Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma (Review)

Ducharme FM, Lasserson TJ, Cates CJ

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[Intervention Review]

Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

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ABSTRACT

Background

Asthma patients who continue to experience symptoms despite being on regular inhaled corticosteroids (ICS) represent a management challenge. Long-acting beta$_2$-agonists (LABA) or anti-leukotrienes (LTRA) are two treatment options that could be considered as add-on therapy to ICS.

Objectives

We compared the efficacy and safety profile of adding either daily LABA or LTRA in adults and children with asthma who remain symptomatic on ICS.

Search methods

We searched the Cochrane Airways Group Specialised Register (up to and including March 2010). We consulted reference lists of all included studies and contacted authors and pharmaceutical manufacturers for other published or unpublished studies.

Selection criteria

We included randomised controlled trials (RCTs) conducted in adults or children with recurrent asthma that was treated with ICS and where a fixed dose of a long-acting beta$_2$-agonist or leukotriene agent was added for a minimum of 28 days.

Data collection and analysis

Two authors independently assessed the risk of bias of included studies and extracted data. We sought unpublished data and further details of study design, where necessary.

Main results

We included 17 RCTs (7032 participants), of which 16 recruited adults and adolescents (6850) and one recruited children aged 6 to 17 years (182). Participants demonstrated substantial reversibility to short-acting beta-agonist at baseline. The studies were at a low risk of bias. The risk of exacerbations requiring systemic corticosteroids was lower with the combination of LABA and ICS compared

with LTRA and ICS, from 11% to 9% (RR 0.83, 95% CI 0.71 to 0.97; six studies, 5571 adults). The number needed to treat (NNT) with LABA compared to LTRA to prevent one exacerbation over 48 weeks was 38 (95% CI 22 to 244). The choice of LTRA did not significantly affect the results. The effect appeared stronger in the trials using a single device to administer ICS and LABA compared to those using two devices. In the absence of data from the paediatric trial and the clinical homogeneity of studies, we could not perform subgroup analyses on age or asthma severity. The addition to ICS of LABA compared to LTRA was associated with a statistically greater improvement from baseline in several of the secondary outcomes, including lung function, functional status measures and quality of life. Serious adverse events were more common with LABA than LTRA, although the estimate was imprecise (RR 1.35, 95% CI 1.00 to 1.82), and the NNT to harm for one additional patient to suffer a serious adverse event on LABA over 48 weeks was 78 (95% CI 33 to infinity). The risk of withdrawal for any reason in adults was significantly lower with LABA and ICS compared to LTRA and ICS (RR 0.84, 95% CI 0.74 to 0.96).

Authors' conclusions

In adults with asthma that is inadequately controlled on low doses of inhaled steroids and showing significant reversibility with beta$_2$-agonists, LABA is superior to LTRA in reducing oral steroid treated exacerbations. Differences favouring LABA in lung function, functional status and quality of life scores are generally modest. There is some evidence of increased risk of SAEs with LABA. The findings support the use of a single inhaler for the delivery of LABA and inhaled corticosteroids. We are unable to draw conclusions about which treatment is better as add-on therapy for children.

PLAIN LANGUAGE SUMMARY

What are the effects of long-acting beta$_2$-agonists compared with anti-leukotrienes when added to inhaled steroids?

People who continue to experience asthma symptoms despite regularly taking inhaled corticosteroids are a challenge for management. It is not clear whether the addition of a long-acting beta$_2$-agonist (LABA) such as formoterol or salmeterol would provide more benefit in comparison with an oral anti-leukotriene agent (LTRA), for example zafirlukast or montelukast.

Seventeen trials (16 in adults and one in children) were included in this review and were of good quality. We found that the addition of a LABA provides significantly greater protection against exacerbations requiring oral steroids when compared with a LTRA for adults. Based on the results of our analyses, approximately 38 adults (with a range of between 22 and 244) would need to be treated with a LABA rather than a LTRA for 48 weeks to prevent one experiencing an exacerbation needing a course of oral steroids. The trial on children did not contribute data on the main outcome and therefore we could not draw any conclusions for children.

LABAs also led to a greater improvement in lung function, improvement in symptoms, use of rescue medication, quality of life and symptoms compared to the use of LTRAs. The magnitude of the improvements was modest. Serious adverse events were more frequent with LABA than with LTRAs although this result was imprecise. Based on our analyses, around 78 people would need to be treated for 48 weeks with a LABA rather than a LTRA for one of them to experience a serious adverse event. However, due to the lack of precision around our result, the true number could be between 33 and infinity. There are currently insufficient data to draw any conclusions about the effects of these drugs in children.

BACKGROUND

Leukotrienes are inflammatory molecules and are one of several substances released by mast cells during the immediate response to an inhaled allergen. They are derived from arachidonic acid, the precursor of prostaglandins (Wasserman 1988; Wenzel 1997). There are two families of leukotrienes. Leukotriene B_4 acts primarily in conditions in which inflammation is dependent on neutrophils, such as cystic fibrosis, inflammatory bowel disease, and psoriasis. The second group (C_4, D_4, E_4), called cysteinyl-leukotrienes, bind to highly selective receptors to induce eosinophil- and mast cell-induced bronchoconstriction and inflammation associated with asthma (Davis 1997). Drugs that can interfere with the production (leukotriene synthesis inhibitors) and activity (leukotriene receptor antagonists) of leukotrienes have been designed. Leukotriene synthesis inhibitors (for example zileu-

ton) inhibit the enzyme 5-lipoxygenase thus blocking the production of many leukotrienes (for example B_4, C_4, D_4, and E_4) (Georgitis 1999). Leukotriene (cysteinyl) receptor antagonists (for example montelukast, zafirlukast, pranlukast) block leukotriene D_4 (LTD_4) receptors (Georgitis 1999). Both types of leukotriene modifiers are administered orally as tablets.

Two Cochrane reviews have concluded that leukotriene receptor antagonists (LTRA) are mild anti-inflammatory agents when used as monotherapy (Ducharme 2004b) and bring modest benefit as add-on therapy to inhaled steroids (Ducharme 2004a). Long-acting beta$_2$ (β_2)-agonists (LABA) have a similar mode of action to that of short-acting β_2-agonists. Some LABAs may have a slightly slower onset of action than short-acting β_2-agonists (SABA, Lotvall 1996) but display prolonged activation of β_2-receptors (Johnson 1995) in bronchial smooth muscle resulting in prolonged duration of action, for up to 12 hours (Rees 1995). LABA are recommended solely as add-on therapy to inhaled corticosteroids (ICS) in patients with moderate to severe asthma who remain symptomatic despite anti-inflammatory therapy (BTS 2009; GINA; Lougheed 2010). A number of concerns have been raised about the safety of LABA, predominantly when used without concomitant ICS (Cates 2008a; Cates 2008b; Salpeter 2006; Walters 2007). Due to evidence of increased risk of severe exacerbations and death, there has been a recent call for the withdrawal of inhalation devices containing only LABA. The combination of LABA with ICS has been carefully examined and is superior to placebo when introduced as a second-line therapy in adults treated with ICS (Ducharme 2010; Ernst 2006). In children already taking ICS and in steroid-naive patients, there remains some uncertainty as to whether additive LABA confers any meaningful benefit (Ni Chroinin 2009a; Ni Chroinin 2009b). Despite non-statistically significant results for outcomes relating to serious adverse events, the data do not prove conclusively that the risk of serious adverse events is abolished by the presence of ICS (Cates 2009a; Cates 2009b).

People with asthma who continue to experience symptoms with ongoing airway obstruction despite taking regular ICS represent a management challenge. Both leukotriene receptor antagonists (LTRAs) and LABA agents may be considered as add-on therapy to ICS (Adams 2007). There are several reasons to support the synergistic effect of either combination at the cellular or pathophysiology level. LABAs reduce airway hyper-responsiveness by means of functional antagonism (Lipworth 2002) while corticosteroids increase the expression of β_2-adrenergic receptors (Baraniuk 1997), which is a good combination for synergy. LTRAs inhibit the production of cysteinyl leukotrienes, important pro-inflammatory mediators in asthma that are unaffected by steroid treatment. LTRAs are particularly effective in allergen-, exercise-, and aspirin-induced asthma (Krawiec 2002). Thus, both the addition of LTRAs or LABA could potentiate the anti-inflammatory effect of inhaled corticosteroids and lead to better asthma control. The current review compares the relative benefits and safety profile of adding either an LTRA or a LABA to the treatment of patients with asthma who are inadequately controlled by ICS and updates a previous Cochrane review (Ducharme 2006).

OBJECTIVES

To compare the safety and efficacy of adding LABA versus LTRA in children and adults with asthma who remain symptomatic in spite of regular treatment with ICS. We specifically wished to examine the relative impact of the two agents on asthma exacerbations, lung function, symptoms, quality of life, adverse health events, and withdrawals.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCT) conducted in adults or children in whom a long-acting β_2−agonist (LABA) or leukotriene receptor antagonist (LTRA) were added, as a fixed-dose combination, to ICS.

Types of participants

Children or adults with recurrent or persistent asthma treated with inhaled steroids (ICS) as the only asthma control medication prior to study entry.

Types of interventions

Interventions included LABA (for example salmeterol or formoterol) or LTRA (for example montelukast, pranlukast, zafirlukast, or zileuton). Participants were required to be on a stable dose of ICS throughout the treatment period. The intervention must have been administered for a minimum of 28 days. Inhaled short-acting β_2-agonists and short courses of oral steroids were permitted as rescue interventions.

Types of outcome measures

Primary outcomes

Number of patients with asthma exacerbations requiring a rescue short course of systemic corticosteroids.

Secondary outcomes

1. Other measures of severity of exacerbations, such as hospital admissions.
2. Measures reflecting chronic asthma control such as pulmonary function tests; symptom scores; days or nights without symptoms, or both; quality of life; use of rescue fast-acting β_2-agonists; and patient satisfaction.
3. Measures of inflammation such as eosinophilia, serum eosinophil cationic protein, and sputum eosinophils.
4. Adverse effects including rates of clinical and biochemical adverse effects.
5. Withdrawal.

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials (searched up to March 2010), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE, and CINAHL; and handsearching of respiratory journals and meeting abstracts (please see the Airways Group search methods for further details). All records in the Specialised Register coded as 'asthma' were searched using the following terms:
(((beta* AND agonist*) AND (long-acting OR "long acting")) OR ((beta* AND adrenergic*) AND (long-acting OR "long acting")) OR (bronchodilat* AND (long-acting OR "long acting")) OR (salmeterol OR formoterol OR eformoterol OR advair OR symbicort)) AND (((steroid* OR glucocorticoid* OR corticosteroid*) AND inhal*) OR (budesonide OR beclomethasone OR fluticasone OR triamcinolone OR flunisolide)) AND (leucotrien* OR leukotrien* OR anti-leukotrien* OR anti-leucotrien* OR *lukast).
An additional search of CENTRAL was completed using the above search strategy.

Searching other resources

We reviewed reference lists of all included studies and reviews to identify potentially relevant citations. We asked authors of included studies and pharmaceutical companies to identify other published or unpublished studies. We searched abstract books of the American Thoracic Society (ATS) and European Respiratory Society (ERS) (1998 to 2005) by hand. For the 2006 and 2010 updates, we accessed a register of study results posted by pharmaceutical manufacturers (www.clinicalstudyresults.org). This website lists study results from the manufacturers of LABAs (GSK, AstraZeneca) and LTRAs (Merck, AstraZeneca).

Data collection and analysis

Selection of studies

Two of us screened the title, abstract or descriptors and excluded all studies that were clearly not RCTs or that clearly did not fit the inclusion criteria. Two of us reviewed the full-text documents of the remaining trials, assessing for inclusion based on population, intervention, study design, and outcome. We searched the bibliographies of articles that we retrieved in full to identify any additional studies.

Data extraction and management

Data for the trials were extracted by two authors and entered into Review Manager 5. Where necessary, expansions of graphic reproductions and estimations from other data presented in the papers were performed.
We contacted primary study authors to confirm methodology and data extraction as well as to provide additional information and clarification, if needed.

Assessment of risk of bias in included studies

We assessed the risk of bias for each study in terms of allocation generation and concealment, blinding, handling of withdrawals, and selective reporting bias (*see* Chapter 8 of the Cochrane Handbook) (Higgins 2008). This replaced the previous methodology for assessing study quality (*see* Differences between protocol and review).
We assessed the risk of bias of each study for the following six items.

1. Allocation generation.
2. Allocation concealment.
3. Blinding.
4. Incomplete data.
5. Selective reporting.
6. Other potential sources of bias.

Our judgments of high, low, and unclear risk of bias were corroborated by quotations from trial reports, correspondence, or summarized information from the relevant sections of the individual study reports.

Assessment of heterogeneity

We measured heterogeneity of effect sizes between studies with the I^2 statistic (Higgins 2003). If heterogeneity was suggested by $I^2 > 25\%$, a random-effects model was applied to the summary estimates and was reported in the results.
Subgroup analyses were planned to explore possible effect modifications associated with a priori identified variables or to explore the cause of heterogeneity of study results, if any, for the main

outcome. Differences in the magnitude of effect attributable to these subgroups were examined with the residual Chi^2 test from the odds ratios (Deeks 2001).

Data synthesis

All included trials were combined using Review Manager 5. For dichotomous variables, we combined data as a pooled fixed-effect model risk ratio (RR) with 95% confidence interval (95% CI). For continuous outcomes we combined data as a pooled fixed-effect model mean difference (MD) or standard mean difference (SMD) with 95% CI. We calculated the number needed to treat (NNT) for the primary outcome using Visual Rx, a web-based programme available via www.nntonline.net (Cates 2002).
Odds ratios were used for NNT as the results are not affected by the selection of the reference treatment (LABA or LTRA). In view of the different duration of the trials, the pooled odds ratio was applied to the average exacerbation rate in the trials to give NNTs for 12 and 48 weeks of treatment.

Subgroup analysis and investigation of heterogeneity

1. Number of inhaler devices used to deliver LABA and ICS therapy (added after publication of the protocol, *see*Differences between protocol and review)
2. Dose and type of long-acting β_2-agonist (salmeterol, formoterol)
3. Dose and type of anti-leukotriene (montelukast, pranlukast, zafirlukast, zileuton)
4. Dose and type of ICS (in beclomethasone-equivalents)
5. Children versus adults
6. Baseline severity of airway obstruction based on the per cent predicted forced expiratory volume in one second (FEV1), or peak expiratory flow (PEF): severe < 60%, moderate 61% to < 80%, mild ≥ 80% (GINA 2009)

Sensitivity analysis

For the primary outcome, we planned to perform the following sensitivity analyses to investigate the potential effect of study duration (≤ 12 weeks, > 12 weeks), publication bias, risk of bias, and funding source (trials funded by producers of LABA, studies funded by producers of LTRA, independently-funded studies) on the study results. Funnel plots were used to test for the presence of publication and other biases for trials contributing data to the main outcomes (Egger 1997).

RESULTS

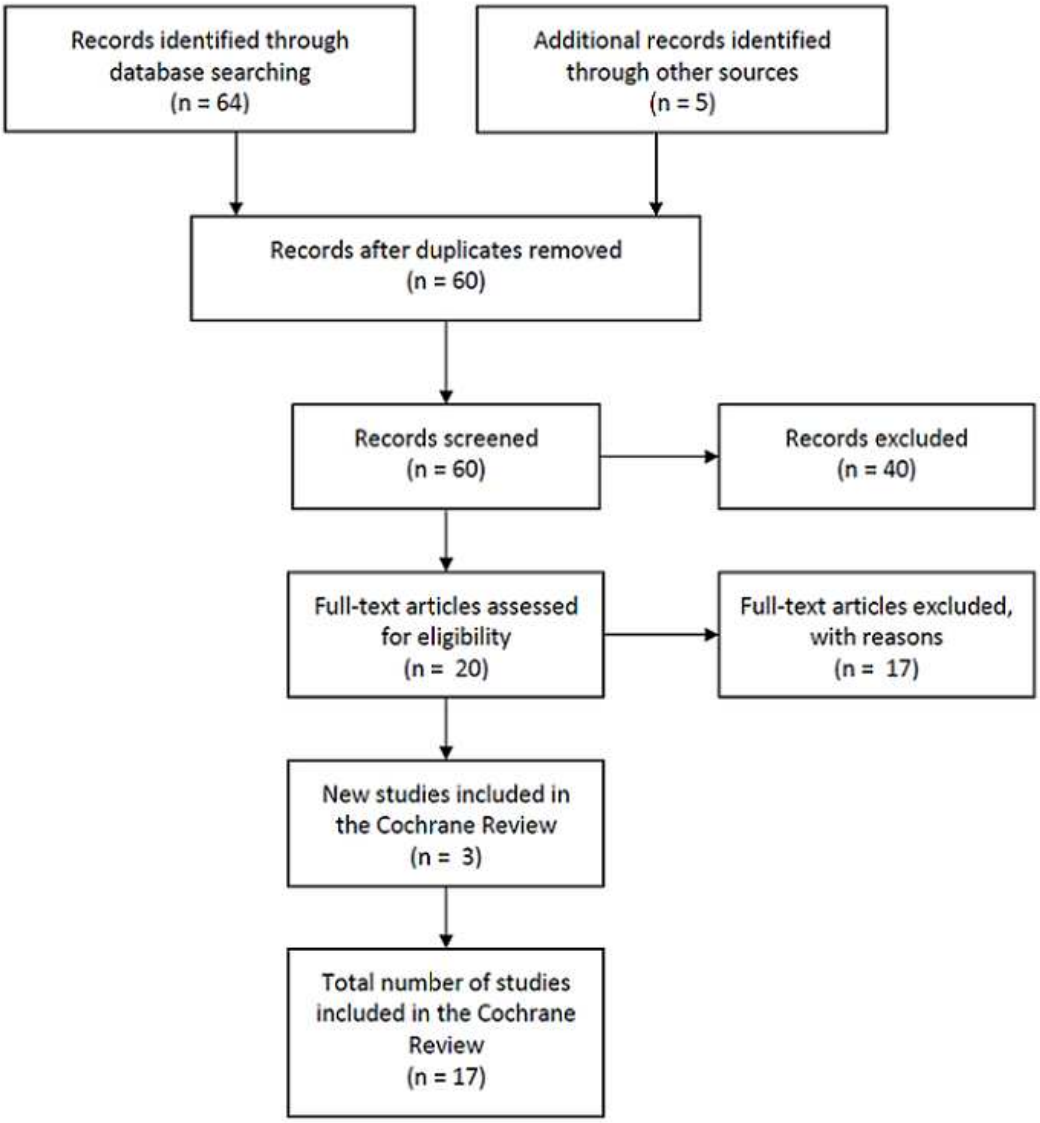
Description of studies

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

Results of the search

See Table 1 for details of the search history which formed the basis of the previous version of the review (all years to January 2006). Three studies from searches conducted between January 2006 and March 2010 met the eligibility criteria of the review (ELEVATE; Lemanske 2010; Pavord 2007). We re-assessed the eligibility of one previously included study and excluded it due to pre-trial exposure to combination therapy (Stelmach 2008). The addition of three new studies and the exclusion of Stelmach 2008 gave a total of 17 included studies reported in 45 publications (*see* Figure 1).

Figure 1. Literature flow diagram for studies included in 2010 update of the Cochrane review.



Included studies

The studies were reported as 13 full-text journal publications (Bjermer 2003; Ceylan 2004; ELEVATE; Fish 2001; Green 2006; Grosclaude 2003; Ilowite 2004; Lemanske 2010; Nelson 2000; Nelson 2001; Pavord 2007; Ringdal 2003; Storms 2004), two unpublished full-text company reports (SAM40030; SD-004-0216) and two conference abstracts (Hendeles 2004; Nsouli 2001). The conference abstracts did not provide data in sufficient detail to contribute to the meta-analyses, and we have not been able to obtain data from the investigators through correspondence. We describe below the characteristics of the 15 included studies which contributed data to the review.

Design

All but one trial employed a parallel-group design. Lemanske 2010 was a three-arm cross-over trial conducted in children. The authors declined our request for additional data to enable inclusion of any data from this study in the review.

Participants

Fourteen trials focused on adults, with mean ages ranging from 35 to 44 years, with similar gender representation and mean asthma duration ranging from 10 to 26 years. One study recruited children aged between six and 17 years (Lemanske 2010). Most trials (Bjermer 2003; Ceylan 2004; Fish 2001; Grosclaude 2003; Ilowite 2004; Nelson 2000; Ringdal 2003; Storms 2004) allowed the inclusion of adolescents aged ≥15 years (or ≥ 12 years for SD-004-0216 and Nelson 2001) although the number of teenagers randomised, if any, was not reported. All but one trial clearly specified that participants could not be steroid naive at enrolment; the remaining study, which failed to specify whether this was a specific criterion for eligibility (Nelson 2001), was still included.

Participants were symptomatic at enrolment despite inhaled steroids at doses of 200 to 1000 µg/day of chlorofluorocarbon (CFC)-propelled beclomethasone or equivalent (CFC-BDP), when ICS doses were reported. Severity of asthma as measured by degree of airway obstruction was available for one study. Based on categorisations outlined by GINA of: mild obstruction, FEV1 80% predicted or higher; moderate, FEV1 60% to 80% predicted; severe, less than 60% predicted, the mean FEV1 indicated that participants had mild airway obstruction in two trials (Lemanske 2010; Storms 2004) and moderate airway obstruction in 11 trials (Bjermer 2003; Ceylan 2004; Fish 2001; Green 2006; Ilowite 2004; Nelson 2000; Nelson 2001; Pavord 2007; Ringdal 2003; SAM40030; SD-004-0216). We were not able to ascertain baseline FEV1 for two studies (ELEVATE; Grosclaude 2003).

Allergy status was reported in two studies (Bjermer 2003; Lemanske 2010) where 65% and 77% respectively of participants were affected at baseline. Three studies (Bjermer 2003; Ceylan 2004; Grosclaude 2003) reported that 60%, 65%, and 51% respectively of participants suffered from allergic rhinitis.

Withdrawal rates varied from 8% to 17% in the LTRA group and 5% to 27% in the LABA group.

Intervention

During the intervention period, all participants remained on a stable dose of inhaled corticosteroids (ICS). For the purposes of this review, we considered low ICS doses to be 400 µg/day or less (CFC-BDP equivalent), moderate doses to be 400 to 800 µg/day (CFC-BDP equivalent) and high doses as 800 µg/day (CFC-BDP equivalent) or higher. Based on these categorisations, most of the studies assessed the addition of LABAs or LTRAs to low and moderate doses of ICS (see Table 2). Two trials failed to report the dose of background ICS (ELEVATE; Nelson 2001).

The LTRAs and doses administered were: zafirlukast 20 mg twice daily (Nelson 2001; SD-004-0216) and montelukast 10 mg once daily (Bjermer 2003; Ceylan 2004; Fish 2001; Green 2006; Grosclaude 2003; Ilowite 2004; Lemanske 2010; Nelson 2000; Pavord 2007; Ringdal 2003; SAM40030; Storms 2004). ELEVATE was a pragmatic study in which study participants were allocated to either montelukast or zafirlukast.

The LABAs used were: salmeterol 50 µg twice daily in seven trials (Bjermer 2003; Fish 2001; Grosclaude 2003; Ilowite 2004; Lemanske 2010; Nelson 2000; Nelson 2001; Pavord 2007; Ringdal 2003; SAM40030; Storms 2004) and formoterol 12 µg twice daily in three trials (Ceylan 2004; Green 2006; SD-004-0216). ELEVATE was a pragmatic study in which study participants were allocated to either formoterol or salmeterol.

In seven studies, the combination therapy (Seretide®, Advair® or Symbicort®) was administered in a single device (Green 2006; Grosclaude 2003; Lemanske 2010; Nelson 2000; Pavord 2007; Ringdal 2003; SAM40030) and by separate inhaler devices in seven studies (Bjermer 2003; Ceylan 2004; Fish 2001; Ilowite 2004; Nelson 2001; SD-004-0216; Storms 2004). We were unable to determine the number of inhalers used to deliver therapy in ELEVATE.

The intervention period varied between four weeks (Nelson 2001; Storms 2004), six weeks (Green 2006), eight weeks (Ceylan 2004; SD-004-0216), 12 weeks (Fish 2001; Grosclaude 2003; Pavord 2007; Nelson 2000; Ringdal 2003; SAM40030), 16 weeks (Lemanske 2010), 48 weeks (Bjermer 2003; Ilowite 2004), and

two years (ELEVATE).

Outcomes

The primary outcome (the number of participants with exacerbations requiring rescue systemic corticosteroids) was available for six trials contributing to the main outcome (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003), representing 77% of the total number of participants (81% of adults and 0% children) randomised to trials included in this review. For four trials we could not satisfactorily identify the requirements for oral steroids as binary data (ELEVATE; Green 2006; Grosclaude 2003; Lemanske 2010). None of the studies identified since the first version of the review contributed additional data to our primary outcome.

Other measures of asthma control (for example pulmonary function tests, symptoms, use of rescue β2-agonist, quality of life), withdrawals and adverse effects were reported by several included studies.

Excluded studies

Of the 69 citations retrieved since the 2006 version of the review, we excluded 66 records because:

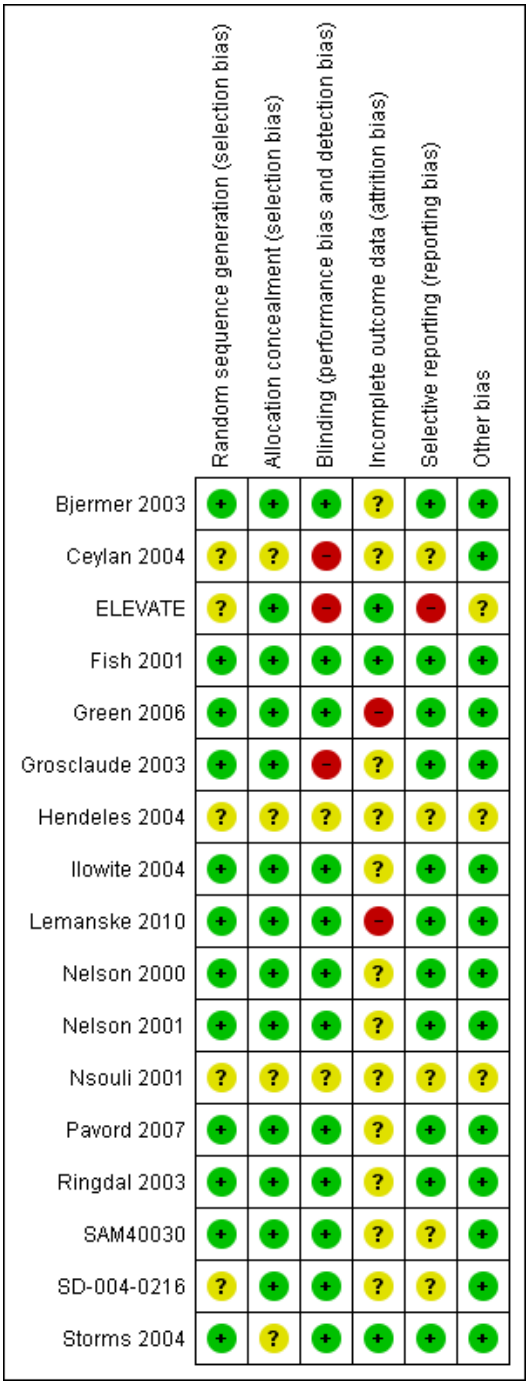
1. the study was a duplicate (i.e. identical citation of a trial report or a subsequent report of a trial), N = 29;
2. the study was not randomised, N = 2;
3. the study was ongoing, N = 5;
4. the administration of either LTRA or LABA was not standardised across treatment groups, N = 3;
5. there was no consistent co-treatment with inhaled glucocorticoids, N = 8;
6. one of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoids, N = 9;
7. one of the tested interventions was not daily LABA as add-on to inhaled glucocorticoids, N = 2;
8. the tested interventions were administered for less than four weeks, N = 1;
9. the study used prohibited co-intervention, N = 3;
10. the study did not recruit participants at the step 2* level, i.e. the study recruited steroid-naive participants or participants on combination therapy, N = 3

* Step 1, 2, and 3 refer to levels of asthma treatment (BTS 2003).

Risk of bias in included studies

An overview of our judgments for the risk of bias of each study is provided in Figure 2.

