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Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma (Review)

Walters EH, Walters JAE, Gibson PG

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[Intervention Review]

Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma

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ABSTRACT

Background

Selective beta-adrenergic agonists for use in asthma are: short acting (2 to 6 hours) and long acting (> 12 hours). There has been little controversy about using short acting beta-agonists intermittently, but long acting beta-agonists are used regularly, and their regular use has been controversial.

Objectives

To determine the benefit or detriment of treatment with regular short- or long acting inhaled beta-agonists in chronic asthma.

Search methods

We carried out a search using the Cochrane Airways Group trial register. We searched bibliographies of identified RCTs for additional relevant RCTs and contacted authors of identified RCTs for other published and unpublished studies.

Selection criteria

All randomised studies of at least two weeks duration, comparing a long acting inhaled beta-agonist given twice daily with any short acting inhaled beta-agonist of equivalent bronchodilator effectiveness given regularly in chronic asthma.

Data collection and analysis

Two reviewers performed data extraction and study quality assessment independently. We contacted authors of studies for missing data.

Main results

Thirty one studies met the inclusion criteria, 24 of parallel group and seven cross over design. Salmeterol xinafoate was used as long acting agent in 22 studies and formoterol fumarate in nine.

Salbutamol was the short acting agent used in 27 studies and terbutaline in five. The treatment period was over two weeks in 29 studies, and at least 12 weeks in 20.

25 studies permitted a variety of co-intervention treatments, usually inhaled corticosteroid or cromones. One study did not permit inhaled corticosteroid.

Long acting beta-agonists were significantly better than short acting for a variety of lung function measurements including morning highest forced expiratory flow measured with a peak flow meter (PEF) (Weighted Mean Difference (WMD) 33 L/min 95% CI 25 to 42) or evening PEF (WMD 26 L/min 95% CI 18 to 33); and had significantly lower scores for day and night time asthma symptom scores and percentage of days and nights without symptoms. They were also associated with a significantly lower use of rescue medication both during the day and night. Risk of exacerbations was not different between the two types of agent, but most studies were of short duration which limits the power to test for such differences.

Authors' conclusions

Long acting inhaled beta-agonists have advantages across a wide range of physiological and clinical outcomes for regular treatment.

PLAIN LANGUAGE SUMMARY

Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma

Patients with chronic asthma are generally treated with a 'preventer medication' to reduce the underlying airways inflammation but often require bronchodilators for their symptoms. Treatment with regular long acting Beta-agonist bronchodilator agents, such as salmeterol (Serevent) or formoterol (Foradil, Oxis), leads to fewer asthma symptoms during the day and the night, less bronchodilator medication requirement for symptoms, better lung function measurements and better quality of life measurements compared to short acting Beta-agonist bronchodilators such as salbutamol (Ventolin, Asmol, Airomir) or terbutaline (Bricanyl). There were no major adverse effects but there is little information on the effects in patients who do not use a 'preventer medication'.

BACKGROUND

Asthma is a common respiratory disease among both adults and children (Pearce 2000), though there are large geographical differences in the prevalence of asthma (Janson 2001), and the prevalence is increasing in many countries. Estimates for asthma prevalence in 1990 varied from 8.5% in Australia to 4% in the USA and 3% in the United Kingdom (Sullivan 1996) and repeat estimates in Australia in 1999 (Woods 2001) gave rates for physician diagnosed asthma of 18% while 10% had used asthma medications in the past year.

As a chronic illness, asthma is responsible for significant economic costs, both direct medical costs and indirect costs. These have been measured and range from direct costs of US\$ 250 million in Australia to US\$ 3.6 billion for total costs. Costs per patient have been estimated at US\$ 326 per patient per year in Australia and US \$ 1,043 per patient per year in the United Kingdom (Sullivan 1996).

Pathophysiological studies have increasingly recognised asthma as an inflammatory airway disease over the past decade. National treatment guidelines for asthma were published in several countries including Britain, USA and Australia (BTS 1993; GINA 1995; BTS 1997; NAC 1998) recommending that doctors responsible for treating patients with asthma should make greater use of inhaled steroids in the management of asthma. In chronic asthma of moderate severity or greater, treatment with topical anti-inflammatory corticosteroids or cromones is recommended as maintenance therapy.

In addition bronchodilator therapy is an essential component of treatment, traditionally used for relief of symptoms as needed. The most widely used bronchodilators are inhaled beta2-agonists that are divided into two groups: those with a short duration of action (2 to 6 hours) and those, introduced more recently, with a longer duration of action (> 12 hours). The major representatives of the short acting beta2-agonist agents in clinical use are salbutamol (known in North America as albuterol), terbutaline and orciprenaline, while the long acting beta2-agonists in use are salmeterol and formoterol.

There has not been any controversy about using beta2-agonists intermittently, for relieving acute asthma symptoms or preventing exercise induced asthma. However in chronic asthma, when used regularly three or four times daily, concerns have been raised (AAACI 1993). It was proposed that excessive use of beta2-agonists might have contributed directly or indirectly to peaks in asthma mortality seen in the 1960's and late 1970's (Sears Rea 1986). A study by Campbell 1976 showed that in four Australian states there was a high correlation between the sales of adrenergic bronchodilator aerosols and the corresponding asthma mortality rates for the periods 1961 to 1963 and 1964 to 1966. Later in 1989 a case control study in New Zealand linked the use of inhaled fenoterol with increased risk of death from asthma (Crane 1989). This was followed soon after by a similar study in Saskatchewan that also showed an association between excessive use of beta2-agonists and the risk of death or near death from asthma (Spitzer 1992).

Excessive use of beta2-agonists in poorly controlled asthma may contribute to deaths (Abramson 2001). This study showed significantly less use of asthma management plans and less use of inhaled corticosteroids in fatal cases.

Increased inflammation in the airways due to inhibition of anti-inflammatory heparin release from mast cell degranulation by beta2-agonists was proposed by Page 1993 as a mechanism for the worsening of asthma with regular use of these agents. Alternatively it was suggested that prolonged dilatation of the airways may allow more penetration of allergen.

The regular use of short acting beta-2 agonist agents was the subject of a Cochrane review in 1999 (Walters 1999). The conclusions were that there is little difference in using short-acting beta2-agonists regularly or as required, but with potentially some small clinical disadvantage to regular use. In general the frequency of use could therefore be left to patient preference.

The development of beta2-agonists with long-acting properties, such as salmeterol (Adkins 1997) and formoterol (Bartow 1998) has provided potential pharmacological advantages over short-acting beta-agonists, such as prolonged bronchodilation and protection against induced bronchospasm. However there remain concerns about adverse effects of regular use of long acting beta2-agonists (Devoy 1995) on bronchial hyper responsiveness (Cockcroft 1993), the development of tolerance (Newnham 1995) and progressively reduced protection against provoking stimuli (Taylor 1997) and masking of deteriorating asthma (McIvor 1998).

Long acting beta-agonists are more expensive than short acting beta agonists, and widespread use of long acting beta2-agonist agents implies a significant increase in drug budgets for asthma. Whether there is any advantage in giving regular beta2-agonist therapy as long or short acting drugs is therefore an important question (Kips 2001).

This review has addressed the comparative benefit or detriment of treatment in chronic asthma with regular short acting versus regular long acting inhaled beta2-agonists.

OBJECTIVES

The objective of the review is to compare the effects of regular inhaled long acting beta agonists with regular use of inhaled short acting beta agonists in chronic asthma.

The specific purpose of the review is to assess whether there are any beneficial or harmful effects from the regular use of inhaled long acting beta agonists compared with inhaled short acting beta agonists on asthma control and symptoms, pulmonary function, airway hyper-reactivity, rate of exacerbations of asthma, and quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised studies, both open and blinded. Ideally, all studies would be blinded, and preferably double blind. The scoring system gives a lower score to open studies, which can be used to weigh the contribution of open studies, or exclude them from analyses. Studies could be either of parallel group or cross-over design.

Types of participants

We included studies in which participants had a clinical diagnosis of asthma present for at least six months. We included both adults and children. We looked specifically for evidence of reversibility of airway obstruction to short-acting inhaled beta(2)-agonists as a diagnostic criterion. We sought to document the severity of participants' asthma at inclusion. Other asthma therapies could be used during the study, and we assessed the level and stability of the dose used. Studies that included some or all participants with other pulmonary diseases, and especially smoking related Chronic Obstructive Pulmonary Disease (COPD) were excluded unless the results for those with asthma alone were available separately.

Types of interventions

Participants in one treatment arm used a long acting inhaled beta agonist; either salmeterol or formoterol, twice daily administered via any inhalational device. The second treatment arm consisted of regular doses of any short acting inhaled beta agonist. The dose, inhalational device and frequency of administration were recorded, with the aim of having equivalence of bronchodilator effectiveness as far as possible. We excluded studies using oral administration of beta2-agonists. The minimum period of treatment was two weeks, to fit the aim of assessing regular use in the chronic asthma setting.

Types of outcome measures

Outcome measures were chosen to reflect asthma control, balanced against side effects.

Planned outcome measures were daytime and night-time asthma symptom scores, bronchodilator use for symptom relief, daily peak flow measurement (PEF), clinic measurements of airway function, airway hyper-reactivity measurement, quality of life score, asthma exacerbation rates, adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Group "Asthma and Wheez" trial register. This was derived from a comprehensive search of MEDLINE, EMBASE, CINAHL. In addition, hand searching of the 20 most productive respiratory care journals has been undertaken and relevant RCTs have been added to the register, including those published in a language other than English.

We searched this database using the following search strategy : (beta and agonist*) or bronchodilat* or salbutamol or albuterol or terbutaline or isoproterenol or reproterol or reproterenol or rimitalerol or fenoterol or ventolin or orciprenaline or metaproterenol or pirbuterol) and (salmeterol or eformoterol or formoterol).

Searching other resources

We reviewed reference lists of all available primary studies and review articles to identify potentially relevant citations. We contacted researchers known to have an interest in the field to identify other relevant past or current studies.

Data collection and analysis

Selection of studies

From the abstracts or titles, two reviewers (JW and FR) independently reviewed literature searches to identify potentially relevant trials for full review. We carried out searches of bibliographies and texts to identify additional studies. Using the specified criteria, we decided inclusion of studies in the review by agreement between the reviewers (JW, EHW and FR).

Data extraction and management

Data were extracted by two authors and entered into Review Manager software by one author. We collected details of the study characteristics and outcomes assessed by seeking information presented in [Appendix 1](#).

Assessment of risk of bias in included studies

The trials were scored using the Cochrane approach to assessment of allocation concealment:

Grade A: Adequate concealment.

Grade B: Unclear concealment.

Grade C: Obviously not adequate concealment.

Each study was also assessed for validity using the method of [Jadad 1996](#), on a 0 to 5 scale as follows:

(1) Was the study described as randomised? (1 = yes, 0 = no)

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

(3) Was there a description of withdrawals and drop outs? (1 = yes, 0 = no)

(4) Was the method of randomisation well described and appropriate? (1 = yes, 0 = no)

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

(6) Deduct 1 point if methods of randomisation or blinding were inappropriate.

Differences were resolved by discussion between the reviewers.

Dealing with missing data

An attempt was made to contact authors with data missing on relevant outcomes. We contacted a total of 17 principal authors of eligible studies. Five replied with data ([Britton 1992](#); [Pearlman 1992](#); [D'Alonzo 1994](#); [De Carli 1995](#); [Bensch 2001](#)) seven replied but were unable to provide data ([Hermansson1995](#); [Juniper 1995](#); [Staehr 1995](#); [Steffensen 1995](#); [Leblanc 1996](#); [Lipworth 1998](#); [Taylor 1998](#)) and no reply was received from the remainder.

Assessment of heterogeneity

For pooled effects a Breslow-Day test of heterogeneity was carried out, and a p value < 0.05 was considered significant, indicating possible differences between studies. If heterogeneity was found an explanation was sought. Investigation of sources for heterogeneity included performing sensitivity analyses using the domains:

(1) Methodological quality - Cochrane criteria A and B versus C ; Jadad score 3 to 5 versus 1 to 2.

(2) Fixed effect versus random effects modelling.

Data synthesis

All included trials were combined using the Review Manager 4.1.1. We analysed data from parallel group and crossover studies separately.

For continuous outcomes, we calculated individual and pooled statistics as weighted mean differences (WMD) with 95% Confidence Intervals (CI) using both fixed and random effects models. Where different scales had been used to measure the outcome the pooled standardised mean differences (SMD), with 95% Confidence Intervals (CI) were calculated. The SMD is a statistic that expresses the difference in means between the two treatment groups in units of the pooled standard deviation. This applied particularly to measures of bronchial reactivity, symptom scores and diurnal variation in PEF.

For dichotomous outcomes, we calculated individual and pooled statistics as odds ratios (OR) with 95% Confidence Intervals (CI), using both fixed and random effects models.

Both a fixed effects model ([Hasselblad 1995](#)) and a random-effects model ([DerSimonian 1986](#)) were used to pool the data, since there does not appear to be general consensus as to which method is superior. In general, the random effects method is a more conservative approach than the fixed effect method and results in larger CIs. The fixed effect result was reported unless a substantial difference was seen, when the random effects result was also quoted.

Funnel plots were used to examine the effects to investigate publication bias.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to assess the effect of treatment in different populations of asthmatics; adults versus children, mild versus moderate asthma severity, asthmatics on regular inhaled corticosteroids versus asthmatics on no co interventions.

The following subgroup analyses were carried out:

1. Asthmatics using regular inhaled corticosteroids
2. Children
3. Severity of asthma (mild, mild-moderate, moderate-severe).

Subgroup analyses of studies over six months length was planned for the next version.

RESULTS

Description of studies

Results of the search

We obtained a total of 868 references via a search performed in April 1999. These were assessed and we checked their reference lists in the full papers for further studies. The reference lists in 31 papers which were included in the earlier Cochrane review ([Walters 1999](#)), were also searched for relevant studies. A total of 208 papers were initially fully assessed. A repeat search, using the same criteria, was performed in February 2001 and we obtained a further 32 out of 459 references for full assessment. We assessed each paper and if it reported a study for inclusion, it was scored by at least two reviewers using the full text of the paper. Agreement on grading

of quality was good. Kappa statistics showed 96% agreement on Cochrane grades and 86% on Jadad grades.

In these 240 papers there were:

- (1) 33 reviews, editorials and background studies (see additional reference list)
- (2) 53 which cited 31 studies meeting agreed inclusion criteria (see table of included studies)
- (3) 154 studies which were excluded for the following reasons (see table of excluded studies):
 - (a) absence of a short-acting beta(2)-agonist group (96),
 - (b) period of treatment less than 2 weeks (43),
 - (c) dose of long-acting beta(2)-agonist varied during study (5),
 - (d) oral short-acting beta(2)-agonist agent used (3),
 - (e) not an RCT (5),
 - (f) only published as an abstract without any further details available or obtainable(2).

Included studies

The long-acting beta(2)-agonist agent was salmeterol xinafoate in 22 studies. The dose used was 50 mcg given twice daily at 12 hour interval in 21 studies and 100 mcg twice daily in one study ([Faurischou 1996](#)). Two studies also used another dose in comparison- 25 mcg in one case and 100 mcg in another. Formoterol fumarate was the long-acting beta(2)-agonist agent used in nine studies, at a dose of 12 mcg twice daily in seven studies; one study used 6 mcg twice daily ([Ekstrom 1998b](#)) and one 24 mcg twice daily ([Kozlik-Feldman 1996](#)). One had three treatment arms ([Lipworth 1998](#)), 6 mcg and 24 mcg in addition to 12 mcg. Where data from studies was combined, the dose of long-acting beta(2)-agonist used was the same or equivalent; salmeterol 50 mcg or formoterol 12 mcg ([Campbell 1999](#)). If another dose was used, the study was included, but the analysis performed with and without that study to assess the effect on the result.

The short-acting inhaled beta(2)-agonist agent used in 26 studies was salbutamol sulphate, at a dose of 200 mcg four times daily in 19 studies, a dose of 200 mcg twice daily in one study of children and a dose of 400 mcg four times daily in six studies. The drug was delivered in a dry powder form in studies using salbutamol 400 mcg, as this was considered by the maker as clinically equivalent to 200 mcg as a pressurised aerosol. Terbutaline sulphate 500 mcg four times daily was used in five studies.

The rescue agent used in 26 studies was salbutamol (albuterol); terbutaline in 2 studies; ipratropium (an anticholinergic agent) in two studies, and in one study the patient's usual agent was continued ([Castle 1993](#)).

Five studies in which the study drug was used as the rescue agent were excluded, on the basis that the dose of both the short-acting beta(2)-agonist agent and long-acting beta(2)-agonist agent was being varied in an unknown manner ([Arvidsson1989](#); [Wallin 1990](#); [Midgren 1992](#); [Newnham 1995](#); [Tattersfield 2001](#)).

INTERVENTION: TREATMENT PERIOD

Any treatment period over two weeks was specified in the protocol and of the 31 included studies the treatment periods were:

- 2 weeks in 2 studies
- 4 weeks in 6 studies
- 6 weeks in 3 studies

- 12 weeks in 17 studies (four of these followed patients up for 12 months collecting limited data in the second period ([Britton 1992](#); [Lundback 1993](#); [De Carli 1995](#); [Lenney 1995](#)))
- 16 weeks in 1 study
- 24 weeks in 2 studies

PARTICIPANTS: AGE

Twenty eight studies used adult or adolescent subjects over the age of 12 and three used children younger than 12 years of age ([Lenney 1995](#); [Kozlik-Feldman 1996](#); [Byrnes 2000](#)). There was little data available in these three publications with subjects aged less than 12 and they did not contribute to any of the major outcomes analyses.

