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Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children (Review)

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Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD004106.
DOI: 10.1002/14651858.CD004106.pub4.

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TABLE OF CONTENTS

[Intervention Review]

Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

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Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2012.
Review content assessed as up-to-date: 24 June 2011.

Citation: Lasserson TJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD004106. DOI: 10.1002/14651858.CD004106.pub4.

ABSTRACT

Background

Long-acting beta-agonists are a common second line treatment in people with asthma inadequately controlled with inhaled corticosteroids. Single device inhalers combine a long-acting beta-agonist with an inhaled steroid delivering both drugs as a maintenance treatment regimen. This updated review compares two fixed-dose options, fluticasone/salmeterol FP/SALand budesonide/formoterol, since this comparison represents a common therapeutic choice.

Objectives

To assess the relative effects of fluticasone/salmeterol and budesonide/formoterol in people with asthma.

Search methods

We searched the Cochrane Airways Group register of trials with prespecified terms. We performed additional hand searching of manufacturers' web sites and online trial registries. Search results are current to June 2011.

Selection criteria

We included randomised studies comparing fixed dose fluticasone/salmeterol and budesonide/formoterol in adults or children with a diagnosis of asthma. Treatment in the studies had to last for a minimum of 12 weeks.

Data collection and analysis

Two authors independently assessed studies for inclusion in the review. We combined continuous data outcomes with a mean difference (MD), and dichotomous data outcomes with an odds ratio (OR). We assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Main results

Five studies met the review entry criteria (5537 adults). Study populations entered the studies having previously been treated with inhaled steroids and had moderate or mild airway obstruction (mean FEV_1 predicted between 65% and 84% at baseline). Most of the studies assessed treatment over a period of six months. The studies were at a low risk of selection and performance/detection bias, although we could not determine whether missing data had an impact on the results. Availablility of outcome data was satisfactory.

Primary outcomes

The odds ratio for exacerbations requiring oral steroids was lower with fluticasone/salmeterol but did not reach statistical significance (OR 0.89, 95% confidence interval (CI) 0.74 to 1.07, four studies, N = 4949). With an assumed risk with budesonide/formoterol of 106/1000 participants requiring oral steroids, treatment with fluticasone/salmeterol would lead to between 25 fewer and seven more people per 1000 experiencing a course of oral steroids. Although the odds of hospital admission was higher with fluticasone/salmeterol, this did not reach statistical significance (OR 1.29, 95% CI 0.68 to 2.47, four studies, 4879 participants). With an assumed risk in the budesonide/formoterol of 7/1000, between three fewer and nine more people per 1000 would be hospitalised on fluticasone/salmeterol. The odds of a serious adverse event related to asthma was higher with fluticasone/salmeterol but did not differ significantly between treatments (OR 1.47, 95% CI 0.75 to 2.86, three studies, 4054 participants). With an assumed risk in the budesonide/formoterol of 7/1000, between two fewer and 13 more people per 1000 would experience a serious adverse event on fluticasone/salmeterol.

Secondary outcomes

Lung function outcomes, symptoms, rescue medication, composite of exacerbations leading to either emergency department visit or hospital admission, withdrawals and adverse events did not differ statistically between treatments. Assessment of quality of life was limited to two studies, both of which gave results that did not reach statistical significance. One study reported one death out of 1000 participants on fluticasone/salmeterol and no deaths in a similar number of participants treated with budesonide/formoterol. No deaths were reported in the other studies.

Authors' conclusions

Statistical imprecision in the effect estimates for exacerbations and serious adverse events do not enable us to conclude that either therapy is superior. The uncertainty around the effect estimates justify further trials to provide more definitive conclusions; the overall quality of evidence based on GRADE recommendations for the three primary outcomes and withdrawals due to serious adverse events was moderate. We rated the quality of evidence for mortality to be low. Results for lung function outcomes showed that the drugs were sufficiently similar that further research is unlikely to change the effects. No trials were identified in the under-12s and research in this population is a high priority. Evaluation of quality of life is a priority for future research.

PLAIN LANGUAGE SUMMARY

Different combinations of inhaled steroids and long-acting beta-agonists for chronic asthma (fluticasone/salmeterol versus budesonide/formoterol)

People with persistent asthma often require an additional treatment to regular inhaled steroids. Some preparations of long-acting beta-agonists are delivered in the same inhaler device as the inhaled corticosteroids. Inhaled steroids help to treat inflammation of the airway and long-acting beta-agonists help the airway to relax, improving symptoms and lung function. This systematic review examined randomised controlled trials comparing two commonly available combinations administered at a fixed dose through a single inhaler, fluticasone/salmeterol and budesonide/formoterol. We included five studies which recruited 5537 people. The trials were generally well designed but only recruited adults and adolescents and not children. Participants were already taking regular inhaled steroids before the studies commenced and had mild or moderate asthma based on tests of their airway. We found that the number of people who required treatment with oral steroids and admission to hospital was similar between the treatments, but due to the statistical uncertainty of this result we could not rule out important differences in favour of either drug combination. Additional trials would enable us to draw more reliable conclusions about how well these drugs work compared with each other. We also looked at serious adverse events. Again, the results did not indicate that one combination was clearly better than the other, but again these results were imprecise so we cannot be certain. However, lung function and rescue medication use were similar between the treatments. We could not assess the relative effects of these drugs on mortality because there were so few deaths which leads to statistical uncertainty; out of the five studies, one person died. Quality of life was measured in different ways in two studies and we could not determine how the treatments compared

in this respect. Further studies are needed to strengthen and better explain these findings. In particular studies which assess the effects of these therapies in children and studies which measure quality of life are a priority.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Combination fluticasone/salmeterol versus budesonide/formoterol for chronic asthma in adults and children

Patient or population: Patients with chronic asthma in adults and children
Settings:
Intervention: combination fluticasone/salmeterol versus budesonide/formoterol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combination budesonide/formoterol	Combination fluticasone/salmeterol				
Participants experiencing exacerbations requiring oral steroid treatment Follow-up: mean 6 months	**106 per 1000**[1]	**95 per 1000** (81 to 113)	**OR 0.89** (0.74 to 1.07)	4949 (4 studies)	⊕⊕⊕○ **moderate**[2]	
Participants experiencing exacerbations requiring admission to hospital Follow-up: mean 6 months	**7 per 1000**[1]	**8 per 1000** (4 to 16)	**OR 1.29** (0.68 to 2.47)	4879 (4 studies)	⊕⊕⊕○ **moderate**[2]	
Asthma-related serious adverse event Follow-up: mean 6 months	**7 per 1000**[1]	**10 per 1000** (5 to 20)	**OR 1.47** (0.75 to 2.86)	4054 (3 studies)	⊕⊕⊕○ **moderate**[2]	

Mortality Follow-up: mean 6 months	*See comment*	*See comment*	*Not estimable*	4819 (5 studies)	⊕⊕◯◯ **low**[3]	The data did not generate a pooled effect estimate as no deaths occurred in four out of the five studies
Withdrawals (adverse events) Follow-up: mean 6 months	**16 per 1000**[1]	**15 per 1000** (10 to 23)	**OR 0.94** (0.6 to 1.46)	5082 (5 studies)	⊕⊕⊕◯ **moderate**[2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] The mean rate of exacerbations across the BUD/F arms of the trials was used to calculate the assumed risk.
[2] Imprecision (-1): the confidence interval is compatible with superiority of either treatment and could change with the addition of new evidence.
[3] Imprecision (-2): The width of the confidence intervals is very wide and reflects the low rate of events in the analysis. One death occurred in 4819 participants.

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory disease of the airways, and anti-inflammatory treatment is a cornerstone of asthma therapy. Treatment with inhaled corticosteroids (ICS) improves lung function and reduces asthma symptoms in asthmatic patients (Adams 2008).

Description of the intervention

Many patients remain symptomatic despite using optimal doses of ICS. There is strong evidence to support the use of long-acting beta-agonists (LABAs) as a means of reducing the requirement for short burst oral steroid therapy improving lung function (Ducharme 2010a; Ducharme 2010b).

The two interventions being assessed in this review combine a LABA and ICS as a fixed-dose maintenance regimen, namely fluticasone and salmeterol (marketed by GSK as 'Seretide', 'Advair' or 'Viani'), and budesonide and formoterol (marketed by AstraZeneca as 'Symbicort').

How the intervention might work

The principal advantage of combining ICS and LABA in one inhaler is the simultaneous delivery of two effective inhaled therapies with complementary anti-inflammatory and bronchodilatory properties. This may facilitate better adherence to fixed dosing regimens, especially given concerns over the use of LABA therapy without a regular background steroid (Walters 2007).

Why it is important to do this review

There is some uncertainty as to which particular combination may be suitable. Previous assessments have considered the addition of any LABA to any ICS when the dose of ICS is increased or when the study drugs are titrated according to symptoms (Ducharme 2010b; Gibson 2005). Although the LABAs commonly used in combination preparations have a similar duration of effect of around 12 hours or more, salmeterol and formoterol also have differing pharmacological properties. The onset of action of formoterol is faster than that of salmeterol (Palmqvist 1997; Van Noord 1996) and has as rapid an onset of action as salbutamol in asthma (Cazzola 2002). Some differences exist also between fluticasone and budesonide despite the shared anti-inflammatory effect (Adams 2007), and so a systematic exploration of the relative efficacy of these different drug combinations is justified.

OBJECTIVES

To compare the combinations of salmeterol/fluticasone and budesonide/formoterol in single inhaler devices in chronic asthma in terms of asthma control, safety and lung function.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with a parallel design, as the minimum wash-out period of inhaled steroids has not been adequately established which precludes the inclusion of crossover trials.

Types of participants

We included trials involving adults and children with a diagnosis of chronic asthma. We accepted trialist-defined asthma. We accepted any severity of asthma and patients on any co-intervention (as long as the co-interventions were not part of the randomised treatment) but we excluded studies on acute asthma.

Types of interventions

The preparations considered by this review were:

1. the combination of the inhaled steroid fluticasone (FP) and long-acting beta-agonist salmeterol (SAL); and
2. the inhaled steroid budesonide (BUD) and long-acting beta-agonist formoterol (F).

