

Addition of anti-leukotriene agents to inhaled corticosteroids in children with persistent asthma (Review)

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Addition of anti-leukotriene agents to inhaled corticosteroids in children with persistent asthma

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ABSTRACT

Background

In the treatment of children with mild persistent asthma, low-dose inhaled corticosteroids (ICS) are recommended as the preferred monotherapy (referred to as step 2 of therapy). In children with inadequate asthma control on low doses of ICS (step 2), asthma management guidelines recommend adding an anti-leukotriene agent to existing ICS as one of three therapeutic options to intensify therapy (step 3).

Objectives

To compare the efficacy and safety of the combination of anti-leukotriene agents and ICS to the use of the same, an increased, or a tapering dose of ICS in children and adolescents with persistent asthma who remain symptomatic despite the use of maintenance ICS. In addition, we wished to determine the characteristics of people or treatments, if any, that influenced the magnitude of response attributable to the addition of anti-leukotrienes.

Search methods

We identified trials from the Cochrane Airways Group Specialised Register of Trials (CAGR), which were derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, AMED, and CINAHL; and the handsearching of respiratory journals and meeting abstracts, as well as the www.clinicaltrials.gov website. The search was conducted until January 2013.

Selection criteria

We considered for inclusion randomised controlled trials (RCTs) conducted in children and adolescents, aged one to 18 years, with asthma, who remained symptomatic despite the use of a stable maintenance dose of ICS and in whom anti-leukotrienes were added to the ICS if they were compared to the same, an increased, or a tapering dose of ICS for at least four weeks.

Data collection and analysis

We used standard methods expected by The Cochrane Collaboration.

Main results

Five paediatric (parallel group or cross-over) trials met the inclusion criteria. We considered two (40%) trials to be at a low risk of bias. Four published trials, representing 559 children (aged $\geq$ six years) and adolescents with mild to moderate asthma, contributed data to the review. No trial enrolled preschoolers. All trials used montelukast as the anti-leukotriene agent administered for between four and 16 weeks. Three trials evaluated the combination of anti-leukotrienes and ICS compared to the same dose of ICS alone (step 3 versus step 2). No statistically significant group difference was observed in the only trial reporting participants with exacerbations requiring oral corticosteroids over four weeks ($N = 268$ participants; risk ratio (RR) 0.80, 95% confidence interval (CI) 0.34 to 1.91). There was

also no statistically significant difference in percentage change in FEV_1 (forced expiratory volume in 1 second) with mean difference (MD) 1.3 (95% CI -0.09 to 2.69) in this trial, but a significant group difference was observed in the morning (AM) and evening (PM) peak expiratory flow rates (PEFR): $N = 218$ participants; MD 9.70 L/min (95% CI 1.27 to 18.13) and MD 10.70 (95% CI 2.41 to 18.99), respectively. One trial compared the combination of anti-leukotrienes and ICS to a higher-dose of ICS (step 3 versus step 3). No significant group difference was observed in this trial for participants with exacerbations requiring rescue oral corticosteroids over 16 weeks ($N = 182$ participants; RR 0.82, 95% CI 0.54 to 1.25), nor was there any significant difference in exacerbations requiring hospitalisation. There was no statistically significant group difference in withdrawals overall or because of any cause with either protocol. No trial explored the impact of adding anti-leukotrienes as a means to taper the dose of ICS.

Authors' conclusions

The addition of anti-leukotrienes to ICS is not associated with a statistically significant reduction in the need for rescue oral corticosteroids or hospital admission compared to the same or an increased dose of ICS in children and adolescents with mild to moderate asthma. Although anti-leukotrienes have been licensed for use in children for over 10 years, the paucity of paediatric trials, the absence of data on preschoolers, and the variability in the reporting of relevant clinical outcomes considerably limit firm conclusions. At present, there is no firm evidence to support the efficacy and safety of anti-leukotrienes as add-on therapy to ICS as a step-3 option in the therapeutic arsenal for children with uncontrolled asthma symptoms on low-dose ICS.

PLAIN LANGUAGE SUMMARY

Is adding an anti-leukotriene to an inhaled corticosteroid better than using an inhaled corticosteroid alone in children with persistent asthma?

Background: Asthma management guidelines recommend low-dose inhaled corticosteroids (ICS) as preferred therapy for children with mild persistent asthma. In children who have inadequate control of their asthma on low doses of ICS, anti-leukotrienes can be added to ICS. Anti-leukotrienes are a class of anti-inflammatory drugs for asthma. Almost a decade ago, a Cochrane review (Ducharme 2004) evaluating the addition of anti-leukotrienes to ICS in children and adults with asthma identified only two studies of children, one of which was only published as an abstract with insufficient information to contribute data. Considering the publication of several additional studies in the past decade, we wished to update the review with the latest literature.

Review question: To compare the effectiveness and safety of the addition of an anti-leukotriene agent to ICS to the use of the same dose of ICS alone, an increased dose of ICS, or a reduced dose of ICS in children aged one to 18 years with persistent asthma who are not well controlled with ICS alone.

Study characteristics: The evidence was updated until January 2013. We found five studies of children with asthma; of them, four studies, representing 559 children (aged six to 18 years) with mild to moderate asthma, contributed data to the review. No study enrolled pre-school children (i.e. aged under six years). Three studies compared the combination of anti-leukotrienes and ICS with the same dose of ICS alone; one study compared the combination of anti-leukotrienes and ICS to a higher dose of ICS; and no study tested whether the addition of anti-leukotriene to ICS could allow the tapering of the dose of ICS while maintaining asthma control. All studies used montelukast as the anti-leukotriene agent, which was administered for four to 16 weeks. Included studies enrolled both girls and boys and between 65% and 69% were boys. All trials enrolled children with mild to moderate airway obstruction.

Results: Whether comparing the addition of anti-leukotrienes to ICS to the same dose or an increased dose of ICS, there was no difference in the number of participants experiencing one or more moderate exacerbations (that is, requiring oral corticosteroids) or severe exacerbations (i.e. requiring a hospital admission). A single study comparing the same ICS dose reported lung function tests and showed no or small group differences depending on the test used.

Conclusion: There is no firm evidence to support that adding montelukast to ICS is safe and effective to reduce the occurrence of moderate or severe asthma attacks in children taking low-dose ICS and whose symptoms remain uncontrolled. After being on the market for more than 10 years, the limited number of available studies testing antileukotrienes in children, the absence of data on preschoolers, and the inconsistency of available trials in reporting of efficacy and safety clinical outcomes is disappointing and limit the conclusions.

Quality of the results: This review is based on a small number of identified trials conducted in children with asthma; none were conducted in preschoolers. As a single study of moderate duration reported all measures of efficacy and most measures of safety, our confidence in the quality of evidence is low. Other important measures of asthma control were either not measured or reported in different formats, so they could not be pooled. In other words, there are too few paediatric trials to conclude firmly whether either treatment is superior to the other.

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

Anti-leukotrienes and inhaled corticosteroids versus same dose of inhaled corticosteroids						
Patient or population: Children with asthma Settings: Outpatients Intervention: Anti-leukotrienes and inhaled corticosteroids Comparison: Same dose of inhaled corticosteroids						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Anti-leukotrienes and inhaled corticosteroids versus same dose of inhaled corticosteroids				
Participants with one or more exacerbations requiring oral corticosteroids Follow-up: mean 4 weeks	See comment	See comment	Risk Ratio 0.80 [0.34, 1.91]	279 (1 study)	⊕⊕○○ low ¹	Single study reported the primary outcome No significant group difference with wide confidence interval
Participants with exacerbations requiring hospital admission Follow-up: mean 4 weeks	See comment	See comment	Not estimable	279 (1 study)	⊕○○○ very low ²	Single study reported the outcome (but no admissions were reported)
Change from baseline FEV₁ (%) Follow-up: mean 4 weeks	3.3% increase from baseline FEV ₁ on placebo	4.6% [2.4%, 6.0%]	1.30% [-0.09%, 2.69%]	279 (1 study)	⊕⊕○○ low ¹	Single study reported the outcome No significant group difference with wide confidence interval

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

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

¹ Single study, wide confidence interval

² There were no admissions to hospital in this study

BACKGROUND

Description of the condition

Asthma is the most common chronic disease of childhood and is one of the leading reasons for emergency department visits (Linzer 2007) and hospitalisations (PHAC 2007). It affects an estimated 235 million individuals worldwide (WHO 2011). Asthma presents as recurrent episodes or persistent symptoms of reversible airway obstruction. It is a complex syndrome that involves bronchospasm, inflammation, secretions, and airway hyperresponsiveness (Busse 2006).