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



Allocation

Randomisation was clearly described and appropriate in all trials with the exception of three trials that contributed data to the review (Ceylan 2004; Grosclaude 2003; SD-004-0216) and the two abstracts not contributing data in sufficient detail to be meta-analysed (Hendeles 2004; Nsouli 2001). All the data included in the primary outcome were drawn from six studies with robust random sequence generation and allocation concealment.

Blinding

Twelve trials reported double blinding with identical 'dummy' treatments, while three trials (Ceylan 2004; Grosclaude 2003; Nsouli 2001) had an open-label design. One trial failed to clearly report the means of blinding (Hendeles 2004).

The methodology was confirmed by the authors of all trials contributing data with the exception of three (Ceylan 2004; Grosclaude 2003; Storms 2004). No confirmation was obtained for two studies reported as abstracts (Hendeles 2004; Nsouli 2001).

The six trials contributing data to the primary outcome were double-blind, double-dummy studies.

Incomplete outcome data

Withdrawal rates were described in all but one study (Nsouli 2001). Withdrawals were not reported in three trials by treatment group (Ceylan 2004; ELEVATE; Lemanske 2010).

The analyses within the studies were frequently described as being by intention to treat. However, further information as to how missing data were handled in the trials was limited. For one trial, data were from patients who completed the study (Nelson 2001).

Selective reporting

The amount of data for the review primary outcome was high when considered as the proportion of the total participants randomised (77%). We were unable to use data from other studies due to their broader definition of exacerbations or inadequate reporting of outcome data (ELEVATE; Green 2006; Grosclaude 2003; Lemanske 2010). In one study, exacerbations were not measured (Pavord 2007) and in another there were no occurrences (Storms 2004). From the remaining five studies, we could not ascertain whether exacerbations were measured.

Effects of interventions

Primary outcome: exacerbations requiring oral (systemic) corticosteroids

Six trials with 5571 adults (no children) contributed data to the primary outcome (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003). The risk of having an exacerbation requiring systemic corticosteroids was statistically significantly lower with the use of LABA and ICS compared to LTRA and ICS (RR 0.83, 95% CI 0.71 to 0.97) (Figure 3). The addition of LABA lowered the risk of an exacerbation from 11% to 9%, a 2% (95% CI 0 to 3%) risk difference in exacerbations requiring systemic steroids over the use of LTRA. The number of patients who needed to be treated (NNT) with the combination of LABA and ICS instead of LTRA and ICS to prevent one exacerbation over 48 weeks was 38 (95% CI; 22 to 244), as shown in a Cates plot in Figure 4. For the shorter 12-week trials the NNT was 106 (95% CI 63 to 676).

Figure 3. Forest plot of comparison: 1 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, outcome: 1.1 Participants with one or more exacerbations requiring systemic corticosteroids.

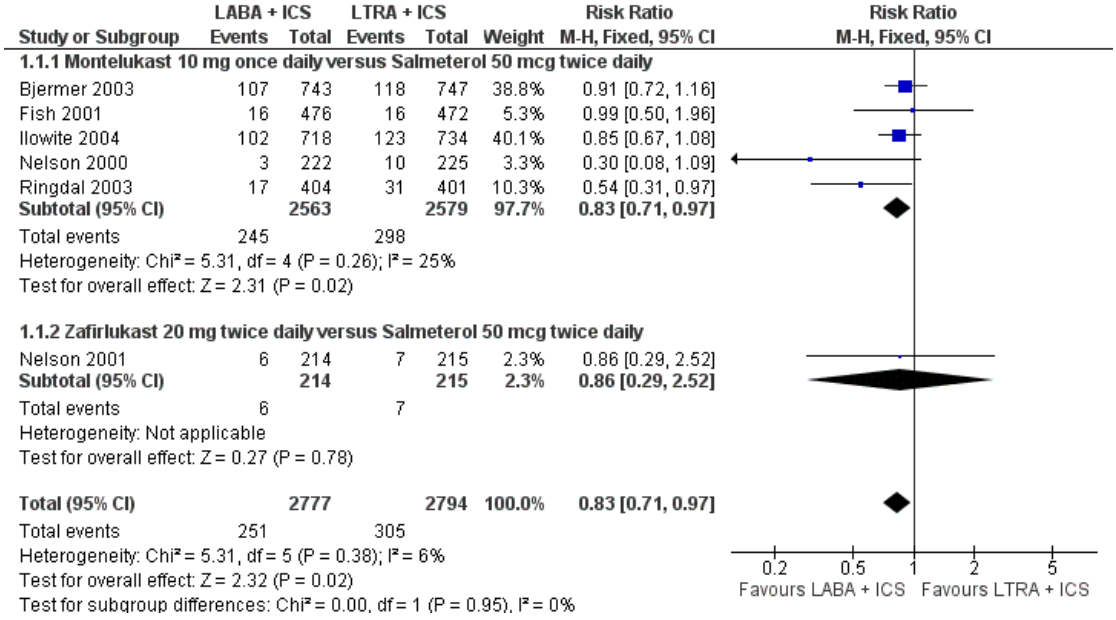
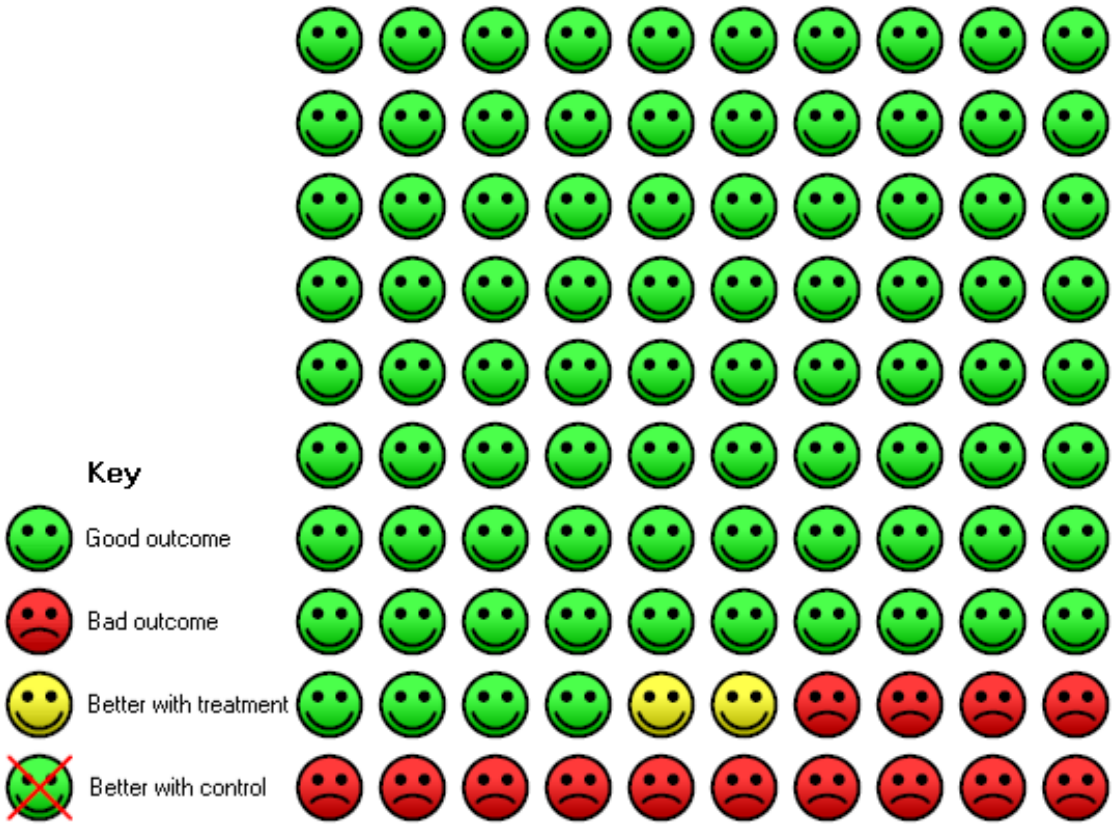
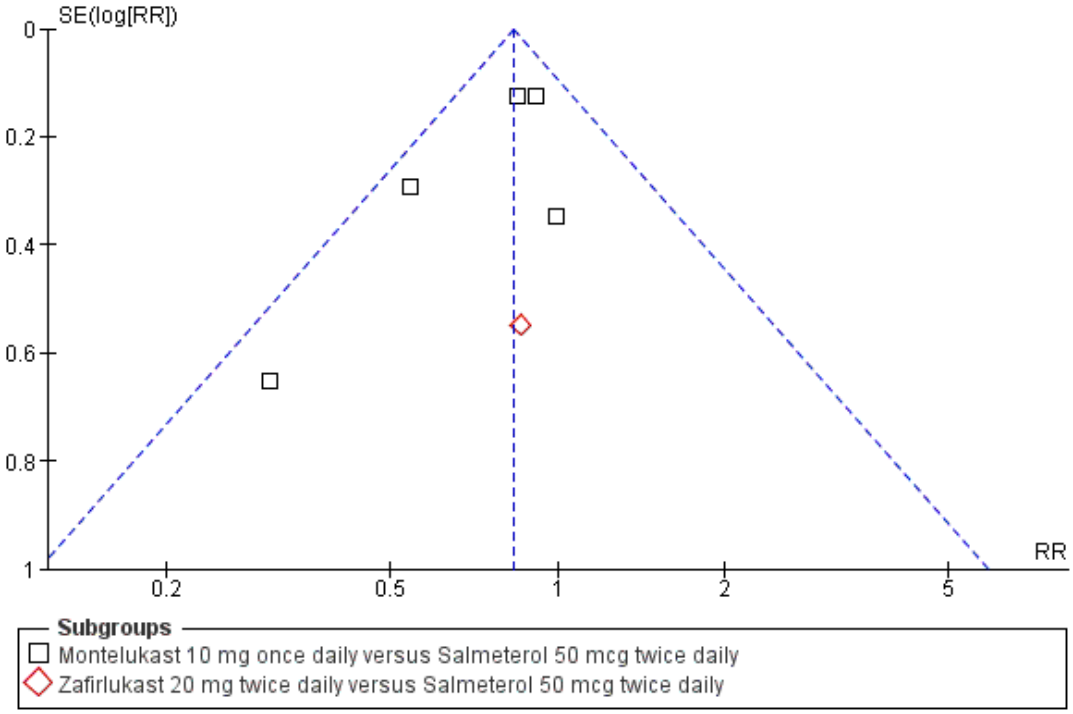


Figure 4. In the LRTA group 16 out of 100 had an exacerbation requiring oral corticosteroids over 48 weeks, compared to 14 (95% CI 12 to 16) for the LABA group. The NNT with LABA to prevent one patient having an exacerbation over 48 weeks is 38 (95% CI 22 to 244).



The results were homogeneous despite the different LABAs and LTRAs used (I^2 = 6%). Although the funnel plot intercept suggested no evidence of publication bias (-0.01, 95% CI -4.23 to 2.10) visual inspection of the funnel plot precludes firm reassurance (Figure 5). The number of unpublished studies with null results needed to overturn the current findings was nine.

Figure 5. Funnel plot of comparison: 1 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, outcome: 1.1 Participants with one or more exacerbations requiring systemic corticosteroids.



Although there was no heterogeneity between trials, we had planned a priori to perform subgroup analyses on the following variables, to explore their possible influence on the magnitude of effect (effect modification). The subgroup comparison between single and combined inhalers was added after publication of the initial protocol as a result of work subsequently published on this topic (Nelson 2003).

1. Number of inhaler devices used to deliver LABA and ICS

Of the six studies contributing outcome data to the primary outcome, there were two studies (Nelson 2000; Ringdal 2003) where LABA and ICS were delivered in one inhaler device and four studies (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2001) where separate inhalers were used. Use of a single inhaler provided significantly greater protection against exacerbations than use of separate inhalers (Analysis 2.1). We calculated the ratio of risk ratios (RRR) as 0.55 (95% CI 0.31 to 0.95; P = 0.04) (Altman 2003). In other words, the protective effect seen with single inhaler devices that combined ICS and LABA on exacerbations requiring rescue oral corticosteroids was almost twice that of the separate inhaler devices as compared to ICA and LTRA. However, this indirect comparison is confounded by other differences between trials, including trial duration and ICS dose.

2.Dose and type of LABA

All included studies contributing data towards the meta-analysis used salmeterol as the LABA, preventing assessment of the within-class effect of LABA.

3. Dose and type of LTRA

The type of LTRA used in the included trials did not appear to make a difference on the primary outcome. The RR of exacerbations when LABA + ICS was compared to montelukast + ICS and zafirlukast + ICS was 0.83 (95% CI 0.71 to 0.97) and 0.86 (95% CI 0.29 to 2.52) respectively, with no statistical difference between the two subgroups (Analysis 1.1).

4. Dose and type of inhaled corticosteroids (in beclomethasone-equivalent doses)

All six studies included in the primary outcome were reported to have used similar doses of inhaled glucocorticoids, ranging from 200 to 282 µg/day of HFA-BDP equivalents. There were no subgroup differences between those with low, moderate, mixed, or unclear ICS dose (Analysis 2.2). Fluticasone was used in four trials

(Bjermer 2003; Ilowite 2004; Nelson 2000; Ringdal 2003). One trial used a variety of ICSs as the authors kept patients on their usual ICS (Fish 2001); and we were unable to obtain details on the ICS used in Nelson 2001.

5. Children versus adults

Since the paediatric trial did not contribute any outcome data to this review, the effect on children versus adults could not be examined.

6. Baseline severity of airway obstruction

As the studies pertained to patients with moderate airway obstruction who were relatively homogeneous in the average baseline FEV1 (all within 66% to 76% of predicted value), subgroup analyses of baseline severity could not be performed.

7. Duration of trials

The two trials of 48 week duration showed a smaller difference in treatment effect ((RR 0.88; 95% CI 0.74 to 1.04) than the other trials of 12 week duration or less (RR 0.65; 95% CI 0.45 to 0.96), although the confidence intervals were overlapping and the difference between the longer and shorter trials was not statistically significant (Chi^2 = 1.93, df = 1, P = 0.16, Analysis 2.3). However, the difference in trial durations could be a confounding factor when considering the subgroup difference between single and separate inhalers.

The studies contributing to the primary outcome were at a low risk of bias, funded by manufacturers of the study drugs, and were all published. The pooled result was not sensitive to bias from any of the sources we assessed and we could not ascertain whether funding source or publication status affected the estimated effect.

Secondary outcomes

Morning peak expiratory flow (PEF) (L/min change from baseline)

Eleven studies in 5723 adults contributed data to the morning PEF results. There was a greater improvement in morning PEF with LABA compared with LTRA (15.36 L/min, 95% CI 11.35 to 19.37) (Analysis 1.2).

Evening PEF (L/min change from baseline)

Ten studies in 4012 adults contributed data to the meta-analysis of evening PEF. There was a significantly greater improvement in evening PEF with LABA compared with LTRA (12.64 L/min, 95% CI 10.11 to 15.17) (Analysis 1.3).

Forced expiratory volume in one second (FEV1) (L/sec change from baseline)

Ten studies in 4538 adults contributed data to changes in FEV1. There was a greater improvement in FEV1 with LABA compared with LTRA (0.08 L/sec, 95% CI 0.06 to 0.10) (Analysis 1.4).

FEV1 (L/sec, % change from baseline)

As only one adult trial contributed date to this outcome (Ceylan 2004), we were unable to pool data (Analysis 1.5).

FEV1 (% predicted)

As one small adult study contributed data to this outcome, we were unable to pool data (Analysis 1.6).

FEV1 (% fall post-exercise)

One small adult study contributed data to this outcome (Analysis 1.7).

Rescue-free days (% change from baseline)

Five studies conducted in 2612 adults contributed data to change in per cent of rescue medication-free days. LABA + ICS showed an increase in the percentage of days with no rescue medication use compared to LTRAs + ICS (MD 9.18, 95% CI 5.39 to 12.98) (Analysis 1.8).

Rescue medication use (puffs/day)

Seven studies in 4055 adults contributed data on rescue medication. The combined overall estimate showed a significant decrease in the use of rescue medication with LABA + ICS (MD -0.49 puffs/day, 95% CI -0.75 to -0.24) (Analysis 1.9).

Change in global asthma quality of life score (higher score is better) - change from baseline

Three studies in 2893 adults reported asthma-specific quality of life using the Juniper's 24-point scale: Bjermer 2003; Ilowite 2004 using montelukast, and Nelson 2001 using zafirlukast. The overall estimate showed an improvement in global asthma quality of life with LABA + ICS that was significantly different to that of LTRA + ICS (MD 0.11, 95% CI 0.05 to 0.17) (Analysis 1.10).

Symptom-free days (% change from baseline)

Six studies with 2692 adults reported symptom-free days (Fish 2001; Grosclaude 2003; Nelson 2000; Nelson 2001; Pavord 2007; Ringdal 2003). The pooled effect estimate showed that the addition of LABA (salmeterol was used in all of these trials) increased

the percentage of symptom-free days by 7.27% (95% CI 4.71 to 9.83) compared with LTRA (Analysis 1.11).

Day-time symptom scores (high score is worse) - change from baseline

Five studies with 3823 adults reported daytime symptom scores (Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003). Four of the studies comparing LABA + ICS to montelukast + ICS showed improvement in day-time symptom score with LABA + ICS (SMD -0.18, 95% CI -0.25 to -0.12) (Analysis 1.12).

Change in morning symptom scores

As only one adult trial contributed date to this outcome (Ceylan 2004), we were unable to pool data (Analysis 1.13).

Night-time symptom score (5-point scale, higher score is worse) - change from baseline

As only one trial contributed date to this outcome (Nelson 2001), we were unable to pool data (Analysis 1.14).

Change in number of night awakenings per week - change from baseline

Four studies with 4214 adults reported night awakenings (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000). The combined overall estimate showed that LABA + ICS led to fewer awakenings than LTRA + ICS (MD -0.12, 95% CI -0.19 to-0.06) (Analysis 1.15).

Change in % of nights with no awakenings per week - change from baseline

Two studies reported this outcome based on data from 673 adults (Grosclaude 2003; Nelson 2001) and showed a greater percentage of awakening-free nights per week with LABA + ICS (MD 6.89%, 95% CI 2.87 to 10.91) (Analysis 1.16).

Change in % rescue-free nights

As only one trial contributed date to this outcome (Grosclaude 2003), we were unable to pool data (Analysis 1.17).

Withdrawals for any reason

Eleven studies involving 6291 adults reported withdrawals due to any reason. Overall, there was a significant reduction in the risk of withdrawal with LABA (12%) compared with LTRA (14%) when added to ICS (RR 0.84, 95% CI 0.74 to 0.96) (Analysis 1.18).

Withdrawals due to adverse effects

Eleven studies in 6291 adults reported withdrawals due to adverse effects. The overall estimate comparing LABA and ICS with LTRA and ICS did not show a significant difference between the groups (RR 1.01, 95% CI 0.79 to 1.29) (Analysis 1.19).

Withdrawals due to poor asthma control (exacerbations)

Eight studies in 5354 participants reported withdrawals due to exacerbations. There were no significant differences in the overall estimate (RR 0.87, 95% CI 0.49 to 1.56; random-effects model) (Analysis 1.20l).

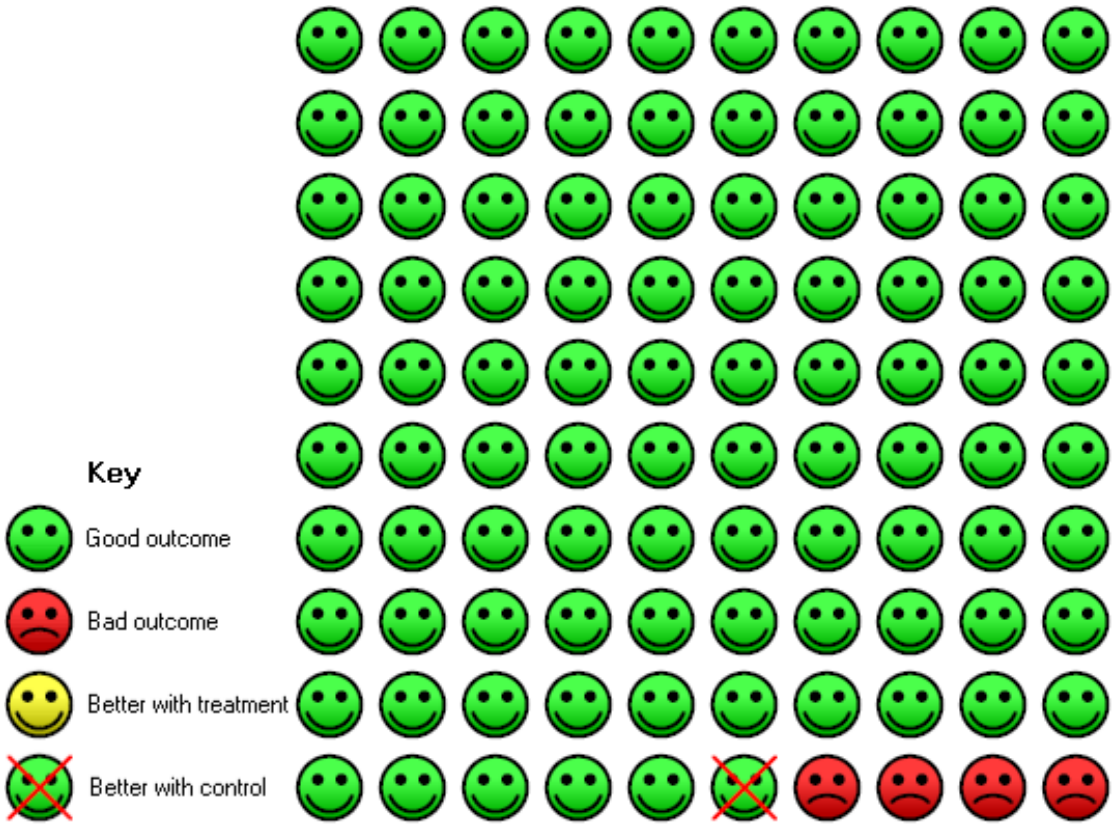
Patients with one or more exacerbations requiring hospital admission

Four studies in 3993 adults contributed data for this outcome (Bjermer 2003; Grosclaude 2003; Ilowite 2004; Ringdal 2003). There was no significant difference between the two study groups (RR 1.31, 95% CI 0.58 to 2.98) (Analysis 1.21).

Serious adverse events

Seven studies in 5658 adults reported this outcome. The pooled result indicated that serious adverse events were significantly more likely to occur with LABAs (3.4%) than with LTRAs (2.5%) (RR 1.35, 95% CI 1.00 to 1.82; P = 0.05) (Analysis 1.22). This is shown as a Cates plot in Figure 6, and the number needed to treat to harm (NNTH) for one additional patient to suffer a serious adverse event on LABA over 48 weeks was 78 (95% CI 33 to infinity). The 12-week NNTH for serious adverse events was 236 (95% CI 100 to infinity).

Figure 6. In the LRTA group 4 people out of 100 had a serious adverse event over 48 weeks, compared to 5 (95% CI 4 to 7) out of 100 for the LABA group. The NNT(H) for one extra patient to suffer a serious adverse event over 48 weeks with LABA is 78 (95% CI 33 to infinity).



In view of the proposed reasons behind the increased risk of serious adverse events (SAEs) with LABAs (Cates 2008a; Cates 2008b; Cates 2009a; Cates 2009b), we undertook a post hoc subgroup analysis of the pooled estimate by exploring the relationship between the number of inhaler devices and the risk of SAEs. The risk ratio of serious adverse events was RR 0.72 (95% CI 0.26 to 1.99) in the three studies using a single inhaler to deliver both LABA and ICS, compared to LTRA and ICS, and RR 1.43 (95% CI 1.04 to 1.97) in the four studies in which LABA and ICS were delivered by separate inhalers (Analysis 2.4). The difference between the two subgroup estimates did not reach statistical significance, with a test for subgroup differences giving: $Chi^2 = 1.61$, df = 1 (P = 0.20); $I^2 = 38.1\%$ (Figure 7).

Deaths

One study reported deaths (Bjermer 2003) with no significant difference between the two study groups (one death occurred in the LABA group) (Analysis 1.23).

Headache

Ten studies with 6187 adults reported headache as an adverse event. There was no significant difference in the overall result or when the two different types of LTRA were compared to LABA and ICS (RR 1.07, 95% CI 0.9 to 1.26) (Analysis 1.24).

Cardiovascular events

Five studies with 5163 adults reported cardiovascular events (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Ringdal 2003). There was no significant difference when LABA and ICS was compared to LTRA and ICS (RR 1.09, 95% CI 0.77 to 1.53) (Analysis 1.25).

Oral moniliasis

Six studies with 5203 adults reported the number of patients with oral moniliasis. The studies compared LABA and ICS to montelukast and ICS, showing an overall significantly increased risk

of oral moniliasis with the addition of LABA compared to montelukast + ICS (RR 1.86, 95% CI 1.00 to 3.44) (Analysis 1.26). Yet, the occurrence rates were low and this represents an average risk of oral moniliasis of 1% for LABA and 0.5% for LTRA. The risk difference for this outcome was 0.01 (95% CI 0 to 0.01).

Osteopenia and osteoporosis

Two studies on 2963 adults reported this outcome (Bjermer 2003; Ilowite 2004) with no significant difference between the study groups (RR 0.56, 95% CI 0.12 to 2.63) (Analysis 1.27).

Elevated liver enzymes

As only one trial contributed data to this outcome (Bjermer 2003), we were unable to pool data (Analysis 1.28).

Overall adverse events

Nine studies with 5977 adults reported adverse events, which did not show a significant difference when LABA and ICS was compared to LTRA and ICS. In fact, the absence of group difference (RR 1.03, 95% CI 0.99 to 1.07) (Analysis 1.29) met our a priori definition of equivalence.

Patient treatment satisfaction

Three studies with 2020 adults (Fish 2001; Nelson 2001; Ringdal 2003) reported significantly higher patient satisfaction with LABA and ICS than with LTRA and ICS (RR 1.12, 95% CI 1.04 to 1.20) (Analysis 1.30). Random-effects modelling was used due to the high level of statistical heterogeneity (I^2 = 61.8%).

Change from baseline in serum eosinophils (x 10e9/L)

Two adult studies reported this outcome (Bjermer 2003; Ilowite 2004), which showed a statistically significant greater decrease in serum eosinophils with LTRA + ICS than with LABA + ICS (MD 0.04, 95% CI 0.02 to 0.05) (Analysis 1.31).

DISCUSSION

Primary outcome

Our review has shown that in adult patients who remain symptomatic on low or moderate doses of inhaled steroids, the addition of a LABA reduces the relative risk of exacerbations requiring oral steroids compared to the addition of a LTRA. The rate of exacerbations requiring oral steroids was 11% in those treated with a combination of LTRA and ICS compared to 9% with the use of LABA; an absolute risk reduction of 2%. Thirty-eight patients need to be treated over 48 weeks with LABA and ICS instead of LTRA and ICS to avoid one patient from experiencing an exacerbation requiring rescue oral steroids. When assessed over 12 weeks this number is 106.

The results were homogeneous between the trials. The choice of LTRA did not appear to affect the magnitude of the benefit related to LABA. When compared to LTRA and ICS, a single inhaler containing both LABA and ICS was associated with a 50% reduction in the risk of exacerbations requiring systemic steroids while a 10% reduction was observed when the two drugs were delivered separately. This difference were statistically significant but should be interpreted cautiously because it is not based on a head-to-head comparison and may be confounded by other differences between the trials that used single or separate inhalers (such as trial duration and ICS dose used). However, the direction of effect is congruent with findings of head-to-head comparisons of single versus separate inhalers (Nelson 2003).

The other characteristics we wished to explore to better guide the selection of treatment for specific patients were similar between the studies, and thus could not be explored. These were age, dose of ICS, degree of airway obstruction, choice of LABA, and study quality. In particular, the absence of paediatric trials contributing data to this outcome prevented any conclusion with regards to the relative effect of LABA versus LTRA as add-on to ICS on the occurrence of exacerbations requiring rescue systemic steroids in children. Treatment duration did not notably affect the direction or magnitude of effect.

