Leukotriene receptor antagonist for prolonged non-specific cough in children (Review)

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[Intervention Review]

Leukotriene receptor antagonist for prolonged non-specific cough in children

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ABSTRACT

Background

Non-specific cough is defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology. It is commonly seen in paediatric practice. These children are treated with a variety of therapies including a variety of asthma medications. The leukotriene pathway is reported to be involved in the sensory (neurogenic) pathway, which is a mechanism thought to be involved in the pathogenesis of chronic cough.

Objectives

To evaluate the effectiveness of leukotriene receptor antagonist (LTRA) in treating children with prolonged non-specific cough.

Search methods

The Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Airways Group Specialised Register, MEDLINE and EMBASE databases were searched by the Cochrane Airways Group. The latest searches were carried out in October 2010.

Selection criteria

All randomised controlled trials comparing LTRA with a placebo medication in children with non-specific cough.

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. Two eligible trials that utilised montelukast were identified but no data was available for meta-analysis. It was not possible to separate results from children with non-specific cough from those without in one study and in the second, the groups were very small (5 in montelukast group and one in placebo group).

Main results

There was no significant difference in all study endpoints between the montelukast and placebo groups (total N=256 plus 6 from second study).

Authors' conclusions

With the lack of evidence, the routine use of LRTA in treating children with non-specific cough cannot be recommended.

PLAIN LANGUAGE SUMMARY

Leukotriene receptor antagonist for prolonged non-specific cough in children

Children with non-specific cough (dry and non-productive cough without any other respiratory symptom, sign or systemic illness) are commonly treated with a variety of medications to treat the symptom of cough. This review examined whether there was any evidence for using leukotriene receptor antagonist in children with non-specific cough. There were two randomised controlled trials that included, but was not restricted to, children with non-specific cough, whereby no significant advantage over placebo was found in both studies. There is no RCT evidence to support the routine use of leukotriene receptor antagonist for the symptom of non-specific cough in children. Further research examining the effects of this treatment using child appropriate cough outcome measures is needed.

BACKGROUND

Cough is the most common symptom presenting to general practitioners (Britt 2002; Cherry 2003) and causes significant anxiety to parents (Cornford 1993). Worldwide the desire to reduce the impact of the symptom of cough is reflected in the billions of dollars spent on over the counter cough and cold medications. Non-specific cough has been defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology (Chang 2001). While some children with chronic non-specific cough have asthma, the majority do not (McKenzie 1994; Chang 1999). In adults, chronic cough is defined as cough of over 8 weeks duration but the definition commonly accepted in children is that of over 3-4 weeks, based on the known differences between paediatric and adults cough (Chang 2005b).

The leukotriene pathway is reported to be involved in the sensory (neurogenic) pathway (Ishikawa 1996) which is a key mechanism thought to be involved in the pathogenesis of chronic cough (Mazzone 2004; Widdicombe 1995). Although leukotriene receptor antagonists (LTRA) are now primarily used for asthma, they have also been shown to reduce respiratory symptoms associated with post respiratory syncytial virus (RSV) infection (Bisgaard 2003). The influence of LTRA in post RSV bronchiolitis is likely through the effect of LTRA on the neurogenic pathway, as demonstrated in animal work (Wedde-Beer 2002). While post RSV bronchiolitis symptoms do not constitute non-specific cough, a similar mechanism involving the neurogenic pathway maybe involved in the pathophysiology of chronic non-specific cough. Thus it is biologically plausible that LTRA may be beneficial in non-specific cough (separate to its anti-asthma properties) through its action on the neurogenic pathway. However like all medications, use of LTRAs may cause adverse events. A systematic review of the benefits (or otherwise) of LTRA on chronic non-specific cough would thus be useful to help guide clinical practice.

OBJECTIVES

To evaluate the effectiveness of LTRA in treating children with prolonged non-specific cough.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing LTRA with a placebo medication with cough as an outcome, where cough is not primarily related to an underlying respiratory disorder such as cystic fibrosis, asthma, suppurative lung disease etc.

Types of participants

Children with chronic (>4 weeks) non-specific cough (dry and non-productive cough without any other respiratory symptom, sign or systemic illness).

