Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children (Review)

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[Intervention Review]

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ABSTRACT

Background

Formoterol has a fast onset of action and can therefore be used to relieve symptoms of asthma. A combination inhaler can deliver formoterol with different doses of inhaled corticosteroid; when used as a reliever both drugs will be delivered more frequently when asthma symptoms increase. This has the potential to treat both bronchoconstriction and inflammation in the early stages of exacerbations.

Objectives

To assess the efficacy and safety of combined inhalers containing both formoterol and an inhaled corticosteroid when used for reliever therapy in adults and children with chronic asthma.

Search methods

We last searched the Cochrane Airways Group trials register in April 2009, and no new studies were found for inclusion in the review.

Selection criteria

Randomised trials in adults and children with chronic asthma, where a combination inhaler containing formoterol and inhaled corticosteroid is compared with fast-acting beta$_2$-agonist alone for the relief of asthma symptoms. This should be the only planned difference between the trial arms.

Data collection and analysis

Two review authors independently extracted the characteristics and results of each study. Authors or manufacturers were asked to supply unpublished data in relation to primary outcomes.

Main results

Three trials involving 5905 participants were included. In patients with mild asthma who do not need maintenance treatment, no clinically important advantages of budesonide/formoterol as reliever were found in comparison to formoterol as reliever.

Two studies enrolled patients with more severe asthma who were not controlled on high doses of inhaled corticosteroids (around 700 mcg/day in adults), and had suffered a clinically important asthma exacerbation in the past year. Hospitalisations related to asthma in the two studies comparing budesonide/formoterol for maintenance and relief with the same dose of budesonide/formoterol for maintenance with terbutaline for relief yielded an odds ratio of 0.68 (95% CI 0.40 to 1.16), which was not a statistically significant reduction. In adults there was a reduction in exacerbations requiring oral corticosteroids compared to terbutaline, odds ratio 0.54 (95% CI 0.44 to 0.65), which translates into a number needed to treat over 12 months of 15 (95% CI 13 to 21). The study in children found less serious adverse events with budesonide/formoterol used for maintenance and relief. There was no significant difference in annual growth in children using budesonide/formoterol reliever in comparison to terbutaline.

Authors' conclusions

In mild asthma it is not yet known whether patients who use a budesonide/formoterol inhaler for relief of asthma symptoms derive any clinically important benefits. In more severe asthma, two studies enrolled patients who were not controlled on inhaled corticosteroids, and had suffered an exacerbation in the previous year, and then had their maintenance inhaled corticosteroids reduced in both arms of the study. Under these conditions the studies demonstrated a reduction in the risk of exacerbations that require oral corticosteroids with budesonide/formoterol for maintenance and relief in comparison with budesonide/formoterol for maintenance and terbutaline or formoterol for relief. The incidence of serious adverse events in children was also less using budesonide/formoterol for maintenance and relief in one study, which similarly enrolled children who were not controlled on inhaled corticosteroids, and who had their maintenance inhaled corticosteroids reduced at the start of the study. This study also compared an explorative maintenance dose of budesonide/formoterol that is not approved for treatment.

PLAIN LANGUAGE SUMMARY

Formoterol and budesonide for the relief of asthma symptoms in adults and children

Combined formoterol and budesonide inhalers can be used for maintenance treatment of asthma and relief of symptoms. Three trials involving 5905 participants were included. We found very little evidence in relation to the use of formoterol and budesonide for relief of symptoms in people with mild asthma, but in people with more severe asthma who had suffered exacerbations in spite of regular treatment with inhaled corticosteroids, we found that reliever formoterol and budesonide compared favourably with terbutaline in reducing asthma exacerbations that required a course of oral corticosteroids. However only a small proportion of the 'severe asthma exacerbations' as defined in the trials led to hospital admissions, and no significant overall benefit has yet been shown for this outcome. In children with asthma that was not controlled with regular inhaled corticosteroids, there were fewer serious adverse events when formoterol and budesonide were used to relieve symptoms as well as for maintenance treatment.

BACKGROUND

People with asthma take preventer therapy to maintain symptom control, improve lung function and reduce the requirement for emergency care. In response to symptoms, reliever medication in the form of short-acting beta-agonists such as salbutamol or terbutaline, or formoterol (a long acting beta-agonist (LABA) with a fast onset of action), can be used on an 'as needed' basis (BTS 2003). A maintenance combination therapy with formoterol in the combination marketed as 'Symbicort' combines preventer and reliever therapy in a single inhaler, and allows both medications to be increased simultaneously when asthma symptoms increase (SMILE). The pharmacological properties of salmeterol used in the Seretide/Advair combination inhaler give bronchodilation with a slower onset, and it is not licensed for use on an 'as needed' basis. The inclusion of inhaled corticosteroid (ICS) in a reliever inhaler for use during episodes of loss of control requires monitoring for safety, efficacy and assessment of overall ICS dose.

Description of the intervention

In patients whose asthma remains poorly controlled on moderate doses of inhaled corticosteroids (ICS), the addition of a LABA has been shown to compare favourably with placebo (Ni Chroinin 2005) and increasing the dose of ICS (Greenstone 2005), and this is a recommended approach in asthma guidelines (BTS 2003).

There are concerns about the impact of LABA on exacerbation rates in children (Bisgaard 2003). Traditionally patients have used an additional short-acting beta$_2$-agonist to relieve symptoms (on top of their regular maintenance preventer treatment). Formoterol is a long-acting beta$_2$-agonist with fast onset of action (Palmqvist 2001). It is therefore also suitable for use in the relief of asthma symptoms, and when taken as reliever therapy in combination with ICS may have the added advantage of allowing the patient to titrate their ICS treatment according to asthma symptoms.

How the intervention might work

The inflammatory component of chronic asthma can be reduced by regular use of inhaled corticosteroids (Adams 2008), but many patients default from treatment (Sovani 2008). Asthma exacerbations are preceded by many days of worsening symptoms (Tattersfield 1999), but doubling inhaled corticosteroids has not been shown to be effective in preventing exacerbations from developing (FitzGerald 2004; Harrison 2004). Deteriorating symptoms may be an early sign of an increase in underlying inflammation, so including inhaled corticosteroids with formoterol in a reliever inhaler is an alternative approach.

Why it is important to do this review

Concerns have been raised about the use of long-acting beta$_2$-agonists in chronic asthma, in particular when used without regular inhaled corticosteroids, in relation to the possible increased risk of severe adverse events such as intubation and asthma-related death (Salpeter 2006; Walters 2007; Cates 2008; Cates 2008a). This review is needed to identify and summarise the results of clinical trials that compared budesonide/formoterol combination inhaler as reliever therapy with other reliever inhalers.

OBJECTIVES

This review has been carried out to assess the efficacy and safety of combined inhalers containing both formoterol and an inhaled corticosteroid, when used for reliever therapy, in adults and children with chronic asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials of parallel group design were included in the review.

Types of participants

Adults and children with a diagnosis of chronic asthma. We accepted trialist-defined asthma, recording the definition of asthma used in the studies, and the entry criteria. We summarised baseline severity of lung function and persistence of symptoms, and we collected data on pre-study maintenance therapies. We did not include studies conducted in an emergency department setting.

Types of interventions

Eligible treatment group intervention

This review included studies which assessed the effects of using a combined formoterol and inhaled steroid delivered through a single inhaler device for relief of symptoms. The intervention was considered in three different drug therapy regimens which we analysed separately:

1. As needed, in addition to regular maintenance therapy with combination inhaled steroid and long-acting beta-agonist (i.e. as needed and regular combination therapy).
2. As needed, in addition to regular maintenance therapy with inhaled steroid only (i.e. as needed combination therapy and regular ICS).
3. As needed only (i.e. combination therapy used without maintenance treatment).

Eligible control group treatment

The control groups for the studies in this review consisted of a prescribed fast-acting beta$_2$-agonist such as terbutaline, salbutamol or formoterol alone, given on an as needed basis. We plan to include future studies which compare reliever therapy with combination formoterol inhalers and other fast-acting beta$_2$-agonists combined in a single inhaler with an inhaled corticosteroid.

The maintenance dose of ICS or combination therapy had to be the same in both treatment groups. Fixed dosing had to remain stable within the control limbs of each of the studies. Study duration had to be greater than 12 weeks.

We did not consider studies that compared different combination therapy inhalers (i.e. seretide versus symbicort), or titration of maintenance dosing of combination therapy based on clinical signs and symptoms.

Types of outcome measures

Primary outcomes

1. Exacerbations of asthma requiring hospitalisation
2. Exacerbations of asthma requiring oral steroids
3. Serious adverse events (including mortality and life-threatening events)

Secondary outcomes

1. Exacerbations (not otherwise specified)
2. Clinic spirometry Fixed Expiratory Volume in one second (FEV_1)
3. Diary card morning and evening peak expiratory flow (PEF)
4. Number of rescue medication puffs required per day
5. Symptoms
6. Quality of life
7. Adverse events
8. 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. All records in the Specialised Register coded as 'asthma' were searched using the following terms: ("single inhaler therapy" or SiT or SMART or relie* or "as need*" or as-need* or prn or flexible or titrat*) and ((combin* or symbicort or viani) or ((steroid* or corticosteroid* or ICS or budesonide or BUD or Pulmicort or beclomethasone or BDP or becotide) and ("beta*agonist" or "beta*adrenergic agonist" or formoterol or eformoterol or oxis or foradil)))

Searching other resources

We contacted trialists and manufacturers in order to confirm data and to establish whether other unpublished or ongoing studies were available for assessment. We handsearched clinical trials 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 independently selected articles on the basis of title or abstract or both for full text scrutiny. The authors agreed a list of articles which were retrieved, and they subsequently assessed each study to determine whether it was a secondary publication of a primary study publication, and to determine whether the study met the entry criteria of the review.

Data extraction and management

We extracted information from each study for the following characteristics:
Design (description of randomisation, blinding, number of study centres and location, number of study withdrawals).
Participants (sample size (N), mean age, age range of the study, baseline lung function, percentage on maintenance ICS or ICS/LABA combination and average daily dose of steroid, entry criteria).
Intervention (type and dose of component ICS and LABA, control limb dosing schedule, inhaler device, study duration and run-in)
Outcomes (type of outcome analysis, outcomes analysed)
We extracted data for each of the outcomes considered by the review from the trial publication(s) or from correspondence with trialists or the manufacturer.

Assessment of risk of bias in included studies

We assessed trial bias protection in the following domains according to whether studies meet the following pre-specified quality criteria (as met, unmet or unclear, Handbook 2006):
1. Sequence Generation;
2. Allocation Concealment;
3. Blinding of participants and investigators;
4. Loss to follow up.

Assessment of heterogeneity

We measured statistical variation between combined studies by the I-squared (I^2) statistic (Higgins 2003).

Data synthesis

Data was combined with RevMan 5.0, using a fixed-effect mean difference (calculated as either a weighted mean difference or a mean difference weighted by generic inverse variance) for continuous data variables, and a fixed-effect odds ratio for dichotomous variables. For the primary outcome of exacerbations we planned to calculate a number needed to treat to benefit (NNTB) for the different levels of risk as represented by control group event rates over a specified time period (www.nntonline.net).

Subgroup analysis and investigation of heterogeneity

We looked at the data from adults and children separately. Adult studies were considered as those which recruited participants from 18 upwards. Adult and adolescent studies were considered as those which recruit participants from 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.

Sensitivity analysis

Sensitivity analysis was planned on the basis of risk of bias in studies and methods of data analysis (fixed and random-effects models).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The original search was out in April 2008 and included 199 abstracts and a new search was also carried out in April 2009 which included 30 further abstracts. Thirty six of the original abstracts were potentially relevant and full text articles were obtained. There were 11 citations relating to the three studies included in the review and 25 citations for the 12 studies that were excluded (*see* Characteristics of included studies and Characteristics of excluded studies for full details).

The updated search did not yield any further studies for inclusion; five potentially relevant full text articles were independently assessed by CJC and TL. Stallberg 2008 was excluded because the two comparison arms used different maintenance regimens (either higher dose budesonide/formoterol or adjustable budesonide and formoterol in separate inhalers). Two references were to existing excluded studies (MONO and SALTO) and Riemersma 2008 was excluded as the comparison was with usual care.

Included studies

The three trials (5905 participants) that are included in this review have been considered as four separate data sources, in order to separate the STAY study into children STAY - Children and adults STAY - Adults. However it has not been possible to obtain separate data for adults and children for all outcomes, so for these the overall data has been entered under the label STAY - All ages.

SOMA

This was a small study on 92 adults with mild asthma who were symptomatic but not taking any inhaled steroids, and had a concentration of nitric oxide in exhaled breath (FeNO) level of more than 20 ppb. The mean pre-bronchodilator FEV_1 was 101% predicted normal. Budesonide/formoterol 200/6 mcg was compared with formoterol 6 mcg as reliever therapy (with no maintenance therapy in either arm) over a 24 week treatment period. The primary outcome for this study was mean change in FeNO, but this was not a pre-specified outcome for this review so the results are not reported here.

