

Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children (Review)

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[Intervention Review]

Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children

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ABSTRACT

Background

Acute asthma presentation in the emergency setting frequently leads to hospital admission. Currently available treatment options include corticosteroid therapy, beta₂-agonists and oxygen. Antileukotriene agents are beneficial in chronic asthma as additional therapy to inhaled steroids. Their value when used orally or intravenously in the acute setting requires evaluation.

Objectives

To determine if the addition of a leukotriene receptor antagonist (LTRA) produces a beneficial effect in children and adults with acute asthma who are currently receiving inhaled bronchodilators and systemic corticosteroids.

Search methods

We searched the Cochrane Airways Group's Specialised Register of trials with predefined terms. Searches are current to February 2012.

Selection criteria

We included randomised trials comparing antileukotrienes and standard acute asthma care versus placebo and standard care in people with acute asthma of any age. We considered any dose and method of delivery of the leukotriene agent.

Data collection and analysis

Two authors independently assessed studies for inclusion in the review and extracted data. We then checked data and resolved disagreements by discussion. We contacted study authors where necessary to provide additional information and data.

Main results

Eight trials, generating 10 treatment-control comparisons, that recruited 1470 adults and 470 children met the entry criteria. These studies were of mixed quality, and there was heterogeneity in the severity of asthma exacerbation.

For oral treatment, there was no significant difference in hospital admission between LTRAs and control in three trials on 194 children (risk ratio (RR) 0.86; 95% confidence interval (CI) 0.21 to 3.52). Using a broader composite outcome which measured requirement for additional care there was no significant difference between treatments (RR 0.87; 95% CI 0.60 to 1.28). Results demonstrated some indication of improvement in lung function with a significant difference in forced expiratory volume in one second (FEV₁) favouring

LTRAs in two trials on 641 adults (mean difference (MD) 0.08; 95% CI 0.01 to 0.14). There were insufficient data to assess this outcome in children. The most common adverse event described was headache; however, there was no significant difference between LTRAs and control (RR 0.81; 95% CI 0.22 to 2.99). Due to insufficient numbers, we were unable to conduct a subgroup analysis based on age.

The combined results of two trials of intravenous treatment in 772 adults and one trial in 276 children demonstrated a reduction in the risk of hospital admission which was not quite statistically significant (RR 0.78; 95% CI 0.61 to 1.01). There was a statistically significant small difference in FEV₁ in the adult studies (MD 0.12; 95% CI 0.06 to 0.17), but not in the single trial in children (MD 0.01; 95% CI -0.06 to 0.08).

Authors' conclusions

Presently, the available evidence does not support routine use of oral LTRAs in acute asthma. Further studies are required to assess whether intravenous treatment can reduce the risk of hospital admission, and what the most appropriate dose regimen is. Additional research is also needed into safety and efficacy of additional doses for those on maintenance therapy, and larger paediatric trials are required to allow subgroup analysis. Prolonged studies would be required to establish other health economic outcomes in admitted patients.

PLAIN LANGUAGE SUMMARY

Does adding antileukotriene agents to usual care when people are suffering an asthma attack in the emergency department help?

Current recommended treatment in the emergency department for people experiencing an asthma attack is beta₂-agonists, systemic corticosteroids and oxygen. Unfortunately, some people do not get better with these standard treatments and so there is interest in developing additional treatments which will help people experiencing an asthma attack. One such treatment is antileukotrienes, which are available in tablet form to be taken orally; this drug is also made in injection form, however the intravenous form is not marketed and therefore not available.

This review considers the effect of antileukotriene agents, (normally used as add-on preventer therapy in chronic asthma), when used during acute asthma treated in emergency settings. We identified eight randomised controlled trials (RCTs) on 1470 adults and 470 children addressing this question, and in most of these studies participants were also given courses of corticosteroids at the time of treatment. We did not find a significant difference in the likelihood of being admitted to hospital between people treated with oral antileukotrienes and placebo or usual care. There was no significant difference in participants requiring additional care (including hospital admission or other treatment options) at the end of the studies between treatment and control groups. There was an improvement in lung function in people taking antileukotrienes compared to those on placebo. More research in this area is required, and the low number of studies recruiting children does not enable us to provide evidence on what effects this class of drugs has in children.

There were two trials that randomised 772 adults and 276 children to receive intravenous antileukotrienes and there was no statistically significant difference in hospital admissions, however there was an improvement in lung function in adults on antileukotrienes.

BACKGROUND

Description of the condition

Acute asthma consistently ranks among the most frequent causes of visits to the emergency department, and hospital admission in

both children and adults.

Many patients with acute asthma exacerbations do not respond fully to standard therapy of beta₂-agonists, systemic corticosteroids and oxygen. Therefore alternative therapeutic avenues need to be explored. The roles of adjunctive therapies such as systemic aminophylline (Parameswaran 2000; Mitra 2005), systemic beta₂-ago-

nists (Travers 2001) and inhaled magnesium sulfate (Blitz 2005) remain unclear; however, systemic magnesium (Rowe 2000) and inhaled anticholinergic (Stoodley 1999; Plotnick 2000) agents have been shown to be effective. The long-term, anti-inflammatory effects of leukotriene receptor antagonists (LTRAs) in chronic asthma are well established, and have been found to have a good safety profile (Ducharme 2004). Antileukotriene agents reach peak serum concentrations within three hours; the onset of action is fast and sustained (Dockhorn 2000). In acute asthma, the leukotriene pathways are activated, as evidenced by increased plasma and urinary leukotrienes (Sampson 1995). More recently, antileukotriene agents have been shown in animal models of acute asthma to have anti-inflammatory effects through suppression of T-helper cytokines (Wu 2003).

Why it is important to do this review

Since the initial publication of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines, several studies have been published evaluating the efficacy of LTRAs in acute asthma. The most recent revisions of both the BTS/SIGN asthma guidelines, the National Asthma Education and Prevention Program expert panel report (NAEPP 2007) and the Global Strategy for Asthma Management and Prevention (GINA 2008) conclude insufficient evidence to make a recommendation about the use of LTRAs. However, to date there has been no published systematic review of the evidence. LTRAs can be administered in acute asthma by the oral or the intravenous route, but intravenous administration is not currently licensed.

OBJECTIVES

To determine if the addition of a leukotriene receptor antagonist (LTRA) produces a beneficial effect in children and adults with acute asthma who are currently receiving inhaled bronchodilators and systemic corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in which an oral or intravenous LTRA was used in addition to standard care compared to standard care with a placebo.

Types of participants

We included children and adults with acute asthma presenting for acute medical care to an emergency department or equivalent setting.

Types of interventions

We included studies where participants were randomised to a LTRA and standard care or placebo and standard care. We allowed all LTRA agents, with similarity assumed; although we planned a sensitivity analysis according to type and dosage of LTRA (see [Data collection and analysis](#)).

We included different standard care protocols. However, eligible interventions must have included initial inhaled beta₂-agonists (titrated to patient response at short intervals) and systemic corticosteroids. We accepted additional treatments (e.g. ipratropium bromide, oxygen) provided they were the same in both the LTRA and placebo arms.

Types of outcome measures

Primary outcomes

Admission to hospital with acute asthma.