How the intervention might work

Daily inhaled corticosteroids (ICS) are recommended as first-line monotherapy in children with mild persistent symptoms, that is, as preferred step-2 therapy (National Asthma Council Australia 2006; BTS 2011; GINA 2011; Loughheed 2012; NAEPP 2007). ICS reduce asthma symptoms, exacerbations, airway inflammation, hyperresponsiveness, and the risk of death, and they improve quality of life (QOL) and lung function (Andersson 2001; Castro-Rodriguez 2009; Enting 2003; Pijnenburg 2005; Suissa 2000).

In case of unsatisfactory control with low doses of ICS, asthma management guidelines recommend one of the following three options as step-3 therapy:

1. increasing the dose of ICS to a moderate dose;
2. adding a long-acting beta₂-agonist (LABA); or
3. adding an anti-leukotriene agent (National Asthma Council Australia 2006; BTS 2011; GINA 2011; Loughheed 2012; NAEPP 2007).

Increasing the dose of ICS is effective, but may be associated with short-term growth suppression in a dose-related, and probably a drug-dependant, fashion in children (de Benedictis 2001; Eid 2002; Sharek 1999). The efficacy of LABAs as adjunct to ICS has been thoroughly evaluated recently (Heuck 2000; Malone 2005; Pohunek 2006; Stelmach 2008). Concerns have been raised about the efficacy of LABAs in children and possibly their safety, not only when used as a monotherapy, which is no longer recommended, but also as adjunct therapy (Cates 2008; Cates 2012). Although the risk of serious adverse events of regular formoterol in children was greater than that observed in adults, the difference between age groups did not reach statistical significance (Cates 2008).

Anti-leukotriene agents (also known as leukotriene receptor antagonists or LRTA) are anti-inflammatory drugs that interfere either with leukotriene production (5-lipoxygenase inhibitors) or with receptors (leukotriene receptors antagonists) (Calhoun 2001). They have the advantage of being administered orally in a single or twice-daily dose, and importantly, they seem to lack some of the dose-dependent adverse effects associated with long-term

ICS, such as growth and adrenal suppression (Muijsers 2002). Anti-leukotrienes have the potential to interfere with the pathophysiology of asthma and improve to some extent the clinical and functional manifestations of asthma (Chauhan 2012; Paggiaro 2011).

Why it is important to do this review

A 2004 Cochrane review (Ducharme 2004) evaluating the addition of anti-leukotrienes to ICS in children and adults with asthma identified only two paediatric trials, one of which was published as an abstract and did not contribute data to the meta-analysis. In the past decade, several additional trials were published that may shed more light on the role of anti-leukotrienes as adjunct therapy to ICS. The original review is not being updated; instead, it has been replaced by the present systematic review in children; a second review pertaining to adults will follow.

OBJECTIVES

To compare the efficacy and safety of the combination of anti-leukotriene agents and ICS to the use of the same, an increased, or a tapering dose of ICS in children and adolescents with persistent asthma who remain symptomatic despite the use of maintenance ICS. In addition, we wished to determine the characteristics of people or treatments, if any, that influenced the magnitude of response attributable to the addition of anti-leukotrienes.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion all randomised controlled trials (RCTs) with either parallel group or cross-over design.

Types of participants

We included children and adolescents aged one to 18 years with persistent asthma who remained symptomatic despite the use of a stable maintenance of ICS (or who were made symptomatic after ICS dose reduction).

Types of interventions

We focused analysis on the following three treatment protocols:

- Anti-leukotrienes and ICS (step 3) versus the same dose of ICS (step 2).
- Anti-leukotrienes and ICS (step 3) versus a higher dose of ICS (step 3).
- Anti-leukotrienes and tapering dose of ICS (step 3) versus a tapering dose of ICS (tapering protocol) (step 3).

We did not permit cointerventions other than rescue beta₂-agonists and oral corticosteroids.

Types of outcome measures

Primary outcomes

1. The number of participants with one or more exacerbations requiring oral corticosteroids (unless both groups were tapering their dose of ICS, in which case, the main outcome was the change from the baseline dose of ICS required to maintain control).

Secondary outcomes

1. Exacerbations:
 - participants with one or more exacerbations leading to a hospital admission; and
 - participants with one or more exacerbations leading to an emergency department or an acute-care visit.
2. Clinical or physiologic outcomes reflecting chronic asthma control including the following:
 - i) change in pulmonary function tests (i.e. Forced expiratory volume in one second (FEV₁), peak expiratory flow rate (PEFR), provocative dose or concentration of the stimulus required to achieve a 20% fall in FEV₁ (PC₂₀), etc);
 - ii) change in symptoms;
 - iii) change in beta₂-agonist use;
 - iv) days (period or change in days) without symptoms;
 - v) days (period or change in days) without rescue treatment;
 - vi) change in night-time awakening; and
 - vii) change in quality of life (as measured by a validated questionnaire).
3. Biological markers of inflammation:
 - i) change in eosinophil count in blood or sputum;
 - ii) change in leukotrienes in biological fluids, exhaled nitric oxide, etc; and
 - iii) change in eosinophilic cationic protein, etc.
4. Clinical and biochemical adverse effects:
 - i) participants with overall adverse effects;

- ii) participants with serious adverse health events (including death);
 - iii) participants with other adverse effects (elevation of liver enzymes, headache, adrenal suppression, etc); and
 - iv) change in growth velocity, basal cortisol, etc.
5. Withdrawal rate:
 - i) overall withdrawals;
 - ii) withdrawals due to poor asthma control/exacerbation; and
 - iii) withdrawals due to adverse effects.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register of Trials (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, AMED (Allied and Complementary Medicine Database), and CINAHL (Cumulative Index to Nursing and Allied Health Literature); and the handsearching of respiratory journals and meeting abstracts (please see [Appendix 1](#) for further details). We searched all records in the CAGR coded as 'asthma' using the following terms: (leukotriene* or leucotriene* or anti-leukotriene or anti-leucotriene or montelukast or singulair or zafirlukast or accolate or pranlukast or azlaire)

AND (((steroid* or corticosteroid* or glucocorticoid*) AND in-hal*) OR (fluticasone or beclomethasone or budesonide or triamcinolone or flunisolide or ciclesonide or bronhalide or becotide or azmacort or aerobid or flixotide or aerobec or flovent or becloforte or pulmicort or beclovent or vancril or alvesco))

AND (child* or paediat* or pediat* or adolescen* or infant* or toddler* or bab* or young* or *school* or newborn* or "new born*" or new-born* or neo-nat* or neonat*)

The search was conducted up to January 2013. There was no restriction on language of publication.

Searching other resources

We checked the clinicaltrials.gov and various pharmaceutical companies' websites for the relevant trials.

Data collection and analysis

Two reviewers (BFC and RBS) independently collected data for analysis.

Selection of studies

Two reviewers (BFC and RBS) reviewed each abstract and annotated them as follows:

1. clearly an eligible RCT;
2. clearly not eligible; or
3. unclear.

We obtained full papers for all those that were clearly an eligible RCT and for those in whom the design or relevance was unclear. We contacted authors to confirm the missing information on selection criteria.

Data extraction and management

Two reviewers (BFC and RBS) independently extracted data and dealt with disagreement by consensus and with the input of a third reviewer (FMD), if needed.

Assessment of risk of bias in included studies

The methodological quality of eligible controlled trials was assessed using The Cochrane Collaboration's 'Risk of bias' tool based on six criteria: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Two reviewers (BFC and FMD) independently assessed methodological quality and deemed a study to have a high methodological quality if the reported randomisation procedures and blinding were adequate and there was a low and balanced group attrition.

Measures of treatment effect

We calculated treatment effects for dichotomous variables as odds ratios (OR), relative risk (RR), risk difference (RD), or a combination of the aforementioned. For continuous outcomes, such as the pulmonary function test, we calculated pooled statistics as mean differences (MD), generic inverse variance (GIV), or standardised mean differences (SMD), as indicated. We summarised differences between groups in event rates using rate ratio. We reported all estimates with 95% confidence intervals (CI). We assumed equivalence if the relative risk estimate and its 95% CI were between 0.9 and 1.1.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

We did not impute missing data. We planned to contact authors to ask for missing data.