We only included studies where both preparations were delivered in one inhaler device. We included studies which assessed the combination of drugs in either metered dose inhalers (MDI) or dry powder inhaler (DPI). We considered fixed-dose comparisons between these preparations only and we have excluded studies evaluating different dosing strategies of budesonide/formoterol ('single inhaler therapy' or 'adjustable maintenance dosing') with fixed dose fluticasone/salmeterol.

We only included trials with a minimum treatment duration of 12 weeks.

Types of outcome measures

Primary outcomes

1. Exacerbations of asthma requiring oral steroids.
2. Exacerbations of asthma requiring hospital admission.
3. Asthma-related serious adverse events (including asthma-related death and intubation).

Secondary outcomes

1. Exacerbations leading to emergency department (ED) visit/admission to hospital.
2. Mortality.
3. Quality of life.
4. Diary card morning and evening peak expiratory flow (PEF).
5. Clinic spirometry (FEV_1, clinic PEF, FVC).
6. Rescue medication use.
7. Symptoms.
8. Adverse events.
9. Study withdrawal.

Search methods for identification of studies

Electronic searches

We identified trials 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 (see Appendix 1 for further details). We searched all records in the Specialised Register coded as 'asthma' using the following terms:

("single inhaler" or symbicort or seretide or advair or viani) or ((steroid* or corticosteroid* or ICS or fluticasone or FP or Flixotide or budesonide or BUD or Pulmicort) and ("long acting beta agonist*" or "*beta-agonist*" or LABA* or salmeterol or serevent or formoterol or eformoterol or oxis or foradil))
Searches are current to June 2011.

Searching other resources

We reviewed reference lists of all primary studies and review articles for additional references. We contacted authors of identified randomised trials to ask about knowledge of other published and unpublished studies. We also contacted manufacturers of combination single inhaler devices regarding other published and unpublished studies.
We contacted trialists and manufacturers in order to obtain unreported data and to establish whether other unpublished or ongoing studies are available for assessment. We undertook additional handsearching of clinical trial web sites (www.clinicalstudyresults.org; www.clinicaltrials.gov; www.fda.gov) and the clinical trial web sites of manufacturers (www.ctr.gsk.co.uk; www.astrazenecaclinicaltrials.com).

Data collection and analysis

Selection of studies

Following electronic literature searches, two review authors (TJL and GF) independently selected articles on the basis of title and/or abstract for full text scrutiny. The authors agreed a list of articles which were retrieved, and they subsequently assessed each reference to determine whether it met the review eligibility criteria.

Data extraction and management

One author (TJL) extracted information from each study for the following characteristics.

- Design (description of randomisation, blinding, number of study centres and location, number of withdrawals).
- Participants (numbers, mean age, age range of the study, gender ratio, baseline lung function, % on maintenance ICS or ICS/LABA combination and average daily dose of steroid (beclomethasone (BDP) equivalent), entry criteria).
- Intervention (type and dose of component ICS and LABA, dosing schedule, inhaler device, study duration and run-in).
- Outcomes (type of outcome analysis, outcomes analysed, numerical data).

A second author double-checked and agreed this information (GF).

Assessment of risk of bias in included studies

We judged the risk of bias (high, low or unclear) for each included study in relation to the following criteria in accordance with recommendations described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

1. Selection bias (allocation sequence generation).
2. Selection bias (concealment of allocation sequence).
3. Performance bias (blinding of study participants and personnel).
4. Detection bias (blinding of outcome assessors).
5. Attrition bias (frequency and nature of withdrawals). This was considered in relation to the outcomes of oral steroid requirement and hospital admission.
6. Publication bias (selective reporting of outcome measures).
7. Other bias (other type of bias).

We noted funding source, but did not consider it to be a source of bias.

Dealing with missing data

We contacted study sponsors for additional data which we required for our primary outcomes of oral steroid-treated exacerbations, and exacerbations leading to hospital admission.

Assessment of heterogeneity

We measured statistical variation between studies by the I^2 statistic (Higgins 2003). We considered possible causes of any statistical variation (see Subgroup analysis and investigation of heterogeneity).

Data synthesis

We combined data with RevMan 2011, using a fixed-effect odds ratio (OR) for dichotomous variables, and a fixed-effect mean difference (MD) (calculated as either a mean difference or a mean difference weighted by generic inverse variance) for continuous data variables.

We presented a Summary of Findings table for the primary outcomes in the review (exacerbations requiring oral steroids, exacerbations leading to hospital admission, and serious adverse events) based on recommendations described in Chapter 11 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We intended to subgroup on age and asthma severity.

We considered adult studies as those which recruited participants from aged 18 upwards. We considered adult and adolescent studies as those which recruited participants from aged 12 upwards. We considered participants in studies where the upper age limit was 12 years as children, and in studies where the upper age limit was 18 years as children and adolescents.

We performed subgroup analyses based on the severity of asthma as assessed according to international guidelines (GINA 2006: controlled, partly controlled, uncontrolled), and we considered trials on patients using oral steroid treatment separately. We restricted subgroup analysis to our primary outcomes.

Sensitivity analysis

We conducted sensitivity analysis on the risk of bias, whereby we removed studies at a high risk of bias based on the assessment of randomisation, blinding, withdrawal or other sources of bias. We also considered the impact of dosing and inhaler devices for both interventions. We produced and inspected funnel plots to assess the presence of publication bias.

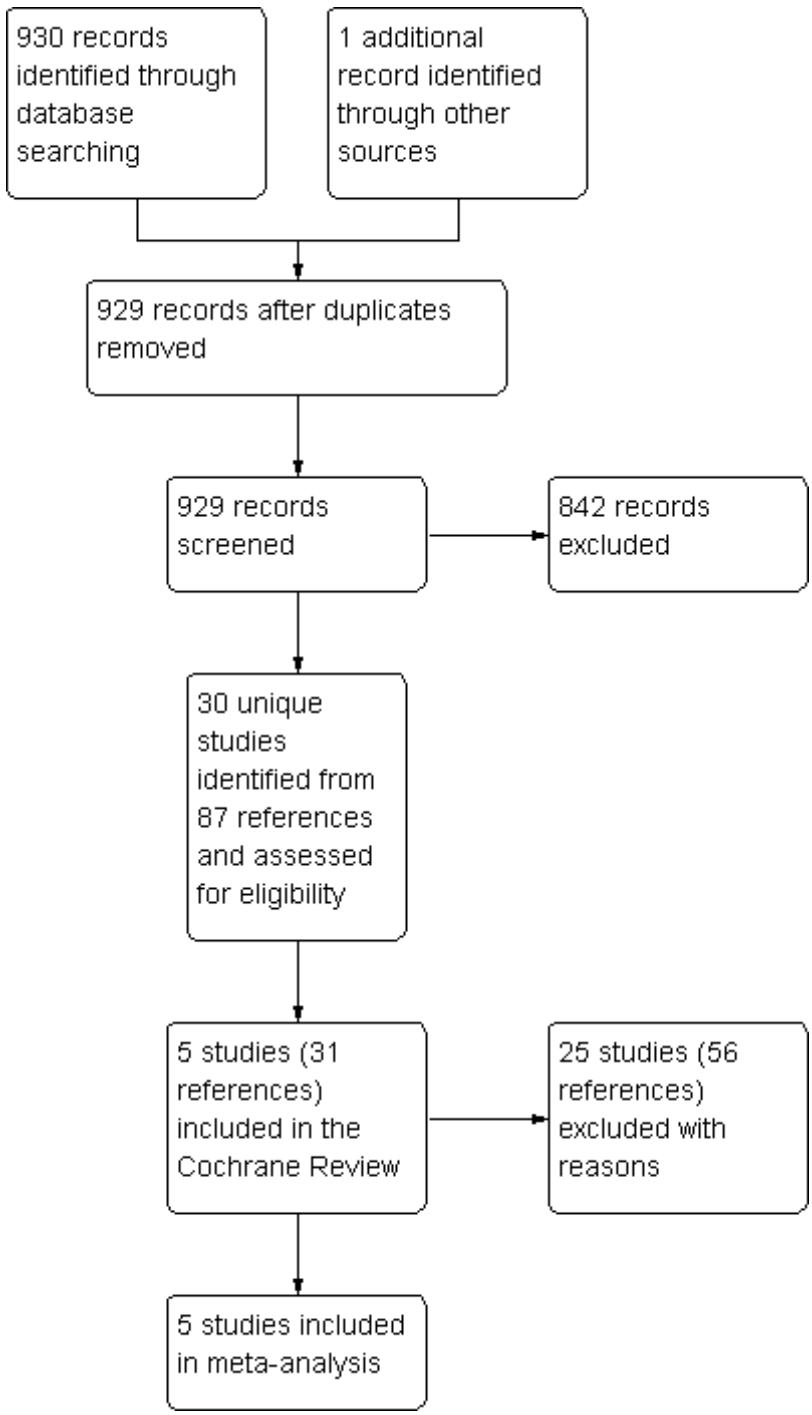
RESULTS

Description of studies

Results of the search

We have provided details of the literature search and study assessment processes up to June 2011 in Figure 1.

Figure 1. Study flow diagram. This represents the results of all literature searches up to June 2011.



The 2011 update search yielded 184 citations. When added to search results from previous years we have identified a total of 931 references up to June 2011. Five studies (reported in 31 articles) met the inclusion criteria of the review. For further details please refer to Characteristics of included studies. Of the five included studies, four are full-text publications, and one is available as a download from a manufacturer's online clinical trial results registry (SAM40048). All of the included studies were industry-sponsored: GlaxoSmithKline (manufacturers of FP/SAL) sponsored EXCEL; SAM40048 and AstraZeneca (manufacturers of BUD/F) sponsored Aalbers 2004; Busse 2008; COMPASS.

Included studies

Population

A total of 5537 adult and adolescent participants were recruited to the studies. The studies required participants to have a history of chronic asthma, treated with maintenance inhaled corticosteroids at moderate to high doses prior to study entry.

In the five studies, participants had to be stable for one month before the run-in period. Once in the run-in phase, participants were further required to demonstrate the need for frequent reliever inhaler use. On the basis of these characteristics we adjudged the trial populations to be partly controlled, since the requirement for relief medication was in addition to chronically applied inhaled steroids (GINA 2006).