Secondary outcomes

1. Requirement for additional care at the end of study protocol.
2. Rate of admission to more intensive care settings.
3. Lung function (forced expiratory volume in one second (FEV₁) and peak expiratory flow rate (PEFR).
4. Changes in clinical score (pulmonary Index).
5. Changes in symptom score.
6. Use of inhaled bronchodilators.
7. Requirement for additional beta₂-agonist.
8. Length of hospital admission.
9. Rate of relapse or return to emergency department.
10. Adverse side effects.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group's Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE,

CINAHL, AMED and PsycINFO (see Appendix 1 for further details). We searched the Specialised Register up to February 2012 with the following terms:

(leukotriene* or leucotriene* or anti-leukotriene* or anti-leucotriene* or *lukast or lukast* OR montelukast* or Singulair OR Zafirlukast* OR accolate or pranlukast* or Ultair) AND (acute* or status* or sever* OR emergenc* or exacerbate* or hospital* or ER or ED).

We applied no language or publication status restrictions.

Searching other resources

We handsearched respiratory journals, and abstracts and annual meetings from the Society for Academic Emergency Medicine (SAEM), American College of Emergency Physicians (ACEP), American Thoracic Society (ATS), European Respiratory Society (ERS), and American College of Chest Physicians (ACCP) for the years 2003 to 2011 inclusive.

We reviewed the reference lists of all selected articles, primary studies and review articles for relevant studies. We contacted primary authors and pharmaceutical companies (Merck Sharp and Dohme (MSD), AstraZeneca, Abbot and GlaxoSmithKline (GSK) for information on additional trials (published and unpublished). We also contacted clinicians, colleagues, collaborators and trialists to identify potentially relevant studies.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, two reviewers (KW, RC) independently reviewed all literature search results to identify potentially relevant trials for full review. From the full-text using specific criteria, the same two reviewers (KW, RC) independently selected trials for inclusion. No disagreement on the inclusion of studies or study quality arose during the course of the review.

Data extraction and management

Two reviewers (KW, RC) independently extracted data. We requested unpublished data from the primary authors when necessary. We used a standard form that documented the following: characteristics of the study (design, methods of randomisation, withdrawals/dropouts); participants (age, gender); intervention (type, dose, route of administration, timing and duration of therapy, co-interventions); control (agent and dose); outcomes (types of outcome measures, timing of outcomes, adverse events); and results. We entered extracted data and pooled results in the Cochrane Collaboration's statistical package [Review Manager 5](#).

Assessment of risk of bias in included studies

Two reviewers (KW, RC) independently completed assessments of quality, with support from the Cochrane Airways Group editorial base. We assessed the risk of bias for each study according to five domains; random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data.

Measures of treatment effect

For dichotomous variables, we expressed both individual and pooled statistics as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous data, we reported individual data as mean differences (MDs) and pooled the data using the MD where the scales reported were identical or where the conversion factor was known (e.g. FEV₁). We used standardised mean differences (SMDs) where different metrics were used to measure outcome and there was no known conversion factor (e.g. symptoms). We reported MDs and SMDs with 95% CIs.

Assessment of heterogeneity

We measured heterogeneity using the I^2 test and compared pooled results using both random-effects and fixed-effect models, where statistical heterogeneity exceeded 20% ([Higgins 2003](#)). We assessed possible sources of heterogeneity by subgroup and sensitivity analyses.

Assessment of reporting biases

We planned to investigate publication bias through inspection of a funnel plot if we had found more than 10 studies contributing to a single meta-analysis.

Data synthesis

In view of the clinical heterogeneity between the studies (wide diversity in the severity of asthma exacerbations among the included studies), we reported the pooled trial results using a random-effects model. We did not combine trials on oral therapy with trials on intravenous therapy.

Subgroup analysis and investigation of heterogeneity

We proposed a priori subgroup analyses to examine the effect of:

1. age - children less than two years; children more than two years; and adults as per British Thoracic Society (BTS) groupings;
2. dose and type of antileukotriene agent;
3. severity of exacerbation of asthma; and
4. co-interventions.

Sensitivity analysis

Sensitivity analyses provide an approach for testing how robust the results of a review are relative to key decisions and assumptions that have been made in the process of conducting the review. We planned to investigate the following three factors:

1. methodological quality - the effects of overall methodological quality on the pooled result was examined using the findings of the risk of bias assessment;
2. statistical testing - random-effects versus fixed-effect; and
3. intention-to-treat status.

RESULTS

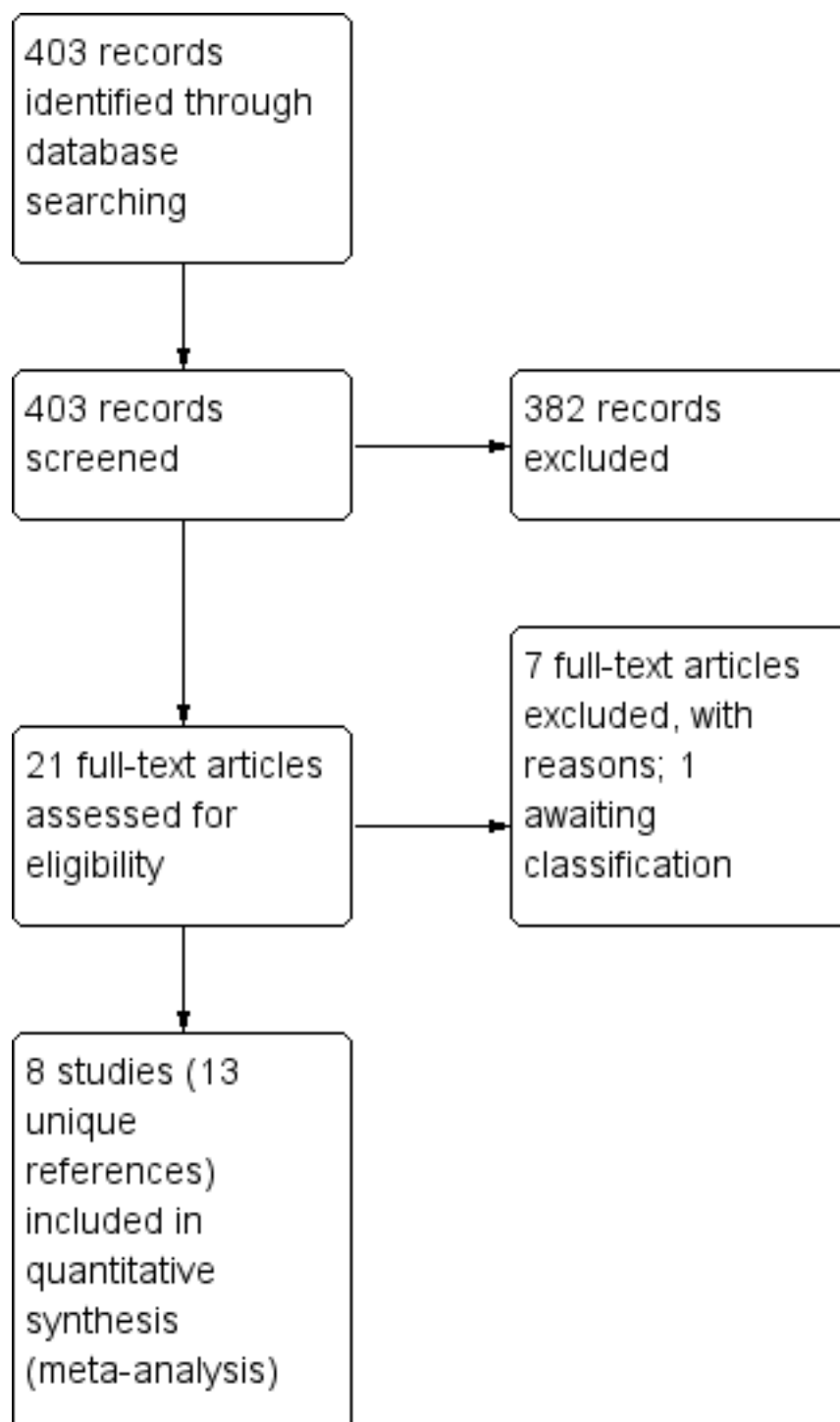
Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