SMILE

This was a large Multicentre study on 3394 adults and adolescents with moderate to severe persistent asthma who had a history of more than one severe asthma exacerbation in the past year, and remained symptomatic on budesonide/formoterol 200/6 one inhalation twice daily during a two week run-in. Their mean pre-bronchodilator FEV_1 was 72% predicted and the mean baseline daily ICS level was 755 mcg/day. Fifty nine per cent of participants were also taking LABA before participating in the study. During the 12 month trial period budesonide/formoterol 200/6 mcg one inhalation twice daily was given as maintenance to all patients (half the average dose of ICS used previously); the same inhaler as reliever was compared to formoterol 6 mcg and terbutaline 500 mcg as reliever in the three arms of the study.

The definition of a severe asthma exacerbation in this study included hospitalisation, emergency room (ER) visits or the need for oral steroids for three days or more. The proportion of patients with a severe exacerbation was the primary outcome used for the power calculation in this study.

STAY - Adults

This was a large Multicentre study on 2419 adults and adolescents with moderate to severe persistent asthma uncontrolled on ICS (400 to 1000 mcg/day) and a history of at least one "clinically important" exacerbation in the past year. Their mean pre-bronchodilator FEV_1 was 73% predicted and the mean baseline daily ICS level was 660 mcg/day. Twenty eight per cent of participants (adults and children) were already taking LABA before participating in the study. To be eligible for randomisation patients had to have used 12 or more inhalations of as-needed medication during the last 10 days of run-in, when they were treated with their previous ICS but LABA was withdrawn. During the 12 month trial period budesonide/formoterol 100/6 mcg one inhalation twice daily was given as maintenance to all patients in two arms of the study (one third of the previously prescribed dose of ICS); the same inhaler as reliever was compared to terbutaline 500 mcg as reliever. The third arm of the study did not contribute data to this review as a higher dose of budesonide was used for maintenance with terbutaline as reliever.

The definition of a severe asthma exacerbation in this study included hospitalisation, emergency room (ER) visits, oral steroid treatment, or morning peak flow of 70% or less of baseline on two consecutive days. The primary efficacy variable was time to first

severe asthma exacerbation.

STAY - Children

This was a subset of data presented from 341 children aged 4 to 11 years in the STAY study. They had moderate to severe persistent asthma uncontrolled on ICS (200 to 500 mcg/day) and a history of at least one "clinically important" exacerbation in the past year. Their mean pre-bronchodilator FEV_1 was 76% predicted and the mean baseline daily ICS level was 315 mcg/day. The proportion of children taking LABA before participating in the study is not reported. To be eligible for randomisation patients had to have used eight or more inhalations of as-needed medication during the last 10 days of run-in, when they were treated with their previous ICS but LABA was withdrawn. During the 12 month trial period budesonide/formoterol 100/6 mcg one inhalation in the evening was given as maintenance to all patients in two arms of the study (effectively one third of the previously prescribed dose of ICS); the same inhaler as reliever was compared to terbutaline 500 mcg. The third arm of the study did not contribute data to this review as a higher dose of budesonide was used for maintenance with terbutaline as reliever.

The definition of a severe asthma exacerbation in this study included hospitalisation, emergency room (ER) visits, oral steroid treatment, or morning peak flow of 70% or less of baseline on two consecutive days. For children an increase in inhaled corticosteroids (via a separate inhaler), or other additional treatment were also classified as severe asthma exacerbations. The primary efficacy variable was time to first severe asthma exacerbation.

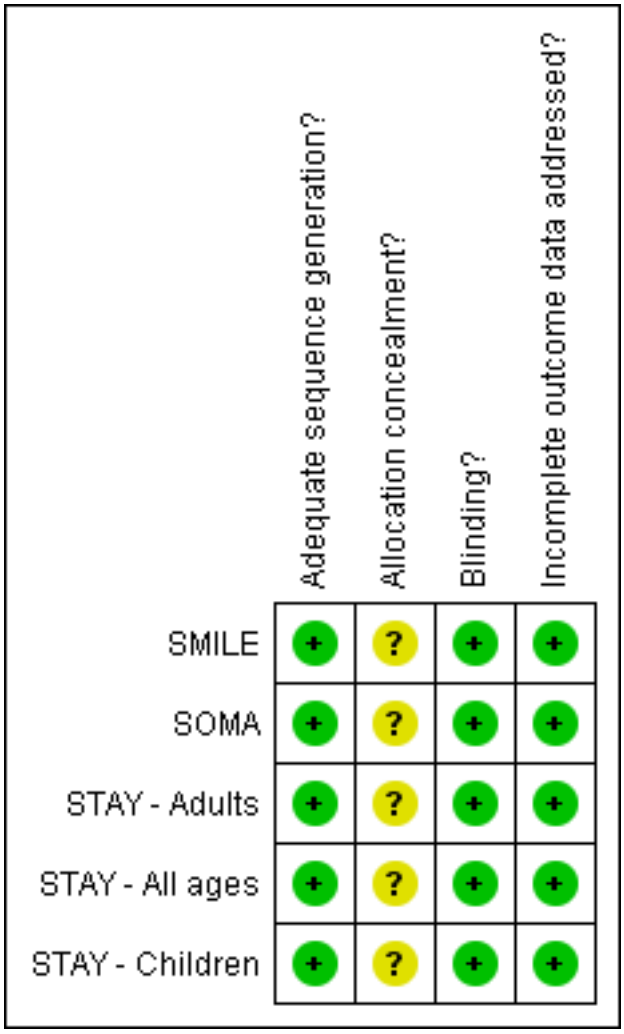
Excluded studies

Three of these studies (Ind 2002; Richter 2007; Tattersfield 2001) used formoterol alone as reliever therapy, and the other studies (Bousquet 2007; COMPASS; COSMOS; Loukides 2005; Lundborg 2006; Scicchitano 2004; SOLO; Sovani 2008; STEAM) were trials of Single Inhaler Therapy with budesonide/formoterol but used different maintenance treatments as well as comparing different reliever therapy.

Risk of bias in included studies

All the included studies had adequate sequence generation and blinding, drop out rates were not high Figure 1. Although allocation concealment was not well-reported, it is likely that it was also adequate in view of the sponsored nature of the studies.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

Budesonide/formoterol as reliever in mild asthma with no maintenance therapy

One small study in adults (SOMA) has looked at the effect of reliever therapy with budesonide/formoterol 200/6 in comparison with formoterol alone. All patients in the study had a baseline FeNO of at least 20 ppb and this was the main outcome measure for this study (but not a pre-specified outcome for this review). No studies were found addressing this comparison in children.

Primary outcomes

There were no reported exacerbations requiring oral corticosteroids in this study and no reported hospitalisations. One patient in the formoterol group took 12 reliever inhalations on one day, and further information is awaited from the sponsors as to whether this resulted in treatment with oral corticosteroids (as specified in the trial protocol). Three serious adverse events were reported for the budesonide/formoterol group (migraine, road traffic accident and hydatidiform molar pregnancy), compared to none in the formoterol group.

Secondary outcomes

Reliever inhaler use rose in both groups from baseline levels of 3.9 inhalations/week to 5.7 inhalations per week for budesonide/formoterol and from 3.2 to 5.9 inhalations/week for formoterol alone. The proportion of rescue free days was 52% and 56% respectively. These differences were not statistically significant.
There were no significant between group differences in morning or evening PEF, asthma symptom scores or asthma free days. FEV_1 increased from 102.4% to 104.2% predicted with budesonide/formoterol, in comparison to a fall from 99.5% to 99.2% predicted with formoterol. This represents a difference of 2.7% (0.7% to 4.7%), which is statistically significant but is of unproven clinical importance.

Budesonide/formoterol as reliever in asthma with ICS maintenance therapy

No trials were found (in adults or children) where ICS alone was used as maintenance therapy at the same dose in both arms of the trial, with budesonide/formoterol compared to $beta_2$-agonist alone as reliever.

Budesonide/formoterol as reliever in asthma with ICS and LABA maintenance therapy compared to terbutaline as reliever

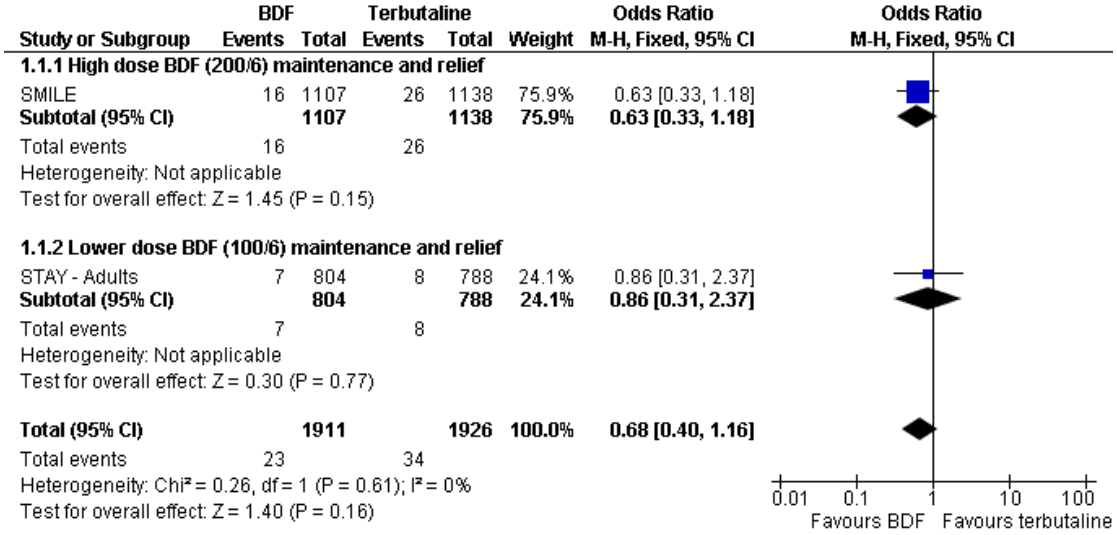
Adults

Two studies contribute to this comparison (SMILE; STAY - Adults). Both studies enrolled patients who were symptomatic on ICS and had a history of previous exacerbations. The SMILE study enrolled patients with a higher previous ICS intake (mean 755 mcg/day) and halved the ICS maintenance by using budesonide/formoterol 200/6 mcg twice daily and compared the same inhaler as reliever to formoterol and terbutaline. In contrast the patients in STAY - Adults had a lower dose of previous ICS (mean 660 mcg/day) and this was reduced by two thirds by using a lower dose of combined inhaler, budesonide/formoterol 100/6 mcg, as twice daily maintenance and reliever compared to the same maintenance with terbutaline reliever. The patients in SMILE had to remain symptomatic on budesonide/formoterol 200/6 mcg twice daily during the run-in period, whereas those in STAY - Adults had to be symptomatic on their previous ICS dosage without LABA.

Primary outcomes

The way that asthma exacerbations have been reported makes full assessment of our primary outcomes impossible without further information. A breakdown of the exacerbation data in both studies has been requested from the sponsors; they have provided information from STAY - Children in relation to the number of patients who had a hospitalisation that was asthma related and additional information from STAY - Adults on patients with one or more courses of oral corticosteroids has now been added. As data on serious adverse events that were asthma related is available from SMILE, we have used this data as a proxy for asthma exacerbations leading to hospital admission, (as almost all serious adverse events are classified as serious due to admission to hospital).
No data was directly available from SMILE in relation to asthma exacerbations leading to hospital admission. Moreover the proportion of severe asthma exacerbations recorded that led to a hospitalisation or ER visit is low in both studies; in SMILE one third of exacerbations fall in this category and in STAY - All ages the proportion is 13% of all severe exacerbations and 19% of those severe exacerbations needing medical intervention. The only current indication of the number of patients who were admitted to hospital for asthma in SMILE comes from asthma-related serious adverse events, of which there were 16 on budesonide/formoterol and 26 on terbutaline . The sponsors have provided hospitalisation data from STAY - All ages and there were seven on budesonide/formoterol and eight on terbutaline. This is a close match to the asthma-related serious adverse events, which yielded seven adults on budesonide/formoterol and nine on terbutaline in this category. The pooled results from both studies yield a combined Odds Ratio of 0.68 (95% CI 0.40 to 1.16), Figure 2.

Figure 2. Forest plot of comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), outcome: 1.1 Adults with an exacerbation causing hospitalisation.



Data on with an asthma exacerbation requiring oral corticosteroids was not originally reported for either study, but has been calculated for SMILE (from Table 2 in the paper publication), by subtracting the number of patients with a hospitalisation or ER visit from the total number that had a severe exacerbation. There was a significant reduction in adults treated with oral corticosteroids in SMILE, and data on this outcome has now been obtained from data on file at AstraZeneca in relation to STAY - Adults. The combined results from these two studies show a reduction in the number of patients needing oral corticosteroids with single inhaler therapy, Odds Ratio 0.54 (95% CI 0.44 to 0.65), Figure 3. This translates into a number needed to treat over 12 months of 15 (95% CI 13 to 21) in order to prevent one patient being treated with oral corticosteroids, Figure 4.