Exclusion criteria: cough related to mycoplasma, pertussis and chlamydia, presence of underlying cardio-respiratory condition,

current or recurrent wheeze (>2 episodes), presence of other respiratory symptoms (productive or wet cough (Chang 2005a), haemoptysis, dyspnoea), presence of other respiratory signs (clubbing, chest wall deformity, respiratory noises such as wheeze on auscultation and other adventitious sounds), presence of any sign of systemic illness (failure to thrive, aspiration, neurological or developmental abnormality), presence of lung function abnormality.

Types of interventions

All randomised controlled comparisons of any type of LTRA. Trials only comparing two or more medications without a placebo comparison group will not be included. Trials that included the use of other medications or interventions were to be included if all participants had equal access to such medications or interventions.

Types of outcome measures

Primary outcomes

Proportions of participants who were not cured or not substantially improved at follow up (clinical failure).

Secondary outcomes

1. Proportions of participants who were not cured at follow up,
2. Proportions of participants who not substantially improved at follow up,
3. Mean difference in cough indices (cough diary, cough frequency, cough scores),
4. Proportions experiencing adverse effects of the intervention, (e.g. seizures, school performance etc),
5. Proportions experiencing complications e.g. requirement for medication change, etc.

The proportions of participants who failed to improve on treatment and the mean clinical improvement were to be determined using the following hierarchy of assessment measures (i.e. where two or more assessment measures are reported in the same study, the outcome measure that is listed first in the hierarchy would have been used).

i) Objective measurements of cough indices (cough frequency, cough receptor sensitivity).

ii) Symptomatic (Quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the patient (adult or child)

iii) Symptomatic (Quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the parents/carers.

iv) Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by clinicians.

v) Relevant airway markers consistent with inflammation.

Search methods for identification of studies

The latest searches were carried out in October 2010.

Electronic searches

The following topic search strategy was used to identify the relevant randomised controlled trials listed on the electronic databases: "cough" OR "bronchitis", all as (textword) or (MeSH) AND "leukotriene receptor" OR "leukotrienes" OR "montelukast" OR "LTRA" OR "zafirlukast", OR "pranlukast"; all as (textword) or (MeSH) (see Appendix 1)

Trials were identified from the following sources:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (to search date)
2. The Cochrane Airways Group Specialised Register (all years)
3. MEDLINE (1966 to search date). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
4. OLDMEDLINE (1950 to 65). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
5. EMBASE (1980 to search date).Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.

Searching other resources

1. The list of references in relevant publication
2. Written communication with the authors of trials included in the review.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, two reviewers (AC, DW) independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, reviewers independently selected trials for inclusion. Agreement would have been measured using kappa statistics. Disagreement would have been resolved by third party adjudication (JA).

Data extraction and management

Trials that satisfied the inclusion criteria were reviewed and the following information was recorded: study setting, year of study, source of funding, patient recruitment details (including number

of eligible subjects), inclusion and exclusion criteria, other symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of intervention, duration of therapy, co-interventions, numbers of patients not followed up, reasons for withdrawals from study protocol (clinical, side-effects, refusal and other), details on side-effects of therapy, and whether intention-to-treat analyses were possible. Data was extracted on the outcomes described previously. Further information was requested from the authors of the single included study (van Adelsberg 2005)

Assessment of risk of bias in included studies

Rias of bias table in Revman was utilised. Aditionally quality assessment of the study included was independently performed by two reviewers (AC, JA). Four components of quality were assessed:

1. Allocation concealment. Trials were scored as: Grade A: Adequate concealment, Grade B: Unclear, Grade C: Clearly inadequate concealment. (Grade A = high quality).
2. Blinding. Trials were scored as: Grade A: Participant and care provider and outcome assessor blinded, Grade B: Outcome assessor blinded, Grade C: Unclear, Grade D: No blinding of outcome assessor (Grade A, B = high quality).
3. Reporting of participants by allocated group. Trials were scored as: Grade A: The progress of all randomised children in each group described, Grade B: Unclear or no mention of withdrawals or dropouts, Grade C: The progress of all randomised children in each group clearly not described. (Grade A = high quality).
4. Follow-up. Trials were scored as: Grade A: Outcomes measured in >90% (where withdrawals due to complications and side-effects are categorised as treatment failures), Grade B: Outcomes measured in 80-90%, Grade C: Unclear, Grade D: Outcomes measured in <80%. (Grade A = high quality).

While only the allocation concealment quality assessment would have been displayed in the meta-analysis figures, all assessments were included in the 'Characteristics of included studies' table.

