Inhaled beta2-agonists for non-specific chronic cough in children (Review)

Tomerak AAT, Vyas H, Lakhanpal M, McGlashan JJM, McKeen M

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Inhaled beta2-agonists for non-specific chronic cough in children (Review)

Tomarak AAT, Vyas H, Lakhanpaul M, McGlashan JJM, McKean M

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ABSTRACT

Background
The pathophysiology of so called 'cough variant asthma' has not received a great deal of research interest and opinion lies divided as to whether it is really asthma or not. The proponents of cough variant asthma suggest a therapeutic trial of medications usually used to treat asthma.

Objectives
To determine the effectiveness of inhaled ß2 agonists in non-specific chronic cough in children over the age of 2 years.

Search strategy
CENTRAL, MEDLINE and EMBASE were searched. Reference lists were checked and trial authors were contacted. 'Grey' literature including theses, internal reports, and non-peer reviewed journals were sought. Searches are current as of February 2006.

Selection criteria
All randomised (randomised and quasi-randomised) controlled clinical trials in which inhaled ß2 agonists were given for chronic cough in children over 2 years of age were included. Two reviewers independently assessed articles for inclusion and methodological quality.

Data collection and analysis
Data for trials of salbutamol versus placebo were extracted by both reviewers and entered into the Cochrane Collaboration software program Review Manager, version 4.2

Main results
In children presenting with isolated chronic cough there was no significant difference between salbutamol treated group and placebo group.

Authors’ conclusions
Salbutamol was no different from placebo in reducing the frequency of cough measured objectively or scored subjectively.

PLAIN LANGUAGE SUMMARY

The existence of cough variant asthma (cough as the only respiratory symptom without any evidence of airway obstruction) is controversial. This review raises the appropriateness of the common practice of using inhaled ß2 agonists in the treatment of children with cough without any other evidence of airway obstruction. The review found that there is nothing at present to suggest that treatment with ß2 agonists will be beneficial in treating nonspecific isolated cough in children.
Chronic cough is generally accepted as a cough that is persistent for more than 3 weeks. All children cough at some time, but for most this is just a normal response to common viral infections of the respiratory tract. Some, however, persist with a troublesome cough. In a child with isolated cough, a detailed history and examination, followed in a small number of cases by targeted investigations, should allow the child to be placed in one of five broad diagnostic categories. These are: a normal child who is chronically exposed to an irritant (e.g. smoke, fresh paints, new carpeting, dry air heating, old pillow, furry pet); a child with a serious illness such as cystic fibrosis, tuberculosis etc.; a child with non-serious, but treatable causes of cough, for example gastro-oesophageal reflux or postnasal drip; a child with an asthma syndrome; and a child where there is an overestimation of symptoms by either the child or family due to psychological or other reasons (Bush 2002). There are those who do not fit into these categories and are labelled as having non-specific chronic cough, that is isolated cough without any other associated manifestations that could be related to a background aetiology.

Inhaled β2 agonists have long been used for the treatment of acute asthma symptoms in both adults and children. To maximize the amount of drug that reaches the airways and minimise systemic absorption and side effects, small doses of the drug can be inhaled in aerosol and powder form (Skoner 2001). The pathophysiology of so called ‘cough variant asthma’ has not received a great deal of research interest and opinion lies divided as to whether it is really asthma or not. Currently there are proponents for (Doan 1992; Cloutier 1981) and against (McKenzie 1995; Ninan 1995) the diagnosis of asthma in children with cough as the sole respiratory symptom, so called ‘cough variant asthma’. The proponents of the entity of cough variant asthma found that in patients presenting solely with chronic cough:

- The diagnosis of asthma was confirmed by an exercise provocation test in some children (Konig 1981);
- Obvious clinical asthma developed in some patients after long-term follow-up (Hannaway 1982);
- Personal and family histories of atopy and blood eosinophilia suggested an allergic diathesis. Chest radiographs showed hyperinflation in many and spirometry showed bronchospasm (Yahav 1982);
- They responded to a therapeutic trial of asthma medication (e.g. inhaled corticosteroids), and relapsed on stopping medications with a second response to recommencing them (Bush 2002).

On this evidence the proponents of cough variant asthma suggest a therapeutic trial of medications usually used to treat asthma (Doan 1992). Wright 1996 on the other hand found that children with recurrent cough in isolation of other symptoms differ significantly from those with asthma, with or without cough, in airway hyperresponsiveness and atopy, among other factors. Another study found that children with persistent cough had less morbidity and less atopy compared with children with wheeze (Faniran 1998). Despite these differences and the unclear pathophysiology, for many general practitioners and paediatricians the most practicable approach to isolated chronic cough is a therapeutic trial of β2-agonists and or inhaled corticosteroids. As β2 agonists are one of the main therapies used for this condition we aim to conduct a systematic review of the evidence that supports their use in chronic cough.