PARTICIPANTS: ASTHMA SEVERITY

Information on the severity of participants' asthma at entry to the study was sought from the paper- mild; mild - moderate; moderate - severe. If it was not directly specified then a grade of mild asthma was given where no preventive agent was used, mild to moderate if the majority of participants were on a preventive agent (usually inhaled corticosteroids or cromones), or moderate - severe if participants were permitted to use oral steroids regularly. Those studies in which no details were available on the participants' asthma severity or any severity was permitted were classed as unknown or 'broad range'.

The majority of studies, 23, used subjects with mild to moderate asthma. Two used subjects with mild asthma only ([Venables 1992](#); [Kozlik-Feldman 1996](#)) and three used subjects with moderate to severe asthma ([Lai 1995](#); [Faurischou 1996](#); [FitzGerald 1999](#)). Three were of unclear or a broad range of severity ([Kesten 1991](#); [Castle 1993](#); [Steffensen 1995](#)).

PARTICIPANTS: CO-INTERVENTIONS

Studies were assessed according to the co-intervention treatment for asthma used by participants during the course of the study. The information was available for all studies, and in most cases the authors specified that the dose was kept constant during the course of the study treatment period.

The majority of studies, 25 of the 30 included, permitted a variety of co-intervention treatments. The most frequently used were inhaled corticosteroid or cromones, but some of these studies also permitted oral steroids at low dose and theophyllines. Full details of treatments permitted in individual studies can be found in the table of included studies.

In six studies all participants were required to use inhaled corticosteroids ([Beach 1993](#); [Lai 1995](#); [Faurischou 1996](#); [Lipworth 1998](#); [FitzGerald 1999](#); [Byrnes 2000](#)). Only one study did not permit inhaled corticosteroid ([Kozlik-Feldman 1996](#)).

METHODOLOGICAL QUALITY

OUTCOMES

Results for parallel group studies have been analysed together, while those from studies with a cross-over design have been grouped as a sub-set. The statistical programme in Review Manager does not allow for the combining of results from studies with differing designs, unless the results from the first period are available alone, when this period only can be included.

Twenty three studies were of parallel group design and seven of cross-over design. There were no cross-over studies in which we were able to extract results independently from the first period.

All the results referred to below are from the twenty three parallel group studies, and are given as weighted mean differences, calculated using the fixed effect model, unless specified otherwise in the text. Results from these and other analyses can be found in additional tables [Table 1](#).

Risk of bias in included studies

The methodological quality of the majority of trials was good and on the Jadad scoring method, three scored five while 23 scored four and one scored three. Four studies were given the lower score of two as they were not blinded by intervention. Lack of information in publications on the methods of randomisation used, meant that allocation concealment could not be confirmed in many cases, so only five studies were graded as confirmed adequate (A), and the remaining 26 were unclear (B).

Effects of interventions

AIRWAY CALIBRE MEASUREMENTS

There were significant advantages for the long acting beta agonist group compared with the regularly treated short acting beta agonist group for all indices of airway calibre.

The long acting beta agonist group showed an advantage of 32.93 L/min (95% CI 24.47 to 41.39, [Analysis 1.1](#)) for morning peak expiratory flow (PEF am). There was no significant heterogeneity.

The evening peak expiratory flow (PEF pm) showed an advantage of 25.62 L/min (95% CI 17.98 to 33.27, [Analysis 1.2](#)) based on eight studies with 1881 subjects. There was significant heterogeneity however, χ^2 was 14.04 df = 7, and on examination the heterogeneity was due to one study [Ekstrom 1998b](#) which used a lower dose of formoterol (6 mcg) than the other studies. When this was excluded from the calculation of the pooled effect, the χ^2 value was not significant 7.37 df = 6.

The mean difference in the change in PEF during treatment was 27.38 L/min (95% CI 22.98 to 31.77, [Analysis 1.3](#)) for morning PEF am and 11.94 L/min (95% CI 7.99 to 15.90, [Analysis 1.4](#)) for evening PEF, based on six studies with 1603 participants. There was no significant heterogeneity seen in this analysis.

There was only one study reporting usable data for participants who all used inhaled corticosteroids ([Pearlman 1992](#)) when the difference was larger for PEF am 60 L/min (CI 0.8 to 109.8), pm 48 L/min (CI 13.8 to 110). The result for participants with asthma of mild to moderate severity was very similar to the that in all studies combined.

Laboratory measures of lung function showed an advantage for long acting beta2-agonists of 0.22 litres (95%CI 0.14 to 0.31) in FEV1 (based on eight studies with 2446 participants) and 0.24 Litres (95% CI 0.13 to 0.36) for FVC (based on three studies with 1118 participants). There was no heterogeneity. One study ([De Carli 1995](#)) had differences in FVC at baseline so this result was excluded.

Maximum mid-expiratory flow (FEF 25-75%) showed a difference of 0.42 L/sec (95% CI 0.18 to 0.66) based on two studies with 305 participants.

There was only one study with data on patients using inhaled corticosteroids and on participants classified as having moderate to severe asthma. The result in studies using participants classified

as having mild to moderate asthma did not differ from the overall analysis (WMD 0.2 (CI 0.13 to 0.28).

SYMPTOM SCORES

There were significant advantages to the long acting beta agonist group compared with the regularly treated short acting beta agonist group for composite symptom scores, measured over the whole day and also day or night scores measured separately. The difference in whole day score was -0.27 units (SMD) (95%CI -0.11 to -0.43), based on three studies with 604 participants (Analysis 1.11).

For daytime only, the difference was -0.15 (95% CI -0.06 to -0.23), and for night time only score, the difference was -0.21 (95%CI -0.1 to -0.31), both in three studies with 701 subjects (Analysis 1.12).

There were also significant advantages to the long acting beta agonist group compared with the regularly treated short acting beta agonist group in the proportion of days and nights affected by asthma symptoms. The difference in the percentage of nights with no awakenings due to asthma was 12.12% (95%CI 7.8 to 16.43) in three studies with 606 participants (Analysis 1.15). The difference in percentage of days with no asthma symptoms was 10.34% (95%CI 1.8 to 18.88) in two studies with 307 participants (Analysis 1.14).

There were no analyses possible in the subgroup of participants using inhaled corticosteroids or with asthma classified as moderate to severe owing to a lack of data. Those with asthma graded as mild to moderate showed very similar results to the overall analysis.

RESCUE BRONCHODILATOR USE

The long acting beta agonist group used significantly less rescue bronchodilator for symptoms compared with the regularly treated short acting beta agonist group during treatment. The amount of rescue medication being used by participants in most of the studies at the start was of the order of four to five puffs each day. This fell during study treatment period, and in three studies that reported figures, the mean change was -2.7 puffs per day in the long acting beta2-agonist group and -2.0 puffs per day in the short acting beta2-agonist group. The difference in mean decrease from baseline use was -0.69 puffs per day (95%CI -0.08 to -1.29) with the group treated with long acting agents showing a greater decrease in use of rescue agent (Analysis 1.19).

Over a 24 hour period the mean difference in number of puffs used was -0.48 puffs (95%CI -0.18 to -0.77) in four studies with 751 participants (Analysis 1.16). For daytime use of rescue agent, the difference between the long acting beta2-agonist group and short acting beta2-agonist group was -0.33 day time puffs/24 hrs (95%CI -0.16 to -0.5) in four studies with 1002 participants (Analysis 1.17). However this analysis showed significant heterogeneity (χ^2 9.87 df = 3), and on investigation, this was mainly due to one study (Steffensen 1995) in which the effect size was larger. This study did not specify the baseline severity of asthma in the participants and the WMD in studies on participants all with mild-moderate asthma was -0.26 puffs/day (CI -0.09 to -0.44). There was no significant heterogeneity in this case (χ^2 4.02 df = 2). The WMD for night time use of rescue short acting beta2-agonist was -0.31 puffs/24 hrs (95%CI -0.19 to -0.43) in four studies with 1002 participants (Analysis 1.18).

The majority of studies contributing to these results used asthmatics with mild to moderate asthma and there was no data

available for subgroup analyses in more mild or more severe asthmatic participants.

QUALITY OF LIFE

Three studies (Juniper 1995; Rutten-van Molken 1995; Wenzel 1998) measured quality of life changes with treatment, using the AQOL scale by Juniper 1992, which contains thirty two questions in four domains; activity limitation, symptoms, emotional function and environmental stimuli, but only in the case of Wenzel 1998 could the results be fully extracted for both treatment groups. De Carli 1995 used the Living with Asthma questionnaire to assess patient-perceived quality of life. This gives a global score, based on 12 questions, with a reduction in score indicating better quality of life (Hyland 1991).

Combining the results from De Carli 1995 and Wenzel 1998 showed a significant advantage to the long acting beta agonist group compared with the regularly treated short acting beta agonist group in overall score, SMD 0.54 (95%CI 0.39, 0.69), N=647 for these two studies. There was significant heterogeneity in this analysis, (χ^2 8.23 df = 1). The studies used different instruments to measure quality of life with different scales and the result is expressed as the SMD, however the different scales to some extent measure different aspects of quality of life and these may be affected in different ways by the study treatment.

The results from Wenzel 1998 for separate domains also gave a significant advantage to the long acting beta agonist group, with the mean difference for symptoms 0.52 (95%CI 0.39 to 0.65), emotions 0.44 (95%CI 0.32 to 0.56), exposure to environmental stimuli 0.21 (95%CI 0.11 to 0.31) and activity limitation 0.21 (95%CI 0.11 to 0.31) with 539 participants in the study. It is known that a mean difference of ≥ 0.5 for overall quality of life and each of the individual domains is clinically important (Juniper 1994). The result for symptoms of asthma reached this level of clinical importance, with that for emotional function approaching the level.

These differences were of similar magnitude to those seen in Juniper 1995, where in all four domains there was a significantly greater improvement in the long acting beta2-agonist group compared to the short acting beta2-agonist group. The magnitude was clinically important for symptoms and emotional function. In Rutten-van Molken 1995 there was a significant improvement in all domains in the long acting beta2-agonist group compared to the short acting beta2-agonist group. This was clinically important in the domains of activity limitation and symptoms.

Subgroup analyses were not possible owing to lack of studies with data.

BRONCHIAL HYPER REACTIVITY

Three studies reported results for bronchial hyper reactivity (BHR), Beach 1993 and FitzGerald 1999, Byrnes 2000 but these used differing methods and timing. Only Beach 1993 had a wash out period after the previous dose of treatment, of 24 hours, to look at underlying changes in reactivity. FitzGerald 1999 tested reactivity two hours after the morning dose of trial medication, and Byrnes 2000 tested twelve hours after the previous dose.

Only Beach 1993 reported both mean and standard deviation, in a study on 20 participants, with a non significant difference in BHR measured as log PD20 methacholine 0.37 (95%CI -1.26 to 0.51) mg/

ml. [FitzGerald 1999](#) reported a non significant difference in degree of bronchoprotection of 1.38 fold (95%CI 0.88 to 2.15) at 12 weeks in 190 participants with moderate or greater asthma. [Byrnes 2000](#), in a crossover study, tested 14 children and found no significant difference between treatments, the ratio of PC20 histamine being 1.54 (95%CI 0.65 to 3.7).

[Lipworth 1998](#) studied the degree of bronchoprotection against methacholine challenge afforded by a long acting beta2-agonist (formoterol 12 mcg) compared with a short acting agent (terbutaline 500 mcg), both after the first dose and after two weeks treatment, in participants on inhaled corticosteroids. The first dose of formoterol gave a two fold greater degree of protection compared to terbutaline, but after two weeks treatment there was no significant difference between the two treatments, and the residual degree of protection was 1.5 fold (95%CI 0.6 to 3.8) for formoterol 12 mcg BD and 1.6 fold (95%CI 0.8 to 4.9) for terbutaline 500 mg QID.

ADVERSE EVENTS

The majority of studies, twenty seven in total, reported on adverse events related to trial medication .The exceptions were [Hekking 1990](#); [Beach 1993](#), [Rutten-van Molken 1995](#), [Lipworth 1998](#), [Taylor 1998](#), and they stated that asthma related events and pharmacologically predicted events occurred at the same rate in both groups. [Taylor 1998](#) reported extensively on asthma exacerbation rates, but this is reported later in the review.

For those studies which reported adverse events data, the odds ratio for any trial medication-related adverse event occurring in the long acting beta agonist group compared with the regularly treated short acting beta agonist group was a non-significant 1.13 (95%CI 0.8 to 1.59) in five studies with 993 participants ([Analysis 1.27](#)).

Specified pharmacologically predictable adverse effects of palpitations, headache, tremor and cramps were assessed and reported in 13 studies. A significant increase in odds ratio was found for headache in the regular long-acting groups OR 1.28 (95%CI 1.02 to 1.62). The differences in other adverse effects were non-significant: palpitations OR 1.04 (95%CI 0.62 to 1.74), tremor OR 0.68 (95%CI 0.43 to 1.07), and muscle cramps OR 2.12 (95%CI 0.99 to 4.54) where the increased odds ratio for the long acting beta agonist group approached statistical significance.

Subgroup analyses did not show any significant differences in the results from those studies using participants with more severe asthma or where all participants used inhaled corticosteroids.

ASTHMA EXACERBATIONS

Data on exacerbations of asthma were reported in fourteen studies. Exacerbations of asthma were defined in eight studies as worsening of asthma symptoms requiring treatment in addition to the study drug and rescue short acting inhaled beta -agonist agent. The number of participants experiencing at least one exacerbation was used as a comparative measure in these studies.

In [Ekstrom 1998b](#) the number of participants discontinuing participation in the study due to deterioration of asthma was recorded, and used as a measure of asthma exacerbations.

In [FitzGerald 1999](#) the number of exacerbation days was measured. These were defined as days when more than eight puffs of rescue

salbutamol were inhaled or the asthma symptoms score was at the maximum on the study scale. The number of patients requiring an increase in corticosteroid cover was recorded and this was used as the measure of major exacerbations for comparison.

In [Steffensen 1995](#) data was collected on adverse events that were possibly drug related, including asthma exacerbations, though no definition of an exacerbation was given.

[De Oliveira 1998](#) reported on withdrawals due to worsening asthma.

[De Carli 1995](#) sent unpublished tables on exacerbations at time points from three to twelve months, but did not define an exacerbation. In [Castle 1993](#) serious drug related adverse events were recorded and data on those that were respiratory and related to asthma were extracted.

[Hekking 1990](#) measured an outcome called 'asthma attacks' with no definition of an attack, though discussion in the paper makes it clear that these were not synonymous with an exacerbation as defined by others. These data have not been combined with other data on exacerbations.

[Taylor 1998](#) studied asthma control during long term treatment, and used a complex scoring system, based on PEF readings, symptoms scores, rescue bronchodilator use and presence of nocturnal waking to define both minor and major exacerbations of asthma. A major exacerbation implied major deterioration over two or more days, with PEF 40-60% of predicted value, increased asthma score and increased rescue use. The protocol stated that if this occurred, participants should commence a short course of oral prednisolone, in addition to increasing their inhaled corticosteroid dose according to their predefined action plan. Data was given as both the percentage of participants temporarily increasing their dose of inhaled corticosteroids and the percentage of participants who used one or more short courses of oral steroids. The outcome entered into the analysis was the number of participants who increased their dose of inhaled corticosteroid. This study also reported a corrected yearly exacerbation rate, for both major and minor exacerbations.

Overall, the odds ratio for experiencing at least one major exacerbation of asthma was lower in the long acting beta agonist group, OR 0.89 (95%CI 0.75 to 1.06) in nine studies with 2,890 participants ([Analysis 1.32](#)). These studies all used a highly comparable definition of an exacerbation. If the studies where the definition was imprecise or the data came from adverse events monitoring, were included in the analysis(N = 14) , there remained a lower risk of exacerbation, OR 0.90 (95%CI 0.78 to 1.03). Neither result achieved statistical significance.

[Taylor 1998](#) was a crossover study design, and was therefore not combined for this outcome with other studies in the analysis, however he reported on the rate of exacerbations and there was a significant difference for the corrected rate of major exacerbations. There was an advantage towards the long acting beta agonist group , WMD -0.29 (95%CI -0.50 to -0.08) exac/patient/year.

In the two studies where all subjects were using inhaled corticosteroids (n = 370) the odds ratio for experiencing at least one major exacerbation was 0.86 (CI 0.5 to 1.84) . The result however was not statistically significant though it was similar to the result from all studies.

GLOBAL ASSESSMENT OF EFFICACY

Six studies reported results of the assessment of efficacy of study treatment, using scales offering the participant a range from very good or very effective to poor or poorly effective. Data was available in five studies for analysis and in [Faurschou 1996](#) the authors stated that more participants rated treatment with salmeterol as effective or very effective when compared to salbutamol and the difference was statistically significant. The odds ratio of patients on long acting beta2-agonists compared with short acting agents, in the five studies with data, for finding treatment very effective or effective was 2.54 (95%CI 1.92 to 3.36, [Analysis 1.38](#)) or as NNT 5 (95% CI 4 to 7).