Measures of treatment effect

It was planned that the dichotomous outcome variables of each individual study, relative and absolute risk reductions will be calculated using a modified intention-to-treat analysis. This analysis would have assumed that children not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies of all the individually analysed studies to examine whether pooling of results (meta-analysis) would have been reasonable was planned. This would have taken into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

Data synthesis

The results from studies that met the inclusion criteria and reported any of the outcomes of interest would have been included in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed-effect model) would have been calculated (Cochrane statistical package, RevMan 4.2). For cross-over studies, mean treatment differences would have been calculated from raw data, extracted or imputed and entered as fixed effects generic inverse variance (GIV) outcome, to provide summary weighted differences and 95% confidence intervals. In cross-over trials, only data from the first arm would have been included in meta analysis if data is combined with parallel studies (Elbourne 2002). Numbers needed to treat (NNT) would have been calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2003). The cough indices would have been assumed to be normally distributed continuous variables so the mean difference in outcomes could be estimated (weighted mean difference). If studies reported outcomes using different measurement scales, the standardised mean difference would have been estimated. Any heterogeneity between the study results would have been described and tested to see if it reached statistical significance using a chi-squared test. The 95% confidence interval estimated using a random-effects model would have been included whenever there are concerns about statistical heterogeneity.

Subgroup analysis and investigation of heterogeneity

An a priori sub-group analysis was planned for children aged less than seven years and seven years and above.

Sensitivity analysis

Sensitivity analyses were planned to assess the impact of the potentially important factors on the overall outcomes:

a) study quality;
b) study size;
c) variation in the inclusion criteria;
d) differences in the medications used in the intervention and comparison groups;
e) differences in outcome measures;
f) analysis using random effects model;
g) analysis by 'treatment received';
h) analysis by 'intention-to-treat'; and

RESULTS

Description of studies

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

Results of the search

The Airways Group Specialised Register/search identified 226 potentially relevant titles in the original search (2005). After assessing the abstracts, 24 papers were retrieved and five potential studies were considered (see Characteristics of excluded studies). For the 2006 and 2007 updates, a further 62 and 40 abstracts were reviewed but no study fulfilled inclusion criteria. The 2008 search identified 63 abstracts of which 5 were obtained but none fulfilled inclusion criteria. The 2009 search identified 62 potential studies from which 9 papers were fully reviewed and only one study (Kooi 2008) had subjects that fulfilled inclusion criteria. Of the 54 potential titles in the 2010 search, 4 papers were described in the 'excluded studies' list.

Two studies (van Adelsberg 2005, Kooi 2008) fulfilled the eligibility criteria. Although the term 'asthma symptoms' which included cough was an inclusion criteria in the first included study (van Adelsberg 2005), it is likely that a number of children would not have fulfilled study criteria of non-specific cough. Data were sought from the corresponding author of the trial but none was received. The study was designed primarily for safety and tolerability of montelukast but analysis included clinical efficacy (see Characteristics of included studies). The study was supported and reported by a commercial interest. The second study (Kooi 2008) included children with cough alone and hence fulfilled inclusion criteria. Raw data provided by the primary author revealed 11 children were in the 'cough only' subgroup of which only 6 (5 in montelukast group and one in placebo group) could be included for this review.

Risk of bias in included studies

Both studies (van Adelsberg 2005, Kooi 2008) scored 'high quality' in two categories of the Quality Assessment scale. See also 'risk of bias table'

Effects of interventions

One study included 256 randomised subjects (van Adelsberg 2005). There was no difference in all study endpoints between the montelukast and placebo groups. As it was not possible to separate children with non-specific cough from those without, no data have been presented in the MetaView. Cough was not reported as an outcome measure, thus cough-specific related outcomes cannot be described. Clinical adverse events were also not different between groups and no serious adverse events occurred in either group. The second study (Kooi 2008) included in this review had a subgroup that fulfilled the criteria (cough only). Relevant data obtained from the raw results provided by the primary data are displayed in the analysis were but the effect of the intervention could not be estimated as the sample size was too small (n=6).

DISCUSSION

Two randomised controlled trial comparing LTRA with a placebo in children with non-specific cough were identified. These studies were included as the inclusion criteria included children with isolated cough (van Adelsberg 2005, Kooi 2008). The authors included symptoms described as 'asthma symptoms' but it is highly controversial if the diagnosis of asthma can be made in the age group (6-24 months) studied (Strunk 2002). However it is likely that only some of the children in the study would have fulfilled the study criteria.