The severity of airway obstruction varied between the trials, with the participants with the lowest percentage predicted of FEV_1 recruited to SAM40048 (65%), Busse 2008, COMPASS and EXCEL recruiting participants with moderate airway obstruction (79%, 73% and 79%, respectively), and participants with milder obstruction represented in Aalbers 2004 (84%).

Interventions & comparisons

Converting the inhaled steroid load to BDP equivalent indicated that the trials assessed high doses of inhaled steroids in both FP/SAL and BUD/F groups, although FP/SAL was higher in BDP equivalence terms than BUD/F (1000 versus 400 to 800 mcg/day). All doses were given twice daily via different inhalers (Diskus and Turbohaler for FP/SAL and BUD/F respectively). Two studies were open label (Aalbers 2004; Busse 2008). In all studies the dose of FP/SAL was 500/100 µg/day, and that of BUD/F was 400/12 to 800/24 µg/day.

Concomitant use of reliever medication was permitted in four studies; terbutaline in COMPASS, salbutamol in Busse 2008 and EXCEL, and terbutaline or salbutamol as preferred in Aalbers 2004. In SAM40048 the reliever medication was not reported.

Outcomes

Four trials measured exacerbations as those treated with oral steroids and hospital admission (Aalbers 2004; Busse 2008; COMPASS; EXCEL). They also gave numerical data for serious adverse events. All studies reported lung function measurements. Data on admission to hospital were made available to the review authors on request from GSK and AZ (Aalbers 2004; COMPASS; EXCEL). We were informed verbally by the study sponsors of SAM40048 that exacerbation outcome data were not collected in a way that was suitable for us to use in our review.

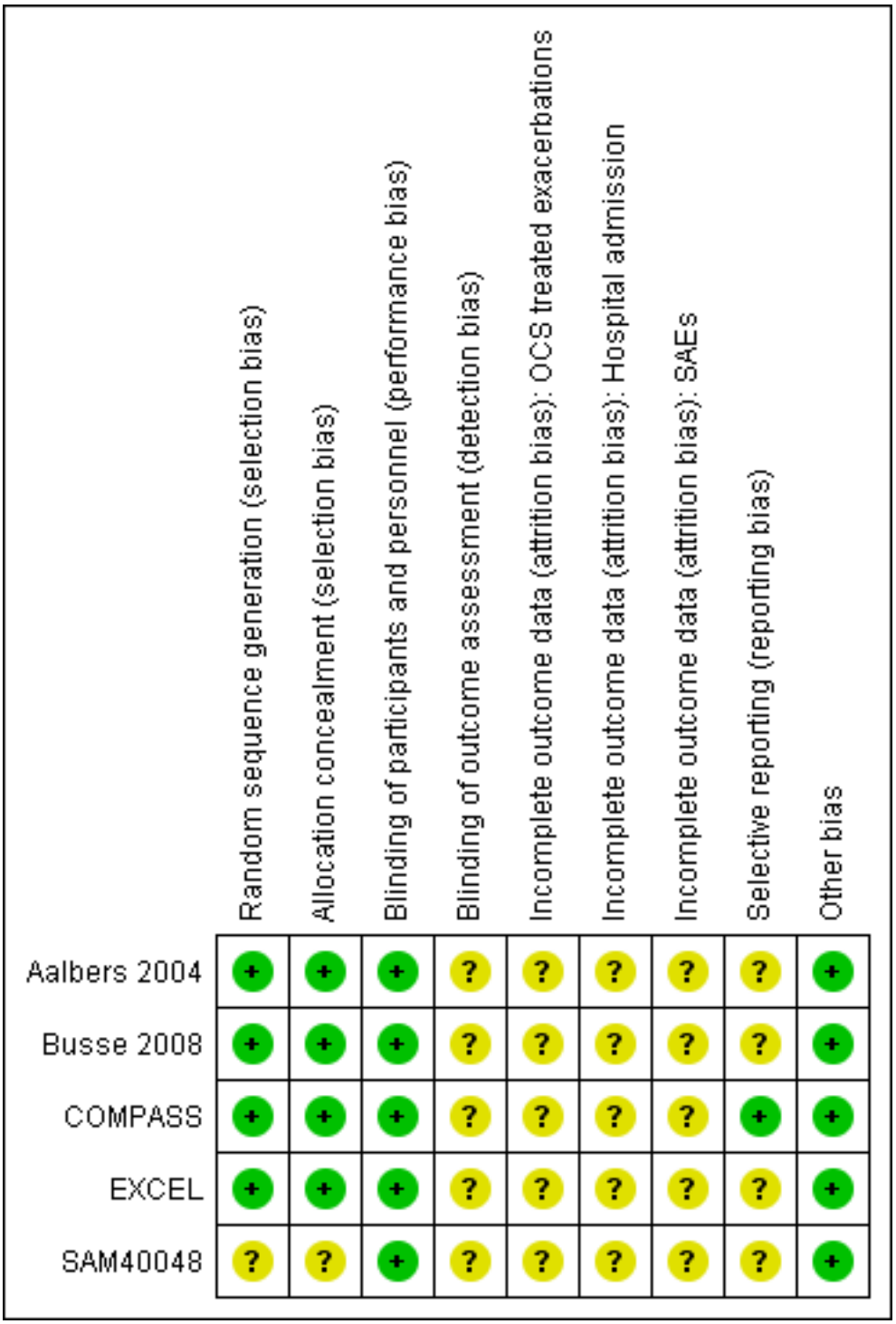
Excluded studies

A total of 25 studies failed to meet the review eligibility criteria. We have provided the reasons for their exclusion in Characteristics of excluded studies.

Risk of bias in included studies

See Figure 2 for a summary of the risk of bias. We have provided additional details in Characteristics of included studies. In general, the studies were well-designed.

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



Allocation

The four studies available as full-text articles reported computer-generated randomisation sequences, with adequate concealment of treatment group allocation. Demographic characteristics of all four of the studies indicated that treatment groups were well balanced at baseline. Details on SAM40048 were not adequately reported for us to establish the appropriateness of the concealment of allocation.

Blinding

We used outcome data from an open label phase in two studies (Aalbers 2004; Busse 2008). We did not consider this aspect of the design to have an important impact on the direction of the effect for the primary outcomes. The remaining studies used a double-dummy design to control for awareness of treatment group allocation. Blinding of outcome assessors was not reported across the studies.

Incomplete outcome data

The intention to treat principle was described in all of the studies, but explicit description of the handling of missing data were not provided. Based on the information provided, we were unable to verify whether participants who withdrew contributed data to numerators for the co-primary outcomes.

Selective reporting

Primary outcome data were either reported in the studies or made available to the authors on request. We needed to contact the study sponsors (AstraZeneca) of Aalbers 2004 and COMPASS for data pertaining to our primary outcomes of exacerbations. The sponsors of EXCEL confirmed data on the primary outcomes, and made data for exacerbations leading to ED visits and admission to hospital available to us (see Published notes). A subsequent trial report associated with Busse 2008 indicated that quality of life (Asthma Quality of Life Questionnaire (AQLQ)) was measured in the original study, but was not available until two years after the initial2008 publication.

Effects of interventions

See: **Summary of findings for the main comparison** Combination fluticasone/salmeterol versus budesonide/formoterol for chronic asthma in adults and children

Using published data and unpublished data obtained through correspondence with study sponsors, we included four of the five eligible trials in the three co-primary outcomes representing 88% of randomised participants.

FP/SAL 500/100 µg/d versus BUD/F 400-800/12-24 µg/d

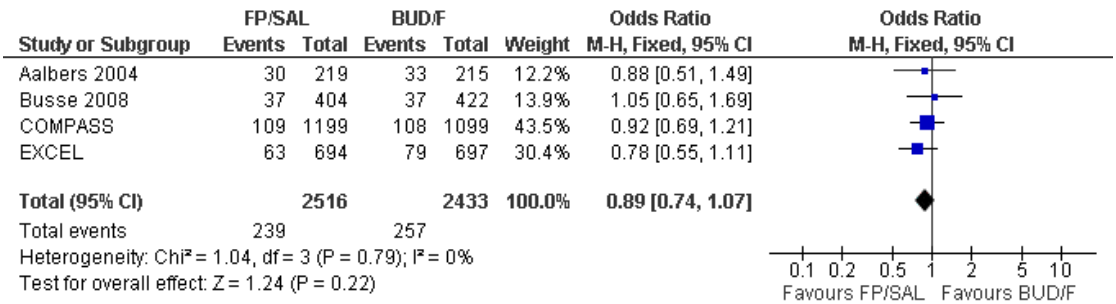
The comparisons are presented such that FP/SAL is the 'intervention' group and BUD/F is the 'control' group.

Primary outcomes

Exacerbations leading to treatment with oral steroids

Treatment with FP/SAL led to a slightly lower odds of experiencing an exacerbation requiring OCS treatment compared with BUD/F, although the wide confidence interval meant that this could have been a chance finding (OR 0.89, 95% CI 0.74 to 1.07, P = 0.22). This result was based on data from four studies conducted over six months in 4949 adults (Figure 3). With an assumed control group rate of 106 per 1000 over six months in the BUD/F group, between 81 and 113 per 1000 participants given FP/SAL would experience an exacerbation (Summary of findings for the main comparison).

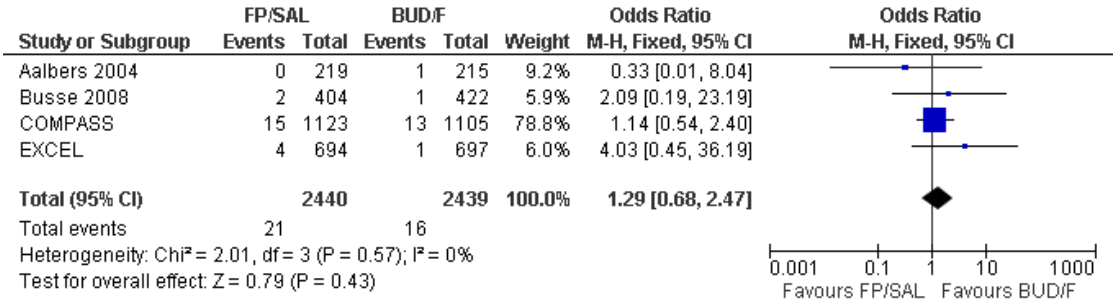
Figure 3. Forest plot of comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol, outcome: 1.1 Participants experiencing exacerbations requiring oral steroid treatment.