**OBJECTIVES**

To determine the effectiveness of inhaled β2 agonists in non-specific chronic cough in children over the age of 2 years.

**CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

**Types of studies**

All randomised (randomised and quasi-randomised) controlled clinical trials in which inhaled β2 agonists were given for chronic cough in children over 2 years of age were included.

**Types of participants**

Children aged 2 years or over presenting with non-specific chronic cough for more than 3 weeks in all settings (inpatient or outpatient, general practice and the home). Studies involving children under the age of 2 years were excluded since different pathophysologies may occur in babies and young infants. Children with associated wheezy chest were also excluded.

**Types of intervention**

Inhaled β2 agonists, delivered by any means; aerosol, nebulised or by metered dose inhaler (MDI); with or without a holding chamber +/- a mask. All doses and dosing regimes were included. Studies including comparison of: β2 agonist with placebo, β2 agonist with any other drug, and comparison between different types of β2 agonists were included.

**Types of outcome measures**

**Primary outcome measure:**

Imoove in cough frequency.

**Secondary outcome measures:**

Cough severity score charts.

Changes in capsaicin cough receptor sensitivity.
Indicators of exacerbations (for example, increased use of bronchodilators, use of oral steroids, hospital admission or physician attendance).
Patient and/or parent assessment.
Physician's assessment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 1 2006; MEDLINE (1966-February 2006) and EMBASE (1980-February 2006) were searched using the search strategies detailed in Table 01.

Additional searching
Reference lists in primary sources were searched. Personal communication with authors and experts in the field were made in order to trace other unpublished sources. “Grey literature” including theses, internal reports, non-peer reviewed journals were sought.

METHODS OF THE REVIEW

Study Selection Process
The full texts of potential studies for inclusion were obtained to decide if they should be included or not by AT. A list of excluded studies was made, with reasons for their exclusion documented. In order to make sure these decisions were made properly, a second reviewer (MM) independently selected the studies to be included as well. No disagreement occurred so a third reviewer was not needed.

Assessment of methodological quality
Studies included underwent quality assessment performed independently by both reviewers, using two methods. The first involves using the Cochrane approach to assessment of allocation of concealment.
Trials were scored using the following principles:
Grade A: Adequate concealment
Grade B: Unclear concealment
Grade C: Clearly inadequate concealment

Secondly, each study was assessed using a 1 to 5 scale described by Jadad 1996 and summarised as follows:
Was the study described as randomised? (1=yes; 0=no)
Was the study described as double blind? (1=yes; 0=no)
Was there a description of withdrawals and dropouts? (1=yes; 0=no)
Was the method of randomisation clearly described and appropriate? (1=yes; 0=no)
Was the method of double blinding well described and appropriate? (1=yes; 0=no).
(Deducting one point when the methods for randomisation or blinding were inappropriate).
Inter-reviewer reliability was measured by using Kappa and weighted Kappa statistics.

Data extraction
Data for trials was extracted by both reviewers and entered into the Cochrane Collaboration software program Review Manager, version 4.2. Since only one study was identified no meta-analysis is possible at present.

Statistical considerations for future updates
All future included trials will be combined using the RevMan Analyses 1.0.2. For dichotomous variables, individual and pooled statistics will be calculated as relative risks with 95% confidence intervals. For continuous outcomes, individual and pooled statistics will be calculated as weighted mean differences or standard mean differences, as indicated, with 95% confidence intervals. We will pool data with a Fixed effect model. Since there does not appear to be consensus as to which method is superior, we will report both models where statistical heterogeneity as measured by the I² statistic is greater than 20%, or where the Chi-squared test for heterogeneity is significant at the P=0.1 level.

Subgroup analysis
Where future heterogeneity is observed, we will explore variation in treatment effects by conducting the following a priori subgroup analyses of clinical characteristics:
• Females versus males
• Age (2-5 years versus 6-18 years)
• Co-interventions versus none
• Different doses of β2-agonists
• Duration of β2-agonists administration (< 6 weeks vs >= 6 weeks administration)

Assessment of statistical heterogeneity
The trial characteristics that may have influenced the observed treatment effect was to be examined. Statistical heterogeneity was to be investigated by sensitivity analysis.