Electronic searches yielded a total of 403 references. Of these, we independently identified 21 citations as being potentially relevant. Eight separate trials met the entry criteria for the review, of which two reported an additional eligible treatment arm ([Camargo 2003a](#); [Camargo 2003b](#); [Silverman 2004a](#); [Silverman 2004b](#)). This gave a total of ten intervention arms which met the review entry criteria ([Cylly 2003](#); [Camargo 2003a](#); [Camargo 2003b](#); [Silverman 2004a](#); [Silverman 2004b](#); [Harmanci 2006](#); [Nelson 2008](#); [Camargo 2010](#); [Morris 2010](#); [Todi 2010](#)). We excluded seven further potentially eligible trials after discussion between the reviewers (see [Characteristics of excluded studies](#)), and one abstract is awaiting classification pending further information ([Adachi 2008](#)). This data is presented in a PRISMA diagram ([Figure 1](#)).

Figure 1. Study flow diagram.



Included studies

Participants

The trials recruited 1470 adults and adolescents above the age of 12 years and 470 children between the age of 2 and 12 years (see [Table 1](#)). Four trials were conducted in children ([Harmanci 2006](#); [Nelson 2008](#); [Morris 2010](#); [Todi 2010](#)). No study included children less than two years. All the participants in the studies had been recruited from emergency treatment settings. Participants had a history of asthma for more than one year in the trials carried out in adults, however the trials in children had different inclusion criteria. One trial carried out in children aged between two and five years required only six months asthma history ([Harmanci 2006](#)), a second trial in children 6 to 14 years allowed children with at least one previous episode of asthma-like symptoms ([Morris 2010](#)) and a third trial included children aged 5 to 15 years seeking treatment for acute moderate to severe asthma in paediatric services of a tertiary hospital in north India ([Todi 2010](#)). Patients were excluded where there were other possible clinical explanations for dyspnoea including pneumonia, congestive cardiac failure, cystic fibrosis and chronic lung disease of prematurity. Although smokers were included in several studies, they all had fewer than ten pack years.

Patients were excluded if they received systemic corticosteroids or leukotriene modifiers in the two weeks preceding the trial in all except four studies ([Silverman 2004a](#); [Nelson 2008](#); [Camargo 2010](#); [Todi 2010](#)), one accepted patients if a maximum of five days of oral corticosteroids had been given ([Silverman 2004a](#)), two accepted patients if they had received leukotriene-modifying medications more than 24 to 48 hours in advance ([Nelson 2008](#); [Morris 2010](#)) and one within one week ([Todi 2010](#)). [Camargo 2010](#) excluded patients given systemic corticosteroids or leukotriene-modifying medications within 12 hours of presentation or during their initial assessment period.

There was heterogeneity in the severity of the asthma exacerbation. One study specifically targeted mild to moderate exacerbations ([Harmanci 2006](#)), others moderate to severe cases ([Camargo 2003a](#); [Silverman 2004a](#); [Camargo 2010](#); [Morris 2010](#); [Todi 2010](#)). Six trials used FEV₁ as entrance criteria ([Cylly 2003](#); [Camargo 2003a](#); [Silverman 2004a](#); [Nelson 2008](#); [Camargo 2010](#); [Morris 2010](#)), four studies accepted patients with FEV₁ less than either 70% or 75% predicted ([Camargo 2003a](#); [Silverman 2004a](#); [Morris 2010](#)), one study enrolled patients with FEV₁ 40% to 80% predicted ([Cylly 2003](#)), one study accepted patients with FEV₁

40% to 70% predicted ([Nelson 2008](#)) and one study accepted patients with FEV₁ 50% predicted or less ([Camargo 2010](#)).

Interventions

Two different antileukotriene agents were assessed in the trials: montelukast ([Cylly 2003](#); [Camargo 2003a](#); [Harmanci 2006](#); [Nelson 2008](#); [Camargo 2010](#); [Morris 2010](#); [Todi 2010](#)); and zafirlukast ([Silverman 2004a](#)). The mode of delivery in three trials was intravenous ([Camargo 2003a](#); [Camargo 2010](#); [Morris 2010](#)); in the remaining studies the leukotriene receptor antagonist (LTRA) was administered orally. Doses of LTRAs are given in the [Characteristics of included studies](#) table. In each trial the drug was administered once, with outcome assessment occurring at regular intervals until the end of the study (around four hours). [Silverman 2004a](#) and [Silverman 2004b](#) also included a post-discharge treatment phase where participants in placebo, high dose and low dose LTRA groups were discharged with a course of study drug. The doses of oral montelukast or zafirlukast employed in the trials are the usual recommended dose for long-term treatment of chronic asthma.

Usual care in all the studies included short-acting beta₂-agonist and systemic steroids.

Outcomes

Seven trials reported the primary outcome of hospitalisation. We opted to also include available data from trials under a composite outcome of requirement for further care, which includes hospitalisation, but also encompasses requirement for further therapies within the emergency department since study drugs failed to manage the acute episode sufficiently. Lung function data were available from six studies. One paediatric study reported change in FEV₁.

Excluded studies

We excluded seven studies with reasons. Full details can be found in [Characteristics of included studies](#).

Risk of bias in included studies

An overview of the judgments for the possible sources of bias in the studies (allocation generation, concealment of allocation and blinding) is given in [Figure 2](#) and full details can be found in the [Characteristics of included studies](#) table.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality 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)
Camargo 2003a	+	+	+	+	+
Camargo 2003b	+	+	+	+	+
Camargo 2010	+	+	+	+	?
Cylly 2003	?	?	-	?	?
Harmanci 2006	?	?	+	?	+
Morris 2010	+	+	?	?	+
Nelson 2008	+	+	+	+	+
Silverman 2004a	+	?	?	?	-
Silverman 2004b	+	?	?	?	-
Todi 2010	+	+	+	?	+

Allocation

The randomisation process was adequate in eight studies which we therefore judged to be at low risk of bias. The process was not adequately described in the remaining two trials (Cylly 2003; Harmanci 2006). Allocation was adequately concealed in six studies (Camargo 2003a; Camargo 2003b; Nelson 2008; Camargo 2010; Morris 2010; Todi 2010) and unclear in the remaining four studies.

Blinding

Identical placebo treatments were adequately described in six trials which lead us to judge that there was a low risk of performance bias for patients and physicians in these trials (Camargo 2003a; Camargo 2003b; Harmanci 2006; Nelson 2008; Camargo 2010; Todi 2010). Three studies were described as double-blind, but with no further details; therefore we judged them to be at unclear risk of bias (Silverman 2004a; Silverman 2004b; Morris 2010). One trial was at high risk of bias because physicians were not blinded (Cylly 2003). Outcome assessors were adequately blinded in four studies (Camargo 2003a; Camargo 2003b; Nelson 2008; Camargo 2010), but we could not be sure for the remaining six trials which we therefore judged to be at unclear risk of bias.