Hospital admission

Treatment with FP/SAL The odds of an exacerbation resulting in admission to hospital were higher with FP/SAL but the difference was not significantly different (four studies, N = 4053; OR 1.29, 95% CI 0.68 to 2.47, P = 0.43; Figure 4). Based on assumed control group rate of seven per 1000 over six months in the BUD/F groups, between four and 16 per 1000 participants would experience hospital admission in the FP/SAL group (Summary of findings for the main comparison).

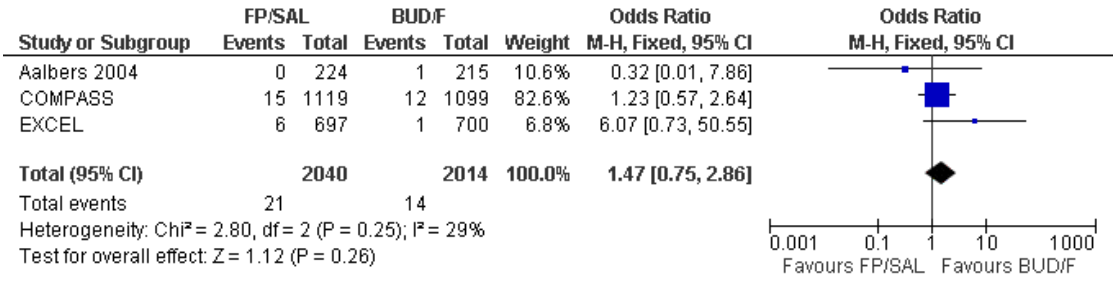
Figure 4. Forest plot of comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol, outcome: 1.2 Participants experiencing exacerbations requiring admission to hospital.



Asthma-related serious adverse events

The risk of an asthma-related serious adverse event was higher with FP/SAL but the confidence interval was wide and the overall result was not statistically significant (three studies, N = 4879; OR 1.47, 95% CI 0.75 to 2.86, P = 0.26; Figure 5). Based on an assumed control group rate of seven per 1000 over six months in the BUD/F groups, between five and 20 people per 1000 given FP/SAL would experience a serious adverse event (Summary of findings for the main comparison).

Figure 5. Forest plot of comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol, outcome: 1.3 Asthma-related serious adverse event.



Secondary outcomes

Exacerbations requiring ED visit/hospital admission (composite)

There was no statistically significant difference in the odds of ED visit/admission to hospital between the treatments (four studies, N = 4861; OR 1.3, 95% CI 0.94 to 1.8; Analysis 1.4).

Mortality

COMPASS reported one death in the FP/SAL group and no deaths in the BUD/F group, and there were no other deaths in any of the studies (Analysis 1.5).

Quality of life

Two studies assessed quality of life withAQLQ. However, differences in the way that this outcome was measured in the studies (mean differences in COMPASS, and the number of participants achieving clinically meaningful change in Busse 2008) precluded us from combining their data. No statistically significant differences between the treatments were reported in either study.

Diary card peak flow

There was no significant difference between treatments in mean change in morning (five studies, N = 5101; 2.24 L/min, 95% CI -0.24 to 4.73; Analysis 1.8) or evening peak flow (four studies, N = 4299; 0.25 L/min, 95% CI -0.80 to 1.30; Analysis 1.9).

FEV_1

There was no significant difference in the change from baseline between treatments (three studies, N = 4845; 0 L, 95% CI -0.02 to 0.02; Analysis 1.10).

Rescue medication use

There was no significant difference between treatments in mean change from baseline in rescue medication use (three studies, N = 3469; -0.06 puffs per day, 95% CI -0.13 to 0.02; Analysis 1.12).

Symptoms

There was no significant difference between treatments in the mean change in symptom scores (three studies, N = 3464; -0.02, 95% CI -0.6 to 0.03; Analysis 1.13), and also in the mean change in symptom-free days (two studies, N = 3027; 1.25 days, 95% CI -1.18 to 3.67; Analysis 1.14).

Adverse events

The odds of experiencing any adverse event were similar between FP/SAL and BUD/F (three studies, N = 3547; OR 1.00, 95% CI 0.88 to 1.15; Analysis 1.16).

Differences between treatments in the odds of headache (OR 1.08, 95% CI 0.82 to 1.43; Analysis 1.17), candidiasis (OR 1.64, 95% CI 0.68 to 4.00; Analysis 1.18), upper respiratory tract infection (OR 1.09, 95% CI 0.81 to 1.47; Analysis 1.19), dysphonia (OR 1.45, 95% CI 0.87 to 2.43; Analysis 1.20) and throat irritation (Analysis 1.22) did not differ significantly between treatments.

Study withdrawals were not significantly more frequent with either treatment in terms of overall discontinuations (Analysis 1.25). We added withdrawals due to adverse events to Summary of findings for the main comparison. The pooled result gave an OR of the withdrawals due to adverse events of 0.94 (95% CI 0.60 to 1.46). With an assumed rate of withdrawal due to adverse events of 16 per 1000 over six months in the BUD/F group the corresponding risk of withdrawal in the FP/SAL group is between 10 and 23 per 1000 participants.

DISCUSSION

Summary of main results

This review summarises evidence from five well-designed industry-sponsored studies randomising over 5000 adults and adolescent patients. We identified three co-primary outcomes, two pertaining to different severities of asthma exacerbation (those requiring oral steroid treatment, and those leading to hospitalisation), and one relating to asthma-related serious adverse events. None of the results for our primary outcomes reached conventional thresholds of statistical significance. Based on our analyses, there remains some uncertainty as to the superiority of either drug combination.

Neither lung function parameters, symptom scores nor rescue medication use identified statistically significant differences between treatments. The estimates for FEV_1 and peak flow are sufficiently close and statistically precise that further research is unlikely to change the similar effect of these drugs on these outcomes. One subsequent trial report for COMPASS reported quality of life on the AQLQ scale. Although the trial was large, the wide confidence intervals for this result make the small difference observed uncertain and further evaluation of this important outcome is required.

Outcome data relating to harms indicated that our analyses were underpowered to detect equivalent or increased risk of candidiasis, loss of voice, respiratory tract infections or headache, with either therapy.

Overall completeness and applicability of evidence

The studies assessed the two drug combinations in predominantly adult populations with mild or moderate airway obstruction partly controlled regular inhaled steroids at baseline. Follow-up was adequate for the key outcomes of interest to the review. The greatest limitation of the evidence base in this area is the absence of data in children under the age of 12 years. However, there is an overriding need to establish the additive benefit of long-acting beta-agonists in children more generally (Ducharme 2011; Ni Chroinin 2009).

The dose comparisons across the studies were similar, except for SAM40048 where the dose of budesonide was half of that in the other studies. Based on UK recommendations, the BUD/F dose was the maximum licensed dosing for asthma in the UK, and the FP/SAL dose is the medium dose recommended in the UK for asthma (BNF 2007).

Quality of the evidence

Five outcomes populate the Summary of findings for the main comparison: oral steroid-treated exacerbations, hospital admission and asthma-related serious adverse events; and for the 2011 update we also included withdrawal due to adverse events and mortality. Based on the GRADE recommendations we did not consider the risk of bias, inconsistency, indirectness or biases of publication/reporting to affect our confidence in the results. However, we downgraded the quality of evidence to 'moderate' for exacerbations and SAEs, and to 'low' for mortality. For all five outcomes we downgraded the quality of the evidence due to statistical imprecision. The low event rate and lack of a pooled estimate for mortality prompted us to downgrade two points rather than one.

Requirement for a course of oral steroid treatment is a treatment-driven rather than a symptom-driven definition, but gives some indication as to whether maintenance therapy reduces inflammation sufficiently to prevent requirement for additional steroid. The ratio of such events was close to one in the four studies, and the BUD/F event rate was similar between the trials (Aalbers 2004: 15%; Busse 2008: 9%; COMPASS: 10%; EXCEL: 11%). Whilst the absence of a statistically significant difference may reflect the effectiveness of adding long-acting beta-agonists to ICS in reducing exacerbations (Ducharme 2010b), the low frequency of this outcome across the studies underpowered our analyses to determine either no important difference between the treatments or superiority of either therapy.

The morbidity associated with hospital admission is considerable, and may indicate severe uncontrolled disease as well as predict future hospitalisation and mortality (Suissa 2001). Superiority of FP over BUD in dose ratio comparisons of 1:1 and 1:2 has been demonstrated for lung function endpoints, but not exacerbation rate data (Adams 2007). In this review the risk of hospitalisation did not differ significantly between therapies, although the confidence interval was wide and further evidence is necessary before a conclusion of equivalence could be drawn reliably.

The relative effects of these treatments on serious harms including death remain to be fully elucidated. Monotherapeutic use of LABAs is discouraged since the bronchodilatory effects of LABAs possibly masks deterioration in underlying airway inflammation (Cates 2008a; Cates 2008b; Walters 2007). However, recent reviews assessing LABAs as additive treatment have also failed to identify an abolition of risk with ICS (Cates 2009a; Cates 2009b). Our analyses lack statistical precision since serious adverse events did not occur very frequently in the studies.

Potential biases in the review process

We limited our analyses to parallel studies on the assumption that optimum washout in steroid trials is uncertain, and that our primary outcome of exacerbations was best measured in long-term studies with a between-patient design. We assumed that requirement for oral steroids and admission to hospital are independent, and that participants who experienced hospital admission after a course of oral steroids would feature in both outcomes. This may not be the case, although it is reasonable to expect that poor asthma control when associated with poor adherence to maintenance inhaled steroids is a useful predictor for the requirement of rescue oral steroid therapy and hospital admission (Williams 2004). Assessment of patient severity was confined to GINA defined con-

trol status, and this categorisation may not be sensitive enough to discern between severities of asthma.