No difference between groups was found in both clinical efficacy or in adverse events in both studies (van Adelsberg 2005, Kooi 2008). In comparison to RCTs in adults (Dicpinigaitis 2002, Spector 2004) using LTRA for cough outcomes whereby LTRAs were found to be effective, this review is inconclusive despite the significantly larger sample size (n=256) in the included study (van Adelsberg 2005) when compared to the study in adults (Dicpinigaitis 2002, Spector 2004) (n= 8 and 14 respectively).

A single cohort study (Kopriva 2004) was also found whereby the time to response was within 3 weeks (mainly within 2 weeks). However this has to interpreted in the context of methodological problems in studies with cough as an outcome measure, specifically the large placebo effect, biased subjective reporting, and period effect (Chang 1999). Given the morbidity associated with chronic cough in children, there is a need for the evaluation of the efficacy of LTRA on non-specific cough in children.

AUTHORS' CONCLUSIONS

Implications for practice

With the lack of evidence, the routine use of LRTA in treating children with non-specific cough cannot be recommended. If LTRA were to be trialled in these children, current cohort data suggest a clinical response (subjective cough severity) usually occurs within two weeks of therapy and definitely within three weeks.

Implications for research

Randomised controlled trials of LTRA to determine the effectiveness in treating children with non-specific cough are clearly needed. Trials should be parallel studies and double blinded, given the known problems in studying cough, specifically the large placebo and time period effects (Chang 1999). Based on cohort data, a short trial of three weeks would suffice. Outcome measures

for the clinical studies on cough should be clearly defined using validated subjective data (including quality of life) and supported by objective data if possible.

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REFERENCES

References to studies included in this review

Kooi 2008 ***{published and unpublished data}***
Kooi EM, Schokker S, Marike Boezen H, de Vries TW, Vaessen-Verberne AA, van der Molen T, Duiverman EJ. Fluticasone or montelukast for preschool children with asthma-like symptoms: Randomized controlled trial. *Pulmonary Pharmacology & Therapeutics* 2008;**21**:798–804.

van Adelsberg 2005 ***{published data only}***
van Adelsberg J, Moy J, Wei LX, Tozzi CA, Knorr B, Reiss TF. Safety, tolerability, and exploratory efficacy of montelukast in 6- to 24-month-old patients with asthma. *Current Medical Research and Opinion* 2005;**21**(6):971–9.

References to studies excluded from this review

Bisgaard 2003 ***{published data only}***
Bisgaard H. A randomized trial of montelukast in respiratory syncytial virus post-bronchiolitis. *American Journal of Respiratory & Critical Care Medicine* 2003;**167**(3):379–83.

Dicpinigaitis 1999 ***{published data only}***
Dicpinigaitis PV. Effect of zafirlukast, a leukotriene-receptor antagonist, on cough reflex sensitivity in healthy volunteers. *Current Therapeutic Research, Clinical & Experimental* 1999; **60**(1):15–19.

Dicpinigaitis 2002 ***{published data only}***
Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *Journal of Asthma* 2002;**39**(4): 291–7.

Ghosh 2006 ***{published data only}***
Ghosh G, Manglik AK, Roy S. Efficacy and safety of montelukast as monotherapy in children with mild persistent asthma. *Indian Pediatrics* 2006;**43**:780–5.

Hallstrand 2002 ***{published data only}***
Hallstrand TS, Moody MW, Wurfel MM, Schwartz LB, Henderson WR, Aitken ML. Inflammatory basis of exercise-induced bronchoconstriction. *American Journal of Respiratory and Critical Care Medicine.* 2005;**172**(6): 679–86.

He 2009 ***{published data only}***
He ZM, Guo YB, Xie CM. Effect of leukotriene receptor antagonist on cough variant asthma. *Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University* 2009; **29**(4):694–6.

Jung 2006 ***{published data only}***
Jung J, Lee J, Kim J. Treatment of inhaled corticosteroid and leukotriene receptor antagonist in Korean young cough variant asthma children [Abstract]. *Journal of Allergy and Clinical Immunology* 2006;**117**(2 Suppl 1):S93.

Kawai 2008 ***{published data only}***
Kawai S, Baba K, Matsubara A, Shiono H, Okada T, Yamaguchi E. The efficacy of montelukast and airway mast cell profiles in patients with cough variant asthma. *Journal of Asthma* 2008;**45**:243–50.

