Treatment of obstructive sleep apnoea for chronic cough in children (Review)

Teoh L, Hurwitz M, Acworth JP, van Asperen P, Chang AB

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Treatment of obstructive sleep apnoea for chronic cough in children (Review)

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Title: Treatment of obstructive sleep apnoea for chronic cough in children

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ABSTRACT

Background
Childhood obstructive sleep apnoea (OSA) is a disorder that is characterised by repeated episodes of partial or complete upper airway obstruction (UAO) during sleep that result in disruption of normal ventilation and sleep patterns. Chronic cough in children is a significant medical problem and in some situations warrants thorough investigation. There may be an association between chronic cough and OSA as suggested in adult studies.

Objectives
To evaluate the efficacy of treatment of OSA leading to the resolution of cough in the management of children with chronic cough.

Search methods
We searched the Cochrane Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE and EMBASE. The latest search was performed in September 2010.

Selection criteria
All randomised controlled trials comparing an intervention for OSA to a control group (placebo or usual treatment) in children with chronic cough.

Data collection and analysis
We reviewed the search results against the pre-determined criteria for inclusion. Two review authors independently selected the studies. No eligible trials were identified and thus no data were available for analysis.

Main results
We found no randomised controlled trials that examined the efficacy of treatment of OSA in the management of children with chronic cough.
Authors’ conclusions

There is currently no evidence that therapies directed for OSA are useful for the management of chronic cough in children. Until further evidence is available, OSA should be managed on its own merits and the presence or absence of cough should not be used as a decision trigger. Further research examining the effects of this intervention is needed.

plain language summary

Does treating obstructive sleep apnoea in children who also have chronic cough improve their cough?

Sleep apnoea (a condition where breathing stops for short spells during sleep) and chronic cough in children are significant medical problems and cause a significant burden of distress to parents. Interventions for sleep apnoea are associated with risks of morbidity and mortality, in addition to substantial costs. This review aimed to examine the effect of the treatment of sleep apnoea in children with chronic cough, however no randomised controlled trials were found. Currently there is no evidence to support the use of interventions for sleep apnoea in children with chronic cough and a randomised controlled trial is needed.

background

Description of the condition

Obstructive sleep apnoea (OSA) has been reported as a cause of chronic cough in adults. Data are scarce in children despite the fact that OSA and chronic cough are relatively common. Also when two symptoms are common, the chance occurrence of having both symptoms is high. Thus the association between cough and OSA symptoms may not be causal.

OSA belongs to the severe end of a spectrum of sleep-disordered breathing (SDB). Within the OSA syndrome (OSAS), a spectrum also exists and some mild OSA may not require treatment (Littner 2007).

Childhood OSA is a disorder that is characterised by repeated episodes of partial or complete upper airway obstruction (UAO) during sleep that result in disruption of normal ventilation and sleep patterns (American Thoracic Society 1996). An obstructive apnoea is a respiratory event where there is absence of airflow with continued respiratory effort, derived from the nasal pressure and the thermistor signal during the polysomnogram. This is associated with an arousal, oxygen desaturation or autonomic activation (Chokroverty 2005). The most common cause for childhood OSA is adenotonsillar hypertrophy, but the large tonsils and adenoids alone cannot account for the entire pathophysiology process. There is accumulating evidence to suggest that OSA is related to an interaction of structural and neuromuscular variables within the upper airway. A recent study revealed that childhood OSA was related to impaired response of the central nervous system to mechanical stimulation of the respiratory system (Huang 2008). Thus, structural factors alone cannot be fully responsible for this condition. The mechanism underlying this condition is related to a combination of three processes: (1) decreased upper airway patency (adenotonsillar hypertrophy, allergies associated with chronic rhinitis or nasal obstruction), (2) reduced capacity to maintain airway patency related to neuromuscular tone (obesity, neuromuscular disorder), and (3) decreased drive to breathe (brainstem injury) (Au 2009). OSA may result in considerable morbidity and perhaps mortality if left untreated. Complications of untreated childhood OSA include possible cardiovascular consequences, inflammatory associations, the metabolic syndrome and growth failure.