Agreements and disagreements with other studies or reviews

A related Cochrane Review on safety issues comparing different long-acting beta-agonists in addition to regular inhaled steroid treatment provides similarly equivocal results on the outcomes of serious harms and mortality (Cates 2010). Our composite analysis of ED visit/hospitalisation gave an effect estimate that was similar in terms of size and direction to that reported by Edwards 2007. However, the confidence interval was narrower in the Edwards 2007 meta-analysis giving a result favouring BUD/F that was statistically significant. The data for that analysis were in part based upon hospitalisation data from EXCEL and did not include additional ED visits.

AUTHORS' CONCLUSIONS

Implications for practice

The results from this review do not provide a strong basis for supporting one therapeutic option over the other. The confidence intervals for the effect estimates in our primary outcomes include no difference, but their width for these endpoints also include possibly meaningful differences between the treatments in either direction. As such, more evidence would help to improve their precision. Serious adverse events were too infrequent to generate findings which could be easily interpreted. Applying GRADE recommendations to our assessments, we rated the quality of evidence in each of the three primary outcomes as moderate. Withdrawal due to adverse events was rated moderate and based on the low rate of mortality in the studies we rated the quality of evidence for death to be low. The lung function outcomes we analysed gave results which suggest that these drugs have similar effects. The evidence base in this area pertains to adults and adolescents whose asthma is not adequately controlled with high doses of inhaled steroids.

Implications for research

The findings of our review would be strengthened by more data on exacerbations from further trials, in particular trials that include visits to emergency departments and hospitalisation. Evidence is required to establish the ratio of serious adverse events between these two drugs with better accuracy. Evidence for the effects of these drugs in children is also required. Assessment and fuller reporting of quality of life should feature in further research.

ACKNOWLEDGEMENTS

We thank Elizabeth Stovold and Susan Hansen for assistance in designing a search strategy and for electronic literature searching, Emma Jackson and Veronica Stewart for assistance in retrieving the papers, and Emma Welsh for managing the editorial process. We are grateful to René Aalbers, Jeff Fletcher and Steve Edwards from AZ in our efforts to obtain data for the Aalbers 2004 and COMPASS. We are grateful to Pim Kon and Richard Fellows from GSK for assisting us in obtaining ED visit data for EXCEL.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aalbers 2004

Methods	Randomised, parallel group trial. Open label design with adjustable dosing criteria 93 centres in Denmark, Finland, Germany, Norway, Sweden, Netherlands Description of withdrawals: stated.
Participants	N screened: not reported (1044 enrolled in run-in period) N randomised: 658: FP/SAL fixed dose: 224; BUD/F fixed dose: 215; BUD/F adjustable maintenance dose: 219 (not included in this review) N completed: 383 M = 205 F = 234 Mean age: 46 Baseline characteristics: FEV_1 % predicted: 84; PEF L/min: 468; % combination LABA/ICS treatment at entry: 45; asthma duration: 12; Average ICS dose (BDP equivalent): 735 GINA status: mild persistent Inclusion criteria: 1. > 12 years; 2. minimum 6 months asthma duration (ATS definition); 3. FEV_1 predicted > 50%; 4. ICS use > 3 months; 5. stable dose +/- LABA. Post-run-in entry criteria: 1. symptom score > 1 on at least 4 of last 7 days of run-in period; 2. mean PEF of 50%-85% predicted; 3. use of PEF meter to record DC data Exclusion criteria: 1. Respiratory infection < 4 weeks prior to study entry; 2. smoking history > 10 pack years; 3. use of systemic steroids within 4 weeks of study entry; 4. significant co-morbidities.
Interventions	1. Combination fluticasone and salmeterol 250/50 µg bid (double-blind phase); 250/50 bid fixed (open label phase). BDP equivalent 1000 µg. 2. Combination budesonide and formoterol 400/12 µg bid (double-blind phase); 400/12 bid fixed (open label phase). BDP equivalent 800 µg. 3. Combination budesonide and formoterol 320/9 µg bid (double-blind phase); 320/9 bid or 160/4.5 bid plus temporary increase if needed (open label period). BDP equivalent 800 µg. Delivery device: BUD/F: Turbuhaler; FP/SAL: Diskus. Treatment period: Double-blind fixed dose period: 4 weeks; open label period: 24 weeks. Run-in: 10-14 days on ICS only. Rescue: Terbutaline or salbutamol as preferred.

Outcomes	Primary outcome: well controlled asthma week. Secondary outcomes: am PEF; pm PEF; FEV_1; rescue medication use; symptoms; exacerbations (requiring OCS treatment on > 3 days; hospitalisation or ER treatment); mortality
Notes	Dose adjustment criteria: step down to one inhalation bid if symptoms controlled for last week of double-blind period; increase to up to four inhalations bid (for 7-14 days) if symptomatic over last week of double-blind period Study sponsors: AstraZeneca

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'The randomisation schedule was generated using a computer programme by a statistician (...) Patients were consecutively allocated to the lowest available patient number and were randomised strictly sequentially in blocks.'
Allocation concealment (selection bias)	Low risk	Third party not involved with primary study.
Blinding of participants and personnel (performance bias) OCS-treatment, hospital admission & asthma-related SAEs	Low risk	Open label study design not a threat to primary outcomes in this review
Blinding of outcome assessment (detection bias) OCS-treatment, admission to hospital & asthma-related SAEs	Unclear risk	Confirmation that outcome assessors were blind to treatment group assignment was not available
Incomplete outcome data (attrition bias) OCS treated exacerbations	Unclear risk	ITT analysis described; no explicit details on how withdrawals were handled
Incomplete outcome data (attrition bias) Hospital admission	Unclear risk	ITT analysis described; no explicit details on how withdrawals were handled
Incomplete outcome data (attrition bias) SAEs	Unclear risk	ITT analysis described; no explicit details on how withdrawals were handled
Selective reporting (reporting bias)	Unclear risk	Unable to ascertain this reliably.
Other bias	Low risk	No other potential sources of bias identified.

Busse 2008

Methods	Randomised, parallel group open label design with adjustable dosing criteria (from month 2 onwards). Participants randomised 2:1 to receive fixed dose BUD/F or FP/SAL. Subsequently BUD/F treated participants were re-randomised to continue with fixed dose regimen or adjustable maintenance dosing 145 centres in USA. Description of withdrawals: stated.
Participants	N screened: 2080, N randomised: 1225 (FP/SAL: 406; initial fixed dose BUD/F: 817 (after one month participants further subdivided between fixed dose (427) and adjustable dose BUD/F: 389) N completed: 1052. M = 490. F = 735. Mean age: 39. Baseline characteristics: FEV_1 79% predicted. Inclusion criteria: 1. > 12 years; 2. ATS defined asthma for 6 months; 3. stable condition; 4. pre-bronchodilator FEV_1 >/= 50% predicted; 5. maintained on a daily medium-dose ICS or ICS/LABA combination for 12 weeks or longer before screening. Exclusion criteria: 1. systemic corticosteroid use within 30 days; 2. 20 pack-year or longer smoking history; 3. significant disease, respiratory tract infection, or illness that might interfere with lung function/study participation.
Interventions	1. Combination fluticasone and salmeterol 250/50 µg BID, BDP equivalent 1000 µg 2. Combination budesonide and formoterol 400/12 µg BID. BDP equivalent 800 µg 3. Combination budesonide and formoterol 400/12 µg QD, with temporary increases as determined by investigator. Delivery device: BUD/F: MDI; FP/SAL: DPI. Treatment period: 7 months. Run-in: 10-14 days. Rescue: prn SABA.
Outcomes	Primary outcome: time to first exacerbation. Secondary outcomes: exacerbations requiring oral corticosteroids; hospitalisation; ED visits; FEV_1; am PEF; symptoms; rescue medication use; adverse events; withdrawals; AQLQ; mortality
Notes	Dose adjustment criteria: step down to one inhalation bid if symptoms controlled for last week and no nocturnal awakening; increase to up to four inhalations bid (for 7-14 days) if symptomatic over last week Study sponsors: AstraZeneca.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	Third party not involved with primary study.
Blinding of participants and personnel (performance bias) OCS-treatment, hospital admission & asthma-related SAEs	Low risk	Open label study design not a threat to primary outcomes in this review
Blinding of outcome assessment (detection bias) OCS-treatment, admission to hospital & asthma-related SAEs	Unclear risk	Confirmation that outcome assessors were blind to treatment group assignment was not available
Incomplete outcome data (attrition bias) OCS treated exacerbations	Unclear risk	Intention to treat population described as: 'Efficacy analyses included randomised patients who received 1 or more doses of randomised study medication and contributed data sufficient to calculate 1 or more primary or secondary efficacy end points.'
Incomplete outcome data (attrition bias) Hospital admission	Unclear risk	Intention to treat population described as: 'Efficacy analyses included randomised patients who received 1 or more doses of randomised study medication and contributed data sufficient to calculate 1 or more primary or secondary efficacy end points.'
Incomplete outcome data (attrition bias) SAEs	Unclear risk	ITT analysis described; no explicit details on how withdrawals were handled
Selective reporting (reporting bias)	Unclear risk	Unable to ascertain this reliably.
Other bias	Low risk	No other potential sources of bias identified.