Assessment of heterogeneity

We tested the homogeneity of effect sizes between studies being pooled with the DerSimonian & Laird method, with $P > 0.05$ or an I^2 statistic $> 40\%$ used as the cut-off level for significance. If one or both methods suggested heterogeneity, we applied a random-effects model to the summary estimates. Unless specified otherwise, we used the fixed-effect model.

Assessment of reporting biases

We examined the funnel plot on the main outcome and conducted the Egger test (Egger 1997) to explore the possibility of bias.

Data synthesis

We reported all effect estimates with their 95% CI. We performed meta-analysis using Review Manager 5.2 (RevMan) (Higgins 2008; RevMan 2011).

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to explore possible reasons for heterogeneity between study results on the primary outcome. We based a priori defined subgroups upon the following:

1. daily dose of ICS in both groups in hydrofluoroalkane beclomethasone dipropionate or equivalent (HFA-BDPeq) (for children aged six to 11 years, ≤ 200 , 201 to 400, and $> 400 \mu\text{g}$ HFA-BDPeq were considered as low-, medium-, and high-dose, while for adolescents aged 12 to 18 years, ≤ 250 , 251 to 500, and $> 500 \mu\text{g}$ HFA-BDPeq were considered as low-, medium-, and high-dose (Lougheed 2012));
2. age (preschool versus school-aged children versus adolescents);
3. severity of baseline airway obstruction (mild: $\text{FEV}_1 \geq 80\%$ of predicted, versus moderate: FEV_1 60% to 79% of predicted, versus severe: $\text{FEV}_1 < 60\%$ of predicted) (GINA 2011);
4. anti-leukotriene agent used (montelukast versus zafirlukast);
5. duration of intervention (four to 12 weeks versus 24 to 52 weeks); and
6. funding source (no funding/academic funding versus pharmaceutical industry funding).

Sensitivity analysis

For the primary outcome, we planned to perform two sensitivity analyses to determine the effect of publication status (abstracts or web reports only versus full peer-reviewed papers) and methodological quality, respectively. We explored a possible publication bias by removing trials not published as full text (i.e. abstracts or web reports) and bias due to poor methodological quality by removing trials not meeting all of the three following criteria: clearly

reported and acceptable random sequence generation, blinding procedure, and balanced and low attrition in both groups.

6. Withdrawals

'Summary of findings' tables

We included a summary of findings table for the two main comparisons in this review. We rated the quality of evidence using recommendations developed by the [GRADE working group](#), presenting our ratings alongside the relative and absolute effects for the following outcomes:

1. Exacerbations
2. FEV₁
3. Quality of life
4. Rescue medication use
5. Adverse events

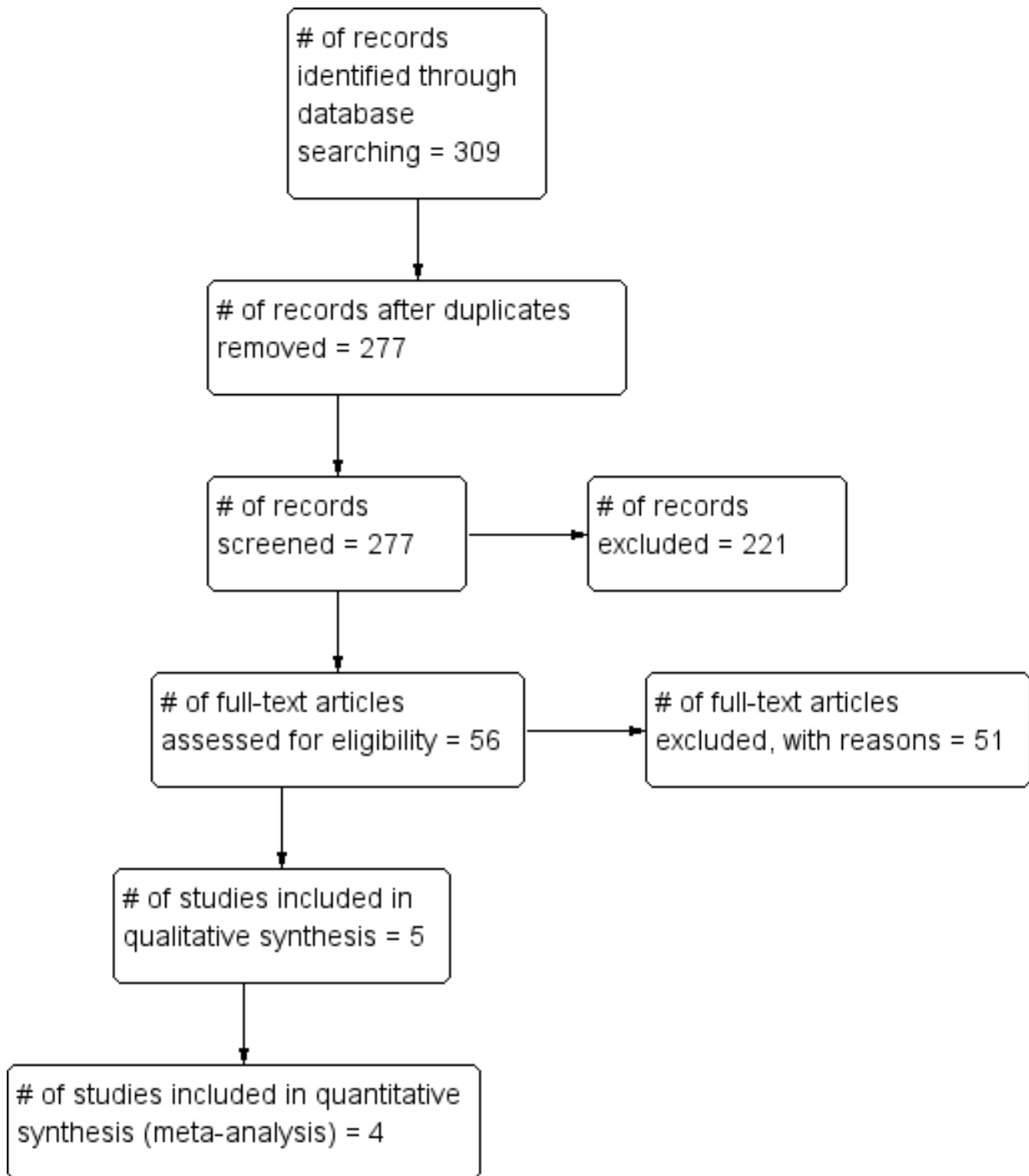
RESULTS

Description of studies

Results of the search

The literature search conducted until January 2013 yielded 309 citations. The reasons for exclusion of various trials are available in the '[Excluded studies](#)' section. We reported the flow of references in a PRISMA diagram ([Figure 1](#)).

Figure 1. Study selection diagram



Included studies

Five trials (Lemanske 2010; Simons 2001; Stelmach 2007; Stelmach 2008; Strauch 2003) met the inclusion criteria for this review. Of these, one trial (Strauch 2003) was eligible but did not contribute data. The following results, except risk of bias in included trials, pertain to four remaining trials that were eligible and contributed data to this review.

The included trials were all published as full-text manuscripts and comprised 559 children (aged $\geq$ six years) and adolescents with mild to moderate asthma. Three trials compared the combination of anti-leukotrienes and ICS with the same dose ICS (Simons 2001; Stelmach 2007; Stelmach 2008), and one trial compared the combination of anti-leukotrienes and ICS with a higher dose ICS (Lemanske 2010). We did not identify studies that assessed the combination of anti-leukotrienes and ICS as a means to taper the dose of ICS.

Design: Two trials (Stelmach 2007; Stelmach 2008) used a parallel group design, while the remaining two trials used a cross-over design.

Participants: Included trials described a gender ratio ranging from 65% to 69% male. One trial (Simons 2001) recruited children aged six to 14 years while remaining trials enrolled children aged $\geq$ six years and adolescents. Stelmach 2007 enrolled children with moderate airway obstruction, and Lemanske 2010 enrolled children with mild to moderate airway obstruction. The remaining two trials did not report the severity of airway obstruction. Stelmach 2007 and Stelmach 2008 recruited children who had confirmed positive skin-prick tests for specific allergens. Both studies compared the combination of anti-leukotriene and ICS to the same dose ICS.

Intervention duration: The duration of intervention varied from four to 16 weeks.