Four of the studies also stated that investigator rated efficacy results were of similar direction and magnitude ([Hekking 1990](#); [Hermansson1995](#); [Steffensen 1995](#); [Faurschou 1996](#)). Only two of these studies quoted the results and the analysis showed significant heterogeneity.

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 a patient's physical and mental well being and to try, through good control, to minimise long term damage to the airways and prevent undue fixed airway obstruction. Treatment is therefore directed at improving physiological endpoints and patient perceived physical and mental health.

This review shows that for assessment of airway calibre, regular treatment with long acting inhaled beta2-agonists gives significantly better results than regular therapy with short acting beta2-agonists. The magnitude of the difference was moderately large: for morning PEF 32 L/min (95% CI 25 to 41) and evening PEF 25 L/min (95% CI 18 to 32). The change from pre-treatment PEF values was also significantly greater for long acting inhaled beta2-agonists, especially in morning values, 27 L/min (95% CI 23 to 31) reflecting the longer duration of action of 12 hours compared to the short acting agents of only 4 to 6 hours. The difference for evening PEF values was a more modest 12 L/min (95% CI 8 to 16), which reflects the diurnal variation of lung function in asthma, with the worst time being on waking or in the hours just prior to waking.

Clinic measured lung function also showed a significant and clinically important benefit for treatment with long acting inhaled beta2-agonists, with an average increase in FEV1 of 220 ml (95% CI 140 to 310), FVC 190 ml (95% CI 90 to 300) and FEF25-75% 0.4 L/sec (95% CI 0.2 to 0.7).

Long acting inhaled beta2-agonists also gave advantages over regular treatment with short acting agents in terms of patient assessed symptoms, and on a variety of scales. The difference in scores for the whole day, expressed using an SMD, was 0.3 (95% CI 0.1 to 0.4) (SMD), daytime alone 0.2 (95%CI 0.1 to 0.2) and night time 0.2 (95% CI 0.1 to 0.3). Interpretation of this improvement in quantitative terms is difficult, but when looking at the percentage of days with no asthma symptoms there was a significant benefit in the long acting inhaled beta2-agonist group of 10% (95% CI 2 to 19), and nights with no asthma awakenings of 12% (95% CI 8 to 18).

The reduction in perceived symptoms was reflected in the amount of additional bronchodilator agent used, usually a short acting beta2-agonist. It was significantly less in the long acting inhaled

beta2-agonist group. The amount of rescue medication being used by participants in most of the studies at the start of the study was of the order of four to five puffs each day. This fell during study treatment period in both the participants groups treated regularly with long acting and short acting agents, and in three studies which reported figures, the mean change was 2.7 puffs per day in the long acting beta2-agonist group and 2.0 puffs per day in the short acting beta2-agonist group. Over a 24 hour period the mean difference in number of puffs was used was 0.5 puffs (95% CI 0.2 to 0.8), 0.3 puffs (95% CI 0.2 to 0.5) for daytime use and 0.3 puffs (95% CI 0.2 to 0.4) for night time use. The difference in mean decrease from baseline use was 0.7 puffs per day (95% CI 0.1 to 1.3).

These commonly used clinical endpoints, forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), symptom scores, use of rescue medication and sleep disturbance are not always good proxies for overall quality of life. Asthma specific measurement of the impact of asthma on patients' quality of life is now possible, using purpose -designed instruments, of proven reliability, validity and responsiveness. These provide a robust reliable measurement of this the global impact of aspect of efficacy of treatment. Two asthma specific measures were used in the studies included herein this review. The Living with Asthma Questionnaire (LWAQ) by [Hyland 1991](#) and Asthma Quality Of Life Score (Asthma Quality Of Life Score (AQOL) based on [Juniper 1992](#). Combining overall results from both studies showed a significantly better quality of life in those using long acting inhaled beta2-agonists, SMD 0.6 (95%CI 0.4, 0.7). This was supported by results for all four domains of the AQLQ, i.e. activity limitation, symptoms, emotional function and environmental stimuli, from three studies, though in only one case were full results of available for both groups. The differences in AQLQ score for the separate domains varied in their clinical importance, with that for asthma symptoms being consistently at a level corresponding to the criterion for a small clinically significant improvement.

Data for underlying bronchial hyper reactivity (BHR) were limited to one study and two studies looked at bronchoprotection to challenge. Laboratory measures of airway reactivity can measure the bronchoprotection to various stimuli that is conferred by regular treatment with both long and short acting beta2-agonists. The direct significance of these changes is not understood but they may provide explanations for adverse effects of treatment that may be observed or postulated from population data on mortality and severe life threatening asthma attacks.

The studies included in this review did not provide any evidence that regular treatment with either long or short acting beta2-agonist agents adversely affects airway reactivity at a level likely to be of clinical importance. This is reassuring to those who have expressed concern over the past decade or more, that regular beta2-agonist use would cause a worsening of underlying airway inflammation and thereby of BHR.

The development of tachyphylaxis to the bronchoprotective effects of beta2-agonist agents to methacholine challenge seen in [Lipworth 1998](#) occurred in spite of concomitant inhaled corticosteroid use. The clinical significance is not certain, and is probably slight at most but, but potentially this sub sensitivity could mean that long acting agents may not give full protection against a given bronchoconstrictor stimulus and extra doses of rescue agent might be required. It would argue against the use of

long acting beta2-agonist agents specifically as relief medication, which is now currently the case in some countries for formoterol.

Risks of treatment and deleterious effects must be taken into account in a comparison of effectiveness between these two treatments, especially any evidence of deterioration in asthma control, particularly in the light of historical concerns about regular use of beta2-agonist agents. Evidence from a recent case control study from one group of patients dying from asthma did not show an increased risk of death with use of inhaled symptomatic medication for an attack, except that there was an increased risk of death (OR 4.1 95%CI 1.7 to 11) for the use of nebulised symptomatic medication for an attack or in the last month. Blood levels of salbutamol were significantly higher in asthma deaths than controls, even in a situation in which controls with life threatening asthma were usually given bronchodilator before assessment. Some of the blood levels detected in the deceased asthmatics were extremely high, suggesting that over reliance on relief beta2-agonists for treatment of severe attacks could be cardio toxic (Abramson 2001).

Only one study (Castle 1993) looked at the safety of a long acting beta2-agonist (salmeterol) compared with a short acting agent (salbutamol) when used regularly over sixteen weeks in a large number of participants. It was the only study reporting figures for mortality from asthma. There was a numerical excess of deaths in the salmeterol group; 0.07% compared with 0.02%, OR 3 (95%CI 0.67 to 13.41). The numbers were very small however, and the difference was not significant with a wide confidence interval. 17% of participants included in the study were classified as having severe asthma, 69% were using inhaled corticosteroids and 4.75 oral steroids, so they formed a more severe population than those included in most of the other studies reviewed the total population. The authors proposed that use of beta agonist was not causal in the deaths reported, but rather general under treatment of their asthma.

The risk of having at least one major exacerbation, (defined as requiring treatment in addition to study treatment, usually with oral steroids) in the long acting beta2-agonist group was not reduced compared with the group using short acting agents, over the relatively short time scale of these studies; OR 0.89 (CI 0.75 to 1.06). There was a similar size difference OR 0.86 (CI 0.5 to 1.48) in the studies which only included participants on inhaled corticosteroids, however the number of participants in these studies was small. There was no evidence of an increased risk of exacerbation of asthma in those taking long acting beta2-agonists regularly.

One study (Taylor 1998) was designed to look more comprehensively at the rate of all exacerbations of asthma, including minor exacerbations. These were defined as a fall in morning PEF to 60 to 75% of best run-in value, with some increase in asthma symptoms or a fall to 40 to 60% of best PEF with no extra symptoms. There was a significantly lower rate of such episodes in the long acting beta2-agonist group, the difference being 0.59 exacerbations/patient /year (95%CI 0.33 to 0.85).

The acceptability of treatment to patients was assessed by patients rating the control of their asthma on treatment and results show a significantly higher odds ratio for assessment as good or very good by patients using long acting beta2-agonists than those using short acting beta2-agonists regularly, OR 2.5 (95%CI 1.9 to 2.4).

In recent times as healthcare resources have been increasingly constrained, treatment must be assessed not only to be clinically effective, acceptable to patients and safe but it must also be cost effective. There are currently few studies comparing the clinical and economic benefits of comparing alternate treatments in asthma, including the subject of this review, long acting with short acting inhaled beta2-agonist agents. At this stage we are therefore unable to comment upon this.

Future studies should use a standardised approach to outcome measurement in addition to cost effectiveness analysis. Perhaps inevitably at this stage, we found that different studies reported lung function parameters in varying ways, and used symptom scores with different scales, so that direct comparisons were difficult. In general the length of intervention studies should be longer to allow more appropriate assessment of effectiveness and also to take into account dropouts from therapy. The burden of asthma is dependent on the severity of the condition, and there is a distinct lack of studies looking at asthma of defined severity at either end of the spectrum, mild or severe. Increasingly, the population of patients with chronic symptomatic asthma requiring regular symptom-controller medication is going to be elderly, and studies are needed specifically in this group to determine both cost effectiveness and safety. The elderly, who might be more vulnerable to the adverse cardiovascular effects of systemic absorption of beta2-agonists, tend to be poorly represented in the studies currently available.

AUTHORS' CONCLUSIONS

Implications for practice

Long acting inhaled beta2-agonists have advantages in clinical outcomes when used regularly over the effects of regular inhaled short acting beta2-agonists. The increased cost of treatment if more long acting beta2-agonists are prescribed will have implications for medical costs, which will only be partially offset by reduced symptom directed use of short acting beta2-agonists.

Implications for research

Increasingly studies are showing that long acting inhaled beta2-agonists have anti-inflammatory and other disease modifying effects, especially in combination with inhaled corticosteroids. Whether similar effects would be present if used without inhaled corticosteroids needs assessment. There are data suggesting that beta2-agonists can enhance the translocation of the CS-CS receptor complex into the nucleus where it can effect changes in transcription, but further work is required to document the full pathophysiological effects of long acting inhaled beta2-agonists, independently and together with inhaled corticosteroids, and to more fully explain these effects.

Further cost effectiveness studies are also required.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Beach 1993

Methods	STUDY DESIGN: Parallel group. 6 week treatment period. Single centre - UK. RANDOMISATION: Yes, method not stated. BLINDING: Double blind using identical inhalers. WITHDRAWALS/DROP OUTS: All subjects completed study.
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Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma (Review)

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Beach 1993 (Continued)

COMPLIANCE: No details.
CONFOUNDERS: None apparent.
QUALITY: Jadad 4. Cochrane B

Participants	N = 20 Adults M = 13, F = 7 Mean age 39 yrs BASELINE SEVERITY: Symptomatic asthma INCLUSION : Taking ICS regularly EXCLUSION: Oral beta agonist/theophylline, ipratropium
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 400 mcg BD DEVICE: Diskhaler TREATMENT PERIOD: 6 weeks RESCUE: Short acting beta2 agonist- salbutamol 400 mcg inhalation PRN CO-INTERVENTIONS: All on, ICS- mean dose 575 & 610 mcg.
Outcomes	OUTCOMES: FEV1, FVC, PEF, PD20 Methacholine.
Notes	

Risk of bias

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

Bensch 2001

Methods	STUDY DESIGN: Parallel group. Multi centre, 26 in USA. 12 week treatment period. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, placebo controlled. Matching capsules and devices. WITHDRAWALS/DROP OUTS: 83 described, 35 due to adverse events. COMPLIANCE: Assessed by counting capsules and weighing canisters, >80% in all groups. CONFOUNDERS: Baseline characteristics similar for all groups. QUALITY: Jadad 4. Cochrane B
Participants	N = 541 randomised, 535 ITT M = 224, F = 317 ADULT Mean age 5.5 yrs (SD14.6) BASELINE SEVERITY: Mild-moderate persistent asthma. INCLUSION : Diagnosis of asthma, requiring daily use of inhaled SABA. Baseline FEV1 40 to 80% predicted, > 15% reversibility to inhaled SABA EXCLUSION: URTI, hospitalization/asthma exacerbation < 4 weeks, serious illness.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12/ 24 mcg BD SHORT ACTING BETA AGONIST: Albuterol 180 mcg QDS PLACEBO: Placebo QDS DEVICE: LABA Aerolizer DP device & SABA MDI TREATMENT PERIOD: 12 weeks RESCUE: Short acting beta2 agonist- albuterol 90 mcg inhalation PRN CO-INTERVENTIONS: ICS 51%, Slow release theophylline 17%.
Outcomes	OUTCOMES: FEV1, FVC, FEV 25 to 75%, PEF, Rescue albuterol, asthma symptom score, asthma exacerbations, adverse events.
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough; scaled 0-4.

Bensch 2001 (Continued)

Risk of bias

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

Boulet 1997

Methods	<p>STUDY DESIGN: Parallel group. Multi centre, Canada. 12 week treatment period.</p> <p>RANDOMISATION: Yes, no method stated.</p> <p>BLINDING: double blind, double dummy, matching devices.</p> <p>WITHDRAWALS/DROP OUTS: 21 described, 4 due to adverse events.</p> <p>COMPLIANCE: Not assessed objectively.</p> <p>CONFOUNDERS: Baseline characteristics similar for all groups.</p> <p>QUALITY: Jadad 4. Cochrane B</p>	
Participants	<p>N = 300 screened, 228 ITT M = 128, F = 100 ADULT Mean age 39 yrs (SD 16)</p> <p>BASELINE SEVERITY: Mild-moderate persistent asthma.</p> <p>INCLUSION : Requiring daily use of inhaled SABA for 6 months. Symptoms in 4/7 days run in. Baseline FEV1 50-80% predicted, >15% reversibility to inhaled SABA</p> <p>EXCLUSION: use of oral steroids, theophylline or ipratropium</p>	
Interventions	<p>LONG ACTING BETA AGONIST Salmeterol 50mcg BD</p> <p>SHORT ACTING BETA AGONIST: Albuterol 180 mcg QDS</p> <p>PLACEBO: Placebo BD</p> <p>DEVICE: MDI</p> <p>TREATMENT PERIOD: 12 weeks</p> <p>RESCUE: Short acting beta2 agonist- salbutamol 100 mcg inhalation PRN</p> <p>CO-INTERVENTIONS: ICS >70%, cromones, anti histamines, immunotherapy</p>	
Outcomes	<p>OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue albuterol, asthma symptom score, night awakenings, asthma exacerbations, adverse events.</p>	
Notes	<p>Symptom Score- breathlessness, chest tightness, wheezing, cough</p> <p>Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.</p>	

Risk of bias

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

Britton 1992

Methods	<p>STUDY DESIGN: Parallel group. Multi centre, Europe- 62 centres . 52 week treatment period.</p> <p>RANDOMISATION: Yes, no method stated.</p> <p>BLINDING: double blind, double dummy, matching devices.</p> <p>WITHDRAWALS/DROP OUTS: 60 described during treatment , mainly due to asthma and poor compliance.</p> <p>COMPLIANCE: Recorded but no published.</p> <p>CONFOUNDERS: Baseline characteristics similar for all groups.</p> <p>QUALITY: Jadad 5. Cochrane A</p>	
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Britton 1992 (Continued)

Participants	N = 796 screened, 667 randomised (ITT) M = 332, F = 335 ADULT Mean age 49 yrs (range 18 to 81) BASELINE SEVERITY: Moderate persistent asthma. INCLUSION : Diagnosis of asthma with regular symptoms, symptoms score > 2 on 4/7 days run in, Base-line FEV1 > 50 predicted, > 15% reversibility to inhaled SABA EXCLUSION: LRTI, hospitalization with asthma < 14 days, use of oral steroids > 20 mg /day, theophylline or ipratropium
Interventions	LONG ACTING BETA AGONIST Salmeterol 50mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: Placebo BD DEVICE: MDI TREATMENT PERIOD: 12weeks RESCUE: Short acting beta2 agonist- salbutamol 100 mcg inhalation PRN CO-INTERVENTIONS: ICS >61%, OS 15%, cromones.
Outcomes	OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue use, asthma symptom score, night awakenings, asthma exacerbations, adverse events.
Notes	Symptom Score- 0 = none to 5 = severe. Exacerbations asthma defined as worsening of asthma symptoms recorded as an AE requiring change in therapy other than inhaled SABA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Byrnes 2000

Methods	STUDY DESIGN: Crossover, 3 way design. 4 week per treatment. Single centre UK. RANDOMISATION: Yes, computer generated random code. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 5 described during treatment , 1 due lack efficacy, 3 FTA. COMPLIANCE: Assessed by counting unused blisters, >80%. CONFOUNDERS: no washout period at cross over, used second 2 week data only.. QUALITY: Jadad 5. Cochrane A
Participants	N = 52 screened, 45 randomised (ITT) CHILDREN. M = 31 F = 14 Mean age 9 yrs (sd 2.8) BASELINE SEVERITY: Symptomatic asthma on medium dose ICS. INCLUSION : Asthma requiring > 400mcg ICS . > 15% reversibility on PEF or FEV1 to inhaled SABA EXCLUSION: URTI/ use of OS/ hospitalization with asthma < 4 weeks, theophylline or ipratropium use.
Interventions	LONG ACTING BETA AGONIST Salmeterol 50/ 100 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: Placebo BD DEVICE: Diskhaler TREATMENT PERIOD: 4 weeks RESCUE: Short acting beta2 agonist- salbutamol 200 mcg inhalation up to 6 times daily CO-INTERVENTIONS: All on ICS >400 mcg.
Outcomes	OUTCOMES: FEV1, FVC, FEV 25-75%, PEF, Rescue use, asthma symptom score, symptom free days, adverse events , BHR (in subgroup).
Notes	No description of asthma score.