Secondary outcomes

Statistically significant improvements were seen with LABA and ICS compared to LTRA and ICS for most secondary outcomes. The average difference in the improvement from baseline in FEV1 between LABA and LTRA was 80 mL (95% CI 60 to 100 mL), namely 215 mL with the addition of LABA to ICS compared to 134 mL with the addition of LTRA to ICS. A change of 200 mL or more in FEV1 is considered a clinically important difference as it exceeds normal intra-subject variation (ATS 1991). However, in the absence of a placebo group these changes from baseline may overestimate an expected improvement as both exceed the previously reported benefit for the additive effect of each drug in comparison with the use of ICS alone. Indeed, previous Cochrane reviews have quantified the magnitude of improvement in FEV1 attributable to each drug over that of ICS and placebo. The addition of LABA to ICS was associated with an increase of 110 to 120 mL (Ducharme 2010), while an increase of 60 mL was observed for the combination of LTRA and ICS over ICS alone (Ducharme 2004b). The clinical importance of the observed differences in favour of LABA over LTRA (80 mL in FEV1, 15 mL in morning PEF, and 12 mL in evening PEF) is debatable, particularly as LABA are specifically meant to achieve bronchodilation.

The outcome measures of rescue-free days, rescue medication use, asthma quality of life, symptom-free days, daytime symptom score, number and per cent of night awakenings, and patient satisfaction were also statistically significantly better with LABA. Moreover, significantly fewer patients allocated to the combination of LABA and ICS withdrew from the study for any reason. Yet, in most secondary outcomes (other than lung function) the magnitude of the observed difference appeared modest. No group difference was observed in the risk of withdrawals due to poor asthma control and hospitalisation.

Only two trials examined the impact of both strategies on inflammatory markers, namely serum eosinophils. The addition of a LTRA to ICS was associated with a greater (4%) reduction from baseline serum eosinophils when compared to LABA and ICS.

The risk of serious adverse events (SAEs) was higher with LABA than LTRA (3.4% with LABA versus 2.5% with LTRA, a risk difference of 1%) but at the limit of statistical significance since the lower limit of the 95% CI equalled the conventional threshold for statistical significance at the 5% level. The apparent increased risk of SAEs with LABA should be regarded as a provisional result. Although the number needed to treat with LABA over 48 weeks for one additional serious adverse event is 78 (95% CI 33 to infinity), the severity of the adverse effects raises concern. We thus performed a post-hoc analysis to explore whether the use of one or two devices for delivering LABA and ICS influenced the risk of severe adverse outcomes. The increased risk may be limited to the studies using two separate inhalers to deliver LABA and ICS. This is concordant with accumulating evidence of an increased risk of SAEs in patients using LABA without ICS and is possibly mediated by non-compliance with concurrent inhaled steroids (Perera 2003). The test for a difference in risk between single and separate inhalers did not show a significant difference between these subgroups (Figure 7).

There was no difference observed between treatments in the risk of cardiovascular events, headaches, and osteopenia or osteoporosis. Only the risk of oral moniliasis was significantly higher in the LABA group than the LTRA group, although the risk difference was clinically small (1% for LABA in comparison with 0.5% for LTRA). The risk of overall adverse effects was similar in both groups, meeting our a priori definition of equivalence and suggesting a similar overall safety profile of the two treatment options. There was no difference between LABA and LTRA in withdrawals due to adverse effects.

One of the entry criteria common to all included trials was the need to demonstrate significant reversibility in FEV1 ($\geq$ 12% improvement post-bronchodilation). It is possible that the requirement to demonstrate a significant reversibility with short-acting β_2−agonists resulted in the selection of patients who were more likely to show a response on lung function outcomes. This may explain the greater differences in favour of LABA that were observed with measures of lung function compared to other outcomes. Although reversibility to a bronchodilator is one of the standard diagnostic criteria of asthma (Boulet 2001; BTS 2003; GINA 2009; USA 2002) only a minority of asthmatic patients display significant reversibility at a given point in time (Storms 2003). It is quite possible that the selection of patients, with significant reversibility, has favoured the combination of LABA and ICS over LTRA and ICS.

The major limitation of the relevant studies in this area is the striking absence of large studies examining the best step three in children. There remains uncertainty as to whether LABAs are effective in reducing the requirement for oral steroids in children (Ni Chroinin 2009b) and a direct comparison of the role of these two drugs in children is urgently required. One well-designed cross-over paediatric trial met the eligibility criteria for inclusion in this review (Lemanske 2010). Unfortunately it reported rescue oral steroids in the context of a composite outcome which did not fit our outcome definition and the authors declined to provide the necessary additional data to allow inclusion of other outcomes in this review. Several other paediatric trials were excluded as they tested add-on therapy in children still on step one or in those already on step three (Stelmach 2007; Stelmach 2008). As wide variations in the definition of exacerbations have been identified as an important difficulty in comparing data across studies, the extraction of data restricted to the use of rescue oral steroids appeared important. Many asthma guidelines still recommend LABAs as an add-on therapy in children. In view of the potential harms associated with LABAs, it is particularly critical for future paediatric studies to carefully examine the best option as add-on therapy for those who remain partially controlled on ICS alone.

The relative homogeneity of adult trials limits the application of the results in children and patients older than 65 years old, smokers, and those with asthma with no significant reversibility to short-acting beta$_2$-agonists. Moreover, how well these add-on therapies perform when added to doses of ICS outside the range of those we have reviewed remains uncertain. Inadequate documentation and reporting also limits generalisation of results to adolescents. We recommend that trialists including adolescents specify the number included and perform subgroup analyses on this age group to begin to address this considerable gap in knowledge. An individual data meta-analysis might provide critical information to determine if the presence of allergic rhinitis modifies the observed superiority of LABA over LTRA as add-on therapy to ICS.

With well-documented decreases in adherence over time (Storms 2003), one wonders whether an undocumented lack of compliance affected the results. Was there poor adherence to a twice daily regimen for LABA? With a flat dose-response curve to inhaled steroids (Powell 2003), one may even wonder whether similar improvement observed with LTRA and LABA is derived from enhanced compliance to inhaled steroids per se, as a result of study participation, rather than the selected add-on therapies. Is the greater improvement associated with concomitant rather than separate delivery of LABA and ICS mostly attributable to better lung deposi-

tion of and interaction between both drugs (Buhl 2003; Rosenhall 2003) or better adherence with ICS? In the absence of adherence measures, these questions remain unanswered. The perception of more rapid and greater benefit by the patients with LABA is often regarded by clinicians as justification for selecting LABA over LTRA as add-on therapy. In the two trials reporting satisfaction, significantly more patients were satisfied in the group receiving LABA + ICS (85%) than those treated with LTRA + ICS (76%). Although derived from close to 6000 patients in six trials, the results of the primary outcome could be reversed by nine additional trials of similar size to those included, showing no group difference. The direction of results may be influenced by patient selection. It is possible that a differential effect of add-on options may be influenced by age, airway reversibility, smoking status, severity of baseline airway obstruction, type of asthma (eosinophilic versus non-eosinophilic), triggers (such as allergic rhinitis), adherence, etc. Future studies should now focus on comparing these add-on strategies in selected groups of patients so that characteristics of responders to either option may be better delineated. Measures of adherence (before and after randomisation) should also be incorporated in to the design of future studies.

The results apply predominantly to adult asthmatics who remain symptomatic despite 200 to 1000 µg/day doses of CFC-BDP or equivalent, and who present with a moderate (baseline FEV1 of 65% to 75% predicted value) reversible airway obstruction. The results should not be regarded as applicable to children and adolescents, or patients over 65 years of age.

The extensive search strategy yielded the identification and voluntary disclosure of data from several relevant trials, including two high-quality unpublished reports, and reduced the risk of publication bias. This assessment is also supported by a negative test for funnel plot asymmetry, although one must acknowledge the low sensitivity of this test in the presence of few trials. The high methodological quality of all trials contributing data and the confirmation of methodology and extracted data by authors or the study sponsors for the studies contributing to the primary outcome strengthen our findings.

AUTHORS' CONCLUSIONS

Implications for practice

In asthmatic adults with mild or moderate airway obstruction who are on low doses of inhaled corticosteroids and who demonstrate significant reversibility to a short-acting bronchodilator, the risk of an exacerbation requiring oral corticosteroids over 12 to 48 weeks was 17% lower in participants treated LABA compared LTRA. This was compatible with a NNT over a 48 week period of 38. Compared to LTRAs, the addition of LABA to inhaled corticosteroids is associated with statistically significant improvements in lung function, symptom-free days, use of rescue β_2-agonists, symptoms, symptom-free days, night awakenings, and quality of life, although the group differences are generally modest. There is evidence that LABAs increase the risk of serious adverse events when compared with LTRAs, from 2.5% to 3.4%. The findings support the use of a single inhaler for the delivery of LABA and inhaled corticosteroids. There are insufficient data to conclude which is the best add-on therapy for children unsatisfactorily controlled on ICS alone.

Implications for research

Future trials should address the main gaps in knowledge, namely the generalisability of results to the following.

1. Children, adolescents, and elderly patients.
2. Patients with severe (or milder) airway obstruction.
3. Asthmatic patients with minimal or no (< 12%) airway reversibility to bronchodilators at time of enrolment but with positive provocation challenge or other convincing criteria of the diagnosis of asthma.
4. Patients with co-morbidities, such as allergic rhinitis, aspirin-induced asthma, smokers or having environmental exposure to cigarette smoke, etc.
5. Add-on therapy to higher dose of inhaled corticosteroids than 200 to 280 µg/day of HFA-BDP, or equivalent.
6. Monitoring of adherence to both combination therapies.
7. Use of single inhalers for delivery of LABA and ICS compared to LTRA and ICS
8. Comparison of LABA and LTRA versus LABA and ICS (in a single device).
9. Measuring and reporting the impact of each adjunct therapy on inflammatory markers (preferably using induced sputum) and airway hyper-responsiveness over time.
10. Careful monitoring and reporting of outcomes that are important to the patient, particularly exacerbations requiring systemic steroids or hospital admission, symptoms, symptom-free days, night awakenings, quality of life, satisfaction, and life-threatening asthma as defined by admission to ICU or requiring intubation or ventilation.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bjermer 2003

Methods	Parallel-group, multicentre trial (148 centres in 37 countries)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: LTRA: 638±285 µg of beclomethasone-equivalent/day LABA: 647±229 µg of beclomethasone-equivalent/day RANDOMISED: 1490 (LTRA: 747; LABA: 743) WITHDRAWALS: LTRA: 125 (17%) LABA: 110 (15%) AGE in years: mean ± SD LTRA: 41.2 ± 13.6 LABA: 41.0± 13.7 GENDER (% male) LTRA: 45.4% LABA: 44.8% SEVERITY: MODERATE asthma BASELINE % PRED FEV1 LTRA: 71.3 ± 13.2 LABA: 72.7 ± 13.9 ALLERGIC RHINITIS: LTRA: 61.7% LABA: 60.4% ALLERGEN TRIGGERS: Not reported ASTHMA DURATION in years: mean ± SD LTRA: 16.3 ± 13.0 LABA: 16.2 ± 12.7 ELIGIBILITY CRITERIA: age: 15-72 years; clear history of chronic asthma for at least 1 year; regular use of inhaled corticosteroids over 8 weeks prior to study entry; FEV1 values between 50% and 90% of predicted; ≥12% improvement in FEV1 or PEFR after ß-agonists; minimum pre-determined level of daytime and night-time inhaled short-acting ß-agonist use (≥ 1 puff/day); minimum asthma symptom score (biweekly score of ≥56 on a scale of 0 to 336); current treatment includes only short-acting beta2-agonists and inhaled corticosteroids (200-1000 µg/day or equivalent); women with negative urine pregnancy test at screening EXCLUSION CRITERIA: emergency treatment for asthma within 1 month of 1st visit; hospitalisation for asthma within 3 months; unresolved upper respiratory tract infection within 3 weeks; active sinus infection; received the following asthma medications: oral corticosteroids within 1 month, cromolyn, nedocromil, leukotriene-receptor antagonists, long-acting or oral ß-agonists, inhaled anticholinergics within 2 weeks, theophylline, terfenadine, fexofenadine, loratadine, or cetirizine within 1 week

Bjermer 2003 (*Continued*)

Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 4 weeks Intervention period: 48 weeks INTERVENTION GROUP 1 LTRA: montelukast @ 10 mg/day p.o. + ICS (FP 100 µg bid, via discus) INTERVENTION GROUP 2 LABA: salmeterol 50 ug bid, via MDI + ICS (FP 100 µg bid, via Discus) 2 inhalers used for combination therapy. CO-TREATMENT: none
Outcomes	INTENTION-TO-TREAT ANALYSES Outcomes used at endpoint or 48 weeks PULMONARY FUNCTION TESTS Change from baseline FEV; change from baseline in am PEFR SYMPTOM SCORES Change from baseline NIGHT-TIME awakenings **EXACERBATIONS Exacerbations requiring systemic steroids; exacerbations requiring hospital admission; exacerbations requiring unscheduled office visit; exacerbations requiring emergency room visit; time to first exacerbation Definition: an asthma attack was defined by one or all of the following, hospitalisation; unscheduled office visit; ER visit; CS use (oral, IM, IV or rectal use) FUNCTIONAL STATUS Change in quality of life; change in night-time awakenings INFLAMMATORY MARKERS Change in serum eosinophils ADVERSE EFFECTS Elevated liver enzymes, headache, nausea, death, neutropenia, increased lymphocytes WITHDRAWALS Due to adverse effects; due to poor control; overall (** denotes primary outcome)
Notes	Full-text report; additional unpublished data provided by Peter Polos, June 2003 Funder: Merck Frost Confirmation of methodology and data extraction: received (Peter Polos, June 2003) User-defined number: 48 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by computer generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation occurred at pharmacy and not conducted by investigator

Bjermer 2003 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Number coded MDI/tablets supplied by pharmacy Tripple-blind (patient, assessor and treating physician); double-dummy (identical placebo)
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	Intention-to-treat analysis reported, but method not available
Selective reporting (reporting bias)	Low risk	Data obtained from investigators
Other bias	Low risk	

Ceylan 2004

Methods	Parallel-group; single centre study (Turkey)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids and SABA prn BASELINE INHALED STEROID DOSAGE Not reported (400µg/d BUD given as standard during 4 week run-in period) RANDOMISED 48. NB baseline data only reported for those who completed the study: LTRA: 20; LABA: 20 WITHDRAWALS: Not stated by treatment group AGE in years, mean: LTRA: 33.2 LABA: 39.1 GENDER (% male): LTRA: 55 LABA: 50 SEVERITY Moderate persistent asthma BASELINE % PRED FEV1 (L): LTRA: 69.7 LABA: 71.2 ALLERGIC RHINITIS (%): LTRA: 60 LABA: 70 ALLERGEN TRIGGERS Not reported ASTHMA DURATION in years: Mean ± SD: LTRA: 8.1± 4 LABA: 9 ± 8.8 ELIGIBILITY CRITERIA: age 15-60 years; diagnosis of asthma (GINA); persistent asthma symptoms for at least 1 year; use of ICS for at least 6 months; post-run in period: FEV1 or PEF ≥60 and ≤80% predicted

	-≥15% reversibility increase in FEV1; mean am PEF value ≤85% max after SABA; use of SABA ≥2 times per day or am/night symptom score ≥2 on 4 or less days per week EXCLUSION CRITERIA: smokers; pregnant or lactating women; life-threatening asthma; patients hospitalised due to asthma in last 3 months; upper/lower RTI
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 4 weeks Intervention period: 8 weeks Outcomes at 4, 8, and 12 weeks INTERVENTION GROUP 1 -LTRA = montelukast @ 10 mg/day p.o.+ BUD 200 µg BID, unclear inhaler device INTERVENTION GROUP 2 -LABA = formoterol 12 µg bid,+ BUD 200 µg BID, unclear inhaler device CO-TREATMENT: -SABA prn
Outcomes	PULMONARY FUNCTION TESTS Change in FEV1 % predicted; change in FEV1 (L); change in am PEF*; change in pm PEF SYMPTOM SCORES Morning symptom scores; night symptom scores EXACERBATIONS Not reported (participants who exacerbated were excluded from the study) FUNCTIONAL STATUS Rescue medication usage (puffs/d); % days without rescue medication usage INFLAMMATORY MARKERS Not reported EXACERBATIONS Need for a drug not included in the protocol ADVERSE EFFECTS Candidiasis; sore throat; voice problems; headache WITHDRAWALS Not clear -Due to ADVERSE EFFECTS Not reported -Due to poor control Not reported -Overall Stated * Main outcome
Notes	Full-text report No funding body User-defined number: 8 weeks

Risk of bias

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

Ceylan 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	Stated ITT for efficacy and safety, however baseline data are only presented for 40 participants who completed the study
Selective reporting (reporting bias)	Unclear risk	Unable to verify whether primary outcome measured in the review
Other bias	Low risk	

ELEVATE

Methods	Parallel group, pragmatic randomised controlled study in primary care population in the UK
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE Not specified RANDOMISED: LTRA: 164 LABA: 176 WITHDRAWALS Not specified (12 participants withdrew from treatment) AGE in years: mean ± SD Not reported GENDER (% male) Not reported SEVERITY Not described BASELINE PEF (% predicted) LTRA: 89.2 LABA: 87 ALLERGEN TRIGGERS Not reported ALLERGIC RHINITIS Not reported ASTHMA DURATION in years Not reported ELIGIBILITY CRITERIA >11 years; PEF predicted >50%; inadequately controlled on inhaled corticosteroids

ELEVATE (*Continued*)

	EXCLUSION CRITERIA Not listed SETTING: primary care
Interventions	DURATION: 2 years 1. LTRA (not specified from abstract) 2. LABA (not specified from abstract)
Outcomes	Asthma quality of life (AQLQ); exacerbations; asthma control questionnaire; PEF % predicted; symptoms; SABA usage; hospital admission; change in ICS (for participants at step 3)
Notes	TJL emailed for data: 22nd April, 2010.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Pragmatic randomised controlled trial
Allocation concealment (selection bias)	Low risk	Centralised 'ring-in' centre for randomisation
Blinding (performance bias and detection bias) All outcomes	High risk	Single-blind (to study personnel)
Incomplete outcome data (attrition bias) Exacerbations	Low risk	Low withdrawal rates (12/352) unlikely to affect results
Selective reporting (reporting bias)	High risk	Study presented as conference abstract. Outcomes within it well reported, but no information presented on exacerbations and SAEs. Trial protocol indicates that exacerbations were measured
Other bias	Unclear risk	No full-text article presenting clinical endpoints available to determine this

Fish 2001

Methods	Parallel-group study, multicentre trial (71 centres in USA and Puerto Rico)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: 84-4000 µg of beclomethasone-equivalent/day RANDOMISED: 948

	LTRA: 472 LABA: 476 WITHDRAWALS: LTRA: 70 (15%) LABA: 61 (13%) AGE in years: mean ± SD LTRA: 39.5 ± 14.0 LABA: 39.9 ± 13.5 GENDER (% male) LTRA: 38% LABA: 39% SEVERITY: Not described BASELINE FEV1 (% pred) LTRA: 68.6 (0.4) SE LABA: 68.1 (0.4) SE ALLERGEN TRIGGERS Not reported ASTHMA DURATION in years: % Less than 10 years LTRA: 26% LABA: 24% Over 10 years LTRA: 74% LABA: 76% ELIGIBILITY CRITERIA: aged ≥15 years; male or non-pregnant, non-lactating female; asthma for ≥ 6months; symptomatic despite ICS for at least 6 weeks prior to screening; 50-80% predicted FEV1; ≥12% increase in FEV1 post-bronchodilator (200 µg albuterol) In the 7 to 14 days prior to randomisation one or more of the following: 1. FEV1 of 50 to 80% of predicted 2. average of 4 or more puffs per day albuterol 3. symptom score of 2 or more for 3 or more days 4. 3 or more nights when patient woke at night due to asthma symptoms EXCLUSION CRITERIA Not described SETTING: outpatients in private and university clinics
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 1-2 weeks Intervention period: 12 weeks INTERVENTION GROUP 1 LTRA: montelukast 10 mg qd + ICS: continued current medication (which included fluticasone, triamcinolone, BDP, BUD and flunisolide) Mean 565 µg in CFC BDP-equivalent) INTERVENTION GROUP 2 LABA: salmeterol 50 µg bid, via Diskus + ICS: continued current medication Mean 546 µg in CFC BDP-equivalent

Fish 2001 (*Continued*)

	2 inhalers used for combination therapy CO-TREATMENT: none permitted
Outcomes	INTENTION-TO-TREAT ANALYSES Outcomes used at endpoint PULMONARY FUNCTION TESTS **Change from baseline in AM PEFR; change from baseline in pm PEFR SYMPTOM SCORES Change from baseline overall symptom scores; change in symptom-free days; patient satisfaction EXACERBATIONS Definition: any worsening of asthma symptoms requiring treatment beyond the use of blinded study drug and/or supplemental albuterol. Patients who experienced an asthma exacerbation were withdrawn from the study FUNCTIONAL STATUS Change from baseline in mean overall use of B2-agonists (puffs/DAY); change from baseline in mean DAYTIME use of B2-agonists (puffs/DAY); change from baseline in mean NIGHT-TIME use of B2-agonists (puffs/DAY); change in rescue-free days; change in night-time awakenings INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Drug related and non-drug related WITHDRAWALS Due to adverse effects reported (** denotes primary outcome)
Notes	Full-text report Received additional unpublished data provided by Karen Richardson, GSK, UK, August 2003 Funded by Glaxo Wellcome, studies SMS40003 & SMS40004 Confirmation of methodology and data extraction received User-defined order: 12 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Methods of randomisation: by computer generated random number
Allocation concealment (selection bias)	Low risk	Means of assignment by number coded inhaler/pills supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy design

Fish 2001 (*Continued*)

Incomplete outcome data (attrition bias) Exacerbations	Low risk	Received additional unpublished data provided by Karen Richardson, GSK, UK, August 2003
Selective reporting (reporting bias)	Low risk	Primary outcome data available for meta-analysis
Other bias	Low risk	

Green 2006

Methods	Crossover, single centre study in UK
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: ≤400 µg BDP equivalent N RANDOMISED: 49 N COMPLETED: 39 M = 25 F = 24 MEAN AGE: 42 SEVERITY: not stated BASELINE FEV1: 74.8% ATOPIC: 93% INCLUSION CRITERIA: 18-75 yrs, diagnosed with asthma; receiving treatment with less than or equal to 400 µg/day CFC-BDP per day ; one or more of 1) >15% increase in FEV1 post-SABA; 2) >20% within-day variability in PEF assessed twice daily over a 2-week period; 3) provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) <8 mg/mL-1; following run-in on 200mcg day BUD, participants were eligible if they had recorded day- or night-time asthma symptoms on their diary cards on at least 4 days in the third or fourth baseline week EXCLUSION: current smokers or smoking history of >10 pack-yrs, significant comorbidity, treated with oral corticosteroids, long-acting ß2-agonists, leukotriene antagonists or theophylline; asthma exacerbation or lower respiratory tract infection within the 4 weeks prior to trial entry
Interventions	LTRA + ICS versus LABA + ICS (Stable low dose of ICS) INTERVENTION GROUP 1 LTRA: oral montelukast 10 mg qd + budesonide 100 mg BID INTERVENTION GROUP 2 LABA: formoterol 12 mg BID + budesonide 100 mg BID TREATMENT PERIOD: 6 weeks (wash-out period: 4 weeks) RUN-IN PERIOD: 4 weeks CO-TREATMENT: not reported
Outcomes	INTENTION-TO-TREAT ANALYSES: Crossover data analysed for completers PULMONARY FUNCTION TESTS: FEV1, PEFR but only improvements when groups compared, no individual group results

	were presented SYMPTOM SCORES: VAS (individual group values not presented, but rather differences between groups) EXACERBATIONS Reported as events FUNCTIONAL STATUS Not stated INFLAMMATORY MARKERS Not stated ADVERSE EFFECTS Not stated WITHDRAWALS Not reported
Notes	Funding source not disclosed Confirmation of methodology and data extraction received User-defined order: 4 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'I believe that this was generated using a computer statistical package generating a random sequence. I don't know the package that was used and unfortunately the individual has left our organisation but had extensive clinical trials expertise.'
Allocation concealment (selection bias)	Low risk	'...this was indeed generated by a third party, namely the pharmacist responsible for dispensing the double blind medication (...) None of the study investigators were aware of the randomisation schedule until the last patient had completed the cross-over study'
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) Exacerbations	High risk	Completers used for analysis
Selective reporting (reporting bias)	Low risk	OCS-treated exacerbations reported. Data could not be extracted as only data on events and not number of participants were made available
Other bias	Low risk	

Grosclaude 2003

Methods	Parallel group, open-label study; multicentre study (115 centres in France)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE 1000 µg CFC Beclomethasone or equivalent daily. RANDOMISED = 253 LTRA: 130 LABA: 123 WITHDRAWALS LTRA: 16 (12%) LABA: 7 (6%) AGE in years: mean ± SD LTRA: 44.6 (18.2) LABA: 43.1 (17.8) GENDER (% male) LTRA: 39 LABA: 39 SEVERITY Not described BASELINE % PRED FEV1 (L) Not reported BASELINE PEF (L/min): LTRA: 327 LABA: 344 ALLERGIC RHINITIS (%): LTRA: 51% LABA: 52% ALLERGEN TRIGGERS Not reported ASTHMA DURATION in years: Mean ± SD Reported as % with asthma duration: <1 year: 6; between 1 and 5 years: 17; between 5 and 10 years: 15; between 10 and 15 years: 19; more than 15 years: 43 ELIGIBILITY CRITERIA: less than or equal to 15 years of age diagnosed asthma; treatment for at least four weeks with CFC BDP equivalent of ≥1000 µg/d and inhaled SABA prn; able to use Mini Wright PEF metre; able to fill in daily record card Over last seven days of run-in: 1. mean am PEF between 60-80% predicted best (as obtained post-BD at visit 2) 2. asthma symptoms on at least two days 3. used SABA at least four times EXCLUSION CRITERIA: use of systemic CS, anti-leukotriene agent, LABA, lower RTI within previous four weeks; hospitalisation within previous 4 weeks; hypersensitivity to one of compound study drugs; serious uncontrolled concurrent disease; allergen specific immunotherapy in incremental phase; smoker or ex-smoker with 10 pack year; participation in clinical study in previous month
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 1-2 weeks Intervention period: 12 weeks

	INTERVENTION GROUP 1 LTRA: montelukast @ 10 mg/day p.o.+ CFC BDP 250 ug two puffs bid, via pMDI INTERVENTION GROUP 2 LABA: salmeterol 50 ug bid, via MDI + FP 250 mcg one puff bid, via diskus (single combination inhaler) CO-TREATMENT: SABA prn
Outcomes	INTENTION-TO-TREAT ANALYSES outcomes used at endpoint or 12 weeks PULMONARY FUNCTION TESTS **change from baseline in AM PEF; change from baseline in pm PEFR SYMPTOM SCORES Change from baseline % nights with awakenings; change from baseline in % days with no symptoms; change from baseline in % nights with no symptoms EXACERBATIONS One or more of: Mild: reduction in AM PEF of >20% of baseline; increased bronchodilator usage; awakenings due to asthma on one or more consecutive nights Moderate: reduction in AM PEF >30% of baseline; change in maintenance therapy or premature termination of trial therapy; oral steroids Severe: hospitalisation FUNCTIONAL STATUS Change from baseline in % nights without rescue medication usage; change from baseline in % days without rescue medication usage; % of patients with good asthma control 10 of 12 weeks as defined by presence of two of: 1. PEF ≥80% predicted 2. no more than four puffs of BD on no more than 2 days 3. symptom free for at least two days; 4. presence of all the following criteria on a weekly basis: no nocturnal awakening; no exacerbation; no unscheduled medical contact; no adverse effect of treatment leading to withdrawal) INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Headache; gastroenteritis; upper respiratory inflammation; pharyngitis; viral respiratory infections; malaise and fatigue; allergic rhinitis; diarrhoea; digestive discomfort & pain; ENT symptoms; muscle cramps and spasms; regurgitation and reflux; nasal inflammation; vertigo; nausea and vomiting; cough; lower respiratory infections; dyspeptic symptoms WITHDRAWALS Due to poor completion of diary cards; due to adverse effects; due to poor control -overall (all reported) (** denotes primary outcome)
Notes	Full-text report and unpublished trial report Received additional unpublished data (SFCF4007) from GSK website Funded by GSK User-defined number: 12 weeks
Risk of bias	

