Asthma and other recurrent wheezing disorders in children (chronic)

Search date June 2010

Stephen W Turner, Amanda J Friend, and Augusta Okpapi

ABSTRACT

INTRODUCTION: Childhood asthma is the most common chronic paediatric illness. There is no cure for asthma but good treatment to palliate symptoms is available. Asthma is more common in children with a personal or family history of atopy, increased severity and frequency of wheezing episodes, and presence of variable airway obstruction or bronchial hyperresponsiveness. Precipitating factors for symptoms and acute episodes include infection, house dust mites, allergens from pet animals, exposure to tobacco smoke, and exercise. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of single-agent prophylaxis in children taking as-needed inhaled beta$_2$ agonists for asthma? What are the effects of additional prophylactic treatments in childhood asthma inadequately controlled by standard-dose inhaled corticosteroids? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 48 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: beta$_2$ agonists (long-acting), corticosteroids (inhaled standard or higher doses), leukotriene receptor antagonists (oral), omalizumab, and theophylline (oral).

QUESTIONS

INTERVENTIONS

SINGLE-AGENT PROPHYLAXIS IN CHILDREN TAKING AS-NEEDED INHALED BETA2 AGONISTS FOR ASTHMA

ASTHMA UNCONTROLLED BY STANDARD-DOSE INHALED CORTICOSTEROIDS

Covered elsewhere in Clinical Evidence

Bronchiolitis

Footnote

*Categorisation based on consensus.

Key points

- Childhood asthma can be difficult to distinguish from viral wheeze and can affect up to 20% of children.
- Regular monotherapy with inhaled corticosteroids improves symptoms, reduces exacerbations, and improves physiological outcomes in children with asthma symptoms requiring regular short-acting beta$_2$ agonist treatment. Their effect on final adult height is minimal and when prescribed within recommended doses have an excellent safety record. Regular monotherapy with other treatments is not superior to low-dose inhaled corticosteroids.
- Leukotriene receptor antagonists may have a role as first-line prophylaxis in very young children.
- There is consensus that long-acting beta$_2$ agonists should not be used for first-line prophylaxis.

  CAUTION: Monotherapy with long-acting beta$_2$ agonists does not reduce asthma exacerbations but may increase the chance of severe asthma episodes.
- Theophylline was used as first-line prevention before the introduction of inhaled corticosteroids. Although there is weak evidence that theophylline is superior to placebo, theophylline should no longer be used as first-line prophylaxis in childhood asthma because of clear evidence of the efficacy and safety of inhaled corticosteroids.

Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded.

- When low-dose inhaled corticosteroids fail to control asthma, most older children will respond to one of the add-on options available, which include addition of long-acting beta$_2$ agonists, addition of leukotriene receptor antagonists, addition of theophylline, or increased dose of inhaled corticosteroid. However, we don't know for certain how effective these additional treatments are because we found no/limited RCT evidence of benefit compared with adding placebo/no additional treatments.

  Addition of long-acting beta$_2$ agonists may reduce symptoms and improve physiological measures compared with increased dose of corticosteroids in older children. Long-acting beta$_2$ agonists are not currently licensed for use in children under 5 years of age.

  Consensus suggests that younger children are likely to benefit from addition of leukotriene receptor antagonists.

  Although there is weak evidence that addition of theophylline to inhaled corticosteroids does improve symptom control and reduce exacerbations, theophylline should only be added to inhaled corticosteroids in children aged over 5 years when the addition of long-acting beta$_2$ agonists and leukotriene receptor antagonists have both been unsuccessful.

- Omalizumab may be indicated in the secondary care setting for older children (aged over 5 years) with poorly controlled allergic asthma despite use of intermediate- and high-dose inhaled corticosteroids once the diagnosis is confirmed and compliance and psychological issues are addressed. However, we need more data to draw firm conclusions.

DEFINITION

Asthma is characterised by episodic wheeze, cough, and shortness of breath in association with exposure to multiple factors including rhinovirus, exercise, and allergens. The diagnosis remains entirely based on the history coupled with a positive response to treatment. Childhood asthma can affect up to 20% of children and can be difficult to diagnose in preschool children, where many individuals have acute episodic wheeze/viral-induced wheeze. Examination of the child with asthma is invariably normal and although physiological testing will characteristically find reversible airway obstruction and atopy, these tests lack precision for asthma and have no benefit in the majority of children. The absence of a widely accepted definition for asthma, a diagnostic test, and lack of a biomarker with which to objectively monitor the condition can make childhood asthma a clinical challenge, especially in young children. In cases of clinical uncertainty or where symptoms persist despite adequate treatment, referral for specialist opinion should be sought. This review deals with pharmacological management of chronic asthma in children only. For information on the management of acute asthma in children see review on Asthma and other recurrent wheezing disorders in children (acute).

INCIDENCE/ PREVALENCE

Asthma prevalence rose in the UK and other Western countries during the 1980s and 1990s, but recent evidence suggests that asthma prevalence is falling; however, lifetime asthma prevalence is still reported as 24% in children aged 9 to 12 years in the UK. [1] [2] Genetic factors are thought to account for 60% of asthma causation, [3] but genetic change cannot explain the rise in asthma prevalence from 4% in 1964 to present day values. The reasons for the rise and early fall in asthma prevalence are not understood but are likely to involve epigenetics and interactions between genetic predispositions and environmental exposures, [4] including tobacco smoke.

AETIOLOGY/ RISK FACTORS

Asthma is a typical complex condition where genetic and environmental factors interact, often at critical stages of development. Genetic factors explain approximately 60% of asthma causation, but there is no single "asthma gene" — rather there are approximately 10 genes, each of which confer a modest increased risk for asthma. Environmental factors implicated in asthma causation include exposure to tobacco smoke, diet (including non-breast feeding), early respiratory infection, and indoor and outdoor air quality. Other non-modifiable risk factors include sex (asthma is more common in boys than girls but more common in women than men) and age (many children apparently "grow out of" their asthma).

PROGNOSIS

A UK longitudinal study of children born in 1970 found that 29% of 5-year-olds wheezing in the past year were still wheezing at the age of 10 years. [5] Another study followed a group of children in Melbourne, Australia, from the age of 7 years (in 1964) into adulthood. The study found that a large proportion (73%) of 14-year-olds with infrequent symptoms had few or no symptoms by the age of 28 years, whereas two-thirds of those 14-year-olds with frequent wheezing still had recurrent attacks at the age of 28 years. [6]

AIMS OF INTERVENTION

To reduce or abolish cough and wheeze; to attain best possible lung function; to reduce the risk of severe attacks; to minimise sleep disturbance and absence from school; to minimise adverse effects of treatment; and to allow normal growth.

OUTCOMES By contrast with other chronic conditions, there is no gold standard outcome for asthma in clinical trials; this can make for difficulties in comparing and contrasting similar clinical trials. We have separated outcomes into 4 domains: **symptom control (clinical assessments):** daily symptom score, daily use of short-acting beta$_2$ agonist, exertional and nocturnal symptoms; **physiological measures:** FEV$_1$, peak flow, bronchial hyperreactivity; **exacerbations:** hospital admission, rescue course of oral corticosteroids, unscheduled presentation to primary care, accident and emergency attendance, and hospitalisation. **Adverse effects**.

METHODS *Clinical Evidence* search and appraisal June 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2010, Embase 1980 to June 2010, and The Cochrane Database of Systematic Reviews, May 2010 [online, searched 2 June 2010] (1966 to date of issue). When editing this review we used The Cochrane Database of Systematic Reviews 2010, Issue 3. An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. We included studies in children aged 1 to 12 years with asthma or recurrent wheeze of unspecified origin. We included studies including older children (>12 years) or younger children (<1 year) if the mean age of children in the study was between 1 and 12 years, or where the majority of children (at least 80%) were aged between 1 and 12 years. We excluded studies mainly in children with wheeze due to other specific respiratory disorders (e.g., bronchiolitis). Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language. RCTs had to be at least single blinded, and contain 20 or more individuals, of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 62). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of single-agent prophylaxis in children taking as-needed inhaled beta2 agonists for asthma?**

OPTION **CORTICOSTEROIDS (INHALED)**

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- Regular monotherapy with inhaled corticosteroids improves symptoms, reduces exacerbations, and improves physiological outcomes in children with asthma symptoms requiring regular short-acting beta$_2$ agonist treatment. Their effect on final adult height is minimal and when prescribed within recommended doses have an excellent safety record.
- Regular monotherapy with other treatments (long-acting beta$_2$ agonists, leukotriene receptor antagonists, or oral theophylline) is not superior to low-dose inhaled corticosteroids.

Benefits and harms

Inhaled corticosteroids versus placebo:

We found three systematic reviews (search dates 1996, 24 RCTs [10/24 RCTs in preschool children]; [7] search date 2007, 13 RCTs; [8] and search date 2008, 14 RCTs in children [9]). The reviews applied different inclusion criteria. The first and second systematic reviews included RCTs on any inhaled corticosteroid versus placebo in children, and identified different RCTs. [7] [8] The third systematic review [9] included RCTs on inhaled fluticasone versus placebo. It identified one RCT in common with the first review, and three RCTs in common with the second review. The first and third reviews pooled the data from the included RCTs. The second review [8] reported the results of

the RCTs narratively and did not pool the data, and so we have only reported on those additional RCTs in this review that met *Clinical Evidence* inclusion criteria for this question, and were not included in the meta-analyses of the other systematic reviews. One of these RCTs was reported in multiple publications. [10] [11] [12] We found three subsequent RCTs [13] [14] [15] and three additional RCTs. [16] [17] [18] For further information on adverse effects from observational studies, see comment.

Symptom control (clinical assessments)

Compared with placebo Regular inhaled corticosteroids seem more effective at improving symptom scores and days without symptoms, and at reducing beta$_2$ agonist use in children with asthma (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Asthma symptoms					
[7] Systematic review	744 children; all receiving usual care, including as-needed inhaled beta$_2$ agonists 15 RCTs in this analysis	**Symptom score , 4 to 88 weeks** with regular inhaled corticosteroids (betamethasone, beclometasone, budesonide, flunisolide, or fluticasone) with placebo Absolute results not reported	Improvement with corticosteroids 50% 95% CI 49% to 51%	○○○	corticosteroids plus usual care
[16] RCT	160 children aged 12 to 47 months, with persistent asthma symptoms	**% symptom-free 24-hour periods , 12 weeks** with fluticasone propionate (inhaled, 100 micrograms twice daily) with placebo Absolute results not reported	OR 0.53 95% CI 0.29 to 0.95 P = 0.035	●○○	fluticasone
[9] Systematic review	353 children with asthma (no oral corticosteroids) 2 RCTs in this analysis	**Change in daily symptom scores from baseline , 12 weeks** with fluticasone (inhaled, 100 micrograms/day) with placebo Absolute results not reported	SMD –0.52 95% CI –0.73 to –0.31	○○○	fluticasone
[9] Systematic review	1083 children with asthma (no oral corticosteroids) 5 RCTs in this analysis	**Change in daily symptom scores from baseline , 12 weeks** with fluticasone (inhaled, 200 micrograms/day) with placebo Absolute results not reported	SMD –0.34 95% CI –0.46 to –0.22	○○○	fluticasone
[13] RCT **3-armed trial**	276 children aged 1 to 4 years, with frequent wheezing The remaining arm evaluated placebo plus beclometasone/salbutamol combination inhaler (800 micrograms/1600 micrograms) taken as required	**% of symptom-free days , 12 weeks** 70% with beclometasone (inhaled using nebuliser, 400 micrograms twice daily) plus salbutamol (inhaled using nebuliser, 2500 micrograms taken as required) 61% with placebo plus salbutamol (inhaled using nebuliser, 2500 micrograms taken as required) Symptom free defined as lack of wheezing, coughing, shortness of breath, and child/parent nocturnal awakening 166 children in analysis	P = 0.034	○○○	regular beclometasone plus as-needed salbutamol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] RCT **3-armed trial**	1041 children aged 5 to 12 years, with mild to moderate asthma, mean pre-study FEV_1 94% predicted, all using salbutamol for asthma symptoms In review [8] The remaining arm evaluated nedocromil (inhaled, 8 mg twice daily) (312 children)	**Change in symptom score, assessed by daily diary-card measures , 4 to 6 years** –0.44 with budesonide (inhaled, 200 micrograms twice daily) –0.37 with placebo	P (budesonide *v* placebo) = 0.005	○○○	budesonide
[14] RCT **3-armed trial**	63 children aged 2 to 6 years with asthma-like symptoms The remaining arm evaluated montelukast	**Change in symptom scores from baseline , 3 months** with fluticasone (inhaled, 100 micrograms twice daily) with placebo (oral, once daily) Absolute results reported graphically Parents rated the child's symptoms (cough, wheeze, and shortness of breath) each morning and evening to give the total daily symptom score	P = 0.021 RCT may have been underpowered; see further information on studies	○○○	fluticasone
[15] RCT **3-armed trial**	238 children aged 12 to 59 months with 2 or more episodes of wheeze in the past year The remaining arm evaluated montelukast (oral, 4 mg once daily) plus placebo (inhaled)	**Proportion of episode-free days, assessed by diary cards , over 12 months** 76% with budesonide (inhaled by nebuliser, 1.0 mg twice daily) plus placebo (oral) 74% with placebo (oral and inhaled) Absolute results not reported Children received treatment for 7 days at the first sign of respiratory tract infection; all children also received salbutamol by inhalation Episode-free day defined as day free from cough, wheeze, trouble breathing, asthma-associated interference with daily activities/awakening from sleep, healthcare use caused by wheezing, and use of asthma-related non-study medications	Direct statistical comparison between budesonide and placebo not reported		
[20] RCT **3-armed trial**	353 children aged 5 to 12 years, with moderate symptomatic asthma, receiving short-acting $beta_2$ agonist on as-needed basis In review [8] The remaining arm evaluated beclometasone dipropionate (inhaled via extrafine aerosol, 80 micrograms/day)	**% of days free from asthma symptoms , week 12** 29.4% with beclometasone dipropionate (inhaled via extrafine aerosol, 160 micrograms/day) 17.6% with placebo Secondary outcome	Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] RCT **3-armed trial**	353 children aged 5 to 12 years, with moderate symptomatic asthma, receiving short-acting beta$_2$ agonist on as-needed basis In review [8] The remaining arm evaluated beclometasone dipropionate (inhaled via extrafine aerosol, 160 micrograms/day)	**% of days free from asthma symptoms , week 12** 32.1% with beclometasone dipropionate (inhaled via extrafine aerosol, 80 micrograms/day) 17.6% with placebo Secondary outcome	P less-than or equal to 0.05	○○○	beclometasone dipropionate (80 micrograms/day)
[17] RCT **4-armed trial** Pre-planned integrated analysis of 2 identically designed double-blind RCTs	1031 children aged 4 to 11 years with persistent asthma The remaining arms evaluated ciclesonide (inhaled, 80 micrograms once daily) and ciclesonide (inhaled, 160 micrograms once daily)	**Mean change from baseline in asthma symptom scores (24-hour) , 12 weeks** with ciclesonide (inhaled, 40 micrograms once daily) with placebo (inhaled, once daily) Absolute results reported graphically Secondary outcome	P <0.01	○○○	ciclesonide (40 micrograms daily)
[17] RCT **4-armed trial** Pre-planned integrated analysis of 2 identically designed double-blind RCTs	1031 children aged 4 to 11 years with persistent asthma The remaining arms evaluated ciclesonide (inhaled, 40 micrograms once daily) and ciclesonide (inhaled, 160 micrograms once daily)	**Mean change from baseline in asthma symptom scores (24-hour) , 12 weeks** with ciclesonide (inhaled, 80 micrograms once daily) with placebo (inhaled, once daily) Absolute results reported graphically Secondary outcome	P <0.001	○○○	ciclesonide (80 micrograms daily)
[17] RCT **4-armed trial** Pre-planned integrated analysis of 2 identically designed double-blind RCTs	1031 children aged 4 to 11 years with persistent asthma The remaining arms evaluated ciclesonide (inhaled, 40 micrograms once daily) and ciclesonide (inhaled, 80 micrograms once daily)	**Mean change from baseline in asthma symptom scores (24-hour) , 12 weeks** with ciclesonide (inhaled, 160 micrograms once daily) with placebo (inhaled, once daily) Absolute results reported graphically Secondary outcome	P <0.001	○○○	ciclesonide (1600 micrograms daily)
Beta-agonist use					
[7] Systematic review	722 children; all receiving usual care, including as-needed inhaled beta$_2$ agonists 14 RCTs in this analysis	**Beta$_2$ agonist use , 4 to 88 weeks** with regular inhaled corticosteroids (betamethasone, beclometasone, budesonide, flunisolide, or fluticasone) with placebo Absolute results not reported	Relative decrease with corticosteroids 37% 95% CI 36% to 38%	●●○	corticosteroids plus usual care

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use The remaining arm evaluated salmeterol (80 children)	**Days and nights without need for salbutamol** 92% with beclometasone (81 children) 83% with placebo (80 children)	P less-than or equal to 0.001	○○○	beclometasone

Exacerbations

Compared with placebo Regular inhaled corticosteroids seem more effective at reducing oral corticosteroid use in children with asthma, and at reducing treatment withdrawals due to exacerbation, hospital admissions, and severe asthma-related events at up to 3 years, in children aged over 5 years (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Asthma exacerbation					
[20] RCT **3-armed trial**	353 children aged 5 to 12 years, with moderate symptomatic asthma, receiving short-acting beta$_2$ agonist on as-needed basis In review [8]	**Time to onset of first asthma exacerbation or increased asthma symptoms , week 12** with beclometasone dipropionate (inhaled via extrafine aerosol, 160 micrograms/day) with beclometasone dipropionate (inhaled via extrafine aerosol, 80 micrograms/day) with placebo Absolute results reported graphically Secondary outcome	No significant difference among the 3 groups (P = 0.18, Kaplan-Meier analysis)	⟷	Not significant
[10] RCT	1981 children aged 5 to 10 years with mild persistent asthma, 1974 children included in analysis In review [8] Subgroup analysis Subgroup of children aged 5 to 10 years from a larger trial (START trial) in people aged 5 to 66 years	**Time to first severe asthma-related event** with budesonide (inhaled, 200 micrograms once daily) added to usual care with placebo (inhaled, once daily) added to usual care Absolute results not reported Severe asthma-related event defined as an event requiring an unscheduled admission to hospital or emergency treatment or which resulted in death due to asthma	Reported as significantly increased with budesonide P value not reported	○○○	budesonide
[10] RCT	1981 children aged 5 to 10 years with mild persistent asthma, 1974 children included in analysis In review [8] Subgroup analysis Subgroup of children aged 5 to 10 years from a larger trial (START trial) in people aged 5 to 66 years	**Number of severe asthma-related events , 3 years** 52 (in 40 children) with budesonide (inhaled, 200 micrograms once daily) added to usual care 82 (in 63 children) with placebo (inhaled, once daily) added to usual care Severe asthma-related event defined as an event requiring an unscheduled admission to hospital or emergency treatment or which resulted in death due to asthma	Reported as significantly reduced risk with budesonide P value not reported	○○○	budesonide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admissions					
[19] RCT **3-armed trial**	1041 children aged 5 to 12 years, with mild to moderate asthma, mean pre-study FEV_1 94% predicted, all using salbutamol for asthma symptoms In review [8] The remaining arm evaluated nedocromil (inhaled, 8 mg twice daily) (312 children)	**Hospital admissions due to asthma per 100 person-years , 4 to 6 years** 2.5 with budesonide (inhaled, 200 micrograms twice daily) (311 children) 4.4 with placebo (418 children)	P (budesonide *v* placebo) = 0.04	○○○	budesonide
[19] RCT **3-armed trial**	1041 children aged 5 to 12 years, with mild to moderate asthma, mean pre-study FEV_1 94% predicted, all using salbutamol for asthma symptoms In review [8] The remaining arm evaluated nedocromil (inhaled, 8 mg twice daily) (312 children)	**Urgent care visits due to asthma per 100 person-years , 4 to 6 years** 12 with budesonide (inhaled, 200 micrograms twice daily) (311 children) 22 with placebo (418 children)	P (budesonide *v* placebo) <0.001	○○○	budesonide
Need for oral corticosteroids					
[7] Systematic review	487 children; all receiving usual care, including as-needed inhaled $beta_2$ agonists 12 RCTs in this analysis	**Oral corticosteroid use , 4 to 88 weeks** with regular inhaled corticosteroids (betamethasone, beclometasone, budesonide, flunisolide, or fluticasone) with placebo Absolute results not reported	Relative decrease with corticosteroids 68% 95% CI 66% to 70%	○○○	corticosteroids plus usual care
[19] RCT **3-armed trial**	1041 children aged 5 to 12 years, with mild to moderate asthma, mean pre-study FEV_1 94% predicted, all using salbutamol for asthma symptoms In review [8] The remaining arm evaluated nedocromil (inhaled, 8 mg twice daily) (312 children)	**Prednisolone courses per 100 person-years , 4 to 6 years** 70 with budesonide (inhaled, 200 micrograms twice daily) 122 with placebo	P (budesonide *v* placebo) <0.001	○○○	budesonide
Treatment withdrawal due to exacerbations					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years The remaining arm evaluated salmeterol (80 children)	**Treatment withdrawals because of exacerbations** 5 with beclometasone (81 children) 15 with placebo (80 children)	P = 0.03	○○○	beclometasone