Byrnes 2000 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Castle 1993

Methods	<p>STUDY DESIGN: Parallel group, general practice setting in UK- 3516 GPs. 16 weeks treatment.</p> <p>RANDOMISATION: Yes, computer generated random code, blocks of 6.</p> <p>BLINDING: double blind, double dummy, matching devices. Monitoring staff unblinded.</p> <p>WITHDRAWALS/DROP OUTS: 6481, causes fully described.</p> <p>COMPLIANCE: Not assessed/ reported.</p> <p>CONFOUNDERS: Groups well balanced by characteristics. Possibility of confounding by severity of asthma.</p> <p>QUALITY: Jadad 5. Cochrane A</p>	
Participants	<p>N = 25180 randomised (TT) Adults, M = 10479 F = 14701 Mean age not reported, range 18 to > 60</p> <p>BASELINE SEVERITY: mild 17%, moderate 65%, severe 17% as categorised at randomisation by GP.</p> <p>INCLUSION : Clinical diagnosis of asthma requiring regular SABA</p> <p>EXCLUSION: Beta blocker use, serious uncontrolled diseases , pregnancy.</p>	
Interventions	<p>LONG ACTING BETA AGONIST Salmeterol 50 mcg BD</p> <p>SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS</p> <p>PLACEBO: Placebo BD</p> <p>DEVICE: MDI</p> <p>TREATMENT PERIOD: 16 weeks</p> <p>RESCUE: Patients usual rescue agent PRN</p> <p>CO-INTERVENTIONS: ICS 69%, OS 4.7%, Theophyllines, cromones, ipratropium- stable doses</p>	
Outcomes	<p>OUTCOMES: Deaths related to asthma, Admission to hospital- respiratory or asthma related. other serious adverse events related to asthma, withdrawals for respiratory or related to asthma.</p>	
Notes	<p>No definition of asthma exacerbation. Serious adverse event related to asthma= event requiring hospital admission, prolonging stay, life threatening or severely disabling.</p>	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

D'Alonzo 1994

Methods	<p>STUDY DESIGN: Three treatment parallel group, multicentre (11) study in USA, 12 wks</p> <p>RANDOMISATION: Yes, method not given.</p> <p>BLINDING: Double blind, double dummy, with 2 matching inhalers.</p> <p>WITHDRAWALS: 42/322 , by groups - 15 in salmeterol , 16 in albuterol, 11 in placebo</p> <p>CONFOUNDERS: differential rates of ICS and cromone use in regular and prn group, use of theophyllines in run in period</p> <p>QUALITY: Jadad = 4, Cochrane B</p>	
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D'Alonzo 1994 (Continued)

Participants	<p>N = 322 Albuterol = 108, placebo = 108, salmeterol = 106</p> <p>AGE- means -albuterol 31(14), placebo 28(12), salmeterol 29(12)</p> <p>BASELINE SEVERITY: Chronic symptomatic asthma.</p> <p>INCLUSION: Diagnosis asthma by ATS criteria, requiring daily drug treatment for > 6 months. Baseline FEV1 50-70% predicted, >15% FEV1 reversibility to SABA.</p> <p>EXCLUSION: Smokers</p>
Interventions	<p>LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD</p> <p>SHORT ACTING BETA AGONIST: Albuterol 180mcg QDS PLACEBO:placebo QDS</p> <p>DEVICE: MDI</p> <p>PERIOD:12 weeks</p> <p>RESCUE:albuterol 90mcg prn</p> <p>CO-INTERVENTIONS:</p> <p>ICS - used by 20% on placebo , 24% on albuterol, 21% on salmeterol</p> <p>ORAL STEROIDS - not at randomisation</p> <p>CROMONES-used by 9% on placebo , 6% on albuterol, 10% on salmeterol</p> <p>THEOPHYLLINES- used only during run in by 46% on placebo , 50% on albuterol, 43% on salmeterol</p> <p>ORAL BETA AGONISTS - not permitted</p>
Outcomes	<p>OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue use, asthma symptom score, symptom free days & nights, adverse events .</p>
Notes	<p>Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.</p> <p>Symptom Score- composite based on individual scores for breathlessness, chest tightness, wheezing, cough. Scale : 0 = none to 5 = severe, activities cancelled.</p>

Risk of bias

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

De Carli 1995

Methods	<p>STUDY DESIGN: Parallel group, multicentre, 27 in Italy. 12 weeks initially, with 12 month follow on.</p> <p>RANDOMISATION: Yes, used PACT computer code, allocation blocks of 2.</p> <p>BLINDING: open label, not blinded.</p> <p>WITHDRAWALS/DROP OUTS: 27 withdrawals detailed in 3mths, 1 in follow up period</p> <p>COMPLIANCE: Not assessed</p> <p>CONFOUNDERS: Groups well balanced by characteristics</p> <p>QUALITY: Jadad 3. Cochrane A</p>
Participants	<p>N = 252 screened RANDOMISED/COMPLETED = 234 ITT, adult, M = 116 F = 118 Mean age: 45 (range 18 to 81)</p> <p>BASELINE SEVERITY: Mild to moderate asthma</p> <p>INCLUSION : Baseline FEV1 50 to 80% predicted, >15% FEV1 reversibility to SABA.</p> <p>EXCLUSION: none specified.</p>
Interventions	<p>LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD</p> <p>SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS</p> <p>PLACEBO: none</p> <p>DEVICE: MDI</p> <p>TREATMENT PERIOD: 12 weeks initial, 12 months follow on.</p> <p>RESCUE Salbutamol prn</p> <p>CO-INTERVENTIONS: ICS 10%, OS < 20mg/day 4%</p>

De Carli 1995 (Continued)

Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, adverse events. Exacerbations. Efficacy score-patient and investigator rated. Asthma QOL score	
Notes	Exacerbations- not defined. Symptom Score- Night-time 0-4 (none - so severe that no sleep possible). Daytime Symptom Score- 0 = none to 5 = severe. LWAQ for QOL measure (Italian version)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

De Oliveira 1998

Methods	STUDY DESIGN: Parallel group, single centre, Brazil, 4 wks. RANDOMISATION: Yes, method not stated. BLINDING: double blind, double dummy. WITHDRAWALS/DROP OUTS: 7 described after randomization. COMPLIANCE: No details CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B	
Participants	N = 136 ENROLLED/ 60 RANDOMISED/53 COMPLETED, ADULT , M=17 F=43 Mean age: 37 (range 18-64) BASELINE SEVERITY: Mild-moderate symptomatic asthma INCLUSION : Diagnosis asthma by ATS criteria, Baseline FEV1 >50% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: Use of theophyllines or anticholinergic, except in acute attack.	
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: placebo BD DEVICE: MDI. TREATMENT PERIOD: 4 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: ICS > 42%,	
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, adverse events,	
Notes	Symptom Score- Night-time 0-4 (none - so severe that no sleep possible). Day-time 0-4 (no symptoms - symptoms so severe normal activities not possible)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Ekstrom 1998a

Methods	STUDY DESIGN: Parallel group, 3 treatment arms; multicentre, 28 centres Scaninavia. 12 wks. RANDOMISATION: Yes, computer generated random order, balanced blocks..	
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Ekstrom 1998a (Continued)

BLINDING: double blind, double dummy, matching devices.
WITHDRAWALS/DROP OUTS: 32 described, due to asthma.
COMPLIANCE: Not assessed/ reported.
CONFOUNDERS: Groups well balanced by characteristics.
QUALITY: Jadad 5. Cochrane A

Participants	N = 343 Adults, M = 164 F = 179 Mean age 48 (RANGE 18 to 82) BASELINE SEVERITY: moderate stable asthma. INCLUSION : Diagnosis asthma by ATS criteria. Baseline FEV1 40 to 80% predicted, >15% FEV1 re- versibility to SABA. EXCLUSION: none stated in paper.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD SHORT ACTING BETA AGONIST: Terbutaline 500mcg QDS PLACEBO: Placebo QDS DEVICE: Dry powder device- turbuhaler. TREATMENT PERIOD: 12 weeks RESCUE: Terbutaline 250 mcg via turbuhaler PRN CO-INTERVENTIONS: ICS 89%, cromones 2% - stable doses OS 2 subjects
Outcomes	OUTCOMES: FEV1, PEF, Rescue use, asthma symptom score, adverse events
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough. Scale :0 - 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Ekstrom 1998b

Methods	STUDY DESIGN: Parallel group, 3 treatment arms; multicentre, 25 centres Norway, Sweden, Spain, Italy. 12 wks. RANDOMISATION: Yes, method not given. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 38 described. 27 to asthma, 11 to adverse events. COMPLIANCE: Not assessed/ reported. CONFOUNDERS: Groups well balanced by characteristics. Excess withdrawals from SABA group, 10 sub- jects did not fully meet inclusion criteria. QUALITY: Jadad 4. Cochrane B
Participants	N = 397 Adults, M = 232 F = 179 Mean age 47 (RANGE 18 to 79) BASELINE SEVERITY: mild - moderate asthma. INCLUSION : Diagnosis asthma by ATS criteria. Baseline FEV1 50-80% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: none stated in paper.
Interventions	LONG ACTING BETA AGONIST: Formoterol 6 mcg BD SHORT ACTING BETA AGONIST: Terbutaline 500mcg QDS PLACEBO: Placebo QDS DEVICE: Dry powder device. TREATMENT PERIOD: 12 weeks RESCUE: Terbutaline 250 mcg via turbuhaler PRN CO-INTERVENTIONS: ICS 80%, cromones 5% (at stable dosages)

Ekstrom 1998b (Continued)

Outcomes	OUTCOMES: FEV1, PEF, Rescue use, asthma symptom score, adverse events. asthma deterioration	
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough. Scale :0 - 3. Asthma deterioration leading to withdrawal reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Faurschou 1996

Methods	STUDY DESIGN: Parallel group, multicentre, 20 centres UK, Norway, Denmark. 6 wks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 17 described. COMPLIANCE: Not assessed/ reported. CONFOUNDERS: Groups well balanced by characteristics. QUALITY: Jadad 4. Cochrane B	
Participants	N = 286 RECRUITED, 190 ENROLLED. Adults, M = 100 F=90 Mean age 51 (RANGE 18-80) BASELINE SEVERITY: moderate to severe symptomatic asthma. INCLUSION : Baseline FEV1 30-75% predicted, >15% FEV1 reversibility to SABA. Symptoms on 4/7 days run in, using > 1200mcg BUD or 1500mcg BDP EXCLUSION: URTI/ Change in asthma medication/ exacerbation asthma within 2 wks. Maintenance with OS.	
Interventions	LONG ACTING BETA AGONIST: Salmeterol 100 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 400mcg QDS PLACEBO: Placebo BD DEVICE: Dry powder device- DISKHALER TREATMENT PERIOD: 6 weeks RESCUE: Salbutamol 200 mcg PRN CO-INTERVENTIONS: ALL ON ICS . theophylline 18% Ipratropium 10%	
Outcomes	OUTCOMES: FEV1, FVC, FEV 25 to 75%, PEF, Rescue use, asthma symptom score, symptom free days & nights, adverse events . Efficacy rating	
Notes	Symptom Score- Night-time 0 to 3 (none - so severe that no sleep possible). Day-time 0-4 (no symptoms - symptoms so severe normal activities not possible). Exacerbations asthma defined as worsening of asthma requiring a change in therapy .	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

FitzGerald 1999

Methods	STUDY DESIGN: Parallel group, multicentre, 15 centres Canada. RANDOMISATION: Yes, no method stated. 24 wks.	
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FitzGerald 1999 (Continued)

BLINDING: double blind, double dummy, matching devices.
WITHDRAWALS/DROP OUTS: 54 described.
COMPLIANCE: Not assessed/ reported.
CONFOUNDERS: Groups well balanced by characteristics.
QUALITY: Jadad 4. Cochrane B

Participants	N = 374 RECRUITED, 271 RANDOMISED. Adults, M = 116 F = 155 Mean age 36 (SD 13) BASELINE SEVERITY: moderate to severe asthma. INCLUSION : Diagnosis asthma by ATS criteria. > 15% FEV1 reversibility to SABA. Using ICS 400 to 1200 mcg for > 1mth. PC20 methacholine < 8mg/ml EXCLUSION: URTI/ Change in asthma medication/ exacerbation asthma within 2 months. Smoking.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD SHORT ACTING BETA AGONIST: Albuterol 200mcg QDS PLACEBO: Placebo QDS DEVICE: Dry powder device. TEATMENT PERIOD: 24 weeks RESCUE:Albuterol 100 mcg PRN CO-INTERVENTIONS: ALL ON ICS . Theophylline, Ipratropium, Cromones, antihistamines- at fixed doses.
Outcomes	OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue use, asthma symptom score, exacerbations asthma, BHR, adverse events .
Notes	Symptom Score- 0 = best to 4 = worst. Exacerbation defined as that requiring increase in corticosteroid cover.

Risk of bias

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

Hekking 1990

Methods	STUDY DESIGN: Parallel group, multicentre, Holland. 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 45 described after randomization. COMPLIANCE: Not assessed / reported. CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B
Participants	N = 301 ENROLLED/ RANDOMISED, ADULT, M = 157 F=144 Mean age: 40 (SD 14) BASELINE SEVERITY: Stable phase asthma INCLUSION : Stable phase asthma, Baseline FEV1 <80% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: Use of theophyllines, oral beta_2 agonists or anticholinergics.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200mcg QDS PLACEBO: placebo BD DEVICE: MDI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: stable dose ICS, cromones.
Outcomes	OUTCOMES: PEF, Rescue use, asthma attacks.

Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma (Review)

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Hekking 1990 (Continued)

Efficacy rating

Notes	Asthma attacks not defined.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Hermansson1995

Methods	STUDY DESIGN: Parallel group, multicentre, 23 centres Europe. 4 wks. RANDOMISATION: Yes, no method stated. BLINDING: open label, not blinded. WITHDRAWALS/DROP OUTS: 15 after randomization. COMPLIANCE: 93 - 96% reported. CONFOUNDERS: Groups well balanced by characteristics. QUALITY: Jadad 2. Cochrane B	
Participants	N = 243 RANDOMISED. Adults, M = 120 F = 123 Mean age 48 (RANGE 18 to 78) BASELINE SEVERITY: mild to moderate asthma. INCLUSION : Baseline FEV1 > 75% predicted, > 15% FEV1 reversibility to SABA. Symptom score >2 on 4/7 days run in EXCLUSION: LRTI/ exacerbation asthma within 1 mth. OS > 20mg/day	
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Terbutaline 500mcg QDS PLACEBO: none DEVICE: Dry powder devices- diskhaler, turbuhaler. TREATMENT PERIOD: 4 weeks RESCUE:Salbutamol 400 mcg PRN CO-INTERVENTIOS: ICS 73% . OS 3% Cromones,	
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, adverse events . Efficacy rating	
Notes	Symptom Score- Night-time 0 to 4 (none - so severe that no sleep possible). Day-time 0 to 5 (no symp- toms - symptoms so severe normal activities not possible)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Juniper 1995

Methods	STUDY DESIGN: 3 way cross over, multicentre, 14 centres Canada, 4 wks. RANDOMISATION: Yes, no method stated. BLINDING: Double blind, double dummy, matching inhalers. WITHDRAWALS/DROP OUTS: 21 described after randomization. COMPLIANCE: >70% reported for all but 7 subjects. CONFOUNDERS:	
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Juniper 1995 (Continued)

QUALITY: Jadad 4. Cochrane B

Participants	N = 140 RANDOMISED. Adults, M = 66 F = 74 Mean age 37.5 (sd 14.5) BASELINE SEVERITY: mild to moderate asthma. INCLUSION : Baseline FEV1 > 60% predicted, > 15% FEV1 reversibility to SABA. Symptom score > 2 on 4/7 days run in EXCLUSION: Exacerbation asthma within 1 mth, emergency room visit > 3 mths, uncontrolled illness, pregnancy. OS within 1mth. Theophylline .
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: placebo QDS DEVICE: MDI. TREATMENT PERIOD: 4 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: ICS 77%. Cromones 15%, 30% none.
Outcomes	OUTCOMES: FEV1, FVC, FEV 25-75%, PEF, Rescue use, asthma symptom score, symptom free days & nights, adverse events, AQOL scores.
Notes	AQOL score measures-symptoms, emotions, activity limitation, environment-overall scores + individual domains

Risk of bias

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

Kemp 1998

Methods	STUDY DESIGN: Parallel group, multicentre, 14 centres Canada, 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: Double blind, double dummy, matching inhalers. WITHDRAWALS/DROP OUTS: 41 described after randomization. COMPLIANCE: > 70% reported for all but 7 subjects. CONFOUNDERS: QUALITY: Jadad 4. Cochrane B
Participants	N = 451 RANDOMISED. Adults, M = 262 F = 189 Mean age 31 (sd 14) BASELINE SEVERITY: mild - moderate asthma. INCLUSION : Diagnosis asthma by ATS criteria. Baseline FEV1 50-80% predicted, >15% FEV1 reversibility to SABA. Requiring daily drug treatment for > 6 mths. EXCLUSION: smoking.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Albuterol 180 mcg QDS PLACEBO: placebo QDS DEVICE: MDI & dry powder device. TREATMENT PERIOD: 12 weeks RESCUE: Albuterol 100 mcg PRN CO-INTERVENTIONS: ICS 55 to 70 % . Cromones 7 to 12 %
Outcomes	OUTCOMES: FEV1, FVC, FEV 25-75%, PEF, Rescue use, asthma symptom score, symptom free days & nights, adverse events, exacerbations.
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough. Scale : 0 to 3.