Figure 3. Forest plot of comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), outcome: 1.2 Adults with an exacerbation treated with oral corticosteroids.

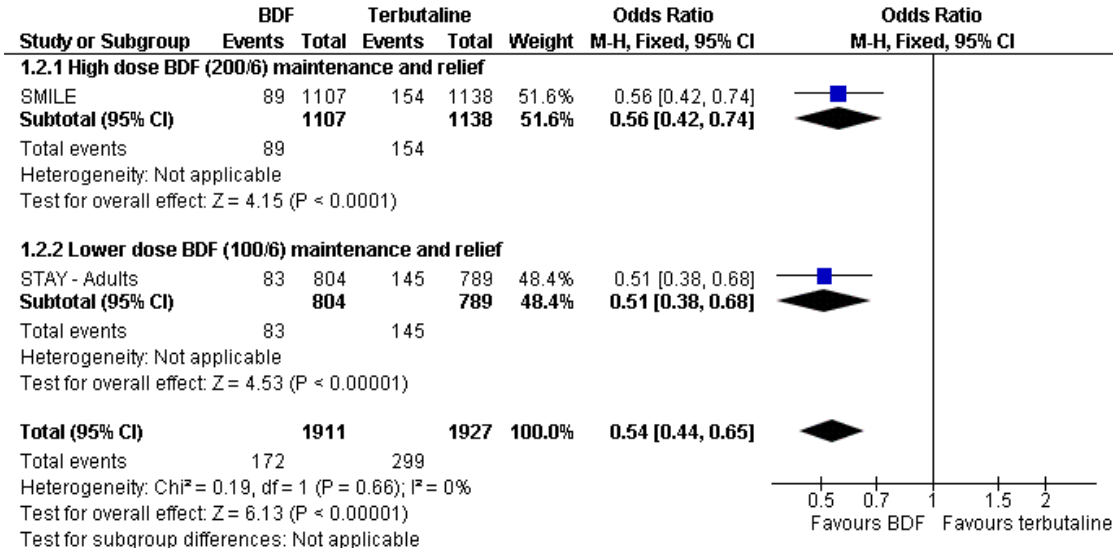
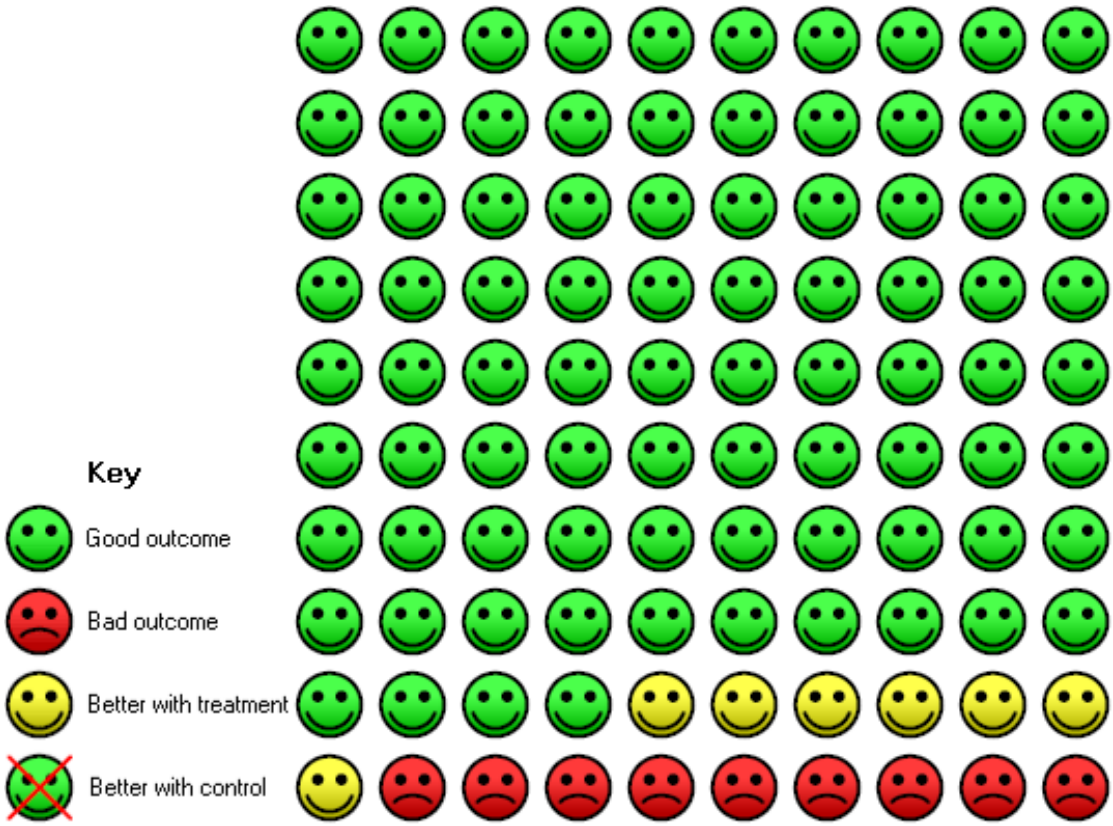


Figure 4. In the control group 16 people out of 100 had asthma exacerbation needing oral steroids over 12 months, compared to 9 (95% CI 8 to 11) out of 100 for the active treatment group using single inhaler therapy compared to terbutaline as reliever over 12 months. NNT(B) 15 (95% CI 13 to 21)



The combined data on adults with all cause serious adverse events from STAY - Adults and SMILE did not show a significant difference between budesonide/formoterol and terbutaline as reliever, Odds Ratio 1.04 (95% CI 0.79 to 1.36), Figure 5. There were four deaths in 1,940 patients on terbutaline from the two studies and one death in 1,914 patients on budesonide/formoterol, giving a pooled Odds Ratio of 0.34 (0.05 to 2.14) for all cause fatal serious adverse events, Figure 6. There were no patients recorded as having an asthma-related fatal event on budesonide/formoterol and one patient on terbutaline, Figure 7.

Figure 5. Forest plot of comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), outcome: 1.3 Adults with non-fatal Serious Adverse Events.

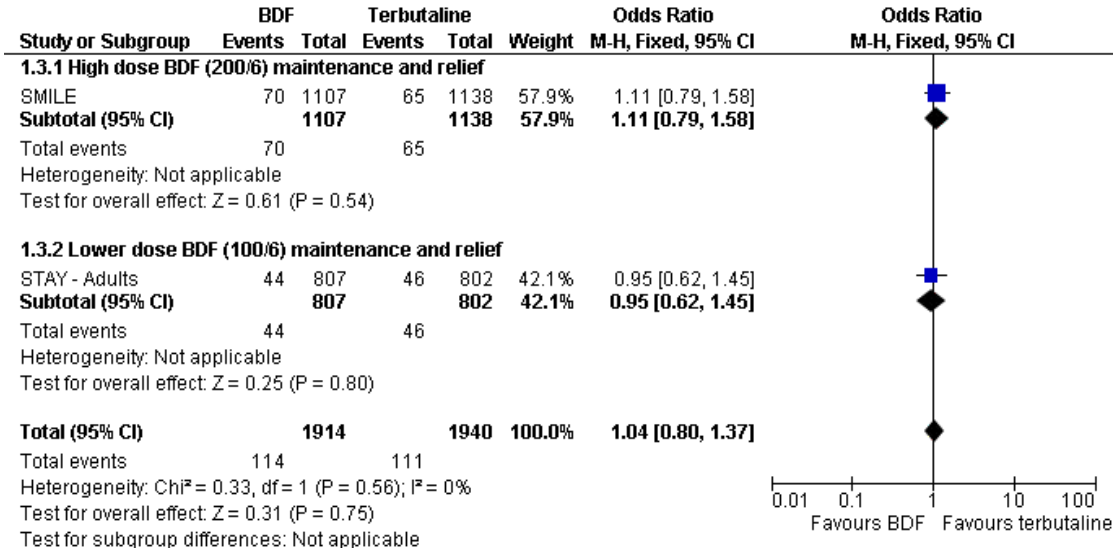


Figure 6. Forest plot of comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), outcome: 1.4 Adults with fatal serious adverse events.

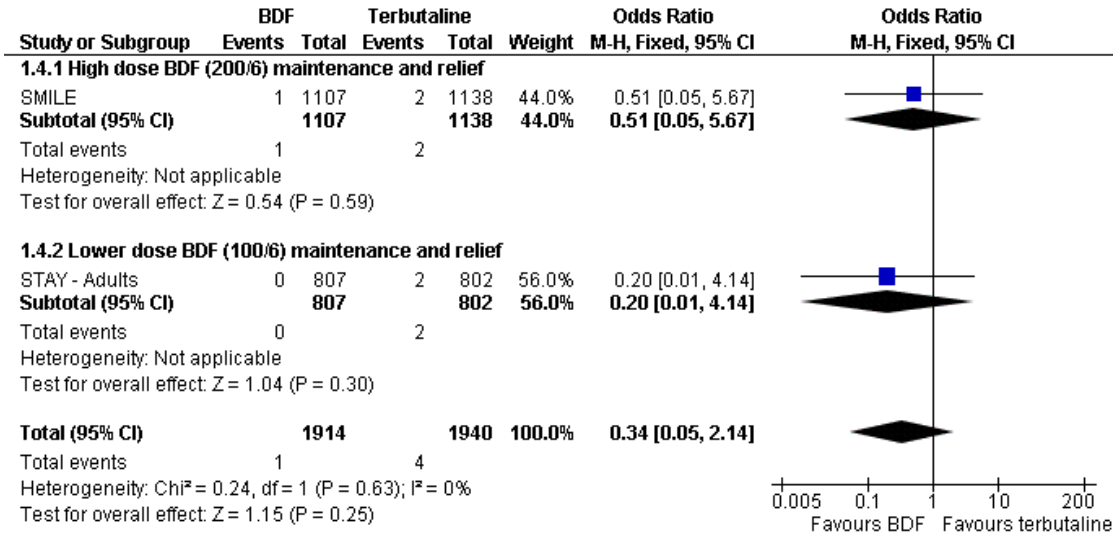
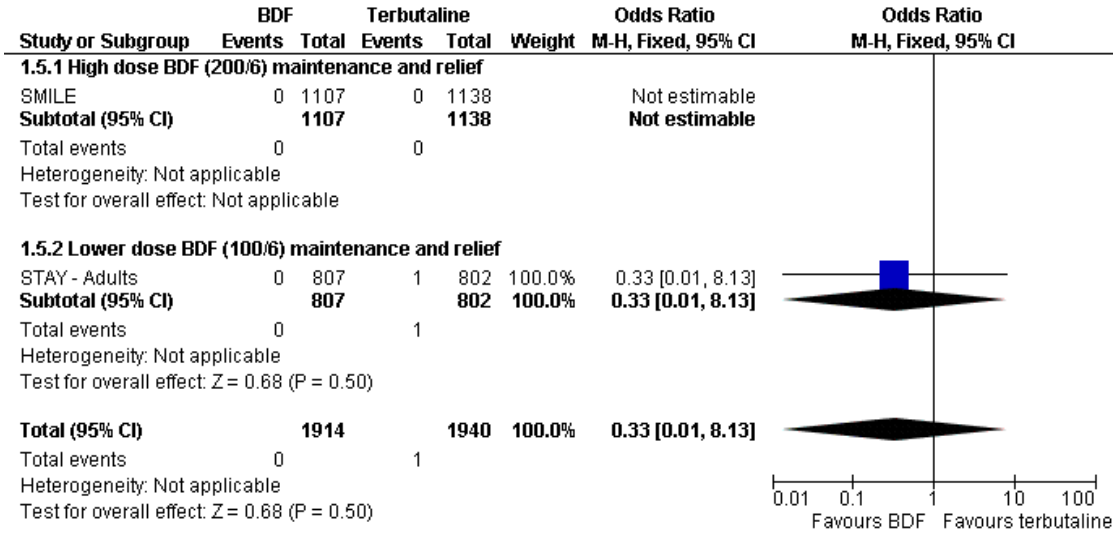


Figure 7. Forest plot of comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), outcome: 1.5 Adults with fatal serious adverse events related to asthma.



Secondary outcomes

The secondary outcomes were not reported separately for adults in STAY - Adults, so as 87% of the total population were adults and adolescents the combined data for all ages was used (STAY - All ages). With the exception of asthma control days (where no significant difference was seen), all the other secondary outcomes favoured budesonide/formoterol as reliever, but the differences were too small to be clinically significant. The pooled difference in FEV_1 for SMILE and STAY - All ages was 0.07 Litres (95% CI 0.05 to 0.09 Litres), Analysis 1.6, and morning peak flow showed a pooled difference of 7.88 Litres/min (95% CI 5.11 to 10.66), Analysis 1.7. The percentage of nights with awakenings fell from 20% in the run-in period to 9% on budesonide/formoterol reliever and 12% in fixed dose budesonide/formoterol with terbutaline reliever in STAY - All ages. Overall the pooled risk difference was -3.16% nights with awakenings (95% CI -4.64 to -1.69), Analysis 1.10.