Sensitivity analysis provides an approach for testing how robust the results of a review are relative to key decisions and assumptions that have been made in the process of conducting the review.
Two factors were to be investigated:
1. Publication bias - the existence of publication bias was to be examined using a funnel plot trial quality;
2. The effects of overall trial quality on the pooled result was to be examined using both the Cochrane approach and that of Jadad 1996.
**DESCRIPTI ON OF STUDIES**

Electronic search: 516 citations retrieved; 506 excluded on basis of abstract: mainly being related to chronic cough of asthmatic subjects and/or adults. Ten papers were obtained in full text form. Nine papers did not meet the inclusion criteria (see table 'Characteristics of Excluded Studies'). Only one publication met the criteria for inclusion in the review (Chang 1998). A detailed description of this study is provided in the included studies table.

**Study design**
The study was a randomised, double-blind parallel group trial. The method of allocation was by sequential random number with treatments assigned based upon the number.

**Population**
43 participants from an outpatient’s clinic were recruited who were not experiencing current chest infections, and had a recent history of persistent cough.

**Interventions**
Participants were randomised to receive inhaled salbutamol or placebo two puffs twice a day (100 mcg salbutamol per puff) for 5-7 days. Therapies administered via a metered dose inhaler (MDI) with a spacer.

**Outcomes assessed**
The principal outcome assessed was the cough frequency. Chang 1998 studied cough frequency over 24 hrs at day 5-7 of the study. Other outcomes reported in the study included symptom scores using cough score charts (both parent and child completed), as well as measuring the lowest capsaicin concentration required to stimulate 2 coughs or more (C2h) and 5 coughs or more (C5). Airway responsiveness was assessed by inhalations of hypertonic saline (4.5%) using an ultrasonic nebuliser (the dose of hypertonic saline was increased successively by doubling the inhalation time). FEV1 was measured 60 seconds after each inhalation time and the test ceased when the FEV1 had fallen by more 15% or more or when a cumulative inhalation time of 15.5 minutes had been achieved. The presence of airway hyper-responsiveness (AHR positive) was defined as a fall in FEV1 of 15% or more from the baseline at any during the hypertonic saline challenge.

**METHODOLOGICAL QUALITY**

The overall quality of reporting of methods in the study included was fair. It was described as randomised and double blind. As assessed by the Jadad method, a score of 3 was given. The number of withdrawals and the reason for withdrawals were clearly stated. The concealment of allocation was not adequate as it was undertaken by the trialists directly.

**RESULTS**

**Inhaled β2-agonists versus placebo**

**Symptoms**
Chang 1998 reported that cough frequency and other outcome variables did not change significantly in either treatment group and there was no significant difference between the groups. There was also no significant difference in the change in cough frequency between the AHR positive and the AHR negative groups. The confidence intervals are wide and this study can neither confirm or rule out clinical benefit from inhaled β2-agonists in chronic cough in children.

**Other outcomes**
There was no significant difference in the change in C2h and C5 (reflecting cough receptor sensitivity) in either group.

Based upon canister weights 28 of the 38 children who completed the study (13 in β2-agonist group, and 15 in the placebo group) were compliant with the treatment protocol.

Withdrawals: Five children (four from the active treatment group and one from the placebo group did not complete the study due to personal reasons (three), use of salbutamol in addition to trial medications (one in the placebo group), and a refusal to take the trial medications (one from the active group). Thirty-eight children completed the study. It is not clear whether the trialists conducted an intention-to-treat analysis.

**DISCUSSION**

This review raises the appropriateness of the common practice of using inhaled β2 agonists in the treatment of children with cough without any other evidence of airway obstruction. Identifying children who are unlikely to benefit from medications used for asthma could not only potentially prevent the diagnostic labelling of asthma in a large group of children but also save these children from the use of unnecessary medications and their associated side effects, as well as save their parents from any unnecessary expense.

The promotion of the diagnosis of asthma based on the symptom of cough alone has led to the overuse of β2 agonists in children with recurrent cough (McKenzie 1995). The findings of a lack of response to inhaled medications used routinely for asthma, irrespective of the presence of AHR, are supported by epidemiological data (Clifford 1989; Lombard 1997). Clifford 1989 found no association between cough and either AHR or atopy after controlling for wheeze, and they suggested that, in the absence of wheeze, the significance of cough and dyspnoea for the diagnosis of asthma in epidemiological studies should be questioned.