Incomplete outcome data

Six trials were judged to be at low risk of bias for incomplete outcome data (Camargo 2003a; Camargo 2003b; Harmanci 2006; Nelson 2008; Morris 2010; Todi 2010) while two were at unclear risk (Cylly 2003; Camargo 2003a). Two trials were judged to be at high risk of bias because the withdrawal rate was around 15% (Silverman 2004a; Silverman 2004b).

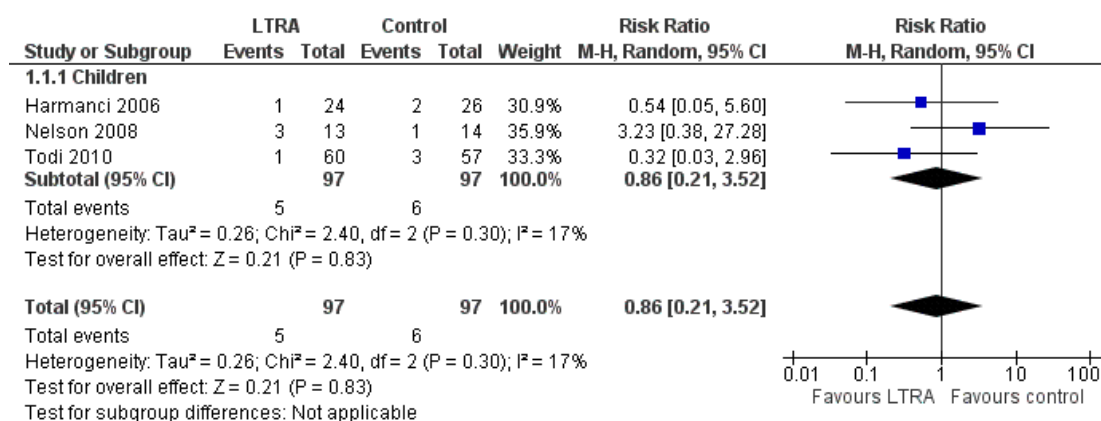
Effects of interventions

Oral montelukast or zafirlukast in addition to usual care

Hospitalisation (primary outcome)

There was no significant difference between oral leukotriene receptor antagonists (LTRAs) and control in the risk of admission to hospital in three studies including 194 children comparing oral montelukast to control in addition to usual care for acute asthma (RR 0.86; 95% CI 0.21 to 3.52; Figure 3).

Figure 3. Forest plot of comparison: I Oral montelukast or zafirlukast in addition to usual care, outcome: I.1 Hospital admission (primary outcome).



Requirement for additional care

A broader composite outcome which measured the requirement of other forms of additional care at the end of the study protocol was

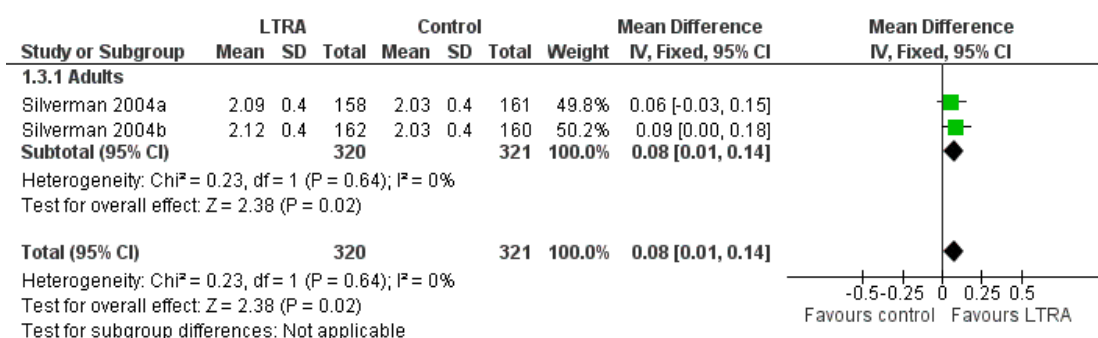
also not significantly different between treatments (RR 0.87; 95% CI 0.60 to 1.28; Analysis 1.2). One study on 641 adults given zafirlukast and one study on 50 children given oral montelukast provided data for this analysis.

Lung function

There was a significant difference in FEV₁ favouring LTRAs in the combined results of a single study on 641 adults on different doses of zafirlukast (MD 0.08; 95% CI 0.01 to 0.14; Figure 4).

In Silverman 2004a 20 mg of zafirlukast was administered orally and in Silverman 2004b the dose was 160 mg.

Figure 4. Forest plot of comparison: I Oral montelukast or zafirlukast in addition to usual care, outcome: 1.3 FEV₁.



Change in predicted FEV₁ did not show a significant effect of LTRAs in a single study of montelukast in 26 children (MD -3.10; 95% CI -12.70 to 6.50; Analysis 1.4).

Pulmonary index scores

Lung function tests are less reliable in young children, especially during acute exacerbation. Therefore one study (Harmanci 2006) used the pulmonary index score based on clinical observation (on 50 children); there was a statistically significant change in pulmonary index score favouring children on LTRAs compared with placebo in this study (MD -1.2; 95% CI -1.37 to -1.03; Analysis 1.5).

Respiratory rate

The same study (Harmanci 2006), reported a small but statistically significant difference in respiratory rate (MD -4.60; 95% CI -6.84 to -2.36; Analysis 1.6).

Beta₂-agonist usage

A single study in 45 adults (Cylly 2003), showed a small but statistically significant reduction in the number of rescue beta₂-agonist administrations with additional oral montelukast (MD -0.80; 95% CI -1.47 to -0.13; Analysis 1.7).

Symptom scores

There was no significant difference in symptom score between LTRAs and controls (SMD -0.09; 95% CI -0.33 to 0.15; Analysis 1.8) in two studies on 686 adults on oral LTRAs.

Adverse effects and withdrawals

The most commonly described adverse event with LTRAs is headache; however, there was no significant difference between LTRAs and control (RR 0.81; 95% CI 0.22 to 2.99, N = 641 adults in a single study; Analysis 1.9) with respect to the occurrence of headache. There was no statistically significant difference in the risk of withdrawals between treatment groups in two studies on 143 children (RR 1.00; 95% CI 0.16 to 6.34; Analysis 1.10).

Relapse

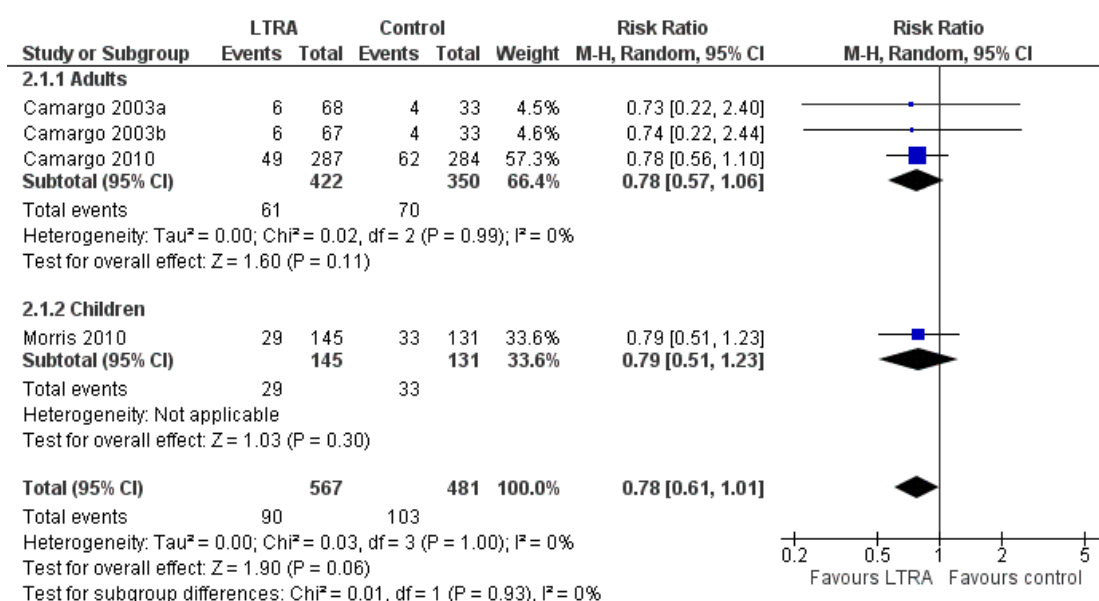
Only one study on 546 adults and one study on 22 children reported relapse data at the end of the follow-up period; these studies did not demonstrate a significant difference between LTRAs and controls (RR 0.81; 95% CI 0.61 to 1.07; Analysis 1.11).