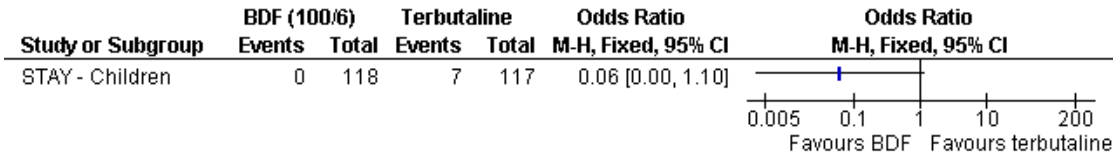
Children

One study included 341 children aged from four to 11 years old (STAY - Children). The children were randomised into three treatment arms, and for the purposes of this review those given budesonide/formoterol 100/6 mcg once daily (in the evening) with the same inhaler to use for relief of symptoms were compared to the same maintenance treatment with terbutaline for symptom relief. The definition of severe exacerbations requiring medical intervention in children was not the same as for adults in this study, but also included an increase in ICS use (via a separate inhaler) and/or additional treatment. Information has been requested from AstraZeneca in order to assess children who had exacerbation by the consequences; separate data on those who were admitted to hospital, attended casualty or received a course of oral steroids are required to do this, for the primary outcome analysis in this review. At present it has only been possible for AstraZeneca to provide data on hospitalisation for asthma.

Primary outcomes

Data provided by AstraZeneca confirmed that there were hospitalisations related to asthma in seven patients on the fixed-dose combination with terbutaline as reliever, but there were none in patients using budesonide/formoterol as reliever, Figure 8. In addition one child given terbutaline as reliever had an asthma-related SAE that did not lead to hospitalisation. This reduction in hospitalisation was large, Odds Ratio 0.06 (0.00 to 1.10) but the confidence interval includes the possibility that this could have arisen by chance (as the number of events was small).

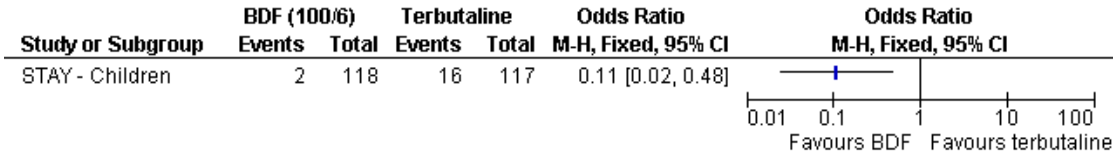
Figure 8. Forest plot of comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), outcome: 2.1 Children with an exacerbation causing hospitalisation.



The number of children with exacerbations requiring oral corticosteroids were not reported in the paper, although the number of days on treatment was less with budesonide/formoterol as reliever (32 versus 320 days, descriptive results only).

Children with serious adverse events of any cause were significantly less with budesonide/formoterol as reliever, (two events in contrast to 16 events with fixed dose budesonide/formoterol and terbutaline as reliever, odds ratio 0.11 (95% CI 0.02 to 0.48), Figure 9. No fatal events were reported in children. It should also be pointed out that the maintenance dose of budesonide/formoterol used with terbutaline as reliever was only 100/6 mcg daily, which the sponsors regard as an experimental dose and not approved for treatment.

Figure 9. Forest plot of comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), outcome: 2.3 Children with non-fatal Serious Adverse Events.



Secondary outcomes

In contrast to the adults, the improvements seen in lung function in this trial were not significant (Analysis 2.4; Analysis 2.5). The use of relievers fell significantly more in the group using budesonide/formoterol as reliever, from an average of 1.6 inhalations per day at baseline to 0.58 per day with budesonide/formoterol and 0.76 per day in the terbutaline reliever group, a reduction of -0.28 puffs per day (95% CI -0.54 to -0.02). Change in percentage nights with awakenings is reported as a significant reduction in the adjusted mean difference in favour of budesonide/formoterol. However this represents 2.4% nights with awakenings on budesonide/formoterol and 4.4% on terbutaline, and the baseline difference between groups is the same size (12.8% and 10.8% respectively), Analysis 2.7. Asthma control days (Analysis 2.8) and annual growth (Analysis 2.9), did not show significant differences between budesonide/formoterol and terbutaline.

Budesonide/formoterol as reliever in asthma with ICS and LABA maintenance therapy compared to formoterol as reliever

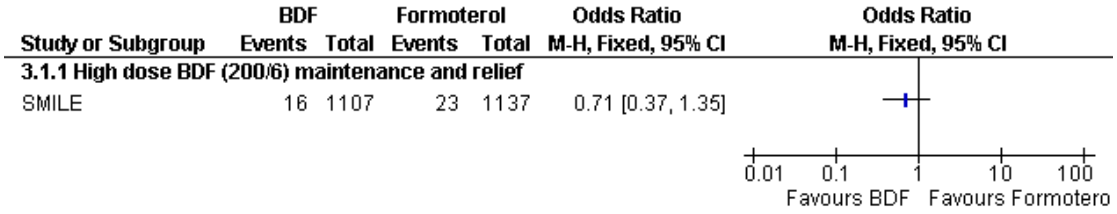
Only the SMILE study in adults contributed to this outcome, as budesonide/formoterol as reliever was compared to formoterol in one of the arms of this trial.

Primary outcomes

As there was no separate reporting of asthma exacerbations leading to hospitalisation in the paper, we used serious adverse events

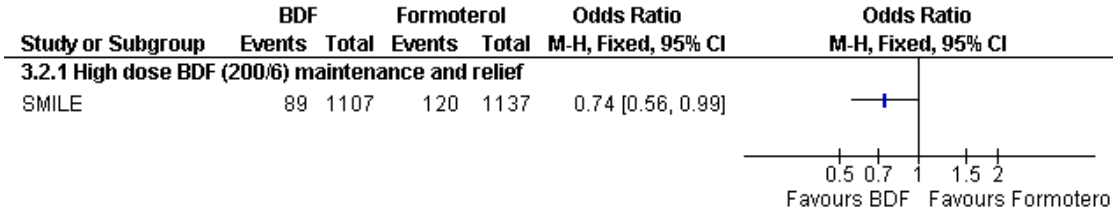
relating to asthma as a measure of hospitalisation. There were 16 patients in the budesonide/formoterol arm in comparison to 23 in the formoterol arm, odds ratio 0.71 (95% CI 0.37 to 1.35), Figure 10.

Figure 10. Forest plot of comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), outcome: 3.1 Adults with an exacerbation causing hospitalisation.



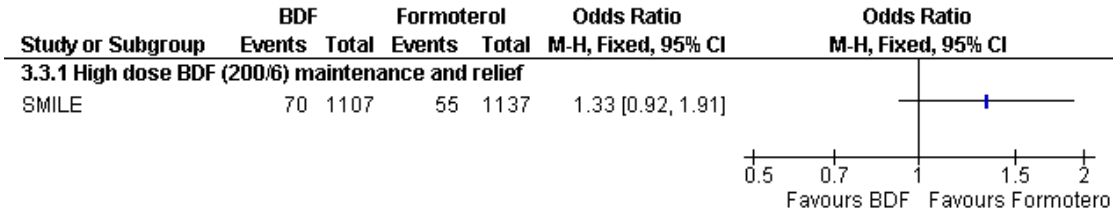
Asthma exacerbations requiring oral corticosteroids were not reported but could be calculated by subtracting the number of patients with admissions/ER visits from the total number with exacerbations. This represented a significant reduction using budesonide/formoterol as reliever from 120 to 89 patients, odds ratio 0.74 (95% CI 0.56 to 0.99), Figure 11 .

Figure 11. Forest plot of comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), outcome: 3.2 Adults with an exacerbation treated with oral corticosteroids.



Non-fatal serious adverse events relating from any cause were not significantly different, budesonide/formoterol 70 participants and formoterol 55 participants, odds ratio 1.33 (95% CI 0.92 to 1.91), Figure 12. There were was one fatal serious adverse event on budesonide/formoterol and one on formoterol, neither was reported as due to asthma.

Figure 12. Forest plot of comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), outcome: 3.3 Adults with non-fatal Serious Adverse Events.



Secondary outcomes

The results for lung function, reliever use and night awakenings were very similar to the findings when budesonide/formoterol was compared to terbutaline, with clinically small, but statistically significant advantages for budesonide/formoterol as reliever. *See* Analysis 3.6 to Analysis 3.10. Again the difference in asthma control days was not statistically significant Analysis 3.11.

There was no significant difference in annual growth in children using budesonide/formoterol reliever in comparison to terbutaline in STAY - Children.

DISCUSSION

Summary of main results

In patients with mild asthma who do not need maintenance treatment, no clinically important advantages of budesonide/formoterol as reliever were found in comparison to formoterol as reliever.

In the two studies on patients with more severe asthma, who had suffered a recent exacerbation in spite of quite high doses of inhaled corticosteroids, a lower maintenance ICS dose (in the form of regular budesonide/formoterol), and budesonide/formoterol as reliever was compared to formoterol or terbutaline as reliever. Hospital admissions make up a small proportion of those reported as having a severe asthma exacerbation, and the combined results yield a non-significant pooled odds ratio of 0.68 (95% CI 0.40 to 1.16). The use of oral corticosteroids was significantly lower in SMILE (both in comparison to formoterol or terbutaline as reliever), but comparative data from STAY - All ages are not currently available. Serious adverse events were not significantly different in adults, but in children there were significantly less serious adverse events in the group using budesonide/formoterol as maintenance and reliever, in comparison to those on budesonide/formoterol maintenance and terbutaline as reliever. However the maintenance dose of budesonide/formoterol used with terbutaline as reliever was only 100/6 mcg daily, which the sponsors regard as an experimental dose and not approved for treatment.

Overall completeness and applicability of evidence

The application of the results of SMILE, STAY - Adults and STAY - Children should be in the light of the patients enrolled in these trials, who all had suffered an asthma exacerbation in the past year, were not controlled on quite high doses of inhaled corticosteroids, and then were all treated with a lower dose of maintenance inhaled corticosteroid treatment. Data for our primary outcome were rarely available in a format usable for meta-analysis as dichotomous data, nor were exacerbation types sub-divided sufficiently to give a complete overview of exacerbations from the studies we included. There remains some uncertainty as to how complete our numerical analyses are.

Quality of the evidence

All the included studies were double blind. Although allocation concealment was not clearly reported, we concluded that the included studies were unlikely to have suffered from selection bias, as they were carried out by the sponsors for regulatory purposes.

Potential biases in the review process

Reporting of serious adverse events was not uniform across the studies, and the use of a composite outcome for exacerbations with no separate reporting of hospital admissions for asthma makes the possibility of publication bias a concern. A report on the manufacturer's controlled trial web site was only found for STAY - All ages and STAY - Children.

Agreements and disagreements with other studies or reviews

The use of budesonide/formoterol as a reliever therapy for asthma is subject to product license, and this is currently restricted; for example use as reliever is restricted to adults over 18 years in the British National Formulary (issue 55).

AUTHORS' CONCLUSIONS

Implications for practice

In mild asthma it is not yet known whether patients who use a budesonide/formoterol inhaler for relief of asthma symptoms derive any clinically important benefits. In more severe asthma, two studies enrolled patients who were not controlled on inhaled corticosteroids, and had suffered an exacerbation in the previous year, and then had their maintenance inhaled corticosteroids reduced in both arms of the study. Under these conditions the studies demonstrated a reduction in the risk of exacerbations that require oral corticosteroids with budesonide/formoterol for maintenance and relief in comparison with budesonide/formoterol for maintenance and terbutaline or formoterol for relief. The incidence of serious adverse events in children was also less using budesonide/formoterol for maintenance and relief in one study, which similarly enrolled children who were not controlled on inhaled corticosteroids, and who had their maintenance inhaled corticosteroids reduced at the start of the study. This study also compared an explorative maintenance dose of budesonide/formoterol that is not approved for treatment.