Kita 2010 ***{published data only}***
Kita T, Fujimura M, Ogawa H, Nakatsumi Y, Nomura S, Ishiura Y, Myou S, Nakao S. Antitussive effects of the leukotriene receptor antagonist montelukast in patients with cough variant asthma and atopic cough. *Allergology International* 2010;**59**(2):185–192.

Kopriva 2004 ***{published data only}***
Kopriva F, Sobolova L, Szotkowska J, Zapalka M. Treatment of chronic cough in children with montelukast,a leukotriene receptor antagonist. *Journal of Asthma* 2004;**41**(7):715–20.

Kowal 2006 ***{published data only}***
Kowal K, Zukowski S, DuBuske LM, Bodzenta-Lukaszyk A. Montelukast and budesonide therapy of asthmatic patients suffering from chronic cough. *European Respiratory Journal* 2006;**28**(Suppl 50):440s [P2563].

Lehtimaki 2009 ***{published data only}***
Lehtimaki L, Petays T, Haahtela T. Montelukast is not effective in controlling allergic symptoms outside the airways: A randomised double-blind placebo-controlled crossover study. *International Archives of Allergy and Immunology* 2009;**149**:150–153.

Proesmans 2009 ***{published data only}***
Proesmans M, Sauer K, Govaere E, Raes M, De Bilderling G, De Boeck K. Montelukast does not prevent reactive airway disease in young children hospitalized for RSV bronchiolitis. *Acta Paediatrica* 2009;**98**(11):1830–4.

Shimonda 2006 ***{published data only}***
Shimonda TT, Kishikawa RR, Shoji SS, Nishima SS. Efficacy of airway anti-inflammatory treatments evaluated with airway inflammation markers in patients with cough

variant asthma budesonide versus montelukast [Abstract].. *Journal of Allergy and Clinical Immunology* 2006;**117**(2 Suppl 1):S176.

Spector 2004 ***{published data only}***
Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. *Annals of Allergy, Asthma & Immunology* 2004;**93**(3):232–6.

Yamaguchi 2009 ***{published data only}***
Yamaguchi M, Niimi A, Matsumoto H, Ito I, Jinnai M, Otsuka K. et al.Comparative effects of low-and high-dose budesonide and montelukast in patients with cough variant asthma [abstract]. *Am J Respir Crit Care Med* 2009;**179**: A2314.

Zedan 2009 ***{published data only}***
Zedan M, Gamil N, El-Chennawi F, Maysara N, Hafeez HA, Nasef N, Fouda A. Evaluation of different asthma phenotype responses to montelukast versus fluticasone treatment. *Pediatric Asthma, Allergy and Immunology* 2009; **22**:63–68.

Additional references

Britt 2002
Britt H, Miller GC, Knox S, Charles J, Valenti L, Henderson J, et al.Bettering the evaluation and care of health - a study of general practice activity. AIHW Cat. No. GEP-10. Australian Institute of Health and Welfare, 2002.

Cates 2003
Cates C. Visual Rx. Online NNT Calculator.. http://www.nntonline.net/: Cates C, 2003.

Chang 1999
Chang AB. Cough, cough receptors, and asthma in children. *Pediatric Pulmonology* 1999;**28**(1):59–70.

Chang 2001
Chang AB, Asher MI. A review of cough in children. *Journal of Asthma* 2001;**38**(4):299–309.

Chang 2005a
Chang AB, Gaffney JT, Eastburn MM, Faoagali J, Cox NC, Masters IB. Cough quality in children: a comparison of subjective vs. bronchoscopic findings. *Respiratory Research* 2005;**6**(1):3.

Chang 2005b
Chang AB. Cough: are children really different to adults?. *Cough* 2005;**1**:7.

Cherry 2003
Cherry DK, Burt CW, Woodwell DA. National Ambulatory Medical Care Survey: 2001 summary. *Advance Data* 2003; **11**(337):1–44.

Cornford 1993
Cornford CS, Morgan M, Ridsdale L. Why do mothers consult when their children cough?. *Family Practice* 1993; **10**(2):193–6.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Ishikawa 1996
Ishikawa J, Ichinose M, Miura M, Kageyama N, Yamauchi H, Tomaki M, et al.Involvement of endogenous tachykinins in LTD4-induced airway responses. *European Respiratory Journal* 1996;**9**(3):486–92.