Kemp 1998 (Continued)

Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

Risk of bias

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

Kesten 1991

Methods	STUDY DESIGN: Parallel group, multicentre, 7 centres Canada & UK. 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: Double blind, double dummy, matching inhalers. WITHDRAWALS/DROP OUTS: 12 described after randomization. COMPLIANCE: assessed by diary card, not reported. CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B
Participants	N = 309 ENROLLED, 145 RANDOMISED. Adults, M = 60 F=85 Mean age NOT REPORTED BASELINE SEVERITY: stable, symptomatic asthma. INCLUSION : Baseline FEV1 >40% predicted, >15% FEV1 reversibility to SABA. Requiring > 2 puffs res-cue/day in run in EXCLUSIONuse of OS, exacerbation asthma within 1mth
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD SHORT ACTING BETA AGONIST: Albuterol 200 mcg QDS PLACEBO: placebo BD DEVICE: MDI. TREATMENT PERIOD: 12 weeks RESCUE: Albuterol 100 mcg PRN CO-INTERVENTIONS: None 32%, ICS 62 % . Cromones 7 % Theophylline 32%
Outcomes	OUTCOMES: FEV1, FVC, FEV 25 to 75%, PEF, Rescue use, rate asthma attacks day & night, adverse events, exacerbations. Efficacy rating

Notes

Risk of bias

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

Kozlik-Feldman 1996

Methods	STUDY DESIGN: Parallel group, single centre Germany, 12 weeks RANDOMISATION: Yes, no method stated. BLINDING: not stated and no details in paper WITHDRAWALS/DROP OUTS: All completed, no withdrawals. COMPLIANCE: Not assessed CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 2. Cochrane B
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Kozlik-Feldman 1996 (Continued)

Participants	N = 22 RANDOMISED/COMPLETED, children, M = 15 F = 7 Mean age: 9.7 (SD 3.5) BASELINE SEVERITY: Mild asthma, not requiring additional therapy other than SABA INCLUSION : Mild asthma, requiring no preventive therapy. EXCLUSION: Requiring additional therapy for asthma.	
Interventions	LONG ACTING BETA AGONIST: Formoterol 24 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: none DEVICE: not specified TREATMENT PERIOD: 12 weeks RESCUE: none required CO-INTERVENTIONS: none	
Outcomes	OUTCOMES: FEV1, FVC, histamine provocation, beta-receptor binding sites on mononuclear leucocytes, adverse events	
Notes	Histamine provocation only until subjective endpoint, not 20% fall in FEV1.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Lai 1995

Methods	STUDY DESIGN: cross over, single centre Hong Kong. 2weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 5 described after randomization. COMPLIANCE: Not assessed CONFOUNDERS: Not analysed by ITT QUALITY: Jadad 4. Cochrane B	
Participants	N = 55 ENROLLED, 25 RANDOMISED, 20 COMPLETED. Adults, M = 14 F = 6 Mean age: 41.7 (SD 3.2) BASELINE SEVERITY: Moderate to severe asthma. INCLUSION : Baseline FEV1 > 30% predicted, > 15% FEV1 reversibility to SABA. Requiring ICS > 800MCG/DAY EXCLUSION: none stated	
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Albuterol 400 mcg QDS PLACEBO: placebo BD DEVICE: Dry powder device- diskhaler TREATMENT PERIOD: 2 weeks RESCUE: Albuterol 400 mcg PRN CO-INTERVENTIONS: ICS all 800-2000 mcg/day , OS.	
Outcomes	OUTCOMES: FEV1, PEF, Rescue use, asthma symptom score, efficacy rating, adverse events.	
Notes	No details on Symptom Score- or scale.	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Lai 1995 (Continued)

Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)
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Leblanc 1996

Methods	STUDY DESIGN: 3 way cross over, multicentre 15 Canada. 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 67 described after randomization. COMPLIANCE: 93% assessed by diary card. CONFOUNDERS: Smokers included QUALITY: Jadad 4. Cochrane B	
Participants	N = ENROLLED, 367 RANDOMISED. Adults, M = 164 F=203 Mean age: 39 (SD 13.9) BASELINE SEVERITY: mild to moderate asthma. INCLUSION : Baseline FEV1 > 60% predicted, > 15% FEV1 reversibility to SABA. Symptoms on 4/7 days run in. EXCLUSION: methylxanthines, anticholinergic, OS	
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: placebo QDS DEVICE: MDI. TEATMENT PERIOD: 12 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: ICS >80% , cromones 7%	
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom free days & nights, adverse events .	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Lenney 1995

Methods	STUDY DESIGN: Parallel group, conducted as 2 separate studies, multicentre 91 in 17 countries. RANDOMISATION: Yes, no method stated. BLINDING: double blind, matching devices. WITHDRAWALS/DROP OUTS: 50 described after randomization. COMPLIANCE: Not assessed. CONFOUNDERS: QUALITY: Jadad 4. Cochrane B	
Participants	N = ENROLLED, 847 RANDOMISED. Children , M = 534 F = 313 Mean age: 10.2 (SD 2.9) BASELINE SEVERITY: Symptomatic asthma requiring inhaled SABA therapy. INCLUSION : > 15% FEV1/PEF reversibility to SABA. Symptoms on 5/7 days run in, requiring SABA 7/14 days. EXCLUSION: Exacerbation asthma requiring hospital/ LRTI within 1 mth, current OS.	
Interventions	LONG ACTING BETA AGONIST: Salmeterol 25 mcg BD or Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg BD	

Lenney 1995 (Continued)

PLACEBO: none
DEVICE: MDI or Diskhaler.
TREATMENT PERIOD: 52 weeks
RESCUE: Salbutamol 100 mcg PRN
CO-INTERVENTIONS: ICS > 60%, cromones 23%

Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom free days & nights, exacerbations, adverse events.
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA. Symptom Score- Night-time 0 to 3 (none - so severe that no sleep possible). Day-time 0 to 3 (no symptoms - symptoms so severe normal activities not possible)

Risk of bias

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

Lipworth 1998

Methods	STUDY DESIGN: Parallel group- 5 groups, 2 centres UK. 2 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 5 described after randomization. COMPLIANCE: assessed by diary card & counting doses not used, >75% CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B
Participants	N= ENROLLED, 72 RANDOMISED.67 COMPLETED. ADULT , M = 38 F = 34 Mean age: 37 (range 16 to 65) BASELINE SEVERITY: Mild to moderate asthma INCLUSION : Diagnosis asthma by ATS criteria. Baseline FEV1 > 60% predicted, > 15% FEV1 reversibility to SABA, PD20 methacholine < 1000mcg EXCLUSION: LRTI within 1 mth, current OS. Smoking within 1 yr, current pollen allergy.
Interventions	LONG ACTING BETA AGONIST: Formoterol 6 mcg BD/ Formoterol 12 mcg BD/ Formoterol 24 mcg BD SHORT ACTING BETA AGONIST Terbutaline 500 mcg QDS PLACEBO: Placebo QDS DEVICE: Dry powder device- turbuhaler. TREATMENT PERIOD: 2 weeks RESCUE: Ipratroprium PRN CO-INTERVENTIONS: All on ICS < 2000 mcg/day , cromones stable dose
Outcomes	OUTCOMES: PEF, PD20 methacholine
Notes	

Risk of bias

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

Lundback 1993

Methods	STUDY DESIGN: Parallel group- multicentre 47 in 11 countries. 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 85 described after randomization. COMPLIANCE: Not assessed CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B
Participants	N = 460 ENROLLED, 388 RANDOMISED. ADULT , M = 187 F = 201 Median age: 44 (range 19 to 79) BASELINE SEVERITY: Mild to moderate asthma INCLUSION : Baseline FEV1 > 50% predicted, > 15% FEV1 reversibility to SABA. Symptoms on 4/7 days run in. EXCLUSION: OS 20mg/day, uncontrolled illness.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: Placebo BD DEVICE: Dry powder device- diskhaler. TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol 200 mcg PRN CO-INTERVENTIONS: ICS 55%, os 10%. cromones stable dose
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, adverse events . exacerbations
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

Risk of bias

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

Pearlman 1992

Methods	STUDY DESIGN: parallel-group(3), multicentre (8) in USA RANDOMISATION: Randomised- means and methods not described. BLINDING: double-blind, placebo controlled using 2 identical inhalers WITHDRAWALS: 33 DESCRIBED COMPLIANCE : Not reported in paper. CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad score = 4. COCHRANE = B
Participants	N = 234, ADULT/ADOLESCENT M = 150, F = 84 Mean age = 27.3. range 12 to 73yr BASELINE SEVERITY: Mild-moderate asthma INCLUSION: Baseline FEV150-80% predicted. Diagnosis asthma by ATS definition,FEV1 reversibility to albuterol >15%. Requiring daily beta agonist treatment during preceeding 6 months. EXCLUSION: smoking, theophylline and oral beta agonist
Interventions	LONG ACTING BETA AGONIST : Salmeterol 42 mcg bd SHORT ACTING BETA AGONIST :Albuterol 180 mcg qds PLACEBO: placebo qds DEVICE:MDI PERIOD TREATMENT: 12 weeks RESCUE: Albuterol 90 mcg PRN

Pearlman 1992 (Continued)

COINTERVENTIONS: ICSS 40%, cromones 7%,

Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, adverse events . exacerbations
Notes	Symptom Score- composite based on individual scores for breathlessness, chest tightness, wheezing, cough. Scale : 0=none to 5= severe, activities cancelled. Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

Risk of bias

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

Rutten-van Molken 1995

Methods	STUDY DESIGN: Parallel group-single centre , Holland. 6 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, matching devices. WITHDRAWALS/DROP OUTS: 13 described after randomization. COMPLIANCE: Not assessed CONFOUNDERS: Groups well balanced by characteristics. Not ITT QUALITY: Jadad 4. Cochrane B
Participants	N = ENROLLED, 120 RANDOMISED. 107 COMPLETED ADULT , M = 60 F = 47 Mean age: 53 (SD 14) BASELINE SEVERITY: Moderate asthma INCLUSION : Baseline FEV1 50 to 70% predicted, > 15% FEV1 reversibility to SABA. EXCLUSION: URTI/ LRTI < 6 WKS. OS, theophyllines, uncontrolled illness.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 400 mcg BD PLACEBO: DEVICE: Dry powder device- diskhaler. TREATMENT PERIOD: 6 weeks RESCUE: Salbutamol 400 mcg PRN CO-INTERVENTIONS: ICS 31%, cromones stable dose
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, efficacy score, AQOL/LWAQ scores, % days with no symptoms ,% nights with no asthma awakenings . Efficacy rating
Notes	Symptom Score- Night-time 0 to 4(none - so severe that no sleep possible). Day-time 0 to 5 (no symptoms - symptoms so severe normal activities not possible)

Risk of bias

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

Staehr 1995

Methods	<p>STUDY DESIGN: 2 period cross over, general practice setting, 29 GPs , Denmark. 4 week treatment period.</p> <p>RANDOMISATION: Yes, no method stated.</p> <p>BLINDING: double blind, double dummy, matching devices.</p> <p>WITHDRAWALS/DROP OUTS: 36 pre-randomisation, 10 described after randomization.</p> <p>COMPLIANCE: Not assessed / reported.</p> <p>CONFOUNDERS: Groups well balanced by characteristics</p> <p>QUALITY: Jadad 4. Cochrane B</p>
Participants	<p>N = 128 ENROLLED/ 92 RANDOMISED, ADULT, M = 36 F=56 Mean age: 40</p> <p>BASELINE SEVERITY: Mild-moderate stable asthma</p> <p>INCLUSION : Stable phase asthma, run-in PEF average >50% predicted, >15% PEF reversibility to SABA.</p> <p>EXCLUSION: uncontrolled disease, pregnancy, Use of theophyllines, oral beta₂ agonists or anticholinergics.</p>
Interventions	<p>LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD</p> <p>SHORT ACTING BETA AGONIST: Salbutamol 400mcg QDS</p> <p>PLACEBO: placebo BD</p> <p>DEVICE: Diskhaler</p> <p>TREATMENT PERIOD: 4 weeks</p> <p>RESCUE: Salbutamol 400 mcg PRN</p> <p>CO-INTERVENTIONS: none 28%, ICS 72%, OS, cromones.</p>
Outcomes	OUTCOMES: PEF, Rescue use, asthma symptom score, adverse events.
Notes	Symptom Score- Night-time 0 to 4 (none - so severe that no sleep possible). Day-time 0 to 5 (no symptoms - symptoms so severe normal activities not possible)

Risk of bias

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

Steffensen 1995

Methods	<p>STUDY DESIGN: Parallel group-multicentre , 20 Scandinavia.12 weeks.</p> <p>RANDOMISATION: Yes, no method stated.</p> <p>BLINDING: double blind, double dummy, matching devices.</p> <p>WITHDRAWALS/DROP OUTS: 42 described after randomization.</p> <p>COMPLIANCE: Not assessed</p> <p>CONFOUNDERS: Groups well balanced by characteristics</p> <p>QUALITY: Jadad 4. Cochrane B</p>
Participants	<p>N = 362 ENROLLED, 304 RANDOMISED. ADULT , M = 60 F = 47 Mean age: 48 (SD 13)</p> <p>BASELINE SEVERITY: not specified, clinically stable.</p> <p>INCLUSION : Baseline FEV1 > 40% predicted, > 15% FEV1 reversibility to SABA. Requiring SABA.</p> <p>EXCLUSION: unstable asthma, altered dose medication.</p>
Interventions	<p>LONG ACTING BETA AGONIST: Formoterol 12 mcg BD</p> <p>SHORT ACTING BETA AGONIST: Salbutamol 400 mcg QDS</p> <p>PLACEBO: placebo QDS</p> <p>DEVICE: Dry powder device.</p> <p>TREATMENT PERIOD: 12 weeks</p> <p>RESCUE: Salbutamol 100 mcg PRN</p> <p>CO-INTERVENTIONS: ICS 84%, OS 6%, cromones stable dose</p>

Steffensen 1995 (Continued)

Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score. adverse events, including asthma exacerbations. Efficacy rating
Notes	Symptom Score- Day: 0 = none, to 3 = very severe symptoms. Night: 0 = none to 3 = almost no sleep due to asthma. No definition of asthma exacerbation recorded as an adverse event given.

Risk of bias

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

Taylor 1998

Methods	STUDY DESIGN: 3 way cross over, 2 centre, New Zealand. 24 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 35 described after randomization and 8 protocol violators. COMPLIANCE: Assessed by counting blisters, > 87% CONFOUNDERS: Not analysed by ITT, Efficacy analysis similar. QUALITY: Jadad 4. Cochrane B
Participants	N = ENROLLED, 165 RANDOMISED, 157 ANALYSED. ADULT , M = 73 F = 92 Mean age: 38 (range 18 to 64) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : > 15% FEV1 reversibility to SABA. PC20 methacholine < 8mg/ml. EXCLUSION: current smokers, requiring OS or theophyllines, SABA requirement > 10 puffs/day, significant illness.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 400 mcg QDS PLACEBO: placebo QDS DEVICE: Dry powder device- diskhaler. TREATMENT PERIOD: 24 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: None 8%, ICS 92%, cromones stable dose
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, exacerbations, daily asthma score.
Notes	Exacerbations- Major = daily asthma score 3, PEF 40 to 60% predicted, requiring OS. Minor- Daily asthma score 2, PEF 61 to 75% predicted, increased rescue use.