Case series on chronic cough in adults have reported that one of the possible aetiological factors is OSA (Birring 2007). A retrospective review on adults with chronic cough reported that OSA was a common finding, even when another cause of cough was identified and that interventions to optimise the SDB led to an improvement in the cough (Sundar 2010). The pathogenesis remains unclear, although patients with OSA also have a high prevalence of gastro-oesophageal reflux disease (Ing 2000). Other aetiological factors associated with OSA may include laryngeal oedema, particularly of the arytenoid cartilages, and changes in cough threshold secondary to changes to laryngeal sensitivity. In a cross-sectional study, snoring in preschool children was found to be significantly associated with both nocturnal cough and asthma (Lu 2003). However symptoms of OSA, particularly snoring in children, are common, with a population prevalence of habitual snoring as high as 12% (Ali 1993). The literature suggests a prevalence of OSA from 0.1% to 13%, but most report a figure between 1% and 4% (Au 2009; Gislason 1995; Redline 1999). Hence the
symptoms may co-exist by chance alone. Nevertheless other biologically plausible mechanisms may also account for the association between cough and OSA. These include recurrent small volume aspiration in association with childhood OSA and priming of cough receptors leading to increased cough sensitivity from mechanical vibration of the airways from snoring.

Description of the intervention
Types of intervention for OSA in children include adenotonsillectomy, non-invasive positive pressure ventilation (NIPPV), leukotriene receptor antagonist, nasal corticosteroid therapy and/or weight loss. Adenotonsillectomy is considered the cardinal treatment of childhood OSA. Nasal corticosteroids have been examined as an alternative to adenotonsillectomy in otherwise healthy children with OSA (Broviñetile 2001; Demain 1995). Nasal corticosteroids work by exerting lympholytic action and effects on inflammation and upper airway oedema (Kiely 2004). In an open-labelled study, the leukotriene receptor antagonist, montelukast was found to be clinically effective in reducing disease severity in children with mild OSA (Goldbart 2005). A combination of intransal steroids and leukotriene modifier was found to be useful in children with residual OSA after adenotonsillectomy (Kheirandish 2006). Nasal continuous positive airway pressure (CPAP) provides positive pressure to the lumen of the airway and decreases airway collapsibility. Weight loss is recommended as supplementary therapy for obese children.

How the intervention might work
The pathophysiology on OSA possibly causing cough is unknown. Possible reasons include increased risk of aspiration during sleep when airway obstruction is present and/or stimulation of cough receptors during the vibrations that occurs with airway collapse. Interventions that remove or decrease airway obstruction during sleep may thus improve cough. Adenotonsillar hypertrophy is the most common cause of childhood OSA, hence adenotonsillectomy to remove the obstruction that causes OSA. In childhood OSA, nasal CPAP or bilevel positive airway pressure (BiPAP) have become established themselves as the second-line treatment or as first-line treatment in cases where adenotonsillectomy is contraindicated (Guilleminault 1986; Marcus 1995; Waters 1995). Nasal CPAP to the lumen of the airway decreases airway collapsibility. Demain 1995 demonstrated that nasal corticosteroids over a 24-week treatment period reduced adenoidal size and improved symptoms of nasal airway obstruction. Nasal corticosteroids with or without leukotriene receptor antagonist are an option for children with mild OSA related to nasal obstruction caused by allergic rhinitis (Au 2009).

Any treatment, however, may demonstrate physiological or placebo-related improvements. In cough-related studies, the period effect (spontaneous resolution of cough) can be as high as 80% (Eccles 2002) and thus comparison to a placebo arm is very important.

Why it is important to do this review
Cough is the most common symptom presenting to general practitioners (Britt 2002; Cherry 2003). 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. Cochrane reviews on other interventions for chronic cough are available (Chang 2007; Schroeder 2004).

General management of children with non-specific cough currently involves the ‘watch, wait, and review’ approach (Chang 2006). For specific cough the intervention is for the presumed aetiology. However some interventions including that for OSA may be invasive (such as adenotonsillectomy) with an associated small but significant risk of morbidity and mortality. Other interventions for OSA such as NIPPV strategies have substantial cost implications. Thus a systematic review of the efficacy of OSA treatments for chronic cough would be useful in assessing the risk versus benefit details of the therapy, in order to help guide clinical practice.

OBJECTIVES
To evaluate the efficacy of treatment of OSA leading to the resolution of cough in the management of children with chronic cough.

METHODS

Criteria for considering studies for this review

Types of studies
All randomised controlled trials comparing any treatment for OSA to a control group (placebo or usual treatment) in children with chronic cough.

Types of participants
Children with chronic (greater than four weeks) cough in association with OSA symptoms (snoring, increased respiratory effort, choking during sleep, restlessness, frequent awakening, excessive sleepiness, tiredness, fatigue, nocturnal enuresis, poor attention span, hyperactivity, poor school performance, aggressiveness, failure to thrive and/or other behavioural disturbances).
Exclusion criteria: acute (less than two weeks) or sub-acute (two to four weeks) cough, cough related to mycoplasma, pertussis and chlamydia, presence of underlying cardio-respiratory condition, current or recurrent wheeze (more than two episodes), presence of other obvious causes of chronic cough (e.g. bronchiectasis) or other respiratory symptoms (e.g. productive cough, haemoptysis, dyspnoea).