Implications for research

More research is needed in the use of budesonide/formoterol for symptom relief in patients with less severe asthma, particularly in those patients who take low doses of inhaled corticosteroids. Asthma exacerbations reporting should include patients with hospital admissions and those treated with oral corticosteroids, the composite of these outcomes, and transparent reporting of serious adverse events.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

SMILE

Methods	Study Design: Randomised, double-blind, parallel group study over a 12 month period in 289 centres in 20 countries (between April 2003 and Dec 2004)
Participants	Population: 3394 asthmatic adults aged 12 years or more with asthma previously on ICS and symptomatic on budesonide/formoterol 200/6 twice daily during 2 week run-in, with more than one exacerbation in the past year. The maintenance treatment was budesonide/formoterol for all patients and terbutaline, formoterol and budesonide/formoterol were compared as reliever therapy Adults Mean age: 42 years. FEV_1 **72%** predicted pre bronchodilator. Mean ICS dose at enrolment ***755*** mcg/day. Hospital admission for asthma in the past year: unknown proportion. Course of oral steroids for asthma in past year: unknown proportion Inclusion Criteria: Outpatients aged 12+ years, clinical diagnosis of asthma with ICS for at least 3 months, and steady dose for at least 4 weeks. More than one severe asthma exacerbation in the past 12 months was required. Prebronchodilator FEV_1 of 50-100% predicted normal value and at least 12% reversibility following Terbutaline. To be included patients had to need at rescue inhalations for 5 or more of the last 7 days of run-in. Adults using ten or more rescue inhalations in a single day or with oral steroid course during previous 4 weeks were not included
Interventions	1. Budesonide/formoterol **200/6 mcg twice daily [400 mcg budesonide/day],** and as needed (one maintenance and one relief Turbuhaler) 2. Budesonide/formoterol **200/6 mcg twice daily [400 mcg budesonide/day],** and Formoterol 6 mcg as needed (one maintenance and one relief Turbuhaler) 3. Budesonide/formoterol **200/6 mcg twice daily [400 mcg budesonide/day],** and Terbutaline 500 mcg as needed (one maintenance and one relief Turbuhaler) Maximum of 10 as needed inhalations could be used per day before contacting the investigator
Outcomes	Primary outcome - time to first severe exacerbations. Secondary outcomes included number of severe exacerbations, number of days with hospitalisation, ER room visit or both, and days of oral steroid use were recorded Exacerbation Definition: Severe - Deterioration in asthma requiring hospital or emergency room treatment, or oral steroids (for 3 days or more). Severe exacerbations did **not** include change in PEF . Mild exacerbation day - defined as PEF 80% or less of baseline this was the average of 10 days before randomisation, relief medication 2 or more inhalations above baseline, (not awakenings due to asthma). Mild exacerbation defined as 2 consecutive mild exacerbation days using the same criteria
Notes	SAE data given (70,55,65) of these (16,23,26) were related to asthma. Deaths given for whole trial (1,1,2) Funding source - AstraZeneca.
Risk of bias	

SMILE (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated by an independent person
Allocation concealment?	Unclear	At each centre, eligible patients were sequentially assigned a randomisation code by the investigator from the computer-generated list
Blinding? All outcomes	Yes	Double blind. All as-needed study medication was given by identical turbuhalers
Incomplete outcome data addressed? All outcomes	Yes	Withdrawals and Dropouts: 2989/3374 (**88%)** completed the study

SOMA

Methods	Study Design: Randomised, double-blind, parallel group study over 24 weeks. In the 14 days of run-in patients had to use a reliever on one to five of the last ten days to be eligible
Participants	Population: 92 asthmatic adults with intermittent mild asthma needing a maximum of two doses of reliever medication per week in the preceding months, with FeNO of at least 20 ppb at enrolment or randomisation. There was no maintenance treatment and formoterol and budesonide/formoterol were compared as reliever therapy Adults Mean age: 36 years. FEV_1 **101%** predicted pre bronchodilator. Mean ICS dose at enrolment ***zero*** mcg/day. Inclusion Criteria: Outpatients aged 15+ years, clinical diagnosis of asthma with no ICS for at least 3 months, and no regular maintenance treatment. Prebronchodilator FEV_1 of over 80% predicted normal value and at least 12% reversibility following terbutaline or salbutamol, or documented fall in FEV_1 of at least 12% after exercise. PEF had to demonstrate at least 15% variability in 2 or more days over 2 weeks, or 15% rise post bronchodilator. To be included patients had to need rescue inhalations for 1 to 5 of the last 10 days of run-in.
Interventions	1. Budesonide/formoterol 200/6 mcg twice as reliever (one Turbuhaler). No maintenance therapy 2. Formoterol 6 mcg as reliever (one Turbuhaler). No maintenance therapy Maximum of 12 as needed inhalations could be used per day before contacting the investigator. Patients taking maximum reliever were treated with oral prednisolone and removed from the study if more asthma medication was needed
Outcomes	Primary outcome - mean change in FeNO. Secondary outcomes included asthma symptom scores, asthma-free days, PEF, FEV_1 and number of inhalations of study drug. No mention is made with regard to courses of oral prednisolone in each group

SOMA (*Continued*)

Notes	SAE data given (0,3), none of these were related to asthma. Funding source - AstraZeneca.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation at each study centre was performed in balanced blocks using a computer programme
Allocation concealment?	Unclear	no details
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	77/93 (83%) completed the study

STAY - Adults

Methods	**Study Design**: Randomised, double-blind, parallel group study over a 12 month period in 246 centres in 22 countries (between Jan 2001 and Jan 2003). In the 14-18 day run-in patients used pre-study ICS with terbutaline for symptom relief (LABA had to be discontinued at least 3 days before run-in)
Participants	**Adult Population**: 2419 asthmatic adults aged 12 years or more with asthma uncontrolled on ICS (400-1000 mcg/day) and a history of at least one "clinically important" exacerbation in the past year. The maintenance ICS dose was cut to about one third with additional Budesonide/formoterol (SiT) compared to terbutaline for relief Adults Mean age: 40 years. FEV_1 **73%** predicted pre bronchodilator. Mean ICS dose at enrolment ***660*** mcg/day. Hospital admission for asthma in the past year: unknown proportion. Course of oral steroids for asthma in past year: unknown proportion Inclusion Criteria: Aged 12-80 years, with a constant dose of ICS (400-1000 mcg/day) at least 3 months. Prebronchodilator FEV_1 of 60-90% predicted normal value and at least 12% reversibility following Terbutaline. To be included patients had to need at least 12 rescue inhalations in the last 10 days of run-in. Adults using ten or more rescue inhalations in a single day or with an exacerbation during run-in were not randomised
Interventions	1. Budesonide/formoterol **100/6 mcg twice daily [200 mcg budesonide/day]** and as needed (one maintenance and one relief Turbuhaler) 2. Budesonide/formoterol **100/6 mcg twice daily [200 mcg budesonide/day]** and Terbutaline as needed (one maintenance and one relief Turbuhaler) 3. Budesonide 400 mcg **twice daily [800 mcg budesonide/day]** and Terbutaline as needed (one maintenance and one relief Turbuhaler) Maximum of 10 as needed inhalations could be used per day before contacting the investigator

STAY - Adults (*Continued*)

Outcomes	**Primary outcome** - time to first severe exacerbations. Secondary outcomes included number of severe exacerbations, time to mild exacerbations, number of mild exacerbations, symptom free days, QOL scores. No particular variable was chosen to assess safety **Exacerbation Definition**: Severe - Deterioration in asthma requiring hospital or emergency room treatment, or oral steroids (or other additional treatment) or morning PEF 70% or less of baseline on two consecutive days. ***Severe exacerbations requiring medical intervention were analysed separately*** . Mild exacerbation day - PEF 80% or less of baseline, relief medication 2 or more inhalations above baseline, or awakenings due to asthma. Mild exacerbation defined as 2 consecutive mild exacerbation days using the same criteria
Notes	**SAE data** (44,46,42) in the adult population; deaths given for whole trial (0,2,1)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation scheme
Allocation concealment?	Unclear	Eligible patients were randomised in balanced blocks by allocating patient numbers in consecutive order
Blinding? All outcomes	Yes	Double blind. All study medication was given by turbuhalers. Maintenance and as needed medication distinguished by the colour of the label and its wording
Incomplete outcome data addressed? All outcomes	Yes	Withdrawals and Dropouts: 2039/2419 (84%) completed the study

STAY - All ages

Methods	see STAY - Adults and STAY - children
Participants	Combined data on Children and Adults aged 4 to 60 years with a history of one or more exacerbations in the past year
Interventions	see STAY - Adults and STAY - children
Outcomes	see STAY - Adults and STAY - children
Notes	Data presented for adults and children. P values based on ANOVA and changes from baseline calculated from Tables 1 and 2 in the primary publication. Standard Errors estimated from P values

Risk of bias

STAY - All ages (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	see STAY - Adults and STAY - children
Allocation concealment?	Unclear	see STAY - Adults and STAY - children
Blinding? All outcomes	Yes	see STAY - Adults and STAY - children
Incomplete outcome data addressed? All outcomes	Yes	see STAY - Adults & STAY - children

STAY - Children

Methods	**Study Design**: Randomised, double-blind, parallel group study over a 12 month period in 41 centres in 12 countries (between Jan 2001 and Jan 2003). In the 14-18 day run-in patients used pre-study ICS with terbutaline for symptom relief (LABA had to be discontinued at least 3 days before run-in)
Participants	**Children in Study**: 341 asthmatic children aged 4-11 years with asthma uncontrolled on ICS (200-500 mcg/day) and a history of at least one "clinically important" exacerbation in the past year Mean age: 8 years. Mean morning PEF: 220 L/min. FEV_1 **76%** predicted pre bronchodilator. Mean ICS dose at enrolment **315** mcg/day. Hospital admission for asthma in the past year: unknown proportion. Course of oral steroids for asthma in past year: unknown proportion Inclusion Criteria: Aged 4-11 years, with a constant dose of ICS (200-500 mcg/day) at least 3 months. Prebronchodilator FEV_1 of 60-100% predicted normal value and at least 12% reversibility following Terbutaline. To be included patients had to need at least **8 rescue inhalations** in the last 10 days of run-in. Children using seven or more rescue inhalations in a single day or with an exacerbation during run-in were not randomised
Interventions	1. Budesonide **100** mcg (80 mcg delivered dose) and Formoterol 4.5 mcg **in the evening** and as needed (one maintenance and one relief Turbuhaler) 2. Budesonide **100** mcg (80 mcg delivered dose) and Formoterol 4.5 mcg **in the evening** and Terbutaline as needed (one maintenance and one relief Turbuhaler) 3. Budesonide **400** mcg (320 mcg delivered dose) **in the evening** and Terbutaline as needed (one maintenance and one relief Turbuhaler)
Outcomes	**Primary outcome** - time to first severe exacerbations. Secondary outcomes included number of severe exacerbations, time to mild exacerbations, number of mild exacerbations, symptom free days, QOL scores. No particular variable was chosen to assess safety Exacerbation Definition: Severe - Deterioration in asthma requiring hospital or emergency room treatment, or oral steroids (**or an increase in ICS or other additional treatment**) or morning PEF 70% or less of baseline on two consecutive days. ***Severe exacerbations requiring medical intervention were analysed separately*** . Mild exacerbation day - PEF 80% or less of baseline, relief medication 2 or more inhalations above baseline, or awakenings due to asthma. Mild exacerbation defined as 2 consecutive mild

STAY - Children (*Continued*)

	exacerbation days using the same criteria
Notes	Adverse Events:SAE data given (2,16,5) of these (0,7,2) were related to asthma. Change from baseline nights with awakenings were the same in both groups, P value in the paper not used as it related to post treatment levels not changes. No SD data published in the paper with respect to growth comparing budesonide/formoterol to Terbutaline as reliever, so SD calculated from the other comparisons presented

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation scheme
Allocation concealment?	Unclear	Eligible patients were randomised in balanced blocks by allocating patient numbers in consecutive order
Blinding? All outcomes	Yes	Double blind. All study medication was given by turbuhalers. Maintenance and as needed medication distinguished by the colour of the label and its wording
Incomplete outcome data addressed? All outcomes	Yes	309/341 (91%) completed the study

FEV1: Forced expiratory volume in one second
ICS: Inhaled corticosteroids
LABA: Long acting beta-agonist
PEF: Peak expiratory flow
SAE: Serious Adverse Event
SD: Standard deviation

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

Study	Reason for exclusion
Balanzat 2004	Overview of three existing trials
Bousquet 2007	Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone
COMPASS	Different doses of Symbicort used for maintenance

(*Continued*)

