i.d. (not stated when).
Outcomes	Daily symptom scores (breathlessness, cough, wheeze), PEFR and FEV1 at end of period, number of patients with exacerabations (all mixed asthma/COPD); treatment related withdrawals (mixed asthma/COPD)
Notes	Mixed asthma/COPD mainly; Boehringer Ingelheim financial support.

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Taylor 1986 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Taytard 1984

Methods	Crossover design, but analysed as 1st period only; each phase 21 days. All patients completed the study (although there is no patient number 2). Said to be double blind (with identical treatments), but no details about the assessor. Concurrent asthma medication: no oral or inhaled steroids, no regular treatment but 8 had theophylline for relief.
Participants	Inclusion criteria: patients had asthma - diagnosis according to ATS criteria; presenting an allergic diathesis and consulting an allergology unit; perennial asthma. Patient details: 16 participants (M/F 9/7); age 14-48 (mean 31); mild asthma; all atopic, no information on concurrent COPD.
Interventions	2 interventions: oxitropium bromide 200µg and placebo; all interventions t.i.d. (08.00, 14.00, 20.00h).
Outcomes	Clinical scores (IPD); rescue medication; patient rating.
Notes	Significant order effect, so used 1st period data only from IPD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Tormey 1995

Methods	Crossover design; each phase 28 days. Not clear if intention to treat. Said to be double blind (vs placebo), but no other details. Concurrent asthma medication: inhaled steroids.
Participants	Inclusion criteria: patients had asthma - no diagnostic evidence; stable asthma medication implied. Patient details: 12 participants; age not stated; moderate asthma; no information on atopy or concurrent COPD.
Interventions	3 interventions: oxitropium bromide 200µg, salbutamol 200µg and placebo; all interventions t.i.d. (not stated when).
Outcomes	Daily symptom scores (unspecified, words only); FEV1 after 4 weeks.
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement

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Tormey 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

van Schayck 1991a

Methods	Crossover design; each phase 1 year
Participants	
Interventions	4 interventions: ipratropium bromide 40µg q.i.d., salbutamol 400µg q.i.d., ipratropium bromide on demand, salbutamol on demand
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

van Schayck 1991b

Methods	See van Schayck 1991a
Participants	
Interventions	
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

van Schayck 1994

Methods	See van Schayck 1991a
Participants	
Interventions	

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van Schayck 1994 *(Continued)*

Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

van Schayck 1995

Methods	See van Schayck 1991a
Participants	
Interventions	
Outcomes	
Notes	This comparison not analysed, so details not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Vaughan 1988

Methods	Crossover design; each phase 2 weeks. All patients assumed to have completed the study. Double blind study (code in sealed envelope). Concurrent asthma medication: 2 groups of patients - 12 had inhaled & oral steroids; 10 had no steroids.
Participants	Inclusion criteria: patients had asthma - diagnosis ATS criteria and >15% reversibiliy. Patient details: 22 participants; age 44-77; moderate-severe asthma (2 homogeneous groups); no information on atopy or concurrent COPD.
Interventions	2 interventions: atropine methonitrate 2mg and placebo, nebulised; both interventions q.i.d. (unclear when).
Outcomes	FEV at 2 weeks; daily symptom scores and PEF not reported in results (but 'no difference').
Notes	Authors stated that the allocation schedule was sealed in envelopes until the study was completed.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Vaughan 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Waite 1987

Methods	Crossover design; each phase 12 weeks. No information on patient withdrawal nor on concurrent asthma medication; no information on withdrawal of bronchodilators. Said to be double blind, but no details.
Participants	Inclusion criteria: patients had asthma - reversibiliy >15% following beta-agonist. Patient details: 12 participants; no further details.
Interventions	2 interventions: Duovent and salbutamol; no further details.
Outcomes	Daily symptom scores; use of inhaled bronchodilator; PEFR am (only descriptive).
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Wheeler 1987

Methods	Crossover design; each phase 4 weeks. 8/39 failed to complete the study and 9/39 patients' results were not analysed. Double blind (identical, masked containers). Concurrent asthma medication: none had oral steroids; 26/31 had inhaled steroids; 22 had methylxanthines.
Participants	Inclusion criteria: patients had asthma - diagnosis >15% reversibiliy (28 had asthma, 2 had COAD). Patient details: 39 participants; age 17-76; mild-severe asthma (severity heterogeneous); no information on concurrent COPD.
Interventions	2 interventions: oxitropium bromide 200µg, and placebo; all interventions b.i.d. (on rising and on retiring).
Outcomes	Daily PEF (am, pm); Symptom scores (day, breathlessness; night, overall); rescue medication (day & night); patient preference; side effects.
Notes	Boehringer Ingelheim study; IPD given but some patients' diary notes were incomplete; partial concealment (randomisation carried out by BI, but list supplied).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

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Wolstenholme 1989

Methods	Crossover design; each phase 4 weeks. All patients completed the study; 13/17 patients' results analysed for PEF. Said to be double blind and double dummy, but no other details. Concurrent asthma medication: steroids (oral and inhaled), cromoglycate; all bronchodilators withdrawn.
Participants	Inclusion criteria: patients had asthma - >15% reversibiliy following beta-agonist; morning dip of >15% for half of the 2 week run-in. Patient details: 17 participants; age 19-39 (median 25); moderate asthma (severity homogeneous); 100% atopy; no information on concurrent COPD (but all were non-smokers).
Interventions	2 interventions: Duovent+placebo and salbutamol 200µg+placebo separate inhalers; both interventions q.i.d. (times not stated).
Outcomes	PEF (daily), daily symptom scores, FEV1, FVC, PEF (at 2 and 4 weeks), nocturnal waking, patient preference, adverse effects (words); standard deviations given.
Notes	Partial allocation concealment - extra communication from the author stated that sealed envelopes were used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

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

Study	Reason for exclusion
Abboud 1987	Wrong comparison
Adinoff 1998	Wrong comparison
Advenier 1984	Review
Alanko 1983	Short term study <24h - included in short term review
Allen 1980a	Short term study <24h - included in short term review
Allen 1980b	Short term study <24h - included in short term review
Alliott 1972	Short term study <24h - included in short term review
Altounyan 1964	Short term study <24h - included in short term review
Andersen 1986	Short term study <24h - included in short term review
Anderson 1980	Short term study <24h - included in short term review
Anderson 1981	Short term study <24h - included in short term review
Anderson 1983	Short term study <24h - included in short term review
Aquilina 1986	Not randomised

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Study	Reason for exclusion
Ariano 1981	COPD
Baigelman 1977	Short term study <24h - included in short term review
Banos 1983	Short term study <24h - included in short term review
Barber 1975	Short term study <24h - included in short term review
Barber 1977	Short term study <24h - included in short term review
Bauer 1973	Short term study <24h - included in short term review
Beasley 1987	Confounded - patients selected who responded to Ipratropium
Bell 1982	Confounded - additional salbutamol given to both arms on a regular basis
Bellia 1987	Not said to be randomised; no further data from authors
Bernabeu 1987	Wrong comparison
Bezel 1987	Short term study <24h - included in short term review
Bish 1997	Confounded - patients selected who responded to Ipratropium
Bohadana 1980	Short term study <24h - included in short term review
Bonsignore 1986	wrong comparison; patients had ongoing attack
Botts 1985	Short term study <24h - included in short term review
Brady 1979	Short term study <24h - included in short term review
Brand 1992	Long term study - mixed asthma and COPD patients; separate data not available for asthma despite request to authors
Bremner 1992	Short term study <24h - included in short term review
Britton 1988	Short term study <24h - included in short term review
Brom 1985	Not anticholinergic trial
Bruderman 1983	Short term study <24h - included in short term review
Brumby 1980	Long term study - not stated if patients in long term study were randomised; no response from authors
Bryant 1990a	Short term study <24h - included in short term review
Bryant 1990b	Short term study <24h - included in short term review
Bryant 1992	Short term study <24h - included in short term review
Burge 1980	Short term study <24h - included in short term review
Burki 1997	Short term study <24h - included in short term review