Grosclaude 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	'The safety population included all subjects who received at least 1 dose of the study medication. The intent-to-treat population (ITT) included all randomised subjects who received at least one dose of the study medication, and from whom daily record card (DRC) data were available during the run-in period and the treatment period.'
Selective reporting (reporting bias)	Low risk	Data for exacerbations reported in pharmaceutical company download. The definition of exacerbation was not explicit and we could not used the outcome data for this study in the meta-analysis
Other bias	Low risk	

Hendeles 2004

Methods	Parallel groups; number of sites and countries unclear
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids and SABA prn with history of EIB at baseline BASELINE INHALED STEROID DOSAGE Not reported RANDOMISED = 91 (unclear allocation between groups) WITHDRAWALS Not reported AGE in years (range) 15-60 GENDER (% male) Not reported SEVERITY Not described BASELINE % PRED FEV1 (L) LTRA: 81.3

	LABA: 78.9 ALLERGIC RHINITIS (%) Not reported ALLERGEN TRIGGERS Not reported ASTHMA DURATION in years: Mean ± SD Not reported ELIGIBILITY CRITERIA: participants with asthma who remained symptomatic on ICS; age 15-60 years; history of EIB EXCLUSION CRITERIA: not reported
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION Intervention period: 4 weeks INTERVENTION GROUP 1 LTRA: montelukast @ 10 mg/day p.o.+ FP 125 µg one puff bid, via inhalation INTERVENTION GROUP 2 LABA: salmeterol 50 µg bid, via MDI + montelukast placebo + ICS = FP 125 µg one puff bid, via inhalation (separate inhalers) CO-TREATMENT Not reported
Outcomes	INTENTION-TO-TREAT ANALYSES: outcomes used at endpoint or 4 weeks PULMONARY FUNCTION TESTS Challenge FEV1 % predicted; change in FEV1 % predicted; rescue bronchodilation SYMPTOM SCORES Not reported EXACERBATIONS Not reported FUNCTIONAL STATUS Not reported INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Not reported WITHDRAWALS Due to adverse events: not reported Due to poor control: not reported Overall: reported Primary outcome not identified
Notes	Unpublished: conference abstract Funded by Merck User-defined number: 4 weeks No data could be used for aggregation

Risk of bias

Bias	Authors' judgement	Support for judgement

Hendeles 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Unable to verify whether primary outcome measured in the review
Other bias	Unclear risk	Not enough details about the study could be ascertained from the abstract available

Ilowite 2004

Methods	Parallel-group study, multicentre trial (132 centres in USA for 48 weeks)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: 220 μg of ICS per day RANDOMISED = 1473 LTRA: 743 LABA: 730 WITHDRAWALS: LTRA: 128/743 LABA: 113/730 AGE in years: mean ± SD LTRA: 39.0 (range 14-73) LABA: 38.1 (range 15-70) GENDER (% male) LTRA: 41.2% LABA: 37.5% SEVERITY Moderate-to-severe persistent asthma BASELINE FEV1 (% pred) LTRA: 74.3 ± (SD 11.5) LABA: 74.3 ± (SD 11.7) ALLERGEN TRIGGERS Not reported ALLERGIC RHINITIS Not reported ASTHMA DURATION in years NS ELIGIBILITY CRITERIA: age 15-65 years; asthma for ≥1 year; ICS use daily for at

	least 8 weeks prior to first visit; baseline FEV1 of 50 to 90% of predicted ≥12 % change in FEV1 after albuterol, and, in the 14 days prior to randomisation one or more of the following: 1. asthma symptom that required the use of ß2-agonist medication on average once per day 2. minimum biweekly daytime symptom score of 56 for a 14-day period) EXCLUSION CRITERIA: emergency department visit in < 1 month; admission for asthma in < 3 months; upper respiratory infection in < 3 weeks of 1st visit or during run-in; pregnant or lactating women; use of LABA within 1 month prior to visit 1; use < 1 month of oral, intravenous, intramuscular, or intra-articular corticosteroids; use < 2 weeks of leukotriene antagonist, cromolyn, or nedocromil, use of theophylline in < 1 week, use in < 2 weeks of oral or inhaled long-acting $ß_2$-agonists or inhaled anti-cholinergics SETTING: not described
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 2 weeks Intervention period: 48 weeks INTERVENTION GROUP 1 LTRA: montelukast 10 mg once daily + fluticasone 125 µg bid via MDI INTERVENTION GROUP 2 LABA: salmeterol 50 µg bid, via MDI + fluticasone 125 µg bid via MDI 2 inhalers used for combination therapy CO-TREATMENT: not specified
Outcomes	INTENTION-TO-TREAT ANALYSES for patients who received at least one dose of medication Outcomes used at endpoint PULMONARY FUNCTION TESTS: **Change from baseline in AM PEFR; change from baseline in PM PEFR; change from baseline in FEV1 SYMPTOM SCORES: Change from baseline DAYTIME symptom scores; change from baseline NIGHTTIME symptom scores EXACERBATIONS Exacerbations requiring systemic steroids FUNCTIONAL STATUS Change from baseline in mean OVERALL use of $beta_2$-agonists (puffs/DAY); change from baseline in mean DAYTIME use of $beta_2$-agonists (puffs/DAY); change from baseline in mean NIGHT-TIME use of $beta_2$-agonists (puffs/DAY); % night-time awakenings INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Drug related and non-drug related WITHDRAWALS Due to adverse effects reported (** denotes trials primary outcome)

Ilowite 2004 (*Continued*)

Notes	Unpublished data Received full disclosure of unpublished data provided by Peter Polos, March 2004 Funded by Merck & Co Confirmation with supportive documents received for methodology and data extraction User-defined number: 48 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was determined by computer generated allocation schedule (block size 4)
Allocation concealment (selection bias)	Low risk	Centralised, third party randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	ITT
Selective reporting (reporting bias)	Low risk	Data available for meta-analysis of primary outcome
Other bias	Low risk	

Lemanske 2010

Methods	Crossover study, multicentre study in USA
Participants	INADEQUATELY controlled children on inhaled corticosteroids at baseline BASELINE INHALED STEROID DOSAGE: 100 µg FP ICS per day during run-in RANDOMISED: 182 WITHDRAWALS: 25 AGE in years: mean ± SD 11 ± 3 GENDER (% male) 68% SEVERITY: Mild-to-moderate asthma BASELINE FEV1 (% pred) 98% ALLERGEN TRIGGERS: +ve aeroallergen test 77% +ve perennial allergen test 70%

	ALLERGIC RHINITIS Not reported ASTHMA DURATION 7 years ELIGIBILITY CRITERIA: age 6 to 17 years; physician diagnosed mild to moderate asthma, based on NAEPP criteria; FEV1 predicted >60%; increase in FEV1 >12% predicted or PC20 12.5mg/mL or less During run-in children had to exhibit uncontrolled asthma, defined as one or more of: 1. diary-reported symptoms (coughing rated as moderate or severe or wheezing rated as mild, moderate, or severe) 2. rescue use of reliever medication (two or more puffs per day, or 3. peak flows under 80% predicted EXCLUSION CRITERIA: corticosteroid treatment within 2 weeks (unless ingested nasally in which case at discretion of investigator; current or prior use of medications known to interact with corticosteroids; more than three hospitalizations for asthma in the past year; lung disease other than asthma; significant medical illness other than asthma; history of cataracts, glaucoma, or medical disorder associated with adverse effects related to corticosteroids; uncontrolled gastroesophageal reflux symptoms; significant asthma exacerbation within 2 weeks of Visit 1 or more than 5 courses of systemic corticosteroids in the past year; life-threatening asthma exacerbation requiring intubation, mechanical ventilation, or resulting in a hypoxic seizure in last 5 years; adverse reactions to ICS, LTRA, or LABA preparations; hyposensitization therapy other than an established maintenance regimen (continuous regimen for >3 months); pregnancy or lactation; failure to practice abstinence or use of an acceptable birth control if of child-bearing potential; inability to perform study procedures; refusal to consent to a genotype evaluation; inability to ingest the study drug; evidence that the family may be unreliable or nonadherent, or may move from the clinical center area before trial completion SETTING: not described
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 2-8 weeks Intervention period: 48 weeks (3 x 16 weeks) INTERVENTION GROUP 1 LTRA: montelukast 5 or 10 mg once daily + fluticasone 100 µg bid via DPI INTERVENTION GROUP 2 LABA: salmeterol 50 µg bid, via MDI + fluticasone 100 µg bid via DPI 1 inhaler used for combination therapy CO-TREATMENT: not specified
Outcomes	INTENTION-TO-TREAT ANALYSES No (completers analysed) PULMONARY FUNCTION TESTS: Collected as part of a composite outcome (differential response**): FEV1 SYMPTOM SCORES: Collected as part of a composite outcome (differential response**): symptom-free days EXACERBATIONS Collected as part of a composite outcome (differential response**): exacerbations requiring systemic steroids FUNCTIONAL STATUS

	Quality of life (AQLQ) INFLAMMATORY MARKERS: Collected ADVERSE EFFECTS Drug related and non-drug related WITHDRAWALS Stated (** denotes trials primary outcome)
Notes	Full-text article Funded by National Heart, Lung, and Blood Institute (HL064307, HL064288, HL064295, HL064287, HL064305, and HL064313), the National Institute of Allergy and Infectious Diseases (T32AI007635), and the Clinical Translational Science Award program of the National Center for Research Resources (UL1-RR025011 [Wisconsin], UL1-RR025780 [Colorado], and UL1-RR024992 [St. Louis]) Confirmation of data: not obtained User-defined number: 16 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation schedule: 'The pattern of treatment assignment will utilize the complete set of orthogonal Latin squares...'
Allocation concealment (selection bias)	Low risk	Centralised randomisation. Investigators dialled into server requesting assignment, and received a packet number which related to a medication
Blinding (performance bias and detection bias) All outcomes	Low risk	'The drug assignments were masked with the use of placebo tablets and dummy disk devices that discharged powder without the active drug' '...investigators and the children, along with their caregivers, will not know which treatment is being received during each treatment period.'
Incomplete outcome data (attrition bias) Exacerbations	High risk	Completers analysed (crossover design)
Selective reporting (reporting bias)	Low risk	Primary outcome analysed as events
Other bias	Low risk	

Nelson 2000

Methods	Parallel-group study, multicentre trial (39 centres)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: For the three week run-in period 100 µg twice daily FP (equivalent to 400 µg daily of beclomethasone) RANDOMISED: 447 LTRA: 225 LABA: 222 WITHDRAWALS: LTRA: 30 (13%) LABA: 24 (11%) AGE in years: mean ± SD LTRA: 43 ± 13.7 LABA: 40.2 ± 14.4 GENDER (% male) LTRA: 40% LABA: 39% SEVERITY Not reported BASELINE FEV1 (% predicted) LTRA: 70.8 ± 0.05 (SEM) LABA: 70.0 ± 0.05 ALLERGEN TRIGGERS Not reported ASTHMA DURATION in years: % Under 10 years LTRA: 23% LABA: 24% 10 years or more LTRA: 77% LABA: 76% ELIGIBILITY CRITERIA: age ≥15 years; asthma ≥ 6 months; low-moderate dose of ICS for ≥ 1month CFC-BDP: 252-420 µg/day; BUD 400 µg/day; FP 176- 220 µg/day; triamcinolone 600 - 800 µg/day); 50-80% of predicted normal ≥12 % increase in FEV1 post-200 µg albuterol; At randomisation: FEV1 50% to 80% of predicted; 1 additional sign of inadequate asthma control in the preceding 7 days: 1. ≥ 4 puffs/day albuterol 2. symptom score ≥2 on a scale of (0-5) for ≥ 3 days 3. ≥3 nights waking for asthma EXCLUSION CRITERIA: pregnant or lactating female patients; life threatening asthma; hospitalised for asthma in the last three months; significant concurrent diseases; <30 days of screening: use of theophylline, other bronchodilators, other leukotriene modifiers, cromolyn or nedocromil SETTING: not specified
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 3 weeks

Nelson 2000 (*Continued*)

	Intervention period: 12 weeks INTERVENTION GROUP 1 LTRA: oral montelukast 10 mg once daily + ICS = FP 100 µg twice daily, via diskus INTERVENTION GROUP 2 LABA: salmeterol 50 µg twice daily, via Diskus + ICS = FP 100 µg twice daily, via Diskus 1 inhaler used for combination therapy CO-TREATMENT: none
Outcomes	Modified INTENTION-TO-TREAT ANALYSES Outcomes used at endpoint for exacerbations and withdrawals only (not available for continuous values) PULMONARY FUNCTION TESTS Change from baseline FEV1; change from baseline in AM PEFR; change from baseline in PM PEFR SYMPTOM SCORES Change from baseline OVERALL symptom scores; change from baseline in nighttime awakenings; change in symptom-free days EXACERBATIONS Exacerbations requiring hospital admission; exacerbations requiring systemic steroids (data provided) FUNCTIONAL STATUS Change from baseline in mean OVERALL use of ß2-agonists (puffs/DAY); change in rescue-free days INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Included oral candidiasis, sore throat, hoarseness, headache WITHDRAWALS Due to adverse effects Due to poor control Overall (reported) (** denotes primary outcome)
Notes	Full-text report Received additional unpublished data provided by Karen Richardson, GSK (July 2003) Funded by Glaxo Wellcome, study SAS40018 Confirmation of methodology and data extraction received User-defined order: 12 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Numbered coded inhaler/pills supplied by pharmacy

Nelson 2000 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	'The primary population for the analyses of demographic/baseline characteristics, efficacy and safety was the Intent-to-Treat (ITT Population), which consisted of all subjects who were randomised to receive study drug.'
Selective reporting (reporting bias)	Low risk	Data available for primary outcome.
Other bias	Low risk	

Nelson 2001

Methods	Parallel-group, multicentre trial (54 centres)
Participants	INADEQUATELY controlled adolescent and adult participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: Not described RANDOMISED = 429 LTRA: 215 LABA: 214 WITHDRAWALS: LTRA: 18 (8%) LABA: 12 (6%) AGE in years: mean ± SD LTRA: 39.3 ± 13.20 LABA: 40.9 ± 13.17 GENDER (% male) LTRA: 44% LABA: 44% SEVERITY Not described BASELINE FEV1 (% predicted) LTRA: 65.86 ± 0.58 (SEM) LABA: 66.62 ± 0.58 ALLERGEN TRIGGERS Not reported ASTHMA DURATION in years: % Under 10 years LTRA: 24% LABA: 24% 10 years or over LTRA: 76%

	LABA: 76% ELIGIBILITY CRITERIA: age ≥12 years; asthma ≥ 6 months; FEV1 50-80% of predicted normal; ≥12 % increase in FEV1 post 200 µg albuterol Following 7-14 day run-in In the six days prior to randomisation one or more of the following: 1. an average of 4 or more puffs/day of albuterol 2. a symptom score of 2 or more on at least 2 days for any of the asthma symptom categories 3. at least one night when the patient woke due to asthma 4. two or more days where pm to am PEF variation was 20% or more * intake of daily inhaled steroids prior to randomisation is NOT specified as inclusion criteria* Patients also must have been using an oral or inhaled SABA for 6 weeks EXCLUSION CRITERIA: not described SETTING: clinical centres
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 1-2 weeks Intervention period: 4 weeks INTERVENTION GROUP 1 LTRA: zafirlukast 20 mg twice daily + ICS: constant dose of existing ICS medication INTERVENTION GROUP 2 LABA: salmeterol 42 µg, 2 puffs twice daily via MDI + ICS = constant dose of existing ICS medication 2 inhalers used for combination therapy CO-TREATMENT: Theophylline or other medications that could potentially interact with study treatment not allowed; Albuterol inhalers provided for use on an as needed basis but all other bronchodilators not permitted; antihistamines, nasal decongestants and intranasal medications for rhinitis were permitted
Outcomes	INTENTION-TO-TREAT ANALYSES: outcomes used at endpoint PULMONARY FUNCTION TESTS Change from baseline FEV1; **change from baseline in am PEFR; change from baseline in PM PEFR; change in PEF variability SYMPTOM SCORES Change from baseline DAYTIME symptom scores; change from baseline NIGHT-TIME symptom scores; change in symptom-free days; patient satisfaction EXACERBATIONS Exacerbations requiring systemic steroids; exacerbations defined as any worsening of asthma symptoms requiring a change in the patients asthma therapy other than increased use of supplemental albuterol. Patients who experienced an exacerbation were withdrawn from the study FUNCTIONAL STATUS Change from baseline in mean DAYTIME use of B2-agonists (/DAY); change from baseline in mean NIGHT-TIME use of ß2-agonists (/DAY); change in rescue-free days; change/absolute in rescue-free nights; change in quality of life; change in night-time awakenings

Nelson 2001 (*Continued*)

	INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Upper respiratory tract infection, headache, nausea WITHDRAWALS Due to adverse effects Due to poor control Overall (reported) (** denotes primary outcome)
Notes	Full-text report Received additional unpublished data provided by Karen Richardson, GSK Funded by Glaxo Wellcome, protocols SLGA5024 & SLGA5025 Confirmation of methodology and data extraction received User-defined order: 4 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	'The ITT population included all subjects who were randomized to study drug.'
Selective reporting (reporting bias)	Low risk	Data available for primary outcome
Other bias	Low risk	

Nsouli 2001

Methods	Unclear if parallel-group or crossover
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: FP 100-300 or CFC BDP 200-550 or BUD 200-400 or flunisolide 500-1000 or triamcinolone 400-1000 RANDOMISED: 30 LTRA: unknown LABA: unknown

	WITHDRAWALS Not described AGE in years: mean ± SD Not described GENDER (% male) Not described SEVERITY Not described BASELINE FEV1 (L OR % PRED) Not described ALLERGEN TRIGGERS Not described ASTHMA DURATION in years: mean ± SD Not described ELIGIBILITY CRITERIA Not described EXCLUSION CRITERIA Not described SETTING Not described
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: not described Intervention period: 8 weeks INTERVENTION GROUP 1 LTRA: montelukast 10 mg QD pm + ICS (low dose ICS) INTERVENTION GROUP 2 LABA: salmeterol 50 µg BID + ICS (low dose ICS) 2 inhalers used for combination therapy CO-TREATMENT Not reported
Outcomes	ANALYSES: not reported PULMONARY FUNCTION TESTS FEV1 and FEF25-75 SYMPTOM SCORES None described EXACERBATIONS Not described FUNCTIONAL STATUS Quality of life INFLAMMATORY MARKERS Not described ADVERSE EFFECTS Not described WITHDRAWALS Not described

Nsouli 2001 (*Continued*)

Notes	Abstract Funding of study unknown Confirmation of methodology and data extraction not obtained User-defined order: 8 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Cannot establish this reliably
Other bias	Unclear risk	Cannot establish this reliably

Pavord 2007

Methods	Parallel-group, multicentre study in the UK
Participants	BASELINE INHALED STEROID DOSE: up to 400 μg (which BDP or HFA) BDP equivalent N SCREENED: 132 N RANDOMISED: 66 N COMPLETED: 54 M = 34 F = 32 MEAN AGE: 35 BASELINE DETAILS: PEF 417 L/min; FEV1 predicted 76% INCLUSION CRITERIA: 18 to 50 years, non-smokers, receiving a stable dose of up to 400 μg of beclomethasone dipropionate (presumed CFC-BDP equivalent) a day or equivalent ICS, requiring further therapy; likelihood of compliance with the protocol requirements and ability to use an Accuhaler and mini-Wright peak flow meter. Post-run in: baseline FEV1 61 to 85% predicted; PC20 < 8 mg/ml with methacholine challenge; at least one of: diary card recording of symptoms on > 4 of the last seven days of the run-in period; recorded use of relief medication on >2 different days during the last seven days of the run-in period; period variation in PEF of >10% over last seven days of run in EXCLUSION: additional medication other than ICS, SABA or OCS in previous 3

	months; acute respiratory infection/exacerbation of asthma within 4 weeks of screening; recent or significant smoking history; pregnancy/lactation; inadequate contraceptive methods in women of child-bearing age
Interventions	1. Combination fluticasone/salmeterol 100/50 µg B.I.D 2. Fluticasone 100mcg B.I.D. plus montelukast 10mg O.D. RUN-IN PERIOD: 2 weeks TREATMENT PERIOD: 12 weeks
Outcomes	INTENTION TO TREAT ANALYSES: no PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOMS: Percentages of symptom-free days and nights FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Neutrophils, eosinophils, macrophages, lymphocytes
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'...consecutively randomised according to a pre-defined randomisation list...'
Allocation concealment (selection bias)	Low risk	'Treatment allocation was concealed from the subject, pharmacist, and investigator.'
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy design employed
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	'All summaries and analyses are for the intention-to-treat population (all subjects receiving at least one dose of the study drug) . No imputations were performed for missing data. Therefore if data were missing for either baseline or one of the time points, it was not possible to calculate a change from baseline. However, all available data have been used for relevant summaries.' Some imbalance between the treatment groups in terms of withdrawal, although denominators for lung function outcomes show N randomised

Pavord 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	The outcomes identified as being those of interest were presented in the article. Data on exacerbations were not identified as being an outcome of interest to the investigators
Other bias	Low risk	

Ringdal 2003

Methods	Parallel-group, multicentre trial (114 centres in 19 countries)
Participants	INADEQUATELY controlled participants on 'moderate or high doses' of inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: 800 µg or more of beclomethasone-equivalent/day (moderate or high dose) RANDOMISED: 806, 81 excluded due to not meeting eligibility criteria for randomisation LTRA: 369 LABA: 356 WITHDRAWALS: LTRA: 37 (10%) LABA: 19 (5%) AGE in years: mean ± SD LTRA: 43 (14-79) LABA: 43 (15-75) GENDER (% male) LTRA: 45% LABA: 46% SEVERITY: MODERATE PERSISTENT asthma BASELINE FEV1 (% PRED) LTRA: 74.3 ± 16.1 LABA: 75.8 ± 15.3 ALLERGEN TRIGGERS Not described ASTHMA DURATION in years: mean ± SD Not described ELIGIBILITY CRITERIA: age ≥15 years; moderate persistent asthma as per the ATS and NAEPP Report 2; using inhaled corticosteroids at moderate or high dose (400-1000 µg/day of CFC-BDP, BUD or flunisolide; or 200-500 µg/day of FP) for at least 4 weeks; history of reversible airway obstruction; ≥15% change in FEV1 after 800 µg of salbutamol; At end of run-in: Mean PEF of 50% to < 85% of value in clinic after 400 µg of salbutamol; cumulative symptom score of ≥8 in past 7 days or ≥4 of the last 7 days of run-in EXCLUSION CRITERIA: Recent change in asthma medication; respiratory tract infection or admission for asthma in < 4 weeks; intake of oral, depot, or parenteral corticosteroids in < 4 weeks or ≥2 occasions in past 12 weeks; cigarette smoking ≥10 pack

	year; pregnancy or lactating women or those likely to become pregnant during study; FEV1 < 50%
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 4 weeks Intervention period: 12 weeks plus a 2-week follow up INTERVENTION GROUP 1 LTRA: montelukast 10 mg/day + ICS: FP 100 ug twice daily, via diskus INTERVENTION GROUP 2 LABA: salmeterol 50 ug bid + ICS: FP 100 µg twice daily, via Diskus 1 inhaler used for combination therapy. CO-TREATMENT: Salbutamol provided for relief of symptoms, no other SABAs permitted Other oral, parenteral or depot CS not allowed except where documented for treatment of exacerbations. Other existing asthma treatment allowed at constant dose
Outcomes	INTENTION-TO-TREAT ANALYSES: yes, but excluding those who were incorrectly randomised because they failed major inclusion criteria; outcomes used at endpoint PULMONARY FUNCTION TESTS Change from baseline in FEV1; **change from baseline in am PEFR; change from baseline in pm PEFR SYMPTOM SCORES Change in total symptom score; % change in symptom-free days and nights; patient satisfaction; physician assessment of effectiveness; compliance with study treatment EXACERBATIONS Exacerbations requiring systemic steroids; exacerbations requiring hospital admission; exacerbations defined as MILD: deterioration in asthma requiring a clinically relevant increase in salbutamol use defined as more than 3 additional inhalations per 24 hour period with respect to baseline for more than 2 consecutive days. MODERATE: requiring oral CS and/or antibiotics. SEVERE: requiring hospitalisation FUNCTIONAL STATUS % rescue-free days; % change in use of rescue medication (puffs/day); % symptom-free days INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Serious adverse events, headache, oral thrush WITHDRAWALS Due to adverse effects Overall (reported) (** denotes primary outcome)
Notes	Full-text report Received additional unpublished data provided by Karen Richardson, GSK Funded by Glaxo SmithKline, study SAS40015 Confirmation of methodology and data extraction received User-defined order: 12 weeks

Ringdal 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Numbered coded inhalers/pills supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	'The ITT population (SFC: 404 subjects; FP+montelukast: 401 subjects), which included all randomised subjects, was used for adverse event and concurrent medication data. The modified ITT population (SFC: 356 subjects; FP+montelukast: 369 subjects), which excluded randomised subjects who did not receive treatment as well as subjects who were incorrectly randomised, was used for efficacy, demography and baseline characteristics data.'
Selective reporting (reporting bias)	Low risk	Data available for primary outcome
Other bias	Low risk	

SAM40030

Methods	Parallel-group, multicentre trial
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: ≤400 µg of BDP/day or equivalent RANDOMISED: 66 LTRA: 33 LABA: 33 WITHDRAWALS: LTRA: 4/33 (12.12%) LABA: 9/33 (27.27%) AGE in years: mean ± SD 35 years GENDER (% male) 52% SEVERITY:

SAM40030 (*Continued*)

	Mild-moderate BASELINE FEV1 (% pred) 76% ALLERGEN TRIGGERS: Not reported ALLERGIC RHINITIS: Not reported ASTHMA DURATION in years Not reported ELIGIBILITY CRITERIA: age 18-50 years; confirmed diagnosis of asthma -have received constant daily dose of up to 400 mcg of inhaled CFC-BDP or equivalent in the last 4 weeks During run-in period: FEV1 61-85% of predicted; ≥20 % fall in FEV1 on methacholine challenge; symptom score of ≥1 on 4/7 days; use of rescue ß2-agonists on ≥2/7 days; ≥10% period variation in PEFR over the last 7 days of run-in EXCLUSION CRITERIA: intake of asthma medication other than inhaled steroids or short-acting beta$_2$-agonists in the past 4 weeks; oral steroids in the past 3 months; respiratory infection within 4 weeks; hospital admission in past 12 months; evidence of underlying chronic lung disease; smoking history of 10 pack-years or more; pregnant or lactating women; other chronic diseases; use of LABA or LTRAs within 1 month prior to visit 1; known intolerance to study drugs or inhaled lactose SETTING: not described
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: not reported Intervention period: 12 weeks INTERVENTION GROUP 1 LTRA: montelukast 10 mg die + fluticasone (Flixotide) 100 bid via MDI INTERVENTION GROUP 2 LABA: salmeterol 50 µg bid via MDI + fluticasone 100 µg bid (in single MDI: Seretide 50) 1 inhaler used for combination therapy CO-TREATMENT: not specified
Outcomes	Modified INTENTION-TO-TREAT ANALYSES Outcomes used at 12 weeks or endpoint PULMONARY FUNCTION TESTS Change from baseline in AM PEFR (L/min); change from baseline in PM PEFR (L/min); change from baseline in FEV1 (L) SYMPTOMS (reported as medians) Change in symptom-free days; change in symptom-free nights EXACERBATIONS REQUIRING SYSTEMIC STEROIDS Not reported FUNCTIONAL STATUS (reported as medians): Change from baseline in mean DAYTIME use of ß2-agonists; change from baseline in mean NIGHT-TIME use of ß2-agonists; change in rescue-free days; change in night-time awakenings INFLAMMATORY MARKERS (reported as medians):

SAM40030 (*Continued*)

	Sputum **eosinophils, neutrophils, total cell counts, C-LT, histamine, IL-8 ADVERSE EFFECTS Reported WITHDRAWALS Reported (** denotes primary outcome)
Notes	Unpublished data Received full disclosure of unpublished data provided by Karen Richardson, GSK (July 2003) Funded by GSK : study #40030 Confirmation with supportive documents received for methodology and data extraction obtained from Karen Richardson, GSK, UK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Opaque consecutive envelopes containing assessment
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	'The intention-to-treat (ITT) sample was used for the efficacy and safety analyses. This consisted of all subjects randomised to and receiving at least one dose of study medication.'
Selective reporting (reporting bias)	Unclear risk	Not clear whether OCS exacerbations collected in the study
Other bias	Low risk	