This review supports growing epidemiological evidence that cough alone is a poor marker for asthma (Ninan 1995; Wright 1996).
McFadden 1975 were the first to describe cough as a presenting symptom of asthma in adults. All subjects in this study had exertional dyspnoea and abnormal baseline expiratory flow volume loops consistent with moderate airways obstruction. Subsequent studies of cough variant asthma included adults and children without any abnormality of their baseline pulmonary function (Cloutier 1981; Cheriyan 1994; Hannaway 1982). Many of these studies used asthma medications for adults and children with cough variant asthma but had no placebo arm, and results were based on subjective reporting of cough, which is known to be unreliable (Hsu 1994, Archer 1985). Cheriyan 1994 was a retrospective study that reported eight of 10 adult patients free from cough while on either oral or inhaled corticosteroids after three months. In the earlier adult (Armitage 1994) and paediatric (Cloutier 1981) studies, the subjects' cough responded to oral theophylline within 2-5 days, in contrast to the prolonged course of corticosteroids used by other studies (Cheriyan 1994). The study included in this review is not comparable to the study of Hannaway 1982 that included children with abnormal baseline lung function or chest physical examination. The subjects in the included study had normal physical examination and spirometry. In the Hannaway 1982 study, a third of the 32 children involved had abnormal physical examination of the chest and 12 of the children who were able to perform pulmonary function tests had abnormalities in the expiratory flow loop. Similarly, in another study (Konig 1981) six of the eight children who were able to perform pulmonary function tests had FEV1 predicted values of approximately 85%.

Some children with persistent cough do not have unrecognised wheeze, either because it is poorly perceived by their parents or it is not present at the time they present to a physician. It has also been suggested that this group has a higher wheeze threshold (Koh 1993). The fact that inhaled corticosteroid has helped the coughers in the study by Davies 1999 does not mean that they necessarily have asthma. It may be that children with recurrent, persistent, and isolated cough occupy an intermediate clinical position between children with no cough and those with wheeze with respect to atopy (Lewis 1989), prognosis for asthma (Wright 1996, Powell 1996), family history of asthma (Ninan 1995), response to bronchodilator (Konig 1981), and episodes of respiratory morbidity (Levy 1984). However, coughers appear to have normal lung function measured by spirometry and airway responsiveness (Chang 1998; Wright 1996).

A positive relation between isolated cough and atopic family history as markers for the later development of wheeze has been noted (Powell 1996), and others have also found that children with cough and no wheeze had more atopy than controls but less than asthmatics (Wright 1996; Lewis 1989). Eczema and hay fever, however, occurred no more in coughers than controls (Ninan 1995).

Although cough is often used as a marker of asthma instability (Isles 1993) the severity of cough has been shown to be unrelated to the airway calibre as measured by FEV1, peak expiratory flow or its variability (Hsu 1994). In the laboratory, medications (e.g. cromolyn, atropine) that inhibit the bronchoconstriction that occurs with broncho- provocative challenges do not alter the cough response (Hansson 1988; Sheppard 1983). Conversely, other medications (lignocaine, codeine) that inhibit the induced cough have no effect on broncho-constriction (Hansson 1988; Fuller 1988).

In human airways, the pathways for cough and bronchoconstriction are distinctly different (Sheppard 1983; Fuller 1988; Shimuzu 1996). While the trigger for cough and airway narrowing may be the same, the symptom of cough may persist despite adequate treatment of bronchoconstriction. It is, therefore, not surprising that the AHR positive children in Chang 1998 study responded to salbutamol and placebo in a similar manner to the AHR negative children.

The number of subjects included in the study included in our review was small, but did achieve a power of 80% based on an expected difference of 70% in the frequency of cough as measured by cough meter. Whether this is generalisable depends on two questions. Firstly, is it safe to assume in a small study that any differences between treatment and placebo would not have been missed? Secondly, is a 70% reduction in cough frequency a reasonable representation of treatment success? The primary outcome of improvement of cough and how it is measured is crucial to this issue. Clearly there are difficulties in measuring cough, especially at night. Any future studies should aim to design a validated tool for assessing cough in order to reduce uncertainty in the measurement of cough. Hence the major problem with the included study is the limited ability to generalise the results based on 80% power. In addition the dose was lower than standard asthma care as outlined in BTS guidelines on asthma (given that the authors has taken a pure asthma slant rather than other possible effects of salbutamol such as possible effects on cough receptors, cough pathway, airway clearance etc).

Chang 1998 recorded cough over 24 hours using a cough diary. By using video recordings in Davies 1999, as with other studies (Picciotto 1998), were able to make observations of children with nocturnal cough in their own homes. This method eliminates difficulties with diary card reporting and the problems associated with recording cough of co-sleepers.

Chang 1998 found that inhaled salbutamol had no significant effect on cough frequency or score, irrespective of the presence of AHR. It could be argued that the infrequent use of salbutamol trial affected the outcome measures. Salbutamol was used twice a day rather than four times a day, with the aim of improving compliance. Moreover, regular use of 82 agonists (three to four times a day) may worsen asthma symptoms, increase the risk of severe asthma or cause enhanced AHR (Busse 1994). As compliance and treatment success were similar in both treatment arms, improved compliance and a larger daily dose of salbutamol are unlikely to alter the final results. In addition, there is no gold standard on acceptable compliance and devices that record the use of the medi-
ication cannot confirm if the medication was actually consumed (Rand 1994).

