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Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma (Review)

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Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma.
Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD001281.
DOI: 10.1002/14651858.CD001281.pub2.

TABLE OF CONTENTS

[Intervention Review]

Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2009.

Citation: Tee A, Koh MS, Gibson PG, Lasserson TJ, Wilson A, Irving LB. Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD001281. DOI: 10.1002/14651858.CD001281.pub2.

ABSTRACT

Background

Theophylline and long acting beta-2 agonists are bronchodilators used for the management of persistent asthma symptoms, especially nocturnal asthma. They represent different classes of drug with differing side-effect profiles.

Objectives

To assess the comparative efficacy, safety and side-effects of long-acting beta-2 agonists and theophylline in the maintenance treatment of adults and adolescents with asthma.

Search methods

We searched the Cochrane Airways Group trials register and reference lists of articles. We also contacted authors of identified RCTs for other relevant published and unpublished studies and pharmaceutical manufacturers. Most recent search: November 2007.

Selection criteria

All included studies were RCTs involving adults and children with clinical evidence of asthma. These studies must have compared oral sustained release and/or dose adjusted theophylline with an inhaled long-acting beta-2 agonist.

Data collection and analysis

In original review, two reviewers independently assessed trial quality and extracted data, similarly in this update two reviewers undertook this. Study authors were contacted for additional information.

Main results

Thirteen studies with a total of 1344 participants met the inclusion criteria of the review. They were of varying quality. There was no significant difference between salmeterol and theophylline in FEV_1 predicted (6.5%; 95% CI -0.84 to 13.83). However, salmeterol treatment led to significantly better morning PEF (mean difference 16.71 L/min, 95% CI 8.91 to 24.51) and evening PEF (mean difference 15.58 L/min, 95% CI 8.33 to 22.83). Salmeterol also reduced the use of rescue medication. Formoterol, used in two studies was reported to be as effective as theophylline. Bitolterol, used in only one study, was reported to be less effective than theophylline. Participants taking salmeterol experienced fewer adverse events than those using theophylline (Parallel studies: Relative Risk 0.44; 95% CI 0.30 to 0.63, Risk

Difference -0.11; 95% CI -0.16 to -0.07, Numbers Needed to Treat (NNT) 9; 95% CI 6 to 14). Significant reductions were reported for central nervous system adverse events (Relative Risk 0.50; 95% CI 0.29 to 0.86, Risk Difference -0.07; 95% CI -0.12 to -0.02, NNT 14; 95% CI 8 to 50) and gastrointestinal adverse events (Relative Risk 0.30; 95% CI 0.17 to 0.55, Risk Difference -0.11; 95% CI -0.16 to -0.06, NNT 9; 95% CI 6 to 16).

Authors' conclusions

Long-acting beta-2 agonists, particularly salmeterol, are more effective than theophylline in improving morning and evening PEF, but are not significantly different in their effect on FEV1. There is evidence of decreased daytime and nighttime short-acting beta-2 agonist requirement with salmeterol. Fewer adverse events occurred in participants using long-acting beta-2 agonists (salmeterol and formoterol) as compared to theophylline.

PLAIN LANGUAGE SUMMARY

Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma

This review compared three asthma medications, salmeterol, formoterol (both long acting beta-agonists) and theophylline. These medications are used to help control symptoms of asthma, especially those which occur during the night. This review found that salmeterol showed a greater improvement in lung function, and reduced the need for extra short-term inhalers in the day and the night. Salmeterol and formoterol are less likely to produce side-effects (such as headaches and nausea) when compared to theophylline.

BACKGROUND

Theophylline is used for the management of asthma in people with persistent symptoms. It is a bronchodilator that relieves bronchospasm and increases airway calibre. The actual mechanism of theophylline is unknown. It inhibits phosphodiesterase, the enzyme that degrades cyclic 3', 5'-adenosine monophosphate (cAMP) and high cAMP concentrations are associated with bronchial smooth muscle relaxation. Theophylline may reduce mucosal permeability and thereby reduce plasma and macromolecular leakage across both the endothelial and epithelial barriers. It may also attenuate development of asthma inflammation after allergen challenge. In clinical practice, theophylline may have a role in the treatment of patients with severe persistent asthma who require multiple asthma therapy. Oral sustained release theophylline is also used in the management of nocturnal asthma.

The benefits of theophylline are limited by its toxicity. It has a narrow therapeutic index requiring dose titration and regular monitoring of serum concentrations to avoid adverse effects. Therapeutic plasma levels are generally accepted to be 55 to 110 micromol/L (10 to 20 mg/L), although recent reports suggest 5 to 15 mg/L as being acceptable. Many patients on theophylline experience toxic systemic effects, even with concentrations in the therapeutic range. Side-effects of theophylline include anorexia, nausea, headache and sleep disturbance. Altered mood and behaviour are sufficiently common to limit theophylline use in young children. There are also concerns that this drug may adversely affect concentration and cognitive skills in children. Theophylline may also aggravate underlying gastro-oesophageal reflux.

Long acting beta-2 agonists produce significant bronchodilation by the same pharmacological mechanism as other beta-2 agonists, i.e. stimulation of beta-2 receptors. These increase cAMP and produces functional antagonism, leading to reversal of bronchoconstriction.

Long-acting beta-2 agonists are added to anti-inflammatory therapy for the long term control of symptoms in persistent asthma, control of nocturnal asthma, and to prevent exercise-induced bronchospasm. The duration of bronchodilation lasts for up to 12 hours after administration. Long-acting beta-2 agonists also protect against a wide range of bronchoconstricting stimuli, inducing exercise, allergen, histamine and methacholine. Side-effects of long-acting beta-2 agonists are similar to those of short acting beta-2 agonists and include tachycardia, tremor, and headaches. With regular use, tachyphylaxis develops to the broncho protective effects of long-acting beta-2 agonists.

Other side effects which can occur with regular short-acting beta-2 agonists use are currently under evaluation. These include worsening airway responsiveness, worsening allergen induced airway inflammation and loss of asthma control. Recently, there is also concern, from a meta-analysis, that use of long-acting beta-2 agonists is associated with more severe and life-threatening exacerbations, as well as asthma-related deaths (Salpeter 2006).

Both theophylline and long-acting beta-2 agonists can be used for control of asthma symptoms, especially nocturnal asthma. They represent different classes of drugs with differing side-effect profiles. This review compares their relative efficacy and safety.

OBJECTIVES

To assess the comparative efficacy and safety of long-acting beta-2 agonists and theophylline in the maintenance treatment of adults and adolescents with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials reporting at least one asthma outcome, and that compared the efficacy of theophylline and long-acting beta-2 agonists.

Types of participants

Participants were adults and adolescents with clinical evidence of asthma.

Types of interventions

Interventions were defined as inhaled long-acting beta-2 agonists: salmeterol; eformoterol; bambuterol or bitolterol, versus oral sustained-release and/or dose-adjusted theophylline.

Types of outcome measures

Forced expiratory volume in one second (FEV1) - increase from baseline
Peak expiratory flow (PEF) - increase from baseline
Participants reporting an adverse event - percentage
Number of adverse events
Participants with a central nervous system adverse event
Participants with a gastrointestinal adverse event
Participants with respiratory adverse events
Participants with a ear, nose or throat adverse event
Participants with a cardiac adverse event
Number of symptom free nights
Rescue medication use during the night
Rescue medication use during the day
Participants waking with asthma symptoms

Only studies which had at least one of the above outcome measures were included for review.

Search methods for identification of studies

Electronic searches

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

((beta* and agonist*) or b*-agonist* or "long-acting beta*" or formoterol or foradil or eformoterol or salmeterol or bambuterol or biloterol or Oxis or Serevent or Bambec) AND (*xanthin* or theophylline* or theodur* or nuelin or aminophylline* or Uniphyllin* or Lasma or Phyllocontin* or Slo-Phyllin or Uniphyl or Theolair or Slo-Bid or Respbid or Theolong or Euphylong)

The most recent search was carried out in November 2007.

Searching other resources

We obtained titles, abstracts and key words of these articles and screened them for relevance. We obtained full text versions of relevant papers and hand searched their reference lists for additional articles. Authors of identified trials were contacted and asked to identify other published and unpublished studies. Manufacturers and experts in the field were also contacted.

Data collection and analysis

Selection of studies

Two review authors independently considered potentially relevant trials if their abstracts stated that the studies were randomised controlled trials and that they were comparing a long-acting beta-2 agonist with theophylline.

In the original review, two independent reviewers established whether each study met the inclusion criteria. There was 100% agreement for inclusion/exclusion of studies.

Data extraction and management

We collected the following information about each of the included studies:

(1) Demographics: age, gender, ethnicity and socioeconomic status.

(2) Type of study: whether parallel group or cross over design.

(3) Type of intervention:
type of long-acting beta-2 agonist used, daily dose, and the period of treatment
daily dose of theophylline and the period of treatment.