COSMOS	Different maintenance regimen in each arm
D5890C00003	SiT compared to higher dose maintenance regimen
Ind 2002	Formoterol v Terbutaline as reliever
Jenkins 2007	budesonide/formoterol dose adjustment with FeNO (not used as reliever)
Jonkers 2006	Single dose study
Loukides 2005	Maintenance with symbicort 200/6 mcg bd in SiT group and Budesonide 200 mcg with Formoterol 12 mg bd with formoterol reliever
Lundborg 2006	Higher dose maintenance therapy in the arm using formoterol as reliever
MONO	SiT compared to conventional best treatment
NCT00235911	Comparison of SiT with usual care
NCT00252863	SiT compared to current best practice
Richter 2007	Formoterol not combination therapy as reliever
Riemersma 2008	SiT compared to usual care
SALTO	SiT compared to conventional best practice
Scicchitano 2004	SiT compared to higher dose budesonide
SOLO	SiT compared to conventional best practice (different maintenance regimen)
Sovani 2008	SiT compared to budesonide (different maintenance regimen)
Stallberg 2008	SiT compared to adjustable maintenance separate budesonide and formoterol inhalers or higher dose combination budesonide/formoterol inhaler
STEAM	SiT compared to higher dose maintenance therapy
STYLE	SiT compared to conventional best practice
Tattersfield 2001	Formoterol versus Terbutaline as reliever

bd: twice daily
FeNO:- exhaled nitric oxide
SiT: Single inhaler therapy

DATA AND ANALYSES

Comparison 1. BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adults with an exacerbation causing hospitalisation	2	3837	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.16]
1.1 High dose BDF (200/6) maintenance and relief	1	2245	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.33, 1.18]
1.2 Lower dose BDF (100/6) maintenance and relief	1	1592	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.31, 2.37]
2 Adults with an exacerbation treated with oral corticosteroids	2	3838	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.44, 0.65]
2.1 High dose BDF (200/6) maintenance and relief	1	2245	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.42, 0.74]
2.2 Lower dose BDF (100/6) maintenance and relief	1	1593	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.38, 0.68]
3 Adults with non-fatal Serious Adverse Events	2	3854	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.80, 1.37]
3.1 High dose BDF (200/6) maintenance and relief	1	2245	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.79, 1.58]
3.2 Lower dose BDF (100/6) maintenance and relief	1	1609	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.62, 1.45]
4 Adults with fatal serious adverse events	2	3854	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.05, 2.14]
4.1 High dose BDF (200/6) maintenance and relief	1	2245	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.67]
4.2 Lower dose BDF (100/6) maintenance and relief	1	1609	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.14]
5 Adults with fatal serious adverse events related to asthma	2	3854	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.13]
5.1 High dose BDF (200/6) maintenance and relief	1	2245	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Lower dose BDF (100/6) maintenance and relief	1	1609	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.13]
6 FEV1 (Change from baseline) Litres	2	3844	Mean Difference (Fixed, 95% CI)	0.07 [0.05, 0.09]
6.1 High dose BDF (200/6) maintenance and relief	1	2245	Mean Difference (Fixed, 95% CI)	0.08 [0.05, 0.11]
6.2 Low dose BDF (100/6) maintenance and relief	1	1599	Mean Difference (Fixed, 95% CI)	0.05 [0.02, 0.08]
7 Morning Peak Flow (Change from baseline) L/min	2	3844	Mean Difference (Fixed, 95% CI)	7.88 [5.11, 10.66]
7.1 High dose BDF (200/6) maintenance and relief	1	2245	Mean Difference (Fixed, 95% CI)	7.5 [4.28, 10.72]
7.2 Low dose BDF (100/6) maintenance and relief	1	1599	Mean Difference (Fixed, 95% CI)	9.0 [3.51, 14.49]

8 Evening Peak Flow (Change from baseline) L/min	2	3844	Mean Difference (Fixed, 95% CI)	7.17 [4.31, 10.03]
8.1 High dose BDF (200/6) maintenance and relief	1	2245	Mean Difference (Fixed, 95% CI)	6.30 [3.13, 9.47]
8.2 Low dose BDF (100/6) maintenance and relief	1	1599	Mean Difference (Fixed, 95% CI)	11.0 [4.34, 17.66]
9 Change in reliever use (puffs per 24 hours)	2	4079	Mean Difference (Fixed, 95% CI)	-0.21 [-0.28, -0.14]
9.1 High dose BDF (200/6) maintenance and relief	1	2245	Mean Difference (Fixed, 95% CI)	-0.2 [-0.28, -0.12]
9.2 Low dose BDF (100/6) maintenance and relief	1	1834	Mean Difference (Fixed, 95% CI)	-0.24 [-0.39, -0.09]
10 Change in % nights with awakenings	2	4079	Mean Difference (Fixed, 95% CI)	-3.16 [-4.64, -1.69]
10.1 High dose BDF (200/6) maintenance and relief	1	2245	Mean Difference (Fixed, 95% CI)	-2.6 [-4.28, -0.92]
10.2 Low dose BDF (100/6) maintenance and relief	1	1834	Mean Difference (Fixed, 95% CI)	-5.0 [-8.04, -1.96]
11 Change in % Asthma Control Days	2	4079	Mean Difference (Fixed, 95% CI)	1.91 [-0.58, 4.40]
11.1 High dose BDF (200/6) maintenance and relief	1	2245	Mean Difference (Fixed, 95% CI)	1.9 [-0.72, 4.52]
11.2 Low dose BDF (100/6) maintenance and relief	1	1834	Mean Difference (Fixed, 95% CI)	2.0 [-5.84, 9.84]

Comparison 2. BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Children with an exacerbation causing hospitalisation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Children with non-fatal Serious Adverse Events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 FEV1 (Change from baseline) Litres	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4 Morning Peak Flow (Change from baseline) L/min	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5 Evening Peak Flow (Change from baseline) L/min	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 Change in reliever use (puffs per 24 hours)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 Change in % nights with awakenings	1		Mean Difference (Fixed, 95% CI)	Totals not selected
8 Change in % Asthma Control Days	1		Mean Difference (Fixed, 95% CI)	Totals not selected
9 Annual Height Gain (cms)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adults with an exacerbation causing hospitalisation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 High dose BDF (200/6) maintenance and relief	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Adults with an exacerbation treated with oral corticosteroids	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 High dose BDF (200/6) maintenance and relief	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Adults with non-fatal Serious Adverse Events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 High dose BDF (200/6) maintenance and relief	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Adults with fatal serious adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 High dose BDF (200/6) maintenance and relief	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Adults with fatal serious adverse events related to asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 High dose BDF (200/6) maintenance and relief	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6 FEV1 (Change from baseline) Litres	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6.1 High dose BDF (200/6) maintenance and relief	1		Mean Difference (Fixed, 95% CI)	Not estimable
7 Morning Peak Flow (Change from baseline) L/min	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7.1 High dose BDF (200/6) maintenance and relief	1		Mean Difference (Fixed, 95% CI)	Not estimable
8 Evening Peak Flow (Change from baseline) L/min	1		Mean Difference (Fixed, 95% CI)	Totals not selected
8.1 High dose BDF (200/6) maintenance and relief	1		Mean Difference (Fixed, 95% CI)	Not estimable
9 Change in reliever use (puffs per 24 hours)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
9.1 High dose BDF (200/6) maintenance and relief	1		Mean Difference (Fixed, 95% CI)	Not estimable
10 Change in nights with awakenings (%)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
10.1 High dose BDF (200/6) maintenance and relief	1		Mean Difference (Fixed, 95% CI)	Not estimable
11 Change in Asthma Control Days (%)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
11.1 High dose BDF (200/6) maintenance and relief	1		Mean Difference (Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 1 Adults with an exacerbation causing hospitalisation.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 1 Adults with an exacerbation causing hospitalisation

Study or subgroup	BDF n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	16/1107	26/1138		75.9 %	0.63 [0.33, 1.18]
Subtotal (95% CI)	**1107**	**1138**		**75.9 %**	**0.63 [0.33, 1.18]**
Total events: 16 (BDF), 26 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
2 Lower dose BDF (100/6) maintenance and relief					
STAY - Adults	7/804	8/788		24.1 %	0.86 [0.31, 2.37]
Subtotal (95% CI)	**804**	**788**		**24.1 %**	**0.86 [0.31, 2.37]**
Total events: 7 (BDF), 8 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.77)					
Total (95% CI)	**1911**	**1926**		**100.0 %**	**0.68 [0.40, 1.16]**
Total events: 23 (BDF), 34 (Terbutaline)					
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.40 (P = 0.16)					

Analysis 1.2. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 2 Adults with an exacerbation treated with oral corticosteroids.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 2 Adults with an exacerbation treated with oral corticosteroids

Study or subgroup	BDF n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	89/1107	154/1138		51.6 %	0.56 [0.42, 0.74]
Subtotal (95% CI)	**1107**	**1138**		**51.6 %**	**0.56 [0.42, 0.74]**
Total events: 89 (BDF), 154 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.15 (P = 0.000034)					
2 Lower dose BDF (100/6) maintenance and relief					
STAY - Adults	83/804	145/789		48.4 %	0.51 [0.38, 0.68]
Subtotal (95% CI)	**804**	**789**		**48.4 %**	**0.51 [0.38, 0.68]**
Total events: 83 (BDF), 145 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.53 (P < 0.00001)					
Total (95% CI)	**1911**	**1927**		**100.0 %**	**0.54 [0.44, 0.65]**
Total events: 172 (BDF), 299 (Terbutaline)					
Heterogeneity: Chi^2 = 0.19, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 6.13 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

Analysis 1.3. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 3 Adults with non-fatal Serious Adverse Events.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 3 Adults with non-fatal Serious Adverse Events

Study or subgroup	BDF n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	70/1107	65/1138		57.9 %	1.11 [0.79, 1.58]
Subtotal (95% CI)	**1107**	**1138**		**57.9 %**	**1.11 [0.79, 1.58]**
Total events: 70 (BDF), 65 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 Lower dose BDF (100/6) maintenance and relief					
STAY - Adults	44/807	46/802		42.1 %	0.95 [0.62, 1.45]
Subtotal (95% CI)	**807**	**802**		**42.1 %**	**0.95 [0.62, 1.45]**
Total events: 44 (BDF), 46 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Total (95% CI)	**1914**	**1940**		**100.0 %**	**1.04 [0.80, 1.37]**
Total events: 114 (BDF), 111 (Terbutaline)					
Heterogeneity: Chi^2 = 0.33, df = 1 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.31 (P = 0.75)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

Analysis 1.4. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 4 Adults with fatal serious adverse events.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 4 Adults with fatal serious adverse events

Study or subgroup	BDF n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	1/1107	2/1138		44.0 %	0.51 [0.05, 5.67]
Subtotal (95% CI)	**1107**	**1138**		**44.0 %**	**0.51 [0.05, 5.67]**
Total events: 1 (BDF), 2 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
2 Lower dose BDF (100/6) maintenance and relief					
STAY - Adults	0/807	2/802		56.0 %	0.20 [0.01, 4.14]
Subtotal (95% CI)	**807**	**802**		**56.0 %**	**0.20 [0.01, 4.14]**
Total events: 0 (BDF), 2 (Terbutaline)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
Total (95% CI)	**1914**	**1940**		**100.0 %**	**0.34 [0.05, 2.14]**
Total events: 1 (BDF), 4 (Terbutaline)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					

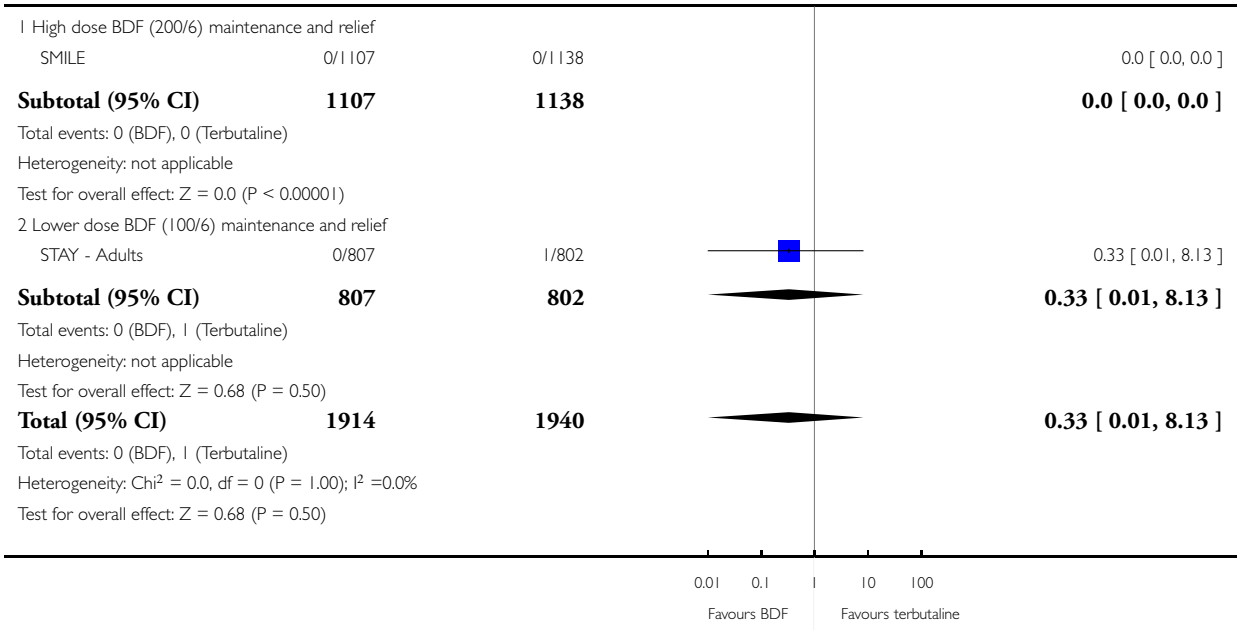
Analysis 1.5. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 5 Adults with fatal serious adverse events related to asthma.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 5 Adults with fatal serious adverse events related to asthma