Risk of bias

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

Venables 1992

Methods	STUDY DESIGN: 2 way cross over, general practice setting, unspecified number practices in UK RANDOMISATION: Yes, no method stated. BLINDING: open, not blinded.
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Venables 1992 (Continued)

WITHDRAWALS/DROP OUTS: 26 pre-randomization, 16 post randomisation (adverse events etc) 28 non compliant.
COMPLIANCE: Assessed by diary card, 28 excluded for non compliance..
CONFOUNDERS:
QUALITY: Jadad 2. Cochrane B

Participants	N = 128 ENROLLED/ 102 RANDOMISED, 58 completed, ADULT, M = 54 F = 48 Mean age: 39 (range 18 to 71) BASELINE SEVERITY: Mild persistent asthma INCLUSION : Adult asthmatics, requiring daily bronchodilator treatment < 800mcg SABA/day. Baseline FEV1 > 75% predicted, > 15% FEV1 reversibility to SABA. Minimum symptom score 1:4 in 4 of 7 days run in. EXCLUSION: Serious uncontrolled diseases, URTI < 2 weeks, pregnancy, lactation, OS within 6 weeks, > 4 courses OS within 12 months.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Terbutaline 500 QDS PLACEBO: none DEVICE: SABA turbuhaler, LABA diskhaler. TREATMENT PERIOD: 4 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: ICS < 400mcg /day 50%, cromones, theophyllines at constant dose
Outcomes	OUTCOMES: FEV1, FVC, PEF, asthma symptom score, nights with asthma, patient assessment, adverse events
Notes	Symptom Score- breathlessness, wheezing, cough. Scale :0 = none to 3=symptoms most of day

Risk of bias

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

Wenzel 1998

Methods	STUDY DESIGN: Parallel group, multicentre, 40, USA. 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 15 described after randomization. COMPLIANCE: Not assessed / reported. CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B
Participants	N = 539 ENROLLED/ RANDOMISED, ADULT/ADOLESCENT , M = 272 F = 266 Mean age: 35.4 (range 12 to 83) BASELINE SEVERITY: Mild to moderate persistent asthma INCLUSION : Diagnosis asthma by ATS criteria, requiring daily bronchodilator treatment > 6 weeks. Baseline FEV1 40 to 80% predicted, > 15% FEV1 reversibility to SABA. EXCLUSION: CF, COPD, current smokers, hospitalized by exacerbation asthma < 6 weeks. Use of theophyllines or cromones.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD SHORT ACTING BETA AGONIST: Albuterol 180mcg QDS PLACEBO: placebo BD DEVICE: MDI. TREATMENT PERIOD: 12 weeks

Wenzel 1998 (Continued)

RESCUE: Albuterol 90 mcg PRN
CO-INTERVENTIONS: ICS 46%,

Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, adverse events, AQOL scores.
Notes	Symptom Score- Night-time 0-3 (none - woke > 3 times). Day-time 0-3 (no symptoms - significant discomfort)

Risk of bias

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

ICS = Inhaled corticosteroids. OS = oral corticosteroids. LABA = long-acting beta2 agonist. SABA = Short-acting beta 2 agonist. Short acting beta 2 agonist salbutamol known in USA as albuterol- dose measured at mouthpiece 90 mcg = 100mcg from inhaler . Bronchial hyperreactivity = BHR, measured as PD20 or PC20 in methacholine or histamine. BDP = beclomethasone dipropionate, BUD = budesonide , FP = fluticasone propionate. Cromones = sodium cromoglycate, nedocromil sodium .

MDI = Metered dose inhaler. Dosages: QDS= 4 times daily, TDS= 3 times daily, BD= twice daily.

AQOL score = Asthma quality of life score, based on Juniper 1992 (Juniper EF, Guyatt GH. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992;47:76-83) value of 1 = maximum impairment, value 7 = no impairment. Results 0.5 = small change, 1.0 = moderate change, 1.5 = large change.

LWAQ = Living with asthma questionnaire (Hyland M. The living with asthma questionnaire. Respir Med 1991;85 supp:13-16.), lower score indicates better quality of life.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adinoff 1998	Intervention- no short acting beta2-agonist group
Akpınarlı 1999	Intervention- no short acting beta2-agonist group
Arvidsson1989	Intervention- dose of long acting beta2-agonist varied during study
Aziz 1999	Intervention- treatment period less than 2 weeks
Aziz 1998	Intervention- treatment period less than 2 weeks
Aziz I Tan 1998	Intervention- treatment period less than 2 weeks
Baki 1998	Intervention- no short acting beta2-agonist group
Becker Simons 1993	Abstract only- no further publication or details on request
Becker 1989	Intervention- treatment period less than 2 weeks
Bhagat 1995	Intervention- treatment period less than 2 weeks
Bishop 1994	Intervention- treatment period less than 2 weeks
Blake 1999	Intervention- treatment period less than 2 weeks
Booth Bish 1996	Intervention- no short acting beta2-agonist group
Booth 1993	Intervention- no short acting beta2-agonist group

Study	Reason for exclusion
Boulet Cartier 1998	Intervention- no short acting beta2-agonist group
Boulet Turcot 1997	Intervention- no short acting beta2-agonist group
Bowers 1997	Not RCT, Review of 8 previously published studies
Boyd 1995	Intervention- no short-acting beta(2)-agonist group
Brambilla 1994	Intervention- oral SR short-acting beta(2)-agonist
Busse 1998	Intervention- no short-acting beta(2)-agonist group
Campbell 2000	Intervention- no short-acting beta(2)-agonist group
Carlsen 1995	Intervention- treatment period less than 2 weeks
Charpin 1992	Intervention- no short-acting beta(2)-agonist group
Chervinsky 1999	Intervention- no short-acting beta(2)-agonist group
Cheung 1992	Intervention- no short-acting beta(2)-agonist group
Clark 1993	Not RCT, Case reports
Clauzel 1998	Not RCT, intervention- no short-acting beta(2)-agonist group
Cockcroft 1997	Intervention- treatment period less than 2 weeks
Dahl 1991	Intervention- no short-acting beta(2)-agonist group
Derom 1992	Intervention- treatment period less than 2 weeks
Di-Lorenzo 1995	Intervention- treatment period less than 2 weeks
Droszcz 1999	Not RCT, intervention- no short-acting beta(2)-agonist group
Faurschou 1991	Intervention- no short-acting beta(2)-agonist group
Faurschou 1992	Abstract only- no publication details available
Faurschou Dahl 1997	Intervention- no short-acting beta(2)-agonist group
Fitzpatrick 1990	Intervention- no short-acting beta(2)-agonist group
Fuglsang 1998	Intervention- no short-acting beta(2)-agonist group
Gardiner 1994	Intervention- no short-acting beta(2)-agonist group
Giannini 1995	Intervention- treatment period less than 2 weeks
Giannini Bacci 1999	Intervention- treatment period less than 2 weeks
Gong 1996	Intervention- treatment period less than 2 weeks
Gotz 1995	Intervention- no short-acting beta(2)-agonist group

Study	Reason for exclusion
Green 1992	Intervention- treatment period less than 2 weeks
Greening 1994	Intervention- no short-acting beta(2)-agonist group
Grove 1995	Intervention- no short-acting beta(2)-agonist group
Grove Lipworth 1996	Intervention- treatment period less than 2 weeks
Hacki 1993	Not RCT, intervention- no short-acting beta(2)-agonist group
Hyland 1994	Intervention- no short-acting beta(2)-agonist group
Jartti 1998	Intervention- no short-acting beta(2)-agonist group
Jones 1994	Intervention- no short-acting beta(2)-agonist group
Juniper 1999	Intervention- no short-acting beta(2)-agonist group
Kalra 1996	Intervention- treatment period less than 2 weeks
Kavuru 2000	Intervention- no short-acting beta(2)-agonist group
Kemp Cook 1998	Intervention- no short-acting beta(2)-agonist group
Kemp 1993	Intervention- treatment period less than 2 weeks
Kemp DeGraff 1999	Intervention- no short-acting beta(2)-agonist group
Kemp Dockhorn 1994	Intervention- treatment period less than 2 weeks
Kesten 1992	Not RCT, intervention- no short-acting beta(2)-agonist group
Kia 1997	Intervention- no short-acting beta(2)-agonist group
Kraft 1997	Intervention- no short-acting beta(2)-agonist group
Langley 1998	Intervention- no short-acting beta(2)-agonist group
Langton 1995	Intervention- no short-acting beta(2)-agonist group
Li Ward 1999	Intervention- no short-acting beta(2)-agonist group
Li 1998	Intervention- no short-acting beta(2)-agonist group
Lipworth Aziz 2000	Intervention- no short-acting beta(2)-agonist group
Lipworth Demps 2000	Intervention- treatment period less than 2 weeks
Lipworth Aziz 1999	Intervention- treatment period less than 2 weeks
Lockey 1999	Intervention- no short-acting beta(2)-agonist group
Lotvall 1992	Not RCT, intervention- no short-acting beta(2)-agonist group
Mahajan 1998	Intervention- no short-acting beta(2)-agonist group

Study	Reason for exclusion
Malo 1992	Intervention- treatment period less than 2 weeks
Malozowski 1998	Intervention- no short-acting beta(2)-agonist group
Mann 1996	Not RCT, cohort study
Martin 1999	Intervention- oral SR short-acting beta(2)-agonist group
McIvor 1998	Intervention- no short-acting beta(2)-agonist group
Meijer 1995	Intervention- no short-acting beta(2)-agonist group
Midgren 1992	Intervention- dose of long acting beta2-agonist varied during study
Molimard 2001	Intervention- no regular short-acting beta(2)-agonist group, not DB
Nathan 1999	Intervention- no short-acting beta(2)-agonist group
Nelson 1999	Intervention- no short-acting beta(2)-agonist group
Nelson 1998	Intervention- no short-acting beta(2)-agonist group
Newnham 1993	Intervention- treatment period less than 2 weeks
Newnham 1994	Intervention- no short-acting beta(2)-agonist group
Newnham 1995	Intervention- dose of long acting beta2-agonist varied during study
Nichol 1990	Intervention- treatment period less than 2 weeks
Nielsen 1999	Intervention- no short-acting beta(2)-agonist group
Nix 1990	Intervention- treatment period less than 2 weeks
Norhaya 1999	Intervention- no short-acting beta(2)-agonist group
Nowak 1992	Intervention- treatment period less than 2 weeks
Palmer 1992	Intervention- no short-acting beta(2)-agonist group
Pauwels 1997	Intervention- no short-acting beta(2)-agonist group
Pearlman 1996	Intervention- no short-acting beta(2)-agonist group
Pearlman 1999	Intervention- no short-acting beta(2)-agonist group
Pederson 1993	Intervention- treatment period less than 2 weeks
Quebe-Fehling 1996	Intervention- treatment period less than 2 weeks
Rabe 1993	Intervention- treatment period less than 2 weeks
Ramage 1994	Intervention- no short-acting beta(2)-agonist group
Ramage Lipworth 1994	Intervention- no short-acting beta(2)-agonist group

Study	Reason for exclusion
Ramsdale 1991	Intervention- treatment period less than 2 weeks
Ringbaek 1996	Intervention- oral SR short-acting beta(2)-agonist group
Roberts 1999	Intervention- no short-acting beta(2)-agonist group
Roberts 1992	Intervention- no short-acting beta(2)-agonist group
Rosenthal 1997	Intervention- no short-acting beta(2)-agonist group
Rosenthal 1999	Intervention- no short-acting beta(2)-agonist group
Russell 1995	Intervention- no short-acting beta(2)-agonist group
Schaaning 1996	Intervention- treatment period less than 2 weeks
Schreurs 1996	Intervention- no short-acting beta(2)-agonist group
Self 1998	Intervention- no short-acting beta(2)-agonist group
Shapiro 2000	Intervention- no short-acting beta(2)-agonist group
Shepherd 1991	Not RCT- letter
Sichletidis 1993	Intervention- treatment period less than 2 weeks
Siergiejko 1998	Intervention- no short-acting beta(2)-agonist group
Simons 1992	Intervention- treatment period less than 2 weeks
Simons 1997	Intervention- no short-acting beta(2)-agonist group
Simons 2 1997	Intervention- no short-acting beta(2)-agonist group
Simons Gerst 1997	Intervention- no short-acting beta(2)-agonist group
Smyth 1993	Intervention- treatment period less than 2 weeks
Starke 1996	Intervention- no short-acting beta(2)-agonist group
Sussman 1995	Intervention- no short-acting beta(2)-agonist group
Tan 1997	Intervention- no short-acting beta(2)-agonist group
Tattersfield 2001	Intervention- dose varied of short-acting and long-acting beta(2)-agonist
Tattersfield 1999	Intervention- no short-acting beta(2)-agonist group
Taylor 1992	Intervention- treatment period less than 2 weeks
Totterman 1998	Intervention- treatment period less than 2 weeks
Turner 1998	Intervention- no short-acting beta(2)-agonist group
Twentyman 1990	Intervention- treatment period less than 2 weeks

Study	Reason for exclusion
Ullman 1988	Intervention- treatment period less than 2 weeks
Ullman 1990	Intervention- no short-acting beta(2)-agonist group
Van der Molen 1996	Intervention- no short-acting beta(2)-agonist group
Van der Molen 1998	Intervention- no short-acting beta(2)-agonist group
Verberne 1991	Intervention- no short-acting beta(2)-agonist group
Verberne 1996	Intervention- treatment period less than 2 weeks
Verberne 1997	Intervention- no short-acting beta(2)-agonist group
Verberne 1998	Intervention- no short-acting beta(2)-agonist group
Verberne 2000	Not RCT , review
Verini 1998	Intervention- treatment period less than 2 weeks
Viskum 1990	Intervention- no short-acting beta(2)-agonist group
Von Berg 1996	Intervention- no short-acting beta(2)-agonist group
Von Berg 1998	Intervention- no short-acting beta(2)-agonist group
Wallaert 1999	Intervention- no short-acting beta(2)-agonist group
Wallin 1999	Intervention- no short-acting beta(2)-agonist group
Wallin 1990	Intervention- dose of long acting beta2-agonist varied during study
Walters 1992	Intervention- no short-acting beta(2)-agonist group
Weinstein 1997	Intervention- treatment period less than 2 weeks
Weinstein 1998	Intervention- no short-acting beta(2)-agonist group
Wilding 1997	Intervention- no short-acting beta(2)-agonist group
Wolfe 2000	Intervention- no short-acting beta(2)-agonist group
Wong 1997	Intervention- treatment period less than 2 weeks
Woolcock 1996	Intervention- no short-acting beta(2)-agonist group
Wronska 1998	Intervention- no short-acting beta(2)-agonist group
Yates 1995	Intervention- no short-acting beta(2)-agonist group
Yates 1997	Intervention- no short-acting beta(2)-agonist group
Zarkovic 1998	Intervention- no short-acting beta(2)-agonist group
Zellweger 1994	Intervention- treatment period less than 2 weeks

DATA AND ANALYSES

Comparison 1. All studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak expiratory flow: morning l/min	14		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Parallel group studies	12	3004	Mean Difference (IV, Fixed, 95% CI)	32.93 [24.47, 41.39]
1.2 Cross over studies	2	120	Mean Difference (IV, Fixed, 95% CI)	16.0 [-55.90, 87.90]
2 Peak expiratory flow: evening l/min	12		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Parallel group studies	10	2798	Mean Difference (IV, Fixed, 95% CI)	25.62 [17.98, 33.27]
2.2 Crossover studies	2	120	Mean Difference (IV, Fixed, 95% CI)	9.0 [-62.90, 80.90]
3 Change in PEF morning	9	2117	Mean Difference (IV, Fixed, 95% CI)	27.38 [22.98, 31.77]
3.1 Parallel group studies	9	2117	Mean Difference (IV, Fixed, 95% CI)	27.38 [22.98, 31.77]
3.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in PEF evening	7	1991	Mean Difference (IV, Fixed, 95% CI)	11.94 [7.99, 15.90]
4.1 Parallel group studies	7	1991	Mean Difference (IV, Fixed, 95% CI)	11.94 [7.99, 15.90]
4.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Amplitude PEF: diurnal variation (l/min or %)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Parallel group studies	2	374	Mean Difference (IV, Fixed, 95% CI)	-16.0 [-21.66, -10.34]
5.2 Cross over studies	1	40	Mean Difference (IV, Fixed, 95% CI)	-2.3 [-5.84, 1.24]
6 FEV1 (litres)	13		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Parallel group studies	11	2446	Mean Difference (IV, Fixed, 95% CI)	0.22 [0.14, 0.31]
6.2 Cross over studies	2	122	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.56, 0.56]
7 % Predicted FEV1	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Parallel group studies	1	22	Mean Difference (IV, Fixed, 95% CI)	12.0 [-1.06, 25.06]
7.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change in FEV (litres)	5	1285	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.12, 0.28]
8.1 Parallel group studies	5	1285	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.12, 0.28]
8.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Forced Vital Capacity (litres)	4	1118	Mean Difference (IV, Fixed, 95% CI)	0.24 [0.13, 0.36]
9.1 Parallel group studies	4	1118	Mean Difference (IV, Fixed, 95% CI)	0.24 [0.13, 0.36]
9.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 FEF25-75 (litres/sec)	2	305	Mean Difference (IV, Fixed, 95% CI)	0.42 [0.18, 0.66]
10.1 Parallel group studies	2	305	Mean Difference (IV, Fixed, 95% CI)	0.42 [0.18, 0.66]
10.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Symptom score - whole day	3	606	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.43, -0.11]
11.1 Parallel group studies	3	606	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.43, -0.11]
11.2 Cross over studies	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Symptom score - day time	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Parallel group studies	5	1061	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.23, -0.06]
12.2 Cross over studies	1	40	Mean Difference (IV, Fixed, 95% CI)	-3.20 [-9.31, 2.91]
13 Symptom score: night time	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 Parallel group studies	5	934	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.31, -0.10]
13.2 Cross over studies	1	40	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-6.39, 0.79]
14 %days without asthma symptoms	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 Parallel group studies	4	601	Mean Difference (IV, Fixed, 95% CI)	10.34 [1.80, 18.88]
14.2 Cross over studies	1	184	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 % nights without asthma awakenings	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Parallel group studies	6	1136	Mean Difference (IV, Fixed, 95% CI)	12.12 [7.80, 16.43]
15.2 Cross over studies	1	184	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Rescue bronchodilator use: whole day	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16.1 Parallel group studies	5	804	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.77, -0.18]
16.2 Cross over studies	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.86, 1.06]
17 Rescue bronchodilator use: day time	7	1469	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.50, -0.16]
17.1 Parallel group studies	7	1469	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.50, -0.16]
17.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Rescue bronchodilator use: night time	7	1468	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.43, -0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Parallel group studies	7	1468	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.43, -0.19]
18.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Change in use of rescue bronchodilator/day	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Parallel group studies	3	606	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-1.29, -0.08]
20 Quality of life score: overall	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 Parallel group studies	2	727	Std. Mean Difference (IV, Fixed, 95% CI)	0.54 [0.39, 0.69]
20.2 Cross over studies	1	1545	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Quality of life score: symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 Parallel group studies	1	539	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-0.65, -0.39]
21.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Quality of life score: emotions	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 Parallel group studies	1	539	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.56, -0.32]
22.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Quality of life score: exposure to environmental stimuli	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
23.1 Parallel group studies	1	539	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.31, -0.11]
23.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Quality of life score: activity limitations	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 Parallel group studies	1	539	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.31, -0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
25.1 Parallel group studies	2	200	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-1.26, 0.51]
25.2 Cross over studies	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Bronchoprotection to methacholine challenge(protection ratio vs. baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
26.1 Parallel group	1	29	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.03, 0.23]
27 Adverse events-all	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 Parallel group studies	5	983	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.80, 1.59]
27.2 Cross over studies	2	264	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.34, 1.59]
28 Adverse events- palpitations	12		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 Parallel group studies	11	3239	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.62, 1.74]
28.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.69]
29 Adverse events-headache	14		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 Parallel group studies	13	3737	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [1.02, 1.61]
29.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
30 Adverse events- tremor	13		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 Parallel group studies	12	3780	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.07]
30.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31 Adverse events- cramps	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 Parallel group studies	4	1334	Odds Ratio (M-H, Fixed, 95% CI)	2.12 [0.99, 4.54]
31.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
32 Exacerbations asthma-major	14	28814	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.78, 1.03]
32.1 Exacerbations (similar definition) - parallel group studies	9	2889	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
32.2 Exacerbations (less precise definition) - parallel group studies	5	25925	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.12]
33 Asthma attacks - day	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
33.1 Parallel group studies	1	301	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-2.26, 0.06]
34 Asthma attacks - night	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
34.1 Parallel group studies	1	1652	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-2.66, -1.34]
35 Major exacerbation rate - yearly (number/patient /year)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
35.1 Parallel group studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.2 Cross over studies	1	314	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.50, -0.08]
36 Minor exacerbation rate (number/patient/year)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
36.1 Cross over studies	1	314	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-0.85, -0.33]
37 Deaths related to asthma	1	25180	Odds Ratio (M-H, Fixed, 95% CI)	3.00 [0.67, 13.41]
38 Global assessment of efficacy by patient - very good/good	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 Parallel group studies	5	1005	Odds Ratio (M-H, Fixed, 95% CI)	2.54 [1.92, 3.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39 Global assessment of efficacy by investigator - very good/good	2	446	Odds Ratio (M-H, Fixed, 95% CI)	2.40 [1.57, 3.66]
39.1 Parallel group studies	2	446	Odds Ratio (M-H, Fixed, 95% CI)	2.40 [1.57, 3.66]
39.2 Crossover studies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 All studies, Outcome 1 Peak expiratory flow: morning l/min.