(4) Severity of asthma: baseline severity of asthma was assessed using FEV1, PEF, exacerbations, use of oral corticosteroids, and the use of inhaled corticosteroids.

(5) Sample size: number of participants eligible, the number randomised and the number completing the study.

(6) Diagnostic criteria for asthma: either American Thoracic Society, doctor diagnosis or objective evidence such as lung function.

(7) Concurrent conditions: any concurrent conditions that warranted exclusion from the study as per the study's protocol.

In the original review, two independent reviewers, extracted data on the intervention and control used in each study and the agreement was 100%. There was also 100% agreement on participant demographics, disease severity and participant numbers. In this update, two reviewers (AT and MK) extracted the data with 100% agreement.

We also sent a request to authors of the primary studies to obtain any missing data. In addition, we sent the authors a copy of the data extracted from their studies and they were asked to verify this.

Assessment of risk of bias in included studies

In the original review, two independent reviewers determined study quality. There was an initial 83% agreement on the quality score using the Jadad system (see the Methodological Quality of the studies). The two disagreements were resolved by discussion. There was 100% agreement using the Cochrane quality score. Similarly, in this update two reviewers (AT and MK) used the Jadad quality score and had 100% agreement. Allocation concealment was ranked using the Cochrane approach:

(1) Concealment of Allocation

Grade A: Adequate concealment - if there was true randomisation, i.e. a central randomisation scheme, randomisation by an external source, or the use of coded containers/envelopes.
Grade B: Uncertain.
Grade C: Clearly inadequate - if there was alternative allocation, reference to case record number, date of birth, day of the week, or an open test or random numbers.

(2) Blinding of Interventions

(3) Withdrawals/Dropouts

(4) Blinding of Outcome Assessment

Data synthesis

We analysed outcomes as continuous or dichotomous variables, using standard statistical techniques:
(1) For continuous outcomes, we calculated a fixed effect mean difference (MD) and 95% confidence intervals with GIV data for crossover and parallel studies.
(2) For dichotomous outcomes, we calculated a fixed effect relative risk with 95% confidence intervals.

Subgroup analysis and investigation of heterogeneity

We conducted a sub-group analysis based on study design:
Cross-over only,
Parallel group only

RESULTS

Description of studies

Results of the search

See Table 1 for details of previous literature searches. An update search run in November 2007 did not identify any new studies which met the eligibility criteria of the review.

Included studies

Thirteen studies with a total of 1344 completed participants met the inclusion criteria (see table 'Characteristics of included studies').

The study population of all the studies was primarily adult, with no participant under the age of 12 years. Ten out of 13 studies included participants who were using inhaled corticosteroids (an average of 60% of participants in these studies were using inhaled corticosteroids). Zwillich 1989; Ukena 1997; Nutini 1998 included participants who were not using steroids. Five studies (Zwillich 1989; Muir 1992; Selby 1997; Ukena 1997; Wiegand 1999) used nocturnal asthma as a specific entry criterion. In most of the studies, asthma severity was described as moderate, with the average baseline FEV1 at 70% of predicted. The treatment duration varied between two weeks (five studies), four weeks (three studies),12 weeks (four studies) and 12 months (one study).

Seven of the studies were cross-over design (Zwillich 1989; Muir 1992; Fjellbirkeland 1994; Selby 1997; Ukena 1997; Wiegand 1999; Filiz 2002). Only the first treatment period data from Wiegand 1999 study was included in this review. Filiz 2002, Fjellbirkeland 1994 and Ukena 1997 used wash-out periods of four weeks, two weeks and seven days, respectively between interventions. Selby 1997 excluded data from days 0 to 7 of each limb, from analysis to avoid carryover effects. Zwillich 1989 did not identify any wash-out period. In the Yurdakul 2002 study only data from groups one and three were used for analysis.

Interventions

Ten studies used salmeterol. Two studies used formoterol (Malolepszy 2002; Yurdakul 2002) as the long acting beta-2 agonist. One study used bitolterol as the long-acting beta-2 agonist (Zwillich 1989) . Theophylline was administered as a slow release formulation (13 studies), and the dose was adjusted using serum levels (12 studies). In one study (Muir 1992) theophylline was combined with ketotifen. Since this agent is a weak bronchodilator, no separate analysis was performed.

Outcomes

The following outcomes were assessed: changes in lung function from baseline including FEV_1 and peak expiratory flow (PEF); the number of adverse events reported; the number of participants reporting adverse events (including central nervous system, gastrointestinal, respiratory, ear,nose and throat, and cardiovascular adverse events); number of symptom free nights; the use of rescue medication; psychometric testing, nocturnal polysomnography and quality of life.

Risk of bias in included studies

In this updated version of the review, two reviewers (AT and MK) assessed the full text versions of the included trials for their methodological quality, with particular emphasis on the allocation concealment which was ranked using the Cochrane approach:

(1) Concealment of Allocation
All studies stated that the treatment allocation was random. Only two studies (Ukena 1997; Yurdakul 2002) mentioned the method for generation of the random sequence. None of the other papers described the methods used to generate random sequences, conceal allocation to groups, or blind outcome assessors, however, Dr Selby has provided this data in his correspondence.

(2) Blinding of Interventions

All the included studies were double-blinded.

(3) Withdrawals/Dropouts

Withdrawals were accounted for in eleven out of thirteen papers.

(4) Blinding of Outcome Assessment

It was noted whether the paper stated if the study outcomes were assessed by a person who was blinded to the treatment allocation.

Effects of interventions

Lung Function

Baseline FEV_1 was presented as mean FEV_1 (1.70 to 2.65 L) in five studies, median FEV_1(L) in one study (Ukena 1997); and FEV_1 % predicted (55 to 72) in four studies. One study, (Selby 1997), did not state the baseline FEV_1. The effects of therapy on lung function was measured and reported as FEV_1 (% predicted) in 12 out of 13 studies and as PEF in 9 out of 13 studies. There was a similar increase in FEV_1 with both theophylline and salmeterol in five studies (Fjellbirkeland 1994; Paggiaro 1996; Pollard 1997; Selby 1997; Nutini 1998), similar increase with formoterol and theophylline in one study (Malolepszy 2002); and no change in FEV_1 with bitolterol in one study (Zwillich 1989). From two studies (Muir 1992; Filiz 2002) there was no significant difference in FEV_1 predicted (MD 6.5% 95% CI -0.84 to 13.83). Pastorello 1998 reported salmeterol to be more effective than theophylline (p = 0.028, by covariance analysis). Except for Muir 1992 and Filiz 2002, data from the majority of trials were not reported adequately for statistical aggregation.

PEF was reported in nine studies. All demonstrated an increase in PEF with both theophylline and salmeterol. Based on analysis of Filiz 2002; Fjellbirkeland 1994; Nutini 1998 and Selby 1997 salmeteorol produced greater morning PEF (MD 16.71 L/min; 95% CI 8.91 to 24.51) and evening PEF (MD 15.63 L/min; 95% CI 8.26 to 22.99) than theophylline. Four studies (Pollard 1997; Ukena 1997; Pastorello 1998; Wiegand 1999) reported statistically significant improvement in PEF with salmeterol as compared to theophylline and one study (Yurdakul 2002) demonstrated greater improvement in PEF with formoterol. It was not possible to aggregate these data for meta-analysis. Muir 1992 commented that the increase in PEF in the theophylline group may have been due to use of more rescue medication (short-acting beta-2 agonist) in the early morning and last part of the night. This may have caused an increase in the morning PEF recording although this was not formally evaluated.

Daytime asthma

Data from three studies indicated that salmeterol was more effective than theophylline in reducing the requirement for short-acting beta-agonists during the day by 0.87 puffs (95% CI 0.06 to 1.67; Filiz 2002; Muir 1992; Ukena 1997). Data from two small trials indicated no significant difference between groups in the proportion of symptom free days on either treatment (4.87% (95% CI -12.1 to 21.83). Pollard 1997 reported that symptoms were reduced more effectively by salmeterol compared with theophylline.

Nocturnal Asthma

Nocturnal asthma was assessed as symptom free nights in seven studies (Muir 1992; Selby 1997; Ukena 1997; Nutini 1998; Pastorello 1998; Filiz 2002; Yurdakul 2002), nocturnal fall in PEF in three studies (Selby 1997; Ukena 1997; Filiz 2002) and rescue beta-2 agonist use during the night in two studies (Muir 1992; Fjellbirkeland 1994). Eight studies stated that salmeterol was significantly more effective than theophylline in reducing nocturnal asthma symptoms and one study stated similar results with formoterol. The studies on theophylline could not be pooled due to different symptom outcome scales used. Selby 1997 found significantly fewer micro arousals during sleep, on salmeterol over theophylline. Zwillich

1989 found no difference between bitolterol and theophylline on nocturnal asthma. Filiz 2002 showed that theophylline was significantly more effective in controlling nocturnal symptoms than salmeterol. Based on meta-analysis from two small studies that reported data as means there was no significant difference between treatments in reducing nocturnal symptoms (5.87% 95% CI -9.73 to 21.47). Pollard 1997 reported that salmeterol reduced the frequency of nocturnal awakenings more effectively than did theophylline.