Intervention drugs: All trials used montelukast (anti-leukotriene agent) at a dose of 5 mg for children aged six to 14 years and 10 mg for adolescents aged 15 years and above. Three trials used budesonide turbuhaler (Simons 2001; Stelmach 2007; Stelmach 2008), and the remaining trial (Lemanske 2010) used fluticasone metered-dose inhaler.

Cointervention: No trials reported the use of additional antiasth-

matic drugs, other than rescue beta₂-agonists and systemic corticosteroids.

Outcomes: Two cross-over trials (Lemanske 2010; Simons 2001) comparing the addition of anti-leukotriene agent to ICS with the same dose or higher dose of ICS, respectively, reported the primary outcome, the number of participants experiencing one or more exacerbations requiring rescue oral corticosteroids.

A small number of trials reported other measures of asthma exacerbation (hospital admissions), lung function (FEV₁, morning PEFR) and asthma control indices (change from baseline in daily use of beta₂-agonists, change in quality of life), and biological markers of inflammation (change from baseline in blood eosinophil counts). All four trials contributing data reported withdrawals and adverse effects.

Excluded studies

Of 309 citations, we excluded 303 citations for the following exclusive reasons: duplicate references (N = 32); not a randomised controlled trial (N = 18); participants did not have asthma (N = 1); the control intervention was not ICS (N = 87); the test intervention was not a combination of ICS and anti-leukotriene (N = 104); participants received non-permitted co-interventions (N = 8); the tested intervention was administered for less than four weeks (N = 3); participants had an acute exacerbation (N = 2); the age of participants was more than 18 years (N = 45); participants were naive to daily ICS before enrolment in the study (N = 2); and inadequate information was available for selection criteria (N = 2). The 'Characteristics of excluded studies' tables provide reasons for exclusion.

Risk of bias in included studies

The 'Characteristics of included studies' tables give full details of the risk of bias for each included trial, with a graphical summary of the 'Risk of bias' judgements in Figure 2. Three of the five included trials provided enough information to assess the method of randomisation.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lemanske 2010	+	+	+	+	+	+	+
Simons 2001	?	?	+	+	+	+	+
Stelmach 2007	+	+	+	+	+	+	+
Stelmach 2008	+	+	+	+	+	+	+
Strauch 2003	?	?	+	+	+	+	+

Allocation

Three of the five trials provided sufficient information to confirm the adequacy of the allocation concealment.

Blinding

The procedures for blinding described in the trial reports were sufficient for us to judge that all the included studies were at a low risk of performance and detection bias..

Incomplete outcome data

All trials reported the number and reasons of withdrawals. We did not observe high or imbalanced withdrawal rate in any comparing groups.

Selective reporting

All trails reported all outcomes as mentioned in the methodology section of the published manuscript without any apparent bias.

Other potential sources of bias

We did not identify any other significant source of bias in included trials.

Effects of interventions

See: [Summary of findings for the main comparison](#) Anti-leukotrienes & ICS versus same dose ICS for asthma; [Summary of findings 2](#) Anti-leukotrienes & ICS versus higher dose ICS for asthma

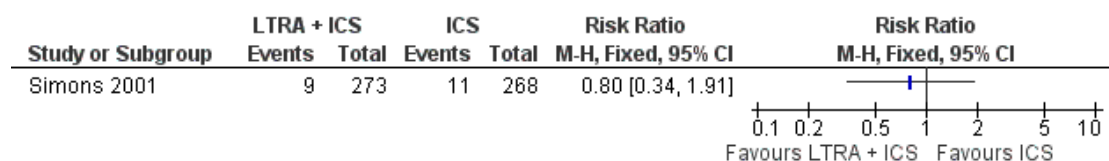
Anti-leukotrienes and ICS versus same dose of ICS (step 3 versus step 2)

See [Summary of findings for the main comparison](#).

Primary outcome: participants with exacerbations requiring oral corticosteroids

There was no statistically significant group difference in the only trial reporting the risk of children (aged six to 14 years) with exacerbations requiring oral corticosteroids over 12 weeks. There were eight children with an exacerbation on anti-leukotrienes, 10 on placebo, and one child who had an exacerbation on both treatments (N = 268 participants; risk ratio (RR) 0.80, 95% CI 0.34 to 1.91; Analysis 1.1; [Figure 3](#)). Because of the lack of trials reporting the primary outcome, we did not perform subgroup analysis, funnel plot, and sensitivity analysis.

Figure 3. Forest plot of comparison: 1 Anti-leukotrienes and ICS versus same dose of ICS, outcome: 1.1 Participants with one or more exacerbations requiring oral corticosteroids



Secondary outcomes

Exacerbations

The only trial that reported this outcome (Analysis 1.2) did not admit any participant to hospital with either treatment strategy due to asthma exacerbation.

Lung functions

No significant group difference was observed in the only trial reporting change from baseline FEV₁ (%) (N = 251 participants; mean difference (MD) 1.30, 95% CI -0.09 to 2.69; Analysis 1.3). Change from baseline in AM PEFR (N = 218 participants; MD 9.70 L/min, 95% CI 1.27 to 18.13; Analysis 1.4) and change from baseline in PM PEFR (N = 218 participants; MD 10.70 L/min, 95% CI 2.41 to 18.99; Analysis 1.5) were reported to be significantly better with anti-leukotriene in this study, but it is not clear whether the PEFR results were based on intention-to-treat or per-

protocol analysis.

Asthma control and biological markers of inflammation

No other included paediatric trials reported other secondary efficacy outcomes. However, the sponsor of one cross-over trial (Simons 2001) provided certain data, which we presented in Table 1. RevMan can not calculate correct treatment effects and 95% CI from such data unless the results of paired t-tests are provided to allow for the within-participant correlation of the treatment effects, so we did not present forest plots for these outcomes.

Safety

Based on only one trial, there were no reported serious adverse effects (Analysis 1.8) or death (Analysis 1.9) in either treatment group. The only trial reporting each of the following outcomes observed no group difference in overall adverse effects (N = 270 participants; OR 0.87, 95% CI 0.62 to 1.23; Analysis 1.10); upper respiratory tract infections (N = 270 participants; OR 0.85, 95% CI 0.46 to 1.54; Analysis 1.111); headache (N = 270 participants; OR 1.02, 95% CI 0.55 to 1.88; Analysis 1.111); nausea (N = 270 participants; OR 0.39, 95% CI 0.07 to 2.00; Analysis 1.111); and elevated liver enzymes (N = 270 participants; OR 1.96, 95% CI 0.18 to 21.70; Analysis 1.11).

Withdrawals

There was no statistically significant group difference in overall withdrawals (N = 368 participants; odds ratio (OR) 1.93, 95% CI 0.74 to 5.05; Analysis 1.6) and in withdrawals due to adverse effects (N = 270 participants; OR 0.49, 95% CI 0.04 to 5.43; Analysis 1.7). No withdrawal was observed due to poor asthma control/exacerbation with either strategy (Analysis 1.7).

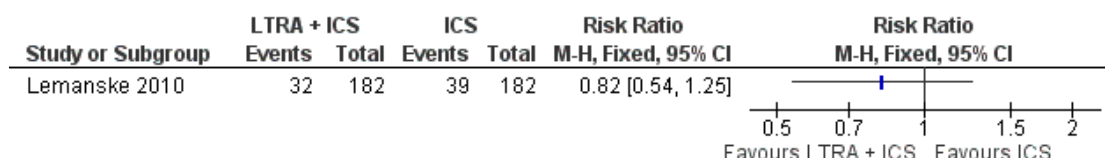
Anti-leukotrienes and ICS versus higher dose of ICS (step 3 versus step 3)

See Summary of findings 2 for the results from the single cross-over study for this comparison (Lemanske 2010).

Primary outcome: participants with exacerbations requiring oral corticosteroids

There was no statistically significant group difference observed in children and adolescents with exacerbations requiring oral corticosteroids over 16 weeks (N = one trial: 182 participants; RR 0.82, 95% CI 0.54 to 1.25; Analysis 2.1; Figure 4). We estimated the number of children who had one or more exacerbations requiring a course of oral corticosteroids by subtracting the number reported as having a second course of oral corticosteroids from the total number of courses on each treatment for one trial (Lemanske 2010). Because of lack of trials reporting the primary outcome, we did not perform subgroup analysis, funnel plot, and sensitivity analysis.

Figure 4. Forest plot of comparison: 2 Anti-leukotrienes and ICS versus higher dose of ICS, outcome: 2.1 Participants with one or more exacerbations requiring oral corticosteroids



Secondary outcomes

Exacerbations

There was no significant difference in exacerbations requiring hospital admission, with a single child admitted on each treatment (N = 182 participants; RR 1.00, 95% CI 0.06 to 15.87; Analysis 2.2).