No data from the following reference on this outcome. [9] [13] [14] [15] [16] [17]

Physiological measures

Compared with placebo Regular inhaled corticosteroids seem more effective at improving peak expiratory flow rate and FEV_1 in children with asthma, and at improving airway hyperresponsiveness, assessed by methacholine challenge test, in children aged 6 to 14 years with clinically stable asthma. We don't know whether regular inhaled corticosteroids are more effective at improving lung function, assessed by interrupter technique (Rint), in children aged 2 to 6 years with asthma-like symptoms (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Peak expiratory flow					
[7] Systematic review	372 children; all receiving usual care, including as-needed inhaled $beta_2$ agonists 5 RCTs in this analysis	**Peak expiratory flow rate , 4 to 12 weeks** with regular inhaled corticosteroids (betamethasone, beclometasone, budesonide, flunisolide, or fluticasone) with placebo Absolute results not reported	Weighted mean improvement: 11% predicted 95% CI 9.5% to 12.5%	○○○	corticosteroids plus usual care
Forced expiratory volume					
[19] RCT **3-armed trial**	1041 children aged 5 to 12 years, with mild to moderate asthma, mean pre-study FEV_1 94% predicted, all using salbutamol for asthma symptoms In review [8] The remaining arm evaluated nedocromil (inhaled, 8 mg twice daily) (312 children)	**Change in FEV_1 (% of predicted) from baseline: before bronchodilator use , 4 to 6 years** 2.9% with budesonide (inhaled, 200 micrograms twice daily) 0.9% with placebo	P = 0.02 (budesonide *v* placebo)	○○○	budesonide
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use The remaining arm evaluated salmeterol (80 children)	**Mean change in FEV_1 as % of predicted , 1 year** 10% with beclometasone (81 children) 5% with placebo (80 children)	P = 0.001 (beclometasone *v* placebo)	○○○	beclometasone
[17] RCT **4-armed trial** Pre-planned integrated analysis of 2 identically designed double-blind RCTs	1031 children aged 4 to 11 years with persistent asthma The remaining arms evaluated ciclesonide (inhaled, 80 micrograms once daily) and ciclesonide (inhaled, 160 micrograms once daily)	**Change in % FEV_1 from baseline , 12 weeks** 22.88% with ciclesonide (inhaled, 40 micrograms once daily) 21.36% with placebo (inhaled, once daily)	Reported no significant difference between groups	⟷	Not significant
[17] RCT **4-armed trial**	1031 children aged 4 to 11 years with persistent asthma The remaining arms evaluated ciclesonide (inhaled,	**Change in % FEV_1 from baseline , 12 weeks** 26.13% with ciclesonide (inhaled, 80 micrograms once daily) 21.36% with placebo (inhaled, once daily)	P <0.05	○○○	ciclesonide (80 micrograms daily)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pre-planned integrated analysis of 2 identically designed double-blind RCTs	40 micrograms once daily) and ciclesonide (inhaled, 160 micrograms once daily)				
[17] RCT **4-armed trial** Pre-planned integrated analysis of 2 identically designed double-blind RCTs	1031 children aged 4 to 11 years with persistent asthma The remaining arms evaluated ciclesonide (inhaled, 40 micrograms once daily) and ciclesonide (inhaled, 80 micrograms once daily)	**Change in % FEV_1 from baseline , 12 weeks** 27.38% with ciclesonide (inhaled, 160 micrograms once daily) 21.36% with placebo (inhaled, once daily)	P <0.01	○○○	ciclesonide (160 micrograms daily)
[20] RCT **3-armed trial**	353 children aged 5 to 12 years, with moderate symptomatic asthma, receiving short-acting $beta_2$ agonist on as-needed basis In review [8] The remaining arm evaluated beclometasone dipropionate (inhaled via extrafine aerosol, 160 micrograms/day)	**Mean change in FEV_1 from baseline (% predicted) , week 12** 9.2% with beclometasone dipropionate (inhaled via extrafine aerosol, 80 micrograms/day) 3.9% with placebo Primary outcome	P less-than or equal to 0.01	○○○	beclometasone dipropionate (80 micrograms/day)
[20] RCT **3-armed trial**	353 children aged 5 to 12 years, with moderate symptomatic asthma, receiving short-acting $beta_2$ agonist on as-needed basis In review [8] The remaining arm evaluated beclometasone dipropionate (inhaled via extrafine aerosol, 80 micrograms/day)	**Mean change in FEV_1 from baseline (% predicted) , week 12** 10.0% with beclometasone dipropionate (inhaled via extrafine aerosol, 160 micrograms/day) 3.9% with placebo Primary outcome	P less-than or equal to 0.01	○○○	beclometasone dipropionate (160 micrograms/day)
Lung function assessed by Rint					
[14] RCT **3-armed trial**	63 children aged 2 to 6 years with asthma-like symptoms The remaining arm evaluated montelukast	**Lung function, assessed by airway resistance (Rint)** with fluticasone (inhaled, 100 micrograms twice daily) with placebo (oral, once daily) Absolute results not reported	Reported no significant difference between groups RCT may have been underpowered; see further information on studies	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Airway hyperresponsiveness					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use The remaining arm evaluated salmeterol (80 children)	**Methacholine PC20, measured 36 hours after study medication , 12 months** with beclometasone with placebo Absolute results reported graphically	P = 0.001 (beclometasone *v* placebo)	○○○	beclometasone

No data from the following reference on this outcome. [9] [13] [15] [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adrenal function					
[7] Systematic review	Children, all receiving usual care, including as-needed inhaled $beta_2$ agonists 12 RCTs in this analysis	**Adrenal function** with inhaled corticosteroids (betamethasone, budesonide, flunisolide, or fluticasone) with placebo Absolute results not reported Reported no evidence of corticosteroid-induced adrenal suppression	Significance assessment not reported		
Oral candidiasis					
[11] RCT	7221 people with mild persistent asthma for <2 years, including 3210 children aged 17 years or younger	**Oral candidiasis , 3 years** 1.2% with once-daily budesonide (200 micrograms once daily from dry-powder inhaler if aged <11 years and 400 micrograms once daily if >11 years) 0.5% with placebo Absolute numbers not reported Reported no difference between groups in any other adverse event			
[7] Systematic review	Children, all receiving usual care, including as-needed inhaled $beta_2$ agonists 4 RCTs in this analysis	**Oral candidiasis** with inhaled corticosteroids (betamethasone, budesonide, flunisolide, or fluticasone) with placebo Absolute results not reported The review found clinical cases of oral candidiasis (one case in each inhaled steroid group)			
Growth suppression					
[19] RCT	1041 children aged 5 to 12 years, with mild to moderate asthma, mean pre-study FEV_1 94%	**Mean increase in height , 4 to 6 years** 22.7 cm with budesonide 400 micrograms	P = 0.005	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	predicted, all using salbutamol for asthma symptoms In review [8] The remaining arm evaluated nedocromil 8 mg twice daily (312 children)	23.8 cm with placebo The difference occurred mainly within the first year of treatment			
[18] RCT **3-armed trial**	241 children aged 6 to 14 years The remaining arm evaluated salmeterol (80 children)	**Mean increase in height** 3.96 cm with beclometasone 5.04 cm with placebo	P = 0.018	○○○	placebo
[21] RCT	94 children aged 7 to 9 years with recurrent viral-induced wheeze In review [22]	**Growth , 7-month treatment period** with inhaled beclometasone 400 micrograms/day with placebo Absolute results not reported	Mean difference in growth: –1 cm 95% CI –1.4 cm to –0.6 cm P <0.0001 No significant catch-up growth during a follow-up 4-month washout period	○○○	placebo
[12] RCT	3195 children aged 5 to 17 years with mild asthma	**Growth rate , 3 years** with budesonide with placebo Absolute results not reported	Mean difference in growth per year: –0.43 cm 95% CI –0.54 cm to –0.32 cm P <0.0001	○○○	placebo
[12] RCT	Children aged <11 years with mild asthma Subgroup analysis	**Growth rate , 3 years** with budesonide (200 micrograms/day) with placebo Absolute results not reported	Differences in growth rate: –0.45 cm/year 95% CI –0.56 cm/year to –0.34 cm/year P <0.0001	○○○	placebo
[12] RCT	Children aged >11 years with mild asthma Subgroup analysis	**Growth rate , 3 years** with budesonide (400 micrograms/day) with placebo Absolute results not reported	Difference in growth rate: –0.40 cm/year 95% CI –0.66 cm/year to –0.14 cm/year P = 0.003	○○○	placebo
[12] RCT	Children aged <11 years with mild asthma Subgroup analysis	**Growth rate , year 1** with budesonide (200 micrograms/day) with placebo Absolute results not reported	Difference in growth rate: –0.58 cm/year 95% CI –0.76 cm/year to –0.40 cm/year P <0.0001	○○○	placebo
[12] RCT	Children aged <11 years with mild asthma Subgroup analysis	**Growth rate , year 3** with budesonide (200 micrograms/day) with placebo Absolute results not reported	Difference in growth rate: –0.33 cm/year 95% CI –0.52 cm/year to –0.14 cm/year P = 0.0005	○○○	placebo
[7] Systematic review	1087 children, 10/24 RCTs in preschool children, all receiving usual care, including as-needed inhaled beta$_2$ agonists 8 RCTs in this analysis	**Growth velocity** with inhaled corticosteroids with placebo Absolute results not reported	Reported no significant difference between groups	⟷	Not significant

Inhaled corticosteroids versus oral leukotriene receptor antagonists:

See option on leukotriene receptor antagonists (oral), p 14 .

Inhaled corticosteroids versus inhaled long-acting beta$_2$ agonist:

See option on long-acting beta$_2$ agonists (inhaled), p 29 .

Inhaled corticosteroids versus oral theophylline:

See option on theophylline (oral), p 35 .

Further information on studies

[14] The RCT reported that it was unable to recruit the number of children (198) required by its power calculation to reach 90% power.

Comment:

A further publication of the START trial [10] reported on a 2-year open-label treatment extension phase with budesonide. [23] A total of 5146 people (aged 5–66 years) from the 3-year double-blind phase of the RCT continued into this extension phase and were treated with budesonide (200 micrograms/day if <11 years, 400 micrograms/day for others). It analysed results over the full 5 years of the study. It found that both groups (budesonide for 5 years and placebo for 3 years followed by budesonide for 2 years) increased % FEV_1 by an average of 3.24%. It found no significant difference between groups. It found that the cumulative risk of severe asthma-related events after 5 years was significantly lower in people treated with budesonide for 5 years compared with people treated with placebo for 3 years followed by budesonide for 2 years.

Adverse effects of inhaled corticosteroids from observational studies:

Observational studies have found little or no biochemical evidence of change in bone metabolism with inhaled corticosteroids. [24] [25] Case reports [26] and a national survey of paediatricians and endocrinologists [27] have indicated the possibility of adrenal suppression leading to adrenal crisis associated with hypoglycaemia in children on high-dose inhaled corticosteroids. Most cases involved fluticasone in daily doses of 500 to 2000 micrograms. Two cross-sectional studies using a slit lamp to screen for lenticular changes in children taking long-term inhaled corticosteroids (beclometasone, budesonide) found no posterior subcapsular cataracts. [28] [29]

One systematic review (search date 1993, 12 studies, 331 children with asthma treated with inhaled beclometasone) found no evidence of growth impairment with inhaled beclometasone. [30] Two related controlled prospective studies assessed the effects of inhaled budesonide on growth. [31] [32] The first study compared 216 children treated with budesonide (400–600 micrograms/day) versus 62 children treated with theophylline or sodium cromoglicate over 3 to 5 years of follow-up. [31] No significant changes in growth velocity were found at doses up to 400 micrograms daily (5.5 cm/year with budesonide *v* 5.6 cm/year with controls).The adult height of 142 of these budesonide-treated children (mean treatment period 9.2 years, mean dosage 412 micrograms/day) was compared with 18 controls never treated with inhaled corticosteroids and 51 healthy siblings. No significant differences were found. Children in all groups attained their target adult height (mean difference between measured and target adult height: +0.3 cm, 95% CI –0.6 cm to +1.2 cm for budesonide-treated children; –0.2 cm, 95% CI –2.4 cm to +2.1 cm for control children with asthma; +0.9 cm, 95% CI –0.4 cm to +2.2 cm for healthy siblings). [32]

Starting dose of inhaled corticosteroid:

We found one systematic review (search date not reported, 5 RCTs in children, 4 RCTs in infants) examining the effects of different initiation doses of inhaled corticosteroids. [33] The review found

no significant difference between intermediate-dose and low-dose inhaled corticosteroid in exacerbations (2 RCTs [1 RCT in children, mean age approximately 9 years; 1 RCT in infants, age range 12–47 months]: proportion of children with exacerbation: 18/193 [9%] with intermediate dose *v* 23/200 [13%] with low dose; RR 0.82, 95% CI 0.47 to 1.43). It found that high-dose budesonide significantly reduced airway hyperresponsiveness, assessed by post-exercise fall in FEV_1, compared with low-dose budesonide (1 RCT, 19 children; absolute numbers not reported in review; P <0.0001).

Inhaled corticosteroids versus placebo post exercise:
We found one crossover RCT (25 children aged 5–14 years) that only assessed post-exercise symptoms. It compared hydrofluoroalkane beclometasone dipropionate (50 or 100 micrograms) once in the evening by autohaler versus placebo. [34] Treatment periods lasted 4 weeks with a 1-week washout period between. The RCT did not report pre-crossover results, but it found no evidence of a carry-over or period effect. It found that both doses of beclometasone significantly reduced the percentage fall in FEV_1 after exercise compared with placebo. It found few adverse effects during treatment with low-dose (50 or 100 micrograms) hydrofluoroalkane beclometasone dipropionate by autohaler or during treatment with placebo. [34]

Clinical guide:
The dose of inhaled corticosteroids should be reviewed at least once every 3 months. If symptoms are controlled, the inhaled corticosteroid dose can be halved or if very low, discontinuation can be considered. Annual measurement of height with plotting on height centile charts should be undertaken in all children receiving treatment with inhaled corticosteroids. Children requiring long-term use of high-dose (off-licence) inhaled corticosteroids should be referred to a specialist.

OPTION LEUKOTRIENE RECEPTOR ANTAGONISTS (ORAL)

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- Regular monotherapy with oral leukotriene receptor antagonists is not superior to low-dose inhaled corticosteroids. Leukotriene receptor antagonists may have a role as first-line prophylaxis in very young children.

Benefits and harms

Oral leukotriene receptor antagonists versus placebo:
We found no systematic review. We found 8 RCTs. [41] [42] [43] [44] [45] [46] [14] [15]

Symptom control (clinical assessments)

Compared with placebo Regular treatment with oral montelukast may be more effective at improving some measures of asthma control (assessed by daily $beta_2$ agonist use) in children aged 6 to 16 years at 8 weeks, but we don't know whether it is more effective at improving other measures (daytime symptom score or nocturnal awakenings). Regular treatment with oral montelukast may be more effective at improving daytime symptom scores in children aged 2 to 5 years at 12 weeks, but we don't know whether it is more effective at improving symptom scores in children aged 2 to 6 years at 12 weeks or at improving days without $beta_2$ agonists in children aged 6 to 24 months at 6 weeks. Intermittent treatment with oral montelukast (treatment at the onset of upper respiratory tract infection or asthma symptoms) may be more effective at improving symptom scores and reducing proportion of nights disturbed in children aged 2 to 14 years with intermittent asthma at 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom scores					
[41] RCT	336 children aged 6 to 16 years with mean FEV_1 72% predicted, concomitant inhaled corticosteroid treatment in 33% of placebo group and 39% of montelukast group	**Daytime asthma symptom score , 8 weeks** with montelukast (oral, 5 mg/day) with placebo Absolute results not reported	Reported no significant difference between groups	⟷	Not significant
[41] RCT	336 children aged 6 to 16 years with mean FEV_1 72% predicted, concomitant inhaled corti-	**Nocturnal awakenings with asthma , 8 weeks** with montelukast (oral, 5 mg/day) with placebo	Reported no significant difference between groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	costeroid treatment in 33% of placebo group and 39% of montelukast group	Absolute results not reported			
[42] RCT	689 children aged 2 to 5 years, concomitant inhaled corticosteroid treatment in 29% of placebo group, 27% of montelukast group, 2:1 ratio montelukast:placebo group	**Improvement in average daytime symptom scores (6-point scale) , 12 weeks** 0.37 with montelukast (oral, 4 mg/day) 0.26 with placebo	P = 0.003	○○○	montelukast
[42] RCT	689 children aged 2 to 5 years, concomitant inhaled corticosteroid treatment in 29% of placebo group, 27% of montelukast group, 2:1 ratio montelukast:placebo group	**Average overnight asthma symptom scores , 12 weeks** with montelukast (oral, 4 mg/day) with placebo Absolute results not reported	Reported no significant difference between groups	⟷	Not significant
[43] RCT	24 children aged 10 to 26 months with probable early childhood asthma, defined as recurrent wheeze, atopy on skin testing, elevated exhaled nitric oxide, and a positive family history of asthma	**Median symptom score (change from baseline)** From 5.5 to 1.5 with montelukast (4 mg) From 3.0 to 4.0 with placebo Symptom score based on cough, wheeze, and shortness of breath, scores range 0 (no symptoms) to 18 (severe symptoms)	Change from baseline with montelukast: P = 0.04 Change from baseline with placebo: P = 0.35		
[45] RCT	220 children aged 2 to 14 years, with intermittent asthma	**Symptom score (mean total symptom score for each episode, assessed by diary cards) , 12 months** 37 with montelukast 43 with placebo Children took either montelukast or placebo at the onset of an upper respiratory tract infection or asthma symptoms, for at least 7 days or until 48 hours after symptom cessation	P = 0.049	○○○	montelukast
[45] RCT	220 children aged 2 to 14 years, with intermittent asthma	**Proportion of nights disturbed per days at risk , 12 months** 1010/29,816 (3.4%) with montelukast 1105/29,840 (3.7%) with placebo Children took either montelukast or placebo at the onset of an upper respiratory tract infection or asthma symptoms, for at least 7 days or until 48 hours after symptom cessation Days at risk defined as the total number of days in the study for all 202 patients who had at least 1 treated episode	Reported 8.6% reduction with montelukast P = 0.043	○○○	montelukast