Withdrawals

There were 200 withdrawals from eight studies, with no withdrawals from five studies. There was no significant difference between treatment groups. Only a small percentage of participants were withdrawn due to adverse events considered by the investigators to be related to either trial medication.

Fjellbirkeland 1994 reported that 43 patients dropped out or withdrew during the trial. Of these, 29 withdrawals were due to adverse events (11 salmeterol and 15 theophylline), but only 15 of these (four salmeterol and nine theophylline) were considered to be drug related. Other adverse events included asthma exacerbations. Eleven more theophylline subjects were withdrawn due to a failure to achieve serum concentration of theophylline. Three participants were withdrawn during the washout period for adverse events. Two participants failed to return and one was withdrawn due to poor compliance, but it is not clear to which treatment group these three participants belonged.

Malolepszy 2002 reported that 12 participants withdrew or dropped out from the trial (seven from theophylline group and five from formoterol group). Six were due to adverse effects, two were taking unallowed medications, two were withdrawn due to poor compliance, one withdrew consent to participate in the trial and two patients withdrew for other reasons.

Muir 1992 reported 15 withdrawals during the first period of the trial. Six of these were from the salmeterol group. Three were due to adverse events (bronchospasm, tachycardia, and exacerbation), two participants were withdrawn because they commenced steroid therapy and one withdrew due to persistence of symptoms. Nine participants were from the theophylline group. Five were due to adverse events (gastrointestinal problems, dizziness, exacerbations, and headaches), two participants commenced steroid therapy, one due to persistent symptoms and one because of lack of compliance.

Nutini 1998 reported 31 withdrawals from the trial. Twelve participants failed to return, 12 participants withdrew due to adverse effects, three patients withdrew due to concomitant diseases and four for other reasons. There were three withdrawals from the salmeterol group and nine from the theophylline group due to adverse events.

Paggiaro 1996 reported nine withdrawals due to adverse events or exacerbations of asthma (four in the salmeterol group and five in the theophylline group).

Pastorello 1998 reported 11 withdrawals from the study. One participant withdrew due to adverse effects, four participants failed to return and six for other reasons.

Pollard 1997 reported 80 dropouts or withdrawals from 484 participants randomised (16 to 17% in each treatment group).

Wiegand 1999 reported that 19 participants withdrew prior to randomisation. Eight participants withdrew due to failure to meet the enrolment criteria, theophylline titration failure (four), adverse events (two), participant decision (two), protocol violation (one), asthma exacerbation (one) and failure to return (one). One of these participants withdrew during theophylline titration after experiencing adverse effects considered to be related to theophylline use. One participant withdrew from the study after randomisation due to asthma exacerbation during the washout following the second treatment period in which salmeterol was administered.

Selby 1997; Ukena 1997; Zwillich 1989 and Yurdakul 2002 stated that all randomised patients completed these studies. Filiz 2002 did not describe number of withdrawals, except that there were no withdrawals due to adverse events.

Adverse Events

A comparison of the number of adverse events was reported in eleven studies. In this meta-analysis, the incidence of adverse events was significantly lower with salmeterol as compared with theophylline.

- Parallel studies: RR 0.44; 95% CI 0.30 to 0.63; RD -0.11; 95% CI -0.16 to -0.07; NNT 9; 95% CI 6 to 14.
- Crossover studies: RR 0.29; 95% CI 0.14 to 0.61; RD -0.26; 95% CI -0.39 to -0.13, NNT 4; 95% CI 3 to 8.

Central Nervous System Adverse Events

Salmeterol was associated with fewer CNS adverse events than theophylline in all of four studies reporting these events (RR 0.50; 95% CI 0.29 to 0.86, RD -0.07 95% CI -0.12 to -0.02, NNT 14 95% CI 8 to 50.

Gastrointestinal Adverse Events

Salmeterol was associated with fewer gastrointestinal diverse events than theophylline in all of the four studies reporting these events (RR 0.30; 95% CI 0.17 to 0.55; RD -0.11; 95% CI -0.16 to -0.06; NNT 9.0; 95% CI 6 to 16.

Other adverse events

There were some respiratory, ear, nose and throat and cardiovascular adverse events, but there were insufficient data to perform a meta-analysis. The trend was for a lower rate in salmeterol treated patients.

Bitolterol

Five of the eight studies included in this review used salmeterol as the long-acting beta-2 agonist, two (Malolepszy 2002; Yurdakul 2002) used formoterol, while one (Zwillich 1989) used bitolterol. Bitolterol appeared less effective than theophylline. Theophylline therapy was associated with a higher FEV_1 while a significant decrease occurred with bitolterol. The theophylline group also showed better sleep quality with fewer wakings with asthma than bitolterol. These results were in contrast to those of the salmeterol studies.

Formoterol

Formoterol was used as the long-acting beta-2 agonist in two studies (Malolepszy 2002; Yurdakul 2002). Both the studies concluded that there was no significant difference in lung function, asthma symptom scores and rescue medication use between the formoterol and theophylline groups. Malolepszy 2002 stated that there was a decrease in serum ECP (Eosinophilic Cationic Protein) concentration in the theophylline group while there was an increase in the formoterol group. This was attributed to the anti-inflammatory effect of theophylline. In Malolepszy 2002, adverse events were significantly fewer in the formoterol group as compared to theophylline. In Yurdakul 2002, the adverse events were similar in both groups.

Results were similar with both fixed and random effects statistical modelling.

DISCUSSION

This review compares long-acting beta-2 agonists with theophylline in the treatment of moderate asthma in 1344 patients in thirteen studies. This review found that salmeterol and theophylline were both effective in treating nocturnal symptoms such as night waking and need for rescue medication. Salmeterol showed a greater improvement in PEF compared to theophylline. The pooled difference in the other beneficial effects of salmeterol over theophylline did not reach statistical significance, but this may relate to the fact that many of the studies did not present data suitable for meta-analysis and all of the individual studies, except Filiz 2002, reported significantly more symptom-free nights with salmeterol over theophylline. This review also reported significantly fewer adverse events with salmeterol as compared to theophylline. With regards to formoterol, another long-acting beta-2 agonist, the two studies found reported it to be as efficacious as theophylline in improving lung function, treating nocturnal asthma symptoms and use of rescue medication, but the number of participants was small. In this review, the efficacy of bitolterol, another long-acting beta-2 agonist was found to be less than theophylline.

The quality of the studies was generally good. All were described as randomised trials with double-blinding. In communication with one author, the generation of random sequence and how it was concealed from the person allocating, was described. The results reported in this review apply to those participants who completed the studies (as stated in the Outcomes section).

The study designs were a mixture of crossover (seven studies) and parallel design (six studies). No differences in results were identified in relation to the different study design.

Nocturnal asthma is characterised by a significant reduction in airway calibre which is most apparent between the hours of 4 am and 7 am. It is frequently associated with disturbed sleep. Several different mechanisms of nocturnal exacerbations of asthma have been investigated, including circadian changes plasma cortisol, adrenal sympathetic hormones, and airway eosinophils. Short-acting bronchodilators provide insufficient protection against nocturnal attacks of asthma. Consequently, studies have investigated different therapies, including long-acting bronchodilators, corticosteroids and anticholinergics.

Salmeterol and theophylline are both effective means of treating asthma symptoms, especially episodes of nocturnal asthma. Salmeterol is an inhaled long-acting beta-2 agonist giving up to 12 hours of protection against bronchoconstricting stimuli. Theophylline is an oral, slow release, or dose-adjusted medication used for the management of asthma in people with persistent symptoms. It is usually monitored and dose adjusted according to the serum levels. Most of the studies in this review used dose-adjusted theophylline.

The studies showed a similar efficacy between salmeterol and theophylline, however salmeterol appeared to perform slightly better in the areas of lung function and nocturnal asthma. Two studies reported formoterol to have a similar efficacy as theophylline with regards to lung function and nocturnal asthma. One study, Zwillich 1989 reported that theophylline was more effective than bitolterol in terms of lung function and nocturnal waking.

Salmeterol is associated with adverse events including tachycardia, tremor, and headaches. Common adverse events associated with theophylline included anorexia, nausea, headache and sleep disturbance. Theophylline may also aggravate underlying gastro-oesophageal reflux. The studies in this review reported salmeterol as having fewer adverse events than theophylline. Meta-analyses of participants reporting adverse events, the total number of adverse events, and the number of participants with central nervous system and gastrointestinal adverse events, showed significantly fewer adverse events in those treated with salmeterol. This trend was also apparent for respiratory, ear, nose and throat, and cardiovascular adverse events, however there was insufficient data to perform a meta-analysis in these areas. One study in this review, Malolepszy 2002 also reported formoterol as having significantly fewer side-effects than theophylline.

There was no heterogeneity regarding the beneficial effects of salmeterol and it's fewer adverse effects as compared to theophylline.