Study or subgroup	BDF n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief				
SMILE	0/1107	0/1138		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1107**	**1138**		**0.0 [0.0, 0.0]**
Total events: 0 (BDF), 0 (Terbutaline)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Lower dose BDF (100/6) maintenance and relief				
STAY - Adults	0/807	1/802		0.33 [0.01, 8.13]
Subtotal (95% CI)	**807**	**802**		**0.33 [0.01, 8.13]**
Total events: 0 (BDF), 1 (Terbutaline)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.68 (P = 0.50)				
Total (95% CI)	**1914**	**1940**		**0.33 [0.01, 8.13]**
Total events: 0 (BDF), 1 (Terbutaline)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.68 (P = 0.50)				



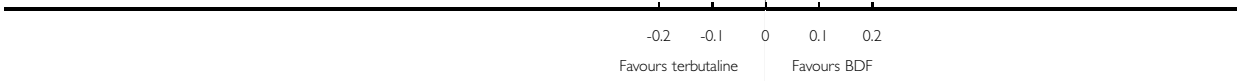
Analysis 1.6. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 6 FEV1 (Change from baseline) Litres.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 6 FEV1 (Change from baseline) Litres

Study or subgroup	BDF N	Terbutaline N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief						
SMILE	1107	1138	0.08 (0.013)		58.1 %	0.08 [0.05, 0.11]
Subtotal (95% CI)					**58.1 %**	**0.08 [0.05, 0.11]**
Heterogeneity: not applicable						
Test for overall effect: Z = 6.15 (P < 0.00001)						
2 Low dose BDF (100/6) maintenance and relief						
STAY - All ages	807	792	0.05 (0.0153)		41.9 %	0.05 [0.02, 0.08]
Subtotal (95% CI)					**41.9 %**	**0.05 [0.02, 0.08]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.27 (P = 0.0011)						
Total (95% CI)					**100.0 %**	**0.07 [0.05, 0.09]**
Heterogeneity: Chi^2 = 2.23, df = 1 (P = 0.14); I^2 =55%						
Test for overall effect: Z = 6.81 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 2.23, df = 1 (P = 0.14), I^2 =55%						



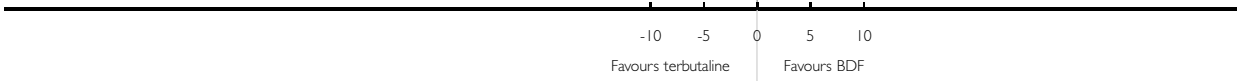
Analysis 1.7. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 7 Morning Peak Flow (Change from baseline) L/min.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 7 Morning Peak Flow (Change from baseline) L/min

Study or subgroup	BDF N	Terbutaline N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief						
SMILE	1107	1138	7.5 (1.642)		74.4 %	7.50 [4.28, 10.72]
Subtotal (95% CI)					**74.4 %**	**7.50 [4.28, 10.72]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.57 (P < 0.00001)						
2 Low dose BDF (100/6) maintenance and relief						
STAY - All ages	807	792	9 (2.8)		25.6 %	9.00 [3.51, 14.49]
Subtotal (95% CI)					**25.6 %**	**9.00 [3.51, 14.49]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.21 (P = 0.0013)						
Total (95% CI)					**100.0 %**	**7.88 [5.11, 10.66]**
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.64); I^2 =0.0%						
Test for overall effect: Z = 5.57 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 0.21, df = 1 (P = 0.64), I^2 =0.0%						



Analysis 1.8. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 8 Evening Peak Flow (Change from baseline) L/min.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 8 Evening Peak Flow (Change from baseline) L/min

Study or subgroup	BDF N	Terbutaline N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief						
SMILE	1107	1138	6.3 (1.616)		81.6 %	6.30 [3.13, 9.47]
Subtotal (95% CI)					**81.6 %**	**6.30 [3.13, 9.47]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.90 (P = 0.000097)						
2 Low dose BDF (100/6) maintenance and relief						
STAY - All ages	807	792	11 (3.4)		18.4 %	11.00 [4.34, 17.66]
Subtotal (95% CI)					**18.4 %**	**11.00 [4.34, 17.66]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.24 (P = 0.0012)						
Total (95% CI)					**100.0 %**	**7.17 [4.31, 10.03]**
Heterogeneity: Chi^2 = 1.56, df = 1 (P = 0.21); I^2 =36%						
Test for overall effect: Z = 4.91 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 1.56, df = 1 (P = 0.21), I^2 =36%						

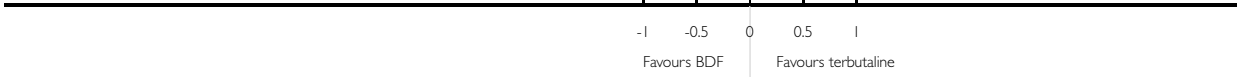
Analysis 1.9. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 9 Change in reliever use (puffs per 24 hours).

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 9 Change in reliever use (puffs per 24 hours)

Study or subgroup	BDF N	Terbutaline N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief						
SMILE	1107	1138	-0.2 (0.0429)		75.3 %	-0.20 [-0.28, -0.12]
Subtotal (95% CI)					**75.3 %**	**-0.20 [-0.28, -0.12]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.66 (P < 0.00001)						
2 Low dose BDF (100/6) maintenance and relief						
STAY - All ages	925	909	-0.24 (0.075)		24.7 %	-0.24 [-0.39, -0.09]
Subtotal (95% CI)					**24.7 %**	**-0.24 [-0.39, -0.09]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.20 (P = 0.0014)						
Total (95% CI)					**100.0 %**	**-0.21 [-0.28, -0.14]**
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.64); I^2 =0.0%						
Test for overall effect: Z = 5.64 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 0.21, df = 1 (P = 0.64), I^2 =0.0%						



Analysis 1.10. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 10 Change in % nights with awakenings.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 10 Change in % nights with awakenings

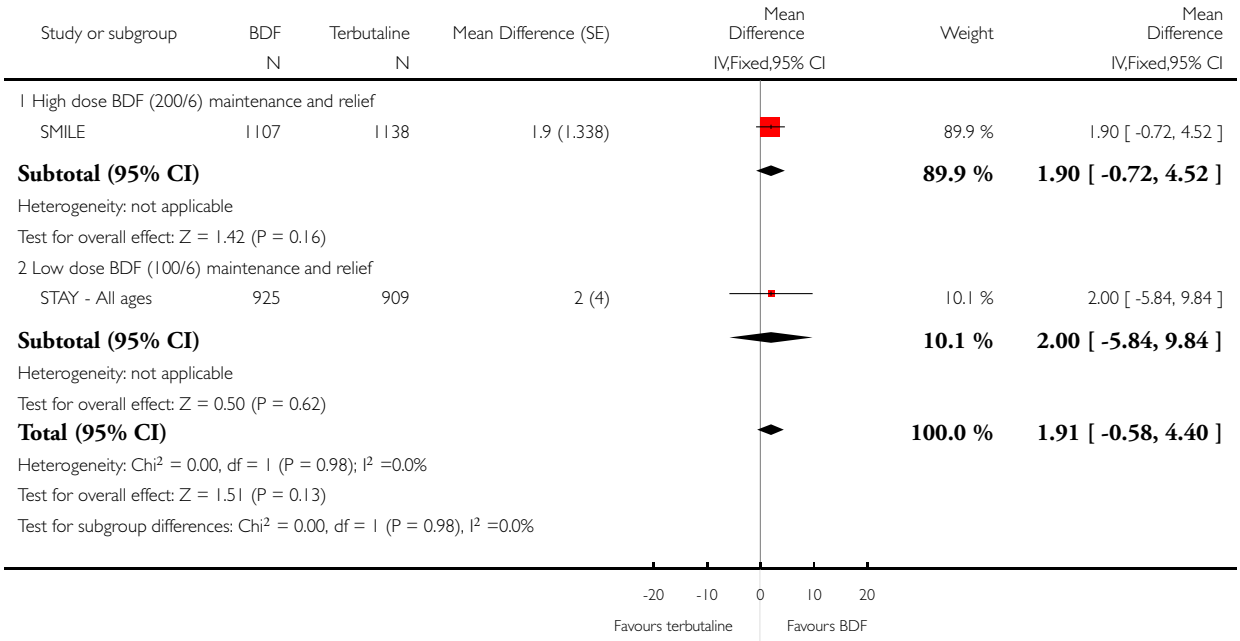
Study or subgroup	BDF N	Terbutaline N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief						
SMILE	1107	1138	-2.6 (0.859)		76.5 %	-2.60 [-4.28, -0.92]
Subtotal (95% CI)					**76.5 %**	**-2.60 [-4.28, -0.92]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.03 (P = 0.0025)						
2 Low dose BDF (100/6) maintenance and relief						
STAY - All ages	925	909	-5 (1.55)		23.5 %	-5.00 [-8.04, -1.96]
Subtotal (95% CI)					**23.5 %**	**-5.00 [-8.04, -1.96]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.23 (P = 0.0013)						
Total (95% CI)					**100.0 %**	**-3.16 [-4.64, -1.69]**
Heterogeneity: Chi^2 = 1.83, df = 1 (P = 0.18); I^2 =45%						
Test for overall effect: Z = 4.21 (P = 0.000025)						
Test for subgroup differences: Chi^2 = 1.83, df = 1 (P = 0.18), I^2 =45%						

Analysis 1.11. Comparison 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance), Outcome 11 Change in % Asthma Control Days.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 1 BDF versus Terbutaline as reliever (Adults with BDF maintenance)

Outcome: 11 Change in % Asthma Control Days

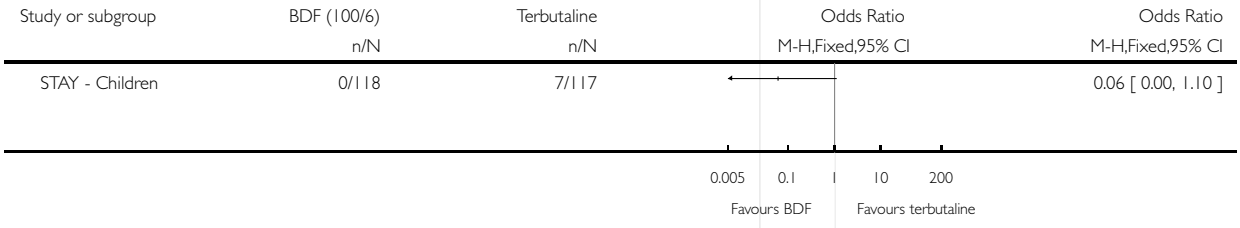


Analysis 2.1. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 1 Children with an exacerbation causing hospitalisation.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 1 Children with an exacerbation causing hospitalisation



Analysis 2.2. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 2 Children with non-fatal Serious Adverse Events.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 2 Children with non-fatal Serious Adverse Events

Study or subgroup	BDF (100/6) n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
STAY - Children	2/118	16/117		0.11 [0.02, 0.48]

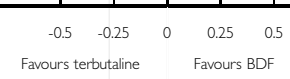
Analysis 2.3. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 3 FEV1 (Change from baseline) Litres.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 3 FEV1 (Change from baseline) Litres

Study or subgroup	BDF N	Terbutaline N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
STAY - Children	118	117	0.06 (0.035)		0.06 [-0.01, 0.13]



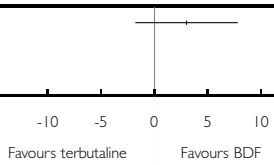
Analysis 2.4. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 4 Morning Peak Flow (Change from baseline) L/min.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 4 Morning Peak Flow (Change from baseline) L/min

Study or subgroup	BDF N	Terbutaline N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
STAY - Children	118	117	3 (2.45)		3.00 [-1.80, 7.80]



Analysis 2.5. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 5 Evening Peak Flow (Change from baseline) L/min.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 5 Evening Peak Flow (Change from baseline) L/min

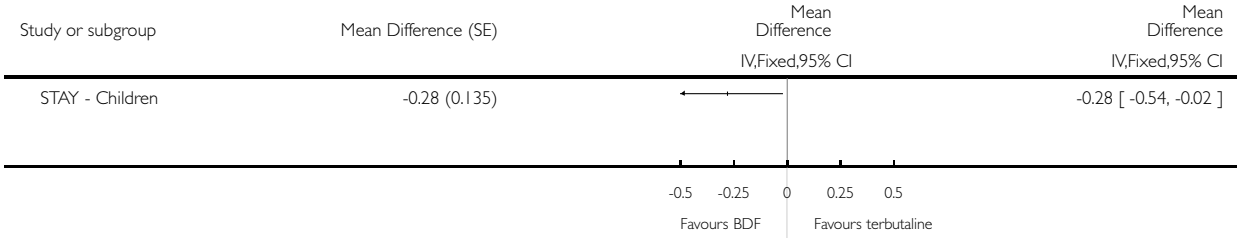
Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
STAY - Children	3 (2.25)		3.00 [-1.41, 7.41]

Analysis 2.6. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 6 Change in reliever use (puffs per 24 hours).