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[46] RCT **Crossover design**	26 children, aged 3 to 6 years, with mild asthma in analysis; unclear how many children randomised	**Change in daytime symptom score from baseline** From 0.98 to 0.63 with montelukast Not reported with placebo Post-crossover results Daily scores were assessed by diary cards on a scale of 0 to 5, where 0 = no symptoms and 5 = very severe symptoms	Reported that montelukast reduced symptoms by 35% compared with placebo, P = 0.033 However, it was unclear from the RCT whether this was an analysis of the change from baseline with montelukast or a direct comparison between montelukast and placebo	○○○	montelukast
[46] RCT **Crossover design**	26 children, aged 3 to 6 years, with mild asthma in analysis; unclear how many children randomised	**Change in night-time symptom score from baseline** From 0.38 to 0.14 with montelukast Not reported with placebo Post-crossover results Night-time scores were assessed by diary cards on a scale of 0 to 2	Reported that montelukast reduced symptoms by 63% compared with placebo, P = 0.022 However, it was unclear from the RCT whether this was an analysis of the change from baseline with montelukast or a direct comparison between montelukast and placebo	○○○	montelukast
[14] RCT **3-armed trial**	63 children aged 2 to 6 years with asthma-like symptoms The remaining arm evaluated fluticasone (inhaled, 100 micrograms twice daily)	**Change in symptom scores from baseline , 3 months** with montelukast (oral, 4 mg/day) with placebo (oral, once daily) Absolute results reported graphically Parents rated the child's symptoms (cough, wheeze, and shortness of breath) each morning and evening to give the total daily symptom score	Reported no significant difference between fluticasone and montelukast P value not reported RCT may have been underpowered; see further information on studies	⟷	Not significant
[15] RCT **3-armed trial**	238 children aged 12 to 59 months with 2 or more episodes of wheeze in the past year The remaining arm evaluated budesonide (inhaled by nebuliser, 1 mg twice daily) plus placebo (oral)	**Proportion of episode-free days, assessed by diary cards , over 12 months** 73% with montelukast (oral, 4 mg once daily) plus placebo (inhaled) 74% with placebo (oral and inhaled) Absolute results not reported Children received treatment for 7 days at the first sign of respiratory tract infection; all children also received salbutamol by inhalation Episode-free day defined as day free from cough, wheeze, trouble breathing, asthma-associated interference with daily activities/awakening from sleep, healthcare use caused by wheezing, and use of asthma-related non-study medications	Direct statistical comparison between montelukast and placebo not reported		
Need for $beta_2$ agonist					
[41] RCT	336 children aged 6 to 16 years with mean FEV_1 72% predicted, concomitant inhaled corticosteroid treatment in 33% of placebo group and 39% of montelukast group	**Total daily $beta_2$ agonist use , 8 weeks** Reduced by 13% with montelukast (oral, 5 mg/day) Increased by 10% with placebo	P = 0.01	○○○	montelukast

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[44] RCT	256 children aged 6 to 24 months with mild asthma	**Days without beta$_2$ agonists , 6 weeks** with montelukast (4 mg oral granules) with placebo Absolute results not reported	Mean difference: +7.4 days 95% CI –0.9 days to +15.6 days	⟷	Not significant

Exacerbations

Compared with placebo Regular treatment with oral montelukast may be more effective at reducing the proportion of children aged 6 to 16 years with an asthma exacerbation at 8 weeks, but we don't know whether it is more effective at reducing the use of oral corticosteroids in these children. Regular treatment with oral montelukast may be more effective at reducing the use of rescue oral corticosteroids at 12 weeks in children aged 2 to 5 years, but we don't know whether it is more effective at reducing asthma attack or unscheduled physician visit for asthma at 6 weeks in children aged 6 to 24 months. Intermittent treatment with oral montelukast (treatment at the onset of upper respiratory tract infection or asthma symptoms) may be more effective at reducing unscheduled acute healthcare resource utilisation, time off school/childcare, and parental time off work in children aged 2 to 14 years with intermittent asthma at 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[41] RCT	336 children aged 6 to 16 years with mean FEV_1 72% predicted, concomitant inhaled corticosteroid treatment in 33% of placebo group and 39% of montelukast group	**Proportion of children with an asthma exacerbation , 8 weeks** 84.8% with montelukast (oral, 5 mg/day) 95.5% with placebo Absolute numbers not reported	P = 0.002	○○○	montelukast
[44] RCT	256 children aged 6 to 24 months with mild asthma	**AR for at least 1 asthma attack , 6 weeks** 16.7% with montelukast (4 mg oral granules) 18.5% with placebo	P = 0.72	⟷	Not significant
[14] RCT **3-armed trial**	63 children aged 2 to 6 years with asthma-like symptoms The remaining arm evaluated fluticasone (inhaled, 100 micrograms twice daily)	**Withdrawal due to asthma exacerbation , 3 months** 1 with montelukast (oral, 4 mg daily) 2 with placebo (oral, once daily) Absolute results reported graphically	Significance assessment not reported		
Unscheduled visit to primary care/hospital					
[44] RCT	256 children aged 6 to 24 months with mild asthma	**AR for at least 1 unscheduled physician visit for asthma , 6 weeks** 10% with montelukast (4 mg oral granules) 15% with placebo	P = 0.12	⟷	Not significant
[45] RCT	220 children aged 2 to 14 years, with intermittent asthma	**Unscheduled acute healthcare resource utilisation specific for asthma , 12 months** 163 with montelukast 228 with placebo	Rate reduction (adjusted for patient cluster, number of days in the study, and rhinitis history) 0.65 95% CI 0.47 to 0.89 P = 0.007	○○○	montelukast

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Children took either montelukast or placebo at the onset of an upper respiratory tract infection or asthma symptoms, for at least 7 days or until 48 hours after symptom cessation; 202 children in intention-to-treat analysis Primary outcome including number of unscheduled visits to a GP, a specialist paediatrician, an emergency department, and admission to hospital			
Rescue oral corticosteroid use					
[41] RCT	336 children aged 6 to 16 years with mean FEV_1 72% predicted, concomitant inhaled corticosteroid treatment in 33% of placebo group and 39% of montelukast group	**Proportion of children with rescue oral corticosteroid use , 8 weeks** 12.1% with montelukast (oral, 5 mg/day) 15.8% with placebo Absolute numbers not reported	P = 0.41	⟷	Not significant
[42] RCT	689 children aged 2 to 5 years, concomitant inhaled corticosteroid treatment in 29% of placebo group, 27% of montelukast group, 2:1 ratio montelukast:placebo group	**Need for rescue oral corticosteroid courses , 12 weeks** 19% with montelukast (oral, 4 mg/day) 28% with placebo Absolute numbers not reported	P = 0.008	○○○	montelukast
Time off school/work					
[45] RCT	220 children aged 2 to 14 years, with intermittent asthma	**Time off school/childcare (proportion of days absent per days at risk) , 12 months** 349/29,816 (1.2%) with montelukast 552/29,840 (1.8%) with placebo Children took either montelukast or placebo at the onset of an upper respiratory tract infection or asthma symptoms, for at least 7 days or until 48 hours after symptom cessation Days at risk defined as the total number of days in the study for all 202 patients who had at least 1 treated episode	Reported reduced by 37% with montelukast P <0.0001	○○○	montelukast
[45] RCT	220 children aged 2 to 14 years, with intermittent asthma	**Parental time off work (proportion of days absent per days at risk) , 12 months** 416/29,816 (1.4%) with montelukast 622/29,840 (2.1%) with placebo Children took either montelukast or placebo at the onset of an upper respiratory tract infection or asthma symptoms, for at least 7 days or until 48 hours after symptom cessation	Reported reduced by 33% with montelukast P <0.0001	○○○	montelukast

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Days at risk defined as the total number of days in the study for all 202 patients who had at least 1 treated episode			

No data from the following reference on this outcome. [43] [46] [15]

Physiological measures

Compared with placebo Regular treatment with oral montelukast may be more effective at improving mean morning lung function (measured by FEV_1) at 8 weeks in children aged 6 to 16 years. Regular treatment with oral montelukast may be more effective at improving bronchial hyperreactivity (assessed by methacholine challenge test) at 4 weeks in children aged 3 to 6 years, but we don't know whether it is more effective at improving lung function, assessed by airway resistance, at 3 months in children aged 2 to 6 years (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume					
[41] RCT	336 children aged 6 to 16 years with mean FEV_1 72% predicted, concomitant inhaled corticosteroid treatment in 33% of placebo group and 39% of montelukast group	**Mean morning FEV_1 , 8 weeks** 8.2% with montelukast (oral, 5 mg/day) 3.6% with placebo	P <0.001	○○○	montelukast
[43] RCT	24 children aged 10 to 26 months with probable early childhood asthma, defined as recurrent wheeze, atopy on skin testing, elevated exhaled nitric oxide, and a positive family history of asthma	**Mean $FEV_{0.5}$ (change from baseline)** 189 mL to 214 mL with montelukast (4 mg) 161 mL to 166 mL with placebo	Change from baseline with montelukast: P = 0.038 Change from baseline with placebo: P = 0.26		
Lung function, assessed by Rint					
[14] RCT **3-armed trial**	63 children aged 2 to 6 years with asthma-like symptoms The remaining arm evaluated fluticasone (inhaled, 100 micrograms twice daily)	**Lung function, assessed by airway resistance (Rint) , 3 months** with montelukast (oral, 4 mg daily) with placebo (oral, once daily) Absolute results reported graphically	Reported no significant difference between montelukast and placebo P value not reported RCT may have been underpowered; see further information on studies	⟷	Not significant
Airway hyperresponsiveness					
[46] RCT **Crossover design**	26 children, aged 3 to 6 years, with mild asthma in analysis; unclear how many children randomised	**Bronchial hyperreactivity (assessed by methacholine challenge test) , 4 weeks** 4.79 mg/mL with montelukast 2.07 mg/mL with placebo Post-crossover results Challenge test results represent the concentration of methacholine causing a 20% decrease in FEV_1 measurements, higher values indicate greater improvement	P = 0.001	○○○	montelukast

No data from the following reference on this outcome. [42] [44] [45] [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT	336 children aged 6 to 16 years with mean FEV_1 72% predicted, concomitant inhaled corticosteroid treatment in 33% of placebo group and 39% of montelukast group	**Adverse effects** with montelukast (oral, 5 mg/day) with placebo	No significant difference reported in the incidence of adverse effects with montelukast versus placebo	⟷	Not significant
[42] RCT	689 children aged 2 to 5 years, concomitant inhaled corticosteroid treatment in 29% of placebo group, 27% of montelukast group, 2:1 ratio montelukast:placebo group	**Adverse effects** with montelukast (oral, 4 mg/day) with placebo	No significant difference reported in the incidence of adverse effects with montelukast versus placebo	⟷	Not significant
[44] RCT	256 children aged 6 to 24 months with mild asthma	**Overall treatment-related adverse effects , 6 weeks** with montelukast (4 mg oral granules) with placebo Absolute results not reported	Reported as no significant difference	⟷	Not significant
[44] RCT	256 children aged 6 to 24 months with mild asthma	**Upper respiratory tract infection , 6 weeks** with montelukast (4 mg oral granules) with placebo Absolute results not reported	Mean difference +11.0% 95% CI –1% to +21%	⟷	Not significant
[44] RCT	256 children aged 6 to 24 months with mild asthma	**Fever , 6 weeks** with montelukast (4 mg oral granules) with placebo Absolute results not reported	Mean difference –0.4% 95% CI –11% to +8%	⟷	Not significant
[44] RCT	256 children aged 6 to 24 months with mild asthma	**Diarrhoea , 6 weeks** with montelukast (4 mg oral granules) with placebo Absolute results not reported	Mean difference –2% 95% CI –11% to +6%	⟷	Not significant
[44] RCT	256 children aged 6 to 24 months with mild asthma	**Vomiting , 6 weeks** with montelukast (4 mg oral granules) with placebo Absolute results not reported	Mean difference –3% 95% CI –12% to +5%	⟷	Not significant

No data from the following reference on this outcome. [43] [45] [46] [14] [15]

Oral leukotriene receptor antagonists versus inhaled corticosteroids:

We found 9 RCTs reported in 10 publications. [47] [48] [35] [36] [37] [38] [15] [14] [39] [40]

Symptom control (clinical assessments)

Compared with inhaled corticosteroids Oral montelukast may be less effective than inhaled fluticasone at improving symptom scores, proportion of parents and physicians reporting satisfaction, and rescue medication-free days at up to 12 weeks, and at improving the composite outcomes of rescue-free days or asthma control days over 48 weeks to 12 months in children aged 6 years or over with asthma. However, we don't know how effective oral montelukast and inhaled budesonide are, compared with each other, at improving episode-free days over 12 months in younger children, aged 1 to 5 years, with asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom score					
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV_1 60% to 80% of predicted	**Mean change in night-time asthma symptom score , 12 weeks** –0.19 with oral montelukast (5 mg chewable tablet once daily) –0.40 with fluticasone propionate (50 micrograms twice daily by multi-dose powder inhaler) Scale 0 to 3, higher score = worse symptoms	P <0.001	●●○	fluticasone
[48] RCT **3-armed trial**	51 newly diagnosed mildly asthmatic children aged 6 to 18 years who were sensitive to house dust mites The remaining arm evaluated high-dose budesonide (800 micrograms/day by dry-powder inhaler)	**Mean symptom score , 6 months** 1.9 with montelukast (oral, 5 mg/day for children aged 6–14 years, 10 mg/day for older children) 1.9 with low-dose budesonide (inhaled, 400 micrograms/day by dry-powder inhaler) Clinical score based on daytime and night-time symptoms, score range 0 (no symptoms or $beta_2$ agonist use) to 9 (severe day and night symptoms plus >3 uses of $beta_2$ agonist)	P >0.12 for each dose of budesonide *v* montelukast	⟷	Not significant
[48] RCT **3-armed trial**	51 newly diagnosed mildly asthmatic children aged 6 to 18 years who were sensitive to house dust mites The remaining arm evaluated low-dose budesonide (400 micrograms/day by dry-powder inhaler)	**Mean symptom score , 6 months** 1.9 with montelukast (oral, 5 mg/day for children aged 6–14 years, 10 mg/day for older children) 2.2 with high-dose budesonide (inhaled, 800 micrograms/day by dry-powder inhaler) Clinical score based on daytime and night-time symptoms, score range 0 (no symptoms or $beta_2$ agonist use) to 9 (severe day and night symptoms plus >3 uses of $beta_2$ agonist)	P >0.12 for each dose of budesonide *v* montelukast	⟷	Not significant
[47] RCT	342 children aged 6 to 12 years with chronic asthma for	**Proportion of parents "very satisfied" , 12 weeks**	P = 0.006	○○○	fluticasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	at least 6 months and FEV_1 60% to 80% of predicted	42% with montelukast (oral, 5 mg chewable tablet once daily) 58% with fluticasone propionate (inhaled, 50 micrograms twice daily) Satisfaction measured on a scale of 0 to 6, unclear what score represented "very satisfied"			
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV_1 60% to 80% of predicted	**Proportion of physicians "very satisfied" , 12 weeks** 29% with montelukast (oral, 5 mg chewable tablet once daily) 48% with fluticasone propionate (inhaled, 50 micrograms twice daily) Satisfaction measured on a scale of 0 to 6, unclear what score represented “very satisfied”	P = 0.016	○○○	fluticasone
[36] RCT	62 children aged 5 to 15 years with newly diagnosed mild, persistent asthma	**Symptom score , 12 weeks** with montelukast (oral, 5 mg/day) plus placebo inhaler with budesonide (inhaled, 200 micrograms twice daily) plus placebo tablets Absolute results not reported Secondary endpoint	Reported no significant difference between groups P value not reported	⟷	Not significant
[37] RCT **Crossover design**	144 children aged 6 to 17 years, with mild to moderate persistent asthma; using only as-needed bronchodilators Further report of reference [38]	**Asthma control days , last 4 weeks of 8 weeks' treatment** 2.1 days/week with montelukast (oral, 5–10 mg [dose dependent on age] at night) 2.8 days/week with fluticasone (inhaled, 100 micrograms twice daily) Results after crossover; see further information on studies	P <0.001	○○○	fluticasone
[15] RCT **3-armed trial**	238 children aged 12 to 59 months with 2 or more episodes of wheeze in the past year The remaining arm evaluated placebo (oral and inhaled)	**Proportion of episode-free days, assessed by diary cards , over 12 months** 73% with montelukast (oral, 4 mg once daily) plus placebo (inhaled) 76% with budesonide (inhaled by nebuliser, 1.0 mg twice daily) plus placebo (oral) Absolute results not reported Children received treatment for 7 days at the first sign of respiratory tract infection; all children also received salbutamol by inhalation Episode-free day defined as day free from cough, wheeze, trouble breathing, asthma-associated interference with daily activities/awakening from sleep, healthcare use caused by wheezing, and use of asthma-related non-study medications	Direct statistical comparison between budesonide and montelukast not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[14] RCT **3-armed trial**	63 children aged 2 to 6 years with asthma-like symptoms The remaining arm evaluated placebo	**Change in symptom scores from baseline , 3 months** with montelukast (oral, 4 mg/day) with fluticasone (inhaled, 100 micrograms twice daily) Absolute results reported graphically Parents rated the child's symptoms (cough, wheeze, and shortness of breath) each morning and evening to give the total daily symptom score	Reported no significant difference between fluticasone and montelukast P value not reported RCT may have been underpowered; see further information on studies	⟷	Not significant
[35] RCT	994 children aged 6 to 14 years, with mild persistent asthma, average FEV_1 87.2% predicted	**% rescue-free days , over 12 months** 84.0% with montelukast (oral, 5 mg) 86.7% with fluticasone (inhaled, 50 micrograms twice daily) Primary outcome Rescue-free day defined as day with no rescue medication (beta$_2$ agonist, systemic corticosteroids, or other asthma rescue medications), and no asthma-related health resource utilisation	Least-squares mean difference –2.8% 95% CI –4.7% to –0.9% P = 0.003 However, non-inferiority satisfied (see further information on studies)	○○○	fluticasone
[40] RCT **3-armed trial**	285 children aged 6 to 14 years, with mild to moderate persistent asthma, using only as-needed salbutamol before randomisation The remaining arm evaluated fluticasone (inhaled, 100 micrograms once daily) plus salmeterol (inhaled, 50 micrograms twice daily)	**% asthma control days , 48 weeks** 52.5% with montelukast (oral, 5 mg once daily) 64.2% with fluticasone (inhaled, 100 micrograms twice daily) Primary outcome Asthma control day defined as day without rescue salbutamol, non-study asthma medications, oral corticosteroids, daytime symptoms, night-time awakenings, unscheduled healthcare visits, emergency departments visits or hospital admissions for asthma, or school absenteeism for asthma	Difference 11.8% 95% CI 3.7% to 19.8% P = 0.004 (fluticasone monotherapy *v* montelukast)	○○○	fluticasone
Need for beta$_2$ agonist					
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV_1 60% to 80% of predicted	**Mean change in daily puffs of salbutamol , 12 weeks** –1.23 with montelukast (oral, 5 mg chewable tablet once daily) –1.43 with fluticasone propionate (50 micrograms twice daily by multi-dose powder inhaler)	P = 0.18	⟷	Not significant
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV_1 60% to 80% of predicted	**Rescue medication-free days , 12 weeks** 35% with montelukast (oral, 5 mg chewable tablet once daily) 45% with fluticasone propionate (inhaled, 50 micrograms twice daily)	P = 0.002	○○○	fluticasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[37] RCT **Crossover design**	144 children aged 6 to 17 years, with mild to moderate persistent asthma; using only as-needed bronchodilators Further report of reference [38]	**Salbutamol use , last 4 weeks of 8 weeks' treatment** 4.4 puffs/weeks with montelukast (oral, 5–10 mg [dose dependent on age] at night) 3.1 puffs/week with fluticasone (inhaled, 100 micrograms twice daily) Results after crossover; see further information on studies	P = 0.0305	○○○	fluticasone

No data from the following reference on this outcome. [39]