Intravenous montelukast in addition to usual care

Hospitalisation (primary outcome)

Three studies on 772 adults and one study on 276 children reported hospital admission using intravenous montelukast. There was no statistically significant difference in the number of hospital admissions in adults (RR 0.78; 95% CI 0.57 to 1.06) or children (RR 0.79; 95% CI 0.51 to 1.23). The pooled result from all age-groups approached statistical significance (RR 0.78; 95% CI 0.61 to 1.01; see Figure 5).

Figure 5. Forest plot of comparison: 2 Intravenous montelukast in addition to usual care, outcome: 2.1 Hospital admission (Primary outcome).



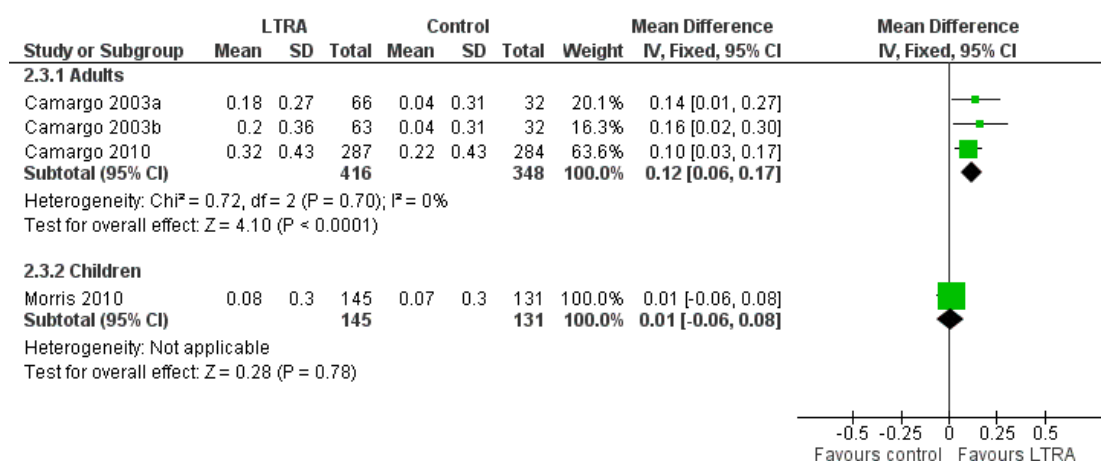
Requirement for additional care

Three studies on 772 adults contributed data to this outcome. There was no statistically significant difference in the requirement for additional treatment in these trials (RR 0.88; 95% CI 0.69 to 1.13; Analysis 2.2).

Change in FEV₁ (litres)

There was a significant benefit in FEV₁ in the three studies with results from 764 adults (MD 0.12; 95% CI 0.06 to 0.17), but not in the study in 276 children (MD 0.01; 95% CI -0.06 to 0.08), see Figure 6. We did not combine the results from the adult and children studies as children have lower expected FEV₁ than adults, and a formal test for differences between adults and children was not performed.

Figure 6. Forest plot of comparison: 2 Intravenous montelukast in addition to usual care, outcome: 2.3 Change in FEV₁ (litres).



Withdrawal from study

The risk of withdrawal was significantly lower for intravenous montelukast in the adult studies (RR 0.56; 95% CI 0.32 to 0.97), but the study in children had much wider CIs (RR 1.13; 95% CI 0.31 to 4.12; Analysis 2.4). There was no significant difference between the results from adults and children (test for subgroup differences: Chi² = 0.97, degrees of freedom (df) = 1 (P = 0.32), I² = 0%).

DISCUSSION

Summary of main results

This systematic review examined all of the available evidence for the effectiveness of adding a leukotriene receptor antagonist (LTRA) to standard treatment for the management of acute asthma in adults and children in the emergency department. Overall, we included 10 unique studies involving 1940 participants in this review. The studies differed in drug preparation and dose, route of administration, symptom severity as well as outcome measurements. The pooled results of oral treatment (currently the only licensed route of administration in the UK), failed to demonstrate a statistically significant or clinically important reduction in need for hospital admission in children. There was a statistically but not clinically significant difference in FEV₁ in the adult studies. There was some indication of an improvement in symptoms and reduction in additional treatment. The studies do not provide any information on impact on length of hospital stay.

The effect of initial disease severity may also be an important factor in determining benefit. The study populations in this review display a wide variation in presenting severity. Early use, initiated by parents of wheezing infants has been shown to have some impact in reducing healthcare utilisation (Robertson 2007). Whilst there appeared to be no significant effect on hospitalisation in the more severe group of patients, other health economic outcomes, including length of stay, clinical dependency scores and morbidity related to additional treatments (intravenous bronchodilators) may also be relevant given the apparent effect on pulmonary function and symptom scores. This effect would need to be addressed in longer studies with adequate power to look at these specific outcomes.

Overall completeness and applicability of evidence

The more recent studies have included children and adults on maintenance LTRAs. With our increasing use of regular LTRAs in patients requiring preventative therapy for asthma, specific studies will be required to look at whether additional or higher doses in the acute setting are beneficial and safe in this group. Patients who seem to benefit from LTRAs for the management of their persistent symptoms may be the patients who would be most likely to respond to LTRAs in the acute setting.

It would not be advisable to apply the results of trials on intravenous administration of LTRAs in acute asthma to clinical practice, where this route of administration is not currently licensed.

Quality of the evidence

The studies overall, were of good methodological quality. Most domains were at low or unclear risk of bias.

Potential biases in the review process

We attempted to minimise bias by undertaking comprehensive literature searches and handsearching references from review articles. Furthermore we screened abstracts and full-text documents, and extracted and entered data in duplicate.

Agreements and disagreements with other studies or reviews

Two studies explored a dose-response relationship; comparing standard and higher than standard dose, there was no clear dose-related response. One large study demonstrated a possible reduction in symptom scores with a high dose strategy of 160 mg zafirlukast compared to 20 mg zafirlukast (Silverman 2004a). The second smaller study (Camargo 2003a) did not show a difference in change in FEV₁ between doses of 7 mg and 14 mg, and in the group's subsequent paper, the lower dose intravenous regime of 7 mg was used (Camargo 2010). It is therefore possible that higher than licensed doses, if safe, may provide better outcomes as suggested in other studies (Ducharme 2004) and further research on this question seems warranted.

AUTHORS' CONCLUSIONS

Implications for practice

At present the evidence does not support routine use of leukotriene receptor antagonists (LTRAs) in acute asthma.