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 6 Change in reliever use (puffs per 24 hours)

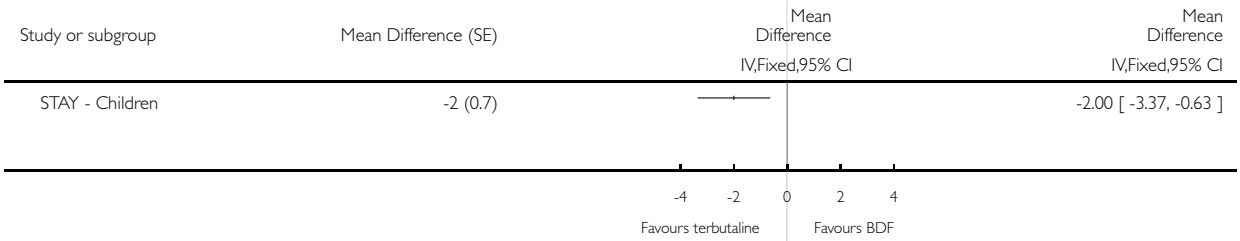


Analysis 2.7. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 7 Change in % nights with awakenings.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 7 Change in % nights with awakenings

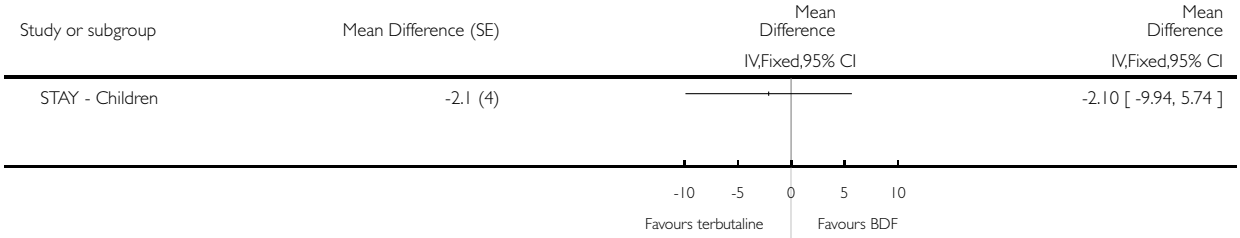


Analysis 2.8. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 8 Change in % Asthma Control Days.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 8 Change in % Asthma Control Days

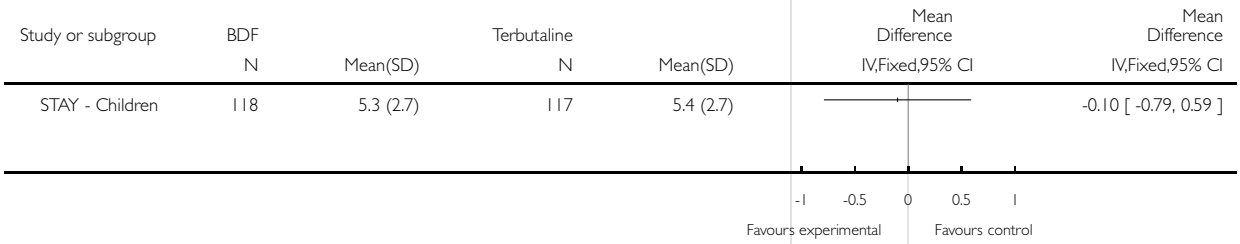


Analysis 2.9. Comparison 2 BDF versus Terbutaline as reliever (Children with BDF maintenance), Outcome 9 Annual Height Gain (cms).

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 2 BDF versus Terbutaline as reliever (Children with BDF maintenance)

Outcome: 9 Annual Height Gain (cms)



Analysis 3.1. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 1 Adults with an exacerbation causing hospitalisation.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 1 Adults with an exacerbation causing hospitalisation

Study or subgroup	BDF n/N	Formoterol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief				
SMILE	16/1107	23/1137		0.71 [0.37, 1.35]

Analysis 3.2. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 2 Adults with an exacerbation treated with oral corticosteroids.

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 2 Adults with an exacerbation treated with oral corticosteroids

Study or subgroup	BDF n/N	Formoterol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief				
SMILE	89/1107	120/1137		0.74 [0.56, 0.99]

Analysis 3.3. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 3 Adults with non-fatal Serious Adverse Events.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 3 Adults with non-fatal Serious Adverse Events

Study or subgroup	BDF n/N	Formoterol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief				
SMILE	70/1107	55/1137		1.33 [0.92, 1.91]

Analysis 3.4. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 4 Adults with fatal serious adverse events.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 4 Adults with fatal serious adverse events

Study or subgroup	BDF n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief				
SMILE	1/1107	1/1138		1.03 [0.06, 16.46]

Analysis 3.5. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 5 Adults with fatal serious adverse events related to asthma.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 5 Adults with fatal serious adverse events related to asthma

Study or subgroup	BDF n/N	Terbutaline n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief				
SMILE	0/1107	0/1138		0.0 [0.0, 0.0]

Analysis 3.6. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 6 FEV1 (Change from baseline) Litres.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 6 FEV1 (Change from baseline) Litres

Study or subgroup	BDF N	Formoterol N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	1107	1137	0.05 (0.015)		0.05 [0.02, 0.08]

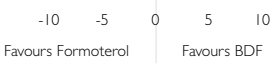
Analysis 3.7. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 7 Morning Peak Flow (Change from baseline) L/min.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 7 Morning Peak Flow (Change from baseline) L/min

Study or subgroup	BDF N	Formoterol N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	1107	1137	4.8 (1.641)		4.80 [1.58, 8.02]



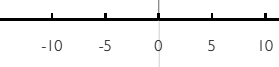
Analysis 3.8. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 8 Evening Peak Flow (Change from baseline) L/min.

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 8 Evening Peak Flow (Change from baseline) L/min

Study or subgroup	BDF N	Formoterol N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	1107	1137	5.4 (1.641)		5.40 [2.18, 8.62]



Analysis 3.9. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 9 Change in reliever use (puffs per 24 hours).

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 9 Change in reliever use (puffs per 24 hours)

Study or subgroup	BDF N	Formoterol N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	1107	1137	-0.17 (0.0429)		-0.17 [-0.25, -0.09]

Analysis 3.10. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 10 Change in nights with awakenings (%).

Review: Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 10 Change in nights with awakenings (%)

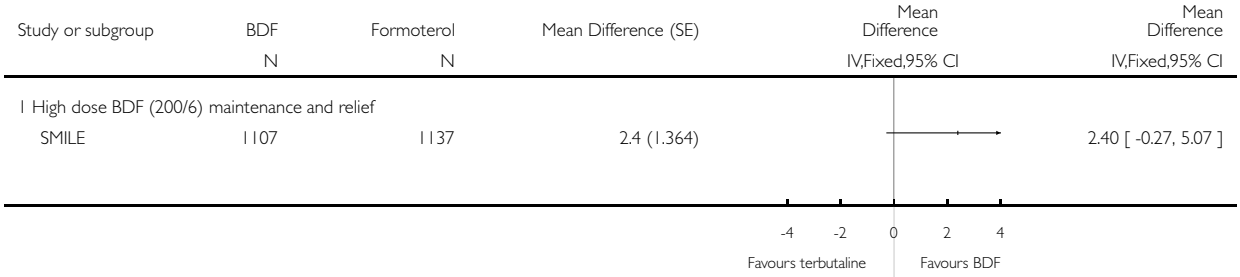
Study or subgroup	BDF N	Formoterol N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 High dose BDF (200/6) maintenance and relief					
SMILE	1107	1137	-2 (0.833)		-2.00 [-3.63, -0.37]

Analysis 3.11. Comparison 3 BDF versus Formoterol as reliever (Adults with BDF maintenance), Outcome 11 Change in Asthma Control Days (%).

Review: Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children

Comparison: 3 BDF versus Formoterol as reliever (Adults with BDF maintenance)

Outcome: 11 Change in Asthma Control Days (%)



FEEDBACK

Study generalisability and interpretational issues, 9 March 2009

Summary

1. The patients recruited to the studies were randomised to receive lower doses of ICS than they had been taking prior to study entry, and would do poorly compared to those that received reliever/ICS. The control groups in both the SMILE and STAY studies are essentially set up to fail. In our opinion, this critical point about the inappropriate treatment given to the control group (although briefly mentioned in the review) was not emphasized enough.

2. The SMILE and STAY studies are really attempting to see if using ICS for relief is worthwhile as both treatment arms get reliever medications; the only difference is that one group receives ICS and the other does not.

3. Did the authors confirm that patients who were hospitalized did not receive oral steroids as well? Did the authors confirm that exacerbations were counted properly? If a patient was first hospitalized for an exacerbation, and then later had another exacerbation not requiring hospitalization (a subsequent event), was the latter counted and reported? And if so was this accounted for in the current review?

4. The authors state that selection bias was unlikely as trials were all double-blinded. As we understand it, double-blinding limits reporting/assessment/concomitant treatment bias and it is allocation concealment procedures that limit selection bias. With regard to implications for research we do not feel that use of a combination reliever in patients with less severe asthma would be of clinical value. If patients only require low dose ICS or no ICS then why expose them to the potential for adverse events of corticosteroids even if it is through intermittent use?

5. The serious adverse event findings did not receive enough emphasis. The suggestion that severe asthmatics derived a benefit from reliever/ICS would only be true if serious adverse events rates were lower for this group compared to the formoterol alone patients. In other words, the reduction in exacerbations requiring oral steroids should have correlated with a reduction in serious adverse events, if the combination produces a net benefit, but it did not. A more appropriate conclusion would have been that no overall health benefit was proven in adults with severe asthma despite the potential reduction in exacerbations requiring steroids.

Reply

We address these comments on a point by point basis as follows:

1. We agree that the study populations recruited were randomised to receive a lower dose of steroid than they had previously been treated with. We have stated this more clearly in the abstract and conclusions of the review, although we have not restated this in the discussion since we feel that this is clearly emphasized already.

2. The corticosteroid is co-delivered with formoterol and compared with terbutaline in most of the studies we included. It is true that both groups of participants receive reliever medications, but essentially the studies are assessing the combination of ICS with a long-acting beta-agonist with a fast onset against a short-acting beta-agonist alone.

3. This point refers to the first published version of the review. Since the review was published, we have received data on OCS-treated exacerbations from the sponsors of the studies and analysed these data as per protocol. The data provided by the sponsors enabled us to add these findings as binary data for both OCS-treated exacerbations and hospital admission in December 2008 (see History of review in the What's new section). The results have been presented as patients with at least one hospital admission or course of oral steroids (as described in the protocol for the review); this is to avoid unit of analysis errors which can arise when multiple events in a single patient are counted as if they came from separate patients.

4. We have clarified that our judgement of selection bias is based on sequence generation and allocation concealment (not on double blinding).

5. We have made the SAE data in the review available for users to make up their own minds about the benefits and risks of treatment. We disagree that we should conclude overall benefit in favour of combination therapy only when SAEs favour this form of therapy. Our primary outcomes included oral steroid use, which favoured combination therapy, and SAEs which did not indicate that either form of relief therapy had an advantage over the other.

We thank Dr Tejani for these comments.

Contributors

Aaron Tejani & Vivian Yih

WHAT'S NEW

Last assessed as up-to-date: 20 April 2008.

Date	Event	Description
15 July 2009	Amended	Correction to contributors who made the comment posted in March 2009

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 1, 2009

Date	Event	Description
21 April 2009	New search has been performed	New search carried out in April 2009 but no new studies found for inclusion

(*Continued*)

9 March 2009	Feedback has been incorporated	Comment submitted relating to study generalisability and interpretational issues. Changes made to emphasis on some of the results, and rebuttal included in the review
11 December 2008	Amended	Additional data incorporated in relation to patients with at least one course of oral corticosteroids in STAY - Adults. The conclusions are unchanged as the results are very similar to the same outcome from SMILE that were already included in the review.
14 March 2008	Amended	Converted to new review format.
14 December 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

CJC: Conception of the idea, study selection and data collection, statistical analysis, and co-writing of the review.

TL: Discussion of concepts, study selection and data collection and co-writing of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NHS R&D, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review authors have included studies with no maintenance therapy, (but not combined the results with other studies of patients on maintenance ICS). Formoterol with ICS is the focus of this review, so salmeterol has been removed from the search terms, as it is not used for reliever therapy. The primary outcome has been modified to patients with exacerbations (rather than rates) that require hospitalisation or courses of oral steroids. All-cause serious adverse events (fatal and non-fatal) have been added as a further primary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adolescent; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Bronchial Diseases [drug therapy]; Bronchodilator Agents [*administration & dosage]; Budesonide [*administration & dosage]; Chronic Disease; Constriction, Pathologic [drug therapy]; Drug Combinations; Ethanolamines [*administration & dosage]; Randomized Controlled Trials as Topic; Terbutaline [administration & dosage]

MeSH check words

Adult; Child; Humans