AUTHORS' CONCLUSIONS

Implications for practice

Long-acting beta-2 agonists, particularly salmeterol, are more effective than theophylline in improving morning and evening PEF, but their effect on FEV1 is not significantly different. There is decreased nocturnal and daytime short-acting beta-2 agonist requirement with salmeterol rather than theophylline. Fewer adverse events occurred in participants using long-acting beta-2 agonists (salmeterol and formoterol) as compared to theophylline.

Implications for research

The following trials need to be done:

(1) Carry out cost analysis of long-acting beta-2 agonists versus theophylline

(2) Compare long-acting beta-2 agonists and theophylline in a paediatric asthma population

ACKNOWLEDGEMENTS

Financial assistance for the previous reviews were provided by the New South Wales Health Department (Australia) and by the (Australian) National Asthma Campaign. The authors would like to acknowledge Melbourne Health for assistance provided for this review. Previous contributors authors on this review were Leena Shah and Jen Coughlan who analysed and wrote-up findings (Shah 2003; Wilson 2000).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Filiz 2002

Methods	Randomised controlled trial (table of random numbers), cross-over.
Participants	15 Participants (5 male; 10 female) with ages ranging from 18 to 51 years, with asthma. number - 15 gender - M:F - 5:10 Baseline FEV1 50-80% predicted. 15% reversibility to inhaled salbutamol.
Interventions	Salmeterol 50 mcg BD versus sustained release theophylline 400-600 mg daily over 4 weeks, cross over with 1 week wash-out period in between.
Outcomes	FEV1, PEF (am and pm), frequency of symptom-free days, symptom-free nights, rescue medications required and side effects.
Notes	All participants had severe asthma requiring 800-1000mg/daily inhaled fluticasone propionate
Risk of bias	

Bias	Authors' judgement	Support for judgement

Filiz 2002 *(Continued)*

Adequate sequence generation?	Low risk	Table of random numbers
Allocation concealment?	Unclear risk	Information not available

Fjellbirkeland 1994

Methods	Randomised controlled trial (method of randomisation unclear), cross-over, double-blind, double-dummy.
Participants	Participants with ages ranging from 18 to 75 (mean age 51) years, with a diagnosis of asthma. 141 randomised, 98 completed. Baseline FEV1 (mean) was 2.05 for the salmeterol group and 2.22 for the theophylline group.
Interventions	Salmeterol 50 mcg BD (MDI) versus dose-adjusted theophylline (oral) over 2 weeks.
Outcomes	FEV1, PEF (am and pm), nocturnal asthma symptoms, nocturnal rescue medication use, daily rescue medication use and adverse events.
Notes	Generation of random sequence not stated. 43 participants were withdrawn or dropped out during this study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Malolepszy 2002

Methods	Multicentre randomised controlled trial (method of randomisation not described) double blind, parallel study.
Participants	Of 93 eligible, 81 participants with ages ranging from 18 to 60 were randomised. Demographic data : values presented as mean (SD) or as appropriate: Formoterol group: number : 41 gender : M:F- 16:25 median age (years) - 41.3 with a range of 18.3 to 60.9. Baseline FEV1(litres)- 2.15. Baseline FVC(litres)-3.03. Baseline PEF(l/sec):4.79. Baseline serum ECP(mcg/l) - 13.78. Theophylline group : number : 40. gender (M:F): 14:26. Median age (years): 44.5 with a range of 22.9 to 60.9. Baseline FEV1(litres) - 2.10. Baseline FVC (litres) - 2.88. Baseline PEF(I/sec) - 4.84.

Malolepszy 2002 *(Continued)*

	Baseline serum ECP(mcg/l) : 12.66.
Interventions	Formoterol 12 mcg BD (MDI) versus oral slow release theophylline 250 or 350 mg twice daily for 12 weeks.
Outcomes	FEV1, change in serum eosinophil cationic protein, asthma scores, rescue medication use and adverse events.
Notes	This study was published in German. Method of randomisation not stated. All participants in this study were on inhaled corticosteroids. 12 participants were withdrawn from the study. The results in this study - FEV1, FVC, PEF and ECP are reported as mean and range.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Muir 1992

Methods	Randomised controlled trial (method of randomisation unclear), double blind, double dummy, cross over.
Participants	Of 96 eligible participants with asthma, 96 were randomised and 80 completed this study. Age range was 17 to 70 years with a mean of 42 (13). The baseline FEV1 (mean+/-SD, %predicted) was 70%+10% for the salmeterol group and 68% +9% for the theophylline group.
Interventions	Salmeterol 50 mcg BD (MDI) versus slow release theophylline 300 mg BD plus ketotifen 1 mg BD (which potentiates the bronchodilating action of theophylline) over 28 days.
Outcomes	FEV1, PEF, nocturnal asthma symptoms, nocturnal rescue medication use, adverse events.
Notes	Parallel group data from treatment period 1 only was used in this analysis. Fifteen participants (6 salmeterol, 9 theophylline) were withdrawn during this period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Nutini 1998

Methods	Randomised controlled trial (method of randomisation unclear) open, parallel group.
Participants	112 participants randomised and 81 completed this study. Demographic data:

Nutini 1998 *(Continued)*

	Values presented as mean (SD) or as appropriate - Salmeterol group: Age (years):45.5(14). Sex (M:F):31:25. Baseline FEV1(litres): 2.21(0.8). Theophylline group: Age : 47.9(16.7). Sex : (M:F) : 37:18. Baseline FEV1(litres): 2.10(0.6).
Interventions	Salmeterol 50 mcg BD (MDI) and dose -adjusted slow release oral theophylline twice daily over 12 months.
Outcomes	FVC, FEV1, PEF(am and pm), daytime and nocturnal asthma symptoms, daily rescue medication use, quality of life and adverse events.
Notes	Method of randomisation not given. 31 participants were withdrawn during this study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Paggiaro 1996

Methods	Randomised controlled trial (method of randomisation unclear), double-blind, double-dummy, parallel group.
Participants	Of 243 eligible participants with asthma, 189 were randomised and 180 completed this study. Ages ranged from 17 to 78. Baseline FEV1 (% predicted) was 68% for the salmeterol and 72% for the theophylline group.
Interventions	Salmeterol 50 mcg BD (MDI) versus dose-adjusted theophylline (oral) over 4 weeks.
Outcomes	FEV1, PEF, nocturnal asthma symptoms, nocturnal rescue medication use, daily medication use, adverse events, physician assessment.
Notes	Method of randomisation was not given. Nine participants (4 salmeterol, 5 theophylline) were withdrawn during the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Pastorello 1998

Methods	Multicentre randomised controlled trial (method of randomisation not described). This was a parallel study.
Participants	Of 97 eligible participants, 86 were enrolled and 75 completed this study. Demographic data: values presented as mean(SD) or as appropriate - Salmeterol group: number - 43. gender - M:F - 22:2 1. age: 44.3(17). baseline PEF(l/m): am - 337.2. pm - 347.8. Theophylline group: number- 43. gender: M:F- 26:17. age(years) - 47(17.2). baseline PEF(l/m): am - 347, pm - 363.1
Interventions	Salmeterol 100 mcg BD (MDI) versus dose -adjusted slow release oral theophylline for 3 months.
Outcomes	FEV1, PEF, symptom scores, rescue medication use and adverse events.
Notes	This study was published in Italian. Method of randomisation not given. All participants were on inhaled steroids. 11 participants withdrew from the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Pollard 1997

Methods	Randomised controlled trial (method of randomisation unclear), double-blind and double-dummy, parallel group.
Participants	Of 638 eligible participants, 484 were randomised and 404 completed this study. All participants had a diagnosis of asthma. Ages ranged from 12 - 80 years. Baseline FEV1 (% predicted) was 72% for the salmeterol and 71% for the theophylline group.
Interventions	Salmeterol 42 mcg BD (MDI) versus dose-adjusted theophylline (oral) over 12 weeks.
Outcomes	FEV1, PEF, asthma symptoms, rescue medication use, patient satisfaction, nocturnal waking with asthma, physician assessment, adverse events.
Notes	This paper is possibly two separate studies with combined results. Generation of random sequence is unclear. 16 - 17% of participants within each treatment group were withdrawn from the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement

Pollard 1997 *(Continued)*

Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Selby 1997

Methods	Randomised controlled trial (method of randomisation unclear), double-blind, double-dummy, cross over.
Participants	Of 30 eligible participants with asthma, 15 were randomised and completed the study. Age range was 17 - 66 years. No baseline lung function was provided.
Interventions	Salmeterol 50 mcg BD (Diskhaler) and dose-adjusted theophylline (oral) over 2 weeks.
Outcomes	FEV1, PEF, Quality of life questionnaire, adverse events, sleep studies, physician assessment, patient assessment, psychometric tests.
Notes	All randomised participants completed the trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Ukena 1997

Methods	Randomised controlled trial (Block randomisation of 4 patients done by Glaxo pharmaceuticals). Placebo-controlled, double-blind, double-dummy, cross-over trial.
Participants	Nocturnal asthma was a specific entry criterion in this study. Of 22 eligible patients with symptomatic asthma, 16 (2 females and 14 males) were randomised and all completed the study. Median age at study was 27 years (range 21-54 years). Baseline FEV1 (litre) in salmeterol group: median 3.08 (range 1.88 - 4.72) Baseline FEV1(litre) in theophylline group: median 3.42 (range 1.96-4.64).
Interventions	Salmeterol 50 mcg BD (MDI) versus theophylline (slow release) 600 mg PO daily were given for periods of 7 days with a wash-out period of 7 days between treatment periods.
Outcomes	FEV1, PEF, FVC, asthma symptoms during day and night, overall effectiveness questionnaire for patients, adverse effects.
Notes	This study was published in German. All randomised patients completed the trial. The results of FEV1 and morning and evening PEF reported as median and range, hence could not be combined with the other data in the meta-analysis.