Implications for research

This systematic review has highlighted the need for additional high quality studies to address several unanswered questions.

1. Are higher than standard doses of oral LTRAs, and intravenous use of LTRAs safe in adults and children in the acute setting?
2. Do additional doses of LTRAs in patients with acute asthma who are already receiving long-term LTRA therapy (i.e. those with a documented response to this treatment modality) offer additional benefits?
3. Do LTRAs used in the acute setting have an impact on health economic and clinical outcomes, including length of hospital stay, dependency scores and morbidity?
4. Do LTRAs started early in an exacerbation of asthma at home or in primary care, alongside beta₂-agonists, reduce healthcare utilisation in adults and children?
5. Is there a difference in response to LTRAs in children with different phenotypes of acute wheeze (multi-trigger wheeze, episodic viral associated wheeze)?

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Camargo 2003a

Methods	Randomised, parallel group trial Withdrawals: stated Intention-to-treat: stated.	
Participants	N: 134 (low dose treatment: 68; control: 66) % females: treatment 56.3%; control 60.6% Mean age: treatment 35.7; control 34.5 Setting: ED Baseline severity: FEV ₁ < 70% or increase/decrease <= 20% points after initial beta ₂ -agonist Inclusion criteria: 15 to 54 years; diagnosis of asthma > 1 year; < 10 pack years smoking history; not currently on systemic steroids/leukotriene modulators/anticholinergics/long-acting beta ₂ -agonists Exclusion criteria: Patients with pneumonia, congestive heart failure, or other clinical explanations for dyspnea were excluded, as were patients with significant comorbid disorders requiring acute management; FEV ₁ > 70% or increase/decrease >= 20% points after initial beta ₂ -agonist	
Interventions	Treatment Intravenous montelukast 7 mg in addition to usual care given over 5 minutes Control Exact matching placebo in addition to usual care <i>Usual care:</i> Nebulised beta ₂ -agonist; O ₂ ; steroids as required; post-discharge: 5-day course of prednisone; follow-up at 14 days ±3 days <i>Study duration:</i> Acute: spirometry at 20 minutes, if improved then discharged, otherwise spirometry repeated at intervals up to 6 hours, F/U 14 days ± 3 days	
Outcomes	Primary outcome: % change in FEV ₁ at 20 mins Secondary outcomes: treatment failure (hospitalisation, need for treatments outside study protocol (anticholinergics, magnesium, systemic beta ₂ -agonist, xanthines, or need for > 6hours active treatment); proportion of participants receiving steroids or beta ₂ -agonists during study period; proportion of participants given > 2 beta ₂ -agonists after study drug	
Notes	Also measured urinary leukotriene E4	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Camargo 2003a (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule with a blocking factor of six to receive study drug
Allocation concealment (selection bias)	Low risk	"Allocation numbers were encoded on labels included with the study drug, and patients were assigned the next available allocation number in sequence at each site"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, investigators, and the in-house research team were not aware of actual treatment allocations at any point during the study. The allocation code was not broken until after the study was completed and the dataset was declared final" "Double-blind (with in-house blinding procedures)" "Intravenous montelukast (7 mg or 14 mg) or exact matching placebo was supplied as a lyophilized powder together with diluent (3.3% dextrose/0.3% normal saline). The study drug was reconstituted by a qualified individual not otherwise involved with the care of the patient and was administered as a manual bolus over 5 minutes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up (intervention: placebo) = 0:0 Small number discontinued intervention A protocol was indicated, but we have not seen it

Camargo 2003b

Methods	This table relates to the second arm of the trial Camargo 2003a See above
Participants	N: 135 (high dose treatment: 67; control: 66) Other demographic details and study entry criteria given above
Interventions	Treatment Intravenous montelukast 14 mg in addition to usual care given over 5 minutes Other details of study drugs given as above

Camargo 2003b (Continued)

Outcomes	See above	
Notes	See above	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See above
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	See above

Camargo 2010

Methods	Randomised, parallel group trial Withdrawals: stated Intention-to-treat: stated
Participants	N: 583 (573 completed treatment: 288 placebo: 285) % females: treatment 53%; control 60% Mean age: treatment 41.1; control 41 Setting: ED Baseline severity: FEV ₁ < 50% Inclusion criteria: > 15 years; diagnosis of asthma > 1 year; < 10 pack years Exclusion criteria: clinically significant, active comorbid disease; a body mass index >35 kg/m ² ; or a smoking history of >15 pack-years. Leukotriene receptor modulators received within 12 hours of initial presentation
Interventions	Treatment Intravenous montelukast 7 mg given over 2 to 5 minutes in addition to usual care Placebo Exact matching placebo in addition to usual care <i>Usual care:</i> Nebulised beta ₂ -agonist and ipratropium bromide; O ₂ ; systemic steroids; follow-up at approximately 14 days

Camargo 2010 (Continued)

	<i>Study duration:</i> Acute: spirometry at 10, 20, 40, 60 minutes, if improved then discharged, otherwise spirometry repeated at intervals up to 3 hours, F/U 14 days	
Outcomes	Primary outcome: change in FEV ₁ at 60 minutes Secondary outcomes: treatment failure (hospitalisation or failure to discharge by 3 hours) ; total dose beta ₂ -agonists	
Notes	Supported by Merck Research Laboratories	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised “according to a computer-generated randomisation schedule with a blocking factor of 4 provided by the study sponsor) during the active treatment period”
Allocation concealment (selection bias)	Low risk	Not clearly described, but sponsored study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Study drug (light-protected lyophilized product reconstituted in 20 mL 3.3% dextrose/0.3% sodium chloride [supplied together with the study drug]) was prepared in a foil-wrapped syringe (to ensure adequate blinding) by a qualified person who was not directly associated with the care of the patients”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Small numbers discontinued intervention (intervention: placebo) = 3:7 A protocol was indicated, but not seen by the reviewers

Cylly 2003

Methods	Randomised, parallel group trial Withdrawals: none occurred Intention-to-treat: all participants accounted for
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Cylly 2003 (Continued)

Participants	N: 45 (treatment: 23; control: 22) % females: treatment: 69.5%; control 68.1% Mean age: treatment 64.0; control 64.6 Setting: ED and OPC Baseline severity: FEV ₁ 40% to 80% predicted with > 15% improvement after agonist Inclusion: diagnosis of chronic asthma for more than 1 year; currently non-smoking Exclusion: po/iv/im steroids last 1/12; long-acting antihistamines in last 2/52, theophylline/long-acting beta ₂ -agonist/sodium cromoglycate in last 1/52; short-acting antihistamine in last 48 hours	
Interventions	Treatment Oral montelukast (10 mg) in addition to usual care Control Usual care <i>Study Duration:</i> (inpatient observation for 24 hours) <i>Usual care:</i> IV steroid 1 mg/kg; 3 x inhaled beta ₂ -agonist via MDI	
Outcomes	Primary outcome: % change in PEFR at time intervals Secondry outcome: borg dyspnoea score, proportion of patients needing rescue Rx	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“allocated randomly” Comment: insufficient information available to determine adequacy of allocation process
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information available to determine concealment of allocation process
Blinding of participants and personnel (performance bias) All outcomes	High risk	“This was a single blind (patient), randomised, placebo controlled study” Comment: physician knowledge of treatment could affect decision to admit and other outcomes Non-identical presentation of treatments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Cylly 2003 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
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Harmanci 2006