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Study	Reason for exclusion
Capel 1964	Short term study <24h - included in short term review
Carpentiere 1986	Wrong comparison Duovent vs placebo
Carratu 1983	Short term study <24h - included in short term review
Casali 1979	Short term study <24h - included in short term review
Catterall 1988	Short term study <24h - included in short term review
Cañete 1991	Asthmatic crisis
Chakravarti 1987	Confounded - patients selected who responded to Ipratropium
Chervinsky 1977	Short term study <24h - included in short term review
Chhabra 2002	Short term study <24h - included in short term review
Chick 1977	Short term study <24h - included in short term review
Chuchalin 1985	Short term study <24h - included in short term review
Ciappi 1986	Short term study <24h - included in short term review
Clauzel 1987	Short term study <24h - included in short term review
Cockcroft 1977	Challenge study
Cox 1984	Not randomised and wrong comparison
Crane 1986a	Short term study <24h - included in short term review
Crane 1986b	Short term study <24h - included in short term review
Crane 1987	Short term study <24h - included in short term review
del Buffalo 1982	Short term study <24h - included in short term review
Donkers 1998	Short term study <24h - included in short term review
Donner 1980	Wrong comparator
Dutt 1990	Study conducted in children
Elwood 1982	Short term study <24h - included in short term review
Emirgil 1975	Short term study <24h - included in short term review
Endoh 1998	Not asthma
Filiz 1994	Not randomised
Firstater 1981	Short term study <24h - included in short term review
Fischbacher 1984	Short term study <24h - included in short term review

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Study	Reason for exclusion
Flint 1983a	Short term study <24h - included in short term review
Flint 1983b	Short term study <24h - included in short term review
Flint 1984	Short term study <24h - included in short term review
Foster 1983	Short term study <24h - included in short term review
Freeman 1992	Challenge study
Frith 1987	Short term study <24h - included in short term review
Gaba 1987	Short term study <24h - included in short term review
Gillies 1987	Challenge study
Ginesu 1983	Short term study <24h - included in short term review
Gotz 1983	Short term study <24h - included in short term review
Grandordy 1988	Short term study <24h - included in short term review
Gross 1975a	Short term study <24h - included in short term review
Gross 1975b	Short term study <24h - included in short term review
Gross 1984	Review
Gross 1987	Not asthma
Gutersohn 1975	Confounded - patients selected who responded to Ipratropium
Guyatt 1986	Asthma not stable
Higgins 1991	Short term study <24h - included in short term review
Hockley 1985	Short term study <24h - included in short term review
Hoffstein 1994	Short term study <24h - included in short term review
Holst 1976	Not stated to be randomised (abstract) - too long ago to write to authors
Huhti 1986	Short term study <24h - included in short term review
Hunt 1983	Short term study <24h - included in short term review
Irsigler 1975	Short term study <24h - included in short term review
Jenkins 1981	Short term study <24h - included in short term review
Jenkins 1982	Short term study <24h - included in short term review
Jindal 1989	Not randomised
Johnson 1989	Short term study <24h - included in short term review

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Study	Reason for exclusion
Jolobe 1981	Not randomised
Kaik 1975	COPD
Kaik 1976	Wrong comparator
Kaik 1979	COPD
Kamburoff 1975	Short term study <24h - included in short term review
Kaptein 1993	As Brand 1992
Kennedy 1964	Short term study <24h - included in short term review
Kerstjens 1992	As Brand 1992
Kerstjens 1993a	As Brand 1992
Kerstjens 1993b	As Brand 1992
Kerstjens 1994	As Brand 1992
Kerstjens 1995	As Brand 1992
Kok-Jensen 1979	Not randomised
Kradjan 1992	Short term study <24h - included in short term review
Kreisman 1984	Short term study <24h - included in short term review
Krivoy 1987	Short term study <24h - included in short term review
Kunkel 1976	COPD
Kunkel 2000	Wrong comparison
Lahdensuo 1975	Short term study <24h - included in short term review
Laitinen 1986	Short term study <24h - included in short term review
Lanser 1975	COPD
Larsson 1987	Challenge study
Lavandier 1987	Short term study <24h - included in short term review
Lawford 1983	Short term study <24h - included in short term review
Lefcoe 1982	Short term study <24h - included in short term review
Lehrer 1993	Short term study <24h - included in short term review
Lehrer 1994	Short term study <24h - included in short term review
Li 2003	

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Study	Reason for exclusion
Lichterfeld 1979	Review
Linehan 1975	Short term study <24h - included in short term review
Maesen 1975a	Short term study <24h - included in short term review
Maesen 1975b	Short term study <24h - included in short term review
Maesen 1982	Short term study <24h - included in short term review
Maesen 1985	Short term study <24h - included in short term review
Mann 1984	Confounded - patients selected who responded to Ipratropium
Marcatili 1984	Short term study <24h - included in short term review
Marin 1987	Short term study <24h - included in short term review
Marlin 1978	Short term study <24h - included in short term review
Marlin 1979	Short term study <24h - included in short term review
Mattila 1966	Short term study <24h - included in short term review
McIntosh 1986a	Short term study <24h - included in short term review
McIntosh 1986b	Short term study <24h - included in short term review
Millar 1990	Short term study <24h - included in short term review
Minette 1979	Short term study <24h - included in short term review
Minette 1985	Short term study <24h - included in short term review
Morrison 1988	Short term study <24h - included in short term review
Morrison 1989	Short term study <24h - included in short term review
Morrison 1991	Challenge study
Morton 1984	Not randomised
Muittari 1968	Short term study <24h - included in short term review
Nishi 1993	Short term study <24h - included in short term review
Nishimura 1999	Wrong comparison oxitropium vs nothing (long term study)
Nolte 1978	Short term study <24h - included in short term review
Osterwalder 1991	Short term study <24h - included in short term review
Pavia 1979	COPD; only 2 patients with asthma
Peel 1984	Short term study <24h - included in short term review

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Study	Reason for exclusion
Peerless 1983	Short term study <24h - included in short term review
Petrie 1975a	Short term study <24h - included in short term review
Petrie 1975b	Short term study <24h - included in short term review
Petro 1981	COPD
Philip-Joet 1986	Acute asthma
Pierce 1979	Short term study <24h - included in short term review
Pounsford 1983	Short term study <24h - included in short term review
Pounsford 2001	Short term study <24h - included in short term review
Rafferty 1987	Short term study <24h - included in short term review
Rebuck 1979	Short term study <24h - included in short term review
Riding 1970	Short term study <24h - included in short term review
Ruffin 1977	Short term study <24h - included in short term review
Ruffin 1978	Short term study <24h - included in short term review
Ruffin 1982	Short term study <24h - included in short term review
Ruffin 1987b	Short term study <24h - included in short term review
Rutkowski 1994	Not reported to be randomised; no response from authors
Rutten-van-Molken 19	As Brand 1992
Sahay 1980	As Bell 1982
Sahlstrom 1986	Short term study <24h - included in short term review
Salome 1988	Challenge study
Schindl 1973	COPD
Schlueter 1978	Short term study <24h - included in short term review
Schroeckenstein 1988	Short term study <24h - included in short term review
Schultze-Werninghaus	Challenge study
Shneerson 1986	Short term study <24h - included in short term review
Simonsson 1979	Review
Smith 1988	Challenge study
Snow 1979	Short term study <24h - included in short term review

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Study	Reason for exclusion
Spector 1975	Short term study <24h - included in short term review
Speirs 1987	Short term study <24h - included in short term review
Stewart 1987	Short term study <24h - included in short term review
Storms 1975a	Short term study <24h - included in short term review
Storms 1975b	Short term study <24h - included in short term review
Stresemann 1975	Short term study <24h - included in short term review
Stresemann 1976a	Short term study <24h - included in short term review
Stresemann1976b	Short term study <24h - included in short term review
Sur 1990	Short term study <24h - included in short term review
Tang 1984	Short term study <24h - included in short term review
Tarlo 1982	Long term study - asthma maintenance medication not stable
Taube 2002	Short term study <24h - included in short term review
Thiessen 1979	Short term study <24h - included in short term review
Trinquet 1975	Short term study <24h - included in short term review
Tukiainen 1985	Short term study <24h - included in short term review
Uffholtz 1975	Short term study <24h - included in short term review
Ullah 1980	Short term study <24h - included in short term review
Ullah 1981	Short term study <24h - included in short term review
Ulmer 1979	One study COPD; other study not randomised (before and after)
Vakil 1985	No comparison
Verstraeten 1974a	Short term study <24h - included in short term review
Verstraeten 1974b	COPD
Verstraeten 1975	Short term study <24h - included in short term review
Villate 1980	Short term study <24h - included in short term review
Vlagopoulos 1975	Short term study <24h - included in short term review
Vlagopoulos 1976	Short term study <24h - included in short term review
Vogt 1974	Short term study <24h - included in short term review
Walker 1987	Short term study <24h - included in short term review