Risk of bias

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

Ukena 1997 *(Continued)*

Adequate sequence generation?	Low risk	Computer generated randomisation schedule
Allocation concealment?	Low risk	Centraliised randomisation process

Wiegand 1999

Methods	Randomised controlled trial (method of randomisation not described), double-blind, double-dummy, three-period crossover.
Participants	Of 38 eligible participants,19 were randomised and18 completed this study. Nocturnal asthma was an entry criterion in this study. Mean age (SD) was 35.6 (2.7) years. Mean (SD) baseline FEV1 was 3.81 (0.17) .
Interventions	Salmeterol 42 mcg BD (MDI) versus dose-adjusted theophylline versus placebo over 15 days.
Outcomes	FEV1, PEF(am and pm), nocturnal asthma symptoms, nighttime awakenings,rescue medication use, daily medication use and adverse effects.
Notes	Method of randomisation was not stated. This study included participants on inhaled corticosteroids. One participant was withdrawn from the study after randomisation whereas 19 patients withdrew prior to randomisation..

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Yurdakul 2002

Methods	Randomised controlled trial (method of randomisation - eligible patients were randomised to each treatment group in rows according to their application month to the hospital.) This was a parallel study.
Participants	64 patients with moderate asthma on inhaled corticosteroids were randomised to three different treatment groups. Demographic data expressed as mean (SD) or as appropriate: Formoterol group: number of patients : 25. Sex : M:F - 17:8. Age in years : 38.3(6). Baseline FEV1 (% predicted) : 66.6(4.8). Baseline PEF(l/min) - morning-288.4(40.5) , evening-352(47.1) . Theophylline group: Number of patients - 20. Sex: M:F: 13:7. Age in years - 37.7(7). Baseline FEV1 (% predicted) - 65.2(6.1). Baseline PEF(l/min): morning -265(47.6),

Yurdakul 2002 *(Continued)*

	evening -357.5(55.4).
Interventions	Formoterol 9 mcg BD (MDI) versus sustained release theophylline 400 mg once daily for 3 months.
Outcomes	FEV1, PEF, asthma symptom scores (day and night-time), rescue medication use and adverse events.
Notes	All randomised participants completed the trial. All participants were on inhaled steroids. Data from groups 1 and 3 only used for this analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	Investigators aware as to order of randomisation

Zwillich 1989

Methods	Randomised, controlled trial (method of randomisation unclear), cross over, double-blind, double-dummy.
Participants	Of 26 eligible participants with asthma, 26 participants were randomised and 26 completed the study. The age range of participants was 17 - 47 with a mean of 32.5 years. Baseline FEV1 for all participants (mean +/-SEM) was 1.84 (0.0096).
Interventions	Bitolterol 1.11 mg (MDI) TDS versus dose-adjusted theophylline BD (oral) over 2 weeks.
Outcomes	FEV1, quality of life questionnaire on sleep, nocturnal asthma symptoms, rescue medication use, sleep variables and patient satisfaction.
Notes	All randomised participants completed the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

BD: Twice a day; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; MDI: Metred-dose inhaler; PEF: Peak expiratory flow; TDS: Three times a day

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

Study	Reason for exclusion
Avidsson 1991	Formoterol versus salbutamol - no theophylline arm
Barnes 1992	Review only
Brogden 1991	Review only
Brogden 1992	Review only
Cheung 1998	Does not compare salmeterol with theophylline

Study	Reason for exclusion
Davies 2000	Review only
Donohue 2001	Review only
Dutta 2002	Review only
Eda 1993	Not a randomised controlled trial
Faulds 1991	Reveiw only
Gokhale 2002	Review only
Hancox 2001	Review only
Holimon 2001	Review only
Hunt 2002	Review only
Kleerup 1997	Review only
Lockey 1999	Compares Salmeterol with placebo, no theophylline arm
Lotvall 1992	Review only
Manchee 1996	Not a randomised controlled trial
Meier 1997	Not a randomised controlled trial
Midgren 1992	Comparing formoterol with salmeterol, no theophylline arm
Morice 1999	Compared short-acting beta-agonist with theophylline
Nelson 1996	Review only
Nightingale 1995	Not a randomised controlled trial
Paciorek 1991	Not a randomised controlled trial
Rossi 2002	Randomised controlled trial in patients with COPD
Skloot 2002	Review only
Taburet 1994	Review only
Taccola 1999	Randomised controlled trial in patients with COPD
Thomson 1998	Review only
Tomac 1996	Controlled clinical trial - Not a randomised controlled trial
Vatrella 2005	Single dose pharmacokinetic, crossover study. No measurable outcome.
Weinstein 1997	No theophylline arm

DATA AND ANALYSES

Comparison 1. Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 predicted	2		% (Fixed, 95% CI)	6.50 [-0.84, 13.83]
2 FEV1 (Litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Change in FEV1 (Litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 PEF	4		L/min (Fixed, 95% CI)	Subtotals only
4.1 Morning PEF	4		L/min (Fixed, 95% CI)	16.71 [8.91, 24.51]
4.2 Evening PEF	4		L/min (Fixed, 95% CI)	15.58 [8.33, 22.83]
5 Morning PEF	4		L/min (Fixed, 95% CI)	16.71 [8.91, 24.51]
5.1 Crossover studies	3		L/min (Fixed, 95% CI)	16.07 [8.15, 23.99]
5.2 Parallel group studies	1		L/min (Fixed, 95% CI)	37.2 [-7.64, 82.04]
6 Evening PEF	4		L/min (Fixed, 95% CI)	15.58 [8.33, 22.83]
6.1 Crossover studies	3		L/min (Fixed, 95% CI)	14.92 [7.58, 22.27]
6.2 Parallel group studies	1		L/min (Fixed, 95% CI)	39.7 [-4.99, 84.39]
8 Change in am PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Change in pm PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Use of rescue medication	4		puffs/day or night (Fixed, 95% CI)	Subtotals only
10.1 Daytime use of rescue medication	4		puffs/day or night (Fixed, 95% CI)	-0.87 [-1.67, -0.06]
10.2 Nocturnal use of medication	2		puffs/day or night (Fixed, 95% CI)	-0.43 [-0.83, -0.03]
11 Change in rescue medication	1		Puffs/d (Fixed, 95% CI)	Totals not selected
12 Symptom-free days	2		% (Fixed, 95% CI)	4.87 [-12.10, 21.83]
13 Symptom-free nights	2		% (Fixed, 95% CI)	5.86 [-9.73, 21.46]
14 Adverse events - CNS (%)	4	527	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.86]

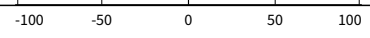
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Parallel studies	1	324	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.20, 1.11]
14.2 Crossover studies	3	203	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.27, 1.04]
15 Adverse events - GI (%)	4	527	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.17, 0.55]
16 Adverse events - any AE (%)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Parallel studies	5	807	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.30, 0.63]
16.2 Crossover studies	4	130	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.14, 0.61]
17 Adverse events - CNS (%)	4	527	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.86]

Analysis 1.1. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 1 FEV1 predicted.

Study or subgroup	Salmeterol N	Theophylline N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Filiz 2002	1	1	-2.1 (7.888)		22.5%	-2.13[-17.59,13.33]
Muir 1992	1	1	9 (4.25)		77.5%	9[0.67,17.33]
Total (95% CI)					**100%**	**6.5[-0.84,13.83]**

Heterogeneity: Tau^2=0; Chi^2=1.54, df=1(P=0.21); I^2=35.2%

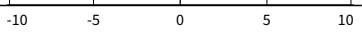
Test for overall effect: Z=1.74(P=0.08)



Favours theophylline — Favours salmeterol

Analysis 1.2. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 2 FEV1 (Litres).