SD-004-0216

Methods	Parallel-group study; multicentre trial (49 centres in 6 countries)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids at baseline BASELINE INHALED STEROID DOSAGE: 400-1000 μg of ICS (not specified)/day RANDOMISED: 236 LTRA: 118 LABA: 118 WITHDRAWALS:

SD-004-0216 (*Continued*)

	LTRA: 19/118 (16%) LABA: 12/118 (10%) AGE in years: mean ± SD LTRA: 38.3 ± NS LABA: 38.1 ± NS GENDER (% male) LTRA: 47 % LABA: 49% SEVERITY: Not described BASELINE FEV1 (% predicted) LTRA: 72.03 ± SD LABA: 69.71 ± SD ALLERGEN TRIGGERS Not reported ALLERGIC RHINITIS Not reported ASTHMA DURATION in years LTRA: 10.1 ± SD LABA: 12.1 ± SD ELIGIBILITY CRITERIA: Male or female outpatient; age 12-70 years; treated for at least 3 mo with 400-1000 µg of inhaled glucocorticoids (presumed CFC-BDP equivalent) ; asthma diagnosis; FEV1 50-80% predicted; ≥12% reversibility in FEV1 and at least 200 mL after inhalation of 1 mg of terbutaline; smoking history of ≤10 pack years In the 7 days prior to randomisation one or more of the following: 1. a symptom score of ≥1 on 4 days 2. awakening on ≥ 1 night due to asthma symptoms 3. use of ß2-agonists ≥10 puffs as weekly mean EXCLUSION CRITERIA: respiratory infection; clinical obstructive pulmonary disease, or pulmonary dysfunction other than asthma; pregnant or lactating women; use of LABA within 1 month prior to visit 1; previous use ever of a leukotriene antagonist; known intolerance to study drugs or inhaled lactose SETTING: not described
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in period: 10-14 days Intervention period: 8 weeks INTERVENTION GROUP 1 LTRA: zafirlukast 20 mg bid + budesonide 200 µg bid via turbuhaler INTERVENTION GROUP 2 LABA: formoterol 12 µg bid, via turbohaler + budesonide 200 µg bid via turbuhaler 2 inhalers used for combination therapy CO-TREATMENT: not specified
Outcomes	Modified INTENTION-TO-TREAT ANALYSES for patients who received at least one dose of medication. Outcomes used at endpoint PULMONARY FUNCTION TESTS **Change from baseline in am PEFR; change from baseline in pm PEFR; change from baseline in FEV1

SD-004-0216 (*Continued*)

	SYMPTOM SCORES Change from baseline DAY-TIME symptom scores; change from baseline NIGHT-TIME symptom scores EXACERBATIONS Exacerbations requiring systemic steroids FUNCTIONAL STATUS Change from baseline in mean OVERALL use of ß2-agonists (puffs/DAY); change from baseline in mean DAYTIME use of ß2-agonists (puffs/DAY); change from baseline in mean NIGHT-TIME use of ß2-agonists (puffs/DAY); % night-time awakenings INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Drug related and non-drug related WITHDRAWALS Due to adverse effects reported (** denotes primary outcome)
Notes	Unpublished data Received full disclosure of unpublished data provided by Roger Metcalf, AstraZeneca, July 2003 Funded by Astra Zeneca. Report #SD-004CR-0216 Confirmation with supportive documents received for methodology and data extraction User-defined number: 12 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented
Allocation concealment (selection bias)	Low risk	Opaque consecutive numbered envelopes containing assignment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) Exacerbations	Unclear risk	Analysis described as modified
Selective reporting (reporting bias)	Unclear risk	Not clear whether the study collected information on exacerbations treated with OCS
Other bias	Low risk	

Storms 2004

Methods	Parallel-group; multicentre study (16 centres in USA)
Participants	INADEQUATELY controlled participants on inhaled glucocorticoids and SABA prn with history of EIB at baseline BASELINE INHALED STEROID DOSAGE Not reported RANDOMISED: 78 LTRA: 39 LABA: 39 WITHDRAWALS LTRA: 0 (0%); LABA: 2 (5%) AGE in years: mean: LTRA: 33.3 LABA: 30 GENDER (% male): LTRA: 29.2 LABA: 41 SEVERITY Not described BASELINE % PRED FEV1 (L) LTRA: 87.5 LABA: 88.1 ALLERGIC RHINITIS (%) Not reported ALLERGEN TRIGGERS Not reported ASTHMA DURATION in years: mean ± SD: LTRA: 17.4 ±11.1 LABA: 19.7 ±12 ELIGIBILITY CRITERIA: age 15-45 years with one year history of asthma; uncontrolled asthma on ICS for at least 2 months; treatment at randomisation with only SABA and ICS; history of EIB (15% drop in FEV1 on ICS, 20% if not on ICS); resting FEV1 $\geq$70% predicted; $\geq$12% increase in baseline FEV1 post-SABA; requirement for SABA on $\geq$3 days of last week of run-in period EXCLUSION CRITERIA: respiratory infection within last 3 weeks and emergency asthma care in previous 3 months; systemic corticosteroids in previous month; patients were required to stop an anti-asthma medication with the exception of ICS two weeks before first study visit; participants requiring oral steroids during the study were withdrawn
Interventions	LTRA + ICS versus LABA + ICS (stable dose of ICS) DURATION: Run-in Period: 1-2 weeks Intervention Period: 4 weeks INTERVENTION GROUP 1 LTRA: montelukast @ 10 mg/day p.o.+ placebo salmeterol inhaler + FP 100 µg bid, via Diskus INTERVENTION GROUP 2 LABA: salmeterol 50 µg bid via MDI + montelukast placebo + FP 100 µg bid, via Diskus (separate inhalers)

Storms 2004 (*Continued*)

	CO-TREATMENT: SABA prn
Outcomes	INTENTION-TO-TREAT ANALYSES - outcomes used at endpoint or 4 weeks PULMONARY FUNCTION TESTS **Challenge FEV1 % predicted; absolute FEV1 % predicted; fall in FEV1 post-exercise (%); rescue bronchodilation SYMPTOM SCORES Clinic exercise assessment score EXACERBATIONS None occurred during the study (requirement for OCS) FUNCTIONAL STATUS Not reported INFLAMMATORY MARKERS Not reported ADVERSE EFFECTS Not reported WITHDRAWALS Reported Due to adverse events: reported Due to poor control: not reported Overall: reported (** denotes primary outcome)
Notes	Full-text report Funded by Merck User-defined number: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy LTRA and LABA
Incomplete outcome data (attrition bias) Exacerbations	Low risk	'A modified intention-to-treat approach was used for efficacy analyses. For FEV1, all randomized patients who had challenge-rescue evaluations at baseline and during treatment were eligible for analyses. There was no imputation of missing values, and prior values were not carried forward.'

Storms 2004 (*Continued*)

Selective reporting (reporting bias)	Low risk	No exacerbations occurred during the study
Other bias	Low risk	

BDP: beclomethasone; DPI: dry powder inhaler; FEV1: forced expiratory volume in one second; FP: fluticasone; GSK: GlaxoSmithKline; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; LTRA: leukotriene receptor antagonist; MDI: metered dose inhaler; PEFR: peak expiratory flow; challenge FEV1 % predicted: FEV1 measured post-SABA after 6 minutes exercise on a treadmill exacerbating heart rate to 80-90% of individual's predicted maximum.

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

Study	Reason for exclusion
Adinoff 1998	One of the interventions was not LTRA + ICS
Anon 1999	Not an RCT - Montelukast vs. zafirlukast review
Anon 2000	Not an RCT (review)
Anon 2001	Not an RCT (review)
Barnes 1997	Not an RCT (review)
Becker 2000	Not an RCT (Review of montelukast)
Bergmann 2004	One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid
Bleecker 2006	Combined analysis of two combination therapy trials versus anti-leukotriene agent alone
Borker 2005	No ICS co-treatment in both groups
Brabson 2002	No co-intervention with ICS
Buchvald 2003	Study duration was less than 28 days.
Caffey 2005	No ICS co-treatment in both groups
Calhoun 2001	Non permitted drugs: study compared montelukast vs. placebo with both group receiving ICS and LABA
Cash 2001	Not an RCT - Commentary on a previously published trial.
Chopra 2005	Comparison between two different LABA + ICS combinations

(*Continued*)

Chuchalin 2002	One of the interventions was not LTRA + ICS
Currie 2002	No systematic co-treatment with ICS
Currie 2003a	Non permitted drug : salmeterol in both groups
Currie 2003b	LTRA in both groups
Currie 2003c	Duration of intervention <30 days
Davis 2001	No co-treatment with ICS and LTRA
Dekhuijzen 2002	Not an RCT but a review article
Delaronde 2005	Intervention is educational (not drug)
Dempsey 2000	Single dose intervention (not > 28 days)
Deykin 2007	Comparison of MON/SAL with FP/SAL
Dicpinigaitis 2002	No systematic co-treatment with ICS
Donohue 2001	Review of combination therapies
Dorinsky 2001	No ICS used
Dorinsky 2002	One of the interventions was not LTRA + ICS
Dorinsky 2002a	One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid (no ICS in LTRA group)
Dorinsky 2004	One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid (no ICS in LTRA group)
Dunn 2001	Review of zafirlukast
Edelman 2000	No co-intervention with ICS
Edin 2002	One of the interventions was not LTRA + ICS
Eliraz 2001	No co-treatment with LTRA - Compares two dry powder inhalers
Eliraz 2002	One of the interventions was not LTRA + ICS
Everden 2002	One of the interventions was not LTRA + ICS
Gabrijelcic 2004	One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid

(*Continued*)

Giannini 2002	One of the interventions was not LTRA + ICS
Grzelewska 2003	One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid
Gupta 2007	Study assessed LTRAs in addition to LABAs.
Havlucu 2005	Not an RCT
Horwitz 1998	Not an RCT (Review)
Houghton 2004	Comparison of propellants in formoterol - no ICS in both groups
Inouhe 2007	Single dose study protocol
Jarvis 1998	Not an RCT (Review of zafirlukast)
Jarvis 1999	Not an RCT but a review article on Zafirlukast.
Jenkins 2005	LTRA and LABA not compared as add on to ICS
Jonsson 2004	One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid
Kalberg 1999	Retrospective data analysis, not an RCT
Kanniess 2002	No systematic co-treatment with ICS
Kanniess 2002b	One of the interventions was not LABA + ICS
Karaman 2007	No prior treatment with ICS.
Kardos 2001	One of the interventions was not LABA + ICS
Keith 2009	Observational study
Kemp 1998	Not an RCT (Review)
Knorr 2001	No consistent co-tx with ICS in all patients (Montelukast vs placebo)
Koenig 2008	Study compared LABA and LTRA without background ICS in either group
Kohrogi 1999	Not an RCT (before and after study)
Laviolette 1999	One of interventions is not LABA + ICS
Lazarus 2001	One of interventions is not LTRA + ICS
Lee 2004	No LTRA and No LABA

(*Continued*)

Lee 2005	RCT testing two types of ICS
Leflein 2002	No systematic co-treatment with ICS
Lipworth 2000	Intervention < 28 days (1 week only)
Liu 1996	No consistent co-treatment with ICS (Zileuton vs. placebo as add-on therapy to ICS)
LOCCS	Comparison of Combination therapy with LRTA alone.
Maspero 2008	Study compared LABA and ICS with LTRA alone.
McCarthy 2002	One of the interventions was not LTRA + ICS
Meltzer 2002	No co-treatment with inhaled corticosteroids
Miraglia del Giudice 2007	No prior ICS treatment.
Mitchell 2005	Intervention is educational (not drug)
Molitor 2005	One of the interventions not LTRA
Naedele-Risha 2001	Not a RCT, review of LABA+ICS therapy
Nathan 2000	Good review of add-on therapy to ICS. Not an RCT.
Nathan 2001b	Not a RCT, review of antileukotriene agents
Nathan 2005	No direct comparison between LABA and LTRA
Nelson 2004	Both treatment groups received FP and Salmeterol (LTRA tested as add-on to LABA)
O'Sullivan 2003	One of the interventions was not LABA + ICS
Ohbayashi 2009	Investigation of addition of anti-leukotriene to combination inhaled steroid and long-acting beta-agonist
Ollendorf 2000	Not an RCT, but an economic evaluation
Oppenheimer 2008	Study assessed addition of anti-leukotriene (montelukast) in addition to combination LABA and ICS in asthma
Ortega-Cisneros 1998	No leukotriene antagonists used in intervention
Paterson 1999	No systematic co-treatment with ICS
Pearlman 2002	No consistent co-tx with ICS (FP + S vs Montelukast alone)

(*Continued*)

Perez 2000	Not RCT - no control group, all patients treated with montelukast
Peroni 2002	Short duration < 28 days
Peroni 2005	Inadequate duration.
Petermann 2004	Review article
Plaza 2005	Intervention is educational (not drug)
Price 2003	One of the interventions was not LABA + ICS
Riccioni 2002	No systematic co-treatment with ICS
Rickard 1998	No systematic co-treatment with ICS
Rosenhall 2003	One of the interventions is not LTRA + ICS
SAS40036	LTRA administered without an ICS.
SAS40037	LTRA administered without an ICS.
SAS40066	LTRA administered without an ICS.
Serrier 2003	One of the interventions is not LTRA + ICS
Sheth 2002	Second report - cost effectiveness analyses
Sims 2003	Intervention < 28 days
Smith 1998	Not an RCT (Review)
Sorkness 2007	LTRA administered without an ICS.
Stanford 2003	LTRA administered without an ICS.
Stelmach 2001	No consistent co-intervention with ICS (RCT of ICS vs. LABA vs. LTRA)
Stelmach 2002	No consistent co-intervention with ICS (RCT of ICS vs. LABA vs. LTRA vs. nedocromil)
Stelmach 2002a	No co-intervention with ICS
Stelmach 2007	Participants were all on combination therapy ICS + LABA prior to enrollment and all controller medication was withdrawn for the 4-week run-in period. Neither before or during the run-in were the participants on ICS alone prior to randomisation
Stelmach 2008	Participants wereall on combination therapy ICS with either LABA or LTRA prior to enrollment and were removed from all controller medications for the 4-week run-in period: consequently they were not on ICS alone prior to enrollment

(*Continued*)

Stempel 1998	Not an RCT (Review)
Stempel 2002	Not an RCT (Review)
Stevenson 2005	No LTRA or LABA given.
Terzano 2001	One of the interventions is not LTRA + ICS
Thien 2000	Not an RCT (Review)
Tolley 2002	One of the interventions was not LTRA + ICS
Vaquerizo 2003	One of the interventions was not LABA + ICS
Volovitz 1999	No consistent co-intervention with ICS in all patients (Montelukast vs. beclomethasone)
Warner 2001	Not an RCT (Review)
Wilson 1999	Only 14 days intervention (not >=28 days)
Wilson 2001	Only 14 days intervention (not >= 28 days)
Wytrychowski 2001	Not an RCT - controlled study
Yurdakul 2002	Not truly randomised as eligible patients were allocated to each treatment group according to their application month to hospital (consecutive alocation not random)
Zarkovic 1998	One of the interventions was not LTRA + ICS
Zimmerman 2002	One of the interventions was not LTRA + ICS

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

Fardon 2002

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	

Fardon 2002 (*Continued*)

Contact information	
Notes	

Fardon 2004

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Price 2001

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	Professor D Price (University of East Anglia, Norwich, NR4 7TJ)
Notes	ISSN: N0254145816.

Ruggins 2003

Trial name or title	
Methods	
Participants	

Ruggins 2003 (*Continued*)

Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with one or more exacerbations requiring systemic corticosteroids	6	5571	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.97]
1.1 Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily	5	5142	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.97]
1.2 Zafirlukast 20 mg twice daily versus Salmeterol 50 mcg twice daily	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.29, 2.52]
2 Morning PEF: L/min change from baseline	11		Mean Difference (Random, 95% CI)	15.36 [11.35, 19.37]
2.1 Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily	8		Mean Difference (Random, 95% CI)	15.91 [13.27, 18.55]
2.2 Zafirlukast 20 mg twice daily versus salmeterol 50 mcg or formoterol 9 mg twice daily	2		Mean Difference (Random, 95% CI)	9.66 [-1.40, 20.73]
2.3 Montelukast 10 mg once daily versus formoterol 18mg twice daily	1		Mean Difference (Random, 95% CI)	23.8 [10.89, 36.71]
3 Evening PEF: L/min change from baseline	10		Mean Difference (Random, 95% CI)	12.64 [10.11, 15.17]
3.1 Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily	7		Mean Difference (Random, 95% CI)	13.29 [10.34, 16.23]
3.2 Zafirlukast 20 mg twice daily versus salmeterol 50 mcg or formoterol 9 mg twice daily	2		Mean Difference (Random, 95% CI)	8.24 [1.99, 14.50]
3.3 Montelukast 10 mg once daily versus formoterol 18mg twice daily	1		Mean Difference (Random, 95% CI)	17.5 [10.16, 24.84]
4 FEV1: L change from baseline	10		Mean Difference (Fixed, 95% CI)	0.08 [0.06, 0.10]
4.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	6		Mean Difference (Fixed, 95% CI)	0.08 [0.06, 0.11]
4.2 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily	2		Mean Difference (Fixed, 95% CI)	0.05 [-0.02, 0.12]
4.3 Montelukast 10 mg once daily versus formoterol 18mg twice daily	2		Mean Difference (Fixed, 95% CI)	0.0 [-0.09, 0.09]
5 FEV1: L % change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

5.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 FEV1: % predicted end of treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Montelukast 5 mg once daily versus formoterol 18mg twice daily	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 % fall in FEV1 POST-EXERCISE	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 Montelukast 10 mg once daily versus salmeterol 50 mcg twice daily	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Zafirlukast 20mg twice daily versus salmeterol 50 mcg or formoterol 9mcg twice daily	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Montelukast 5 mg once daily versus formoterol 18mg twice daily	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Rescue-free days: % change from baseline	5	2612	Mean Difference (IV, Random, 95% CI)	9.18 [5.39, 12.98]
8.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	4	2183	Mean Difference (IV, Random, 95% CI)	7.33 [4.41, 10.26]
8.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Mean Difference (IV, Random, 95% CI)	15.0 [9.43, 20.57]
9 Rescue medication use: puffs/day change from baseline	7	4055	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.75, -0.24]
9.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	4	3353	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.56, -0.19]
9.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg or Formoterol 9 mg twice daily	2	662	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.72, 0.00]
9.3 Montelukast 10 mg once daily versus formoterol 18mg twice daily	1	40	Mean Difference (IV, Random, 95% CI)	-1.4 [-1.81, -0.99]
10 Change in Global asthma QoL AQLQ Score (higher is better) - change from baseline	3	2893	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.05, 0.17]

10.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	2	2464	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.03, 0.16]
10.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.02, 0.36]
11 Symptom free days: % change from baseline	6		Mean Difference (Fixed, 95% CI)	7.27 [4.71, 9.83]
11.1 Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily	5		Mean Difference (Fixed, 95% CI)	5.87 [2.86, 8.87]
11.2 Zafirlukast 20 mg twice daily versus Salmeterol 50 mcg twice daily	1		Mean Difference (Fixed, 95% CI)	11.0 [6.10, 15.90]
12 Day-time symptom scores (high is worse) - change from baseline	5	3823	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.25, -0.12]
12.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	4	3394	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.24, -0.10]
12.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.48, -0.10]
13 Morning symptoms - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Montelukast 10 mg once daily versus formoterol 18mg twice daily	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Night-time symptom score (5pt scale, higher score is worse) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Change in number of night awakenings per week - change from baseline	4	4214	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.19, -0.06]
15.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	3	3785	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.26, -0.05]
15.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Mean Difference (IV, Fixed, 95% CI)	-0.1 [-0.18, -0.02]
16 Change in % of nights with no awakenings per week - change from baseline	2	673	Mean Difference (IV, Fixed, 95% CI)	6.89 [2.87, 10.91]
16.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	1	244	Mean Difference (IV, Fixed, 95% CI)	6.60 [-1.06, 14.26]

16.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Mean Difference (IV, Fixed, 95% CI)	7.0 [2.28, 11.72]
17 Rescue-free nights (%) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Withdrawals for any reason	11	6291	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.96]
18.1 Montelukast 10mg/day vs Salmeterol 50ug twice daily	9	5626	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.98]
18.2 Zafirlukast 20 mg twice daily vs Salmeterol 50 mcg twice daily	2	665	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.40, 1.06]
18.3 Montelukast 10mg/d versus Formoterol 18mcg/d	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Withdrawals due to adverse events	11	6291	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.29]
19.1 Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily	9	5626	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.78, 1.32]
19.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	2	665	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.41, 2.05]
20 Withdrawals due to poor asthma control/asthma exacerbation	8	5354	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.49, 1.56]
20.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	6	4689	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.50, 2.07]
20.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	2	665	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.19, 1.32]
21 Patients with one or more exacerbations requiring hospital admission	4	3993	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.58, 2.98]
21.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	4	3993	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.58, 2.98]
22 Serious Adverse events	7	5658	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.00, 1.82]
22.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	6	5229	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.00, 1.83]
22.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.96]
23 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

23.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Headache	10	6187	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.90, 1.26]
24.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	7	5482	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.92, 1.29]
24.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	2	665	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.36, 1.57]
24.3 Montelukast 10 mg once daily versus formoterol 18mg twice daily	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
25 Cardiovascular events	5	5163	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.77, 1.53]
25.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	5	5163	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.77, 1.53]
26 Oral moniliasis	6	5203	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.00, 3.44]
26.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	5	5163	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.02, 3.61]
26.2 Montelukast 10 mg once daily versus formoterol 18mg twice daily	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
27 Osteopenia/osteoporosis	2	2963	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.12, 2.63]
27.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	2	2963	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.12, 2.63]
28 Elevated liver enzymes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
28.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Overall adverse events	9	5977	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.99, 1.07]
29.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	8	5548	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.99, 1.07]
29.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.81, 1.31]
30 Patient treatment satisfaction	3	2020	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.04, 1.20]
30.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	2	1591	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.05, 1.14]
30.2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily	1	429	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.10, 1.47]
31 Change from baseline in serum eosinophils (x 10e9/L)	2	2787	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.02, 0.05]
31.1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily	2	2787	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.02, 0.05]

Comparison 2. Subgroup and sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with one or more exacerbations requiring systemic corticosteroids: number of inhaler devices	6		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1 Single device for LABA + ICS	2	1252	Risk Ratio (IV, Fixed, 95% CI)	0.49 [0.29, 0.83]
1.2 Two devices for LABA + ICS	4	4319	Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.75, 1.04]
2 Participants with one or more exacerbations requiring systemic corticosteroids: dose of ICS	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low dose of ICS	3	2742	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.00]
2.2 Medium dose of ICS	1	1452	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.67, 1.08]
2.3 Mixed	1	948	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.50, 1.96]
2.4 Unclear	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.29, 2.52]
3 Participants with one or more exacerbations requiring systemic corticosteroids: study duration	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 12 weeks or less	4	2629	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.45, 0.96]
3.2 48 weeks	2	2942	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.04]
4 Serious adverse effects stratified by number of inhaler devices used for LABA + ICS	7		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1 Single device for LABA + ICS	3	1318	Risk Ratio (IV, Fixed, 95% CI)	0.72 [0.26, 1.99]
4.2 Two devices for LABA + ICS	4	4340	Risk Ratio (IV, Fixed, 95% CI)	1.43 [1.04, 1.97]

Comparison 3. MD archive from previous review version

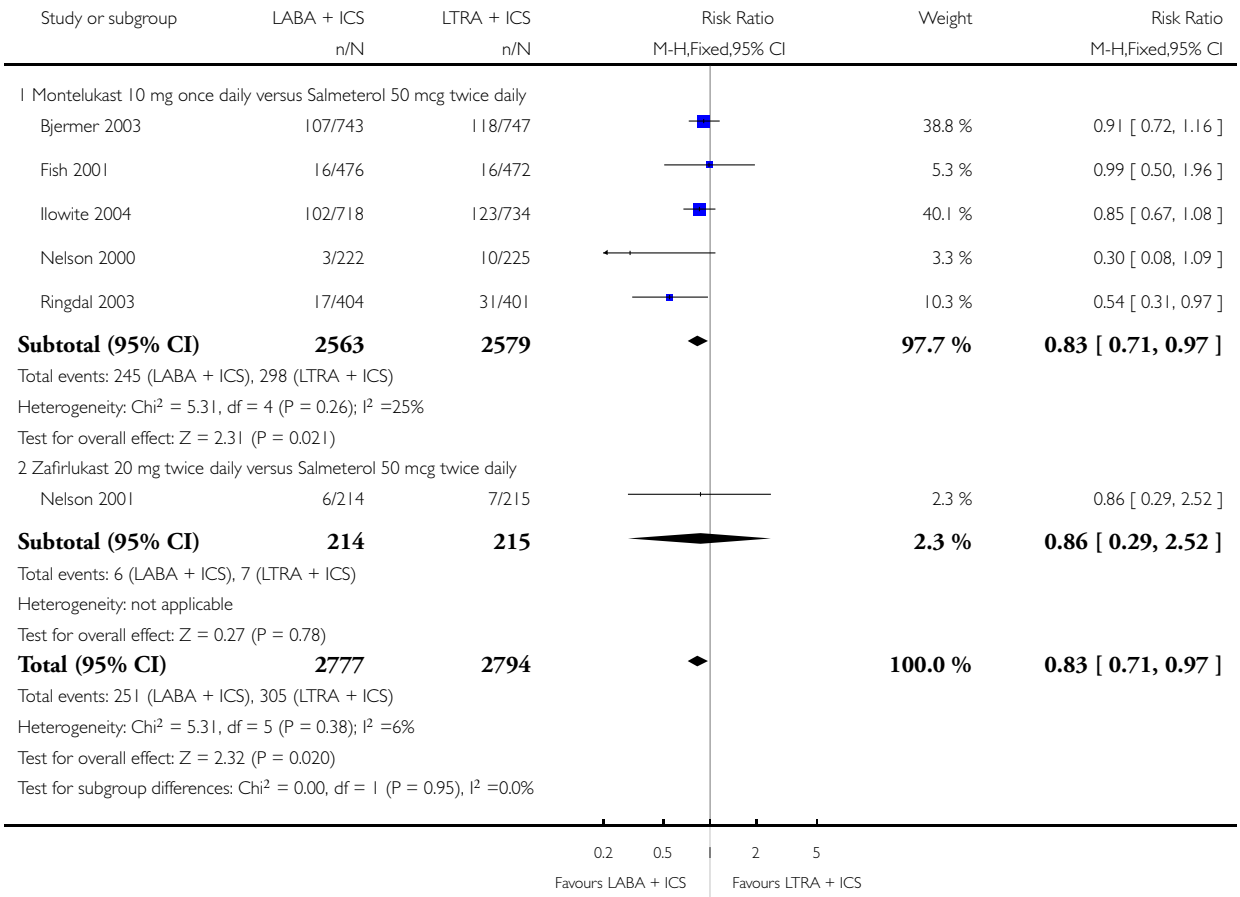
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Morning PEF (L/min) - change from baseline	10		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Evening PEF (L/min) - change from baseline	9		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 FEV1 (L) - change from baseline	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Symptom free days (%) - change from baseline	5		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 1 Participants with one or more exacerbations requiring systemic corticosteroids.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 1 Participants with one or more exacerbations requiring systemic corticosteroids



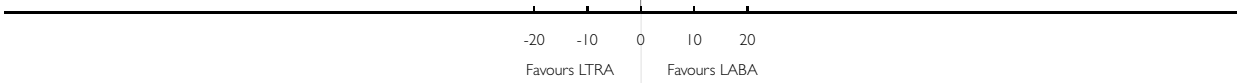
Analysis 1.2. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 2 Morning PEF: L/min change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 2 Morning PEF: L/min change from baseline