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Study	Reason for exclusion
Ward 1987	Acute asthma
Watson 1992	Not asthma
Wegener 1987a	Short term study <24h - included in short term review
Wegener 1987b	Short term study <24h - included in short term review
Wempe 1992	Short term study <24h - included in short term review
Wesolowski 1985	Children
Wildbolz 1977	Short term study <24h - included in short term review
Wilson 1978	Not randomised
Windom 1990	Short term study <24h - included in short term review
Yanai 1991	Short term study <24h - included in short term review
Yang 1989	Short term study <24h - included in short term review
Yeager 1976	Short term study <24h - included in short term review
Zanen 1995	Not randomised and wrong comparator
Zaritsky 1999	Children; acute asthma
Zuck 1987	Confounded - patients selected who responded to Ipratropium

DATA AND ANALYSES

Comparison 1. Longer term AC+BA vs BA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals due to treatment failure/side effects	2	256	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.69, 2.84]
1.1 Medium/long term, parallel, BA alone dose = 2 x comb dose	2	256	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.69, 2.84]
2 No of patients with side effects	2	256	Odds Ratio (M-H, Fixed, 95% CI)	4.51 [0.96, 21.27]
2.1 Parallel studies, overall side effects, BA alone dose = 2 x comb dose	2	256	Odds Ratio (M-H, Fixed, 95% CI)	4.51 [0.96, 21.27]

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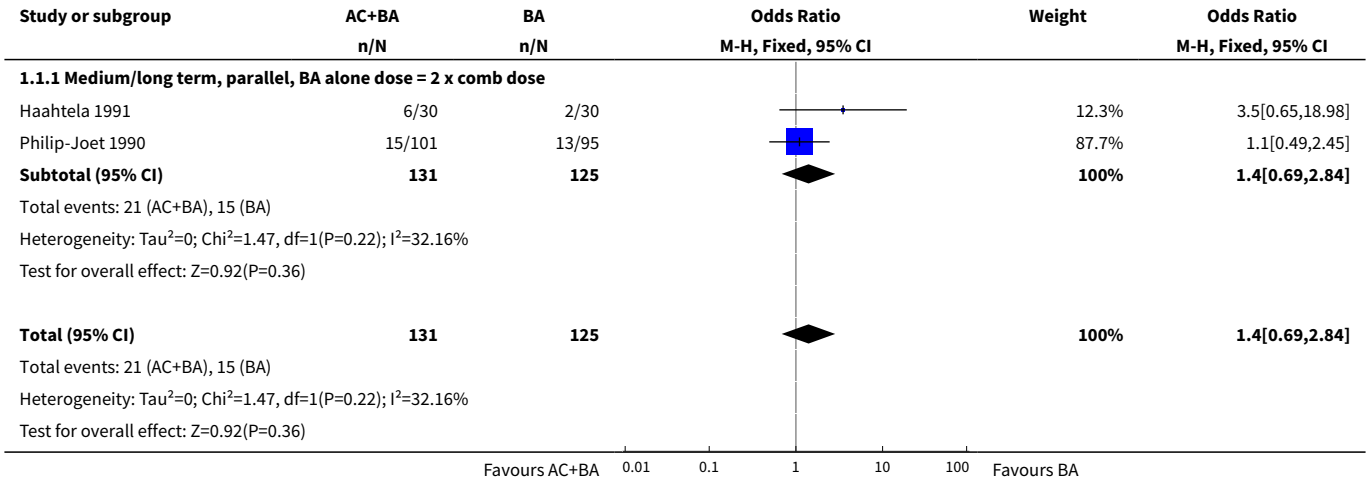
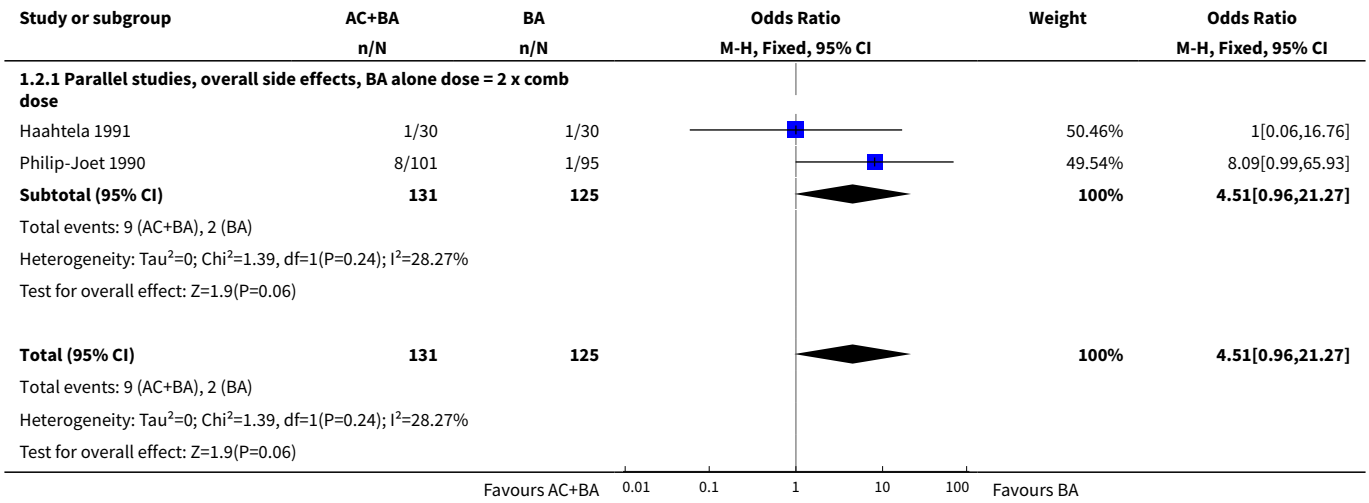
Analysis 1.1. Comparison 1 Longer term AC+BA vs BA, Outcome 1 Withdrawals due to treatment failure/side effects.



Analysis 1.2. Comparison 1 Longer term AC+BA vs BA, Outcome 2 No of patients with side effects.



Comparison 2. Longer Term AC vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom score paired mean difference (Scale -1 to +1)	3		Symptom score diff (Fixed, 95% CI)	Subtotals only
1.1 Symptom score (daily average) up to 28 days dyspnoea, daytime, IB 40	3		Symptom score diff (Fixed, 95% CI)	-0.09 [-0.14, -0.04]
1.2 Symptom score (daily) <28 days dyspnoea, daytime, IB 40; no Salorinne	2		Symptom score diff (Fixed, 95% CI)	-0.07 [-0.13, -0.02]

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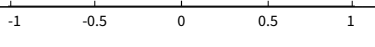
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Symptom score (daily average) medium term overall score, night	1		Symptom score diff (Fixed, 95% CI)	0.09 [-0.09, 0.26]
2 PEF paired analysis (scale -100 to +100 l/min)	3		Mean Difference L/mn (Fixed, 95% CI)	Subtotals only
2.1 PEF am	3		Mean Difference L/mn (Fixed, 95% CI)	14.38 [7.69, 21.08]
2.2 PEF am (without Salorinne)	2		Mean Difference L/mn (Fixed, 95% CI)	16.26 [9.21, 23.31]
2.3 PEF pm, short term	3		Mean Difference L/mn (Fixed, 95% CI)	23.48 [12.32, 34.65]
2.4 PEF am, short term, post bronchodilator	2		Mean Difference L/mn (Fixed, 95% CI)	34.91 [20.13, 49.70]
2.5 PEF pm, short term, post bronchodilator	1		Mean Difference L/mn (Fixed, 95% CI)	23.94 [5.20, 42.68]
3 Patient preference	2	96	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [0.68, 3.94]
4 Number of patients dropping out	2	90	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.13, 3.72]
5 Adverse effects - number of patients	2	104	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [0.51, 6.81]
5.1 overall	2	104	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [0.51, 6.81]

Analysis 2.1. Comparison 2 Longer Term AC vs placebo, Outcome 1 Symptom score paired mean difference (Scale -1 to +1).