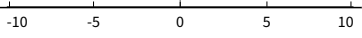
Study or subgroup	Salmeterol N	Salmeterol Mean(SD)	Theophylline N	Theophylline Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Fjellbirkeland 1994	63	2.3 (0)	51	2.3 (0)		Not estimable



Favours theophylline — Favours salmeterol

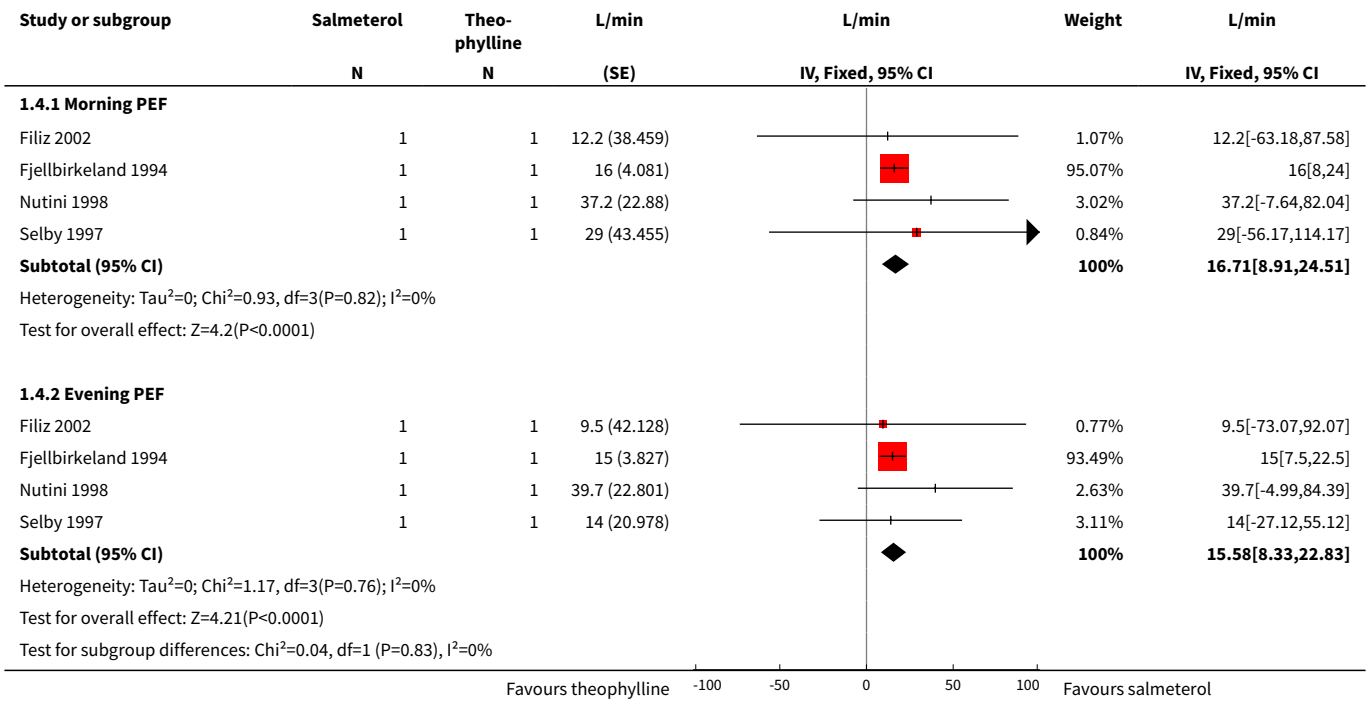
Analysis 1.3. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 3 Change in FEV1 (Litres).

Study or subgroup	Salmeterol N	Salmeterol Mean(SD)	Theophylline N	Theophylline Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Pollard 1997	162	0.2 (0)	162	0.7 (0)		Not estimable

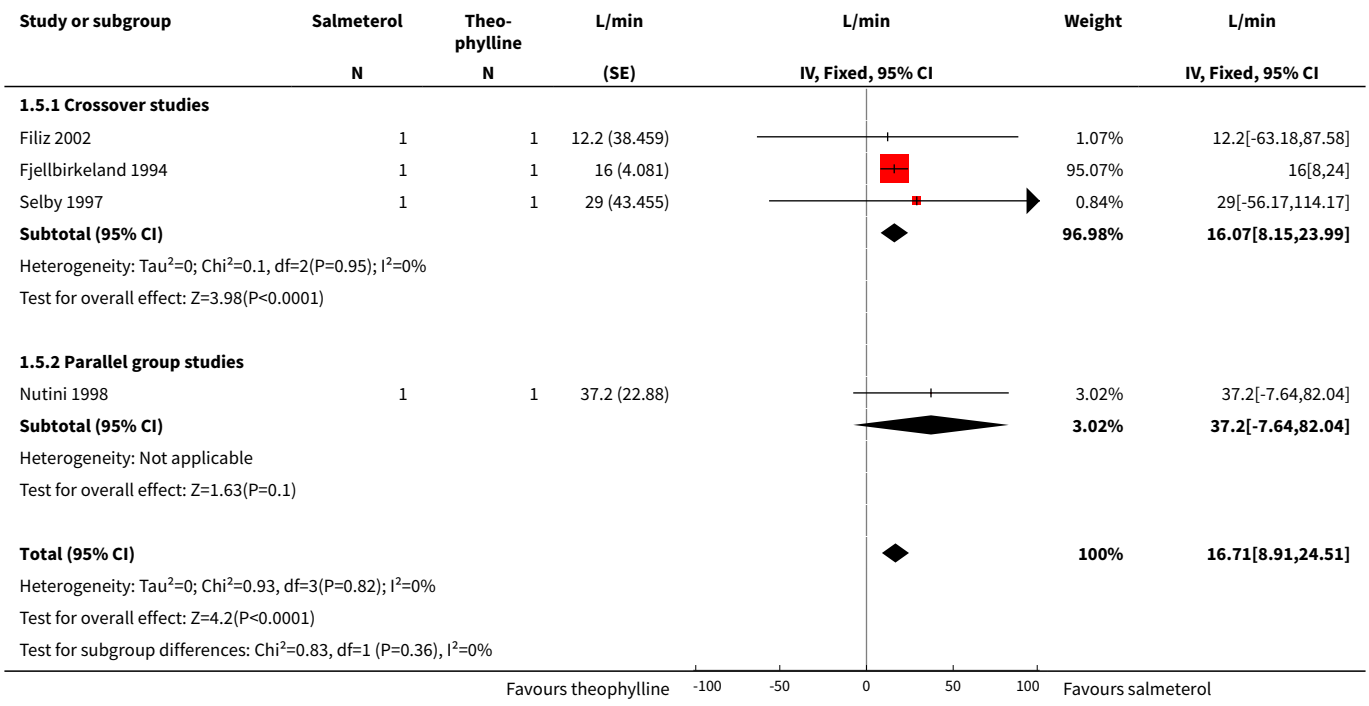


Favours theophylline — Favours salmeterol

Analysis 1.4. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 4 PEF.

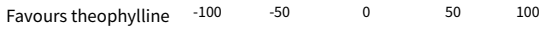


Analysis 1.5. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 5 Morning PEF.



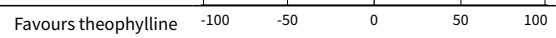
Analysis 1.6. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 6 Evening PEF.

Study or subgroup	Salmeterol N	Theo-phylline N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
1.6.1 Crossover studies						
Filiz 2002	1	1	9.5 (42.128)		0.77%	9.5[-73.07,92.07]
Fjellbirkeland 1994	1	1	15 (3.827)		93.49%	15[7.5,22.5]
Selby 1997	1	1	14 (20.978)		3.11%	14[-27.12,55.12]
Subtotal (95% CI)					**97.37%**	**14.92[7.58,22.27]**
Heterogeneity: Tau²=0; Chi²=0.02, df=2(P=0.99); I²=0%						
Test for overall effect: Z=3.98(P<0.0001)						
1.6.2 Parallel group studies						
Nutini 1998	1	1	39.7 (22.801)		2.63%	39.7[-4.99,84.39]
Subtotal (95% CI)					**2.63%**	**39.7[-4.99,84.39]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.74(P=0.08)						
Total (95% CI)					**100%**	**15.58[8.33,22.83]**
Heterogeneity: Tau²=0; Chi²=1.17, df=3(P=0.76); I²=0%						
Test for overall effect: Z=4.21(P<0.0001)						
Test for subgroup differences: Chi²=1.15, df=1 (P=0.28), I²=13.01%						



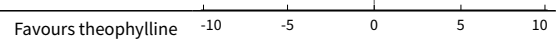
Analysis 1.8. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 8 Change in am PEF (L/min).

Study or subgroup	Salmeterol N	Salmeterol Mean(SD)	Theophyllline N	Theophyllline Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Pollard 1997	162	10.3 (50)	162	-4.5 (50)		14.8[3.91,25.69]



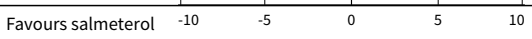
Analysis 1.9. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 9 Change in pm PEF (L/min).