Lung function and asthma control

No trials reported lung function or asthma control parameters with sufficient details to be used.

Withdrawals

There was no statistically significant group difference in overall withdrawals (N = 182 participants; OR 1.30, 95% CI 0.47, 3.57;

Analysis 2.3). No trial reported withdrawals due to adverse effects, poor asthma control/exacerbations, or any safety parameters.

Anti-leukotrienes and ICS versus tapering dose of ICS

No trial reported the comparison of the combination of anti-leukotriene and ICS with tapering dose of ICS.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Anti-leukotrienes and inhaled corticosteroids versus higher dose of inhaled corticosteroids						
Patient or population: Children with asthma Settings: Outpatients Intervention: Anti-leukotrienes and inhaled corticosteroids Comparison: Higher dose of inhaled corticosteroids						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Anti-leukotrienes and inhaled corticosteroids versus higher dose of inhaled corticosteroids				
Participants with one or more exacerbations requiring oral corticosteroids Follow-up: 16 weeks	See comment	See comment	Risk Ratio 0.82 [0.54, 1.25]	182 (1 study)	⊕⊕○○ low ¹	Single study reported the primary outcome No significant group of difference with wide confidence interval
Participants with exacerbations requiring hospital admission Follow-up: 16 weeks	See comment	See comment	Risk Ratio 1.00 [0.06, 15.87]	182 (1 study)	⊕⊕○○ low ¹	Single study reported the outcome No significant group of difference with wide confidence interval
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI) CI: Confidence interval; OR: Odds ratio						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

¹ Single study, wide confidence interval

DISCUSSION

Summary of main results

In children who remain symptomatic with low-dose ICS, there were insufficient data to determine the effect of adding anti-leukotrienes to ICS on the number of participants with one or more exacerbations requiring oral corticosteroids. There were no data on secondary efficacy outcomes to derive any firm conclusion favouring either strategy, whether comparing the same dose or a higher-dose ICS. The limited available data revealed no significant group difference in withdrawals and safety profile, but did not meet the criteria of equivalence. No trial explored the addition of anti-leukotrienes as a strategy to taper the dose of ICS. The paucity of paediatric trials in this area and the inconsistent measurement of key outcomes preclude firm conclusions regarding the efficacy and safety of adjunctive anti-leukotriene agents in children.

Only one trial in each protocol (Lemanske 2010; Simons 2001) reported the number of participants requiring rescue oral corticosteroids. In both cases, there was no statistically significant group difference. The wide confidence intervals did not demonstrate equivalence. In the comparison testing the combination of anti-leukotrienes and ICS versus the same dose of ICS alone (step 3 versus step 2), a cross-over trial (Simons 2001) evaluated certain secondary efficacy outcomes, including lung function parameters

(FEV₁ and PEFR), change in use of rescue medication, and quality of life. We could not use this data in RevMan as we did not have information on the within-participant correlation between the treatment periods. In the comparison examining the combination of anti-leukotrienes and ICS versus a higher dose of ICS (step 3 versus step 3), a cross-over trial (Lemanske 2010) reported both the main outcome and participants with exacerbation requiring hospital admission; no other secondary efficacy outcomes were reported. In other words, insufficient reporting prevented the aggregation of efficacy data in all protocols.

In both treatment protocols, the only safety outcome that we could aggregate was overall withdrawal; no significant group difference was observed with wide confidence intervals. No serious adverse events were observed in these small studies.

In view of the paucity of trials and inadequate reporting, there is inconclusive evidence to support the use of anti-leukotrienes as adjunct therapy to ICS (step-3 option) in children and adolescents (no data on preschoolers). Limited data on withdrawals prevent firm conclusions as to the safety of this strategy compared to using the same dose (step 2) or a higher dose (step 3) ICS alone.

Overall completeness and applicability of evidence

Of note is the strikingly low number of paediatric studies examining the best step-up therapy with anti-leukotrienes in children inadequately controlled with a low daily maintenance dose of ICS.

We excluded four paediatric trials because we could not confirm that children were insufficiently controlled or because they included either well-controlled children on daily ICS or participants naive to ICS (Finn 2000; Jat 2006; Karaman 2007; Miraglia del Giudice 2007). Moreover, of the five eligible trials, one did not contribute data in the format required. Of interest, the only study (Strauch 2003) evaluating the clinical efficacy on bronchial inflammation, of adjunct treatment with leukotriene receptor antagonists in children with asthma on ICS, showed a significant reduction in airway inflammation and improved quality of life.

We identified only five eligible paediatric trials: The trials recruited 559 children, aged six years and above, and adolescents. No trial focused on preschoolers. Of the included studies, four trials reported only a limited number of outcomes of interest. The majority of secondary outcomes were measured as end of treatment values rather than change from the baseline, thus, limiting the interpretation of findings. We emphasise the need for further trials with complete reporting of efficacy outcomes, specifically exacerbations requiring rescue oral corticosteroids, hospital admission, and change from baseline in asthma control parameters.

Quality of the evidence

Our confidence in the effect estimates is limited by statistical imprecision due to the low number of studies and low power of our analysis.

Potential biases in the review process

There were insufficient data to assess the potential for bias relating to study quality and publication bias.

Agreements and disagreements with other studies or reviews

The Cochrane review on addition of anti-leukotriene agents to ICS for chronic asthma in children and adults published in 2004 concluded that in symptomatic people, the addition of licensed doses of anti-leukotrienes to ICS resulted in a non-significant reduction in the risk of exacerbations requiring systemic steroids (RR 0.64, 95% CI 0.38 to 1.07) with modest improvement in lung function (PEFR MD 7.7 L/min, 95% CI 3.6 to 11.8) and a

decrease in the use of rescue short-acting beta₂-agonist use (MD 1 puff/week, 95% CI 0.5 to 2). With only 3 trials comparing the use of licensed doses of anti-leukotrienes with increasing the dose of ICS, no firm conclusion could be drawn about the equivalence of both treatment options (Ducharme 2004).

The prior review was heavily weighted towards adults and did not firmly conclude on the efficacy and safety of addition of anti-

leukotrienes to ICS. The current review supports the same conclusion in paediatrics.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of anti-leukotriene agents as step-3 therapy in children and adolescents with mild to moderate asthma. Despite the fact that anti-leukotrienes have been licensed for over 10 years for children in many countries, there are major limitations with the evidence base: There is an appalling paucity of paediatric trials, an absence of data on preschoolers, and the reporting of clinically relevant outcomes is highly variable. These limitations prevent firm conclusions. At present, there is no firm evidence to support the efficacy and safety of anti-leukotrienes as add-on therapy to ICS as a step-3 option in the therapeutic arsenal for children with uncontrolled asthma symptoms on low-dose ICS. Consequently, should a clinician wish to add anti-leukotrienes to the therapeutic regimen, it should be considered as a therapeutic trial and the clinical impact on asthma control and exacerbations should be documented in the specific person before considering prolonged therapy.

Implications for research

We emphasise the urgent need for further paediatric trials (including preschoolers) with sub-optimal asthma control on inhaled corticosteroids, comparing the addition of anti-leukotriene agents to existing ICS to either the same or a higher ICS. We call for complete reporting of efficacy outcomes, especially with regard to people with one or more exacerbations requiring rescue oral corticosteroids, hospital admissions, and change from baseline in asthma control indices. We also suggest considering the following issues while designing a paediatric trial:

- children with mild to moderate persistent asthma incompletely controlled on daily inhaled corticosteroids;
- including all paediatric age groups, including preschool-aged children;
- favouring a parallel group design with a minimum of 24-week treatment duration;
- measurement and reporting of participants with exacerbation requiring oral corticosteroids and hospital admission separately;
- analysis and reporting of efficacy outcomes (including asthma control) as change from baseline or as overall period effect (instead of end of study value) (Reddel 2009);
- measurement and reporting of severe adverse events, including anticipated adverse effects of both treatment strategies including headache, growth, behavioural changes, etc;
- reporting of overall withdrawals with their reasons;
- documentation of compliance; and
- use of anti-leukotriene agents as a means to taper the dose of ICS (protocol 3).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Lemanske 2010