Exacerbations

Compared with inhaled corticosteroids Oral montelukast may be less effective than inhaled fluticasone at reducing the number of children aged 6 years or over who withdraw due to asthma exacerbation up to 12 to 16 weeks, the proportion with an asthma attack up to 12 months, and oral prednisolone use over 48 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV_1 60% to 80% of predicted	**Withdrawal due to asthma exacerbation , 12 weeks** 14/170 (8%) with oral montelukast (5 mg chewable tablet once daily) 9/172 (5%) with fluticasone propionate (50 micrograms twice daily by multi-dose powder inhaler)	Statistical assessment not performed		
[38] RCT **Crossover design**	144 children aged 6 to 17 years, with mild to moderate persistent asthma; using only as-needed bronchodilators	**Number of people who withdrew due to asthma exacerbation , 16 weeks** 10 with montelukast (oral, 5 mg or 10 mg) 2 with fluticasone (100 micrograms twice daily)	P = 0.019	○○○	fluticasone
[35] RCT	994 children aged 6 to 14 years, with mild persistent asthma, average FEV_1 87.2% predicted	**Proportion of people with an asthma attack , over 12 months** 32.2% with montelukast (oral, 5 mg) 25.6% with fluticasone (inhaled, 50 micrograms twice daily) Absolute numbers not reported Secondary outcome	RR 1.26 95% CI 1.04 to 1.52	●○○	fluticasone
[40] RCT **3-armed trial**	285 children aged 6 to 14 years, with mild to moderate persistent asthma, using only as-needed salbutamol before randomisation The remaining arm evaluated fluticasone (inhaled, 100 micrograms once daily) plus salmeterol (inhaled, 50	**Proportion of people not having oral prednisolone , over 48 weeks** with montelukast (oral, 5 mg once daily) with fluticasone (inhaled, 100 micrograms twice daily) Absolute results reported graphically Kaplan-Meier analysis	P = 0.002	○○○	fluticasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	micrograms twice daily)				

No data from the following reference on this outcome. [14] [15] [48] [36] [39]

Physiological measures

Compared with inhaled corticosteroids Oral montelukast may be less effective than inhaled fluticasone at improving morning peak expiratory flow (PEF) and FEV_1 measures in children aged 6 years or over with asthma; however, we don't know whether it is more or less effective at improving lung function, assessed by airway resistance (Rint). We don't know how effective oral montelukast and inhaled budesonide are, compared with each other, at improving lung function, assessed by Rint, at 4 weeks in younger children, aged 2 to 6 years, with asthma-like symptoms (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume					
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV_1 60% to 80% of predicted	**Proportion with >5% increase in FEV_1 , 12 weeks** 43% with oral montelukast (5 mg chewable tablet once daily) 63% with fluticasone propionate (50 micrograms twice daily by multi-dose powder inhaler)	P = 0.002	○○○	fluticasone
[48] RCT **3-armed trial**	51 newly diagnosed mildly asthmatic children aged 6 to 18 years who were sensitive to house dust mites The remaining arm evaluated high-dose budesonide (800 micrograms/day by dry-powder inhaler)	**FEV_1 as % predicted , 6 months** 90.9% with montelukast (oral, 5 mg/day for children aged 6–14 years, 10 mg/day for older children) 93.4% with low-dose budesonide (400 micrograms/day by dry-powder inhaler)	P >0.07 for each dose of budesonide *v* montelukast	⟷	Not significant
[48] RCT **3-armed trial**	51 newly diagnosed mildly asthmatic children aged 6 to 18 years who were sensitive to house dust mites The remaining arm evaluated low-dose budesonide (400 micrograms/day by dry-powder inhaler)	**FEV_1 as % predicted , 6 months** 90.9% with montelukast (oral, 5 mg/day for children aged 6–14 years, 10 mg/day for older children) 93.0% with budesonide (inhaled, 800 micrograms/day)	P >0.07 for each dose of budesonide *v* montelukast	⟷	Not significant
[38] RCT **Crossover design**	144 children aged 6 to 17 years, with mild to moderate persistent asthma; using only as-needed bronchodilators	**Improvement in FEV_1 , last 4 weeks of 8 weeks' treatment** 1.9% with montelukast (oral, 5–10 mg [dose dependent on age] at night) 6.8% with fluticasone (inhaled, 100 micrograms twice daily) Results after crossover; see further information on studies	P <0.0001	○○○	fluticasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[36] RCT	62 children aged 5 to 15 years with newly diagnosed mild, persistent asthma	**Change in FEV_1, % predicted, from baseline , 12 weeks** with montelukast (oral, 5 mg/day) plus placebo inhaler with budesonide (inhaled, 200 micrograms twice daily) plus placebo tablets Absolute results reported graphically Primary endpoint	Reported no significant difference between groups	⟷	Not significant
[35] RCT	994 children aged 6 to 14 years, with mild persistent asthma, average FEV_1 87.2% predicted	**Change in FEV_1, % of predicted from baseline , over 12 months** 0.6% with montelukast (oral, 5 mg) 2.7% with fluticasone (inhaled, 50 micrograms twice daily) Absolute numbers not reported Secondary outcome	Least-squares mean difference –2.2% 95% CI –3.6% to –0.7% P = 0.004	●○○	fluticasone
[40] RCT **3-armed trial**	285 children aged 6 to 14 years, with mild to moderate persistent asthma, using only as-needed salbutamol before randomisation The remaining arm evaluated fluticasone (inhaled, 100 micrograms once daily) plus salmeterol (inhaled, 50 micrograms twice daily)	**Change in (pre-bronchodilator) FEV_1, % of predicted from baseline , 48 weeks** –0.58% with montelukast (oral, 5 mg once daily) 6.32% with fluticasone (inhaled, 100 micrograms twice daily)	Difference 6.90% 95% CI 3.92% to 9.88% P <0.001	○○○	fluticasone
Peak expiratory flow					
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV_1 60% to 80% of predicted	**Mean change in morning peak expiratory flow (PEF) , 12 weeks** 23.0 L/minute with oral montelukast (5 mg chewable tablet once daily) 39.9 L/minute with fluticasone propionate (50 micrograms twice daily by multi-dose powder inhaler)	P = 0.004	○○○	fluticasone
[40] RCT **3-armed trial**	285 children aged 6 to 14 years, with mild to moderate persistent asthma, using only as-needed salbutamol before randomisation The remaining arm evaluated fluticasone (inhaled, 100 micrograms once daily) plus salmeterol (inhaled, 50 micrograms twice daily)	**Mean change in morning PEF, % predicted , 48 weeks** 0.65% with montelukast (oral, 5 mg once daily) 5.18% with fluticasone (inhaled, 100 micrograms twice daily)	Difference 4.54% 95% CI 1.67% to 7.41% P = 0.002	○○○	fluticasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function, assessed by Rint					
[39] RCT **5-armed trial**	145 children aged 6 to 18 years with moderate atopic asthma, which was stable for the previous 6 months treated with inhaled corticosteroid and long-acting beta$_2$ agonist The remaining arms evaluated budesonide plus montelukast, budesonide plus formoterol, or placebo	**Pulmonary function, % of predicted value as assessed by resistance by the interrupter technique (Rint) , 4 weeks** 126.0% with montelukast (oral, 5 mg once daily for children aged 6–14 years or 10 mg once daily for adolescents aged >14 years) 120.5% with budesonide (inhaled, 200 micrograms per day)	Between-group statistical assessment not reported		
[14] RCT **3-armed trial**	63 children aged 2 to 6 years with asthma-like symptoms The remaining arm evaluated placebo	**Lung function, assessed by airway resistance (Rint)** with montelukast (oral, 4 mg/day) with fluticasone (inhaled, 100 micrograms twice daily) Absolute results not reported	Reported no significant difference between groups RCT may have been underpowered; see further information on studies	⟷	Not significant

No data from the following reference on this outcome. [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV$_1$ 60% to 80% of predicted	**Treatment-related adverse events** 6% with montelukast 7% with fluticasone	Statistical assessment not performed		
[47] RCT	342 children aged 6 to 12 years with chronic asthma for at least 6 months and FEV$_1$ 60% to 80% of predicted	**Withdrawals due to adverse effect** 2% with montelukast 2% with fluticasone	Statistical assessment not performed		
[35] RCT	994 children aged 6 to 14 years, with mild persistent asthma, average FEV$_1$ 87.2% predicted	**Adverse effects (considered drug-related) , over 12 months** 22/495 (4%) with montelukast (oral, 5 mg) 16/499 (3%) with fluticasone (inhaled, 50 micrograms twice daily) The most common adverse effects in both groups were headache and asthma			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[35] RCT	994 children aged 6 to 14 years, with mild persistent asthma, average FEV_1 87.2% predicted	**Overall growth rate , over 12 months** 6.18 cm/year with montelukast (oral, 5 mg) 5.81 cm/year with fluticasone (inhaled, 50 micrograms twice daily)	Difference 0.41 cm/year 95% CI 0.07 cm/year to 0.75 cm/year	○○○	montelukast
[36] RCT	62 children aged 5 to 15 years with newly diagnosed mild, persistent asthma	**Adverse effects , 12 weeks** with montelukast (oral, 5 mg/day) plus placebo inhaler with budesonide (inhaled, 200 micrograms twice daily) plus placebo tablets Absolute results reported graphically 2 people in each group developed skin rashes, and 2 people in budesonide group reported sedation	Significance assessment not reported		
[40] RCT **3-armed trial**	285 children aged 6 to 14 years, with mild to moderate persistent asthma, using only as-needed salbutamol before randomisation The remaining arm evaluated fluticasone (inhaled, 100 micrograms once daily) plus salmeterol (inhaled, 50 micrograms twice daily)	**Linear growth , 48 weeks** 5.72 cm with montelukast (oral, 5 mg once daily) 5.32 cm with fluticasone (inhaled, 100 micrograms twice daily)	Difference –0.40 cm 95% CI –0.93 cm to +0.13 cm P = 0.13	⟷	Not significant

No data from the following reference on this outcome. [14] [15] [48] [38] [39]

Further information on studies

[14] The RCT reported that it was unable to recruit the number of children (198) required by its power calculation to reach 90% power. The RCT found that only montelukast significantly decreased circulating eosinophils from baseline. It found that montelukast significantly reduced eosinophils compared with placebo (P = 0.045).

[35] The RCT calculated a non-inferiority limit for the treatment difference of –7% points corresponding to approximately 2 asthma rescue-free days in 1 month.

[37] [38] The RCT did not include a washout period but used the first 4 weeks of each treatment period as a "pseudo-washout" period. Only results from the second 4 weeks of each treatment period were included in the analysis. The RCT also reported on the proportion of people who responded to treatment (defined as >7.5% improvement in FEV_1). It found that 17% of people responded to both treatments, 23% of people responded only to fluticasone, 5% only to montelukast, and 55% responded to neither; most individuals respond to neither treatment.

Comment: We found another RCT (395 children aged 2–8 years with mild asthma or recurrent wheezing) comparing budesonide versus montelukast, which did not satisfy *Clinical Evidence* inclusion criteria because it was an open-label trial. [49] However, we have included a comment on this study because it reported on exacerbations as an outcome and there was a paucity of such data for this comparison.

It found that budesonide (inhaled via nebuliser, 500 micrograms/day) significantly reduced exacerbations compared with montelukast (oral, 4 mg/day or 5 mg/day) over 52 weeks. [49]

Clinical guide:
In older children, leukotriene receptor antagonists are less effective than inhaled corticosteroids as monotherapy for control of symptoms and preventing exacerbations.

OPTION LONG-ACTING BETA2 AGONISTS (INHALED)

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- There is consensus that long-acting beta$_2$ agonists should not be used for first-line prophylaxis.
- CAUTION: Monotherapy with long-acting beta$_2$ agonists does not reduce asthma exacerbations but may increase the chance of severe asthma episodes when those episodes occur.

Benefits and harms

Inhaled long-acting beta$_2$ agonist versus placebo:

We found one systematic review (search date 2008, 40 RCTs, 9 RCTs in children and adolescents), which reported on asthma exacerbations with long-acting beta$_2$ agonist versus placebo. [50] Some of the RCTs in the review included children who were taking additional asthma medications and the review did not present a separate analysis for children who were only using as-needed beta$_2$ agonist. The review also did not report on the outcomes of symptoms or physiological measures and so we have additionally reported these outcomes from those RCTs included in the review that also satisfied *Clinical Evidence* inclusion criteria for this question. [18] [51] We found another two systematic reviews (search dates 2008) assessing serious adverse effects associated with regular treatment with salmeterol compared with placebo [52] and with regular treatment with formoterol compared with placebo. [53]

Symptom control (clinical assessments)

Compared with placebo We don't know whether adding inhaled salmeterol to usual care is more effective than placebo added to usual care at reducing salbutamol use or the number of nights without awakenings in children aged over 4 years (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms/night-time awakening					
[51] RCT	207 children aged 4 to 11 years with asthma diagnosed according to American Thoracic Society (ATS) guidelines, receiving as-needed inhaled beta$_2$ agonists, FEV$_1$ (without medication) 50% to 80% predicted In review [50]	**Number of nights without awakenings , 12 weeks** with salmeterol (inhaled, 50 micrograms twice daily) with placebo Absolute results not reported	Reported no significant difference between groups	⟷	Not significant
Need for beta$_2$ agonist					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use In review [50] The remaining arm evaluated beclometasone (81 children)	**Days and nights without need for salbutamol** 88% with salmeterol (80 children) 83% with placebo (80 children)	P = 0.09	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[51] RCT	207 children aged 4 to 11 years with asthma diagnosed according to ATS guidelines, receiving as-needed inhaled beta$_2$ agonists, FEV$_1$ (without medication) 50% to 80% predicted In review [50]	**Change in supplemental salbutamol use , 12 weeks** –0.8 with salmeterol (inhaled, 50 micrograms twice daily) –0.3 with placebo	P = 0.004	○○○	salmeterol

No data from the following reference on this outcome. [50]

Exacerbations

Compared with placebo We don't know whether long-acting beta$_2$ agonists (salmeterol or formoterol) are more effective at reducing exacerbations requiring systemic corticosteroids in children with asthma who are/are not taking additional asthma medications (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[50] Systematic review	Children with asthma, unclear how many RCTs or children included in analysis Some of the RCTs in the review included children who were taking additional asthma medications including inhaled corticosteroids; see further information on studies	**Exacerbations requiring systemic corticosteroids** with long-acting beta$_2$ agonist (salmeterol or formoterol) with placebo Absolute results not reported	RR 0.99 95% 0.80 to 1.22 See further information on studies	⟷	Not significant

Physiological measures

Compared with placebo Adding inhaled salmeterol to usual care is more effective than adding placebo to usual care at improving FEV$_1$ at 1 year and mean morning and evening peak expiratory flow rate (PEFR) at 12 weeks, in children aged over 4 years (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use In review [50] The remaining arm evaluated beclometasone (81 children)	**Mean change in FEV$_1$ as % of predicted , 1 year** 10% with salmeterol (80 children) 5% with placebo (80 children)	P <0.001	○○○	salmeterol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Peak expiratory flow rate					
[51] RCT	207 children aged 4 to 11 years with asthma diagnosed according to American Thoracic Society (ATS) guidelines, receiving as-needed inhaled beta$_2$ agonists, FEV$_1$ (without medication) 50% to 80% predicted In review [50]	**Mean morning peak expiratory flow rate (PEFR) , 12 weeks** 25 L/minute with salmeterol (inhaled, 50 micrograms twice daily) 13.2 L/minute with placebo	P <0.001	○○○	salmeterol
[51] RCT	207 children aged 4 to 11 years with asthma diagnosed according to ATS guidelines, receiving as-needed inhaled beta$_2$ agonists, FEV$_1$ (without medication) 50% to 80% predicted In review [50]	**Mean evening PEFR , 12 weeks** 20 L/minute with salmeterol (inhaled, 50 micrograms twice daily) 10.1 L/minute with placebo	P = 0.01	○○○	salmeterol

No data from the following reference on this outcome. [50]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[52] Systematic review	1333 children aged 4 to 16 years, concurrent inhaled corticosteroid use varied from 0% to 57% and concurrent cromones 0% to 25% in included studies 5 RCTs in this analysis	**Non-fatal serious adverse effects** 46/725 (6.3%) with salmeterol 34/608 (5.6%) with placebo The review defined non-fatal "serious" adverse effects as a life-threatening adverse event, hospital admission, a disability/incapacity, or a congenital anomaly in the offspring of a patient who received medication	OR 1.30 95% CI 0.82 to 2.05	⟷	Not significant
[53] Systematic review	1335 children aged 5 to 17 years, concurrent inhaled corticosteroid use varied from 0% to 100% in included studies 5 RCTs in this analysis	**Non-fatal serious adverse effects** 34/843 (4%) with formoterol 6/492 (1%) with placebo The review defined non-fatal "serious" adverse effects as a life-threatening adverse event, hospital admission, a disability/incapacity, or a congenital anomaly in the offspring of a patient who received medication	OR 2.48 95% CI 1.27 to 4.83	●●○	placebo

No data from the following reference on this outcome. [50]

Inhaled long-acting beta$_2$ agonists versus inhaled corticosteroids:

We found two RCTs. [18] [54]

Symptom control (clinical assessments)

Compared with corticosteroids We don't know how inhaled salmeterol and beclometasone compare at increasing the proportion of children who are asymptomatic, but salmeterol may be less effective than beclometasone at reducing the need for beta$_2$ agonists after 1 year, in children aged over 6 years with asthma (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Asthma symptoms					
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Proportion of children asymptomatic (change from before trial) , 1 year** From 3% to 36% with salmeterol (inhaled, 50 micrograms twice daily) From 6% to 55% with beclometasone (inhaled, 200 micrograms twice daily) Absolute numbers not reported	Significance assessment not reported		
Need for beta$_2$ agonists					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use The remaining arm evaluated placebo (80 children)	**Days and nights without need for salbutamol** 88% with salmeterol (80 children) 92% with beclometasone (81 children)	Between-group significance assessment not reported		
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Use of rescue salbutamol , 54 weeks** 0.44 uses/day with salmeterol (inhaled, 50 micrograms twice daily) 0.07 uses/day with beclometasone (inhaled, 200 micrograms twice daily)	P less-than or equal to 0.001	○○○	beclometasone

Exacerbations

Compared with inhaled corticosteroids We don't know how inhaled salmeterol and beclometasone compare at reducing exacerbations requiring oral corticosteroids or exacerbations requiring withdrawal from the study in children aged over 6 years, because the RCTs did not present a direct statistical comparison; however, a higher number of exacerbations were found with salmeterol (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations requiring oral corticosteroids					
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Exacerbations requiring oral corticosteroid treatment , 1 year** 17/32 (53%) with salmeterol (inhaled, 50 micrograms twice daily) 2/35 (6%) with beclometasone (inhaled, 200 micrograms twice daily)	Significance assessment not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment withdrawals because of exacerbations					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use The remaining arm evaluated placebo (80 children)	**Treatment withdrawals because of exacerbations** 15 with salmeterol (80 children) 5 with beclometasone (81 children)	Between-group significance assessment not reported		
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Treatment withdrawals because of exacerbations , 1 year** 6/32 (19%) with salmeterol (inhaled, 50 micrograms twice daily) 1/35 (3%) with beclometasone (inhaled, 200 micrograms twice daily)	Significance assessment not reported		

Physiological measures

Compared with inhaled corticosteroids We don't know how inhaled salmeterol and beclometasone compare at improving FEV_1 or peak expiratory flow rate after about 1 year in children aged over 6 years with asthma. However, inhaled salmeterol may be less effective than inhaled beclometasone at improving airway hyperresponsiveness to methacholine (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use The remaining arm evaluated placebo (80 children)	**Mean change in FEV_1 , as % of predicted , 1 year** 10% with salmeterol (80 children) 10% with beclometasone (81 children)	Between-group significance assessment not reported		
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Mean change of FEV_1 predicted , 54 weeks** –4.5% with salmeterol (inhaled, 50 micrograms twice daily) +10% with beclometasone (inhaled, 200 micrograms twice daily)	Mean difference beclometasone *v* salmeterol: 14.2% 95% CI 8.3% to 20.0%	○○○	beclometasone
Peak expiratory flow rate					
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Improvement in morning peak expiratory flow rate , 1 year** 49 L/minute with salmeterol (inhaled, 50 micrograms twice daily) 61 L/minute with beclometasone (inhaled, 200 micrograms twice daily)	Reported no significant difference between groups	⟷	Not significant
Airway hyperresponsiveness					
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use	**Methacholine PC20 36 hours after study medication , 12 months** with salmeterol with beclometasone	P = 0.009	○○○	beclometasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated placebo (80 children)	Absolute results reported graphically			
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Airway responsiveness , end of the treatment period** –0.73 doubling dose with salmeterol (inhaled, 50 micrograms twice daily) +2.02 doubling dose with beclometasone (inhaled, 200 micrograms twice daily) Airway responsiveness to methacholine defined as a 20% fall in FEV_1 after inhalation of methacholine dose, and expressed as numbers of doubling doses of methacholine	Difference between groups 2.79 doubling dose 95% CI 1.75 to 3.84 P <0.0001 See further information on studies	○○○	beclometasone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Growth suppression					
[54] RCT	67 children aged 6 to 16 years (mean age about 10.5 years), with mild to moderate asthma, not currently using inhaled corticosteroids	**Linear growth , 1 year of treatment** 5.4 cm with salmeterol (inhaled, 50 micrograms twice daily) 4.0 cm with beclometasone (inhaled, 200 micrograms twice daily)	P = 0.004	○○○	salmeterol
[18] RCT **3-armed trial**	241 children aged 6 to 14 years with clinically stable asthma and <1 month of prior corticosteroid use The remaining arm evaluated placebo (80 children)	**Linear growth , 1 year of treatment** 6.1 cm with salmeterol (80 children) 4.7 cm with beclometasone (81 children)	P = 0.007 (beclometasone *v* salmeterol)	○○○	salmeterol

Further information on studies

[50] Some of the RCTs in the review included children who were taking additional medications including inhaled corticosteroids, sodium cromoglicate, and others. The review carried out an indirect comparison and interactive test examining whether long-acting $beta_2$ agonists increased exacerbations in children compared with adults. It found increased exacerbation rates requiring systemic corticosteroids in children compared with adults; however, this was of borderline significance (number of RCTs and people in analysis not reported; RR 1.26, 95% CI 1.00 to 1.60; absolute numbers not reported).