A potential criticism for the study included in this review is that silent gastro-oesophageal reflux and sinusitis were not thoroughly investigated. In children, these diagnoses as a cause of cough, rather than an association, are controversial. In adults with gastro-oesophageal reflux (but no respiratory symptoms), reflux was found to be a cofactor and not the cause of cough (Ferrari 1995). The exclusion of sinusitis is extremely difficult. In a prospective study, 50% of the 137 children younger than 13 years (Diament 1987) had computed tomography sinus scans consistent with sinusitis but all were asymptomatic.

One of the most important observations made in the studies included in this review is that children improved on placebo. Of those who were followed up, most continued with improved symptoms. Since follow up was six months to one year after the study, this could simply reflect the natural history of the tendency of cough to improve with time (Brooke 1995).

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

While cough is associated with asthma (McFadden 1975), when no other evidence of airway obstruction is present one small study has shown that irrespective of the presence of AHR, inhaled salbutamol provided no advantage over placebo in reducing the frequency of cough measured objectively or scored subjectively. However, on the basis of one small trial we cannot exclude the possibility that in children with recurrent cough without other evidence of airway obstruction inhaled β2-agonist might be beneficial. Until there is a greater body of evidence on the treatment of non-specific cough, no recommendation can be made.

**Implications for research**

The common problem of cough in childhood and its relation with airway obstruction deserves further investigation.

More randomised controlled studies are needed to study the efficacy of asthma medications in isolated chronic cough. Since no benefit has been shown from 2 puffs twice a day (100 mcg salbutamol per puff) of inhaled salbutamol it might be worth undertaking a larger study using higher doses of inhaled salbutamol or other types of β2 agonists to investigate whether a subgroup of children with non-specific chronic cough who have never wheezed, are likely to benefit. However the adverse events of using higher doses (e.g. tachycardia, tremor, anxiety, etc) could be problematic. It might also be worth comparing the pros and cons of Inhaled corticosteroids versus inhaled β2 agonists in these cases. Key to the successful study of non-specific cough is exclusion of asthma and it is recommended that in children able to perform lung function, reversible airways obstruction and/or airway hyperresponsiveness is studied as part of assessment for suitability in a study of non-specific cough.

**POTENTIAL CONFLICT OF INTEREST**

None known.

**ACKNOWLEDGEMENTS**

We would like to thank the support staff of the Cochrane Airways Group (Toby Laserson & Liz Arnold) for assistance in the electronic search and retrieval of papers. We would like to thank Dr Anne Chang who was kind enough to supply us with extra details concerning her study.

**SOURCES OF SUPPORT**

**External sources of support**

• No sources of support supplied

**Internal sources of support**

• No sources of support supplied
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References to studies included in this review

Chang 1998  [published data only]

References to studies excluded from this review

Belcher 1986

Davies 1999

de Benedictis 1986

Ellul-Micallef 1983

Irwin 1997
Irwin RS, French CT, Smyrnios NA, Curley FJ. Interpretation of positive Results of a methacholine Inhalation Challenge and 1 week of Inhaled Bronchodilator Use in Diagnosing and Treating cough-variant asthma. *Archives of Internal Medicine* 1997;157:1981–7.

Lowry 1987

Lui 1996

Mulrennan 2002

Spelman 1991

Additional references

Archer 1985
Archer LN, Simpson H. Night cough counts and diary card scores in asthma. *Archives of Disease in Childhood* 1985;60:473–4.