Types of interventions
All randomised controlled trials comparing an intervention for OSA to a control group (placebo or usual treatment) with cough determined as an outcome. These interventions will be grouped into pharmaceutical therapy such as nasal corticosteroids and leukotriene receptor antagonists, NIPPV and surgery (adenotonsillectomy).

Types of outcome measures

Primary outcomes
a) proportions of participants who were not cured or not substantially improved at follow-up (clinical failure).

Secondary outcomes
b) proportions of participants who were not cured at follow-up,
c) proportions of participants who were not substantially improved at follow-up,
d) mean difference in cough-specific indices (quality of life, cough diary, cough frequency, cough scores),
e) proportions experiencing adverse effects of the intervention,
f) 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 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 was listed first in the hierarchy was 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/careers.

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

Search methods for identification of studies

Electronic searches
We used the following topic search strategy to identify the relevant randomised controlled trials listed on the electronic databases: ("cough" OR "bronchitis", all as (textword) or (MeSH )) AND ("sleep" AND ("apnea" OR "apnoea" OR "hypopnea" OR "hypopnoea" OR "obstructive" OR "disorder" OR "disturbance" OR "disordered breathing" OR "snore" OR "snoring" OR "breathing" all as (textword) or (MeSH )) AND ("child" OR "children" OR "pediatrics" OR "paediatrics" all as (textword) or (MeSH )).

We sought trials from the following sources:
1. The current Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), which includes the Cochrane Airways Group Specialised Trials Register.
2. MEDLINE (1966 to current).
3. OLDMEDLINE (1950 to 1965).
4. EMBASE (1980 to current).

Searching other resources
5. The list of references in relevant publications.
6. Written communication with the authors of trials included in the review.

The search was performed in September 2010.

Data collection and analysis

Selection of studies
Retrieval of studies: From the title, abstract, or descriptors, two authors (LT and AC) 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, the same two authors independently assessed trials for inclusion. Disagreement was resolved by consensus.

Data extraction and management
We planned to review eligible studies and record the following information: 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. We also planned to extract data on the previously described outcomes. Further information would have been requested from the trial authors where required.

Assessment of risk of bias in included studies
We planned to assess the risk of bias using the ‘risk of bias tool’ in RevMan 5 according to recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008; Review Manager). Two authors (LT and AC) would have independently assessed the quality of the included studies using the following headings: 1) sequence generation; 2) allocation concealment; 3) blinding; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other bias. Each domain would have been assessed as either high, low or unclear risk of bias. Inter-reviewer reliability for the identification of high quality studies for each component would have been measured by the Kappa statistic.

Dealing with missing data
We planned to request further information from the trial authors where required.

Assessment of heterogeneity
We planned to describe any heterogeneity between the study results and test this to see if it reached statistical significance using the Chi² test. We consider heterogeneity to be significant when the P value is less than 0.10 (Higgins 2008).

Assessment of reporting biases
If combining the data and meta-analysis had been possible, we planned to assess publication bias using a funnel plot when relevant (greater than five trials). We also planned to identify and report on any selective reporting in the included trials.

Data synthesis
For the dichotomous outcome variables of each individual study, relative and absolute risk reductions would have been calculated using a modified intention-to-treat analysis. This analysis assumes 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 would have examined whether pooling of results (meta-analysis) was reasonable. This would take into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

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) were to be calculated using RevMan 5. Numbers needed to treat (NNT) were to be calculated from the pooled odds ratio and its 95% confidence interval applied to a specified baseline risk using an online calculator (Cates 2003). The average cough indices were to be assumed to be normally distributed continuous variables so the mean difference in outcomes can be estimated (weighted mean difference). If studies reported outcomes using different measurement scales, the standardised mean difference was to be estimated. Any heterogeneity between the study results was to be described and tested to see if it reached statistical significance using a Chi² test. For cross-over trials, only those not involving surgery were to be included if the washout period was deemed adequate (at least eight weeks for medication trials and four weeks for CPAP). Generic inverse variance (GIV) of paired data were to be used for cross-overs and could have been combined with parallel studies. The 95% confidence interval estimated using a random-effects model was to be included as part of a sensitivity analysis whenever there were concerns about statistical heterogeneity.

Subgroup analysis and investigation of heterogeneity
We planned an a priori sub-group analysis for:
1. children with a syndrome (e.g. Down’s syndrome) versus non-syndromic;
2. combined versus mono interventions.