[54] Symptom improvement in the salmeterol group was accompanied by significant deterioration in bronchial reactivity, indicating a failure to control underlying bronchial inflammation.

Comment: **Clinical guide:**
Given 1) the lack of clear superiority of long-acting beta$_2$ agonists over inhaled corticosteroid monotherapy, 2) the effectiveness and safety of low-dose inhaled corticosteroid monotherapy, and 3) the concern about increased exacerbations associated with long-acting beta$_2$ agonist monotherapy (extrapolated from adult studies), consensus is that long-acting beta$_2$ agonists should not be used first line as monotherapy in any age group.

OPTION THEOPHYLLINE (ORAL)

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- Theophylline was used as first-line prevention before the introduction of inhaled corticosteroids. Although there is weak evidence that theophylline is superior to placebo, theophylline should no longer be used as first-line prophylaxis in childhood asthma because of clear evidence of the efficacy and safety of inhaled corticosteroids.
- Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded.

Benefits and harms

Oral theophylline versus placebo:

We found one RCT comparing once daily oral sustained-release theophylline (mean theophylline level of 11.2 mg/L) versus placebo for 6 weeks. [55] We found one systematic review (search date not reported, 12 studies) assessing the behavioural and cognitive effects of theophylline. [56]

Symptom control (clinical assessments)

Compared with placebo Oral theophylline added to usual care including as-needed inhaled beta$_2$ agonists may be more effective than adding placebo to usual care at reducing the mean number of doses of bronchodilator used in children aged 6 to 15 years experiencing at least 2 night awakenings per week; however, evidence is weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for other asthma medications					
[55] RCT **Crossover design**	24 children aged 6 to 15 years experiencing at least 2 night awakenings/week, receiving usual care, including as-needed inhaled beta$_2$ agonists	**Mean number of doses of bronchodilator used** 6.5 with once-daily oral sustained release theophylline (mean theophylline level of 11.2 mg/L) 23.7 with placebo	P <0.001	◌◌◌	theophylline

Exacerbations

Compared with placebo Oral theophylline added to usual care including as-needed inhaled beta$_2$ agonists may be more effective than adding placebo to usual care at reducing the mean number of acute night-time attacks in children aged 6 to 15 years experiencing at least 2 night awakenings per week; however, evidence is weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[55] RCT **Crossover design**	24 children aged 6 to 15 years (mean age 9.2 years) experiencing at least 2 night awakenings/week, receiving usual care, including as-needed inhaled beta$_2$ agonists	**Mean number of acute night-time attacks** 3.2 with once-daily oral sustained release theophylline (mean theophylline level of 11.2 mg/L) 10.7 with placebo	P <0.001	◌◌◌	theophylline

Physiological measures

Compared with placebo Oral theophylline added to usual care including as-needed inhaled beta$_2$ agonists may be more effective than adding placebo to usual care at increasing mean morning peak expiratory flow rate in children aged 6 to 15 years experiencing at least 2 night awakenings per week; however, evidence is weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Peak expiratory flow					
[55] RCT **Crossover design**	24 children aged 6 to 15 years experiencing at least 2 night awakenings/week, receiving usual care, including as-needed inhaled beta$_2$ agonists	**Mean morning peak expiratory flow rate** 244 L/minute with once-daily oral sustained release theophylline (mean theophylline level of 11.2 mg/L) 207 L/minute with placebo	P <0.001	○○○	theophylline

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[55] RCT **Crossover design**	24 children aged 6 to 15 years experiencing at least 2 night awakenings/week, receiving usual care, including as-needed inhaled beta$_2$ agonists	**Gastric symptoms (including dyspepsia, nausea, and vomiting)** 30% with oral sustained-release theophylline 6% with placebo Absolute numbers not reported	P <0.001	○○○	placebo
[56] Systematic review	340 children	**Adverse effects** with theophylline No evidence of significant adverse effects with theophylline were found			

Oral theophylline versus inhaled corticosteroids:

We found no systematic review. We found one RCT, which compared oral theophylline versus inhaled beclometasone. [57]

Symptom control (clinical assessments)

Compared with inhaled corticosteroids We don't know how oral theophylline and inhaled beclometasone compare at improving asthma symptom score in children aged 6 to 16 years with asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom score					
[57] RCT	195 children aged 6 to 16 years (mean age 11.9 years) receiving usual care, including as-needed in-	**Mean asthma symptom score (change from baseline) , 12 months** From 0.6 to 0.9 with theophylline (oral)	Reported no significant difference between groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	haled beta$_2$ agonists, followed for 12 months Subgroup analysis	From 0.5 to 0.8 with beclometasone (inhaled, 360 micrograms/day) Scale: 0 = no symptoms, 6 = incapacitating symptoms; scores were low			

Exacerbations

Compared with inhaled corticosteroids We don't know how oral theophylline and inhaled beclometasone compare at reducing the proportion of children, aged 6 to 16 years, with one or more emergency department visits or hospital admissions for asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[57] RCT	195 children aged 6 to 16 years (mean age 11.9 years) receiving usual care, including as-needed inhaled beta$_2$ agonists, followed for 12 months Subgroup analysis	**Proportion of children with 1 or more emergency department visits or hospital admissions for asthma , 12 months** 11.8% with theophylline (oral) 4.9% with beclometasone (inhaled, 360 micrograms/day) Absolute numbers not reported	Reported no significant difference between groups	⟷	Not significant

Physiological measures

Compared with inhaled corticosteroids We don't know how oral theophylline and inhaled beclometasone compare at improving FEV_1 or methacholine sensitivity in children aged 6 to 16 years with asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume					
[57] RCT	195 children aged 6 to 16 years (mean age 11.9 years) receiving usual care, including as-needed inhaled beta$_2$ agonists, followed for 12 months Subgroup analysis	**Pre-bronchodilator mean FEV_1 (% predicted) , 36 weeks** with beclometasone (inhaled, 360 micrograms/day) with theophylline (oral) Absolute results reported graphically	Reported no significant difference between groups	⟷	Not significant
Airway hyperresponsiveness					
[57] RCT	195 children aged 6 to 16 years (mean age 11.9 years) receiving usual care, including as-needed inhaled beta$_2$ agonists, followed for 12 months Subgroup analysis	**Change in methacholine sensitivity from baseline , 6 weeks** 0.48 with beclometasone (inhaled, 360 micrograms/day) 0 with theophylline (oral) Concentration of methacholine producing a 20% fall in FEV_1 (PD_{20}) in puff × micrograms/mL	Reported no significant difference between groups	⟷	Not significant
[57] RCT	195 children aged 6 to 16 years (mean age 11.9 years) receiving usual care, including as-needed in-	**Methacholine sensitivity (PD_{20}) , final visit** 14.79 with beclometasone (inhaled, 360 micrograms/day) 8.71 with theophylline (oral)	Reported no significant difference between groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	haled beta$_2$ agonists, followed for 12 months Subgroup analysis	Concentration of methacholine producing a 20% fall in FEV$_1$ (PD$_{20}$) in puff × micrograms/mL Total study duration 12 months			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Growth suppression					
[57] RCT	195 children aged 6 to 16 years (mean age 11.9 years) receiving usual care, including as-needed inhaled beta$_2$ agonists, followed for 12 months Subgroup analysis	**Mean rate of growth in prepubescent boys , 1 year** 6.2 cm/year with oral theophylline 4.3 cm/year with inhaled beclometasone 360 micrograms/day This effect was not sufficient to be noticed by the children or by their parents, and no child was withdrawn from the study on this account			

Further information on studies

Comment: Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded. [58]

Clinical guide:
Theophylline was used as first-line prevention before the introduction of corticosteroids; however, it is not to be used first line any more. There is no evidence of superiority between inhaled corticosteroids and theophylline monotherapy. Given 1) the lack of clear superiority of theophylline over inhaled corticosteroid monotherapy, 2) the effectiveness and safety of low-dose inhaled corticosteroid monotherapy, and 3) the long-recognised adverse effects associated with theophylline treatment (at therapeutic levels nausea and at toxic levels cardiac arrhythmias and convulsions), consensus is that theophylline should not be used as monotherapy in any age group.

QUESTION What are the effects of additional prophylactic treatments in childhood asthma inadequately controlled by standard-dose inhaled corticosteroids?

OPTION INCREASED DOSE OF INHALED CORTICOSTEROID

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- When low-dose inhaled corticosteroids fail to control asthma, most older children will respond to one of the add-on options available, which include addition of long-acting beta$_2$ agonists, addition of leukotriene receptor antagonists, addition of theophylline, or increased dose of inhaled corticosteroid. However, we don't know for certain how effective these additional treatments are because we found no/limited RCT evidence of benefit compared with adding placebo/no additional treatments.
- Increasing the dose of corticosteroids in older children may be less effective than adding long-acting beta2 agonists for reducing symptoms and improving physiological measures.

Benefits and harms

Increased dose of inhaled corticosteroid versus low-dose corticosteroid:

We found two systematic reviews (search dates 1999 [59] and 2008 [60]). The first systematic review [59] examined different doses of inhaled beclometasone versus each other. It included only two RCTs in children and did not pool the data. We have therefore reported directly from the one RCT that satisfied *Clinical Evidence* inclusion criteria. [61] The second systematic review [60] examined the effects of different doses of inhaled fluticasone versus each other in adults and children. The review did not present a separate analysis based on previous inhaled corticosteroid use, and so we have only included the analyses where the majority of children were from RCTs that specified previous inhaled corticosteroid use.

Symptom control (clinical assessments)

Increased dose of inhaled corticosteroid versus low-dose corticosteroid We don't know whether adding a higher dose of inhaled beclometasone is more effective than adding placebo in children aged 6 to 16 years with asthma, who were already taking low-dose inhaled beclometasone (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom scores					
[61] RCT **3-armed trial**	177 children aged 6 to 16 years, mean pre-bronchodilator FEV_1 86% predicted The third arm evaluated the addition of salmeterol (50 micrograms twice daily)	**Proportion of children with no symptoms , 1 year** 39% with additional beclometasone (200 micrograms twice daily) 35% with placebo Absolute results not reported 117 children in this analysis. All children already taking beclometasone (200 micrograms twice daily)	No direct comparison of increased corticosteroid versus placebo No significant difference among groups was found in these children, whose compliance with pre-existing medication was good		

Exacerbations

Increased dose of inhaled corticosteroid versus low-dose corticosteroid We don't know whether a second dose of inhaled beclometasone is more effective than adding placebo at reducing exacerbations at 1 year, in children aged 6 to 16 years with asthma, who were already taking inhaled beclometasone twice daily. Increased dose of inhaled fluticasone (400–500 micrograms/day) seems no more effective than lower dose of inhaled fluticasone (200 micrograms/day) at reducing exacerbations requiring oral corticosteroids in children with asthma who were all previously using inhaled corticosteroids (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[61] RCT **3-armed trial**	177 children aged 6 to 16 years, mean pre-bronchodilator FEV_1 86% predicted The third arm evaluated the addition of salmeterol (50 micrograms twice daily)	**Exacerbation rates , 1 year** with additional beclometasone (200 micrograms twice daily) with placebo Absolute results not reported 117 children in this analysis. All children already taking beclometasone (200 micrograms twice daily)	No direct comparison of increased corticosteroid versus placebo No significant difference among groups was found in these children, whose compliance with pre-existing medication was good		
[60] Systematic review	883 children (aged 4–11 years or about 8 years) with asthma, all using inhaled corticosteroids and either remaining symptomatic or with at least 1 asthma exacerbation in the	**Exacerbations requiring oral corticosteroids** 33/442 (7.5%) with fluticasone (200 micrograms/day) 28/441 (6.3%) with fluticasone (400–500 micrograms/day)	OR 1.21 95% CI 0.72 to 2.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	previous 12 months 2 RCTs in this analysis				

Physiological measures

Increased dose of inhaled corticosteroid versus low-dose corticosteroid We don't know whether a second dose of inhaled beclometasone is more effective than adding placebo at improving lung function assessed by FEV_1, bronchial reactivity, or airway responsiveness at 1 year, in children aged 6 to 16 years with asthma, who were already taking inhaled beclometasone twice daily. Increased dose of inhaled fluticasone (400–500 micrograms/day) may be more effective than lower dose of inhaled fluticasone (200 micrograms/day) at improving mean morning peak expiratory flow rate in children with asthma who were all previously using inhaled corticosteroids; however, we don't know whether increased dose is more effective at improving FEV_1 in children with asthma, the majority of whom were previously using inhaled corticosteroids (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume					
[61] RCT **3-armed trial**	177 children aged 6 to 16 years, mean pre-bronchodilator FEV_1 86% predicted The remaining arm evaluated salmeterol (50 micrograms twice daily)	**Lung function (mean change in FEV_1) , at 1 year** 5.8% predicted with additional beclometasone (200 micrograms twice daily) 4.3% predicted with placebo 117 children in this analysis. All children already taking beclometasone (200 micrograms twice daily)	No direct comparison of increased corticosteroid versus placebo No significant difference among groups was found in these children, whose compliance with pre-existing medication was good		
[60] Systematic review	114 children 2 RCTs in this analysis 1 RCT: 89 children (aged 4–16 years) all previously taking inhaled corticosteroids with "frequent episodic" asthma; 1 RCT: 25 children (aged 6–14 years) with asthma not using inhaled corticosteroids in previous 4 months	**FEV_1, % predicted** with fluticasone (200 micrograms/day) with fluticasone (400–500 micrograms/day) Absolute results not reported	WMD –2.48 95% CI –8.60 to +3.64	⟷	Not significant
Peak expiratory flow					
[60] Systematic review	876 children (aged 4–11 years or about 8 years) with asthma, all using inhaled corticosteroids and either remaining symptomatic or with at least 1 asthma exacerbation in the previous 12 months 2 RCTs in this analysis	**Change in morning peak expiratory flow rate (PEFR) from baseline** with fluticasone (200 micrograms/day) with fluticasone (400–500 micrograms/day) Absolute results not reported	Difference –7.9 L/minute 95% CI –12.9 L/minute to –2.9 L/minute	○○○	fluticasone (400–500 micrograms/day)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Airway hyperresponsiveness					
[61] RCT **3-armed trial**	177 children aged 6 to 16 years, mean pre-bronchodilator FEV_1 86% predicted The remaining arm evaluated salmeterol (50 micrograms twice daily)	**Bronchial reactivity , 1 year** with additional beclometasone (200 micrograms twice daily) with placebo Absolute results not reported 117 children in this analysis. All children already taking beclometasone (200 micrograms twice daily)	No direct comparison of increased corticosteroid versus placebo No significant difference among groups was found in these children, whose compliance with pre-existing medication was good		
[61] RCT **3-armed trial**	177 children aged 6 to 16 years, mean pre-bronchodilator FEV_1 86% predicted The remaining arm evaluated salmeterol (50 micrograms twice daily)	**Changes in airway responsiveness , 1 year** with additional beclometasone (200 micrograms twice daily) with placebo Absolute results not reported 117 children in this analysis. All children already taking beclometasone (200 micrograms twice daily)	No direct comparison of increased corticosteroid versus placebo No significant difference among groups was found in these children, whose compliance with pre-existing medication was good		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Growth suppression					
[61] RCT **3-armed trial**	177 children aged 6 to 16 years, mean pre-bronchodilator FEV_1 86% predicted	**Mean height increase , 1 year** 3.6 cm with additional beclometasone (200 micrograms twice daily) 4.5 cm with placebo All children already taking beclometasone (200 micrograms twice daily)	P = 0.02	○○○	placebo

Increased dose of inhaled corticosteroid versus adding $beta_2$ agonist:

See option on addition of long-acting $beta_2$ agonist, p 42 .

Increased dose of inhaled corticosteroid versus adding oral leukotriene receptor antagonists:

See option on addition of oral leukotriene receptor antagonists, p 52 .

Further information on studies

Comment: Doses of inhaled corticosteroids are often increased from low dose to higher doses despite lack of evidence of benefit. For the population as a whole, there is likely to be a ceiling effect where total daily doses in excess of 400 micrograms budesonide (or equivalent) do not provide benefit. There have been case reports of serious adrenal crisis in children receiving high doses of inhaler corticosteroid, principally fluticasone in doses above 500 micrograms.

OPTION ADDITION OF REGULAR (DAILY) LONG-ACTING BETA2 AGONIST

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- When low-dose inhaled corticosteroids fail to control asthma, most older children will respond to one of the add-on options available, which include addition of long-acting beta$_2$ agonists, addition of leukotriene receptor antagonists, addition of theophylline, or increased dose of inhaled corticosteroid. However, we don't know for certain how effective these additional treatments are because we found no/limited evidence of benefit compared with adding placebo/no additional treatments.
- Addition of long-acting beta$_2$ agonists may reduce symptoms and improve physiological measures compared with increased dose of corticosteroids in older children.
- Long-acting beta$_2$ agonists are not currently licensed for use in children under 5 years of age.
- Long-acting beta$_2$ adrenergic agonists may increase the chance of severe asthma episodes.

Benefits and harms

Addition of long-acting beta$_2$ agonist versus addition of placebo to inhaled corticosteroid:

We found one systematic review (search date 2008, 16 RCTs, 24 comparisons, 4625 children) comparing adding regular long-acting beta$_2$ agonist to inhaled corticosteroid versus adding placebo to the same dose of inhaled corticosteroid. [62] For further information on adverse effects, see long-acting beta$_2$ agonists (inhaled) under question on prophylaxis, p 29 and comments below.