Analysis 1.2. Comparison 1 All studies, Outcome 2 Peak expiratory flow: evening l/min.

Analysis 1.3. Comparison 1 All studies, Outcome 3 Change in PEF morning.

Analysis 1.4. Comparison 1 All studies, Outcome 4 Change in PEF evening.

Analysis 1.5. Comparison 1 All studies, Outcome 5 Amplitude PEF: diurnal variation (l/min or %).

Analysis 1.6. Comparison 1 All studies, Outcome 6 FEV1 (litres).

Analysis 1.7. Comparison 1 All studies, Outcome 7 % Predicted FEV1.

Analysis 1.8. Comparison 1 All studies, Outcome 8 Change in FEV (litres).

Analysis 1.9. Comparison 1 All studies, Outcome 9 Forced Vital Capacity (litres).

Analysis 1.10. Comparison 1 All studies, Outcome 10 FEF25-75 (litres/sec).

Analysis 1.11. Comparison 1 All studies, Outcome 11 Symptom score - whole day.

Analysis 1.12. Comparison 1 All studies, Outcome 12 Symptom score - day time.

Analysis 1.13. Comparison 1 All studies, Outcome 13 Symptom score: night time.

Analysis 1.14. Comparison 1 All studies, Outcome 14 %days without asthma symptoms.

Analysis 1.15. Comparison 1 All studies, Outcome 15 % nights without asthma awakenings.

Analysis 1.16. Comparison 1 All studies, Outcome 16 Rescue bronchodilator use: whole day.

Analysis 1.17. Comparison 1 All studies, Outcome 17 Rescue bronchodilator use: day time.

Analysis 1.18. Comparison 1 All studies, Outcome 18 Rescue bronchodilator use: night time.

Analysis 1.19. Comparison 1 All studies, Outcome 19 Change in use of rescue bronchodilator/day.

Analysis 1.20. Comparison 1 All studies, Outcome 20 Quality of life score: overall.

Study or subgroup	Long acting		Short acting		Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Subtotal ***	1405		140				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							
<div> <div>Short acting better</div> <div>-1-0.500.51</div> <div>Long acting better</div> </div>							

Analysis 1.21. Comparison 1 All studies, Outcome 21 Quality of life score: symptoms.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.21.1 Parallel group studies							
Wenzel 1998	264	-1 (0.8)	275	-0.5 (0.7)		100%	-0.52[-0.65,-0.39]
Subtotal ***	264		275			100%	-0.52[-0.65,-0.39]
Heterogeneity: Not applicable							
Test for overall effect: Z=8.15(P<0.0001)							
1.21.2 Cross over studies							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							
<div><div>Long acting better</div><div>-1-0.500.51</div><div>Short acting better</div></div>							

Analysis 1.22. Comparison 1 All studies, Outcome 22 Quality of life score: emotions.

Study or subgroup	Long acting		Short acting		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.22.1 Parallel group studies							
Wenzel 1998	264	-0.9 (0.7)	275	-0.4 (0.7)		100%	-0.44[-0.56,-0.32]
Subtotal ***	264		275			100%	-0.44[-0.56,-0.32]
Heterogeneity: Not applicable							
Test for overall effect: Z=7.33(P<0.0001)							
1.22.2 Cross over studies							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							
<div><div>Long acting better</div><div>-1-0.5000.51</div><div>Short acting better</div></div>							

Analysis 1.23. Comparison 1 All studies, Outcome 23 Quality of life score: exposure to environmental stimuli.

Analysis 1.24. Comparison 1 All studies, Outcome 24 Quality of life score: activity limitations.

Analysis 1.25. Comparison 1 All studies, Outcome 25 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine.

Analysis 1.26. Comparison 1 All studies, Outcome 26 Bronchoprotection to methacholine challenge(protection ratio vs. baseline).

Analysis 1.27. Comparison 1 All studies, Outcome 27 Adverse events-all.

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Analysis 1.28. Comparison 1 All studies, Outcome 28 Adverse events- palpitations.

Analysis 1.29. Comparison 1 All studies, Outcome 29 Adverse events-headache.

Analysis 1.30. Comparison 1 All studies, Outcome 30 Adverse events- tremor.

Analysis 1.31. Comparison 1 All studies, Outcome 31 Adverse events- cramps.

Analysis 1.32. Comparison 1 All studies, Outcome 32 Exacerbations asthma-major.

Analysis 1.33. Comparison 1 All studies, Outcome 33 Asthma attacks - day.

Analysis 1.34. Comparison 1 All studies, Outcome 34 Asthma attacks - night.

Analysis 1.35. Comparison 1 All studies, Outcome 35 Major exacerbation rate - yearly (number/patient /year).

Analysis 1.36. Comparison 1 All studies, Outcome 36 Minor exacerbation rate (number/patient/year).

Analysis 1.37. Comparison 1 All studies, Outcome 37 Deaths related to asthma.

Analysis 1.38. Comparison 1 All studies, Outcome 38 Global assessment of efficacy by patient - very good/good.

Analysis 1.39. Comparison 1 All studies, Outcome 39 Global assessment of efficacy by investigator - very good/good.

Comparison 2. Studies with all subjects using ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak expiratory flow: morning l/min	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Parallel group studies	3	240	Mean Difference (IV, Fixed, 95% CI)	60.0 [0.80, 119.20]
1.2 Cross over studies	2	120	Mean Difference (IV, Fixed, 95% CI)	16.0 [-55.90, 87.90]
2 Peak expiratory flow: evening l/min	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Parallel group studies	1	40	Mean Difference (IV, Fixed, 95% CI)	48.0 [-13.76, 109.76]
2.2 Crossover studies	2	120	Mean Difference (IV, Fixed, 95% CI)	9.0 [-62.90, 80.90]
3 Change in PEF morning	2	438	Mean Difference (IV, Fixed, 95% CI)	29.60 [21.18, 38.02]
3.1 Parallel group studies	2	438	Mean Difference (IV, Fixed, 95% CI)	29.60 [21.18, 38.02]
3.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in PEF evening	2	438	Mean Difference (IV, Fixed, 95% CI)	10.77 [3.50, 18.05]
4.1 Parallel group studies	2	438	Mean Difference (IV, Fixed, 95% CI)	10.77 [3.50, 18.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Amplitude PEF: diurnal variation	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Parallel group studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Cross over studies	1	40	Mean Difference (IV, Fixed, 95% CI)	-2.3 [-5.84, 1.24]
6 FEV1 litres	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Parallel group studies	1	20	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.39, 0.75]
6.2 Cross over studies	2	122	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.56, 0.56]
7 Change in FEV1	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Parallel group studies	1	248	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.00, 0.28]
7.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Symptom score- day time	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Parallel group studies	1	180	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Symptom score: night time	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Parallel group studies	1	180	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Cross over studies	1	40	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-6.39, 0.79]
10 Rescue bronchodilator use: whole day	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Parallel group studies	1	35	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-2.53, 0.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Cross over studies	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.86, 1.06]
11 Rescue bronchodilator use: day-time	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Parallel group studies	1	180	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Rescue bronchodilator use: night time	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 Parallel group studies	1	180	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Quality of life score: overall	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 Parallel group studies	1	248	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.57, -0.07]
13.2 Cross over studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Bronchial hyperreactivity	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 Parallel group studies	2	200	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-1.26, 0.51]
14.2 Cross over studies	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Adverse events - all	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Parallel group studies	1	180	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.53, 2.95]
15.2 Cross over studies	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.19, 1.44]
16 Adverse events - palpitations	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Parallel group studies	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.03]
16.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.69]
17 Adverse events - headache	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Parallel group studies	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.17, 2.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
18 Adverse events - tremor	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Parallel group studies	1	190	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.24, 9.09]
18.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
19 Adverse events - cramps	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Parallel group studies	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.43]
19.2 Cross over studies	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
20 Exacerbations asthma - major	2	370	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.50, 1.48]
20.1 Parallel group studies	2	370	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.50, 1.48]
20.2 Cross over studies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Studies with all subjects using ICS, Outcome 1 Peak expiratory flow: morning l/min.

Analysis 2.2. Comparison 2 Studies with all subjects using ICS, Outcome 2 Peak expiratory flow: evening l/min.

Analysis 2.3. Comparison 2 Studies with all subjects using ICS, Outcome 3 Change in PEF morning.

Analysis 2.4. Comparison 2 Studies with all subjects using ICS, Outcome 4 Change in PEF evening.

Analysis 2.5. Comparison 2 Studies with all subjects using ICS, Outcome 5 Amplitude PEF: diurnal variation.

Analysis 2.6. Comparison 2 Studies with all subjects using ICS, Outcome 6 FEV1 litres.

Analysis 2.7. Comparison 2 Studies with all subjects using ICS, Outcome 7 Change in FEV1.

Analysis 2.8. Comparison 2 Studies with all subjects using ICS, Outcome 8 Symptom score- day time.

Analysis 2.9. Comparison 2 Studies with all subjects using ICS, Outcome 9 Symptom score: night time.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI			
	N	Mean(SD)	N	Mean(SD)						
Test for overall effect: Z=1.53(P=0.13)										
Test for subgroup differences: Not applicable										
					-10	-5	0	5	10	
					Long acting better				Short acting better	

Analysis 2.10. Comparison 2 Studies with all subjects using ICS, Outcome 10 Rescue bronchodilator use: whole day.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
2.10.1 Parallel group studies							
D'Alonzo 1994	15	1.4 (1.6)	20	2.5 (2.7)		100%	-1.1[-2.53,0.33]
Subtotal ***	15		20			100%	-1.1[-2.53,0.33]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.5(P=0.13)							
2.10.2 Cross over studies							
Lai 1995	20	1.4 (2.4)	20	1.8 (2.3)		100%	-0.4[-1.86,1.06]
Subtotal ***	20		20			100%	-0.4[-1.86,1.06]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.54(P=0.59)							
Test for subgroup differences: Chi²=0.45, df=1 (P=0.5), I²=0%							
<div>long acting better</div> <div>-4 -2 0 2 4</div> <div>Short acting better</div>							

Analysis 2.11. Comparison 2 Studies with all subjects using ICS, Outcome 11 Rescue bronchodilator use: day-time.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
2.11.1 Parallel group studies							
FitzGerald 1999	89	0.7 (0)	91	0.9 (0)			Not estimable
Subtotal ***	89		91				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.11.2 Cross over studies							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							
<div><div></div><div>Long acting better</div><div>-4-2024</div><div>Short acting better</div></div>							

Analysis 2.12. Comparison 2 Studies with all subjects using ICS, Outcome 12 Rescue bronchodilator use: night time.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
2.12.1 Parallel group studies							
<div><div></div><div>Long acting better</div><div>-4-2024</div><div>Short acting better</div></div>

Analysis 2.13. Comparison 2 Studies with all subjects using ICS, Outcome 13 Quality of life score: overall.

Analysis 2.14. Comparison 2 Studies with all subjects using ICS, Outcome 14 Bronchial hyperreactivity.

Analysis 2.15. Comparison 2 Studies with all subjects using ICS, Outcome 15 Adverse events - all.

Analysis 2.16. Comparison 2 Studies with all subjects using ICS, Outcome 16 Adverse events - palpitations.

Analysis 2.17. Comparison 2 Studies with all subjects using ICS, Outcome 17 Adverse events - headache.

Analysis 2.18. Comparison 2 Studies with all subjects using ICS, Outcome 18 Adverse events - tremor.

Analysis 2.19. Comparison 2 Studies with all subjects using ICS, Outcome 19 Adverse events - cramps.

Analysis 2.20. Comparison 2 Studies with all subjects using ICS, Outcome 20 Exacerbations asthma - major.

Comparison 3. Childrens studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events - palpitations	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Parallel group studies	1	568	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.19, 4.79]
1.2 Cross over studies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events - headache	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Parallel group studies	1	568	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.85, 2.04]
2.2 Cross over studies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events - tremor	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Parallel group studies	1	568	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.19, 4.79]
3.2 Cross over studies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Exacerbations asthma - major	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Parallel group studies	1	568	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.74, 1.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Cross over studies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events-all	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Parallel group studies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Cross over studies	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.19, 1.44]
6 Peak expiratory flow: morning l/min	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Parallel group studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Cross over studies	1	80	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Peak expiratory flow: evening l/min	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Parallel group studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Crossover studies	1	80	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 FEV1 litres	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Parallel group studies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Cross over studies	1	82	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Bronchial hyperreactivity - log PD/PC 20 methacholine or histamine	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Parallel group studies	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Cross over studies	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Childrens studies, Outcome 1 Adverse events - palpitations.

Study or subgroup	Long acting n/N	Short acting n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 Parallel group studies					
Lenney 1995	3/290	3/278		100%	0.96[0.19,4.79]
Long acting better					Short acting better

Analysis 3.2. Comparison 3 Childrens studies, Outcome 2 Adverse events - headache.

Analysis 3.3. Comparison 3 Childrens studies, Outcome 3 Adverse events - tremor.

Analysis 3.4. Comparison 3 Childrens studies, Outcome 4 Exacerbations asthma - major.

Analysis 3.5. Comparison 3 Childrens studies, Outcome 5 Adverse events-all.

Analysis 3.6. Comparison 3 Childrens studies, Outcome 6 Peak expiratory flow: morning l/min.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Subtotal ***	40		40				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							
<div> Short acting better -10 -5 0 5 10 Long acting better </div>							

Analysis 3.7. Comparison 3 Childrens studies, Outcome 7 Peak expiratory flow: evening l/min.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
3.7.1 Parallel group studies							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.7.2 Crossover studies							
Byrnes 2000	40	268 (0)	40	261.6 (0)			Not estimable
Subtotal ***	40		40				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							
<div> Short acting better -10 -5 0 5 10 Long acting better </div>							

Analysis 3.8. Comparison 3 Childrens studies, Outcome 8 FEV1 litres.

Study or subgroup	Long acting		Short acting		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
3.8.1 Parallel group studies							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.8.2 Cross over studies							
Byrnes 2000	41	1.8 (0)	41	1.7 (0)			Not estimable
Subtotal ***	41		41				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							
<div> Short acting better -10 -5 0 5 10 Long acting better </div>							

Analysis 3.9. Comparison 3 Childrens studies, Outcome 9 Bronchial hyperreactivity - log PD/PC 20 methacholine or histamine.