Sensitivity analysis
We planned sensitivity analyses to assess the impact of potentially important factors on the overall outcomes:
1. variation in the inclusion criteria;
2. differences in intervention types for the active arm and comparison groups;
3. differences in outcome measures;
4. analysis using random-effects model;
5. analysis by ‘treatment received’; and
6. analysis by ‘intention-to-treat’.

Results of the search

Description of studies
The Airways Group search identified 138 potentially relevant titles. After assessing the abstracts, we retrieved eight studies (including from references of reviews) for possible inclusion into review but none fulfilled the study eligibility criteria.

**Excluded studies**

There were few controlled studies on OSA in children. Those available did not report on any cough severity measures, see Excluded studies table. The main reason for excluding the studies related to absence of any data on cough. One study evaluated cough in asthmatic children who had nasal obstruction and mouth breathing and not OSA (Henriksen 1984). Another described use of antibiotics in children with chronic rhino-sinusitis, some of whom had snoring but OSA was not described (El-Hennawi 2006). The authors of two studies (El-Hennawi 2006; Li 2009) confirmed they had no data relating to cough and snoring interventions.

**Risk of bias in included studies**

There were no included studies and hence risk of bias is not applicable.

**Effects of interventions**

There were no eligible studies.

**DISCUSSION**

We identified no randomised controlled trials of OSA treatments leading to the resolution of cough in children with chronic cough. One study did evaluate the effect of an intranasal corticosteroid (budesonide) in asthmatic children with a history of nasal obstruction and mouth breathing (Henriksen 1984). The study examined its effect on asthma scores (which included cough) but did not include children with OSA.

There is a lack of relevant data on children with cough associated with OSA despite the commonality of snoring and cough in children. The few RCTs on OSA did not examine cough, likely reflecting the infrequency of cough in children with OSA. However cough has been reported in children in non-randomised controlled trials; one case report described a three year-old boy who had chronic nocturnal cough secondary to OSA (Teng 1997). Nasal CPAP alleviated the persistent nocturnal coughing in this child (Teng 1997). In a cross-sectional study, snoring in preschool children was found to be significantly associated with both nocturnal cough and asthma (Lu 2003). Because snoring, asthma and nocturnal cough may have a common aetiology, Lu 2003 concluded that it is possible that effective treatment of one symptom may lead to reductions in the presence or severity of the other symptoms. In adults with asthma, treatment of snoring and otherwise mild OSA with nasal CPAP can lead to improvements in asthma (Chan 1988).

In children, snoring is also said to be associated with chronic rhino-sinusitis (El-Hennawi 2006). However as there are no cough receptors proximal to the larynx, it is likely but remains unknown that reports of this association may reflect presence of protracted bacterial bronchitis in children. Improvement of cough associated with use of antibiotics for chronic rhino-sinusitis may reflect successful treatment for cough associated with protracted bacterial bronchitis (Marchant 2006 and hence the improvement. Snoring was associated with chronic bronchitis in a prospective cohort study on adults (Baik 2008). The causal relationship between snoring and chronic bronchitis remains unclear, and the mechanisms underlying the association are largely unknown. Given the association of the severity of lower airway inflammation with upper airway inflammation and with systemic inflammation (Hurst 2006), snoring may be linked to lower airway inflammation. In addition, airway pressure gradients, which are triggered by intermittent airway obstruction occurring in snoring, may be transmitted to the respiratory system, causing mechanical stress and resulting in inflammation (Salerno 2004).

**Agreements and disagreements with other studies or reviews**

Case series on chronic cough in adults have reported that one of the possible aetiological factors is OSA (Birring 2007). There were only four adult patients in this study, all of whom had a rapid improvement of their cough with CPAP therapy. A retrospective evaluation of management of adults with chronic cough reported that OSA was a common finding, even when another cause of cough was identified and that CPAP therapy lead to an improvement in the cough (Sundar 2010). Corbo 1989 found that respiratory symptoms in school aged children such as rhinitis and cough or sputum production, previous tonsillectomy, and passive parental smoking were associated with an increased prevalence of snoring. Bloom 1988 reported the same association (snoring and cough or sputum production) in adults. In univariate analysis Zhang 2009 also found increased allergic and other respiratory symptoms as well as smoking and nitric nitrogen dioxide exposure (in winter) in children with snoring.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

There is currently no evidence to support or refute the efficacy of treatment of OSA for the management of cough in children with...
chronic cough. Children with OSA should be managed according to the severity of the OSA and not on the basis of cough until further evidence is available. Mild OSA is not always treated (Littner 2007). Interventions for mild OSA such as nasal CPAP or surgery are only indicated for failed treatment in highly selected cases (Littner 2007). The associated small but significant risk of morbidity and mortality of some interventions for OSA (such as adenotonsillectomy) must be considered if OSA therapies are used for the outcome of cough. Other interventions for OSA such as NIPPV have substantial cost implications and should also be considered.