Study or subgroup	Salmeterol N	Salmeterol Mean(SD)	Theophyllline N	Theophyllline Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Pollard 1997	162	5.3 (0)	162	-3.5 (0)		Not estimable



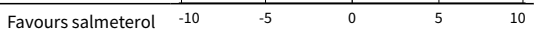
Analysis 1.10. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 10 Use of rescue medication.

Study or subgroup	Salmeterol N	Theo-phylline N	puffs/day or night (SE)	puffs/day or night IV, Fixed, 95% CI	Weight	puffs/day or night IV, Fixed, 95% CI
1.10.1 Daytime use of rescue medication						
Filiz 2002	1	1	-2 (3.37)		1.48%	-2.02[-8.63,4.59]
Muir 1992	1	1	-1.1 (0.486)		70.97%	-1.1[-2.05,-0.15]
Pollard 1997	1	1	-0.5 (0)			Not estimable
Ukena 1997	1	1	-0.2 (0.78)		27.55%	-0.2[-1.73,1.33]
Subtotal (95% CI)					**100%**	**-0.87[-1.67,-0.06]**
Heterogeneity: Tau²=0; Chi²=1.08, df=2(P=0.58); I²=0%						
Test for overall effect: Z=2.11(P=0.03)						
1.10.2 Nocturnal use of medication						
Muir 1992	1	1	-0.5 (0.219)		86.31%	-0.5[-0.93,-0.07]
Ukena 1997	1	1	0 (0.55)		13.69%	0[-1.08,1.08]
Subtotal (95% CI)					**100%**	**-0.43[-0.83,-0.03]**
Heterogeneity: Tau²=0; Chi²=0.71, df=1(P=0.4); I²=0%						
Test for overall effect: Z=2.12(P=0.03)						
Test for subgroup differences: Chi²=0.9, df=1 (P=0.34), I²=0%						



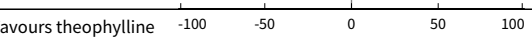
Analysis 1.11. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 11 Change in rescue medication.

Study or subgroup	Salmeterol N	Theophylline N	Puffs/d (SE)	Puffs/d IV, Fixed, 95% CI	Puffs/d IV, Fixed, 95% CI
Pollard 1997	1	1	-1.7 (0.727)		-1.7[-3.12,-0.28]



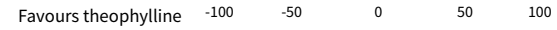
Analysis 1.12. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 12 Symptom-free days.

Study or subgroup	Salmeterol N	Theo-phylline N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Filiz 2002	1	1	-5.3 (13.117)		43.52%	-5.3[-31.01,20.41]
Ukena 1997	1	1	12.7 (11.515)		56.48%	12.7[-9.87,35.27]
Total (95% CI)					**100%**	**4.87[-12.1,21.83]**
Heterogeneity: Tau²=0; Chi²=1.06, df=1(P=0.3); I²=5.97%						
Test for overall effect: Z=0.56(P=0.57)						



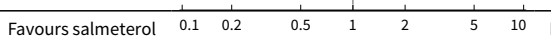
Analysis 1.13. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 13 Symptom-free nights.

Study or subgroup	Salmeterol N	Theo-phylline N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Filiz 2002	1	1	-7.8 (11.76)		45.78%	-7.8[-30.85,15.25]
Ukena 1997	1	1	17.4 (10.806)		54.22%	17.4[-3.78,38.58]
Total (95% CI)					**100%**	**5.86[-9.73,21.46]**
Heterogeneity: Tau²=0; Chi²=2.49, df=1(P=0.11); I²=59.83%						
Test for overall effect: Z=0.74(P=0.46)						



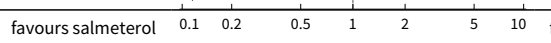
Analysis 1.14. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 14 Adverse events - CNS (%).

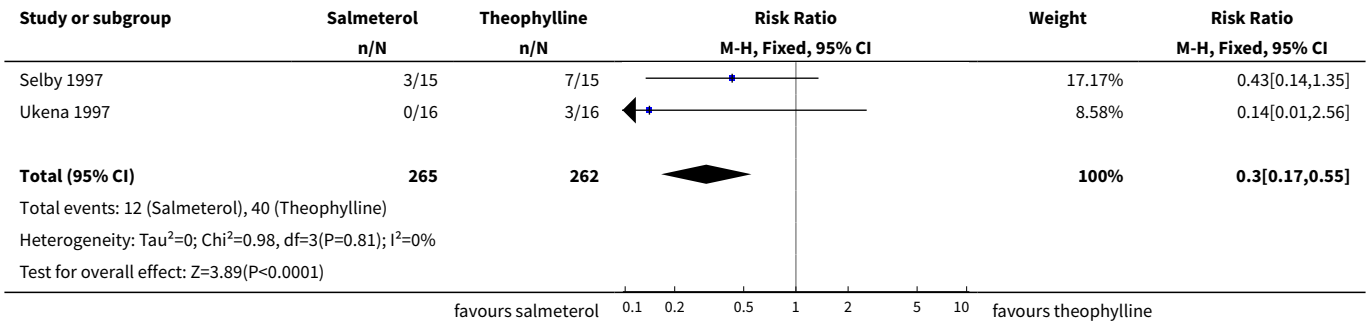
Study or subgroup	Salmeterol n/N	Theophylline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Parallel studies					
Pollard 1997	7/162	15/162		42.44%	0.47[0.2,1.11]
Subtotal (95% CI)	**162**	**162**		**42.44%**	**0.47[0.2,1.11]**
Total events: 7 (Salmeterol), 15 (Theophylline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.72(P=0.09)					
1.14.2 Crossover studies					
Fjellbirkeland 1994	10/72	16/69		46.24%	0.6[0.29,1.23]
Selby 1997	0/15	2/15		7.07%	0.2[0.01,3.85]
Ukena 1997	0/16	1/16		4.24%	0.33[0.01,7.62]
Subtotal (95% CI)	**103**	**100**		**57.56%**	**0.53[0.27,1.04]**
Total events: 10 (Salmeterol), 19 (Theophylline)					
Heterogeneity: Tau²=0; Chi²=0.61, df=2(P=0.74); I²=0%					
Test for overall effect: Z=1.84(P=0.07)					
Total (95% CI)	**265**	**262**		**100%**	**0.5[0.29,0.86]**
Total events: 17 (Salmeterol), 34 (Theophylline)					
Heterogeneity: Tau²=0; Chi²=0.7, df=3(P=0.87); I²=0%					
Test for overall effect: Z=2.51(P=0.01)					
Test for subgroup differences: Not applicable					



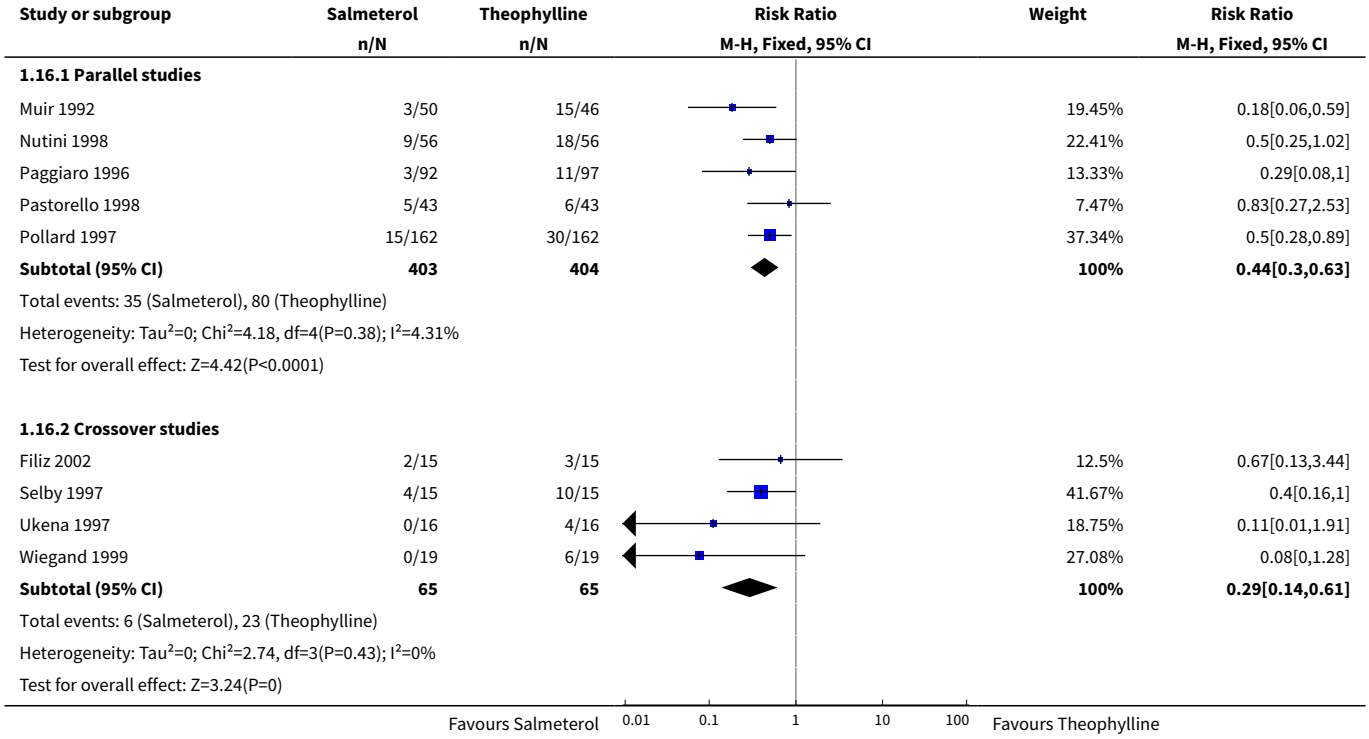
Analysis 1.15. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 15 Adverse events - GI (%).