Armitage 1994

Brooke 1995

BTS 1997

Bush 2002

Busse 1994

Census 1991

Chang 1996

Chang 1997

Chang 1997a

Cheriyan 1994

Clifford 1989

Cloutier 1981

Diament 1987

Doan 1992

East London 1996
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**Tables**

**Characteristics of included studies**

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<td><strong>Methods</strong></td>
<td>Setting: outpatient department; Randomisation: RCT; blocks of 6; Masking: DB; Design: P. Excluded: adequately stated (12); Withdrawal: adequately stated (5); Jadad score: 3. Allocation was by sequential random number with treatments assigned based upon the number. The process of allocation was undertaken by the trialist.</td>
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<tr>
<td><strong>Participants</strong></td>
<td>Total eligible for inclusion: 55; Number enrolled: 43; Participants: males: 19; Females: 24; Number completed study: 38; Age: 6-17 years; Ethnicity: not given; Treatment groups: PHASE 1: SAL: 21; PLA: 22. PHASE 2: BDP: 22; PLA: 21. Baseline characteristics: well balanced. Inclusion criteria: Recurrent cough: two episodes of cough, each lasting two weeks in the past 12 months; experiencing an episode of cough. Exclusion criteria: Moist, productive cough; bronchiectasis; whooping cough; immunodeficiency; clinical gastro-oesophageal reflux; history of cardiac or neonatal pulmonary problems; abnormal cardiopulmonary physical examination and abnormal chest x-ray.</td>
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<td><strong>Interventions</strong></td>
<td>Phase 1: SAL versus PLA Phase 2: BDP versus PLA (participants re-randomised in second phase to treatment groups. SAL/BDP: 2 puffs bd; 100 micgm per puff) PLA: 2 puffs bd Length of intervention: SAL: 5-7 days; BDP: 4-5 weeks (8-9 weeks in a subgroup)</td>
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<td><strong>Outcomes</strong></td>
<td>Number of coughs per 24 hrs measured objectively (24 hrs Holter monitor); subjective cough scores (charts/parent/child completed); CRS; PD15; compliance if reduction more than 70% of canisters weight</td>
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<td><strong>Notes</strong></td>
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DB = double-blind; P = parallel; PLA = placebo; SAL = salbutamol; BDP = beclomethasone; bd = 2 x daily

**Characteristics of excluded studies**

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<tr>
<td>Davies 1999</td>
<td>RCT of steroids in paediatric cough</td>
</tr>
<tr>
<td>Ellul-Micallef 1983</td>
<td>Study conducted on adults</td>
</tr>
<tr>
<td>Irwin 1997</td>
<td>Study conducted on adults</td>
</tr>
<tr>
<td>Lowry 1987</td>
<td>Study conducted on adults and induced cough in normal subjects</td>
</tr>
<tr>
<td>Lui 1996</td>
<td>Study conducted on adults and induced cough</td>
</tr>
<tr>
<td>Mulrennan 2002</td>
<td>Study conducted in healthy adult smokers</td>
</tr>
<tr>
<td>Spelman 1991</td>
<td>Not RCT</td>
</tr>
<tr>
<td>de Benedictis 1986</td>
<td>Not RCT therapeutic trial</td>
</tr>
</tbody>
</table>
Table 01. Search strategies used for Medline, Embase and Central

<table>
<thead>
<tr>
<th>Database searched</th>
<th>Terms used</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL</td>
<td>#1. COUGH explode all trees (MeSH); #2. cough*; #3. (#1 or #2); #4. ADRENERGIC BETA-AGONISTS explode tree 2 (MeSH); #5. agonist*; #6. (receptor next agonist*); #7. (adrenergic next agonist*); #8. beta-2; #9. b2; #10. (#8 or #9); #11. (#5 or #6 or #7); #12. (#10 and #11); #13. (bronchodilator* near agent*); #14. (albuterol or aminophylline* or atropine* or bricanyl or budesonide or clenbuterol or cromakalim or dyphylline or ephedrine or epinephrine or fenoterol or hexoprenaline or ipratropium or isoetharine or isoproterenol or khellin or (nitric next oxide) or orciprenaline or procaterol or s-nitrosoglutathione or nitrosothiols or salbutamol or terbutaline or theobromine or theophylline or tretinoquinol or ventolin); #15. (#4 or #12 or #13 or #14); #16. NEBULIZERS AND VAPORIZERS explode tree 1 (MeSH); #17. ADMINISTRATION INHALATION explode tree 1 (MeSH); #18. (aerosol* or inhal* or atomi* or nebuli* or volatili*); #19. (#16 or #17 or #18); #20. (#3 and #15 and #19) #21. (child* or paediat* or pediat* or adolesc* or infant* or toddler* or bab* or young* or preschool* or pre-school or (pre next school) or newborn* or new-born* or (new next born*) or neonat* or neo-nat*); #22. (#20 and #21)</td>
</tr>
<tr>
<td>MEDLINE</td>
<td>1. exp COUGH/ 2. cough$.mp. 3. 1 or 2 4. exp Child/ or exp infant/ or exp adolescent/ 5. exp Pediatrics/ 6. (paediatric$ or pediatric$ or child$ or adolescen$ or infant$ or young$ or preschool$ or pre-school$ or newborn$ or new-born$ or neonat$ or neo-nat$).mp. 7. 4 or 5 or 6</td>
</tr>
</tbody>
</table>
Table 01. Search strategies used for Medline, Embase and Central