Study or subgroup	AC N	Placebo N	Symptom score diff (SE)	Symptom score diff IV, Fixed, 95% CI	Weight	Symptom score diff IV, Fixed, 95% CI
2.1.1 Symptom score (daily average) up to 28 days dyspnoea, daytime, IB 40						
Ahonen 1978	1	1	-0.1 (0.03)		71.26%	-0.07[-0.13,-0.02]
Salorinne 1988	1	1	-0.2 (0.062)		17.18%	-0.16[-0.28,-0.04]
Wheeler 1987	1	1	-0.1 (0.075)		11.55%	-0.07[-0.22,0.07]
Subtotal (95% CI)					**100%**	**-0.09[-0.14,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=1.6, df=2(P=0.45); I^2=0%						
Test for overall effect: Z=3.5(P=0)						
2.1.2 Symptom score (daily) <28 days dyspnoea, daytime, IB 40; no Salorinne						
Ahonen 1978	1	1	-0.1 (0.03)		86.05%	-0.07[-0.13,-0.02]
Wheeler 1987	1	1	-0.1 (0.075)		13.95%	-0.07[-0.22,0.07]



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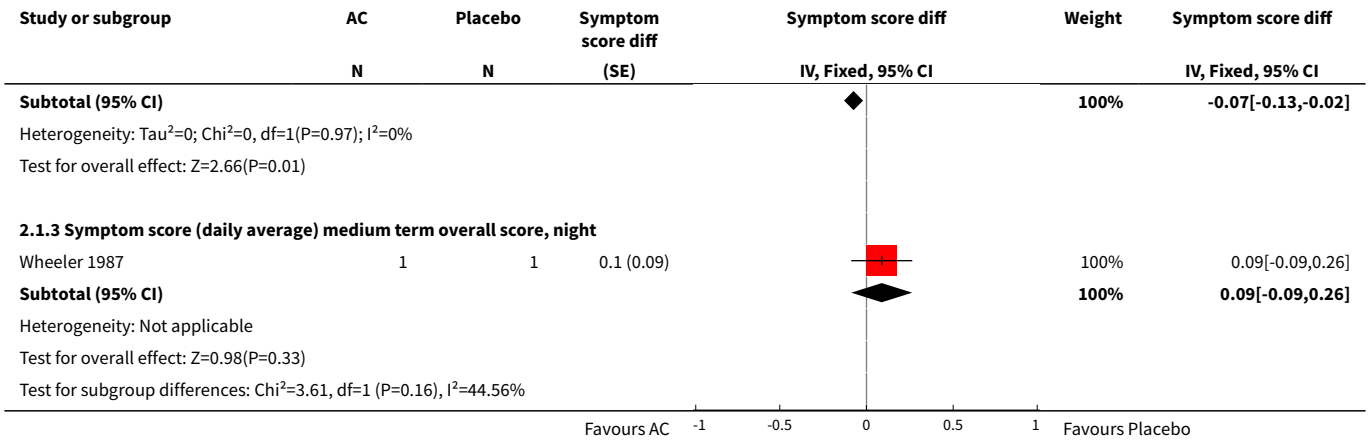
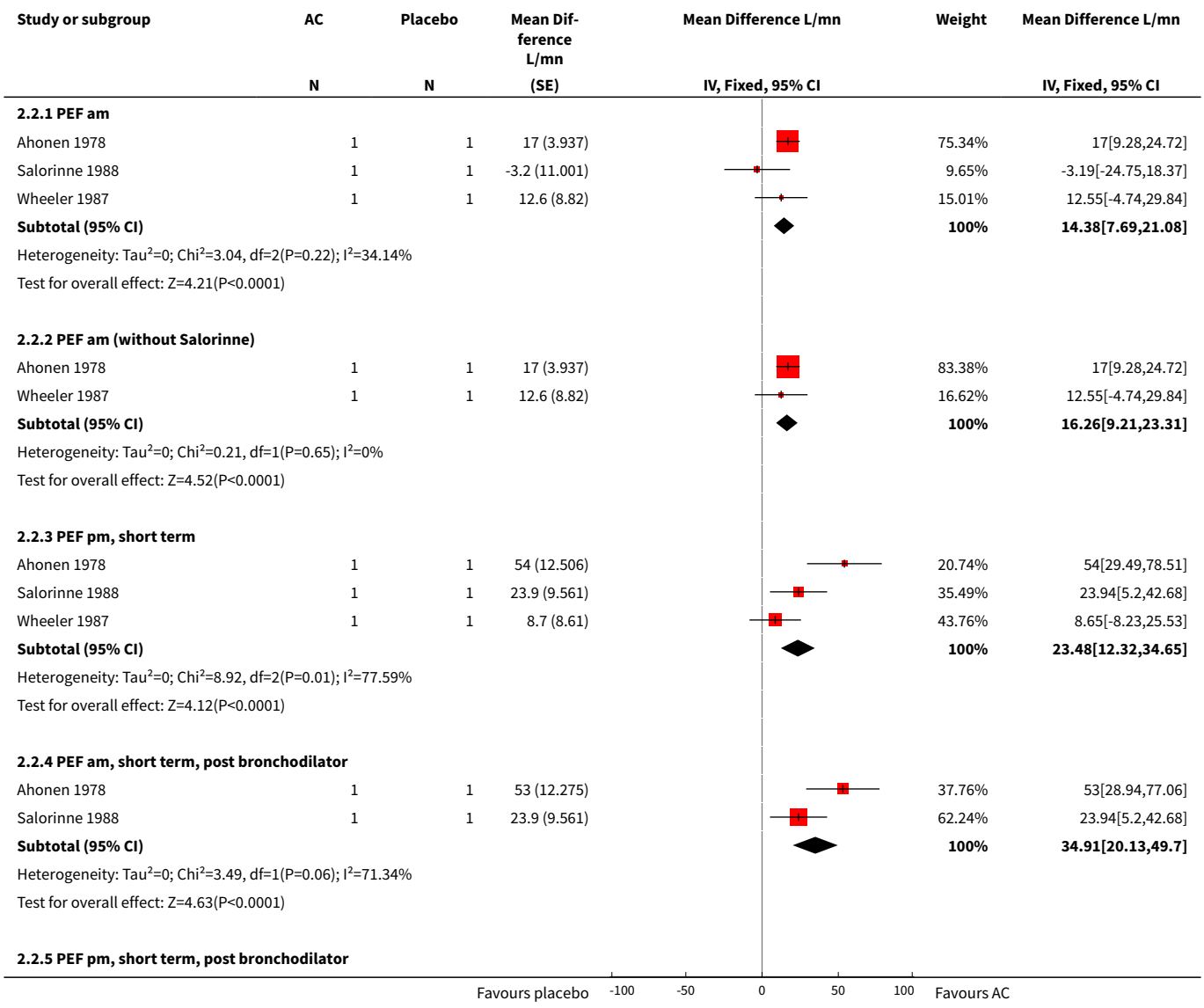


Analysis 2.2. Comparison 2 Longer Term AC vs placebo, Outcome 2 PEF paired analysis (scale -100 to +100 l/min).