COMPASS

Methods	Randomised, parallel group trial. Double-blind, treble-dummy design 235 centres in 16 countries. Description of withdrawals: stated.
Participants	N screened: not reported (4399 enrolled). N randomised: 2228 (two treatment groups: FP/SAL: 1123; BUD/F: 1105; one treatment group not considered by this review: BUD/F (plus BUD/F as needed): 1107) N completed: 2120. M = 932. F = 1296. Mean age: 38 (N 12-17 years: 424; > 18 years: 1696). Baseline characteristics: FEV_1 predicted: 73%; mean ICS consumption at baseline: 747 µg/d; Inclusion criteria: 1. > 12 years; 2. ATS defined asthma for > 6 months; 3. use of ICS > 3 months (500 µg/d FP or equivalent); 4. > 50% predicted FEV_1; 5. > 1 exacerbation in previous 12 months; 6. use of reliever medication > 5 days of previous 7 during run-in. Exclusion criteria: 1. > puffs/d rescue medication on any day of run-in; 2. asthma exacerbation during run-in; 3. use of systemic corticosteroids/respiratory infection affecting asthma control within 30 days of study entry.
Interventions	1. Combination fluticasone and salmeterol 250/50 µg bid. BDP equivalent 1000 µg. 2. Combination budesonide and formoterol 400/12 µg bid. BDP equivalent 800 µg. 3. Combination budesonide/formoterol 200/6 µg bid (plus additional puffs as required). Delivery device: FP/SAL: MDI; BUD/F: DPI. Treatment period: 24 weeks. Run-in: 2 weeks - regular ICS therapy plus terbutaline prn. Rescue: Terbutaline.
Outcomes	Primary outcome: time to first severe exacerbation. Secondary outcomes: exacerbations; lung function (FEV_1; diary card PEF); rescue medication use; symptom scores; mortality; AQLQ
Notes	Dose adjustment criteria: symptoms and rescue medication use determined whether treatment should be increased. If absence of symptoms & rescue medication use (>/= 6 puffs/d or nocturnal symptoms) then maintenance treatment was stepped down Study sponsors: AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement

COMPASS (*Continued*)

Random sequence generation (selection bias)	Low risk	'The randomisation schedule was computer-generated at AstraZeneca Research and Development, Charnwood, UK. Within each centre, patients were randomised strictly sequentially as they became eligible.'
Allocation concealment (selection bias)	Low risk	Third party not involved in the primary study: 'Individual treatment codes and code envelopes (indicating the treatment allocation for each randomised patient) were provided, but code envelopes were to be opened only in case of medical emergencies.'
Blinding of participants and personnel (performance bias) OCS-treatment, hospital admission & asthma-related SAEs	Low risk	Double-dummy design likely to have protected against biased results for subjective outcomes. Objective outcomes not likely to have been affected by the comparison
Blinding of outcome assessment (detection bias) OCS-treatment, admission to hospital & asthma-related SAEs	Unclear risk	Confirmation that outcome assessors were blind to treatment group assignment was not available
Incomplete outcome data (attrition bias) OCS treated exacerbations	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data (attrition bias) Hospital admission	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data (attrition bias) SAEs	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Selective reporting (reporting bias)	Low risk	Unable to ascertain this reliably.
Other bias	Low risk	No other potential sources of bias identified.

EXCEL

Methods	Randomised, parallel group trial. Double-blind, double-dummy design 178 centres in 18 countries. Description of withdrawals: stated.
Participants	N screened: 1769. N randomised: 1397 (FP/SAL: 700; BUD/F: 697). N completed: 1258. M = 595. F = 796. Mean age: 46. Baseline characteristics: FEV_1 predicted: 79%; 353 L/min am PEF. Inclusion criteria: 1. > 18 years; 2. clinical history of asthma (> 6 months); 3. 1000-2000mcg/d BDP equivalent; 4. reversibility of 12% & 200mL or more post SABA; 5. 2 or more episodes of asthma during day/night on 4 of last 7 days of run-in. Exclusion criteria: 1. upper/lower RTI; 2. hospitalisation with asthma in 4 weeks prior to baseline visit; 3. oral steroids within 4 weeks/depot steroids within 12 weeks of baseline visit; 4. FEV_1 < 50% predicted; smoking history of > 10 pack years.
Interventions	1. Combination fluticasone and salmeterol 250/50 µg bid (+ placebo turbuhaler). BDP equivalent 1000 µg. 2. Combination budesonide and formoterol 400/12 µg bid (+ placebo Diskus). BDP equivalent 800 µg. Delivery device: FP/SAL: Diskus; BUD/F: Turbuhaler. Treatment period: 24 weeks. Run-in: ICS + salbutamol prn (2 weeks). Rescue: Salbutamol.
Outcomes	Primary outcome: exacerbations. Secondary outcomes: exacerbations (use of oral steroids; hospitalisations); asthma symptoms; rescue medication use; am PEF; pm PEF; FEV_1; withdrawals; adverse events; mortality.
Notes	Study sponsors: GSK.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Patients were assigned to study treatment in accordance with the randomisation schedule from the Interactive Voice Recognition System, which was part of the GSK

EXCEL (*Continued*)

		System for the Central Allocation of Medication.'
Allocation concealment (selection bias)	Low risk	Third party not involved with primary study.
Blinding of participants and personnel (performance bias) OCS-treatment, hospital admission & asthma-related SAEs	Low risk	Double-dummy design likely to have protected against bias of results for primary outcomes
Blinding of outcome assessment (detection bias) OCS-treatment, admission to hospital & asthma-related SAEs	Unclear risk	Confirmation that outcome assessors were blind to treatment group assignment was not available
Incomplete outcome data (attrition bias) OCS treated exacerbations	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data (attrition bias) Hospital admission	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data (attrition bias) SAEs	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Selective reporting (reporting bias)	Unclear risk	Unable to ascertain this reliably.
Other bias	Low risk	No other potential sources of bias identified.

SAM40048

Methods	Randomised, parallel group trial. Double-blind, double dummy design 27 centres in Germany. Description of withdrawals: stated.
Participants	N screened: not reported. N randomised: 248 (ITT population: 241). N completed: 235. M = 102 (based on ITT). F = 139 (based on ITT). Mean age: 48. Baseline characteristics: FEV_1 predicted: 65%; am PEF 310 L/min. Inclusion criteria: 1. 'moderate' asthma; 2. > 18 years;

	3. FEV_1 50%-80% predicted; 4. > 15% reversibility; 5. ICS dose 1000 µg/d (BDP equivalent); 6. symptomatic (symptom score of 1 on 7 days of the run-in period). Exclusion criteria: 1. exacerbations/emergency visits during 4-week pre-study period; 2. smoking (> 20 cigarettes/d).
Interventions	1. Combination fluticasone and salmeterol 250/50 µg bid + placebo Turbohaler. BDP equivalent 1000 µg. 2. Combination budesonide and formoterol 200/6 µg bid + placebo Diskus inhaler. BDP equivalent 400 µg. Delivery device: FP/SAL: Diskus; BUD/F: Turbohaler. Treatment period: 12 weeks. Run-in: 2 weeks (treatment not clear). Rescue: not reported.
Outcomes	Primary outcome: FEV_1 predicted. Secondary outcomes: Morning PEF; evening PEF; daytime and evening asthma symptoms; symptom-free days; rescue medication-free days; safety; mortality
Notes	Study sponsors: GSK.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) OCS-treatment, hospital admission & asthma-related SAEs	Low risk	Double-dummy design likely to have protected against biased results for subjective outcomes. Objective outcomes not likely to have been affected by the comparison
Blinding of outcome assessment (detection bias) OCS-treatment, admission to hospital & asthma-related SAEs	Unclear risk	Confirmation that outcome assessors were blind to treatment group assignment was not available
Incomplete outcome data (attrition bias) OCS treated exacerbations	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described

SAM40048 (*Continued*)

Incomplete outcome data (attrition bias) Hospital admission	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data (attrition bias) SAEs	Unclear risk	ITT analysis described. Explicit details of how withdrawals handled were not described
Selective reporting (reporting bias)	Unclear risk	Unable to ascertain this reliably,
Other bias	Low risk	No other potential sources of bias identified.

AQLQ: asthma quality of life questionnaire; ATS: American Thoracic Society; BDP: beclomethasone; BID: twice daily; BUD/F: budesonide and formoterol; DC: diary card; DPI: dry powder inhaler; ED: emergency department ; FEV_1: forced expiratory volume in 1 second; FP/SAL: fluticasone propionate/salmeterol combination; GINA: Global Initiative for asthma; ICS: inhaled corticosteroid; LABA: long-acting beat2-aginist; MDI: metered dose inhaler; OCS: oral corticosteroids; PEF: peak expiratory flow; prn: pro re nata (Latin for 'take as needed'); RTI: Respiratory tract infection; SABA: Short-acting beta-agonist.

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

Study	Reason for exclusion
Adachi 2008	Study compared combination FP/SAL with FP and theophylline.
AHEAD	Study comparing FP/SAL with BUD/F as an adjustable dosing strategy
ALLIANCE	Combinations assessed not relevant to this review.
Ambrose 2007	Study compared different doses of BUD/F. No comparison with FP/SAL
Bleecker 2007	Study randomised participants to FP/SAL or SAL. No comparison with BUD/F
Bodzenta-Lukaszyk 2010a	Comparison of FP/F with FP/SAL.
Bodzenta-Lukaszyk 2010b	Comparison of FP/F with FP/SAL.
Bodzenta-Lukaszyk 2011	Comparison of FP/F with FP/SAL.
Brambilla 2003	Separate inhalers: formoterol versus salmeterol as add on to ICS
CONCEPT	Assessment of combination FP/SAL against BUD/F given as an adjustable dosing strategy
Creemers 2002	Study summarised data from two studies comparing BUD/F with ICS alone

(*Continued*)

EDICT	Combination FP/SAL versus BUD and F given via separate inhalers
Gogtay 2010	Comparison does not include the combination of SAL with FP.
Hampel 2007	Report of two crossover studies: ineligible design.
Jenkins 2000	Study assessed FP/SAL with ICS alone.
Kaik 2002	Separate F and BUD preparations versus combination FP/SAL.
Lee 2003	Crossover design.
Lötvall 2002	Summary of two crossover studies.
Maspero 2010	Comparison of Mometasone/F and FP/SAL.
Menendez 2011	Inadequate duration.
Palmqvist 2001	Crossover design.
SAM40042	Crossover design.
SAM40047	Crossover design.
SAM40062	Crossover design.
Vogelmeier 2005	Comparison of FP/SAL with BUD/F as maintenance and relief.

BUD/F; budesonide and formoterol; FP/SAL: fluticasone propionate and salmeterol; ICS: inhaled corticosteroids.