<table>
<thead>
<tr>
<th>Database searched</th>
<th>Terms used</th>
</tr>
</thead>
</table>
| **Medline**       | 8. exp Adrenergic beta-Agonists/  
|                   | 9. agonist$.mp.  
|                   | 10. (receptor adj5 agonist$).mp.  
|                   | 11. (adrenergic adj5 agonist$).mp.  
|                   | 12. (beta-2 or beta2 or b2).mp.  
|                   | 13. 9 or 10 or 11  
|                   | 14. 12 and 13  
|                   | 15. (bronchodilat$ adj5 agent$).mp.  
|                   | 16. (albuterol or aminophylline$ or bricanyl or budesonide or clenbuterol or cromakalim or dyphylline or ephedrine or epinephrine or fenoterol or hexoprenaline or ipratropium or isoetharine or isoproterenol or khellin or (nitric adj3 oxide) or orciprenaline or procaterol or s-nitrosoglutathione or nitrosothiols or salbutamol or terbutaline or theobromine or theophylline or tretoquinol or ventolin).mp.  
|                   | 17. 8 or 14 or 15 or 16  
|                   | 18. exp "Nebulizers and Vaporizers"/  
|                   | 19. exp administration inhalation/  
|                   | 20. (aerosol$ or inhal$ or atomi$ or nebuli$ or volatili$).mp.  
|                   | 21. 18 or 19 or 20  
|                   | 22. 3 and 17 and 21  
|                   | 23. 22 and 7 |
| **EMBASE**        | 1. exp COUGHING/  
| (combined with RCT filter) | 2. cough$.mp.  
|                   | 3. 1 or 2  
|                   | 4. exp Child/ or exp infant/ or exp adolescent/  
|                   | 5. exp PEDIATRICS/  
|                   | 6. (paediatric$ or pediatric$ or child$ or adolescent$ or infant$ or young$ or preschool$ or pre-school$ or newborn$ or new-born$ or neonat$ or neo-nat$).mp.  
|                   | 7. 4 or 5 or 6  
|                   | 8. exp Beta Adrenergic Receptor Stimulating Agent/  
|                   | 9. agonist$.mp.  
|                   | 10. (receptor adj5 agonist$).mp.  
|                   | 11. (adrenergic adj5 agonist$).mp.  
|                   | 12. (beta-2 or beta2 or b2).mp.  
|                   | 13. 9 or 10 or 11  
|                   | 14. 12 and 13  
|                   | 15. (bronchodilat$ adj5 agent$).mp.  
|                   | 16. (albuterol or aminophylline$ or bricanyl or budesonide or clenbuterol or cromakalim or dyphylline or ephedrine or epinephrine}
<table>
<thead>
<tr>
<th>Database searched</th>
<th>Terms used</th>
</tr>
</thead>
<tbody>
<tr>
<td>or fenoterol or hexoprenaline or ipratropium or isoetharine or isoproterenol or khellin or (nitric adj3 oxide) or orciprenaline or procaterol or s-nitrosoglutathione or nitrosothiols or salbutamol or terbutaline or theobromine or theophylline or tretoquinol or ventolin).mp.</td>
<td></td>
</tr>
</tbody>
</table>
17. 8 or 14 or 15 or 16  
18. exp NEBULIZER/  
19. exp VAPORIZER/  
20. exp Inhalational Drug Administration/  
21. (aerosol$ or inhal$ or atomi$ or nebuli$ or volatili$).mp.  
22. 18 or 19 or 20 or 21  
23. 3 or 17 or 22  
24. 7 and 23 |
## ANALYSES

**Comparison 01. Inhaled salbutamol (400 mcg/day) vs placebo**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Cough frequency in 24 hrs</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>02 Symptom score (parent completed)</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>03 Symptom score (child completed)</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>04 C5 (lowest concentration of capsaicin required to stimulate 5 coughs or more)</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>05 Cth (lowest concentration of capsaicin required to stimulate 2 coughs or more)</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>06 Compliance (N deemed compliant by trialists)</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>07 Withdrawals</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

## INDEX TERMS

**Medical Subject Headings (MeSH)**

Administration, Inhalation; Adrenergic beta-Agonists [*administration & dosage*]; Albuterol [*administration & dosage*]; Chronic Disease; Cough [*drug therapy*]; Randomized Controlled Trials

**McSH check words**

Child; Humans

## COVER SHEET

**Title**

Inhaled beta2-agonists for non-specific chronic cough in children

**Authors**

Tomerak AAT, Vyas H, Lakanpaul M, McGlaskan JJM, McKean M

**Contribution of author(s)**

AT: Protocol initiation, search result assessment, data extraction and analysis, write-up and interpretation
MM: Protocol development, search result assessment, data extraction and analysis, interpretation
HV: interpretation
JM: interpretation
ML: interpretation

**Issue protocol first published**

2003/2

**Review first published**

2005/3

**Date of most recent amendment**

17 February 2006

**Date of most recent SUBSTANTIVE amendment**

19 May 2005

**What’s New**

Information not supplied by author
Date new studies sought but none found
08 February 2006

Date new studies found but not yet included/excluded
Information not supplied by author