Symptom control (clinical assessments)

Addition of regular (daily) long-acting beta$_2$ agonist compared with adding placebo Adding long-acting beta$_2$ agonist to inhaled corticosteroid seems no more effective than adding placebo to the same dose of inhaled corticosteroid at improving symptom scores in children aged 4 to 16 years with persistent seasonal asthma, who were previously treated with inhaled corticosteroids (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom scores					
[62] Systematic review	1119 children with persistent asthma who received daily inhaled corticosteroid (ICS) for at least 28 days before study entry 4 RCTs in this analysis	**Mean change in symptom scores** with ICS plus long-acting beta$_2$ agonist (LABA; salmeterol or formoterol) with ICS plus placebo Absolute results not reported Both groups received a similar dose of ICS	SMD –0.04 95% CI –0.16 to +0.08	⟷	Not significant

Exacerbations

Addition of regular (daily) long-acting beta$_2$ agonist compared with adding placebo Adding long-acting beta$_2$ agonist to inhaled corticosteroid is no more effective than adding placebo to the same dose of inhaled corticosteroid at reducing exacerbations requiring oral corticosteroids in children with persistent asthma, who were previously treated with inhaled corticosteroids (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations requiring oral corticosteroids					
[62] Systematic review	1084 children with persistent asthma who received daily inhaled corticosteroid (ICS) for at least 28 days before study entry 7 RCTs in this analysis	**Proportion of children with exacerbation requiring oral corticosteroids** 34/540 (6%) with ICS plus long-acting beta$_2$ agonist (LABA; salmeterol or formoterol) 37/544 (7%) with ICS plus placebo Both groups received a similar dose of ICS	RR 0.92 95% CI 0.60 to 1.40	⟷	Not significant

Physiological measures

Addition of regular (daily) long-acting beta$_2$ agonist compared with adding placebo Adding long-acting beta$_2$ agonist to inhaled corticosteroid seems more effective than adding placebo to the same dose of inhaled corticosteroid at improving FEV$_1$ in children with persistent asthma, who were previously treated with inhaled corticosteroids (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume					
[62] Systematic review	1235 children with persistent asthma who received daily inhaled corticosteroid (ICS) for at least 28 days before study entry 9 RCTs in this analysis	**Improvement in FEV$_1$ from baseline** with ICS plus long-acting beta$_2$ agonist (LABA; salmeterol or formoterol) with ICS plus placebo Absolute results not reported Both groups received a similar dose of ICS	Difference 80 mL 95% CI 60 mL to 110 mL	○○○	addition of LABA

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[61] RCT **3-armed trial**	177 children aged 6 to 16 years, 1 year of follow-up, mean pre-bronchodilator FEV$_1$ 86% predicted In review [62] The remaining arm evaluated additional dose of beclometasone	**Mean height increase , 1 year** 5.1 cm with additional salmeterol (50 micrograms twice daily) 4.5 cm with placebo All children already taking beclometasone (200 micrograms twice daily)	Between-group significance assessment not reported		
[62] Systematic review	3284 children with persistent asthma who received daily inhaled corticosteroid (ICS) for at least 28 days before study entry 15 RCTs in this analysis	**Overall adverse effects** 1054/1855 (57%) with ICS plus long-acting beta$_2$ agonist (LABA; salmeterol or formoterol) 782/1429 (55%) with ICS plus placebo Both groups received a similar dose of ICS	RR 1.04 95% 0.98 to 1.10	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[62] Systematic review	1155 children with persistent asthma who received daily ICS for at least 28 days before study entry 2 RCTs in this analysis	**Oral candidiasis** 5/677 (0.7%) with ICS plus LABA (salmeterol or formoterol) 1/478 (0.2%) with ICS plus placebo Both groups received a similar dose of ICS	RR 3.78 95% CI 0.63 to 22.75 The review advised that results should be interpreted with caution because of a large confidence interval and small number of reporting trials	⟷	Not significant
[62] Systematic review	1467 children with persistent asthma who received daily ICS for at least 28 days before study entry 4 RCTs in this analysis	**Tremor** 3/777 (0.4%) with ICS plus LABA (salmeterol or formoterol) 0/690 (0%) with ICS plus placebo Both groups received a similar dose of ICS	RR 3.07 95% CI 0.38 to 25.05 The review advised that results should be interpreted with caution because of a large confidence interval and small number of reporting trials	⟷	Not significant
[62] Systematic review	1052 children with persistent asthma who received daily ICS for at least 28 days before study entry 2 RCTs in this analysis	**Palpitations** 1/575 (0.2%) with ICS plus LABA (salmeterol or formoterol) 2/477 (0.4%) with ICS plus placebo Both groups received a similar dose of ICS	RR 0.4 95% CI 0.05 to 3.25 The review advised that results should be interpreted with caution because of a large confidence interval and small number of reporting trials	⟷	Not significant
[62] Systematic review	2966 children with persistent asthma who received daily ICS for at least 28 days before study entry 14 RCTs in this analysis	**Headache** 200/1645 (12%) with ICS plus LABA (salmeterol or formoterol) 144/1321 (11%) with ICS plus placebo Both groups received a similar dose of ICS	RR 1.10 95% CI 0.90 to 1.33	⟷	Not significant

Addition of long-acting beta$_2$ agonist versus increased dose of corticosteroid:

We found one systematic review (search date 2008, 7 RCTs, 1048 children) comparing addition of long-acting beta$_2$ agonist to inhaled corticosteroid treatment versus increased dose of inhaled corticosteroid in the control group. [62] We found two subsequent RCTs. [63] [64] For further information on adverse effects (death and hospital admission) with formoterol, see comments.

Symptom control (clinical assessments)

Addition of regular (daily) long-acting beta$_2$ agonist compared with adding increased dose of inhaled corticosteroid

Adding salmeterol to fluticasone may be more effective than increased dose of fluticasone at improving some symptom measures including symptom-free days and days without salbutamol in children aged 4 to 16 years with symptomatic persistent seasonal or perennial asthma, previously treated with inhaled corticosteroids, and at improving the composite outcome of best response to treatment in children aged 6 to 17 years with mild to moderate asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms					
[64] RCT	283 children and adolescents, aged 4 to 16 years (mean age 9.5 years), with symptomatic persistent seasonal or perennial asthma; all children previously	**% of symptom-free days** 41.5% with salmeterol (50 micrograms) plus fluticasone (100 micrograms) (inhaled, twice daily) 33.3% with fluticasone (inhaled, 200 micrograms twice daily) Secondary outcome	Difference 8.7% 95% CI 1.2% to 16.3% Intention-to-treat (ITT) analysis (281 people in analysis)	○○○	salmeterol plus fluticasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	treated with inhaled corticosteroids				
[64] RCT	283 children and adolescents, aged 4 to 16 years (mean age 9.5 years), with symptomatic persistent seasonal or perennial asthma; all children previously treated with inhaled corticosteroids	**% days without salbutamol treatment** with salmeterol (50 micrograms) plus fluticasone (100 micrograms) (inhaled, twice daily) with fluticasone (inhaled, 200 micrograms twice daily) Absolute results not reported Secondary outcome	Difference 8% 95% CI 0.6% to 15.3% ITT analysis (281 people in analysis)	○○○	salmeterol plus fluticasone
[63] RCT **Crossover design** **3-armed trial**	182 children aged 6 to 17 years with mild to moderate asthma; asthma uncontrolled while receiving fluticasone (100 micrograms twice daily) The remaining arm evaluated fluticasone propionate plus leukotriene receptor antagonist	**Proportion of children with best response to each treatment** 54% with fluticasone (100 micrograms) plus salmeterol (50 micrograms) (inhaled, twice daily) 32% with fluticasone (250 micrograms; inhaled, twice daily) Absolute results reported graphically Primary outcome: differential response based on a composite score of oral corticosteroid use, number of asthma control days, and FEV_1	P = 0.004	○○○	fluticasone plus salmeterol

No data from the following reference on this outcome. [62]

Exacerbations

Addition of regular (daily) long-acting beta$_2$ agonist compared with adding increased dose of inhaled corticosteroid

We don't know whether adding long-acting beta$_2$ agonist (salmeterol or formoterol) to inhaled corticosteroid is more or less effective than increased dose of inhaled corticosteroid at reducing exacerbations requiring oral corticosteroids, in children with persistent asthma previously treated with inhaled corticosteroids (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[62] Systematic review	441 children with persistent asthma and having received daily inhaled corticosteroid (ICS) treatment for at least 28 days before study entry 2 RCTs in this analysis	**Proportion of children with exacerbation requiring oral corticosteroids** 12/220 (5%) with ICS plus long-acting beta$_2$ agonist (salmeterol or formoterol) 8/221 (4%) with increased dose of ICS plus placebo	RR 1.50 95% CI 0.65 to 3.48	⟷	Not significant
[64] RCT	283 children and adolescents, aged 4 to 16 years (mean age 9.5 years), with symptomatic persistent seasonal or perennial asthma; all	**Exacerbations** 3 with salmeterol (50 micrograms) plus fluticasone (100 micrograms) (inhaled, twice daily) 6 with fluticasone (inhaled, 200 micrograms twice daily)	Significance assessment not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	children previously treated with ICS				

No data from the following reference on this outcome. [63]

Physiological measures

Addition of regular (daily) long-acting beta$_2$ agonist compared with adding increased dose of inhaled corticosteroid

Adding long-acting beta$_2$ agonist (salmeterol or formoterol) to inhaled corticosteroid may be more effective than increased dose of inhaled corticosteroid at improving peak expiratory flow measurements in children with symptomatic persistent seasonal or perennial asthma or persistent asthma previously treated with inhaled corticosteroids. However, we don't know whether it is more or less effective at improving FEV$_1$ measurements (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Forced expiratory volume measures					
[62] Systematic review	526 children with persistent asthma and having received daily inhaled corticosteroid (ICS) treatment for at least 28 days before study entry 2 RCTs in this analysis	**Change from baseline in FEV$_1$** with ICS plus long-acting beta$_2$ agonist (LABA; salmeterol or formoterol) with increased dose of ICS plus placebo Absolute results not reported	WMD +0.01 95% CI –0.03 to +0.05	⟷	Not significant
Peak expiratory flow measures					
[62] Systematic review	1002 children with persistent asthma and having received daily ICS treatment for at least 28 days before study entry 4 RCTs in this analysis	**Change in morning peak expiratory flow (L/minute)** with ICS plus LABA (salmeterol or formoterol) with increased dose of ICS plus placebo Absolute results not reported	WMD 7.55 95% CI 3.57 to 11.53	○○○	ICS plus LABA
[64] RCT	283 children and adolescents, aged 4 to 16 years (mean age 9.5 years), with symptomatic persistent seasonal or perennial asthma; all children previously treated with ICS	**Change in morning peak flow from baseline , week 8** 24.6 L/minute with salmeterol (50 micrograms) plus fluticasone (100 micrograms) (inhaled, twice daily) 16.0 L/minute with fluticasone (inhaled, 200 micrograms twice daily) Primary endpoint: see further information on studies	Difference 8.6 L/minute 95% CI 1.3 to 15.9 L/minute Intention-to-treat analysis (281 people in analysis)	○○○	salmeterol plus fluticasone

No data from the following reference on this outcome. [63]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[64] RCT	283 children and adolescents, aged 4 to 16 years (mean age 9.5 years), with symptomatic persistent seasonal or perennial asthma; all children previously treated with inhaled corticosteroids (ICS)	**Adverse effects, considered to be drug related** with salmeterol (50 micrograms) plus fluticasone (100 micrograms) (inhaled, twice daily) with fluticasone (inhaled, 200 micrograms twice daily) 1 child with severe tachycardia and hypokalaemia and another child with mild rash with salmeterol plus fluticasone; 1 child with mild laryngitis with high-dose fluticasone			
[62] Systematic review	814 children with persistent asthma and having received daily ICS treatment for at least 28 days before study entry 4 RCTs in this analysis	**Overall adverse effects** 254/403 (63%) with ICS plus long-acting beta$_2$ agonist (LABA; salmeterol or formoterol) 256/411 (62%) with increased dose of ICS plus placebo	RR 1.05 95% CI 0.90 to 1.23	⟷	Not significant
[62] Systematic review	790 children with persistent asthma and having received daily ICS treatment for at least 28 days before study entry 3 RCTs in this analysis	**Headache** 66/391 (17%) with ICS plus LABA (salmeterol or formoterol) 49/399 (12%) with increased dose of ICS plus placebo	RR 1.37 95% CI 0.98 to 1.90	⟷	Not significant
[62] Systematic review	Children with persistent asthma and having received daily ICS treatment for at least 28 days before study entry 2 RCTs in this analysis	**Linear growth , 1 year** with ICS plus LABA (salmeterol or formoterol) with increased dose of ICS plus placebo Absolute results not reported	WMD 1.2 cm/year 95% CI 0.72 cm/year to 1.7 cm/year	○○○	ICS plus LABA

No data from the following reference on this outcome. [63]

Addition of long-acting beta$_2$ agonist versus addition of leukotriene receptor antagonist:

We found one RCT. [63]

Symptom control (clinical assessments)

Addition of long-acting beta$_2$ agonist compared with addition of leukotriene receptor antagonist Adding salmeterol to fluticasone may be more effective than adding montelukast to fluticasone at improving the composite outcome of best response to treatment in children aged 6 to 17 years with mild to moderate asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms					
[63] RCT **Crossover design** **3-armed trial**	182 children aged 6 to 17 years with mild to moderate asthma; asthma uncontrolled while receiving fluticasone (100 micrograms twice daily) The remaining arm evaluated high-dose fluticasone propionate	**Proportion of children with best response to each treatment** 52% with fluticasone (100 micrograms) plus salmeterol (50 micrograms) (both inhaled, twice daily) 34% with fluticasone (inhaled, 100 micrograms twice daily) plus montelukast (orally, 5 mg or 10 mg once daily) Absolute results reported graphically Primary outcome: differential response based on a composite score of oral corticosteroid use, number of asthma control days, and FEV_1	P = 0.02	○○○	fluticasone plus salmeterol

Exacerbations

No data from the following reference on this outcome. [63]

Physiological measures

No data from the following reference on this outcome. [63]

Further information on studies

[62] The review reported that most RCTs were funded by manufacturers of both long-acting $beta_2$ agonist and inhaled corticosteroid inhalers.

[64] The primary outcome of the trial involved the primary endpoint in the per-protocol population; however, this included only 178/283 (63%) of people who had at least 47 days of treatment without missing diary recordings or protocol deviations, and so did not fulfil *Clinical Evidence* reporting criteria. The per-protocol analysis found similar results to the intention-to-treat analysis.

Comment: We found another systematic review (search date 2008 [50]), which identified 9 RCTs in children, all of which were also identified by the review. [62] This second review pooled the data for addition of long-acting $beta_2$ agonist (LABA) to inhaled corticosteroid (ICS) versus the same dose of ICS and versus an increased dose of ICS. It found no significant difference in exacerbations requiring hospital admission in the subgroup of children with LABA plus ICS compared with ICS alone (3 RCTs; number of children in analysis not reported; RR 3.38, 95% 0.94 to 12.15; absolute numbers not reported). However, it also carried out an indirect comparison and interactive test examining whether adding LABA to ICS increased exacerbations in children versus in adults. It found that the addition of LABA to ICS was associated with increased exacerbation rates in children compared with adults (number of RCTs and people in analysis not reported; RR 6.7; P = 0.004; absolute numbers not reported). [50]

Different dosage regimens of ICS/LABA combinations:
One RCT [65] identified by the review [62] assessed the "SMART" regimen of ICS/LABA. In the SMART regimen an ICS/LABA combination inhaler is used on an as-required basis, depending on symptoms. This differs from the conventional "fixed regimen" for ICS/LABA. The RCT (subgroup analysis of 341 children aged 4–11 years) found that the SMART regimen (once daily plus as-required budesonide/formoterol inhaler combination) was superior to the fixed-combination regimen (once daily budesonide/formoterol combination inhaler), and once daily higher dose ICS (budesonide) in terms of exacerbations and early morning peak expiratory flow. Many of the indices of symptom control (clinical measures) were similar across the three arms of the study, with the exception of night-time awakenings, which were reduced in the SMART group. The children in this RCT had mild disease (<40% had an exacerbation during the 12-month follow-up).

Deaths and asthma-related hospital admission
We found another systematic review (search date 2007), which pooled safety data from AstraZeneca-sponsored RCTs comparing formoterol versus non-LABA treatment. [66] It pooled data on 11,849 children and adolescents treated with formoterol in 41 clinical trials (about 45% of people aged <12 years, about 80% of people taking formoterol in combination with ICS). It found no significant difference in asthma-related hospital admissions between people taking formoterol and people taking non-LABA treatments. It found only one asthma-related death (in the formoterol/ICS group). [66]

OPTION ADDITION OF ORAL THEOPHYLLINE

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- When low-dose inhaled corticosteroids fail to control asthma, most older children will respond to one of the add-on options available, which include addition of long-acting beta$_2$ agonists, addition of leukotriene receptor antagonists, addition of theophylline, or increased dose of inhaled corticosteroid. However, we don't know for certain how effective these additional treatments are because we found no/limited evidence of benefit compared with adding placebo/no additional treatments.
- Although there is weak evidence that addition of theophylline to inhaled corticosteroids does improve symptom control and reduce exacerbations, theophylline should only be added to inhaled corticosteroids in children aged over 5 years when the addition of long-acting beta$_2$ agonists and leukotriene receptor antagonists have both been unsuccessful.
- Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded.

Benefits and harms

Addition of oral theophylline versus addition of placebo:

We found no systematic review but found two RCTs. [67] [68]

Symptom control (clinical assessments)

Addition of oral theophylline compared with addition of placebo Adding oral theophylline may be more effective than adding placebo to existing treatment at increasing the mean number of symptom-free days and reducing the use of additional beta$_2$ agonist (orciprenaline), but we don't know whether it is more effective at improving symptoms as recorded on diary cards in children aged 6 years or over with asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms					
[67] RCT **Crossover design**	33 children aged 6 to 19 years, recruited from a hospital asthma clinic; 22 children (mean age 13.6 years) using inhaled beclometasone (mean 533 micrograms/day), 11 children (mean age 11.8 years) using oral prednisolone	**Mean number of symptom-free days** 63% with addition of oral theophylline (serum concentration 10–20 micrograms/mL) for 4 weeks 42% with placebo Absolute numbers not reported Post-crossover results	P less-than or equal to 0.01	○○○	addition of oral theophylline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(mean 30 mg alternate days)				
[68] RCT	36 children, parallel groups, mean age 12.5 years, using inhaled corticosteroids for at least 6 months before study entry	**Symptoms (as recorded on diary cards) or use of rescue medication** with adding theophylline (10 mg/kg bodyweight) with adding placebo Absolute results not reported	Reported no significant difference between groups P value not reported	⟷	Not significant
[67] RCT **Crossover design**	33 children aged 6 to 19 years, recruited from a hospital asthma clinic; 22 children (mean age 13.6 years) using inhaled beclometasone (mean 533 micrograms/day), 11 children (mean age 11.8 years) using oral prednisolone (mean 30 mg alternate days)	**Need for inhaled beta$_2$ agonist (orciprenaline)** 0.5 doses/day with addition of oral theophylline (serum concentration 10–20 micrograms/mL) for 4 weeks 1.0 doses/day with placebo Post-crossover results	P less-than or equal to 0.01	○○○	addition of oral theophylline

Exacerbations

Addition of oral theophylline compared with addition of placebo Adding oral theophylline may be more effective than adding placebo to existing treatment at reducing the proportion of children aged 6 years or over needing additional daily prednisolone; however, evidence is weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for oral corticosteroids					
[67] RCT **Crossover design**	33 children aged 6 to 19 years, recruited from a hospital asthma clinic; 22 children (mean age 13.6 years) using inhaled beclometasone (mean 533 micrograms/day), 11 children (mean age 11.8 years) using oral prednisolone (mean 30 mg alternate days)	**Proportion of children needing additional daily prednisolone** 3/32 (9%) with addition of oral theophylline (serum concentration 10–20 micrograms/mL) for 4 weeks 10/32 (31%) with placebo Post-crossover results	P = 0.02	○○○	addition of oral theophylline

No data from the following reference on this outcome. [68]

Physiological measures

Addition of oral theophylline compared with addition of placebo We don't know whether adding oral theophylline is more effective than adding placebo to existing treatment at improving mean peak expiratory flow in children aged about 12 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Peak expiratory flow					
[68] RCT	36 children, parallel groups, mean age 12.5 years, using inhaled corticosteroids for at least 6 months before study entry	**Change in mean peak expiratory flow from baseline , 12 weeks** From 85% to 95% with adding theophylline (10 mg/kg bodyweight) Not reported with adding placebo	No between-group comparison		

No data from the following reference on this outcome. [67]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[67] RCT **Crossover design**	33 children aged 6 to 19 years, recruited from a hospital asthma clinic; 22 children (mean age 13.6 years) using inhaled beclometasone (mean 533 micrograms/day), 11 children (mean age 11.8 years) using oral prednisolone (mean 30 mg alternate days)	**Adverse effects** with addition of oral theophylline (serum concentration 10–20 micrograms/mL) for 4 weeks with placebo Short-term adverse effects included mild transient headache and nausea in 6 children after the crossover from placebo to the theophylline dose that they had previously tolerated			
[68] RCT	36 children, parallel groups, mean age 12.5 years, using inhaled corticosteroids for at least 6 months before study entry	**Adverse effects** with adding theophylline (10 mg/kg bodyweight) with adding placebo 1 child withdrew from the theophylline group with nausea and vomiting			

No data from the following reference on this outcome. [68]

Further information on studies

[67] One child was excluded from the analysis because of poor compliance. The RCT was too small and brief to comprehensively assess harms.