Mazzone 2004
Mazzone SB. Sensory regulation of the cough reflex. *Pulmonary Pharmacology & Therapeutics* 2004;**17**(6):361–8.

McKenzie 1994
McKenzie S. Cough - but is it asthma?. *Archives of Disease in Childhood* 1994;**70**(1):1–2.

Strunk 2002
Strunk RC. Defining asthma in the preschool-aged child. *Pediatrics* 2002;**109**(2 Suppl):357–61.

Wedde-Beer 2002
Wedde-Beer K, Hu C, Rodriguez MM, Piedimonte G. Leukotrienes mediate neurogenic inflammation in lungs of young rats infected with respiratory syncytial virus. *American Journal of Physiology. Lung Cellular and Molecular Physiology.* 2002;**282**(5):L1143–50.

Widdicombe 1995
Widdicombe JG. Neurophysiology of the cough reflex. *European Respiratory Journal* 1995;**8**(7):1193–202.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Kooi 2008

Methods	Multicenter, randomized, placebo-controlled, double-blind, double-dummy parallel trial ICS or LTRA use was not allowed for a period of 4 weeks preceding the trial. Other exclusion criteria were as follows: use of systemic corticosteroids in the last 2 months; hospitalization for asthma-related symptoms in the last 2 weeks; respiratory disorders other than asthma and poorly controlled systemic diseases. Subsequently, eligible children entered a run-in period of 2 weeks in which the caregivers of the child recorded their child's respiratory symptoms in a diary. Children with symptoms on less than 4 days of the 2-week run-in period or children who used anti-inflammatory medication in this period were excluded at the second visit Quality Assessment: B, A, A, B; high quality score of 2.
Participants	Children were recruited from three outpatient clinics (secondary care) in The Netherlands. Children aged 2-5 years with asthma-like symptoms (wheeze, cough and/or shortness of breath) of sufficient severity to justify the use of prophylactic asthma treatment were eligible for inclusion.63 aged 2-6 years with asthma-like symptoms were included Number of participants in whole study: Fluticasone (n=25), Montelukast (n=18) or placebo (n=20). Mean age (years and SD) in respective groups were 3.8 (71.4) 3.9 (71. 1) and 3.8 (71.3) respectively Number of 'cough only' participants in study: Fluticasone (n=5), Montelukast (n=5) or placebo (n=1)
Interventions	Fluticasone (100 ug twice daily via metered dose inhaler and a spacer (Aerochamber)), Montelukast (4mg daily) or placebo (dummy MDI and dummy tablet) for 3 months
Outcomes	The primary outcome was the daily symptom score (wheeze, cough, shortness of breath) as recorded by caregivers in a symptom diary card which were filled out twice daily during the run-in period and 1 month prior to each follow-up visit. Parents rated their child's night-time and day-time symptoms (cough, wheeze and shortness of breath) on a scale from 0 (no symptoms) to 3 (severe symptoms) each morning and evening. Thus, the total daily symptom score ranged from 0 to 18 Secondary endpoints were rescue medication free days, blood eosinophils and lung function (interrupter technique and forced oscillation technique (FOT)). Data on rescue medication use were derived from the dairy card. The percentage of days on which no rescue medication (salbutamol) was used was calculated. Eosinophils were measured in venous blood at baseline and after 3 months. Lung function was measured using two non-invasive techniques: the interrupter technique and the FOT Adverse events and concomitant medication use were obtained from the diary card
Notes	Raw data relevant to children with cough and no wheeze were kindly provided by Dr Kooi

Kooi 2008 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not described in paper
Blinding? All outcomes	Yes	Double blinded, double dummy trial
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs and reasons provided
Free of selective reporting?	Yes	
Free of other bias?	Yes	Baseline data for groups (montelukast vs placebo) were similar. Study supported by Merck Sharp and Dohme (manufacturer of montelukast) but authors had no financial conflicts of interest