Date new studies found and included/excluded
Information not supplied by author

Date authors’ conclusions section amended
Information not supplied by author

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CD005373

Editorial group
Cochrane Airways Group

Editorial group code
HM-AIRWAYS

Analysis 01.01. Comparison 01 Inhaled salbutamol(400 micgm/day) vs placebo, Outcome 01 Cough frequency in 24 hrs

<table>
<thead>
<tr>
<th>Study</th>
<th>Beta-agonist</th>
<th>Placebo</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>Chang 1998</td>
<td>17 -45.00 (283.60)</td>
<td>21 -34.00 (81.30)</td>
<td>-11.00 [-150.22, 128.22]</td>
<td></td>
</tr>
</tbody>
</table>

Favours beta-agonist Favours placebo

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### Analysis 01.02. Comparison 01 Inhaled salbutamol(400 micgm/day) vs placebo, Outcome 02 Symptom score (parent completed)

<table>
<thead>
<tr>
<th>Study</th>
<th>ß2-agonist N Mean(SD)</th>
<th>Placebo N Mean(SD)</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 1998</td>
<td>17 -0.90 (2.70)</td>
<td>21 -0.50 (2.60)</td>
<td>-0.40</td>
<td>[-2.10, 1.30]</td>
<td></td>
</tr>
</tbody>
</table>

 Favours ß2-agonist  

### Analysis 01.03. Comparison 01 Inhaled salbutamol(400 micgm/day) vs placebo, Outcome 03 Symptom score (child completed)

<table>
<thead>
<tr>
<th>Study</th>
<th>ß2-agonist N Mean(SD)</th>
<th>Placebo N Mean(SD)</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 1998</td>
<td>17 -0.90 (2.40)</td>
<td>21 -1.20 (2.60)</td>
<td>0.30</td>
<td>[-1.29, 1.89]</td>
<td></td>
</tr>
</tbody>
</table>

 Favours ß2-agonist  

### Analysis 01.04. Comparison 01 Inhaled salbutamol(400 micgm/day) vs placebo, Outcome 04 C5 (lowest concentration of capsaicin required to stimulate 5 coughs or more)

<table>
<thead>
<tr>
<th>Study</th>
<th>ß2-agonist N Mean(SD)</th>
<th>Placebo N Mean(SD)</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 1998</td>
<td>17 0.20 (0.69)</td>
<td>21 0.16 (0.79)</td>
<td>0.04</td>
<td>[-0.43, 0.51]</td>
<td></td>
</tr>
</tbody>
</table>

 Favours placebo  

Inhaled beta2-agonists for non-specific chronic cough in children (Review)  

Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
Analysis 01.05. Comparison 01 Inhaled salbutamol (400 micg/day) vs placebo, Outcome 05 Cth (lowest concentration of capsaicin required to stimulate 2 coughs or more)

Review: Inhaled beta2-agonists for non-specific chronic cough in children
Comparison: 01 Inhaled salbutamol (400 micg/day) vs placebo
Outcome: 05 Cth (lowest concentration of capsaicin required to stimulate 2 coughs or more)

<table>
<thead>
<tr>
<th>Study</th>
<th>ß2-agonist</th>
<th>Placebo</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Chang 1998</td>
<td>17</td>
<td>0.14 (0.58)</td>
<td>0.07 [-0.33, 0.47]</td>
</tr>
</tbody>
</table>

Favours placebo Favours ß2-agonist

Analysis 01.06. Comparison 01 Inhaled salbutamol (400 micg/day) vs placebo, Outcome 06 Compliance (N deemed compliant by trialists)

Review: Inhaled beta2-agonists for non-specific chronic cough in children
Comparison: 01 Inhaled salbutamol (400 micg/day) vs placebo
Outcome: 06 Compliance (N deemed compliant by trialists)

<table>
<thead>
<tr>
<th>Study</th>
<th>ß2-agonist</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
</tr>
<tr>
<td>Chang 1998</td>
<td>13/21</td>
<td>15/22</td>
<td>0.91 [0.58, 1.41]</td>
</tr>
</tbody>
</table>

Favours placebo Favours ß2-agonist

Analysis 01.07. Comparison 01 Inhaled salbutamol (400 micg/day) vs placebo, Outcome 07 Withdrawals

Review: Inhaled beta2-agonists for non-specific chronic cough in children
Comparison: 01 Inhaled salbutamol (400 micg/day) vs placebo
Outcome: 07 Withdrawals

<table>
<thead>
<tr>
<th>Study</th>
<th>ß2-agonist</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
</tr>
<tr>
<td>Chang 1998</td>
<td>4/21</td>
<td>1/22</td>
<td>4.19 [0.51, 34.50]</td>
</tr>
</tbody>
</table>

Favours ß2-agonist Favours placebo