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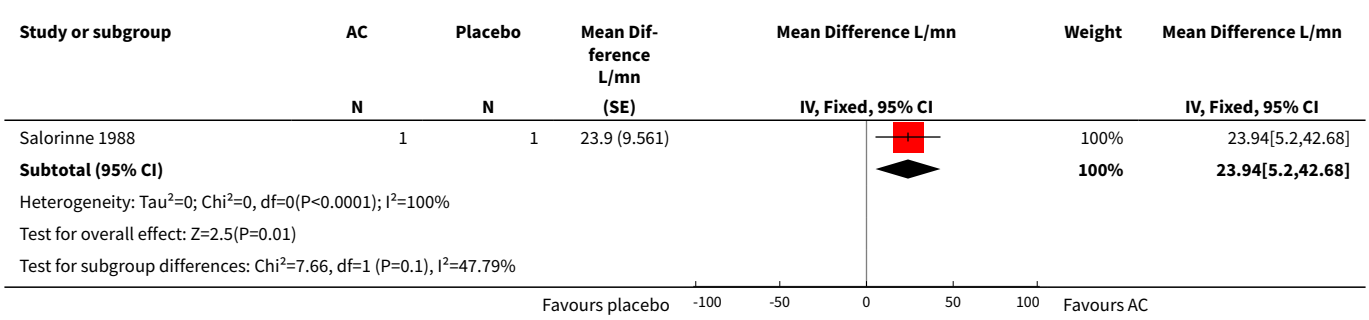
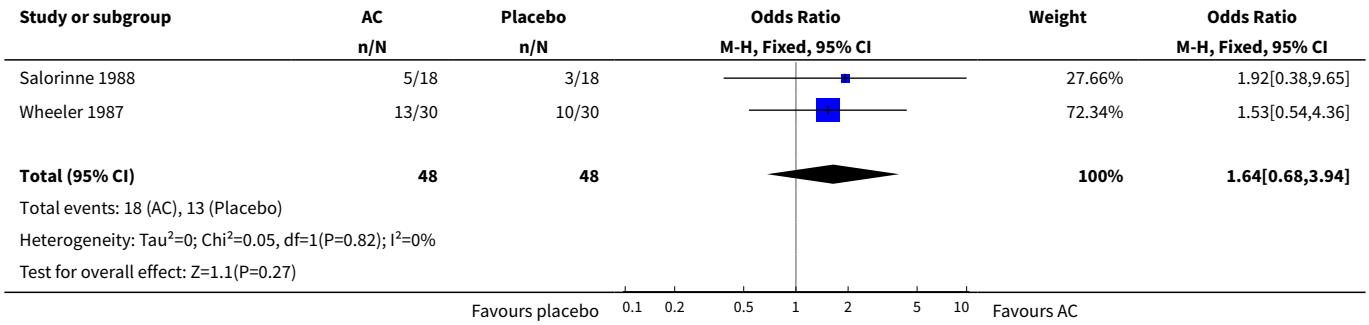
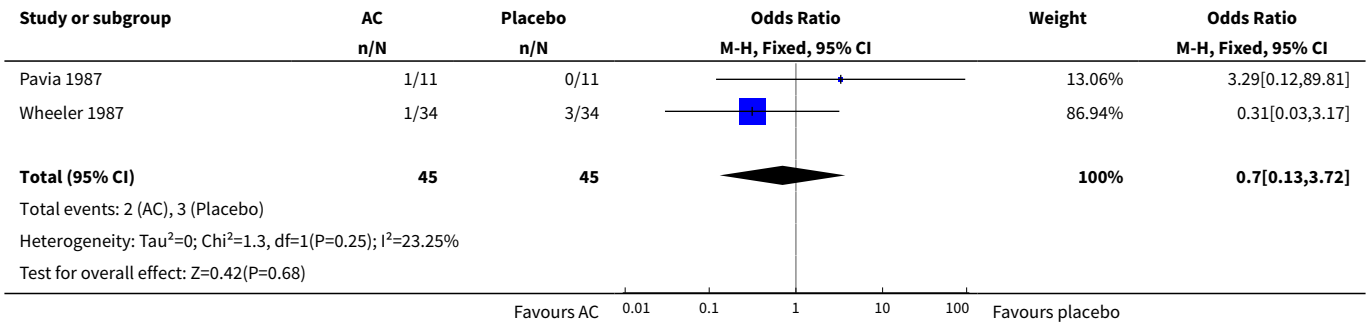


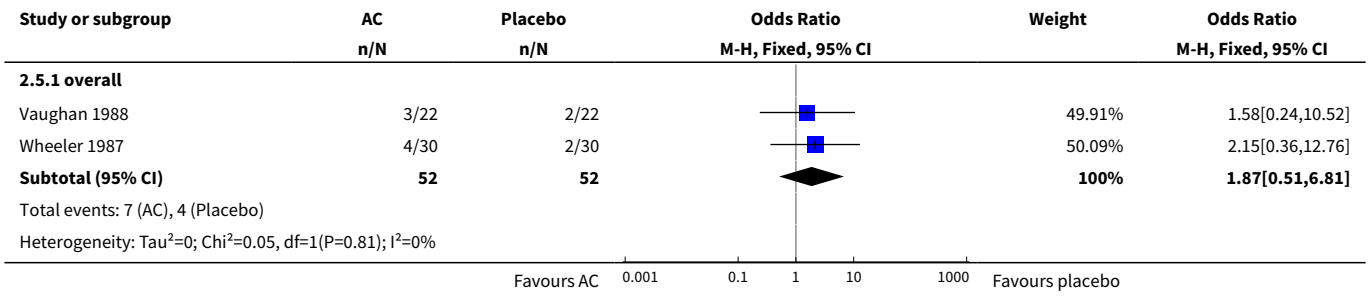
Analysis 2.3. Comparison 2 Longer Term AC vs placebo, Outcome 3 Patient preference.



Analysis 2.4. Comparison 2 Longer Term AC vs placebo, Outcome 4 Number of patients dropping out.



Analysis 2.5. Comparison 2 Longer Term AC vs placebo, Outcome 5 Adverse effects - number of patients.



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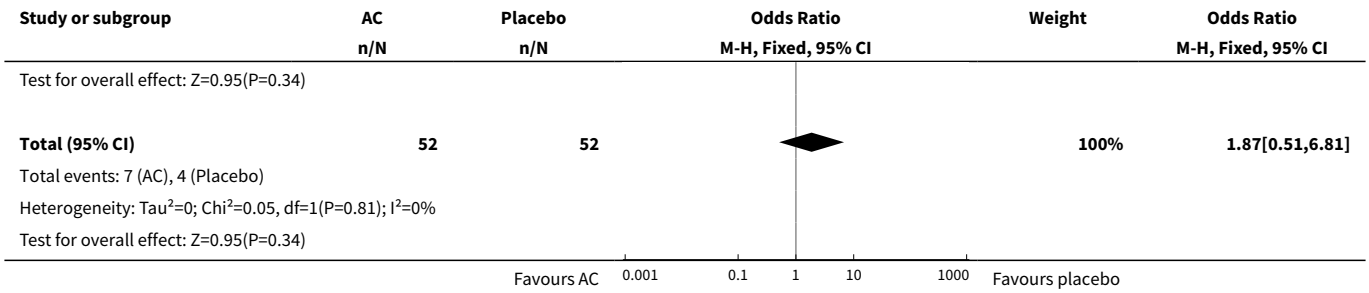
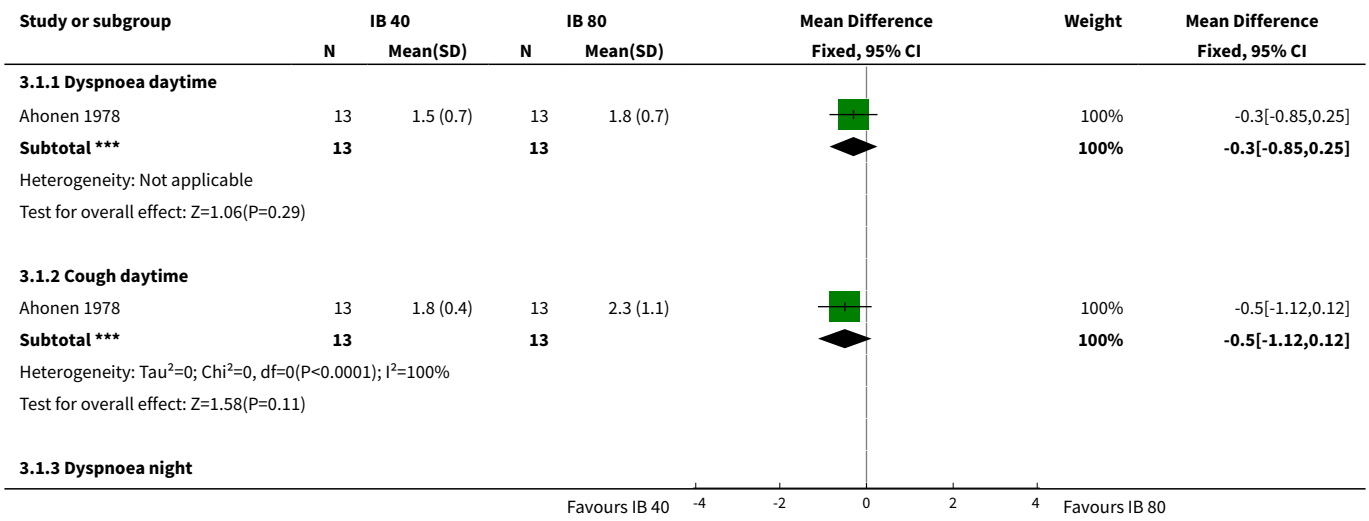