Methods	Randomised, parallel group trial Withdrawals: stated Intention-to-treat: all participants accounted for in follow-up
Participants	N: 51 (treatment: 25 (1 excluded); controls: 26) % females: treatment: 50%; control 73% Mean age: treatment: 3.9; control: 3.8 years Setting: ED Baseline severity: PI score > 6 and mild to moderate exacerbation according to Global Initiative for Asthma Guideline) Inclusion criteria: clinical history of intermittent asthma; using PRN beta ₂ -agonists Exclusion criteria: Inhaled/parental steroids or LTRA last 1/12; previous severe/life-threatening asthma attacks; preterm/low birthweight infants; infants of mothers smoking during pregnancy; Hx RDS; BPD/GOR/CF)
Interventions	Treatment Oral montelukast (4 mg) given in addition to usual care Control Exact matching placebo tablet in addition to usual care (see above) <i>Study duration:</i> 240 minutes (hospitalisation if O ₂ sats < 92%, sustained RR > 50, or PI > 6) <i>Usual care:</i> Nebulised beta ₂ -agonists at entry, 20 minutes, 40 minutes, 180 minutes; oral steroid at 1 hour if PI remained 4+
Outcomes	PI scores, RR, HR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The allocation schedule was also created and concealed at the Faculty of Pharmacy and broken at the end of the study"
Allocation concealment (selection bias)	Unclear risk	See above. No details of how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Monteleukast and placebo tablets were identical in appearance and prepared in the laboratories of the Faculty of Pharmacy"

Harmanci 2006 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“broken at the end of study” implied that assessors were blinded, but no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient dropped out due to vomiting after 15 minutes of taking study drug

Morris 2010

Methods	Randomised, parallel group trial Withdrawals: stated Intention-to-treat: stated	
Participants	N: 276 (277 completed; treatment: 144; placebo: 128) % females: treatment: 37.9%; control 38.2% Mean age: treatment: 9.2 years; control: 8.9 years Setting: ED Baseline severity: $FEV_1 < 75\%$ predictive value and modified PI Score ≥ 5 Inclusion criteria: 6 to 14 years; history of asthma-like symptoms on 1+ occasion in last 3 months Exclusion criteria: pneumonia, CF or other respiratory illness; asthma with life-threatening features; use of LTRA < 12 hours	
Interventions	Treatment Intravenous montelukast (5.25 mg) given in addition to usual care Control Exact matching placebo in addition to usual care (see above) <i>Study duration:</i> spirometry at 15 minute intervals in first hour then at 2 hours; follow-up at 14 days <i>Usual care:</i> Nebulised beta ₂ -agonists +/- anticholinergic, oxygen, systemic steroids	
Outcomes	Primary outcome: time-weighted change in FEV_1 at 60 minutes Secondary outcome: treatment failure (hospitalisation or failure to discharge at 2 hours); PI Score at 60 minutes	
Notes	Sponsored by Merck Research Laboratories	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Computer generated schedule”
Allocation concealment (selection bias)	Low risk	No clear details, assume done as sponsored trial

Morris 2010 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	“double blind” “Matching placebo”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Discontinued intervention (intervention: placebo) = 5:4 Included in analysis (intervention: placebo) = 99.3%:96.9% Protocol written, not seen

Nelson 2008

Methods	Randomised, parallel group trial Withdrawals: stated Intention-to-treat analysis: not done	
Participants	N: 26 M/F: 6/20 Mean age: montelukast: 9; placebo: 12.5 Setting: ED Baseline severity: PEF 40% to 70% predicted Entry criteria: 6 to 14 years; seeking care for acute asthma; at least one previous episode of wheeze treated with bronchodilators; Exclusion: severe exacerbations; pre-existing diagnosis of: pregnancy; CF; GOR; liver disease; BPD; prematurity (< 34 weeks); leukotriene modifying medication in previous 48 hours; theophylline in previous 4 weeks	
Interventions	Treatment group 5 mg montelukast tablet (mixed with strawberry powder) Control group Placebo (strawberry powder alone) <i>Usual care:</i> Protocol within institution which included nebulised beta ₂ -agonists; ipratropium bromide; all patients had steroids (usually prednisolone), O ₂ as required	
Outcomes	Primary outcome: mean change in FEV ₁ predicted (3 hours post-treatment) Secondary outcomes: hospitalisation; relapse; subsequent hospitalisation after discharge	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

Nelson 2008 (Continued)

Random sequence generation (selection bias)	Low risk	"Our statistician had prepared a computer-generated randomisation table with blocks of randomly ordered size..."
Allocation concealment (selection bias)	Low risk	Randomisation sequence: ' which was then maintained by the hospital pharmacists allowing concealed assignment of study group (...) At no time during the study did the research or ED personnel see the randomisation log"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"According to the randomisation scheme, hospital pharmacists independently prepared study medication as either a 5 mg montelukast tablet crushed and mixed with strawberry powder, or a matching volume of strawberry powder alone. Placebo and active drug were indistinguishable in volume, colour, consistency, and taste"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Left ED before completing study procedure (intervention: placebo) = 1:2 Study protocol written, not seen by reviewers

Silverman 2004a

Methods	Randomised, parallel group trial Withdrawals: stated Intention-to-treat analysis: yes
Participants	N: 479 (low dose treatment: 158; control: 321) % females: 57 Mean age: 32 Setting: ED Baseline severity: FEV ₁ : 36% predicted; Borg: 6.8; prior hospitalisation in previous year: 73%. 14-day medication history Theophylline: 10%; OCS: 7%; ICS: 36%; LABA: 7% Entry criteria: 12 to 65 years; presentation to ED with acute asthma; FEV ₁ < 70% predicted (25 minutes post-SABA); willing to remain in ED for 4 hours and willingness to participate in 28 day outpatient treatment program. Exclusion criteria: > 10 pack year smoking history; +ve pregnancy result; recent OCS usage (<= 5 days); treatment with antileukotriene agent within 2 weeks prior to ED presentation; requirement for intubation prior to randomisation; pneumonia or elevated temperature; chronic lung disease other than asthma; diabetes

Interventions	Treatment Oral zafirlukast 20 mg in addition to usual care Control group Placebo in addition to usual care Study follow-up: 28 days (participants allocated to zafirlukast high and low dose continued with 20 mg/d of BID; participants on placebo were given matching placebo). All participants discharged with 7 day course of prednisone <i>Usual care:</i> nebulised SABA at entry and 60 mg dose prednisone post-treatment. Repeat nebulisation at 60, 120 and 180 minutes post-study entry. Study protocol ended at 4 hours if participants required additional treatment	
Outcomes	Primary outcome: time to relapse in outpatient period “Because potential to influence when patients sought care for worsening asthma, additional relapse criteria were applied on visit days. Specifically, if patients indicated that they would have sought urgent care had their clinic visit not been scheduled, relapse was recorded.” (deterioration requiring unscheduled office visit or return to ED until final outpatient clinic attendance; had FEV ₁ < 40% on day of scheduled appointment; participant felt worse relative to ED visit; FEV ₁ < ED visit; diary card data indicated worsening in 72 hours prior to clinic attendance) Secondary outcomes: rate of extended care post-treatment; FEV ₁ ; dyspnea; diary card data on PEF, symptoms, beta ₂ -agonist use; adverse events	
Notes		
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Computer-generated randomisation schedule and each site had its own separate randomisation scheme”
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded study with matching placebo Comment: not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“Patients, all study investigators, and ED staff were blinded to the intervention” Comment: not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrew (intervention 20 mg and 160 mg combined: placebo) = 38:51 Included in analysis (intervention: placebo) = 86:84%