Methods	Randomised, 3-period cross-over trial, double-blind, clinical study
Participants	Children aged 6 to 17 years of age with mild to moderate asthma diagnosed by a physician on the basis of criteria recommended by the National Asthma Education and Prevention Program % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMISED: 37.9% Reasons for exclusion during run-in: • had compliance issues • had asthma exacerbation • had consent withdrawn • had asthma symptoms controlled • did not meet reversibility or PC 2 0 criteria • had FEV₁ • < 60% of predicted • were lost to follow up • were withdrawn by physician • were ineligible at first visit • were unable to perform pulmonary function tests (PFTs) • had medical condition other than asthma • had other reasons RANDOMISED: 182 (cross-over trial) LTRA + ICS: 182 ICS alone: 182 WITHDRAWALS: reported AGE in years: mean = 11.9 years GENDER (% men): 59.5% SEVERITY: mild to moderate persistent asthma MEAN AGE WHEN ASTHMA DIAGNOSED: 4 years BASELINE % PREDICTED FEV₁ (mean): 96.8% MEAN (± SD) beta₂-AGONIST USE (puffs per day): not reported BASELINE DOSE OF ICS: not reported ATOPY (%): 77% positive perennial skin test ELIGIBILITY CRITERIA: • Children aged 6 to 17 years with mild to moderate asthma diagnosed by a physician on the basis of criteria recommended by the National Asthma Education and Prevention Program • Ability to perform reproducible spirometry, an FEV₁ • of at least 60% before bronchodilation, and an increase in the FEV₁ • of at least 12% (bronchodilator reversibility) or a methacholine provocation concentration causing a 20% fall (PC)

	² ⁰) in the FEV ₁ ¹ of 12.5 mg per mL or less ● Occurrence of at least 1 of the following for more than 2 days per week on average during a 2-week period: diary-reported symptoms (coughing rated as moderate or severe or wheezing rated as mild, moderate, or severe), rescue use of an inhaled bronchodilator with 2 or more puffs per day, or peak flows under 80% of the predetermined reference value EXCLUSION CRITERIA: not reported
Interventions	PROTOCOL: LTRA + ICS versus ICS alone OUTCOMES: reported at 16 weeks RUN-IN: 2 to 8 weeks INTERVENTION GROUP: 100 µg of fluticasone twice daily plus 5 or 10 mg of montelukast daily CONTROL GROUP: 250 µg of fluticasone (Flovent Diskus, GlaxoSmithKline) twice daily DEVICE: Flovent Diskus COMPLIANCE: reported (84% for study tablets and 87% for study inhalers) COTREATMENT: reported CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: The primary analysis was analysed using a 1-sided exact test for binomial proportions and a rank-ordered logistic regression OUTCOMES: % of participants responded (not change from baseline) PULMONARY FUNCTION TEST: FEV ₁ FUNCTIONAL STATUS: the need for treatment with oral prednisone for acute asthma exacerbations, the number of asthma control days INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: reported with following reasons: ● dropped out during treatment phase ● withdrew consent ● were lost to follow up or were no longer interested ● were unable to continue for personal reasons or because moved out of the area ● was dissatisfied with asthma control ● was unable to continue owing to medical condition other than asthma ● were withdrawn by physician ● had other reasons
Notes	Full-text publication Source of funding: several grants reported Confirmation of methodology and data: not obtained
<i>Risk of bias</i>	
Bias	Authors' judgement
	Support for judgement

Lemanske 2010 (Continued)

Random sequence generation (selection bias)	Low risk	Centralised random sequence using a 3 x 3 cross-over design
Allocation concealment (selection bias)	Low risk	Placebo tablets and dummy disk devices were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced low withdrawals in the study
Selective reporting (reporting bias)	Low risk	Study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review reported in the pre-specified way
Other bias	Low risk	No apparent bias was observed

Simons 2001

Methods	Randomised, cross-over, double-blind, clinical study
Participants	Children aged 6 to 14 years with persistent asthma % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMISED: not reported RANDOMISED: 279 (cross-over trial) LTRA + ICS: 279 ICS alone: 279 WITHDRAWALS: 15 AGE in years: mean = 10.4 years GENDER (% men) = 67% SEVERITY: not specified MEAN AGE WHEN ASTHMA DIAGNOSED: not reported BASELINE % PREDICTED FEV₁ (mean): 77.7% (10.6) MEAN RESCUE-beta₂-AGONIST USE (mean +/- SD): 2.9 +/- 2.0 puffs per day BASELINE DOSE OF ICS: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: Children aged 6 to 14 years with persistent asthma who had been treated with an ICS for at least 6 weeks before the study at doses of 200 to 800 µg daily of budesonide, beclomethasone dipropionate, triamcinolone acetonide, or flunisolide, or 100 to 500 µg daily of fluticasone propionate

	- During the run-in, despite treatment with 200 µg budesonide twice daily, they were required to have FEV₁ ≥ 60% and ≤ 85% of the predicted value, a ≥ 12% improvement in FEV₁ 20 to 30 minutes after short-acting beta₂-agonist administration, and asthma symptoms requiring a minimum average of at least 2 puffs per day of a beta₂-agonist in the 14 days immediately before randomisation EXCLUSION CRITERIA: - Active upper respiratory tract infection within 3 weeks - Active sinus disease requiring antibiotic treatment within 1 week - Emergency department treatment for asthma within 1 month - Prior intubation for asthma or hospitalisation for asthma within 3 months before the prestudy (screening) visit - Excluded medications included astemizole within 3 months; oral inhaled or parenteral corticosteroids within 1 month; cromolyn, nedocromil, beta₂-agonists (oral or long-acting), antihistamines cimetidine, metoclopramide, phenobarbital, phenytoin, terfenadine, loratadine, or anticholinergic agents within 2 weeks; and theophylline within 1 week before the prestudy visit - People receiving immunotherapy had to maintain therapy at a constant dosage during the study, and therapy had to have begun at least 6 months before the prestudy visit
Interventions	PROTOCOL: LTRA + ICS versus ICS alone OUTCOMES: reported at 4 weeks (3 periods of 4 weeks) RUN-IN: 4 weeks INTERVENTION GROUP: 5 mg chewable montelukast tablet once daily at bedtime in addition to 200 µg of budesonide twice daily CONTROL GROUP: matching placebo once daily at bedtime in addition to 200 µg of budesonide twice daily COMPLIANCE: mentioned COTREATMENT: Short-acting beta₂-adrenergic agonists were used as needed but were withheld for 6 hours before visits CRITERIA FOR WITHDRAWAL FROM STUDY: presented.
Outcomes	ANALYSIS: intention-to-treat analysis OUTCOMES: mean % change from baseline for all parameters PULMONARY FUNCTION TEST: FEV₁, morning and evening PEF. FUNCTIONAL STATUS: change from baseline in average beta₂-adrenergic agonist use, mean percentage of asthma exacerbation days, quality of life measurement, global evaluations or asthma attacks INFLAMMATORY MARKERS: blood eosinophil counts ADVERSE EFFECTS: reported WITHDRAWALS: reported with following reasons: - discontinued because of deviation from the protocol - clinical adverse events - miscellaneous reasons
Notes	Full-text publication Source of funding: not reported Confirmation of methodology and data: not obtained

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although study was randomised, insufficient information was provided on means of randomisation
Allocation concealment (selection bias)	Unclear risk	No details were provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. Matching placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few withdrawals. Reasons for missing outcome data unlikely to be related to true outcomes
Selective reporting (reporting bias)	Low risk	Study protocol was not available, but the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	No apparent bias was observed

Stelmach 2007

Methods	Randomised, double-blind, placebo-controlled, parallel group trial
Participants	Children with a typical history of moderate asthma who were sensitive to house dust mites as shown by positive skin-prick tests and by the presence of specific IgE to <i>Dermatophagoides pteronyssinus</i> or <i>Dermatophagoides farinae</i> % ELIGIBLE OF SCREENED POPULATION: reported % RUN-IN PARTICIPANTS RANDOMISED: reported RANDOMISED: 58 LTRA + ICS: 29 ICS alone: 29 WITHDRAWALS: reported AGE in years: mean = 11.5 years GENDER (% men): 69% SEVERITY: moderate asthma MEAN AGE WHEN ASTHMA DIAGNOSED: not reported