[68] The RCT found that serum eosinophilic cationic protein was significantly decreased from baseline with theophylline after 12 weeks, but it found no significant change from baseline with placebo (reported no between-group comparison). The RCT was too small and brief to comprehensively assess harms.

Comment: Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded. [58]

OPTION ADDITION OF ORAL LEUKOTRIENE RECEPTOR ANTAGONISTS

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- When low-dose inhaled corticosteroids fail to control asthma, most older children will respond to one of the add-on options available, which include addition of long-acting beta$_2$ agonists, addition of leukotriene receptor antagonists, addition of theophylline, or increased dose of inhaled corticosteroid. However, we don't know for certain how effective these additional treatments are because we found no/limited evidence of benefit compared with adding placebo/no additional treatments.
- Consensus suggests that younger children are likely to benefit from addition of leukotriene receptor antagonists.

Benefits and harms

Addition of oral leukotriene receptor antagonists versus addition of placebo:

We found one systematic review (search date 2003) examining the addition of leukotriene receptor antagonists to inhaled corticosteroids for chronic asthma in adults and children. It identified two RCTs in children; however, it did not present a separate analysis in children. [69] One of the RCTs was published only in abstract form and so we have not included it in this *Clinical Evidence* review. The other RCT was a crossover RCT, which compared adding oral montelukast versus adding placebo to inhaled budesonide over 4 weeks. [70] For further information on the risk of suicidality, see comment.

Symptom control (clinical assessments)

Addition of oral leukotriene receptor antagonist compared with addition of placebo We don't know whether adding oral montelukast to inhaled budesonide is more effective than adding placebo to inhaled budesonide at improving global evaluation or quality of life measurements after up to 4 weeks in children, aged 6 to 14 years, with persistent asthma who had been taking inhaled budesonide for at least 6 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom scores					
[70] RCT **Crossover design**	279 children aged 6 to 14 years previously treated with inhaled corticosteroid for at least 6 weeks, with mean FEV_1 78% predicted after 1 month run-in with budesonide 200 micrograms	**Quality of life measurements** with adding oral montelukast to inhaled budesonide over 4 weeks with adding placebo to inhaled budesonide over 4 weeks Absolute results not reported	Reported no significant difference between groups	⟷	Not significant
[70] RCT **Crossover design**	279 children aged 6 to 14 years previously treated with inhaled corticosteroid for at least 6 weeks, with mean FEV_1 78% predicted after 1 month run-in with budesonide 200 micrograms	**Global evaluations** with adding oral montelukast to inhaled budesonide over 4 weeks with adding placebo to inhaled budesonide over 4 weeks Absolute results not reported	Reported no significant difference between groups	⟷	Not significant

Exacerbations

Addition of oral leukotriene receptor antagonist compared with addition of placebo Adding oral montelukast to inhaled budesonide may be more effective than adding placebo to inhaled budesonide at reducing asthma exacerbation days, but we don't know whether it is more effective at reducing asthma attacks requiring unscheduled medical intervention or treatment with oral corticosteroid after up to 4 weeks in children, aged 6 to 14 years, with persistent asthma who had been taking inhaled budesonide for at least 6 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[70] RCT **Crossover design**	279 children aged 6 to 14 years previously treated with inhaled corticosteroid for at least 6 weeks, with mean FEV_1 78% predicted after 1 month run-in with budesonide 200 micrograms	**Asthma attacks requiring unscheduled medical intervention or treatment with oral corticosteroid** with adding oral montelukast to inhaled budesonide over 4 weeks with adding placebo to inhaled budesonide over 4 weeks Absolute results not reported	Reported no significant difference between groups	⟷	Not significant
[70] RCT **Crossover design**	279 children aged 6 to 14 years previously treated with inhaled corticosteroid for at least 6 weeks, with mean FEV_1 78% predicted after 1 month run-in with budesonide 200 micrograms	**Asthma exacerbation days (decrease from baseline peak flow of >20%, or increase from baseline of $beta_2$ agonist use of >70%)** 12% with adding oral montelukast to inhaled budesonide over 4 weeks 16% with adding placebo to inhaled budesonide over 4 weeks Absolute results not reported	P <0.001	○○○	addition of montelukast

Physiological measures

No data from the following reference on this outcome. [70]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[70] RCT **Crossover design**	279 children aged 6 to 14 years previously treated with inhaled corticosteroid for at least 6 weeks, with mean FEV_1 78% predicted after 1 month run-in with budesonide 200 micrograms	**Adverse effects (asthma exacerbation, upper respiratory tract infection, headache, cough, pharyngitis, and fever)** with adding oral montelukast to inhaled budesonide over 4 weeks with adding placebo to inhaled budesonide over 4 weeks Absolute results not reported	Reported no significant difference between groups	⟷	Not significant

Addition of oral leukotriene receptor antagonists versus increased corticosteroid dose:

We found one crossover RCT comparing addition of oral montelukast to inhaled corticosteroids versus increasing inhaled corticosteroid dose. [63]

Symptom control (clinical assessments)

Addition of oral leukotriene receptor antagonist compared with increased corticosteroid dose We don't know how effective adding montelukast to fluticasone and increased dose of fluticasone are, compared with each other, at improving the composite outcome of best response to treatment in children aged 6 to 17 years with mild to moderate asthma (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms					
[63] RCT **Crossover design** **3-armed trial**	182 children aged 6 to 17 years with mild to moderate asthma; asthma uncontrolled while receiving fluticasone (100 micrograms twice daily) The remaining arm evaluated fluticasone propionate plus long-acting beta$_2$ agonist	**Proportion of children with best response to each treatment** with fluticasone (inhaled, 100 micrograms twice daily) plus montelukast (orally, 5 mg or 10 mg once daily) with fluticasone (inhaled, 250 micrograms twice daily) Absolute results reported graphically Primary outcome: differential response based on a composite score of oral corticosteroid use, number of asthma control days, and FEV$_1$	Reported as similar for adding montelukast versus increased dose of fluticasone Significance assessment not reported		

Exacerbations

No data from the following reference on this outcome. [63]

Physiological measures

No data from the following reference on this outcome. [63]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[63] RCT **Crossover design** **3-armed trial**	182 children aged 6 to 17 years with mild to moderate asthma The remaining arm evaluated fluticasone propionate plus long-acting beta$_2$ agonist	**Adverse effects** with fluticasone (inhaled, 100 micrograms twice daily) plus montelukast (orally, 5 mg or 10 mg once daily) with fluticasone (inhaled, 250 micrograms twice daily) 2 children on high-dose inhaled corticosteroid developed oral candidiasis, compared with none on leukotriene receptor antagonist			

Addition of leukotriene receptor antagonist versus addition of long-acting beta$_2$ agonist:
See option on addition of long-acting beta$_2$ agonist, p 42 .

Further information on studies

[70] The RCT in children was brief (4 weeks of treatment). The RCT was funded by the manufacturers of montelukast.

Comment: We found two further RCTs, which did not fulfil *Clinical Evidence* inclusion criteria. However, we have included a brief comment here, because of paucity of data on this intervention in children taking inhaled corticosteroids. The first open-label RCT (84 children aged 6–14 years, on low-dose inhaled corticosteroids) compared addition of montelukast versus addition of theophylline for 4 weeks. [71] It found that additional montelukast significantly improved peak expiratory flow measurements compared with additional theophylline at 4 weeks. However, it found no significant difference between groups in inhaled beta$_2$ agonist use or in mild asthma attacks. [71]

The second RCT (194 children aged 2–14 years with asthma, about 90% currently taking inhaled corticosteroid alone or with long-acting beta$_2$ agonist) compared montelukast versus placebo in addition to usual asthma care, during what is historically know to be a time of increased exacerbation risk (September and October in the USA). It found that montelukast significantly reduced worsening asthma days compared with placebo over 45 days. The number needed to treat was not given and this study was funded by the manufacturer of montelukast. [72]

Risk of suicidality

We found one review (search date 2008,116 RCTs or open-label studies with or without a control group, 37,764 adults or children), which examined adverse effects related to suicidality with montelukast. It found only one case of suicidal ideation with montelukast in paediatric studies. This was in a 12-year-old boy with pre-existing behaviour problems in one open-label study (open-label studies: suicidal ideation: 1/1487 with montelukast *v* 0/900 with other drugs). [73]

OPTION ADDITION OF OMALIZUMAB New

- For GRADE evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic), see table, p 62 .
- Omalizumab may be indicated in the secondary care setting for older children (aged over 5 years) with poorly controlled allergic asthma despite use of intermediate- and high-dose inhaled corticosteroids once the diagnosis is confirmed and compliance and psychological issues are addressed. However, we need more data to draw firm conclusions.

Benefits and harms

Adding omalizumab versus adding placebo:

We found one systematic review (search date 2006), [74] which identified one RCT in children only, which was reported in several publications. [75] [76] [77] We found one subsequent RCT. [78]

Symptom control (clinical assessments)

Addition of omalizumab compared with addition of placebo Adding omalizumab to inhaled corticosteroid seems no more effective than adding placebo to inhaled corticosteroid at improving clinical measures of symptom control including asthma scores, dose of short-acting beta$_2$ agonist, or asthma quality of life scores, in children aged 6 to 12 years with moderate to severe allergic asthma (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom scores					
[75] RCT	334 children, aged 6 to 12 years, with moderate to severe allergic asthma, previously treated with inhaled corticosteroids and bronchodilator treatment for at least 3 months	**Asthma symptom scores , 16 weeks** with adding omalizumab (subcutaneous) to beclometasone (inhaled, stable dose for 16 weeks) with adding placebo to beclometasone (inhaled, stable dose for 16 weeks) Absolute results not reported	The RCT reported that there was little change in asthma symptom scores during the stable-corticosteroid dose phase, with minimal difference between groups Significance assessment not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT involved a stable-corticosteroid dose phase (16 weeks) followed by a corticosteroid dose-reduction phase (12 weeks); see further information on studies			
[76] RCT	334 children, aged 6 to 12 years, with moderate to severe allergic asthma, previously treated with inhaled corticosteroids and bronchodilator treatment for at least 3 months Further report of reference [75]	**Asthma quality of life, assessed by Paediatric Asthma Quality of Life Questionnaire (PAQLQ) score , 16 weeks** with adding omalizumab (subcutaneous) to beclometasone (inhaled, stable dose for 16 weeks) with adding placebo to beclometasone (inhaled, stable dose for 16 weeks) Absolute results reported graphically The RCT involved a stable-corticosteroid dose phase (16 weeks) followed by a corticosteroid dose-reduction phase (12 weeks); see further information on studies	Reported no significant difference between groups	⟷	Not significant
[76] RCT	334 children, aged 6 to 12 years, with moderate to severe allergic asthma, previously treated with inhaled corticosteroids and bronchodilator treatment for at least 3 months Further report of reference [75]	**Proportion of children with a large change (defined as a change in score >1.5) in overall PAQLQ score , 16 weeks** 9.5% with adding omalizumab (subcutaneous) to beclometasone (inhaled, stable dose for 16 weeks) 6.6% with adding placebo to beclometasone (inhaled, stable dose for 16 weeks) Absolute numbers not reported The RCT involved a stable-corticosteroid dose phase (16 weeks) followed by a corticosteroid dose-reduction phase (12 weeks); see further information on studies	Reported no significant difference between groups	⟷	Not significant
[78] RCT	627 children, aged 6 to 12 years, with moderate to severe allergic asthma that was not controlled despite at least fluticasone propionate 200 micrograms daily via dry powder inhaler, or equivalent	**Change in nocturnal asthma score from baseline , 24 weeks** –0.63 with adding omalizumab (subcutaneous) to corticosteroid (inhaled, constant dose unless adjustment for exacerbation, daily) –0.50 with adding placebo to corticosteroid (inhaled, constant dose unless adjustment for exacerbation, daily) Scale of 0 to 4, where 0 = no symptoms and 4 = breathing problems resulting in nocturnal symptoms despite use of rescue medication The RCT involved a stable-corticosteroid dose phase (24 weeks) followed by a corticosteroid dose-reduction phase (28 weeks)	P = 0.114	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[78] RCT	627 children, aged 6 to 12 years, with moderate to severe allergic asthma that was not controlled despite at least fluticasone propionate 200 micrograms daily via dry powder inhaler, or equivalent	**Reduction in number of doses of short-acting beta$_2$ agonist per day , 24 weeks** –1.3 with adding omalizumab (subcutaneous) to corticosteroid (inhaled, constant dose unless adjustment for exacerbation, daily) –1.0 with adding placebo to corticosteroid (inhaled, constant dose unless adjustment for exacerbation, daily)	P = 0.047 Reported as not significant; see further information on studies	⟷	Not significant

Exacerbations

Addition of omalizumab compared with addition of placebo Adding omalizumab to fixed-dose inhaled corticosteroid may be more effective than adding placebo to fixed-dose inhaled corticosteroid at reducing exacerbations in children aged 6 to 12 years with moderate to severe allergic asthma (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbations					
[75] RCT	334 children, aged 6 to 12 years, with moderate to severe allergic asthma, previously treated with inhaled corticosteroids and bronchodilator treatment for at least 3 months	**Proportion of children with exacerbations treated with systemic corticosteroids , 16 weeks** 28/225 (12%) with adding omalizumab (subcutaneous) to beclometasone (inhaled, stable dose for 16 weeks) 20/109 (18%) with adding placebo to beclometasone (inhaled, stable dose for 16 weeks) The RCT involved a stable-corticosteroid dose phase (16 weeks) followed by a corticosteroid dose-reduction phase (12 weeks); see further information on studies	Significance assessment not reported		
[78] RCT	627 children, aged 6 to 12 years, with moderate to severe allergic asthma that was not controlled despite at least fluticasone propionate 200 micrograms daily via dry powder inhaler, or equivalent	**Rate of clinically significant exacerbation , during 24 weeks' treatment** 0.45 with adding omalizumab (subcutaneous) to corticosteroid (inhaled, constant dose unless adjustment for exacerbation, daily) 0.64 with adding placebo to corticosteroid (inhaled, constant dose unless adjustment for exacerbation, daily) Primary outcome Exacerbation defined as worsening of symptoms requiring doubling of inhaled or oral corticosteroid for at least 3 days	RR 0.69 95% CI 0.53 to 0.90 P = 0.007	●○○	omalizumab

No data from the following reference on this outcome. [76]

Physiological measures

Addition of omalizumab compared with addition of placebo We don't know whether adding omalizumab to inhaled corticosteroid is more effective than adding placebo to inhaled corticosteroid at improving measures of pulmonary

function including peak expiratory flow (PEF), FEV_1, FVC, or forced expiratory flow between 25% and 75% of vital capacity (FEF25–75%), in children aged 6 to 12 years with moderate to severe allergic asthma (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pulmonary function					
[75] RCT	334 children, aged 6 to 12 years, with moderate to severe allergic asthma, previously treated with inhaled corticosteroids and bronchodilator treatment for at least 3 months	**Pulmonary function , 16 weeks** with adding omalizumab (subcutaneous) to beclometasone (inhaled, stable dose for 16 weeks) with adding placebo to beclometasone (inhaled, stable dose for 16 weeks) Absolute results not reported The RCT involved a stable-corticosteroid dose phase (16 weeks) followed by a corticosteroid dose-reduction phase (12 weeks); see further information on studies	The RCT reported that there was little change in peak expiratory flow (PEF), FEV_1 , FVC, or forced expiratory flow between 25% and 75% of vital capacity (FEF25–75%) during the stable-corticosteroid dose phase, with minimal difference between groups Significance assessment not reported		

No data from the following reference on this outcome. [76] [78]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[77] RCT	334 children, aged 6 to 12 years, with moderate to severe allergic asthma, previously treated with inhaled corticosteroids and bronchodilator treatment for at least 3 months Further report of reference [75]	**Total number of children with an adverse effect , 28 weeks** 201/225 (89%) with addition of omalizumab (subcutaneous) to beclometasone (inhaled, stable dose for 16 weeks, reducing dose for 12 weeks) 95/109 (87%) with addition of placebo to beclometasone (inhaled, stable dose for 16 weeks, reducing dose for 12 weeks) The RCT involved a stable-corticosteroid dose phase (16 weeks) followed by a corticosteroid dose-reduction phase (12 weeks); see further information on studies	No significant difference between groups; see further information on studies	⟷	Not significant

No data from the following reference on this outcome. [76] [78]

Further information on studies

[75] The RCT also examined the corticosteroid-sparing effects of omalizumab in a corticosteroid dose-reduction phase (final 12 weeks of the study). During the first 8 weeks of this phase, the dose of inhaled beclometasone was reduced step-wise (reduced by about 25% of the baseline dose every 2 weeks until elimination or worsening of asthma symptoms), to establish the minimum effective dose of beclometasone, which was then maintained for the final 4 weeks of the trial. The RCT found that omalizumab allowed a significantly greater reduction in corticosteroid dose compared with placebo (median reduction: 100% with omalizumab *v* 67% with placebo; P = 0.001). It also found that a significantly higher proportion of people taking omalizumab were able to stop taking inhaled corticosteroid completely without worsening asthma symptoms (55% with omalizumab *v* 39%

with placebo; P = 0.004). The RCT found that a small number of people withdrew from the trial because of needle fear.

[77] The RCT found no development of anti-omalizumab antibodies or serum sickness during the 28 weeks of the double-blind phase of the trial.

[78] All people in the RCT used fixed-dose inhaled corticosteroid for 24 weeks (constant dose unless adjustment required for exacerbation), and then used adjustable-dose inhaled corticosteroid for 28 weeks (dose reduction allowed dependent on symptoms). The RCT reported that the significance level was set at P <0.025 for all secondary outcomes to take account of multiple testing.

Comment: **Clinical guide:**
Addition of monthly infusions of omalizumab is associated with reduced inhaled corticosteroid dose and reduced exacerbations. The effect of omalizumab on pulmonary function is not known. Many of the children included in clinical trials were already in receipt of intermediate-dose inhaled corticosteroid and long-acting beta$_2$ agonist, suggesting a potential role for omalizumab in the management of moderate to severe asthma. The efficacy of omalizumab against high-dose inhaled corticosteroid and oral corticosteroids remains unknown. In children with moderate to severe asthma symptoms, issues of diagnostic accuracy, compliance with treatment, and behavioural/psychological problems need to be addressed.

GLOSSARY

Forced expiratory volume in 1 second (FEV$_1$) The volume breathed out in the first second of forceful blowing into a spirometer, measured in litres.

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

Low-quality evidence 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.

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

Orciprenaline This is known as metaproterenol in the USA; it is a non-selective beta agonist.

Peak expiratory flow rate (PEFR) The maximum rate that gas is expired from the lungs when blowing into a peak flow meter or a spirometer. It is measured at an instant, but the units are expressed as litres per minute.

Salbutamol This is known as albuterol in the USA; it is a short-acting selective beta$_2$ agonist.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Addition of omalizumab New option added. [74] [75] [76] [77] [78] Categorised as Unknown effectiveness because evidence from two RCTs, one reported in several publications, is insufficient to assess the effects of this intervention.

Corticosteroids (inhaled) New evidence added. [8] [9] [13] [14] [15] [16] [17] [20] [10] [35] [36] [37] [38] [39] [40] Categorisation unchanged (Beneficial).

Increased dose of inhaled corticosteroid New evidence added. [59] [60] [62] [63] [64] Categorisation unchanged (Unknown effectiveness) because evidence remains insufficient to assess the effects of this intervention.