Comparison 3. IB 40 vs IB 80

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom score (scale -4 to +4)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Dyspnoea daytime	1	26	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.85, 0.25]
1.2 Cough daytime	1	26	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.12, 0.12]
1.3 Dyspnoea night	1	26	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.91, 0.51]
2 PEF (scale -100 to +100 l/min)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 PEF am	1	26	Mean Difference (IV, Fixed, 95% CI)	34.0 [-4.06, 72.06]
2.2 PEF pm	1	26	Mean Difference (IV, Fixed, 95% CI)	24.0 [-19.16, 67.16]
2.3 PEF post dose, am	1	26	Mean Difference (IV, Fixed, 95% CI)	29.00 [-11.21, 69.21]

Analysis 3.1. Comparison 3 IB 40 vs IB 80, Outcome 1 Symptom score (scale -4 to +4).



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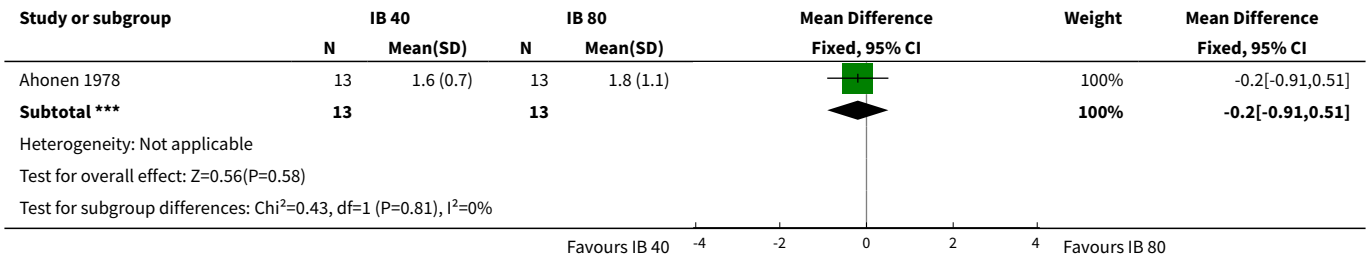
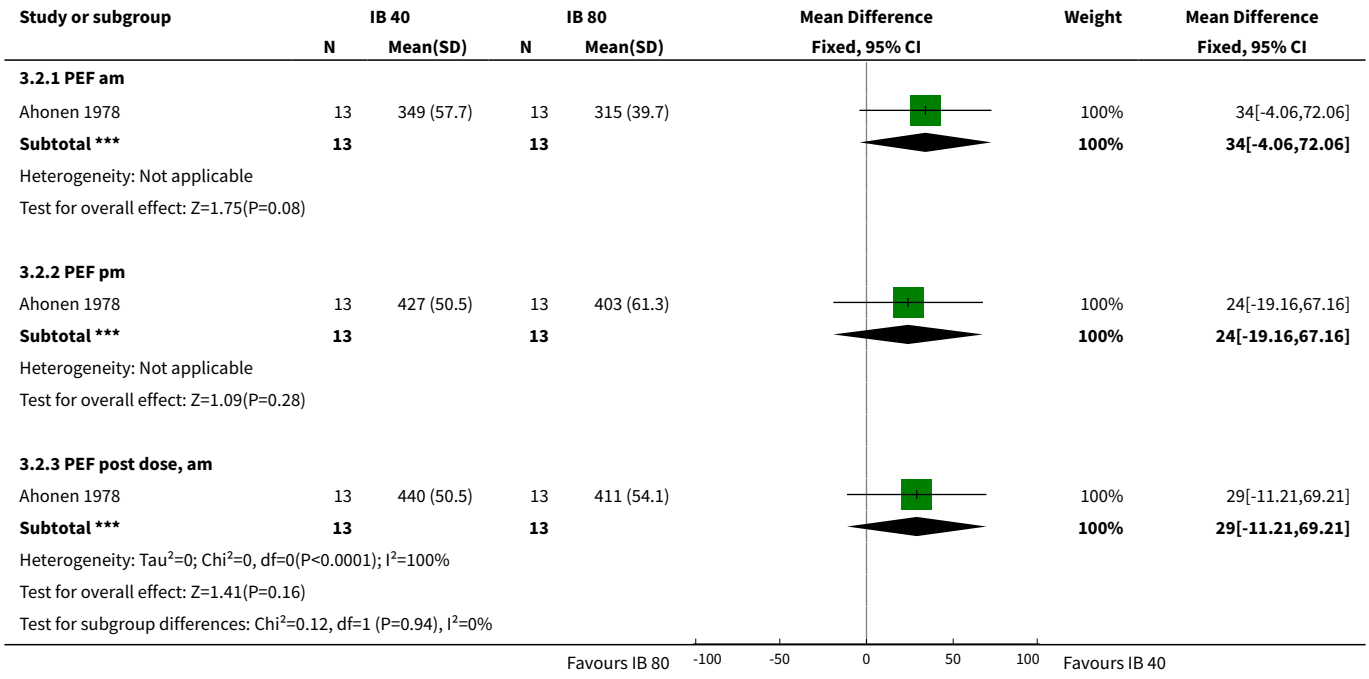


Analysis 3.2. Comparison 3 IB 40 vs IB 80, Outcome 2 PEF (scale -100 to +100 l/min).



ADDITIONAL TABLES

Table 1. Comparison of Ahonen study (IB 40 vs IB 80)

Outcome	Mean difference	% MD of IB 80	95% CI
Daily Symptom score - daytime dyspnoea	-0.30	17% decrease	-0.85, 0.25; not statistically significant
Daily Symptom score - daytime cough	-0.50	22% decrease	-1.12, 0.12; not statistically significant
Daily Symptom score - night dyspnoea	-0.20	11% decrease	-0.91, 0.51; not statistically significant
Daily PEFR - am pre-dose	34 litres/min	11% increase	-4.06, 74.06; not statistically significant

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Table 1. Comparison of Ahonen study (IB 40 vs IB 80) *(Continued)*

Daily PEFR - pm pre-dose	24 litres/min	6% increase	-19.16, 67.16; not statistically significant
Daily PEFR - am post-dose	29 litres/min	7% increase	-11.21, 69.21; not statistically significant

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Table 2. Anticholinergic versus placebo - symptom scores