DATA AND ANALYSES

Comparison 1. Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants experiencing exacerbations requiring oral steroid treatment	4	4949	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.07]
2 Participants experiencing exacerbations requiring admission to hospital	4	4879	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.68, 2.47]
3 Asthma-related serious adverse event	3	4054	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [0.75, 2.86]
4 Participants experiencing exacerbations requiring ED visit/hospitalisation	4	4861	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.94, 1.80]
5 Mortality	5		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Asthma Quality of Life Questionnaire	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 N with improvement in Asthma Quality of Life Questionnaire	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Change in am PEF	5	5101	L/min (Fixed, 95% CI)	2.24 [-0.24, 4.73]
9 Change in pm PEF	4	4299	L/min (Fixed, 95% CI)	0.25 [-0.80, 1.30]
10 Change in FEV_1	4	4845	L (Fixed, 95% CI)	0.00 [-0.02, 0.02]
11 Change in FEV_1 predicted (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Change in rescue medication use	3	3469	Puffs/d (Fixed, 95% CI)	-0.06 [-0.13, 0.02]
13 Change in daytime symptoms	3	3464	Symptoms (Fixed, 95% CI)	-0.02 [-0.06, 0.03]
14 Change in symptom-free days	2	3027	Symptoms (Fixed, 95% CI)	1.25 [-1.18, 3.67]
15 Change in nocturnal awakenings	1		Symptoms (Fixed, 95% CI)	Totals not selected
16 Adverse events	3	3547	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.88, 1.15]
17 Headache	4	2916	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.43]
18 Candidiasis	2	1272	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [0.68, 4.00]
19 Upper respiratory tract infection	2	1644	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.81, 1.47]
20 Dysphonia	3	2669	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.87, 2.43]
21 Rhinitis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
22 Throat irritation	2	1644	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.82, 2.35]
23 Cough	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
24 Tremor	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
25 Withdrawals	5	5082	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.20]
26 Withdrawals (adverse events)	5	5082	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.60, 1.46]
27 Withdrawals (lack of efficacy)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 1 Participants experiencing exacerbations requiring oral steroid treatment.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 1 Participants experiencing exacerbations requiring oral steroid treatment

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	30/219	33/215		12.2 %	0.88 [0.51, 1.49]
Busse 2008	37/404	37/422		13.9 %	1.05 [0.65, 1.69]
COMPASS	109/1199	108/1099		43.5 %	0.92 [0.69, 1.21]
EXCEL	63/694	79/697		30.4 %	0.78 [0.55, 1.11]
Total (95% CI)	**2516**	**2433**		**100.0 %**	**0.89 [0.74, 1.07]**

Total events: 239 (FP/SAL), 257 (BUD/F)

Heterogeneity: $Chi^2 = 1.04$, df = 3 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 1.24 (P = 0.22)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 2 Participants experiencing exacerbations requiring admission to hospital.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 2 Participants experiencing exacerbations requiring admission to hospital

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	0/219	1/215		9.2 %	0.33 [0.01, 8.04]
Busse 2008	2/404	1/422		5.9 %	2.09 [0.19, 23.19]
COMPASS	15/1123	13/1105		78.8 %	1.14 [0.54, 2.40]
EXCEL	4/694	1/697		6.0 %	4.03 [0.45, 36.19]
Total (95% CI)	**2440**	**2439**		**100.0 %**	**1.29 [0.68, 2.47]**

Total events: 21 (FP/SAL), 16 (BUD/F)

Heterogeneity: $Chi^2 = 2.01$, df = 3 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 3 Asthma-related serious adverse event.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 3 Asthma-related serious adverse event

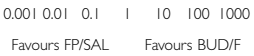
Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	0/224	1/215		10.6 %	0.32 [0.01, 7.86]
COMPASS	15/1119	12/1099		82.6 %	1.23 [0.57, 2.64]
EXCEL	6/697	1/700		6.8 %	6.07 [0.73, 50.55]
Total (95% CI)	**2040**	**2014**		**100.0 %**	**1.47 [0.75, 2.86]**

Total events: 21 (FP/SAL), 14 (BUD/F)

Heterogeneity: $Chi^2 = 2.80$, df = 2 (P = 0.25); $I^2 = 29\%$

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 4 Participants experiencing exacerbations requiring ED visit/hospitalisation.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 4 Participants experiencing exacerbations requiring ED visit/hospitalisation

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	7/219	3/215		4.6 %	2.33 [0.60, 9.14]
Busse 2008	2/404	4/422		6.1 %	0.52 [0.09, 2.85]
COMPASS	70/1123	50/1105		73.9 %	1.40 [0.97, 2.04]
EXCEL	8/686	10/687		15.4 %	0.80 [0.31, 2.04]
Total (95% CI)	**2432**	**2429**		**100.0 %**	**1.30 [0.94, 1.80]**
Total events: 87 (FP/SAL), 67 (BUD/F)					
Heterogeneity: Chi^2 = 3.02, df = 3 (P = 0.39); I^2 =1%					
Test for overall effect: Z = 1.57 (P = 0.12)					
Test for subgroup differences: Not applicable					

Analysis 1.5. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 5 Mortality.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 5 Mortality

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	0/224	0/215		Not estimable
Busse 2008	0/406	0/427		Not estimable
COMPASS	1/962	0/941		2.94 [0.12, 72.20]
EXCEL	0/697	0/700		Not estimable
SAM40048	0/121	0/126		Not estimable

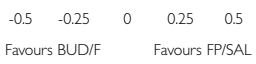
Analysis 1.6. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 6 Asthma Quality of Life Questionnaire.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 6 Asthma Quality of Life Questionnaire

Study or subgroup	FP/SAL N	BUD/F N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
COMPASS	962	941	0.032 (0.04158163)		0.03 [-0.05, 0.11]



Analysis 1.7. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 7 N with improvement in Asthma Quality of Life Questionnaire.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 7 N with improvement in Asthma Quality of Life Questionnaire

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Busse 2008	207/335	212/337		0.95 [0.70, 1.30]

Analysis 1.8. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 8 Change in am PEF.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 8 Change in am PEF

Study or subgroup	FP/SAL N	BUD/F N	L/min (SE)	L/min IV,Fixed,95% CI	Weight	L/min IV,Fixed,95% CI
Aalbers 2004	224	215	0.9 (3.74)		11.5 %	0.90 [-6.43, 8.23]
Busse 2008	397	405	4.34 (3.2602)		15.2 %	4.34 [-2.05, 10.73]
COMPASS	1123	1105	2.5 (1.8878)		45.2 %	2.50 [-1.20, 6.20]
EXCEL	694	697	0.4 (2.4745)		26.3 %	0.40 [-4.45, 5.25]
SAM40048	116	125	14.04 (9.5714)		1.8 %	14.04 [-4.72, 32.80]
Total (95% CI)	**2554**	**2547**			**100.0 %**	**2.24 [-0.24, 4.73]**

Heterogeneity: Chi^2 = 2.64, df = 4 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 1.77 (P = 0.077)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 9 Change in pm PEF.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

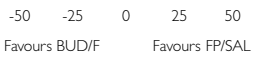
Outcome: 9 Change in pm PEF

Study or subgroup	FP/SAL N	BUD/F N	L/min (SE)	L/min IV,Fixed,95% CI	Weight	L/min IV,Fixed,95% CI
Aalbers 2004	224	215	-1.1 (3.45)		2.4 %	-1.10 [-7.86, 5.66]
COMPASS	1123	1105	0.7 (1.8622)		8.2 %	0.70 [-2.95, 4.35]
EXCEL	694	697	0.2 (0.5663)		89.1 %	0.20 [-0.91, 1.31]
SAM40048	116	125	14.42 (9.9642)		0.3 %	14.42 [-5.11, 33.95]
Total (95% CI)	**2157**	**2142**			**100.0 %**	**0.25 [-0.80, 1.30]**

Heterogeneity: $Chi^2 = 2.24$, df = 3 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 10 Change in FEV1.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 10 Change in FEV_1

Study or subgroup	FP/SAL N	BUD/F N	L (SE)	L IV,Fixed,95% CI	Weight	L IV,Fixed,95% CI
Aalbers 2004	224	215	-0.06 (0.03)		12.9 %	-0.06 [-0.12, 0.00]
Busse 2008	391	396	0.02 (0.0204)		28.0 %	0.02 [-0.02, 0.06]
COMPASS	1123	1105	0 (0.0158)		46.6 %	0.0 [-0.03, 0.03]
EXCEL	694	697	0.02 (0.0306)		12.4 %	0.02 [-0.04, 0.08]
Total (95% CI)	**2432**	**2413**			**100.0 %**	**0.00 [-0.02, 0.02]**

Heterogeneity: $Chi^2 = 5.39$, df = 3 (P = 0.15); $I^2 = 44\%$

Test for overall effect: Z = 0.03 (P = 0.98)

Test for subgroup differences: Not applicable

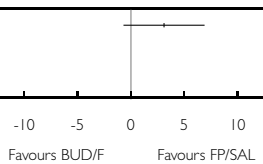
Analysis 1.11. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 11 Change in FEV1 predicted (%).

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 11 Change in FEV_1 predicted (%)

Study or subgroup	FP/SAL N	Mean(SD)	BUD/F N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
SAM40048	116	14 (16.4)	125	10.9 (13.3)		3.10 [-0.69, 6.89]



Analysis 1.12. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 12 Change in rescue medication use.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

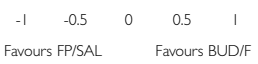
Outcome: 12 Change in rescue medication use

Study or subgroup	FP/SAL N	BUD/F N	Puffs/d (SE)	Puffs/d IV,Fixed,95% CI	Weight	Puffs/d IV,Fixed,95% CI
Aalbers 2004	224	215	-0.03 (0.11)		12.0 %	-0.03 [-0.25, 0.19]
Busse 2008	396	406	0.07 (0.0867)		19.3 %	0.07 [-0.10, 0.24]
COMPASS	1123	1105	-0.1 (0.0459)		68.8 %	-0.10 [-0.19, -0.01]
Total (95% CI)	**1743**	**1726**			**100.0 %**	**-0.06 [-0.13, 0.02]**

Heterogeneity: Chi^2 = 3.08, df = 2 (P = 0.21); I^2 =35%

Test for overall effect: Z = 1.55 (P = 0.12)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 13 Change in daytime symptoms.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