Leukotriene receptor antagonists (oral) New evidence added. [14] [15] [45] [46] [35] [36] [37] [38] [39] [40] Categorisation unchanged (Likely to be beneficial).

Addition of long-acting beta$_2$ agonist New evidence added. [62] [63] [64] Categorisation changed (from Unknown effectiveness to Likely to be beneficial).

Addition of oral leukotriene receptor antagonists New evidence added, [69] which identified no new RCTs. New evidence added. [63] Existing evidence re-evaluated and categorisation changed (from Unknown effectiveness to Likely to be beneficial by consensus).

Long-acting beta$_2$ agonists New evidence added. [50] [52] [53] Categorisation changed (from Trade-off between benefits and harms to Likely to be ineffective or harmful).

Theophylline (oral) No new evidence added but existing evidence re-evaluated. Categorisation changed (from Trade-off between benefits and harms to Likely to be ineffective or harmful).

REFERENCES

1. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.[PubMed]

2. Malik G, Tagiyeva N, Aucott L, et al. Changing trends in asthma in 9-12 year olds between 1964 and 2009. *Arch Dis Child* 2011;96:227–231.[PubMed]
3. Carroll W. Asthma genetics: pitfalls and triumphs. *Paediatr Respir Rev* 2005;6:68–74.[PubMed]
4. McLeish S, Turner SW. Gene-environment interactions in asthma. *Arch Dis Child* 2007;92:1032–1035.[PubMed]
5. Park ES, Golding J, Carswell F, et al. Pre-school wheezing and prognosis at 10. *Arch Dis Child* 1986;61:642–646.[PubMed]
6. Kelly WJW, Hudson I, Phelan PD, et al. Childhood asthma in adult life: a further study at 28 years of age. *BMJ* 1987;294:1059–1062.[PubMed]
7. Calpin C, Macarthur C, Stephens D, et al. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systematic review of the literature. *J Allergy Clin Immunol* 1997;100:452–457. Search date 1996.[PubMed]
8. Rachelefsky G. Inhaled corticosteroids and asthma control in children: assessing impairment and risk.*Pediatrics* 2009;123:353–366.[PubMed]
9. Adams NP, Bestall JC, Lasserson TJ, et al. Fluticasone versus placebo for chronic asthma in adults and children. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
10. Chen Y-Z, Busse WW, Pedersen S, et al. Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: the Steroid Treatment As Regular Therapy in early asthma (START) trial. *Pediatr Allergy Immunol* 2006;17:7–13.[PubMed]
11. Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily budesonide in patients with early onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. *Ann Allergy Asthma Immunol* 2005;94:48–54.[PubMed]
12. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071–1076.[PubMed]
13. Papi A, Nicolini G, Baraldi E, et al. Regular vs prn nebulized treatment in wheeze preschool children. *Allergy* 2009;64:1463–1471.[PubMed]
14. Kooi EM, Schokker S, Marike Boezen H, et al. Fluticasone or montelukast for preschool children with asthma-like symptoms: randomized controlled trial. *Pulm Pharmacol Ther* 2008;21:798–804.[PubMed]
15. Bacharier LB, Phillips BR, Zeiger RS, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127–1135.[PubMed]
16. Carlsen KC, Stick S, Kamin W, et al. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. *Respir Med* 2005;99:1393–1402.[PubMed]
17. Gelfand EW, Georgitis JW, Noonan M, et al. Once-daily ciclesonide in children: efficacy and safety in asthma. *J Pediatr* 2006;148:377–383.[PubMed]
18. Simons FER, The Canadian Beclomethasone Diproprionate–Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol and placebo in children with asthma. *N Engl J Med* 1997;337:1659–1665.[PubMed]
19. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054–1063.[PubMed]
20. Nayak A, Lanier R, Weinstein S, et al. Efficacy and safety of beclomethasone dipropionate extrafine aerosol in childhood asthma: a 12-week, randomized, double-blind, placebo-controlled study. *Chest* 2002;122:1956–1965.[PubMed]
21. Doull IJ, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclometasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715–1719.[PubMed]
22. Sharek PJ, Bergman DA. Beclomethasone for asthma in children: effects on linear growth. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 1999.
23. Busse WW, Pedersen S, Pauwels RA, et al. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 2008;121:1167–1174.[PubMed]
24. Wolthers OD, Riis BJ, Pedersen S. Bone turnover in asthmatic children treated with oral prednisolone or inhaled budesonide. *Pediatr Pulmonol* 1993;16:341–346.[PubMed]
25. Reilly SM, Hambleton G, Adams JE, et al. Bone density in asthmatic children treated with inhaled corticosteroids. *Arch Dis Child* 2001;84:183–184.[PubMed]
26. Drake AJ, Howells RJ, Shield JPH, et al. Symptomatic adrenal insufficiency presenting with hypoglycaemia in children with asthma receiving high dose inhaled fluticasone proprionate. *BMJ* 2002;324:1081–1083.[PubMed]
27. Todd GR, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;87:457–461.[PubMed]
28. Simons FE, Persaud MP, Gillespie CA, et al. Absence of posterior subcapsular cataracts in young patients treated with inhaled corticosteroids. *Lancet* 1993;342:776–778.[PubMed]
29. Abuektish F, Kirkpatrick JN, Russell G. Posterior subcapsular cataract and inhaled steroid therapy. *Thorax* 1995;50:674–676.[PubMed]
30. Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled steroids on growth. *J Allergy Clin Immunol* 1994;93:967–976. Search date 1993.[PubMed]
31. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373–381.[PubMed]
32. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343:1064–1069.[PubMed]
33. Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date not reported.
34. Petersen R, Agertoft L, Pedersen S, et al. Treatment of exercise-induced asthma with beclomethasone dipropionate in children with asthma. *Eur Respir J* 2004;24:932–937.[PubMed]
35. Garcia Garcia ML, Wahn U, Gilles L, et al. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics* 2005;116:360–369.[PubMed]
36. Kumar V, Ramesh P, Lodha R, et al. Montelukast vs. inhaled low-dose budesonide as monotherapy in the treatment of mild persistent asthma: a randomized double blind controlled trial. *J Trop Pediatr* 2007;53:325–330.[PubMed]
37. Zeiger RS, Szefler SJ, Phillips BR, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol* 2006;117:45–52.[PubMed]
38. Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233–242.[PubMed]
39. Stelmach I, Grzelewski T, Bobrowska-Korzeniowska M, et al. A randomized, double-blind trial of the effect of anti-asthma treatment on lung function in children with asthma. *Pulm Pharmacol Ther* 2007;20:691–700.[PubMed]
40. Sorkness CA, Lemanske RF, Mauger DT, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller trial. *J Allergy Clin Immunol* 2007;119:64–72.[PubMed]
41. Knorr B, Matz J, Bernstein JA, et al. Montelukast for chronic asthma in 6–14 year old children. *JAMA* 1998;279:1181–1186.[PubMed]
42. Knorr B, Franchi LM, Bisgaard H, et al. Montelukast, a leukotriene receptor antagonist for the treatment of persistent asthma in children aged 2–5 years. *Pediatrics* 2001;108:E48.[PubMed]
43. Straub DA, Moeller A, Minocchieri S, et al. The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. *Eur Respir J* 2005;25:289–294.[PubMed]
44. Van Adelsberg J, Moy J, Wei L, et al. Safety, tolerability, and exploratory efficacy of montelukast in 6–24 month-old patients with asthma. *Curr Med Res Opin* 2005;21:971–979.[PubMed]
45. Robertson CF, Price D, Henry R, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;175:323–329.[PubMed]
46. Hakim F, Vilozni D, Adler A, et al. The effect of montelukast on bronchial hyperreactivity in preschool children. *Chest* 2007;131:180–186.[PubMed]
47. Ostrom NK, Decotiis BA, Lincourt WR, et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr* 2005;147:213–220.[PubMed]
48. Stelmach I, Bobrowska-Korzeniowska M, Majak P, et al. The effect of montelukast and different doses of budesonide in IgE serum levels and clinical parameters in children with newly diagnosed asthma. *Pulmon Pharmacol Ther* 2005;18:374–380.[PubMed]
49. Szefler SJ, Baker JW, Uryniak T, et al. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. *J Allergy Clin Immunol* 2007;120:1043–1050.[PubMed]
50. Rodrigo GJ, Moral VP, Marcos LG, et al. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. *Pulm Pharmacol Ther* 2009;22:9–19.[PubMed]
51. Weinstein S, Pearlman D, Bronsky E, et al. Efficacy of salmeterol xinafoate powder in children with chronic persistent asthma. *Ann Allergy Asthma Immunol* 1998;81:51–58.[PubMed]
52. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.[PubMed]
53. Cates CJ, Cates MJ, Lasserson TJ. Regular treatment with formoterol for chronic asthma: serious adverse events. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
54. Verberne A, Frost C, Roorda R, et al. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;156:688–695.[PubMed]
55. Pedersen S. Treatment of nocturnal asthma in children with a single dose of sustained release theophylline taken after supper. *Clin Allergy* 1985;15:79–85.[PubMed]
56. Stein MA, Krasowski M, Leventhal BL, et al. Behavioural and cognitive effects of theophylline and caffeine. *Arch Pediatr Adolesc Med* 1996;50:284–288. Search date not reported.
57. Tinkelman DG, Reed C, Nelson H, et al. Aerosol beclomethasone diproprionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64–77.[PubMed]
58. Tsiu SJ, Self TH, Burns R. Theophylline toxicity: update. *Ann Allergy* 1990;64:241–257.[PubMed]
59. Adams N, Bestall J, Jones P, et al. Beclomethasone at different doses for chronic asthma. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 1999.
60. Adams NP, Bestall JC, Jones P, et al. Fluticasone at different doses for chronic asthma in adults and children. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
61. Verberne A, Frost C, Duiverman E, et al. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. *Am J Respir Crit Care* Med 1998;158:213–219.[PubMed]
62. Ni Chroinin M, Lasserson TJ, Greenstone I, et al. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
63. Lemanske RF, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975–985.[PubMed]
64. Gappa M, Zachgo W, von Berg A, et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). *Pediatr Pulmonol* 2009;44:1132–1142.[PubMed]

65. Bisgaard H, Le Roux P, Bjamer D, et al. Budesonide/formoterol maintenance plus reliver therapy: a new strategy in pediatric asthma. *Chest* 2006;130:1733–1743.[PubMed]
66. Price JF, Radner F, Lenney W, et al. Safety of formoterol in children and adolescents: experience from asthma clinical trials. *Arch Dis Child* 2010;95:1047–1053.[PubMed]
67. Nassif EG, Weinberger M, Thompson R, et al. The value of maintenance theophylline in steroid dependent asthma. *N Engl J Med* 1981;304:71–75.[PubMed]
68. Suessmuth S, Freihorst J, Gappa M. Low-dose theophylline in childhood asthma: a placebo-controlled, double-blind study. *Pediatr Allergy Immunol* 2003;14:394–400.[PubMed]
69. Ducharme F, Schwartz Z, Hicks G, et al. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003.
70. Simons FER, Villa JR, Lee BW, et al. Montelukast added to budesonide in children with persistent asthma: a randomized double blind crossover study. *J Pediatr* 2001;138:694–698.[PubMed]
71. Kondo N, Katsunuma T, Odajima Y, et al. A randomized open-label comparative study of montelukast versus theophylline added to inhaled corticosteroid in asthmatic children. *Allergol Int* 2006;55:287–293.[PubMed]
72. Johnston NW, Mandhane PJ, Dai J, et al. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007;120:e702–e712.[PubMed]
73. Philip G, Hustad C, Noonan G, et al. Reports of suicidality in clinical trials of montelukast. *J Allergy Clin Immunol* 2009;124:691–696.[PubMed]
74. Walker S, Monteil M, Phelan K, et al. Anti-IgE for chronic asthma in adults and children. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
75. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001;108:E36.[PubMed]
76. Lemanske RF, Nayak A, McAlary M, et al. Omalizumab improves asthma-related quality of life in children with allergic asthma. *Pediatrics* 2002;110:e55.[PubMed]
77. Berger W, Gupta N, McAlary M, et al. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003;91:182–188.[PubMed]
78. Lanier B, Bridges T, Kulus M, et al. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009;124:1210–1216.[PubMed]

Stephen William Turner
Senior Clinical Lecturer in Child Health and Honorary Consultant Paediatrician
University of Aberdeen
Aberdeen
UK

Amanda Jane Friend
University of Aberdeen
Aberdeen
UK

Augusta Okpapi
Speciality Trainee in Paediatrics
Royal Aberdeen Children's Hospital
Aberdeen
UK

Competing interests: SWT, AJF, and AO declare that they have no competing interests.
We would like to acknowledge the previous contributors of this review: Duncan Keeley and Michael McKean.

Disclaimer

GRADE **Evaluation of interventions for Asthma and other recurrent wheezing disorders in children (chronic).**

Important outcomes	Exacerbations, Physiological measures, Symptom control (clinical assessments)								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of single-agent prophylaxis in children taking as-needed inhaled beta$_2$ agonists for asthma?									
<30 (<5230) [7] [9] [13] [14] [15] [16] [17] [18] [19] [20]	Symptom control (clinical assessments)	Inhaled corticosteroids versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
16 (<4103) [7] [10] [18] [19] [20]	Exacerbations	Inhaled corticosteroids versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
10 (<3101) [7] [14] [17] [18] [19] [20]	Physiological measures	Inhaled corticosteroids versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (<1852) [14] [15] [41] [42] [43] [44] [45] [46]	Symptom control (clinical assessments)	Oral leukotriene receptor antagonists versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes and between studies
5 (<1564) [14] [41] [42] [44] [45]	Exacerbations	Oral leukotriene receptor antagonists versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes and between studies
4 (<449) [14] [41] [43] [46]	Physiological measures	Oral leukotriene receptor antagonists versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes and between studies
8 (<2179) [14] [15] [47] [48] [35] [36] [37] [40]	Symptom control (clinical assessments)	Oral leukotriene receptor antagonists versus inhaled corticosteroids	4	0	–1	–2	0	Very low	Consistency point deducted for different results for different outcomes, time points, and for different corticosteroids. Directness points deducted for no direct statistical comparison between groups in some RCTs and composite outcomes used
4 (<1765) [47] [35] [38] [40]	Exacerbations	Oral leukotriene receptor antagonists versus inhaled corticosteroids	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups in some RCTs
8 (<2086) [14] [47] [48] [35] [38] [39] [36] [40]	Physiological measures	Oral leukotriene receptor antagonists versus inhaled corticosteroids	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes, time points, and for different corticosteroids
2 (367) [18] [51]	Symptom control (clinical assessments)	Inhaled long-acting beta$_2$ agonist versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different studies and outcomes
unclear how many RCTs (unclear how many children) [50]	Exacerbations	Inhaled long-acting beta$_2$ agonist versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and uncertainty about the number of children or RCTs included in analysis. Directness point deducted for inclusion of studies in which some children were taking additional medications for asthma

Important outcomes	Exacerbations, Physiological measures, Symptom control (clinical assessments)								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (367) [18] [51]	Physiological measures	Inhaled long-acting beta$_2$ agonist versus placebo	4	0	0	0	0	High	
2 (228) [18] [54]	Symptom control (clinical assessments)	Inhaled long-acting beta$_2$ agonists versus inhaled corticosteroids	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups
2 (228) [18] [54]	Exacerbations	Inhaled long-acting beta$_2$ agonists versus inhaled corticosteroids	4	0	0	–1	0	Moderate	Directness point deducted for no direct statistical comparison between groups
2 (228) [18] [54]	Physiological measures	Inhaled long-acting beta$_2$ agonists versus inhaled corticosteroids	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups
1 (24) [55]	Symptom control (clinical assessments)	Oral theophylline versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and crossover design. Directness points deducted for uncertainty about other treatments used and restricted population (high number of night-time awakenings due to asthma before randomisation)
1 (24) [55]	Exacerbations	Oral theophylline versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and crossover design. Directness points deducted for uncertainty about other treatments used and restricted population (high number of night-time awakenings due to asthma before randomisation)
1 (24) [55]	Physiological measures	Oral theophylline versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and crossover design. Directness points deducted for uncertainty about other treatments used and restricted population (high number of night-time awakenings due to asthma before randomisation)
1 (195) [57]	Symptom control (clinical assessments)	Oral theophylline versus inhaled corticosteroids	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and subgroup analysis. Directness point deducted for uncertainty about clinical significance of effect due to low symptom scores in this study
1 (195) [57]	Exacerbations	Oral theophylline versus inhaled corticosteroids	4	–3	0	0	0	Very low	Quality points deducted for sparse data, subgroup analysis, and incomplete reporting of results
1 (195) [57]	Physiological measures	Oral theophylline versus inhaled corticosteroids	4	–3	0	0	0	Very low	Quality points deducted for sparse data, subgroup analysis, and incomplete reporting of results
What are the effects of additional prophylactic treatments in childhood asthma inadequately controlled by standard-dose inhaled corticosteroids?									
1 (117) [61]	Symptom control (clinical assessments)	Increased dose of inhaled corticosteroid versus low-dose corticosteroid	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups
3 (1000) [60] [61]	Exacerbations	Increased dose of inhaled corticosteroid versus low-dose corticosteroid	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes	Exacerbations, Physiological measures, Symptom control (clinical assessments)								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (993) [60] [61]	Physiological measures	Increased dose of inhaled corticosteroid versus low-dose corticosteroid	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results between studies and outcomes
4 (1119) [62]	Symptom control (clinical assessments)	Addition of long-acting beta$_2$ agonist versus addition of placebo to inhaled corticosteroid	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (1084) [62]	Exacerbations	Addition of long-acting beta$_2$ agonist versus addition of placebo to inhaled corticosteroid	4	0	0	0	0	High	
9 (1235) [62]	Physiological measures	Addition of long-acting beta$_2$ agonist versus addition of placebo to inhaled corticosteroid	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (465) [63] [64]	Symptom control (clinical assessments)	Addition of long-acting beta$_2$ agonist versus increased dose of corticosteroid	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and crossover design of 1 RCT. Directness point deducted for composite outcome used in 1 RCT
3 (724) [62] [64]	Exacerbations	Addition of long-acting beta$_2$ agonist versus increased dose of corticosteroid	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no statistical comparison between groups in 1 RCT
at least 5 (at least 1285) [62] [64]	Physiological measures	Addition of long-acting beta$_2$ agonist versus increased dose of corticosteroid	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes
1 (<182) [63]	Symptom control (clinical assessments)	Addition of long-acting beta$_2$ agonist versus addition of leukotriene receptor antagonist	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting, and crossover design. Directness point deducted for use of composite outcome
2 (69) [67] [68]	Symptom control (clinical assessments)	Addition of oral theophylline versus addition of placebo	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, results after crossover, and incomplete reporting of results. Directness points deducted for regular use of oral corticosteroids instead of inhaled corticosteroids and no direct statistical comparison between groups in 1 RCT
1 (32) [67]	Exacerbations	Addition of oral theophylline versus addition of placebo	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and results after crossover. Directness points deducted for regular use of oral corticosteroids instead of inhaled corticosteroids and no direct statistical comparison between groups
1 (36) [68]	Physiological measures	Addition of oral theophylline versus addition of placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups
1 (279) [70]	Symptom control (clinical assessments)	Addition of oral leukotriene receptor antagonists versus addition of placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and results after crossover. Directness point deducted for no long-term results

Important outcomes	Exacerbations, Physiological measures, Symptom control (clinical assessments)								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (279) [70]	Exacerbations	Addition of oral leukotriene receptor antagonists versus addition of placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and results after crossover. Directness point deducted for no long-term results
1 (<182) [63]	Symptom control (clinical assessments)	Addition of oral leukotriene receptor antagonists versus increased corticosteroid dose	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting, and crossover design. Directness point deducted for use of composite outcome
2 (961) [75] [76] [78]	Symptom control (clinical assessments)	Adding omalizumab versus adding placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results in 1 RCT
2 (961) [75] [78]	Exacerbations	Adding omalizumab versus adding placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups in 1 RCT
1 (334) [75]	Physiological measures	Adding omalizumab versus adding placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.