Silverman 2004b

Methods	As above
Participants	N: 489 (treatment high dose: 162; control group: 321) Other demographic details and study entry criteria given above
Interventions	Treatment Oral zafirlukast 160 mg in addition to usual care Other details of study drugs given as above
Outcomes	As above
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See above
Allocation concealment (selection bias)	Unclear risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	High risk	See above

Todi 2010

Methods	Randomised, parallel group trial Withdrawals: stated Intention-to-treat analysis: yes
Participants	N: 122 (117 randomised, treatment: 59 (1 failed to complete); control: 57) % females: treatment: 31.6%; placebo: 31.5% Mean age: treatment: 8.63 years; placebo: 8.3 years Setting: ED Baseline severity: total modified PI Score ≥ 9 Entry criteria: 5 to 15 years; seeking treatment with moderate to severe asthma in paediatric ED; PI Score ≥ 9 Exclusion criteria: children with life-threatening asthma; chronic respiratory conditions (congenital lung abnormalities, TB, CF) History of use of LTRA within 1 week

Interventions	Treatment Oral montelukast 5 mg, 5 to 12 years; 10 mg > 12 years Control group Placebo in addition to usual care Study follow-up: measured PI Score at hourly intervals until 4 hours, FEV ₁ at baseline and 4 hours Usual care: as per British Thoracic Society guidelines (including oral steroids, beta ₂ -agonist +/- ipratropium bromide, oxygen)	
Outcomes	Primary outcome: decrease in PI Score Secondary outcome: change in FEV ₁ ; need for hospitalisation at 4 hours; adverse effects	
Notes	Drugs provided by Cipla Limited who did not have any involvement in study design or data analysis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Randomisation was done in variable size block by an individual not involved in the study using computer program, Stata 9.0”
Allocation concealment (selection bias)	Low risk	“The medication packets were labelled serially for each of the strata for allocation concealment” Comment - not sure if participants or personal could see study packets
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“For blinding, similar looking and similar tasting tablets of montelukast and placebo were used.” “Study codes were revealed only at time of analysis”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“Study codes were revealed only at time of analysis”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal number did not complete study (intervention: placebo) = 1:0

ED: Emergency department; FEV₁: forced expiratory volume in one second; F/U: follow up; LTRA: leukotriene receptor antagonist; OPC: outpatient clinic; PEF: peak expiratory flow; PI: pulmonary index; MDI: metered dose inhaler; PEF: peak expiratory flow rate; po: per os, oral administration; iv: intravenous; im: intramuscular injection; BID: bis in die, Latin for "twice daily"; PRN: taken as needed; Hx: medical history; RDS: respiratory distress syndrome; BPD bronchopulmonary dysplasia; GOR: gastroesophageal reflux; CF: cystic fibrosis; TB: tuberculosis; SABA: short-acting beta₂-agonist; HR: heart rate; OCS: oral corticosteroid; ICS: inhaled corticosteroid; LABA: long-acting beta₂-agonist; RR: respiratory rate.

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

Study	Reason for exclusion
Bacharier 2008	Pre-hospital care
Gulati 2005	Hospitalised patients
Matsunga 2004	Mild asthma, no steroids
Ramsay 2007	Hospitalised patients
Robertson 2007	Pre-hospital care
Schuh 2009	Post-discharge comparison with prednisolone
Zubairi 2007	Abstract only. Hospitalised patients

DATA AND ANALYSES

Comparison 1. Oral montelukast or zafirlukast in addition to usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission (primary outcome)	3	194	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.21, 3.52]
1.1 Children	3	194	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.21, 3.52]
2 Requirement for additional care at end of study	3	691	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.60, 1.28]
2.1 Adults	2	641	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.53, 1.43]
2.2 Children	1	50	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.05, 5.60]
3 FEV ₁	2	641	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.01, 0.14]
3.1 Adults	2	641	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.01, 0.14]
4 Change in FEV ₁ (predicted)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4.1 Children	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in pulmonary index score (final assessment)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Children	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Change in respiratory rate (final assessment)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Children	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Number of beta ₂ -agonist administrations	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 Adults	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Symptom scores	3	686	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.33, 0.15]
8.1 Adults	3	686	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.33, 0.15]
9 Headache	2	641	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.22, 2.99]
9.1 Adults	2	641	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.22, 2.99]
10 Withdrawals	2	143	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.16, 6.34]
10.1 Children	2	143	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.16, 6.34]
11 Relapse (within 7 days)	2	568	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.07]
11.1 Adults	1	546	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.08]
11.2 Children	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 8.73]

Comparison 2. Intravenous montelukast in addition to usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission (Primary outcome)	4	1048	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.61, 1.01]
1.1 Adults	3	772	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.57, 1.06]
1.2 Children	1	276	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.51, 1.23]

2 Requirement for additional care at end of study	3	772	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.13]
2.1 Adults	3	772	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.13]
3 Change in FEV ₁ (litres)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Adults	3	764	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.06, 0.17]
3.2 Children	1	276	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.06, 0.08]
4 Withdrawals	4	1060	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.37, 1.04]
4.1 Adults	3	784	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.32, 0.97]
4.2 Children	1	276	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.31, 4.12]

ADDITIONAL TABLES

Table 1. Study characteristics

Study	Intervention	Standard treatment	Age	Participants
Camargo 2003a , Camargo 2003b	IV	Nebulised beta ₂ -agonist; O ₂ ; steroids as required; post-discharge: 5-day course of prednisone; follow-up at 14 days ±3 days	Adults	201
Camargo 2010	IV	Nebulised beta ₂ -agonist and ipratropium bromide; O ₂ ; systemic steroids; follow-up at approx. 14 days	Adults	583
Cylly 2003	oral	IV steroid 1 mg/kg; 3 x inhaled beta ₂ -agonist via metered dose inhaler (MDI)	Adults	45
Harmanci 2006	oral	Nebulised beta ₂ -agonists at entry, 20, 40, and 180 minutes; oral steroid at 1 hour if PI remained 4+	Children	51
Morris 2010	IV	Oxygen, short-acting beta ₂ -agonist, inhaled anticholinergics, systemic corticosteroids	Children	276
Nelson 2008	oral	Protocol within institution which included nebulised beta ₂ -agonists; ipratropium bromide; all patients had steroids (usually prednisolone); O ₂ as required	Children	26
Silverman 2004a , Silverman 2004b	oral	Nebulised short-acting beta ₂ -agonist at	Adults	641

Table 1. Study characteristics (Continued)

		entry and 60 mg dose prednisone post-treatment. Repeat nebulisation at 60, 120 and 180 minutes post-study entry. Study protocol ended at 4 hours if participants required additional treatment		
Todi 2010	oral	Standard therapy including oral prednisolone (1 mg/kg)	Children	117

IV: intravenous; mg: milligrams; O₂: oxygen; PI: pulmonary index

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 5, 2012

CONTRIBUTIONS OF AUTHORS

KW (primary author): Protocol initiation and development; study assessment; data extraction and entry; and analysis and interpretation.

RC: Protocol development; study assessment; data extraction and entry; and analysis and interpretation.

DECLARATIONS OF INTEREST

None known. The authors are neither involved with the makers of antileukotriene agents nor involved in the primary publications included in the review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol for this review we intended to assess study quality using the Jadad score, and the Cochrane Collaboration grading scale for allocation concealment. We have revised this in line with recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) for assessing the risk of bias in each eligible study.

We decided not to combine trials of oral LTRA treatment with trials of intravenous treatment in this review.