	BASELINE % PREDICTED FEV₁ (mean): 94.6% MEAN RESCUE-beta₂ -AGONIST USE (mean +/- SD): not reported BASELINE DOSE OF ICS: not reported ATOPY (%): 100% ELIGIBILITY CRITERIA: • Male and female outpatients, aged 6 to 18 with a clinical diagnosis of bronchial asthma with a duration of at least 6 months before the first visit and with current history of moderate persistent asthma • Patients and their parents were required to do reproducible spirometry, whole body plethysmography, and interrupter technique EXCLUSION CRITERIA: • With active upper respiratory tract infection within 3 weeks before the study and acute sinus disease requiring antibiotic treatment within 1 month before the study • Previous intubation or asthma hospitalisation during the 3 months before the first visit • Clinically significant pulmonary, hematologic, hepatic, gastrointestinal, renal, endocrine, neurologic, cardiovascular, and/or psychiatric diseases, or malignancy that either put the participant at risk when participating in the study or could have influenced the results of the study or the participant's ability to participate in the study as judged by the investigator • Excluded medications were beta₂-blockers (eye drops included), astemizole within 3 months, or oral corticosteroids within 1 month before the first visit. People who were receiving immunotherapy were also excluded
Interventions	PROTOCOL: LTRA + ICS versus ICS alone OUTCOMES: reported on 4 weeks RUN-IN: 4 weeks INTERVENTION GROUP: 200 µg per day budesonide + 5 mg montelukast, formoterol placebo CONTROL GROUP: 200 µg per day budesonide, montelukast placebo, formoterol placebo COMPLIANCE: not mentioned COTREATMENT: inhaled beta₂-agonist 100 mg/dose 'as-needed' for symptomatic relief purposes CRITERIA FOR WITHDRAWAL FROM STUDY: presented
Outcomes	ANALYSIS: not with intention-to-treat analysis OUTCOMES: mean absolute values and change from baseline for all parameters PULMONARY FUNCTION TEST: FEF_{25-75%}, FEV₁, R_{int} and SR_{aw} FUNCTIONAL STATUS: not reported INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: not reported WITHDRAWALS: all enrolled participants completed the trial
Notes	Full-text publication Source of funding: grant from Medical University of Lodz, Poland Confirmation of methodology and data: not obtained

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence was used
Allocation concealment (selection bias)	Low risk	Matching placebo and drug were blinded by the central hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. Double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few withdrawals
Selective reporting (reporting bias)	Low risk	Study protocol was not available, but the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	No apparent bias was observed

Stelmach 2008

Methods	Randomised, double-blind, placebo-controlled, parallel group trial
Participants	Children 6 to 18 years of age with atopic asthma, who were sensitive only to house dust mites as shown by positive skin prick tests to <i>Dermatophagoides pteronyssinus</i>, <i>Dermatophagoides farinae</i>, or both % ELIGIBLE OF SCREENED POPULATION: reported % RUN-IN PARTICIPANTS RANDOMISED: reported RANDOMISED: 40 LTRA + ICS: 20 ICS alone: 20 WITHDRAWALS: reported AGE in years: mean = 12.05 years GENDER (% men): not reported SEVERITY: not reported MEAN AGE WHEN ASTHMA DIAGNOSED: not reported BASELINE % PREDICTED FEV₁ (mean): 91.2% MEAN RESCUE-beta₂-AGONIST USE (mean +/- SD): not reported

	BASELINE DOSE OF ICS: not reported ATOPY (%): 100% ELIGIBILITY CRITERIA: • Male and female outpatients age 6 to 18 with a clinical diagnosis of bronchial asthma with a duration of at least 6 months before the first visit were enrolled • Participants had to have a resting FEV₁ of 70% or more and a documented decrease in FEV₁ of 20% or more after a standard exercise challenge test EXCLUSION CRITERIA: • With active upper respiratory tract infection within 3 weeks before the study and acute sinus disease requiring antibiotic treatment within 1 month before the study • Previous intubation or asthma hospitalisations during the 3 months before the prestudy visit • With other clinically significant pulmonary, hematologic, hepatic, gastrointestinal, renal, endocrine, neurologic, cardiovascular, and/or psychiatric diseases, or malignancy that either put the participant at risk when participating in the study or could have influenced the results of the study or the participant's ability to participate in the study as judged by the investigator • On medications like beta₂-blockers (eye drops included) or oral corticosteroids within 1 month before the first visit • People receiving immunotherapy
Interventions	PROTOCOL: LTRA + ICS versus ICS alone OUTCOMES: reported at 4 weeks RUN-IN: 4 weeks INTERVENTION GROUP: 100 µg budesonide twice daily + 5 mg montelukast, formoterol placebo CONTROL GROUP: 100 µg budesonide twice daily + montelukast placebo, formoterol placebo COMPLIANCE: not mentioned COTREATMENT: inhaled beta₂-agonist 'as needed' for symptomatic relief purposes CRITERIA FOR WITHDRAWAL FROM STUDY: presented
Outcomes	ANALYSIS: not with intention-to-treat analysis OUTCOMES: mean absolute values and change from baseline for all parameters PULMONARY FUNCTION TEST: FEV₁, area under the curve for exercise induced fall in FEV₁ FUNCTIONAL STATUS: not reported INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: not reported WITHDRAWALS: reported with following reasons • asthma exacerbation (caused by respiratory tract infection)
Notes	Full-text publication Source of funding: not reported Confirmation of methodology and data: not obtained
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence was used
Allocation concealment (selection bias)	Low risk	Matching placebo and drug were blinded by the central hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. Double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	The balanced withdrawals were observed in both comparing groups
Selective reporting (reporting bias)	Low risk	Study protocol was not available, but the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	No apparent bias was observed

Strauch 2003

Methods	Randomised, double-blind, placebo-controlled, parallel group trial
Participants	Children having mild to moderate asthma as per the American Thoracic Society % ELIGIBLE OF SCREENED POPULATION: reported % RUN-IN PARTICIPANTS RANDOMISED: reported RANDOMISED: 25 WITHDRAWALS: reported but not per group AGE in years: reported for all participants individually for every included participant GENDER (% men): reported SEVERITY: reported individually for every included participant MEAN AGE WHEN ASTHMA DIAGNOSED: not reported BASELINE % PREDICTED FEV₁ (mean): reported for all participants individually for every included participant MEAN RESCUE-beta₂-AGONIST USE (mean +/- SD): not reported BASELINE DOSE OF ICS: reported for all participants individually for every included participant ATOPY (%): 100% reported in inclusion criteria ELIGIBILITY CRITERIA: Children having mild to moderate asthma as per the American Thoracic Society

	● On ICS at doses between 200 and 400 μg budesonide twice daily regularly for at least 12 weeks ● Aged 6 to 14 years ● All children who were allergic to common inhalant allergens ● Free of respiratory infections or an asthma exacerbation for at least 4 weeks before enrolment ● Bronchial inflammation demonstrated on the basis of a sputum ECP level > 100 μg/L EXCLUSION CRITERIA: ● People using systemic corticosteroids, cromolyn sodium, nedocromil, anticholinergics, theophylline, antihistamines, or an anti-leukotriene medication, such as montelukast	
Interventions	PROTOCOL: LTRA + ICS versus ICS alone OUTCOMES: reported on 4 weeks RUN-IN: 7 to 10 days INTERVENTION GROUP: 200 and 400 μ g budesonide twice daily + 5 mg montelukast orally, once daily CONTROL GROUP: 200 and 400 μ g budesonide twice daily + placebo COMPLIANCE: reported CO-TREATMENT: inhaled beta $_2$ -agonist 'as needed' for symptomatic relief was permitted CRITERIA FOR WITHDRAWAL FROM STUDY: presented	
Outcomes	ANALYSIS: not with intention-to-treat analysis OUTCOMES: absolute values and change from baseline for all parameters PULMONARY FUNCTION TEST: FEV $_1$ (%) FUNCTIONAL STATUS: overall QOL, symptoms, activities, emotions INFLAMMATORY MARKERS: exhaled nitric oxide, sputum eosinophil cationic protein, sputum eosinophil count, urinary excretion of eosinophil protein X ADVERSE EFFECTS: reported WITHDRAWALS: reported	
Notes	Full-text publication Source of funding: not reported Confirmation of methodology and data: not obtained	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although study was randomised, insufficient information was provided on means of randomisation
Allocation concealment (selection bias)	Unclear risk	No details were provided on allocation concealment

Strauch 2003 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. Double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few dropouts
Selective reporting (reporting bias)	Low risk	Study protocol was not available, but the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	No apparent bias was observed