Study or subgroup	Salmeterol n/N	Theophylline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Fjellbirkeland 1994	5/72	13/69		32.56%	0.37[0.14,0.98]
Pollard 1997	4/162	17/162		41.69%	0.24[0.08,0.68]

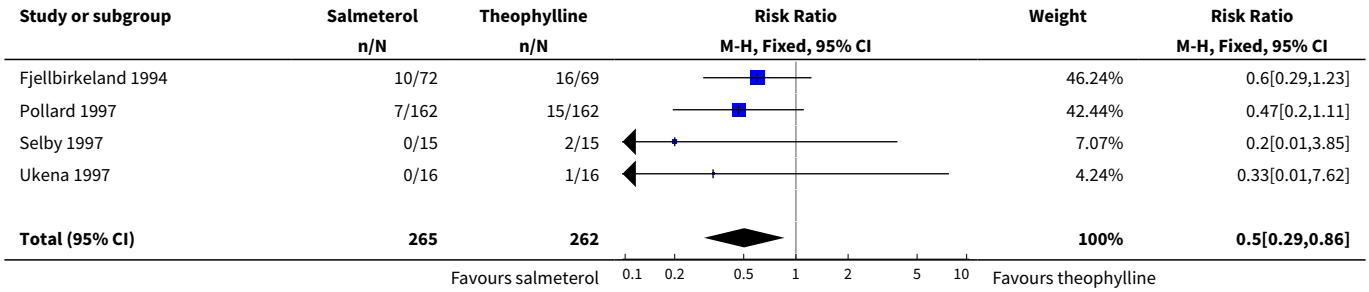


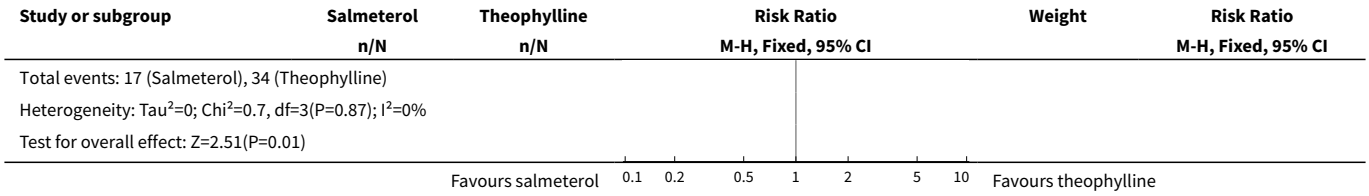


Analysis 1.16. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 16 Adverse events - any AE (%).



Analysis 1.17. Comparison 1 Salmeterol 50 mcg BD versus dose-adjusted, SR theophylline, Outcome 17 Adverse events - CNS (%).

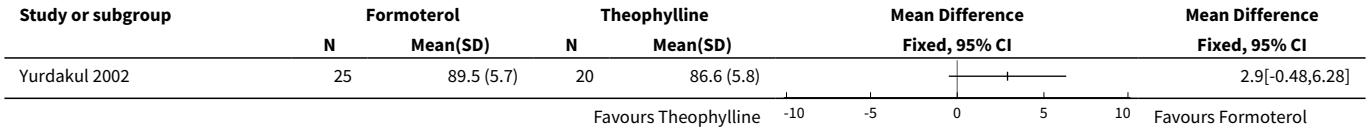




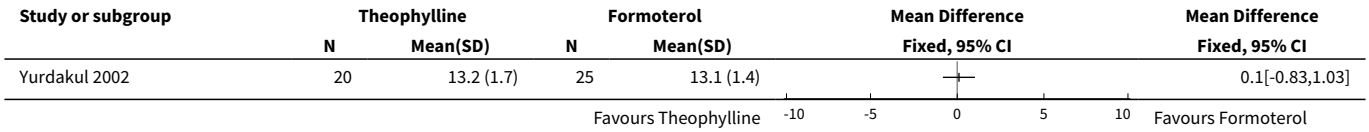
Comparison 2. Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1(% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 PEF variability	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Use of rescue medication	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Symptom score (daytime)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Symptom score (nighttime)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Adverse events - Any	2	126	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.21, 0.95]
7 Serum ECP value (mcg/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline, Outcome 1 FEV1(% predicted).

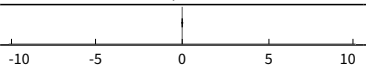


Analysis 2.2. Comparison 2 Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline, Outcome 2 PEF variability.



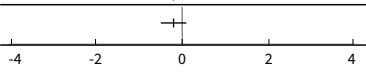
Analysis 2.3. Comparison 2 Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline, Outcome 3 Use of rescue medication.

Study or subgroup	Formoterol		Theophylline		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Yurdakul 2002	25	0.2 (0.1)	20	0.2 (0.1)		0[-0.06,0.06]



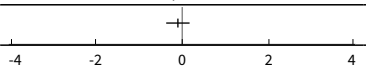
Analysis 2.4. Comparison 2 Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline, Outcome 4 Symptom score (day-time).

Study or subgroup	Formoterol		Theophylline		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Yurdakul 2002	25	0.5 (0.5)	20	0.7 (0.5)		-0.2[-0.49,0.09]



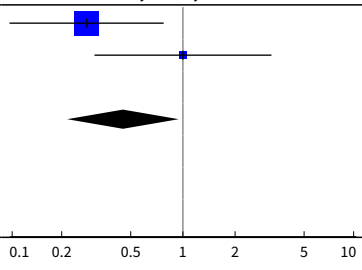
Analysis 2.5. Comparison 2 Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline, Outcome 5 Symptom score (night-time).

Study or subgroup	Formoterol		Theophylline		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Yurdakul 2002	25	0.2 (0.4)	20	0.3 (0.5)		-0.1[-0.37,0.17]



Analysis 2.6. Comparison 2 Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline, Outcome 6 Adverse events - Any.

Study or subgroup	Formoterol	Theophylline	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Malolepszy 2002	4/41	14/40		76.13%	0.28[0.1,0.77]
Yurdakul 2002	5/25	4/20		23.87%	1[0.31,3.24]
Total (95% CI)	**66**	**60**		**100%**	**0.45[0.21,0.95]**
Total events: 9 (Formoterol), 18 (Theophylline)					
Heterogeneity: Tau^2=0; Chi^2=2.61, df=1(P=0.11); I^2=61.72%					
Test for overall effect: Z=2.11(P=0.04)					



Analysis 2.7. Comparison 2 Formoterol 9-12 mcg BD versus dose-adjusted, SR theophylline, Outcome 7 Serum ECP value (mcg/l).

Study or subgroup	Formoterol		Theophylline		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Malolepszy 2002	41	6.1 (19.4)	40	0.6 (10)		5.47[-1.23,12.17]

ADDITIONAL TABLES

Table 1. Search history

Years: 1966-1998	Papers retrieved: 24 Excluded: 18 Included: 6 Authors providing data: 3 (Dr Selby, Dr Fjellbirkeland and Dr Paggiaro)
Years: 1997-January 2003	Papers retrieved: 20 Excluded: 14 Included: 6 Total included: 12
2002-November 2006	Papers retrieved: 1 Excluded: 0 Included: 1 Total included: 13

WHAT'S NEW

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

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 2, 2000

Date	Event	Description
11 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AT and MK updated the review by screening the 37 citations and evaluating the 2 new studies for eligibility and adding data to the analyses. AT amended the Synopsis, Abstract, Background, Search Strategy, Methods, Results, Discussion, Conclusions and References in the light of new evidence.TJL assisted with the analysis in the update of the review by extracting entering and analysing data with generic inverse variance. LI provided supervision, editing and analysis of data. PG edited the original review. AW authored the original review. Other contributors to previous versions of this review: Jen Coughlan; Leena Shah

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.
- Melbourne Health, Australia.

External sources

- New South Wales Health Department, Australia.
- National Asthma Campaign, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [*therapeutic use]; Albuterol [*analogs & derivatives] [therapeutic use]; Asthma [drug therapy] [*prevention & control]; Bronchodilator Agents [*therapeutic use]; Delayed-Action Preparations; Randomized Controlled Trials as Topic; Theophylline [*therapeutic use]

MeSH check words

Adult; Humans