Study or subgroup	Mean Difference (SE)	Weight	Mean Difference IV,Random,95% CI
1 Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily			
Bjermer 2003	16.86 (2.397959)	13.3 %	16.86 [12.16, 21.56]
Fish 2001	13.3 (2.882653)	12.3 %	13.30 [7.65, 18.95]
Grosclaude 2003	13.2 (5.515306)	7.5 %	13.20 [2.39, 24.01]
Ilowite 2004	14.2 (3.959184)	10.1 %	14.20 [6.44, 21.96]
Nelson 2000	16.4 (3.816327)	10.4 %	16.40 [8.92, 23.88]
Pavord 2007	33.3 (10.0255102)	3.3 %	33.30 [13.65, 52.95]
Ringdal 2003	16 (3.678571)	10.7 %	16.00 [8.79, 23.21]
SAM40030	31.9 (10.88776)	2.9 %	31.90 [10.56, 53.24]
Subtotal (95% CI)		**70.4 %**	**15.91 [13.27, 18.55]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.59$, df = 7 (P = 0.47); $I^2 = 0.0\%$			
Test for overall effect: Z = 11.82 (P < 0.00001)			
2 Zafirlukast 20 mg twice daily versus salmeterol 50 mcg or formoterol 9 mg twice daily			
Nelson 2001	15.8 (3.984694)	10.1 %	15.80 [7.99, 23.61]
SD-004-0216	4.47 (2.280612)	13.5 %	4.47 [0.00, 8.94]
Subtotal (95% CI)		**23.6 %**	**9.66 [-1.40, 20.73]**
Heterogeneity: $Tau^2 = 53.64$; $Chi^2 = 6.09$, df = 1 (P = 0.01); $I^2 = 84\%$			
Test for overall effect: Z = 1.71 (P = 0.087)			
3 Montelukast 10 mg once daily versus formoterol 18mg twice daily			
Ceylan 2004	23.8 (6.586735)	6.1 %	23.80 [10.89, 36.71]
Subtotal (95% CI)		**6.1 %**	**23.80 [10.89, 36.71]**
Heterogeneity: not applicable			
Test for overall effect: Z = 3.61 (P = 0.00030)			
Total (95% CI)		**100.0 %**	**15.36 [11.35, 19.37]**
Heterogeneity: $Tau^2 = 25.79$; $Chi^2 = 28.25$, df = 10 (P = 0.002); $I^2 = 65\%$			
Test for overall effect: Z = 7.51 (P < 0.00001)			
Test for subgroup differences: $Chi^2 = 2.66$, df = 2 (P = 0.26), $I^2 = 25\%$			

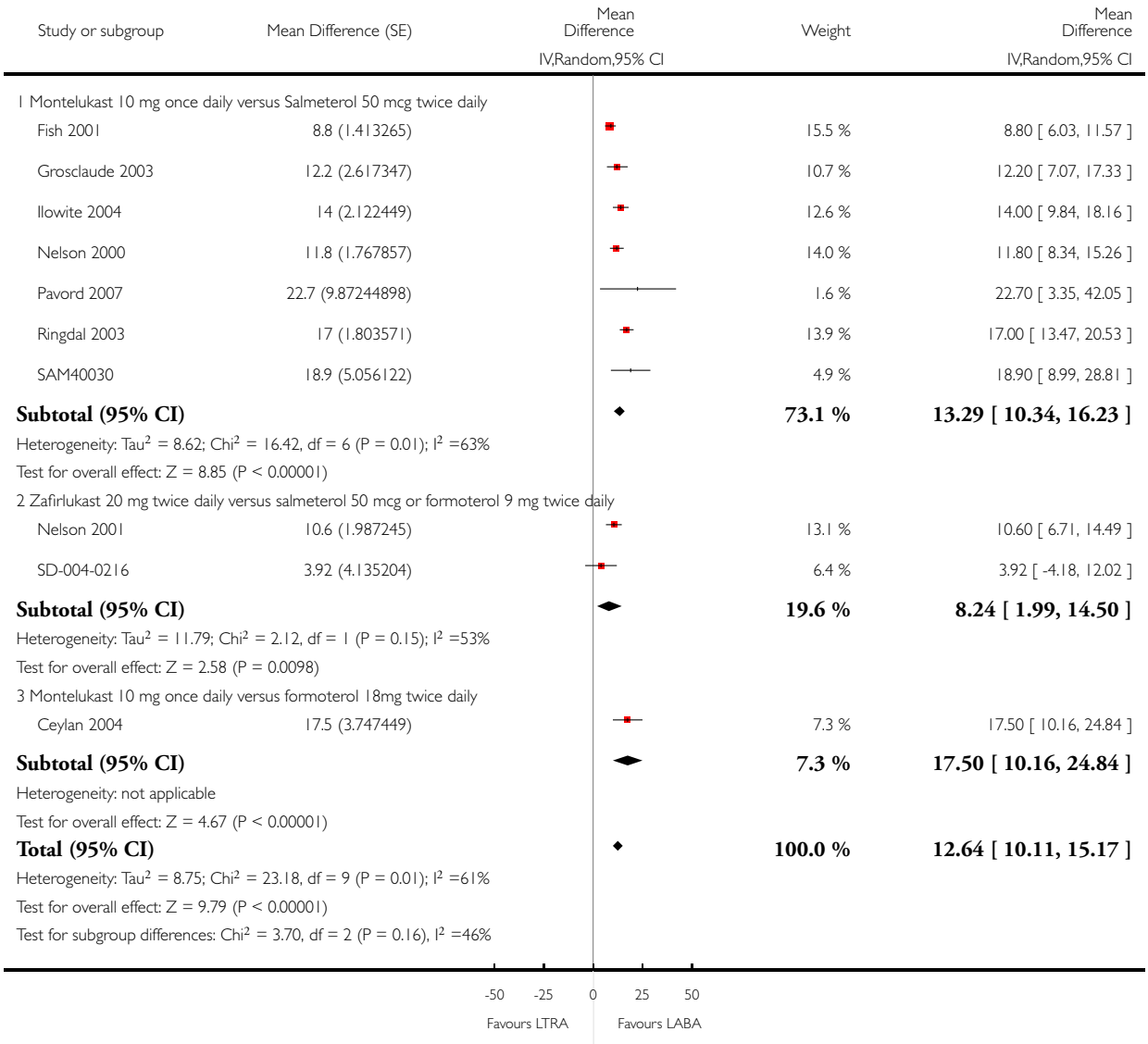


Analysis 1.3. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 3 Evening PEF: L/min change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 3 Evening PEF: L/min change from baseline

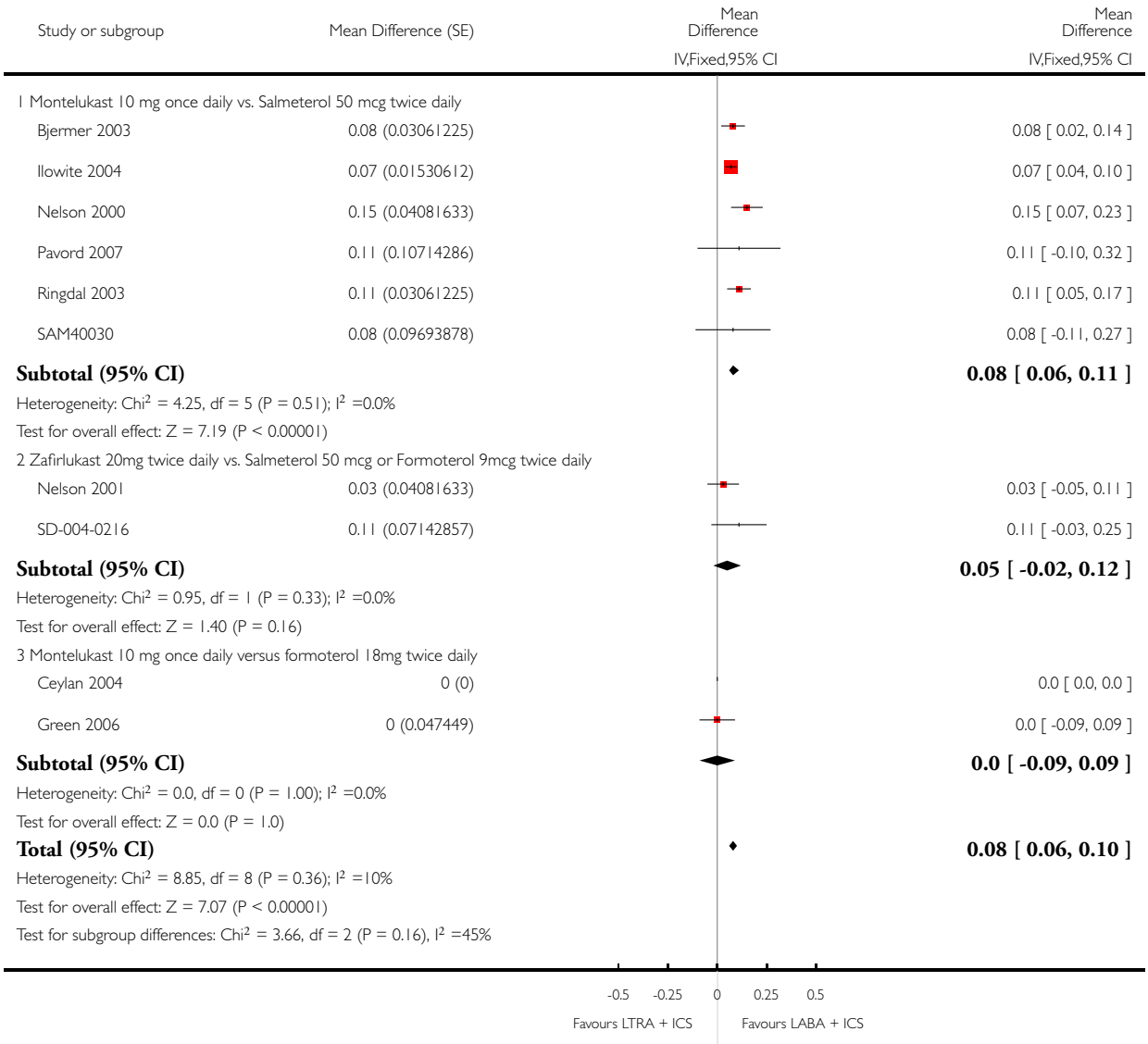


Analysis 1.4. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 4 FEV1: L change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 4 FEV1: L change from baseline



Analysis 1.5. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 5 FEV1: L % change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 5 FEV1: L % change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily						
Storms 2004	34	1.7 (9.5)	36	10.9 (8.5)		-9.20 [-13.43, -4.97]
2 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily						

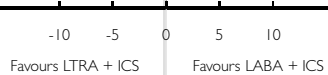
Analysis 1.6. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 6 FEV1: % predicted end of treatment.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 6 FEV1: % predicted end of treatment

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily						
Storms 2004	34	91.2 (10.1)	36	86.6 (11)		4.60 [-0.34, 9.54]
2 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily						
3 Montelukast 5 mg once daily versus formoterol 18mg twice daily						



Analysis 1.7. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 7 % fall in FEV1 POST-EXERCISE.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 7 % fall in FEV1 POST-EXERCISE

Study or subgroup	LABA +ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Montelukast 10 mg once daily versus salmeterol 50 mcg twice daily						
Storms 2004	34	10.5 (10)	36	7.7 (8.1)		2.80 [-1.48, 7.08]
2 Zafirlukast 20mg twice daily versus salmeterol 50 mcg or formoterol 9mcg twice daily						
3 Montelukast 5 mg once daily versus formoterol 18mg twice daily						

Analysis 1.8. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 8 Rescue-free days: % change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 8 Rescue-free days: % change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily							
Ringdal 2003	337	32 (38.55)	326	28 (41.53)		20.1 %	4.00 [-2.10, 10.10]
Fish 2001	451	27.4 (34)	443	20.1 (29.5)		27.8 %	7.30 [3.13, 11.47]
Nelson 2000	196	32.7 (39.2)	189	23 (37.12)		15.6 %	9.70 [2.08, 17.32]
Grosclaude 2003	117	40.4 (30.9)	124	29.8 (32.6)		14.6 %	10.60 [2.58, 18.62]
Subtotal (95% CI)	**1101**		**1082**			**78.0 %**	**7.33 [4.41, 10.26]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.15$, df = 3 (P = 0.54); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.92 (P < 0.00001)							
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily							

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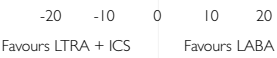
Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Nelson 2001	214	27 (32.2)	215	12 (26.4)		22.0 %	15.00 [9.43, 20.57]
Subtotal (95% CI)	**214**		**215**			**22.0 %**	**15.00 [9.43, 20.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.27 (P < 0.00001)							
Total (95% CI)	**1315**		**1297**			**100.0 %**	**9.18 [5.39, 12.98]**
Heterogeneity: Tau^2 = 8.97; Chi^2 = 7.85, df = 4 (P = 0.10); I^2 =49%							
Test for overall effect: Z = 4.74 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 5.70, df = 1 (P = 0.02), I^2 =82%							



Analysis 1.9. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 9 Rescue medication use: puffs/day change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 9 Rescue medication use: puffs/day change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily							
Fish 2001	451	-1.9 (2.12)	443	-1.66 (2.32)		15.2 %	-0.24 [-0.53, 0.05]
Ringdal 2003	337	-0.98 (1.84)	326	-0.78 (1.26)		16.3 %	-0.20 [-0.44, 0.04]
Nelson 2000	196	-1.86 (2.24)	189	-1.3 (2.06)		12.3 %	-0.56 [-0.99, -0.13]
Ilowite 2004	702	-1.66 (1.59)	709	-1.15 (1.6)		17.6 %	-0.51 [-0.68, -0.34]
Subtotal (95% CI)	**1686**		**1667**			**61.4 %**	**-0.37 [-0.56, -0.19]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.03, df = 3 (P = 0.11); I^2 =50%							
Test for overall effect: Z = 3.93 (P = 0.000086)							
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg or Formoterol 9 mg twice daily							
Nelson 2001	214	-1.46 (1.9)	215	-0.95 (1.47)		14.6 %	-0.51 [-0.83, -0.19]
SD-004-0216	117	-1.86 (1.84)	116	-1.73 (1.83)		11.4 %	-0.13 [-0.60, 0.34]

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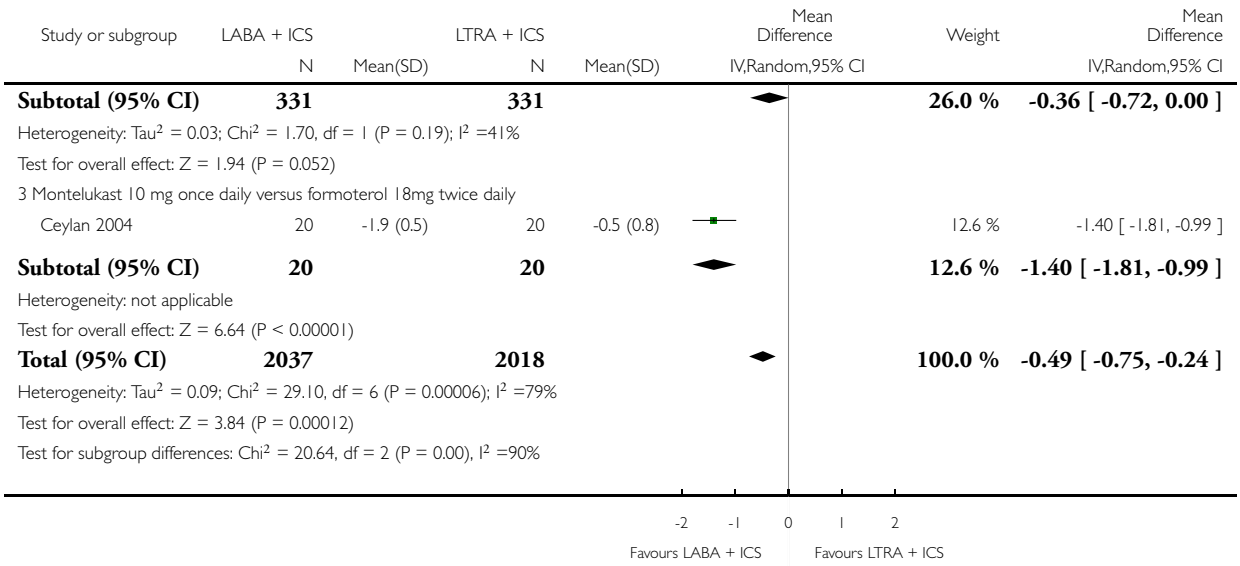


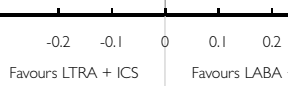
Analysis 1.10. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 10 Change in Global asthma QoL AQLQ Score (higher is better) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 10 Change in Global asthma QoL AQLQ Score (higher is better) - change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily							
Ilowite 2004	647	0.9 (0.76)	655	0.78 (0.77)		55.1 %	0.12 [0.04, 0.20]
Bjermer 2003	581	0.76 (0.96)	581	0.71 (0.96)		31.2 %	0.05 [-0.06, 0.16]
Subtotal (95% CI)	**1228**		**1236**			**86.3 %**	**0.09 [0.03, 0.16]**
Heterogeneity: Chi^2 = 0.99, df = 1 (P = 0.32); I^2 =0.0%							
Test for overall effect: Z = 2.79 (P = 0.0052)							
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily							
Nelson 2001	214	0.76 (0.88)	215	0.57 (0.88)		13.7 %	0.19 [0.02, 0.36]
Subtotal (95% CI)	**214**		**215**			**13.7 %**	**0.19 [0.02, 0.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.24 (P = 0.025)							
Total (95% CI)	**1442**		**1451**			**100.0 %**	**0.11 [0.05, 0.17]**
Heterogeneity: Chi^2 = 2.07, df = 2 (P = 0.35); I^2 =3%							
Test for overall effect: Z = 3.42 (P = 0.00062)							
Test for subgroup differences: Chi^2 = 1.09, df = 1 (P = 0.30), I^2 =8%							

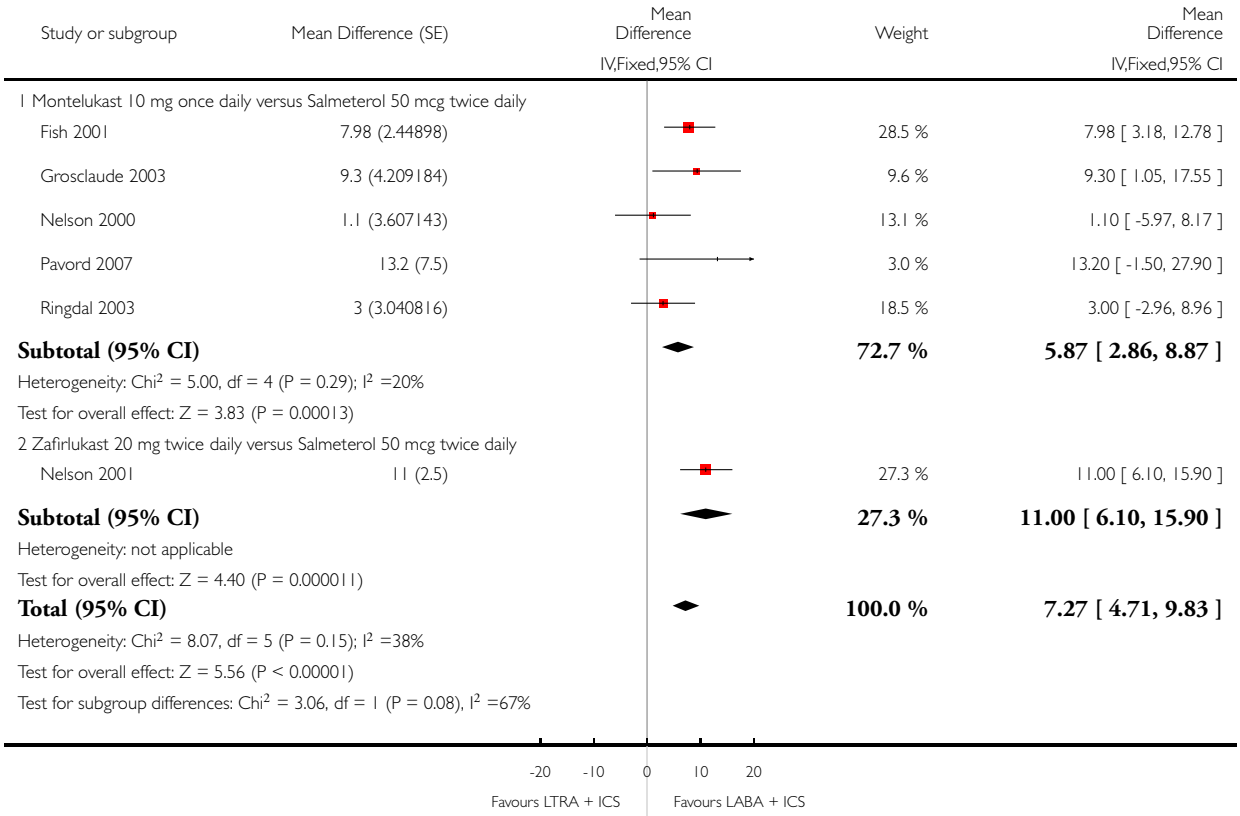


Analysis 1.11. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 11 Symptom free days: % change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 11 Symptom free days: % change from baseline

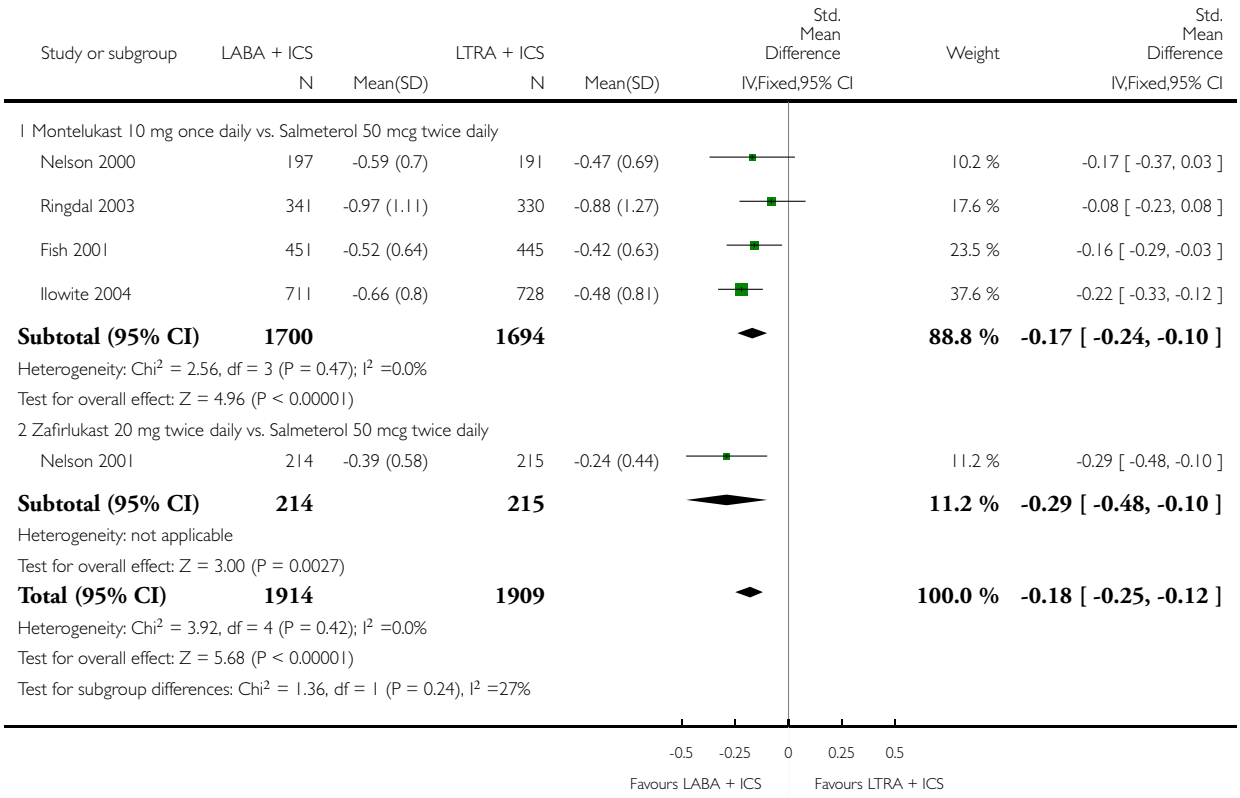


Analysis 1.12. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 12 Day-time symptom scores (high is worse) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 12 Day-time symptom scores (high is worse) - change from baseline



Analysis 1.13. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 13 Morning symptoms - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 13 Morning symptoms - change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Montelukast 10 mg once daily versus formoterol 18mg twice daily						
Ceylan 2004	20	-2.6 (0.7)	20	-0.8 (0.6)		-1.80 [-2.20, -1.40]

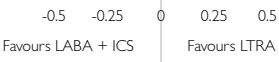
Analysis 1.14. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 14 Night-time symptom score (5pt scale, higher score is worse) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 14 Night-time symptom score (5pt scale, higher score is worse) - change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily						
Nelson 2001	214	-0.43 (0.59)	215	-0.25 (0.59)		-0.18 [-0.29, -0.07]



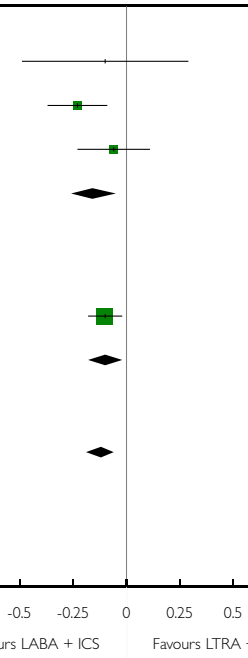
Analysis 1.15. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 15 Change in number of night awakenings per week - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 15 Change in number of night awakenings per week - change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily							
Fish 2001	451	-1.42 (2.76)	443	-1.32 (3.16)		2.8 %	-0.10 [-0.49, 0.29]
Ilowite 2004	709	-1.02 (1.33)	727	-0.79 (1.35)		21.8 %	-0.23 [-0.37, -0.09]
Bjermer 2003	724	-1.74 (1.61)	731	-1.68 (1.62)		15.2 %	-0.06 [-0.23, 0.11]
Subtotal (95% CI)	**1884**		**1901**			**39.7 %**	**-0.16 [-0.26, -0.05]**
Heterogeneity: Chi^2 = 2.46, df = 2 (P = 0.29); I^2 =19%							
Test for overall effect: Z = 2.98 (P = 0.0029)							
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily							
Nelson 2000	214	-0.19 (0.44)	215	-0.09 (0.44)		60.3 %	-0.10 [-0.18, -0.02]
Subtotal (95% CI)	**214**		**215**			**60.3 %**	**-0.10 [-0.18, -0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.35 (P = 0.019)							
Total (95% CI)	**2098**		**2116**			**100.0 %**	**-0.12 [-0.19, -0.06]**
Heterogeneity: Chi^2 = 3.15, df = 3 (P = 0.37); I^2 =5%							
Test for overall effect: Z = 3.70 (P = 0.00021)							
Test for subgroup differences: Chi^2 = 0.69, df = 1 (P = 0.41), I^2 =0.0%							



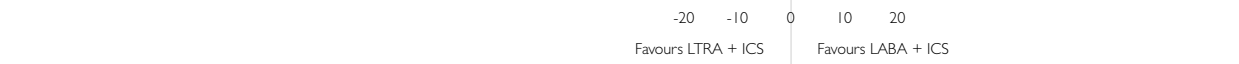
Analysis 1.16. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 16 Change in % of nights with no awakenings per week - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 16 Change in % of nights with no awakenings per week - change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily							
Grosclaude 2003	118	26.4 (31)	126	19.8 (30)		27.5 %	6.60 [-1.06, 14.26]
Subtotal (95% CI)	**118**		**126**			**27.5 %**	**6.60 [-1.06, 14.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.69 (P = 0.091)							
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily							
Nelson 2001	214	15 (26.3)	215	8 (23.5)		72.5 %	7.00 [2.28, 11.72]
Subtotal (95% CI)	**214**		**215**			**72.5 %**	**7.00 [2.28, 11.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.91 (P = 0.0037)							
Total (95% CI)	**332**		**341**			**100.0 %**	**6.89 [2.87, 10.91]**
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%							
Test for overall effect: Z = 3.36 (P = 0.00078)							
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 =0.0%							