van Adelsberg 2005

Methods	Randomised, double blind, placebo-controlled, parallel, multicentre study, comparing 6 weeks of montelukast with placebo in children aged 6-24 months with 'asthma symptoms' including cough. The study was designed primarily for safety and tolerability of montelukast; number allocated to montelukast to placebo was 2:1. Study was carried out, supported and reported by a commercial interest (Merck Research Laboratories) Randomisation by computer generated schedule, method of blinding and allocation concealment not described. Adherence not mentioned. Dropouts: montelukast=6 (3. 4%), placebo= 7 (8.4%) Quality Assessment: B, A, A, B; high quality score of 2.
Participants	256 children (359 screened) aged 6-24 months were recruited from 65 centres (Africa, Asia, Europe, North America, South America). Participants were reviewed 2 weekly. Method of recruitment not specified Montelukast group: 51 (29%) aged 6-12 months, 124 (70.9%) aged 12.1-24 months; 59 boys, 22 girls. Placebo group: 33 (40.7.%) aged 6-12 months, 48 (59.3%) aged 12. 1-24 months; 116 boys, 59 girls Inclusion criteria: history of 'asthma-like' symptoms, including but not limited to cough, wheezing, and shortness of breath; or a history of physician-diagnosed asthma Exclusion: born premature, unresolved respiratory tract infection, any serious condition requiring hospitalisation or emergency room visits in the within 4 weeks, or an asthma exacerbation within 2 weeks of pre-study visit
Interventions	6 weeks of 4mg montelukast (oral granules) or matching placebo, given once a day. Trial medications were given with one tablespoon of apple sauce at bedtime

van Adelsberg 2005 (*Continued*)

Outcomes	Safety and tolerability of trial medications. Secondary endpoints were efficacy endpoints: days without beta agonist use, beta agonist use per day, total peripheral blood eosinophil count, number of unscheduled physician, emergency room or hospital visits due to worsening 'asthma' symptoms, oral corticosteroid rescues for asthma' symptoms, asthma attacks (composite of unscheduled visits and oral steroid rescues) and discontinuations due to worsening 'asthma symptoms'. Carers recorded details daily on a modified calender. Authors considered secondary endpoints exploratory outcomes
Notes	Study was included as cough was an inclusion factor and diagnosis of asthma in the age group of participants is controversial Study's primary author was contacted but did not respond to request for additional data

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Study was carried out, supported and reported by a commercial interest (Merck Research Laboratories)

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

Study	Reason for exclusion
Bisgaard 2003	Young children (3-36 months) were recruited from hospitalised episodes of bronchiolitis. Hence children did not have non-specific cough
Dicpinigaitis 1999	Study in healthy adults
Dicpinigaitis 2002	RCT cross-over design in 8 adults on the effect of a 14-day course zafirlukast on subjective cough score and cough-reflex sensitivity
Ghosh 2006	Non RCT. Some children' with cough variant asthma' were included in the study but the study was not a randomised controlled study

(*Continued*)

Hallstrand 2002	RCT using montelukast and loratadine or placebo for exercise induced bronchoconstriction in adults
He 2009	Case control study involving 4 weeks of terbutaline and montelukast compared to terbutaline
Jung 2006	Non-placebo control study comparing inhaled budesonide (nebulised 500ug bd), montelukast and salbutamol
Kawai 2008	Non-RCT in adults
Kita 2010	Study on adults with 'atopic cough' randomised to montelukast or placebo, and 'cough variant asthma' randomised to montelukast, clenbuterol, or montelukast plus clenbuterol
Kopriva 2004	Non randomised trial. Cohort study on 22 children given montelukast (5mg daily) for 4 weeks. Cough ceased in 14 (68%) of children by week 3 of treatment
Kowal 2006	Study on adults with asthma
Lehtimaki 2009	A randomised, double-blind, placebo-controlled crossover study on the effect of montelukast in atopic syndrome. Cough was not an outcome measure
Proesmans 2009	Study on young children randomised to montelukast or placebo post bronchiolitis. Study found no statistical significant differences between the two groups for symptom-free (cough and wheeze) days and nights
Shimonda 2006	Non placebo trial
Spector 2004	RCT in 14 adults with a 7- to 10-day baseline period and a 4-week treatment period with montelukast, 10 mg, or placebo daily
Yamaguchi 2009	Study on adults with 'cough variant asthma'. Participants randomly assigned to receive daily doses of budesonide (BUD) 400 mcg (n=22), BUD 1200 mcg (22) or montelukast 10 mg
Zedan 2009	Prospective case control study comparing montelukast to fluticasone for reducing symptoms (including cough) and other asthma markers in children

DATA AND ANALYSES

Comparison 1. Cough outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Day-time cough	1	6	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Night-time cough	1	6	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 2. Rescue medications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Salbutamol use	1	6	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Cough outcomes, Outcome 1 Day-time cough.