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abadoglu 2005	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Abdel-wahab 2009	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
ALAACRC 2007	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Allen-Ramey 2003	Not a randomised controlled trial; it was a cohort study
Anonymous 2010	Control group was not inhaled corticosteroid
Bacharier 2008	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Baek 2011	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Barnes 2007	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Barnes 2007a	Study participants were adults
Basu 2010	Control group was not inhaled corticosteroid
Becker 2006	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Benitez 2005	Control group was not inhaled corticosteroid

(Continued)

Bjermer 2000	Control group was not inhaled corticosteroid
Bjermer 2003	Control group was not inhaled corticosteroid
Bleecker 2000	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Bousquet 2005	Control group was not inhaled corticosteroid
Bozek 2012	Received non-permitted drug (LABA) in both comparing groups
Buchvald 2002	Duplication: Buchvald et al. Comparisons of the complementary effect on exhaled nitric oxide of salmeterol vs montelukast in asthmatic children taking regular inhaled budesonide. <i>Annals of Allergy, Asthma & Immunology</i> . 2003; 91(3):309-313
Buchvald 2003	Intervention was administered for < 4 weeks
Bukstein 2003	Not a randomised controlled trial
Busse 1999	Study participants were adults
Busse 2001	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Caffey 2005	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Cakmak 2004	Study participants were adults
Costa-Katz 2012	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Currie 2003	Study participants were adults
Currie 2003a	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Davies 2004	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Dempsey 2002	Study participants were adults
Dempsey 2002a	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Deschildre 2012	Control group was not inhaled corticosteroid
Djukanović 2010	Study participants were adults
Duong 2012	Intervention was administered for < 4 weeks
Eakin 2012	Control group was not inhaled corticosteroid
Farber 2010	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid

(Continued)

Finn 2000	Lack of information to decide whether participants were inadequately controlled with daily ICS before enrolment (step 2)
Fogel 2010	Control group was not inhaled corticosteroid
Fritsch 2006	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Ghiro 2001	Duplication: Ghiro et al. Effect of montelukast added to inhaled corticosteroids on fractional exhaled nitric oxide in asthmatic children. <i>European Respiratory Journal</i> . 2002; 20(3):630-4
Ghiro 2002	Intervention was administered for < 4 weeks
Igde 2009	Control group was not inhaled corticosteroid
Ilowite 2004	Study participants were adults
Irvin 2007	Study participants were adults
Jat 2006	Lack of information to decide whether participants were inadequately controlled with daily ICS before enrolment (step 2)
Jayaram 2005	Study participants were adults
Jenkins 2005	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Johnston 2007	Use of non-permitted drug in subgroup of participants
Jung 2006	Control group was not inhaled corticosteroid
Kamenov 2007	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Karaman 2007	Participants were naive to daily ICS
Keith 2009	Control group was not inhaled corticosteroid
Kondo 2006	Control group was not inhaled corticosteroid
Laviolette 1999	Study participants were adults
Lee 2004	Study participants were adults
Lipworth 2000	Study participants were adults
Marogna 2010	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Matsuse 2012	Control group was not inhaled corticosteroid

(Continued)

Mendes 2004	Study participants were adults
Miraglia del Giudice 2007	Participants were naive to daily ICS
Nathan 2001	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Nelson 2000	Control group was not inhaled corticosteroid
Nelson 2006	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Ng 2007	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
O'Connor 2006	Control group was not inhaled corticosteroid
O'Sullivan 2003	Study participants were adults
Ostrom 2003	Duplication: Ostrom et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. Journal of Pediatrics. 2005; 147(2):213-20
Ostrom 2005	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Papadopoulos 2009	Received non-permitted drugs (nedocromil, antihistamines). Only 40% of included children were on inhaled corticosteroids
Patel 2010	Study participants were adults
Pedersen 2007	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Peroni 2005	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Philip 2011	Study participants were adults
Phipatanakul 2003	Received non-permitted drugs (topical nasal corticosteroids, antihistamines)
Price 2003	Study participants were adults
Price 2011	Study participants were adults
Reiss 1997	Control group was not inhaled corticosteroid
Riccioni 2005	Study participants were adults
Robinson 2001	Study participants were adults
SAM40030	Study participants were adults
SAS40036	Study participants were adults

(Continued)

SD-004CR-0216	Study participants were adults
Shah 2006	Study participants were adults
Sims 2003	Study participants were adults
Smith 2012	Control group was not inhaled corticosteroid
Smugar 2009	Control group was not inhaled corticosteroid
Stelmach 2002	Control group was not inhaled corticosteroid
Stelmach 2005	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Storms 2004	Study participants were adults
Tognella 2004	Study participants were adults
Tohda 2002	Study participants were adults
Tsuchida 2005	Study participants were adults
Ulrik 2010	Study participants were adults
Verini 2010	Control group was not inhaled corticosteroid
Virchow 2000	Study participants were adults
Virnig 2008	Duplication: Johnston et al. Attenuation of the September epidemic of asthma exacerbations in children: a randomised, controlled trial of montelukast added to usual therapy. EMBASE 2007433958. Pediatrics. 2007; 120(3):e702-e712
Weiss 2010	No consistent treatment with inhaled corticosteroid in both comparing groups
Williams 2001	Intervention was not a combination of anti-leukotriene and inhaled corticosteroid
Wilson 2001	Study participants were adults
Wilson 2010	Study participants were adults
Yaldiz 2000	Study participants were adults
Yasui 2012	Received non-permitted drug (LABA) in both comparing groups
Yildirim 2004	Study participants were adults

DATA AND ANALYSES

Comparison 1. Anti-leukotrienes and inhaled corticosteroids versus same dose of inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with 1 or more exacerbations requiring oral corticosteroids	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Participants with exacerbations requiring hospital admission	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Change from baseline FEV ₁ (%)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4 Change from baseline AM PEFR (L/min)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5 Change from baseline PM PEFR (L/min)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 Overall withdrawals	3	643	Odds Ratio (M-H, Fixed, 95% CI)	1.93 [0.74, 5.05]
7 Withdrawal because of specific reasons	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Withdrawal due to adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Withdrawal due to poor asthma control/exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Serious adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Death	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Overall adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Specific adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Upper respiratory tract infections	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Headache	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Nausea	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.4 Elevated liver enzymes	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Anti-leukotrienes and inhaled corticosteroids versus higher dose of inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with 1 or more exacerbations requiring oral corticosteroids	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Participants with exacerbations requiring hospital admission	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Overall withdrawals	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

ADDITIONAL TABLES

Table 1. Secondary outcomes reported in cross-over trial (Simons 2001)

Outcome		LTRA + ICS			ICS		
		Mean difference	SD	Total	Mean difference	SD	Total
Change from baseline FEV ₁ (L)	from	0.07	0.25	251	0.04	0.25	251
Change from baseline AM PEFR (L/min)	from	37.5	72.8	218	28.1	76.4	218
Change from baseline mean daily use of beta ₂ -agonists (puffs/day)	from	-1.36	2.08	225	-1.03	2.44	225
Change in quality of life		0.54	0.95	148	0.45	0.94	148
Change from baseline eosinophil counts ($\times 10^9/L$)	from	-0.07	0.32	232	0.04	0.36	232

CONTRIBUTIONS OF AUTHORS

Dr Bhupendrasinh Chauhan wrote the protocol, reviewed the literature search until January 2013, identified and reviewed all citations for relevance, reviewed methodological quality, extracted data, analysed and interpreted the results of the meta-analysis, wrote all versions of the manuscript, and approved the final version of the manuscript.

Raja Ben Salah identified and reviewed all relevant citations with BFC and extracted data.

Prof Francine Ducharme supervised and approved the protocol, verified the extracted data, provided input in case of disagreement regarding the inclusion of trials, reviewed the methodological assessment and the interpretation of data, edited all versions of the manuscript, and approved the final version of the manuscript.

DECLARATIONS OF INTEREST

Dr Bhupendrasinh Chauhan received a postdoctoral research fellowship from one of Prof Francine Ducharme's CIHR funded projects.

Raja Ben Salah has no declarations of interest.

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- Dr Bhupendrasinh Chauhan, Canada.

received a postdoctoral scholarship from the Canadian Institute of Health Research, Canada.

- Raja Ben Salah, Canada.

received a scholarship from the Canadian Institute of Health Research, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We increased the cut-off point for significant heterogeneity from I^2 statistic > 25% to I^2 statistic > 40%. We added boundaries to classify trials as either short- or long-term.

NOTES

None.