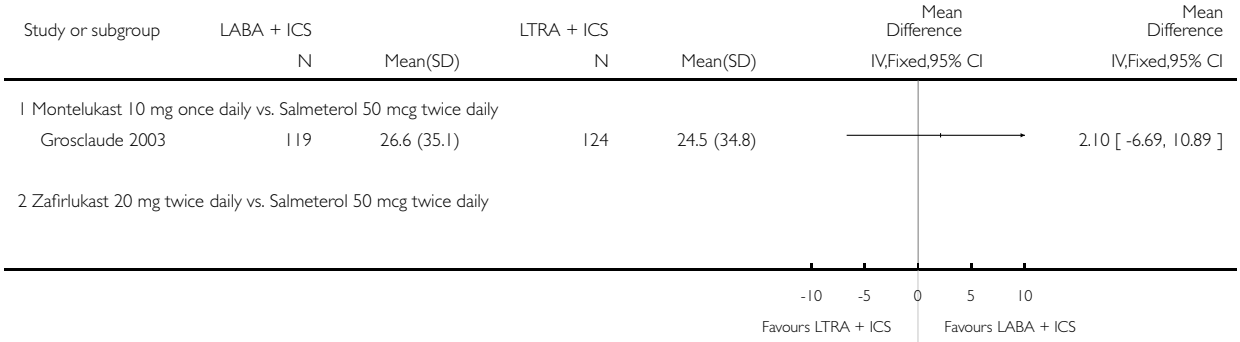


Analysis 1.17. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 17 Rescue-free nights (%) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 17 Rescue-free nights (%) - change from baseline

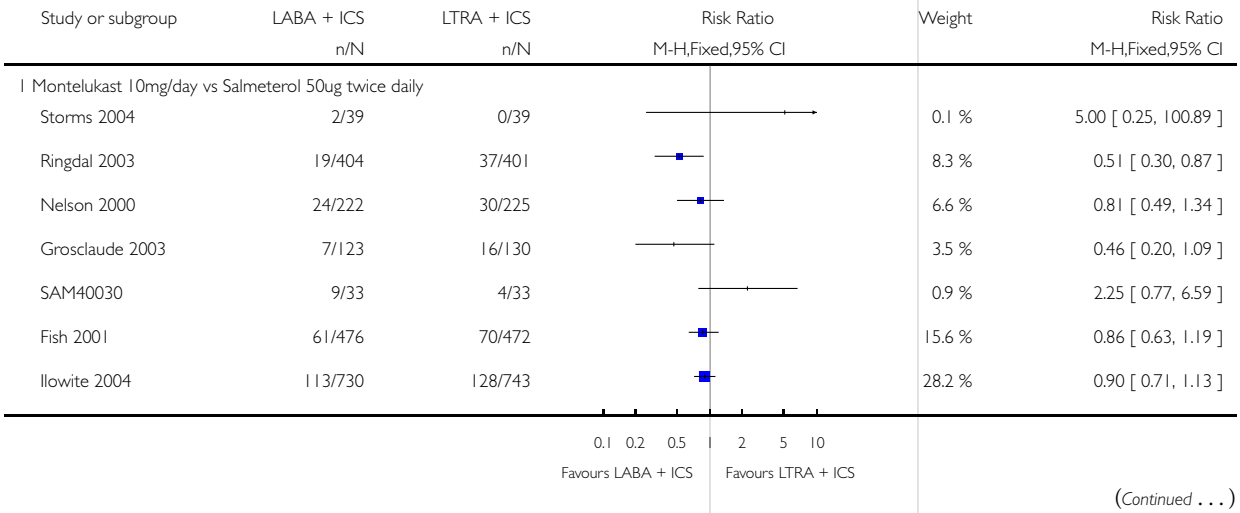


Analysis 1.18. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 18 Withdrawals for any reason.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 18 Withdrawals for any reason



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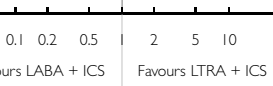
Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bjermer 2003	110/743	125/747		27.7 %	0.88 [0.70, 1.12]
Pavord 2007	9/33	4/33		0.9 %	2.25 [0.77, 6.59]
Subtotal (95% CI)	**2803**	**2823**		**91.8 %**	**0.86 [0.76, 0.98]**
Total events: 354 (LABA + ICS), 414 (LTRA + ICS)					
Heterogeneity: Chi^2 = 13.41, df = 8 (P = 0.10); I^2 =40%					
Test for overall effect: Z = 2.22 (P = 0.026)					
2 Zafirlukast 20 mg twice daily vs Salmeterol 50 mcg twice daily					
Nelson 2001	12/214	18/215		4.0 %	0.67 [0.33, 1.36]
SD-004-0216	12/118	19/118		4.2 %	0.63 [0.32, 1.24]
Subtotal (95% CI)	**332**	**333**		**8.2 %**	**0.65 [0.40, 1.06]**
Total events: 24 (LABA + ICS), 37 (LTRA + ICS)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 1.73 (P = 0.084)					
3 Montelukast 10mg/d versus Formoterol 18mcg/d					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (LABA + ICS), 0 (LTRA + ICS)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**3135**	**3156**		**100.0 %**	**0.84 [0.74, 0.96]**
Total events: 378 (LABA + ICS), 451 (LTRA + ICS)					
Heterogeneity: Chi^2 = 14.66, df = 10 (P = 0.14); I^2 =32%					
Test for overall effect: Z = 2.61 (P = 0.0089)					
Test for subgroup differences: Chi^2 = 1.19, df = 1 (P = 0.27), I^2 =16%					



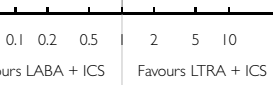
Analysis 1.19. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 19 Withdrawals due to adverse events.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 19 Withdrawals due to adverse events

Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily					
Storms 2004	1/39	0/39		0.4 %	3.00 [0.13, 71.46]
Fish 2001	13/476	13/472		11.0 %	0.99 [0.46, 2.12]
Nelson 2000	6/222	4/225		3.3 %	1.52 [0.43, 5.31]
Grosclaude 2003	3/123	5/130		4.1 %	0.63 [0.15, 2.60]
SAM40030	2/33	4/33		3.4 %	0.50 [0.10, 2.55]
Ringdal 2003	13/404	19/401		16.0 %	0.68 [0.34, 1.36]
Ilowite 2004	32/730	20/743		16.6 %	1.63 [0.94, 2.82]
Bjermer 2003	36/743	38/747		31.8 %	0.95 [0.61, 1.49]
Pavord 2007	2/33	4/33		3.4 %	0.50 [0.10, 2.55]
Subtotal (95% CI)	**2803**	**2823**		**89.9 %**	**1.02 [0.78, 1.32]**
Total events: 108 (LABA + ICS), 107 (LTRA + ICS)					
Heterogeneity: Chi² = 6.96, df = 8 (P = 0.54); I² =0.0%					
Test for overall effect: Z = 0.12 (P = 0.91)					
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily					
Nelson 2001	7/214	7/215		5.9 %	1.00 [0.36, 2.82]
SD-004-0216	4/118	5/118		4.2 %	0.80 [0.22, 2.91]
Subtotal (95% CI)	**332**	**333**		**10.1 %**	**0.92 [0.41, 2.05]**
Total events: 11 (LABA + ICS), 12 (LTRA + ICS)					
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 0.21 (P = 0.84)					
Total (95% CI)	**3135**	**3156**		**100.0 %**	**1.01 [0.79, 1.29]**
Total events: 119 (LABA + ICS), 119 (LTRA + ICS)					
Heterogeneity: Chi² = 7.08, df = 10 (P = 0.72); I² =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² =0.0%					

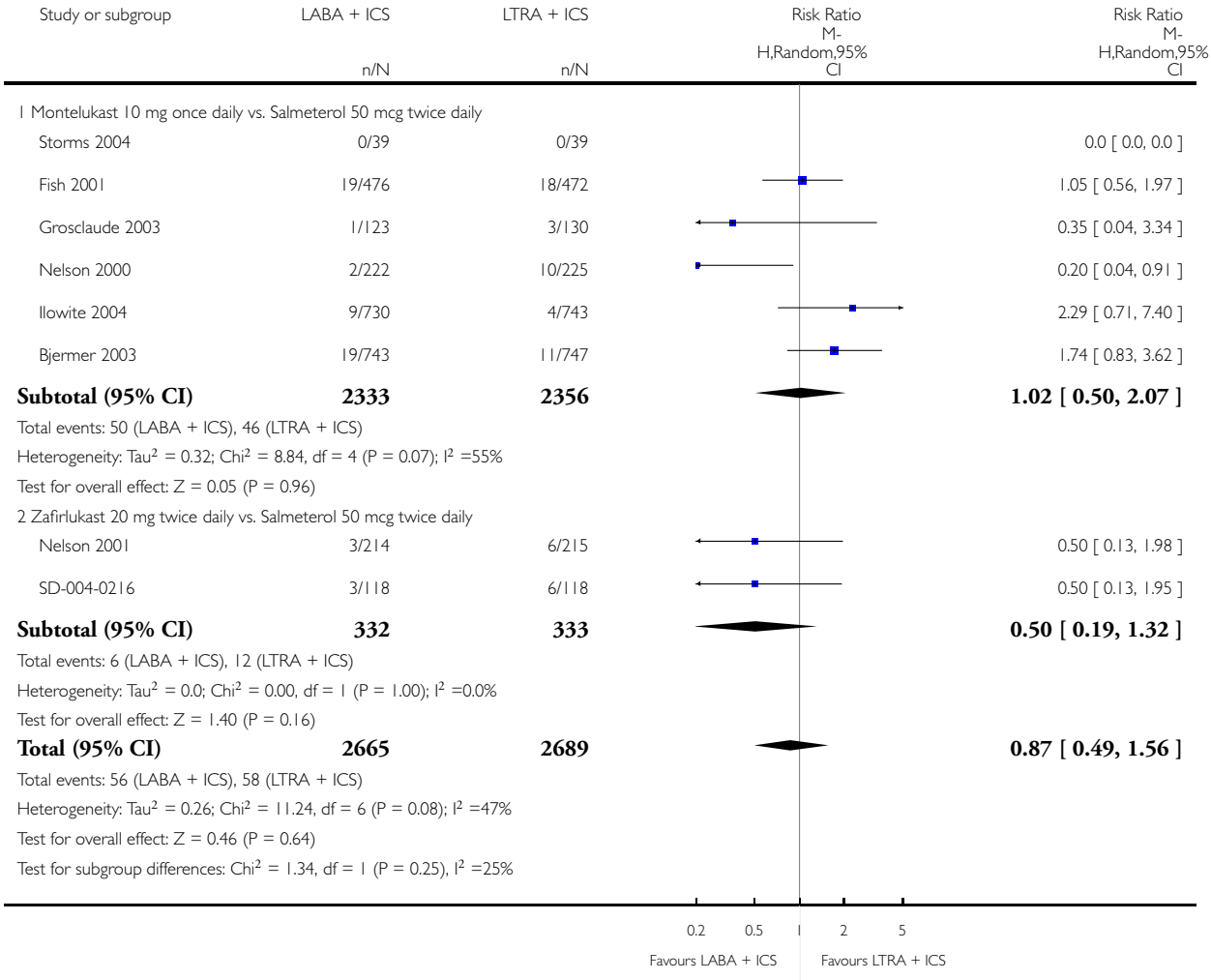


Analysis 1.20. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 20 Withdrawals due to poor asthma control/asthma exacerbation.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 20 Withdrawals due to poor asthma control/asthma exacerbation

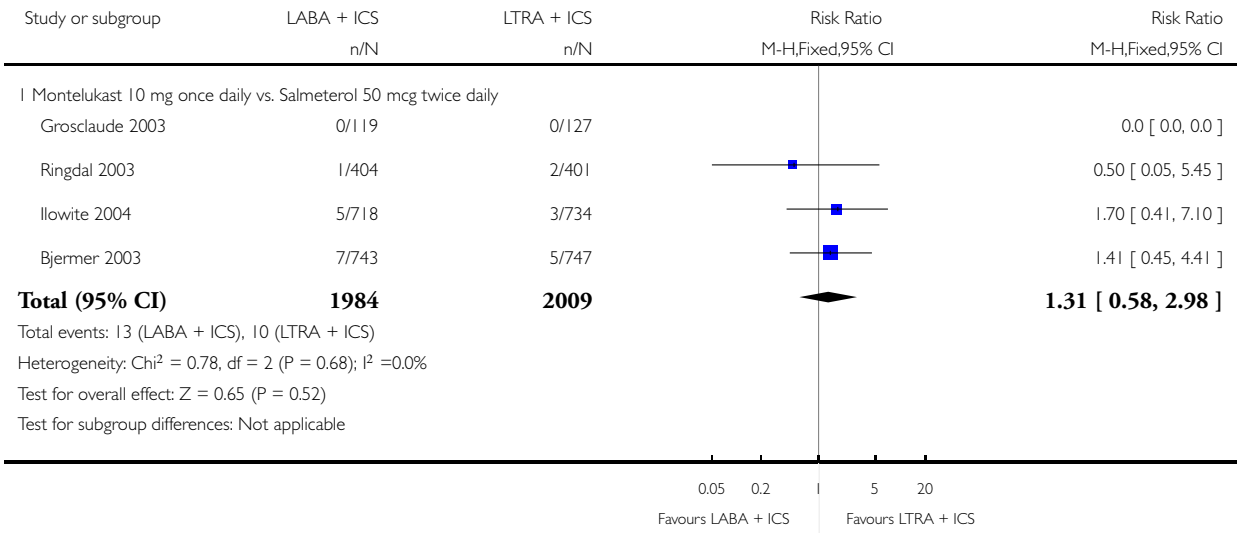


Analysis 1.21. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 21 Patients with one or more exacerbations requiring hospital admission.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 21 Patients with one or more exacerbations requiring hospital admission



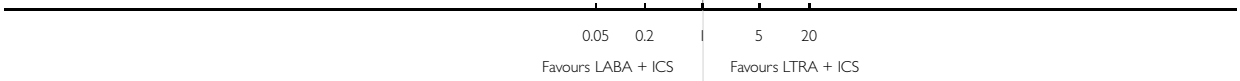
Analysis 1.22. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 22 Serious Adverse events.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 22 Serious Adverse events

Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily					
Fish 2001	5/476	5/472		7.0 %	0.99 [0.29, 3.40]
Ringdal 2003	4/404	7/401		9.9 %	0.57 [0.17, 1.92]
Nelson 2000	1/222	2/225		2.8 %	0.51 [0.05, 5.55]
Ilowite 2004	27/730	22/743		30.6 %	1.25 [0.72, 2.17]
Bjermer 2003	55/743	34/747		47.6 %	1.63 [1.07, 2.46]
Pavord 2007	2/33	0/33		0.7 %	5.00 [0.25, 100.32]
Subtotal (95% CI)	**2608**	**2621**		**98.6 %**	**1.35 [1.00, 1.83]**
Total events: 94 (LABA + ICS), 70 (LTRA + ICS)					
Heterogeneity: Chi^2 = 4.40, df = 5 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 1.95 (P = 0.051)					
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily					
Nelson 2001	1/214	1/215		1.4 %	1.00 [0.06, 15.96]
Subtotal (95% CI)	**214**	**215**		**1.4 %**	**1.00 [0.06, 15.96]**
Total events: 1 (LABA + ICS), 1 (LTRA + ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.0)					
Total (95% CI)	**2822**	**2836**		**100.0 %**	**1.35 [1.00, 1.82]**
Total events: 95 (LABA + ICS), 71 (LTRA + ICS)					
Heterogeneity: Chi^2 = 4.45, df = 6 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.94 (P = 0.053)					
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.83), I^2 =0.0%					



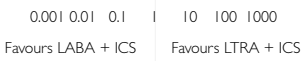
Analysis 1.23. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 23 Death.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 23 Death

Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily				
Bjermer 2003	1/743	0/747		3.02 [0.12, 73.92]



Analysis 1.24. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 24 Headache.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 24 Headache

Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily					
Ringdal 2003	12/404	18/401		7.4 %	0.66 [0.32, 1.36]
Nelson 2000	20/222	10/225		4.1 %	2.03 [0.97, 4.23]
Fish 2001	48/476	44/472		18.2 %	1.08 [0.73, 1.60]
Grosclaude 2003	1/123	4/130		1.6 %	0.26 [0.03, 2.33]
SAM40030	1/33	1/33		0.4 %	1.00 [0.07, 15.33]
Bjermer 2003	93/743	90/747		36.9 %	1.04 [0.79, 1.36]
Ilowite 2004	71/730	60/743		24.4 %	1.20 [0.87, 1.67]
Subtotal (95% CI)	**2731**	**2751**		**93.0 %**	**1.09 [0.92, 1.29]**
Total events: 246 (LABA + ICS), 227 (LTRA + ICS)					
Heterogeneity: Chi^2 = 6.70, df = 6 (P = 0.35); I^2 =10%					
Test for overall effect: Z = 0.99 (P = 0.32)					

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Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily					
Nelson 2001	6/214	11/215		4.5 %	0.55 [0.21, 1.46]
SD-004-0216	6/118	5/118		2.1 %	1.20 [0.38, 3.82]
Subtotal (95% CI)	**332**	**333**		**6.6 %**	**0.75 [0.36, 1.57]**
Total events: 12 (LABA + ICS), 16 (LTRA + ICS)					
Heterogeneity: Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%					
Test for overall effect: Z = 0.76 (P = 0.45)					
3 Montelukast 10 mg once daily versus formoterol 18mg twice daily					
Ceylan 2004	1/20	1/20		0.4 %	1.00 [0.07, 14.90]
Subtotal (95% CI)	**20**	**20**		**0.4 %**	**1.00 [0.07, 14.90]**
Total events: 1 (LABA + ICS), 1 (LTRA + ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Total (95% CI)	**3083**	**3104**		**100.0 %**	**1.07 [0.90, 1.26]**
Total events: 259 (LABA + ICS), 244 (LTRA + ICS)					
Heterogeneity: Chi^2 = 8.60, df = 9 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					
Test for subgroup differences: Chi^2 = 0.94, df = 2 (P = 0.63), I^2 =0.0%					

Analysis 1.25. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 25 Cardiovascular events.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 25 Cardiovascular events

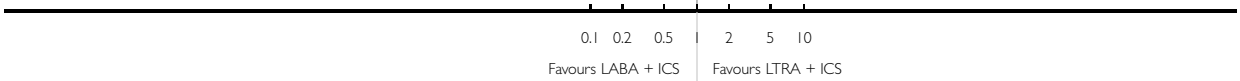
Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily					
Fish 2001	4/476	8/472		13.2 %	0.50 [0.15, 1.64]
Ringdal 2003	6/404	9/401		14.8 %	0.66 [0.24, 1.84]
Nelson 2000	3/222	1/225		1.6 %	3.04 [0.32, 29.01]
Ilowite 2004	22/730	18/743		29.3 %	1.24 [0.67, 2.30]
Bjermer 2003	31/743	25/747		41.0 %	1.25 [0.74, 2.09]
Total (95% CI)	**2575**	**2588**		**100.0 %**	**1.09 [0.77, 1.53]**

Total events: 66 (LABA + ICS), 61 (LTRA + ICS)

Heterogeneity: $Chi^2 = 3.82$, df = 4 (P = 0.43); $I^2 = 0.0\%$

Test for overall effect: Z = 0.49 (P = 0.63)

Test for subgroup differences: Not applicable

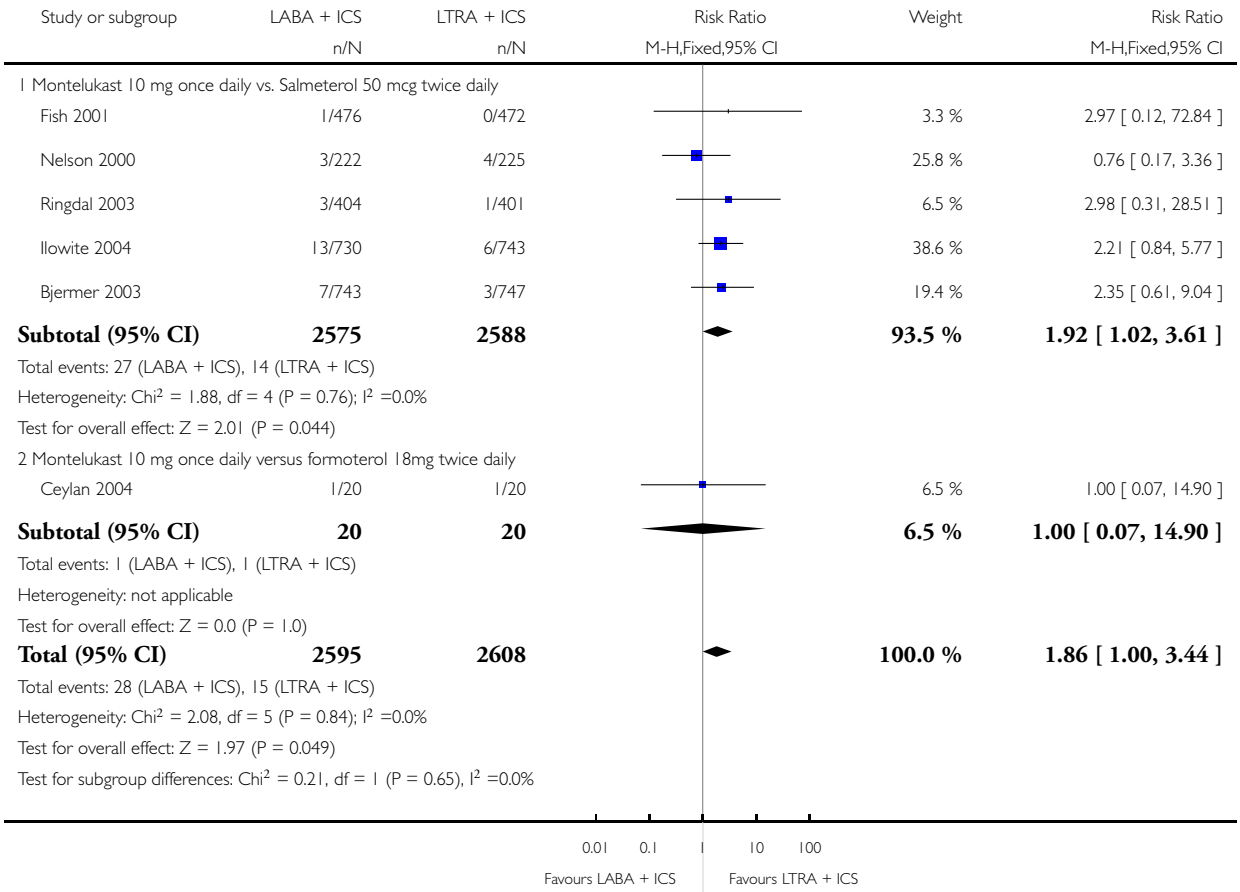


Analysis 1.26. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 26 Oral moniliasis.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 26 Oral moniliasis

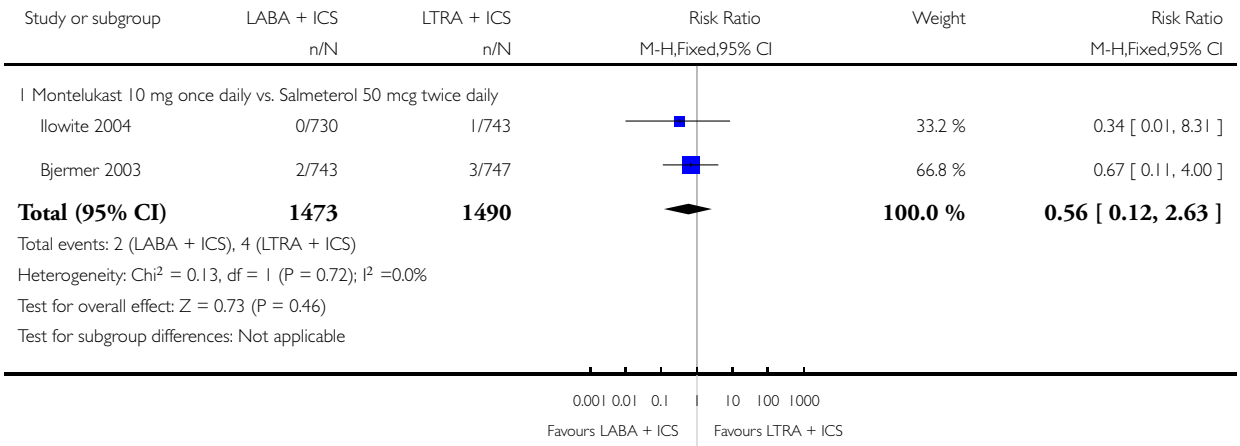


Analysis 1.27. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 27 Osteopenia/osteoporosis.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 27 Osteopenia/osteoporosis

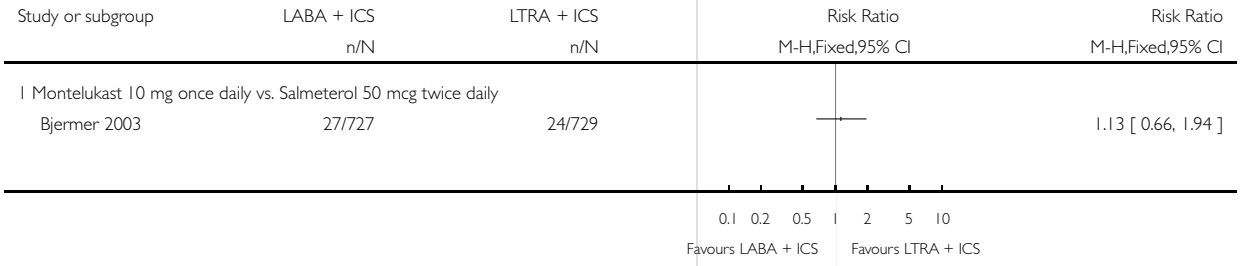


Analysis 1.28. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 28 Elevated liver enzymes.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 28 Elevated liver enzymes

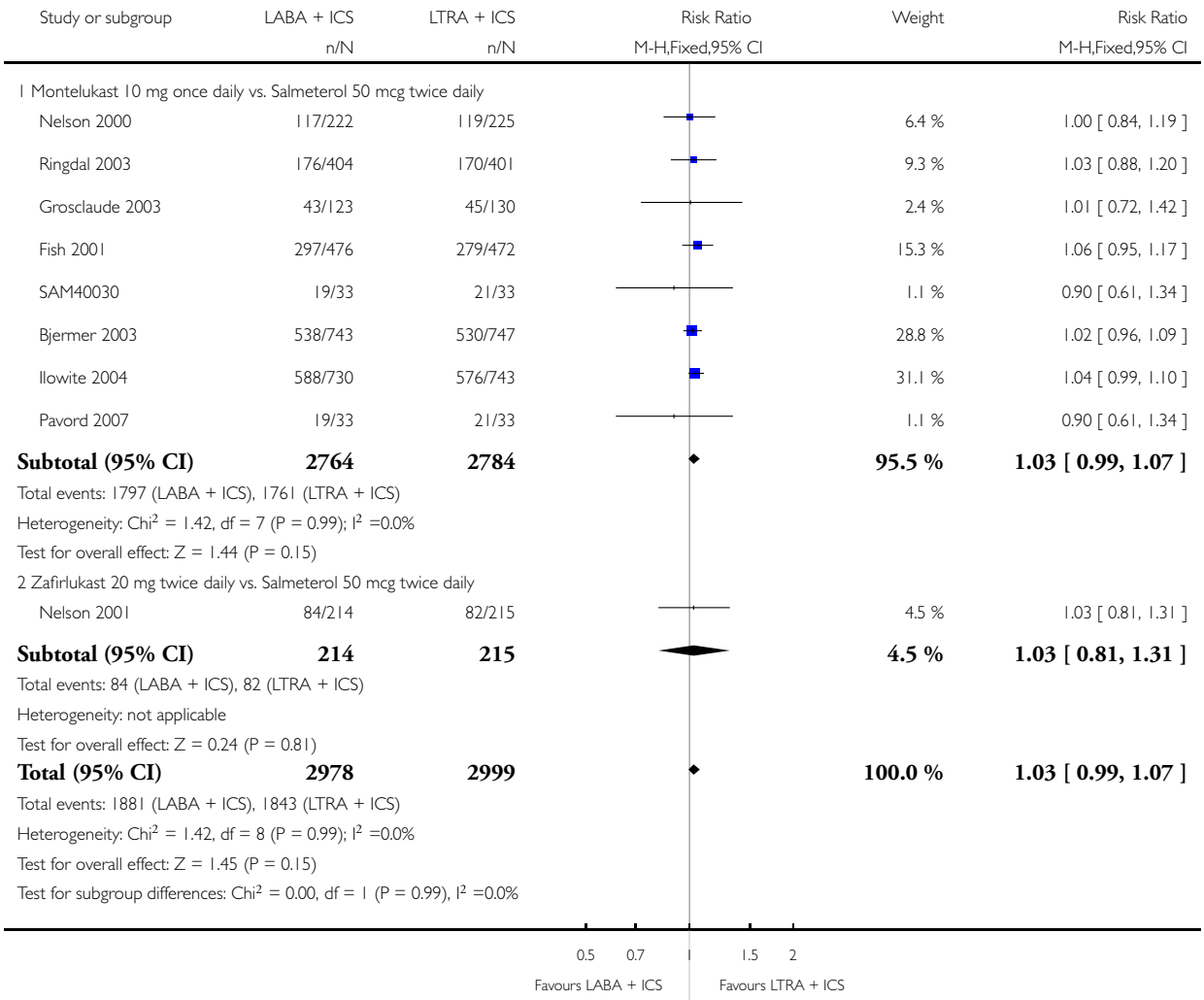


Analysis 1.29. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 29 Overall adverse events.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 29 Overall adverse events