Review: Leukotriene receptor antagonist for prolonged non-specific cough in children

Comparison: 1 Cough outcomes

Outcome: 1 Day-time cough

Study or subgroup	Montelukast N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kooi 2008	5	13 (7.25)	1	25 (0)			Not estimable
Total (95% CI)	**5**		**1**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Test for subgroup differences: Not applicable							

Analysis 1.2. Comparison 1 Cough outcomes, Outcome 2 Night-time cough.

Review: Leukotriene receptor antagonist for prolonged non-specific cough in children

Comparison: 1 Cough outcomes

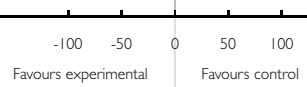
Outcome: 2 Night-time cough

Study or subgroup	Montelukast N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kooi 2008	5	9 (9.75)	1	25 (0)			Not estimable
Total (95% CI)	**5**		**1**				**Not estimable**

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Rescue medications, Outcome 1 Salbutamol use.

Review: Leukotriene receptor antagonist for prolonged non-specific cough in children

Comparison: 2 Rescue medications

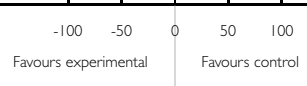
Outcome: 1 Salbutamol use

Study or subgroup	Montelukast N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kooi 2008	5	3.2 (5.63)	1	0 (0)			Not estimable
Total (95% CI)	**5**		**1**				**Not estimable**

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

Database	Search
CENTRAL	#1. COUGH single term (MeSH) #2. BRONCHITIS explode tree 1 (MeSH) #3. cough* #4. bronchiti* #5. (#1 or #2 or #3 or #4) #6. LEUKOTRIENE ANTAGONISTS single term (MeSH) #7. leukotriene* #8. leucotriene* #9. montelukast* #10. zafirlukast* #11. ltra #12. anti-leukotriene* #13. (anti next leukotriene*) #14 pranlukast* #15. (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14) #16. (#5 and #15)
MEDLINE/OLDMEDLINE (Combined with RCT filter as described in the Airways Group Module)	1. exp cough/ 2. exp bronchitis/ 3. cough$.tw. 4. bronchiti$.tw. 5. or/1-4 6. leukotriene antagonists/ 7. leukotriene$.tw. 8. leucotriene$.tw. 9. montelukast$.tw. 10. zafirlukast$.tw. 11. pranlukast$.tw. 12. LTRA.tw. 13. anti-leukotriene$.tw. 14. anti-leucotriene$.tw. 15. or/6-14 16. 5 and 15
EMBASE (Combined with RCT filter as described in the Airways Group Module)	1. exp coughing/ 2. exp bronchitis/ 3. cough$.tw. 4. bronchiti$.tw. 5. or/1-4 6. exp Leukotriene Receptor Blocking Agent/ 7. leukotriene$.tw. 8. leucotriene$.tw. 9. montelukast$.tw. 10. zafirlukast$.tw.

(*Continued*)

	11. pranlukast$.tw. 12. LTRA.tw. 13. anti-leukotriene$.tw. 14. anti-leucotriene$.tw. 15. or/6-14 16. 5 and 15
Airways Group Register	(cough* or bronchiti*) AND (leukotriene* or leucotriene* or anti-leukotriene* or anti-leucotriene* or montelukast* or zafirlukast* or pranlukast* or LTRA)

WHAT'S NEW

Last assessed as up-to-date: 28 October 2010.

Date	Event	Description
29 October 2010	New search has been performed	Updated search. No new studies included

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 4, 2006

Date	Event	Description
25 October 2009	New search has been performed	New search and new study added
24 March 2009	Amended	Contact details changed
24 October 2008	New search has been performed	Literature search re-run; no new studies found
23 October 2008	New search has been performed	No new studies
1 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

For the protocol: Protocol was written by AC, based on previous protocols on cough in children. JW and DW reviewed protocol. For the review: AC: selection of articles from search, data extraction, data analysis and writing of review. JA and DW: selection of articles from search, review of articles for inclusion, and writing of review.

DECLARATIONS OF INTEREST

None declared.

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Internal sources

- Royal Children's Hospital Foundation, Brisbane, Australia.

External sources

- National Health and Medical Research Council, Australia.

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INDEX TERMS

Medical Subject Headings (MeSH)

Acetates [*therapeutic use]; Cough [*drug therapy]; Leukotriene Antagonists [*therapeutic use]; Quinolines [*therapeutic use]

MeSH check words

Child; Humans