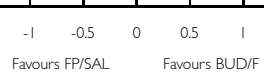
Outcome: 13 Change in daytime symptoms

Study or subgroup	FP/SAL N	BUD/F N	Symptoms (SE)	Symptoms IV,Fixed,95% CI	Weight	Symptoms IV,Fixed,95% CI
Aalbers 2004	224	215	-0.05 (0.06)		14.1 %	-0.05 [-0.17, 0.07]
Busse 2008	395	402	0.02 (0.0357)		39.8 %	0.02 [-0.05, 0.09]
COMPASS	1123	1105	-0.04 (0.0332)		46.1 %	-0.04 [-0.11, 0.03]
Total (95% CI)	**1742**	**1722**			**100.0 %**	**-0.02 [-0.06, 0.03]**

Heterogeneity: Chi^2 = 1.86, df = 2 (P = 0.40); I^2 =0.0%

Test for overall effect: Z = 0.78 (P = 0.44)

Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 14 Change in symptom-free days.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 14 Change in symptom-free days

Study or subgroup	FP/SAL N	BUD/F N	Symptoms (SE)	Symptoms IV,Fixed,95% CI	Weight	Symptoms IV,Fixed,95% CI
Busse 2008	395	404	0.18 (2.4821)		24.9 %	0.18 [-4.68, 5.04]
COMPASS	1123	1105	1.6 (1.4286)		75.1 %	1.60 [-1.20, 4.40]
Total (95% CI)	**1518**	**1509**			**100.0 %**	**1.25 [-1.18, 3.67]**

Heterogeneity: Chi^2 = 0.25, df = 1 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

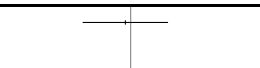
Analysis 1.15. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 15 Change in nocturnal awakenings.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 15 Change in nocturnal awakenings

Study or subgroup	FP/SAL N	BUD/F N	Symptoms (SE)	Symptoms IV,Fixed,95% CI	Symptoms IV,Fixed,95% CI
COMPASS	1123	1105	-0.2 (0.8163)		-0.20 [-1.80, 1.40]



Analysis 1.16. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 16 Adverse events.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 16 Adverse events

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
COMPASS	381/962	387/941		55.0 %	0.94 [0.78, 1.13]
EXCEL	384/697	377/700		39.3 %	1.05 [0.85, 1.30]
SAM40048	44/121	39/126		5.7 %	1.27 [0.75, 2.16]
Total (95% CI)	**1780**	**1767**		**100.0 %**	**1.00 [0.88, 1.15]**

Total events: 809 (FP/SAL), 803 (BUD/F)

Heterogeneity: $Chi^2 = 1.48$, df = 2 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 0.03 (P = 0.98)

Test for subgroup differences: Not applicable

Analysis 1.17. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 17 Headache.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 17 Headache

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	9/224	4/215		4.2 %	2.21 [0.67, 7.28]
Busse 2008	3/406	6/427		6.2 %	0.52 [0.13, 2.10]
EXCEL	101/697	95/700		86.5 %	1.08 [0.80, 1.46]
SAM40048	2/121	3/126		3.1 %	0.69 [0.11, 4.20]
Total (95% CI)	**1448**	**1468**		**100.0 %**	**1.08 [0.82, 1.43]**

Total events: 115 (FP/SAL), 108 (BUD/F)

Heterogeneity: $Chi^2 = 2.66$, df = 3 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 18 Candidiasis.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 18 Candidiasis

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	7/224	4/215		50.7 %	1.70 [0.49, 5.90]
Busse 2008	6/406	4/427		49.3 %	1.59 [0.44, 5.66]
Total (95% CI)	**630**	**642**		**100.0 %**	**1.64 [0.68, 4.00]**

Total events: 13 (FP/SAL), 8 (BUD/F)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 19 Upper respiratory tract infection.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 19 Upper respiratory tract infection

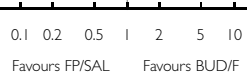
Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
EXCEL	101/697	94/700		96.5 %	1.09 [0.81, 1.48]
SAM40048	3/121	3/126		3.5 %	1.04 [0.21, 5.27]
Total (95% CI)	**818**	**826**		**100.0 %**	**1.09 [0.81, 1.47]**

Total events: 104 (FP/SAL), 97 (BUD/F)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 0.57 (P = 0.57)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 20 Dysphonia.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 20 Dysphonia

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	16/224	2/215		7.8 %	8.19 [1.86, 36.07]
Busse 2008	3/406	7/427		27.9 %	0.45 [0.11, 1.74]
EXCEL	17/697	16/700		64.2 %	1.07 [0.54, 2.13]
Total (95% CI)	**1327**	**1342**		**100.0 %**	**1.45 [0.87, 2.43]**

Total events: 36 (FP/SAL), 25 (BUD/F)

Heterogeneity: Chi^2 = 8.88, df = 2 (P = 0.01); I^2 =77%

Test for overall effect: Z = 1.41 (P = 0.16)

Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 21 Rhinitis.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 21 Rhinitis

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
EXCEL	45/697	34/700		1.35 [0.85, 2.14]

Analysis 1.22. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 22 Throat irritation.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 22 Throat irritation

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
EXCEL	32/697	23/700		91.9 %	1.42 [0.82, 2.45]
SAM40048	2/121	2/126		8.1 %	1.04 [0.14, 7.52]
Total (95% CI)	**818**	**826**		**100.0 %**	**1.39 [0.82, 2.35]**

Total events: 34 (FP/SAL), 25 (BUD/F)

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Not applicable

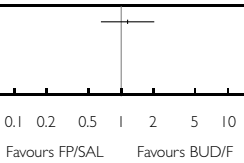
Analysis 1.23. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 23 Cough.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 23 Cough

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
EXCEL	25/697	22/700		1.15 [0.64, 2.05]



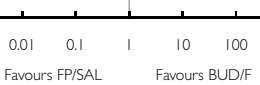
Analysis 1.24. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 24 Tremor.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 24 Tremor

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Busse 2008	1/406	8/427		0.13 [0.02, 1.04]



Analysis 1.25. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 25 Withdrawals.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 25 Withdrawals

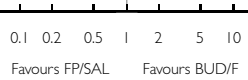
Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	25/224	31/215		16.1 %	0.75 [0.42, 1.31]
Busse 2008	37/391	37/389		19.3 %	0.99 [0.62, 1.61]
COMPASS	45/1119	53/1099		29.5 %	0.83 [0.55, 1.24]
EXCEL	71/697	62/700		31.9 %	1.17 [0.82, 1.67]
SAM40048	7/121	6/127		3.2 %	1.24 [0.40, 3.80]
Total (95% CI)	**2552**	**2530**		**100.0 %**	**0.97 [0.78, 1.20]**

Total events: 185 (FP/SAL), 189 (BUD/F)

Heterogeneity: $Chi^2 = 2.65$, df = 4 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 26 Withdrawals (adverse events).

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 26 Withdrawals (adverse events)

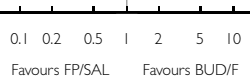
Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Aalbers 2004	9/224	10/215		24.2 %	0.86 [0.34, 2.15]
Busse 2008	5/391	5/389		12.2 %	0.99 [0.29, 3.46]
COMPASS	10/1119	13/1099		32.2 %	0.75 [0.33, 1.73]
EXCEL	13/697	10/700		24.2 %	1.31 [0.57, 3.01]
SAM40048	2/121	3/127		7.1 %	0.69 [0.11, 4.23]
Total (95% CI)	**2552**	**2530**		**100.0 %**	**0.94 [0.60, 1.46]**

Total events: 39 (FP/SAL), 41 (BUD/F)

Heterogeneity: Chi^2 = 1.04, df = 4 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 27 Withdrawals (lack of efficacy).

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 27 Withdrawals (lack of efficacy)

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
EXCEL	5/697	2/700		2.52 [0.49, 13.04]

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

WHAT'S NEW

Last assessed as up-to-date: 24 June 2011.

Date	Event	Description
17 November 2011	Amended	Correction to event rates with FP/SAL in text to match estimates reported in Summary of Findings table

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 3, 2008

Date	Event	Description
25 August 2011	New citation required but conclusions have not changed	Additional outcome data identified for Busse 2008 and COMPASS. Abstract, PLS and SoF table revised. Standardised and reformatted outcome reporting in main results Dr Chris Cates has stepped off the author line.
25 August 2011	New search has been performed	Literature search re-run.
8 May 2009	New search has been performed	Literature search re-run: no new studies identified. Risk of bias table completed and Summary of Findings table added
19 June 2008	Amended	Data from Aalbers 2004 added to the primary endpoint (OCS-treated exacerbations)
13 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

TJL devised the protocol with editorial support from CJC; assessed studies, extracted data, contacted trialists and study sponsors for additional outcome data; analysis and write-up

GF developed the protocol; wrote up study characteristics, extracted data and assisted with development of discussion section.

LC developed discussion section.

We acknowledge the input of Chris Cates who helped with data extraction and checking, interpretation and guidance on conceptual issues in earlier versions of this review.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Cochrane Editorial Unit, UK.

External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Added items to the risk of bias tool (allocation generation, selective reporting bias & other bias domains). This amendment reflects current recommendations regarding the risk of bias assessment from *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

2. Added mortality as an outcome measure. In view of possible concerns raised by related Cochrane Reviews in the area of harms, we included this outcome in the 2011 update of the review.

3. Summary of findings table has been added and quality of evidence assessed based on recommendations developed by GRADE. In the 2011 version we included withdrawals due to adverse events and mortality in this table. Both of these outcomes are potentially important in healthcare decision-making.

NOTES

A previous version of this review was withdrawn prior to publication following the identification of incomplete data by GSK for the outcome ED visit/admission to hospital. The data included in the original version of the review indicated a significant increase in the odds of ED visit/hospitalisation with FP/SAL. However, this reflected data that were drawn from those participants who were admitted to hospital only. The pooled outcome data did not an accurately represent the composite outcome of presentation at ED or hospital admission (EXCEL). We have now included data made available to us by GSK which are an accurate record of ED visit or admission to hospital.

INDEX TERMS

Medical Subject Headings (MeSH)

Albuterol [administration & dosage; analogs & derivatives]; Androstadienes [administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Budesonide [administration & dosage]; Drug Combinations; Ethanolamines [administration & dosage]; Fluticasone; Formoterol Fumarate; Randomized Controlled Trials as Topic; Salmeterol Xinafoate

MeSH check words

Adolescent; Adult; Child; Humans