Outcome	Scale	Studies	Pooled summary stats	Hetero-geneity	Single study results	Stat sig?	% change on placebo	Comments
Symptom score - dyspnoea daytime		Ahonen 1978 Salorinne 1988 Wheeler 1987	Paired mean difference -0.09 (95%CI -0.14, -0.04)	p = 0.45, I-squared = 0%		Y	15% decrease (i.e., favours anticholinergic)	Wheeler: rho = 0.817
Symptom score - dyspnoea daytime (no Salorinne)	1-4 0-3	Ahonen 1978 Wheeler 1987	Paired mean difference -0.07 (95%CI -0.13, -0.02)	p = 0.97, I-squared = 0%		Y	12% decrease	Wheeler: rho = 0.817
Symptom score - cough daytime	1-4 0-3	Ahonen 1978 Salorinne 1988			Mean difference Aho -0.05 (95%CI -0.16, 0.06) Sal -0.05 (no SDs)	N	10% decrease 11% decrease	
Symptom score - dyspnoea night-time	1-4 0-3	Ahonen 1978 Salorinne 1988			Mean difference Aho -0.13 (95%CI -0.27, 0.01) Sal -0.09 (no SDs)	N	24% decrease 26% decrease	
Symptom score - cough night-time	0-3	Salorinne 1988			Mean difference +0.04 (no SDs)	N	14% Increase (i.e. anticholinergic worse than placebo)	
Symptom score - night-time overall score	0-3	Wheeler 1987			Paired mean difference +0.09 (95%CI -0.09, 0.26)	N	28% Increase	Wheeler: rho = 0.611
Clinical score - day and night (change score)	0-13	Taytard 1984			Mean difference (parallel trial) -0.72 (95%CI -1.37, -0.07)	Y	71% decrease	

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Table 3. Anticholinergic versus placebo - daily peak flows

Outcome	Time (post dose)	Studies	Pooled summary stats	Hetero-geneity	Single study re-sults	Stat sig?	% on place-bo mean	Comments
Daily PEFR am pre-bronchodilator	07.00 (6h) 08.00 (10h) "on rising" (12h)	Ahonen 1978 Salorinne 1988 Wheeler 1987	Paired mean difference 14.38 L/min (95%CI 7.69, 21.08)	p = 0.22 I-squared = 34%		Y	7% increase (i.e. favours Antichol)	Wheeler: rho = 0.919
Daily PEFR am pre-bronchodilator (no Salorinne)	07.00 (6h) "on rising" (12h)	Ahonen 1978 Wheeler 1987	Paired mean difference 16.26 l/min (95%CI 9.21, 23.31)	p = 0.65 I-squared = 0%		Y	5% increase	
Daily PEFR pm pre-bronchodilator	22.00 (3h) 22.00 (4h) "on retiring" (12h)	Ahonen 1978 Salorinne 1988 Wheeler 1987	Paired mean difference 23.48 l/min (95%CI 12.32, 34.65)	p = 0.01 I-squared = 78%		Y	7% increase	Wheeler: rho = 0.911
Daily PEFR am post-bronchodilator	10.00 (3h) 10.00 (2h)	Ahonen 1978 Salorinne 1988	Paired mean difference 34.91 l/min (95%CI 20.13, 49.70)	p = 0.06 I-squared = 71%		Y	9% increase	
Daily PEFR pm post-bronchodilator	00.00 (2h)	Salorinne 1988			Paired mean diff. 23.94 L/min (95%CI 5.20, 42.68)	Y	7% increase	

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Table 4. Anticholinergic versus placebo - other outcomes

Outcome	Studies	Pooled summary stats	Hetero-geneity	Single study results	Stat sig?	Interpretation
Number of patients withdrawing	Pavia 1987 Wheeler 1987	OR 0.70 (95%CI 0.13, 3.72)	p = 0.25 I-squared = 23%		N	About two thirds the odds for withdrawal with anticholinergic as placebo
Patient preference (crossover studies)	Salorinne 1988 Wheeler 1987	OR 1.64 (95%CI 0.68, 3.94)	p = 0.82 I-squared = 0%		N	About 1.5 times the odds for patients preferring anticholinergic as placebo
No. patients using rescue medication	Wheeler			Daytime OR 0.66 (95%CI 0.18, 2.36) Night OR 0.58 (95%CI 0.21, 1.62)	N N	About half the odds for using rescue medication with anticholinergic as placebo

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Table 5. Anticholinergic vs placebo - Adverse effects

Effect	Outcome	Studies	Pooled summary stats	Single study results	Stat sig?	Comments
Overall adverse effects	Number of patients	Vaughan 1988 Wheeler 1987	OR 1.87 (95%CI 0.51, 6.81) p = 0.81, I-squared = 0%		N	About twice the odds for patients having adverse effects with AC as with placebo
Gastric irritation	Number of patients	Wheeler 1987		OR 3.10 (95%CI 0.12, 79.23)	N	Authors: "no major differences"
Irritation	Number of days/pt	Ahonen 1978		anticholinergic = 1; placebo =2.5		
	Symptom scores	Salorinne 1988		anticholinergic = 8; placebo = 4	"N"	
Headache	Symptom scores	Salorinne 1988		anticholinergic = 7; placebo = 14	N	
Unpleasant taste	Number of patients	Wheeler 1987		OR 2.07 (95%CI 0.18, 24.15)		
Mouth dryness	Number of patients	Vaughan 1988		OR 1.00 (95%CI 0.13, 7.81)	N	Authors; "not statistically significantly different"
	Symptom scores	Salorinne		anticholinerg = 44; placebo = 19	"N"	
Weight gain	Number of patients	Wheeler 1987		OR 3.10 (95%CI 0.12, 79.23)	N	Authors: "no major differences"
Tremor	Number of days/pt	Ahonen 1978		anticholinergic = 0; placebo =6		
Tremor	Symptom scores	Salorinne 1988		anticholinergic = 0; placebo = 6	"N"	
Anxiety / fear Palpitations	Number of days/pt Symptom scores	Ahonen 1978 Salorinne 1988		anticholinergic = 2; placebo =0 anticholinerg = 10; placebo = 11	"N"	Authors: "no major differences"
Urinary hesitancy	Number of patients	Vaughan 1988		OR 3.14 (95%CI 0.12, 81.35)	N	

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Table 6. Anticholinergic-Beta agonist combination versus BA alone - Symptom scores

Studies	Study design	BA Ratio (comb:sing)	Outcome	Single study results	Stat sig?	% change on BA
Haahtela 1991	Parallel 12 weeks	1:2 (Berodual/Sal)	Daytime Dyspnoea	Mean difference -0.04 (minus = favours AC/BA)	"N" (authors)	6% decrease
			Daytime Cough	+0.03 (NB all symptom scores include large baseline differences)	"N" (authors)	5% increase
		1:2 (Duovent/Sal)	Daytime Dyspnoea	+0.26		26% increase
			Daytime Cough	+0.40		80% increase
Haahtela 1991	Parallel 12 weeks	1:1 (Duovent/Sal)	Daytime Dyspnoea	+0.26 (NB all symptom scores include large baseline differences)	"N" (authors)	27% increase
			Daytime Cough	+0.30	"N" (authors)	50% increase
Macaluso 1986	Crossover 2 weeks	1:1 (Duovent/Sal)	Daytime Dyspnoea	WMD -0.13 (95%CI -0.55, +0.29)	N	37% decrease relative to BA
				WMD -0.06 (95%CI -0.54, +0.42)	N	12% decrease
			Daytime Cough	WMD -0.10 (95%CI -0.54, +0.34)	N	27% decrease
			Night Dyspnoea	WMD -0.03 (95%CI -0.46, +0.40)	N	7% decease
			Night Cough			
Tammivaara	Crossover 3 weeks	1:1 (IB+oral CR terbutaline/ oral Ter)	Daytime Dyspnoea Night Dyspnoea	WMD +0.11 (95%CI -0.24, +0.46)	N	19% increase
				WMD +0.01 (95%CI -0.28, +0.30)	N	2% increase
Wolstenholme	Crossover 4 weeks	1:1 (Duovent/Sal)	Night Dyspnoea	WMD +0.16 (95%CI -0.30, +0.62)	N	22% increase
			Night Cough	WMD +0.12 (95%CI -0.24, +0.48)	N	28% increase
			Night Wheeze	WMD +0.01 (95%CI -0.54, +0.56)	N	2% increase

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Table 7. AC/BA Combination versus BA alone - daily peak flows