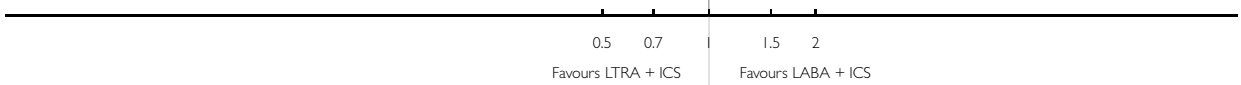
Analysis 1.30. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 30 Patient treatment satisfaction.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 30 Patient treatment satisfaction

Study or subgroup	LABA +ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily					
Ringdal 2003	375/404	335/401		44.3 %	1.11 [1.06, 1.17]
Fish 2001	337/400	306/386		38.6 %	1.06 [0.99, 1.14]
Subtotal (95% CI)	**804**	**787**		**82.9 %**	**1.09 [1.05, 1.14]**
Total events: 712 (LABA +ICS), 641 (LTRA + ICS)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.13, df = 1 (P = 0.29); I^2 =12%					
Test for overall effect: Z = 3.98 (P = 0.000070)					
2 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily					
Nelson 2001	152/214	120/215		17.1 %	1.27 [1.10, 1.47]
Subtotal (95% CI)	**214**	**215**		**17.1 %**	**1.27 [1.10, 1.47]**
Total events: 152 (LABA +ICS), 120 (LTRA + ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.22 (P = 0.0013)					
Total (95% CI)	**1018**	**1002**		**100.0 %**	**1.12 [1.04, 1.20]**
Total events: 864 (LABA +ICS), 761 (LTRA + ICS)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.23, df = 2 (P = 0.07); I^2 =62%					
Test for overall effect: Z = 3.01 (P = 0.0026)					
Test for subgroup differences: Chi^2 = 3.85, df = 1 (P = 0.05), I^2 =74%					

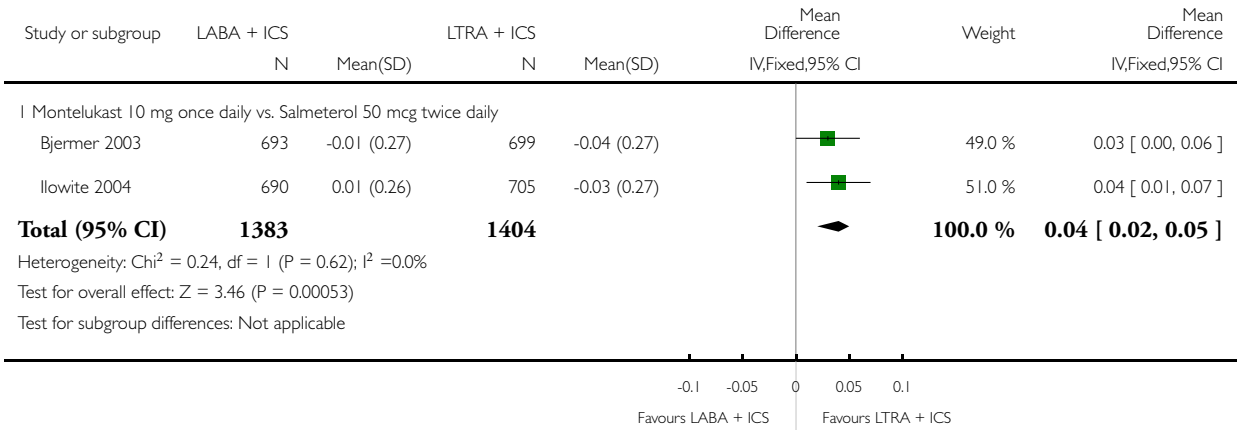


Analysis 1.31. Comparison 1 Long-acting ß2-agonists + ICS versus leukotriene receptor antagonists + ICS, Outcome 31 Change from baseline in serum eosinophils (x 10e9/L).

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 1 Long-acting 2-agonists + ICS versus leukotriene receptor antagonists + ICS

Outcome: 31 Change from baseline in serum eosinophils (x 10e9/L)



Analysis 2.1. Comparison 2 Subgroup and sensitivity analyses, Outcome 1 Participants with one or more exacerbations requiring systemic corticosteroids: number of inhaler devices.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 1 Participants with one or more exacerbations requiring systemic corticosteroids: number of inhaler devices

Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Single device for LABA + ICS					
Ringdal 2003	17/404	31/401		83.1 %	0.54 [0.31, 0.97]
Nelson 2000	3/222	10/225		16.9 %	0.30 [0.08, 1.09]
Subtotal (95% CI)	**626**	**626**		**100.0 %**	**0.49 [0.29, 0.83]**
Total events: 20 (LABA + ICS), 41 (LTRA + ICS)					
Heterogeneity: Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 2.64 (P = 0.0083)					
2 Two devices for LABA + ICS					
Nelson 2001	6/214	7/215		2.3 %	0.86 [0.29, 2.52]
Fish 2001	16/476	16/472		5.8 %	0.99 [0.50, 1.96]
Bjermer 2003	107/743	118/747		46.0 %	0.91 [0.72, 1.16]
Ilowite 2004	102/718	123/734		45.9 %	0.85 [0.67, 1.08]
Subtotal (95% CI)	**2151**	**2168**		**100.0 %**	**0.88 [0.75, 1.04]**
Total events: 231 (LABA + ICS), 264 (LTRA + ICS)					
Heterogeneity: Chi^2 = 0.29, df = 3 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 1.47 (P = 0.14)					
Test for subgroup differences: Chi^2 = 4.34, df = 1 (P = 0.04), I^2 =77%					

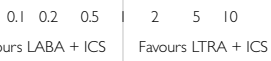
Analysis 2.2. Comparison 2 Subgroup and sensitivity analyses, Outcome 2 Participants with one or more exacerbations requiring systemic corticosteroids: dose of ICS.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 2 Participants with one or more exacerbations requiring systemic corticosteroids: dose of ICS

Study or subgroup	LABA + ICS n/N	LTRA + ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low dose of ICS					
Bjermer 2003	107/743	118/747		74.1 %	0.91 [0.72, 1.16]
Nelson 2000	3/222	10/225		6.3 %	0.30 [0.08, 1.09]
Ringdal 2003	17/404	31/401		19.6 %	0.54 [0.31, 0.97]
Subtotal (95% CI)	**1369**	**1373**		**100.0 %**	**0.80 [0.64, 1.00]**
Total events: 127 (LABA + ICS), 159 (LTRA + ICS)					
Heterogeneity: Chi² = 5.05, df = 2 (P = 0.08); I² =60%					
Test for overall effect: Z = 1.99 (P = 0.047)					
2 Medium dose of ICS					
Ilowite 2004	102/718	123/734		100.0 %	0.85 [0.67, 1.08]
Subtotal (95% CI)	**718**	**734**		**100.0 %**	**0.85 [0.67, 1.08]**
Total events: 102 (LABA + ICS), 123 (LTRA + ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
3 Mixed					
Fish 2001	16/476	16/472		100.0 %	0.99 [0.50, 1.96]
Subtotal (95% CI)	**476**	**472**		**100.0 %**	**0.99 [0.50, 1.96]**
Total events: 16 (LABA + ICS), 16 (LTRA + ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
4 Unclear					
Nelson 2001	6/214	7/215		100.0 %	0.86 [0.29, 2.52]
Subtotal (95% CI)	**214**	**215**		**100.0 %**	**0.86 [0.29, 2.52]**
Total events: 6 (LABA + ICS), 7 (LTRA + ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.78)					
Test for subgroup differences: Chi² = 0.39, df = 3 (P = 0.94), I² =0.0%					

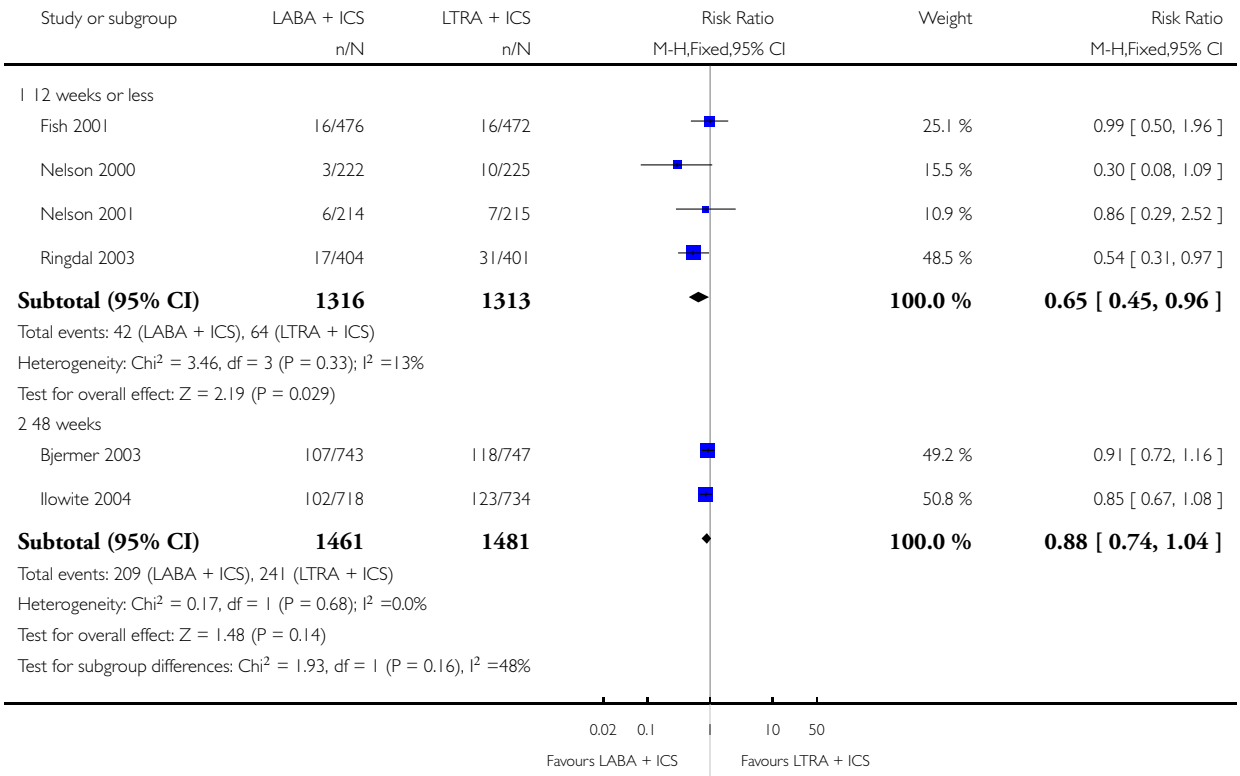


Analysis 2.3. Comparison 2 Subgroup and sensitivity analyses, Outcome 3 Participants with one or more exacerbations requiring systemic corticosteroids: study duration.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 3 Participants with one or more exacerbations requiring systemic corticosteroids: study duration

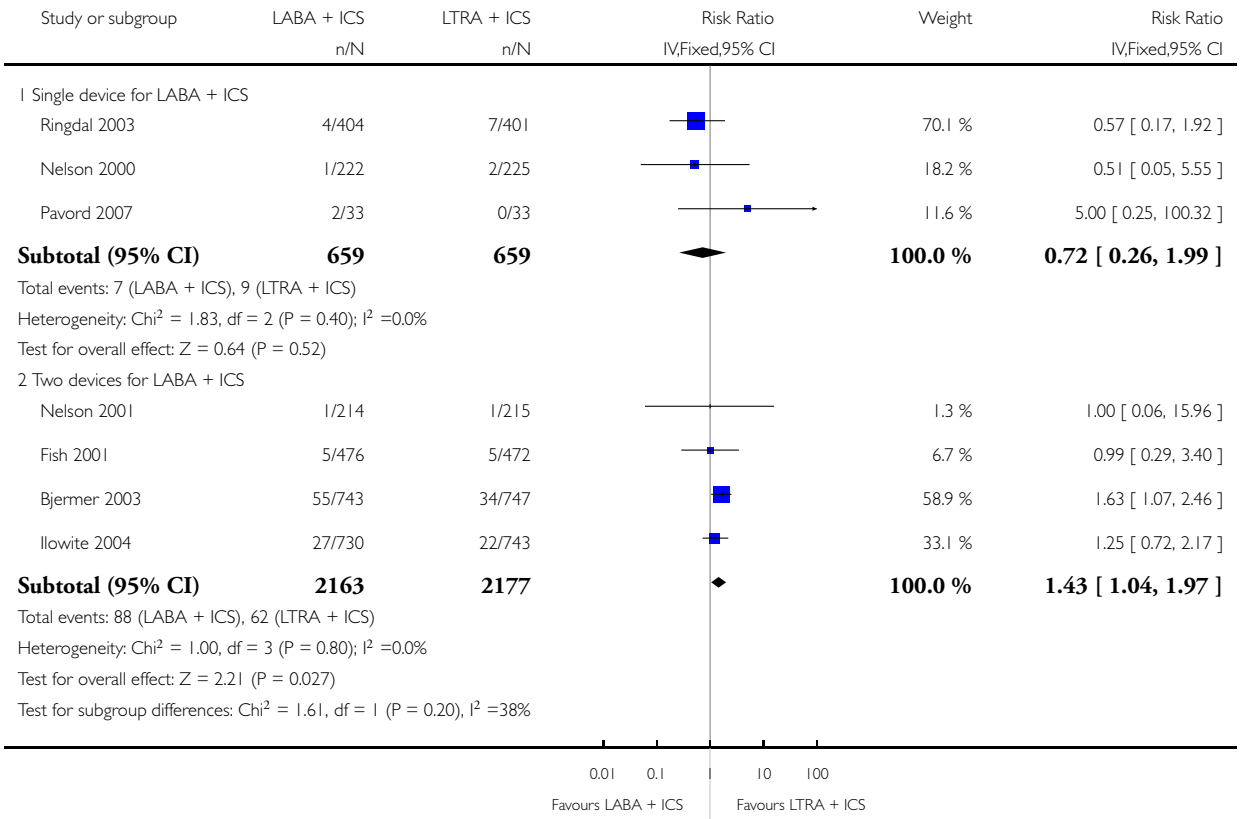


Analysis 2.4. Comparison 2 Subgroup and sensitivity analyses, Outcome 4 Serious adverse effects stratified by number of inhaler devices used for LABA + ICS.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 4 Serious adverse effects stratified by number of inhaler devices used for LABA + ICS



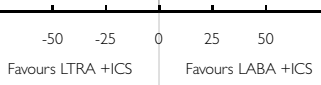
Analysis 3.1. Comparison 3 MD archive from previous review version, Outcome 1 Morning PEF (L/min) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 3 MD archive from previous review version

Outcome: 1 Morning PEF (L/min) - change from baseline

Study or subgroup	LABA +ICS N	Mean(SD)	LTRA +ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Nelson 2001	214	28.8 (45.4)	214	13 (36.6)		15.80 [7.99, 23.61]
SD-004-0216	117	33.86 (63.71)	116	29.39 (63.87)		4.47 [-11.91, 20.85]
Grosclaude 2003	119	44.2 (43.63)	127	31 (42.82)		13.20 [2.39, 24.01]
SAM40030	33	61.5 (37.3)	33	29.6 (50.2)		31.90 [10.56, 53.24]
Fish 2001	476	35 (44.6)	472	21.7 (44.2)		13.30 [7.65, 18.95]
Ilowite 2004	646	55 (71.17)	651	40.8 (71.44)		14.20 [6.44, 21.96]
Ringdal 2003	288	42 (42.43)	279	26 (45.1)		16.00 [8.79, 23.21]
Bjermer 2003	725	34.59 (45.77)	732	17.73 (45.72)		16.86 [12.16, 21.56]
Nelson 2000	197	29.6 (37.89)	190	13.2 (37.22)		16.40 [8.92, 23.88]
Ceylan 2004	20	54.3 (15.1)	20	30.5 (25.3)		23.80 [10.89, 36.71]



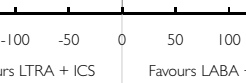
Analysis 3.2. Comparison 3 MD archive from previous review version, Outcome 2 Evening PEF (L/min) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 3 MD archive from previous review version

Outcome: 2 Evening PEF (L/min) - change from baseline

Study or subgroup	LABA + ICS		LTR + ICS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Ceylan 2004	20	44.5 (23.3)	20	27 (24.1)		17.50 [2.81, 32.19]
SAM40030	33	40 (44.8)	33	21.1 (37)		18.90 [-0.92, 38.72]
Ilowite 2004	564	47.4 (71.25)	579	33.4 (72.19)		14.00 [5.68, 22.32]
Fish 2001	451	27.8 (42.5)	444	19 (42.1)		8.80 [3.26, 14.34]
Nelson 2000	197	21.8 (35.09)	191	10 (34.55)		11.80 [4.87, 18.73]
Grosclaude 2003	119	37.4 (40.36)	127	25.2 (41.7)		12.20 [1.94, 22.46]
Ringdal 2003	271	37 (41.16)	250	20 (41.11)		17.00 [9.93, 24.07]
Nelson 2001	213	21.8 (43.8)	213	11.2 (38)		10.60 [2.81, 18.39]
SD-004-0216	117	24.02 (63.6)	116	20.1 (62.68)		3.92 [-12.29, 20.13]



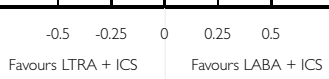
Analysis 3.3. Comparison 3 MD archive from previous review version, Outcome 3 FEV1 (L) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 3 MD archive from previous review version

Outcome: 3 FEV1 (L) - change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
SD-004-0216	117	0.22 (0.54)	116	0.11 (0.54)		0.11 [-0.03, 0.25]
Nelson 2001	214	0.26 (0.44)	215	0.23 (0.44)		0.03 [-0.05, 0.11]
Ceylan 2004	20	0.36 (0)	20	0.19 (0)		0.0 [0.0, 0.0]
Ilowite 2004	602	0.18 (0.25)	621	0.11 (0.25)		0.07 [0.04, 0.10]
Bjermer 2003	695	0.19 (0.53)	688	0.11 (0.52)		0.08 [0.02, 0.14]
Ringdal 2003	364	0.28 (0.38)	355	0.17 (0.38)		0.11 [0.05, 0.17]
SAM40030	33	0.39 (0.36)	33	0.31 (0.43)		0.08 [-0.11, 0.27]
Nelson 2000	197	0.35 (0.42)	195	0.2 (0.42)		0.15 [0.07, 0.23]



Analysis 3.4. Comparison 3 MD archive from previous review version, Outcome 4 Symptom free days (%) - change from baseline.

Review: Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma

Comparison: 3 MD archive from previous review version

Outcome: 4 Symptom free days (%) - change from baseline

Study or subgroup	LABA + ICS N	Mean(SD)	LTRA + ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fish 2001	451	24.1 (31.9)	445	16.12 (40.8)		7.98 [3.18, 12.78]
Grosclaude 2003	117	42.7 (31.3)	125	33.4 (34.2)		9.30 [1.05, 17.55]
Nelson 2000	197	25.1 (36.49)	191	24 (34.55)		1.10 [-5.97, 8.17]
Nelson 2001	214	20 (29.3)	215	9 (22)		11.00 [6.10, 15.90]
Ringdal 2003	341	38 (38.78)	330	35 (39.96)		3.00 [-2.96, 8.96]

ADDITIONAL TABLES

Table 1. Search history

Years	Detail
All years to January 2004	Citations: 184 (181 from the literature search and three unpublished trials provided by pharmaceutical companies for a total of 184 citations) Citations excluded: 172: (1) duplicate citations (N=29), (2) abstracts of considered full-text publications or secondary analyses of the same study (N = 18), (3) not a randomised controlled trial (N = 72), (4) protocol of ongoing trial (N=1), (5) no consistent co-treatment with inhaled glucocorticoids (N = 21), (6) one of the tested interventions was not daily LTRA (N = 18), (7) one of the tested interventions was not daily LABA (N= 5), (8) interventions were administered for less than 4 weeks (N = 6), and (9) use of prohibited co-interventions such as LABA in both groups (N=2). Studies meeting the entry criteria of the review: 12 (six full-text publications (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003), two unpublished full-text reports (Hultquist 2000; McCarthy 2003) and four abstracts (Gold (abs) 2001; Green (abs) 2002; Leibman (abs) 2002; Nsouli 2001). The abstracts did not provide data in sufficient detail to contribute to the meta-analyses
January 2004 to January 2006	Citations: 60. Citations excluded: 55: the study was a duplicate (i.e. identical citation of one trial report, or a subsequent report of a trial) (N = 22); the study was not randomised (N = 2); the study was ongoing (N = 5); the administration of either LTRA or LABA was not standardised across treatment groups (N = 3); there was no consistent co-treatment with inhaled glucocorticoids (N = 8); one

Table 1. Search history (*Continued*)

	of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoids (N = 9); one of the tested interventions was not daily LABA as add-on to inhaled glucocorticoids (N = 2); the tested interventions were administered for less than 4 weeks (N = 1); the study used prohibited co-intervention (i.e., maintenance oral steroids, theophylline, non-steroidal anti-inflammatory drugs, anticholinergics) (N = 3)

Table 2. ICS at CFC-BDP equivalent dose (µg/day)

Study	Actual dose of ICS (total per day)	CFC- BDP equivalent / day	Population	Low/medium/high
Bjermer 2003	200mcg fluticasone	400mcg	Adults	Low
Ceylan 2004	400mcg budesonide	400mcg	Adults	Low
Fish 2001	Range of doses between 175 to 1700mcg	560µg (range 175-1700)	Adults	Mixed
Gold 2001	100mcg fluticasone	200mcg	Adults	Low
Green 2006	200mcg budesonide	200mcg	Adults	Low
Grosclaude 2003	1000mcg CFC BDP and fluticasone 500mcg	1000mcg	Adults	High
Hendeles 2004	250mcg fluticasone	500mcg	Adults	Medium
Ilowite 2004	250mcg fluticasone	500mcg	Adults	Medium
Lemanske 2010	200mcg fluticasone	400mcg	Children	Low
Nelson 2000	200mcg fluticasone	400mcg	Adults	Low
Nelson 2001	not specified	requested from author 08/03	Adults	Unclear
Nsouli 2001	Unclear	500mcg	Adults	Unclear
Pavord 2007	200mcg fluticasone	400mcg	Adults	Low
Ringdal 2003	200mcg fluticasone	400mcg	Adults	Low
SAM40030	200mcg fluticasone	400mcg	Adults	Low
SD-004-0216	400mcg budesonide	400mcg	Adults	Low
ELEVATE	Unclear	Unclear	Adults	Unclear

Table 2. ICS at CFC-BDP equivalent dose (µg/day) (*Continued*)

Storms 2004	200mcg fluticasone	400mcg	Adults	Low

APPENDICES

Appendix 1. GSK randomisation procedures

The procedures for randomising GSK sponsored studies has been detailed in correspondence between Richard Follows and TL, the details of which are given below:
The randomisation software is a computer-generated, centralised programme (RandAll). After verification that the randomisation sequence is suitable for the study design (crossover, block or stratification), Clinical Supplies then package the treatments according the randomisation list generated. Concealment of allocation is maintained by a third party, since the sites phone in and are allocated treatments on that basis. Alternatively a third party may dispense the drug at the sites. Unblinding of data for interim analyses can only be done through RandAll, and are restricted so that only those reviewing the data are unblinded to treatment group allocation.

WHAT'S NEW

Last assessed as up-to-date: 16 March 2010.

Date	Event	Description
5 July 2011	Amended	Clarification made to abstract regarding subgroup analysis.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 1, 2005

Date	Event	Description
2 February 2011	New citation required and conclusions have changed	Full risk of bias assessment has been incorporated into the review Data on secondary outcomes were provided by the new studies. Serious adverse events are more common with LABA and ICS than LTRA and ICS. This result is not definitive and could be influenced by separate administration of LABA and ICS

(*Continued*)

17 March 2010	New search has been performed	Literature search re-run. Three new studies were included (Lemanske 2010; Pavord 2007; ELEVATE). One previously included study was excluded (Stelmach 2008); this study had not contributed data to the primary outcome
4 August 2008	Amended	Converted to new review format.
20 June 2006	New citation required and conclusions have changed	Five new studies met the entry criteria of the review (Ceylan 2004; Grosclaude 2003; Hendeles 2004; Stelmach 2008a; Storms 2004). Of these, two studies contributed data to this updated review. The additional data did not alter the conclusions of the review

CONTRIBUTIONS OF AUTHORS

Francine M Ducharme reviewed the protocol design; supervised the literature search; reviewed all citations; participated in the selection of trials, methodology assessment, and data extraction; corresponded with authors and pharmaceutical companies to identify other relevant trials, verify methodology and data extraction, and request additional information; analysed and interpreted results of the meta-analysis; and edited the final review.

Toby Lasserson (update 2006, 2010) assessed studies for inclusion or exclusion, extracted and entered data, revised results and discussion sections, and solicited additional data from authors.

Christopher Cates edited the review, checked the methodology, and contributed to writing up the final review.

Felix Ram participated in the initial version of the review (2005): protocol design, identified and reviewed the full-text publication of all citations of potential or potentially eligible RCTs, extracted the methodology and data, analysed and interpreted results of the meta-analysis, and wrote the first draft of the review.

DECLARATIONS OF INTEREST

Francine M Ducharme has received travel support for meeting attendance, research funds, fees for speaking and consulting fees from Merck Frosst Inc (producer of montelukast), GlaxoSmithKline (producer of fluticasone, beclomethasone, salmeterol), Novartis (producer of formoterol) and Nycomed (producer of combination of mometasone and formoterol). No conflict was reported by Toby Lasserson or Christopher Cates.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Nederlands Astma Fonds, Netherlands.
- Francine M. Ducharme, Canada.
- NHS Research and Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. In the protocol published in April 2001, we had planned to examine the impact of the inhaled glucocorticoids (subgroups 3) and of baseline severity (subgroups 5) as sensitivity analyses but changed to subgroup analyses because this enhanced the clarity of interpretation. The last two subgroup analyses (6 & 7), not initially considered in 2001, were added to the list subsequently as recent data indicated that the number of inhaler devices to deliver LABA + ICS might be an important effect modifier (Nelson 2003), and a peer reviewer suggested that differences might not be the same over 12 and 48 weeks.

2. Due to recent concerns over the association between LABAs and serious adverse events, we included a subgroup analysis of the data by the number of inhaler devices.

3. Study assessment was amended to reflect changes in the recommended approach to risk of bias evaluation. In the original protocol and first version of the review we assessed studies with the Jadad scale, and by grading concealment of allocation. For the 2010 update we have used a tool for assessing the degree of protection offered by the study design against systematic error. This is outlined in the section: Assessment of risk of bias in included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Adrenergic beta-2 Receptor Agonists [*therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Chronic Disease; Drug Therapy, Combination; Leukotriene Antagonists [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Humans