Study or subgroup	Long acting		Short acting		Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI		
	N	Mean(SD)	N	Mean(SD)					
3.9.1 Parallel group studies									
Subtotal ***	0		0				Not estimable		
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
3.9.2 Cross over studies									
Byrnes 2000	14	0.3 (0)	16	0.5 (0)			Not estimable		
Subtotal ***	14		16				Not estimable		
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
Test for subgroup differences: Not applicable									
				-10	-5	0	5	10	
				Short acting better				Long acting better	

Short acting better -10 -5 0 5 10 Long acting better

Comparison 4. Asthma severity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak expiratory flow: morning l/min	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Mild to moderate asthma	8	2185	Mean Difference (IV, Fixed, 95% CI)	30.48 [23.72, 37.24]
1.3 Moderate - severe asthma	1	180	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Peak expiratory flow: evening l/min	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Mild - moderate asthma	8	2460	Mean Difference (IV, Fixed, 95% CI)	18.30 [12.31, 24.29]
2.3 Moderate - severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in PEF morning	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Mild - moderate asthma	7	1659	Mean Difference (IV, Fixed, 95% CI)	32.07 [26.89, 37.26]
3.3 Moderate - severe asthma	1	190	Mean Difference (IV, Fixed, 95% CI)	29.0 [12.13, 45.87]
4 Change in PEF evening	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Mild - moderate asthma	5	1533	Mean Difference (IV, Fixed, 95% CI)	13.29 [8.56, 18.02]
4.3 Severe asthma	1	190	Mean Difference (IV, Fixed, 95% CI)	10.0 [-1.43, 21.43]
5 Amplitude PEF: diurnal variation (l/min or %)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Mild - moderate asthma	2	231	Mean Difference (IV, Fixed, 95% CI)	-16.0 [-21.66, -10.34]
5.3 Moderate - severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 FEV1 (litres)	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Mild - moderate asthma	8	1909	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.13, 0.28]
6.3 Moderate - severe asthma	1	180	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.13, 0.37]
7 % Predicted FEV1	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Mild asthma	1	22	Mean Difference (IV, Fixed, 95% CI)	12.0 [-1.06, 25.06]
7.2 Mild - moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Moderate - severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Change in FEV (litres)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Mild - moderate asthma	5	1285	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.12, 0.28]
9 Forced Vital Capacity (litres)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Mild - moderate asthma	4	1118	Mean Difference (IV, Fixed, 95% CI)	0.24 [0.13, 0.36]
10 FEF25-75 (litres/sec)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Mild - moderate asthma	2	305	Mean Difference (IV, Fixed, 95% CI)	0.42 [0.18, 0.66]
11 Symptom score - whole day	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Mild - moderate asthma	3	606	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.43, -0.11]
12 Symptom score - day time	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 Mild - moderate asthma	3	678	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.24, -0.05]
12.2 Severe asthma	1	180	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Symptom score: night time	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 Mild - moderate asthma	4	731	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.33, -0.09]
14 %days without asthma symptoms	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 Mild - moderate asthma	3	414	Mean Difference (IV, Fixed, 95% CI)	10.34 [1.80, 18.88]
15 % nights without asthma awakenings	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Mild - moderate asthma	5	943	Mean Difference (IV, Fixed, 95% CI)	12.12 [7.80, 16.43]
16 Rescue bronchodilator use: whole day	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Mild - moderate asthma	4	659	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.90, -0.19]
17 Rescue bronchodilator use: day time	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 Mild - moderate asthma	5	1086	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.44, -0.09]
18 Rescue bronchodilator use: night time	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 Mild - moderate asthma	5	1086	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.42, -0.17]
19 Quality of life score: overall	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Mild - moderate asthma	1	248	Mean Difference (IV, Fixed, 95% CI)	0.32 [0.07, 0.57]
20 Bronchial hyperreactivity	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 Mild - moderate asthma	1	20	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-1.26, 0.51]
20.2 Moderate - severe asthma	1	180	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Adverse events - all	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Mild - moderate asthma	2	369	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.66, 1.75]
21.2 Moderate - severe asthma	1	180	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.53, 2.95]
22 Adverse events - palpitations	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Mild - moderate asthma	9	2815	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.61, 1.78]
22.2 Moderate - severe asthma	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.03]
23 Adverse events - headache	12		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Mild - moderate asthma	11	3313	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [1.01, 1.62]
23.2 Moderate - severe asthma	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.17, 2.34]
24 Adverse events - tremor	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 Mild - moderate asthma	10	3356	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.03]
24.2 Moderate - severe asthma	1	190	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.24, 9.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Adverse events - cramps	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 Mild - moderate asthma	2	910	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [1.07, 5.97]
25.2 Moderate - severe asthma	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.43]
26 Exacerbations asthma - major	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Mild asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Mild - moderate asthma	9	2847	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.04]
26.3 Moderate - severe asthma	2	370	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.50, 1.48]
27 Global assessment of efficacy by patient - very good/good	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 Mild - moderate asthma	3	657	Odds Ratio (M-H, Fixed, 95% CI)	3.08 [2.19, 4.32]

Analysis 4.1. Comparison 4 Asthma severity, Outcome 1 Peak expiratory flow: morning l/min.

Analysis 4.2. Comparison 4 Asthma severity, Outcome 2 Peak expiratory flow: evening l/min.

Analysis 4.3. Comparison 4 Asthma severity, Outcome 3 Change in PEF morning.

Analysis 4.4. Comparison 4 Asthma severity, Outcome 4 Change in PEF evening.

Analysis 4.5. Comparison 4 Asthma severity, Outcome 5 Amplitude PEF: diurnal variation (l/min or %).

Analysis 4.6. Comparison 4 Asthma severity, Outcome 6 FEV1 (litres).

Analysis 4.7. Comparison 4 Asthma severity, Outcome 7 % Predicted FEV1.

Analysis 4.8. Comparison 4 Asthma severity, Outcome 8 Change in FEV (litres).

Analysis 4.9. Comparison 4 Asthma severity, Outcome 9 Forced Vital Capacity (litres).

Analysis 4.10. Comparison 4 Asthma severity, Outcome 10 FEF25-75 (litres/sec).

Analysis 4.11. Comparison 4 Asthma severity, Outcome 11 Symptom score - whole day.

Analysis 4.12. Comparison 4 Asthma severity, Outcome 12 Symptom score - day time.

Analysis 4.13. Comparison 4 Asthma severity, Outcome 13 Symptom score: night time.

Analysis 4.14. Comparison 4 Asthma severity, Outcome 14 %days without asthma symptoms.

Analysis 4.15. Comparison 4 Asthma severity, Outcome 15 % nights without asthma awakenings.

Analysis 4.16. Comparison 4 Asthma severity, Outcome 16 Rescue bronchodilator use: whole day.

Analysis 4.17. Comparison 4 Asthma severity, Outcome 17 Rescue bronchodilator use: day time.

Analysis 4.18. Comparison 4 Asthma severity, Outcome 18 Rescue bronchodilator use: night time.

Analysis 4.19. Comparison 4 Asthma severity, Outcome 19 Quality of life score: overall.

Analysis 4.20. Comparison 4 Asthma severity, Outcome 20 Bronchial hyperreactivity.

Analysis 4.21. Comparison 4 Asthma severity, Outcome 21 Adverse events - all.

Analysis 4.22. Comparison 4 Asthma severity, Outcome 22 Adverse events - palpitations.

Analysis 4.23. Comparison 4 Asthma severity, Outcome 23 Adverse events - headache.

Study or subgroup	Long acting n/N	Short acting n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable Test for overall effect: $Z=0.68(P=0.5)$					
<div>Long acting better</div> <div>0.1 0.2 0.5 1 2 5 10</div> <div>Short acting better</div>					

Analysis 4.24. Comparison 4 Asthma severity, Outcome 24 Adverse events - tremor.

Analysis 4.25. Comparison 4 Asthma severity, Outcome 25 Adverse events - cramps.

Analysis 4.26. Comparison 4 Asthma severity, Outcome 26 Exacerbations asthma - major.

Analysis 4.27. Comparison 4 Asthma severity, Outcome 27 Global assessment of efficacy by patient - very good/good.

ADDITIONAL TABLES

Table 1. Results by subgroup (WMD fixed 95%CI) *indicates non significant result

Outcome	All studies	#stud- ies/ #pts	Heterogeneity chi2	All on ICS	#stud- ies/ #pts	Mild-moderate asthma	#stud- ies/ #pts	Mod- severe asthma	#stud- ies/ #pts
PEF am l/m	32.93 (24.78,41.35)	8/1881	8.61 df7 NS	60.0 (0.8, 119.2)	1/40	30.48 (23.72,37.24)	6/1348		
PEF pm l/m	25.62 (17.98,33.27)	8/1878	14.04 df7, 7.37 df6 NS	48.0 (13.77,109.77)	1/40	18.3 (12.31,24.29)	7/1872		
Change PEFam	27.38 (22.98,31.77)	6/1602	7.31 df5, 6.47 df4 NS	29.6 (26.85,36.76)	2/439	32.67 (26.89,37.26)	4/1034	29.0 (12.13,45.87)	1/190
Change PEFpm	11.94 (7.99,15.90)	6/1603	7.31 df5, 6.47 df4 NS	10.77 (3.5,18.05)	2/438	13.29 (8.56,18.02)	4/1035	*10.0 (-1.43,21.43)	1/190
FEV1 L	0.22 (0.14,0.31)	8/1397	14.79 df7 8.70 df6 NS	*0.18 (-0.39,0.75)	1/20	0.20 (0.13,0.28)	6/1104	*0.12 (-0.13,0.37)	1/180
% pred FEV1	*12.0 (-1.06,25.06)	1/22							
Change in FEV1	0.2 (0.12,0.28)	3/844	8.6 df2, 5.45 df1 SIG	0.14 (0.0, 0.28)	1/248	0.2 (0.12, 0.28)	3/844		
FVC L	0.19 (0.09,0.30)	4/760	8.45 df3 SIG			0.24 (0.13,0.36)	3/548		
FEF 25-75% l/sec	0.42 (0.18,0.66)	2/305	0.26 df1 NS			0.42 (0.18,0.66)	2/305		
Sympt score - 24hr	SMD -0.27 (-0.11,-0.43)	3/604	2.12 df2 NS			-0.27 (-0.11,-0.43)	3/604		
Sympt score - day	-0.15 (-0.06,-0.23)	3/701	0.64 df2 NS			-0.14 (-0.05,-0.24)	2/498		
Sympt score - night	-0.21 (-0.1,-0.31)	3/701	0.8 df2 NS			-0.21 (-0.09,-0.33)	2/498		
% days no asthma symptoms	10.34 (1.8,18.88)	2/307	0.2 df1 NS			10.34 (1.8,18.88)	2/307		
% nights no asth- ma awakenings	12.12 (7.8,16.43)	3/606	2.34 df2 NS			12.12 (7.8,16.43)	3/606		
Rescue SABA 24hrs No. puffs	-0.48 (-0.18,-0.77)	4/751	1.94 df3 NS	*-1.10 (0.33,-2.53)	1/35	-0.55 (-0.19,-0.9)	3/606		

Table 1. Results by subgroup (WMD fixed 95%CI) *indicates non significant result (Continued)

Rescue SABA day-time	-0.33 (-0.16,-0.5)	4/1002	9.87 df3 SIG			-0.26 (-0.09,-0.44)	3/799		
Rescue SABA night-time	-0.31 (-0.19, -0.43)	4/1002	1.02 df3 NS			-0.3 (-0.17,-0.42)	3/799		
QOL -overall score	SMD 0.54 (0.39, 0.69)	2/647	8.23 df1 SIG			0.32 (0.07, 0.57)	1/539		
QOL-symptoms	0.52 (0.39,0.65)	1/539				0.52 (0.39,0.65)	1/539		
QOL - emotions	0.44 (0.32, 0.56)	1/539				0.44 (0.32, 0.56)	1/539		
QOL - exposure to environmental stimuli	0.21 (0.11, 0.31)	1/539				0.21 (0.11, 0.31)	1/539		
QOL - activity limitation	0.21 (0.11, 0.31)	1/539				0.21 (0.11, 0.31)	1/539		
BHR (log PD20)	*0.37 (-1.26, 0.51)	1/20				*0.37 (-1.26, 0.51)	1/20		
Any adverse event	*OR 1.13 (0.8, 1.59)	5/993	6.76 df4 NS	*OR 1.24 (0.53,2.95)	1/180	*OR 1.08 (0.66, 1.75)	2/369	*OR 1.24 (0.53, 2.95)	1/170
AE - palpitations	*OR 1.04 (0.62,1.74)	11/3239	8.94 df 10 NS	*OR 0.32 (0.01,8.03)	1/190	*OR 1.05 (0.61,1.78)	9/2815	*OR 0.96 (0.19,4.79)	1/568
AE - headache	OR 1.28 (1.02,1.62)	13/3737	14.5 df12 NS	*OR 0.64 (0.17,2.34)	1/190	OR 1.28 (1.01,1.61)	11/3313	*OR 0.64 (0.17,2.34)	1/568
AE - tremor	*OR 0.68 (0.43,1.07)	11/3546	13.33 df10 NS	*OR 1.48 (0.24,9.09)	2/370	*OR 0.64 (0.4, 1.03)	10/3356	*OR 1.48 (0.24,9.09)	1/170
AE - cramps	*OR 2.12 (0.99,4.54)	4/1234	3.38 df3 NS	*OR 0.48 (0.04,5.43)	1/190	OR 2.53 (1.07,5.97)	2/910	*OR 0.48 (0.04,5.43)	1/170
> 1 major exacerbation (similarly defined)	*OR 0.89 (0.75,1.06)	9/2890	2.65 df8 NS	*OR 0.86 (1.48, 0.5)	2/370	*OR 0.82 (0.67,1.01)	8/2279	*OR 0.86 (0.5,1.48)	2/370

Table 1. Results by subgroup (WMD fixed 95%CI) *indicates non significant result *(Continued)*

> 1 major exacerbation (definition less precise)	*OR 0.90 (0.78,1.03)	14/28814	8.44 df13 NS
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APPENDICES

Appendix 1. Information collected from eligible studies

Methods-study design, location and setting, method of randomisation and blinding, withdrawals/drop outs, compliance, confounders and quality score.

Participants- total number of subjects (N), numbers of males and females, the mean age and range, baseline severity of asthma, inclusion and exclusion criteria.

Interventions- the long acting beta agonist and short acting beta agonist used, with dose and frequency of dosing, the device used to administer drug, the treatment period, the additional rescue agent used if any, any co-intervention used during study by participants, with its dose and whether dose remained stable.

Outcomes- which outcomes were measured, which reported, in what form and whether they were complete, the standard deviation or other measure of variability.

Studies could use a variety of measures of asthma control and we specifically extracted results for the following 35 outcomes where available:

Peak expiratory flow (PEF): morning

(PEF): evening

% Predicted (PEF): morning

% Predicted (PEF): evening

Change in PEF: morning

Change in PEF: evening

Amplitude of diurnal variation in PEF

FEV1

% Predicted forced expiratory flow in one second (FEV1)

Change in FEV1

Forced Vital Capacity (FVC)

FEF25-75 (forced expiratory flow over the middle half of the FVC, that is the average flow from the point from where 25% of the FVC has been exhaled to the point where 75% has been exhaled.

Symptom score: whole day

Symptom score: day time

Symptom score: night time

%days without asthma symptoms

% nights without asthma awakenings

Rescue bronchodilator use: whole day

Rescue bronchodilator use: day time

Rescue bronchodilator use: night time

Quality of life score: overall

Quality of life score: symptoms

Quality of life score: emotions

Quality of life score: exposure to environmental stimuli

Quality of life score: activity limitations

Bronchial hyper reactivity

Adverse events: all

Adverse events: palpitations

Adverse events: headache

Adverse events: tremor

Adverse events: cramps

Exacerbations of asthma

Deaths related to asthma

Overall efficacy of treatment

We decided that measures of airway inflammation, obtained by bronchoscopy or sputum analysis would not be included in the review at this stage, because there were insufficient studies reporting them.

WHAT'S NEW

Date	Event	Description
20 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2000

Date	Event	Description
24 April 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Julia Walters cooperated in writing the protocol, carried out the initial study selection, study grading, data extraction and analysis, and writing of the first draft and subsequent revisions.

Haydn Walters cooperated in writing the protocol, grading studies, data checking and analysis, writing and revising drafts of the review.

Peter Gibson advised on protocol formulation and writing the first and subsequent revisions of the review.

DECLARATIONS OF INTEREST

E H Walters has taken part in collaborative clinical pharmacology studies with a number of pharmaceutical companies including GlaxoWellcome, Astra Zeneca, Pfizer, Boehringer, Schering Plough, SKB, and Novartis. He has, in the past, held consultancies with GlaxoWellcome, Pfizer and Zeneca. He has had sponsorship to meetings from a number of the companies listed over the past 15 years.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [*therapeutic use]; Albuterol [*analogs & derivatives] [therapeutic use]; Asthma [*drug therapy]; Bronchodilator Agents [*therapeutic use]; Ethanolamines [therapeutic use]; Formoterol Fumarate; Randomized Controlled Trials as Topic; Salmeterol Xinafoate

MeSH check words

Adult; Child; Humans