Studies	Design&Duration	Ratio BA	Outcome	Time (post dose)	Single study results	Stat sig?	%change on BA
Philip-Joet 1990	Parallel design 1 week measurements only used (see text)	1:2 Comb : single	PEFR am	NS (NS but qid, so guess 6h)	Mean difference 4.65 l/m (95%CI -26.24, 35.54)	N	2% increase (i.e. in favour of combination)
			PEFR pm	Not Stated (NS)	MD 8.17 l/m (95%CI -24.08, 40.42)	N	3% increase
			PEFR am post dose	NS (20 mins)	MD 3.31 l/m (95%CI -29.78, 36.40)	N	1% increase
			PEFR pm post dose	NS (20 mins)	MD -4.61 l/m (95%CI -37.93, 28.71)	N	1% decrease
Haahtela 1991	Parallel design 12 weeks	1:2 Comb : Single	PEFR am	07.00h (NS but qid so guess 6h)	Mean difference +2 (Duovent/Sal) Mean difference -4 l/m (Berodual/Sal)	"N" authors "N" authors	1% increase 1% decrease
			PEFR pm	19.00h (NS)	Mean difference 6 l/m (Duovent/Sal) Mean difference 2 l/m (Berodual/Sal)	"N" authors	1% increase 1% increase
			PEFR am post dose	07.00h (1h post dose)	Mean difference 10.5 l/m (Duo/Sal) Mean difference -2 l/m (Bero/Sal)	"N" authors	2% increase 0.5% decrease
			PEFR pm post dose	19.00h (1h post dose)	Mean difference 10 l/m (Duo/Sal) Mean difference -2.5 l/m (Bero/Sal)		2% increase 1% decrease
Haahtela 1991	Parallel design 12 weeks	1:1 Comb : single	PEFR am	07.00h (NS but qid so guess 6h)	Mean difference +1.5 litres/min	"N" authors	0.5% increase
			PEFR pm	19.00h (NS)	Mean difference 9.5 l/m	"N" authors "N" authors	2% increase
			PEFR am post dose	07.00h (1h post dose)	Mean difference 15 l/m	"N" authors	3% increase
			PEFR pm post dose	19.00h (1h post dose)	Mean difference 14 l/m		3% increase
Wolstenholme 1989	Crossover design 4 weeks	1:1 Comb : single	PEFR am	NS (NS but qid so guess 6h)	Mean difference -8.70 l/m (95%CI -83.66, 66.26)	N	3% decrease
			PEFR pm	NS (NS)	Mean difference -1.70 l/m (95%CI -89.35, 85.95)	N	0.5% decrease
			PEFR am	NS (30mins)	Mean difference	N	1% decrease

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Table 7. AC/BA Combination versus BA alone - daily peak flows *(Continued)*

			post dose		-3.00 l/m (95%CI -78.77, 72.77)		
			PEFR pm post dose	NS (30 mins)	Mean difference -4.20 l/m (95%CI -76.47, 68.07)	N	1% decrease
Tammivaara 1993	Crossover design 3 weeks beta-agonist was oral CR terbutaline	1:1 Comb : single	PEFR am PEFR pm	08.00h (12h post dose) 20.00h (4h post ipratropium, 12h after oral terbutaline)	Mean difference -5.00 l/m (95%CI -50.72, 40.72) Mean difference 0.00 l/m (95%CI -47.48, 47.48)	N N	1% decrease no difference
Pierce 1982	Crossover design 4 weeks	1:1 Comb : single	Flow am	08.00h (6h post dose)	Mean difference 3.40 litres (95%CI -4.18, 10.98)	N	48% increase
FLOW not peak flow			Flow pm	19.00h (NS; probably 5-6h post dose) 20.00h (1h post dose)	Mean difference 6.86 litres (95%CI -5.03, 18.75)	N	48% increase
			Flow pm post dose		Mean difference 11.59 litres (95%CI -4.61, 27.79)	N	57% increase

Table 8. AC/BA combination vs BA - other outcomes

Study	Design&Duration	Comb:BA ratio	Outcomes	Pooled summary stats	SIngle study results	Stat sig?	Comment
Wolstenholme 1989	Crossover trial 4 weeks	1:1	Patient preference		OR 0.79 95%CI 0.20, 3.06	N	1.3 times worse with AC/BA
Tammivaara 1993	Crossover trial 3 weeks	1:1 ORAL CR terbutaline			OR 1.70 95%CI 0.40, 7.20	N	1.7 times better with AC/BA
Philip Joet 1990	Parallel design 8 weeks	1:2	Number of patients with exacerbations		OR 1.70 95%CI 0.64, 4.51	N	1.7 times worse with AC/BA
Tammivaara 1993	Crossover trial 3 weeks	1:1 CR ORAL terbutaline	Number of patients with exacerbations		OR 0.32 95%CI 0.01, 8.24	N	3 times better with AC/BA
			No. withdrawing due to treatment failure		OR 0.32 95%CI 0.01, 8.24	N	3 times better with AC/BA

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Table 8. AC/BA combination vs BA - other outcomes *(Continued)*

Rebuck 1983	Crossover trial 4 weeks	1:1	No. withdrawing due to treatment failure		OR 2.10 95%CI 0.18, 25.01	N	2 times worse with AC/BA
Haahtela 1991	Parallel trial 12 weeks	1:1 Duovent / Sal	No. withdrawing due to treatment failure		OR 5.09 95%CI 0.98, 26.43	N	5 times worse with AC/BA
Haahtela 1991 Philip-Joet 1990	Parallel trial 12 weeks Parallel trial 8 weeks	1:2 Berod/Sal 1:2 Berod/Sal	Number of patients withdrawing due to treatment failure	OR 1.40 95%CI 0.69, 2.84 2 studies, 256 patients; Heterogen. p=0.22, I-squared =32.2%		N	1.4 times worse with AC/BA

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Table 9. AC/BA combination vs BA - adverse effects

Effect	Outcome	Study	Details	Single study stats	Stat sig?	Comments
Overall side effects	Number of patients	Rebuck 1983	Crossover 1:1	OR 1.35 (95%CI 0.30, 6.13)	N	Combination worse
	Number of patients	Tammivaara 1993	Crossover 1:1 Oral terbutaline	OR 0.81 (95%CI 0.23, 2.88)	N	Combination better
Overall side effects	No. of pts withdrawn for side effects	Haahtela 1991	Parallel 1:1	OR 3.10 (95%CI 0.12, 79.23)	N	Combination worse
	Number of side effects			Combination 39; BA 25		Combination worse
Overall side effects	Number of patients withdrawn for side effects	Haahtela 1991	Parallel 1:2 Duovent:Salbutamol Berodual:Salbutamol	OR 1.00 (95%CI 0.06, 16.76) OR 5.35 (95%CI 0.25, 116.31)	N	No difference Combination worse
	No. of side effects		Duovent:Salbutamol Berodual:Salbutamol	Duovent 39; Salbutamol 34 Berodual 28; Salbutamol 25		Similar Similar
Tremor Palpitation Bad taste Drying Paresthesia Somnolence	Incidence	Mazzei 1985	Crossover; 1:1	Combination 4; BA 1 Combination 4; BA 8 Combination 3; BA 3 Combination 3; BA 1 Combination 1; BA 0 Combination 0; BA 2 cont.		Mixed effects
Insommnia Excitation				Combination 2; BA 0 Combination 2; BA 3		

WHAT'S NEW

Date	Event	Description
11 July 2017	Amended	The previous what's new event was deleted. This review is no longer being updated.

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 3, 2004

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Date	Event	Description
19 September 2008	New search has been performed	Literature search re-run between August 2005 and August 2008; no new studies found.
30 June 2008	Amended	Converted to new review format.
14 May 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Airways group conceived the idea for the review and MW and MB formulated the question and wrote the protocol, with additional input from PG. Decisions about prioritisation in the review and splitting of the original protocol into two reviews were made by MW and MB in consultation with PG. MW devised the MS Access database, managed the studies and wrote to the authors for missing data. MW and MB carried out the inclusion of studies, quality assessment and data extraction procedures. MW entered the data into RevMan and conducted the analysis. MW and MB wrote the review, with additional input from PG.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Daphne Jackson Trust, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [therapeutic use]; Asthma [*drug therapy]; Cholinergic Antagonists [*therapeutic use]; Drug Therapy, Combination; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans

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