Implications for research

OSA will always need to be treated on its own merits. However, in mild OSA where cough is present, randomised controlled studies to determine the effectiveness of OSA treatments in such settings leading to the resolution of cough in children with chronic cough are needed. Given the difference in aetiologies for both chronic cough and OSA between adults and children, child-specific trials are required. Trials should be parallel and preferably multi-centre studies. In these trials, outcome measures should include cough resolution rates in addition to clinical outcomes. Outcome measures for the clinical trials on cough should be clearly defined using validated subjective data (including quality of life and cough diaries) and supported by objective data (such as cough frequency). Analysis of costs and possible risks and/or adverse effects of interventions for OSA such as adenotonsillectomy, NIPPV and/or pharmaceutical therapy would also provide additional useful information.

References to studies excluded from this review

Brouillette 2001 (published data only)

Don 2005 (published data only)

El-Hennawi 2006 (published data only (unpublished sought but not used))

El-Hennawi 2010 (unpublished data only)
El-Hennawi DM, Ahmed MR. Pediatric subacute rhinosinusitis under 2 years. The Egyptian Society of Ear, Nose, Throat, and Allied Sciences in press.

Henriksen 1984 (published data only)
Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. American Review of Respiratory Disease 1984;130:1014–8.

Kheirandish-Gozal 2008 (published data only (unpublished sought but not used))

Li 2009 (published data only (unpublished sought but not used))

Lojander 1996 (published data only)

McLean 2005 (published data only)

Additional references

Ali 1993
American Thoracic Society 1996

Au 2009

Baik 2007

Birring 2007

Bloom 1988

Britt 2002

Cates 2003 [Computer program]

Chan 1988

Chang 2006

Chang 2007

Cherry 2003

Chokroverty 2005

Corbo 1989

Demain 1995

Eccles 2002

Gislason 1995

Goldbart 2005

Guilleminault 1986

Higgins 2008

Huang 2008

Hurst 2006

Ing 2000

Kheirandish 2006

Kicy 2004
Littner 2007

Lu 2003

Marchant 2006

Marcus 1995

Redline 1999

Review Manager [Computer program]

Salerno 2004

Schroeder 2004

Sundar 2010

Teng 1997

Waters 1995

Zhang 2009

* Indicates the major publication for the study
### Characteristics of excluded studies

[ordered by study ID]

<table>
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<th>Study</th>
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<tr>
<td>Brouillette 2001</td>
<td>Randomised, triple-blind, placebo-controlled, parallel-group trial examining the effect of an intranasal corticosteroid (fluticasone propionate) in 25 children with OSA. No cough outcomes measured</td>
</tr>
<tr>
<td>Don 2005</td>
<td>Randomised, double-blind trial evaluating the efficacy of a broad spectrum antibiotic (azithromycin) in the management of adenotonsillar hypertrophy and OSA in 22 children. No cough outcomes measured</td>
</tr>
<tr>
<td>El-Hennawi 2006</td>
<td>Randomised controlled study in 60 children with persistent nasal discharge and nasal obstruction (and other related symptoms e.g. chronic cough, snoring). The study did not assess children with OSA</td>
</tr>
<tr>
<td>El-Hennawi 2010</td>
<td>Non-randomised study in 180 children &lt;2 years of age with subacute rhino-sinusitis (and other related symptoms including chronic cough and snoring). The study was non-randomised and did not assess children with OSA</td>
</tr>
<tr>
<td>Henriksen 1984</td>
<td>Randomised, double-blind, parallel study examining the effect of an intranasal corticosteroid (budesonide) on nasal symptoms, mode of respiration (nasal versus mouth breathing) and asthma in 37 asthmatic children who were mouth breathers because of chronic nasal obstruction. Cough was measured but the study did not assess children with OSA</td>
</tr>
<tr>
<td>Kheirandish-Gozal  2008</td>
<td>Randomised, double-blind, crossover trial examining the use of an intranasal corticosteroid (budesonide) in 62 children with mild OSA syndrome. No cough outcomes mentioned or measured</td>
</tr>
<tr>
<td>Li 2009</td>
<td>Randomised, double-blind, placebo-controlled study in 44 children with stable asthma and persistent allergic rhinitis. No cough outcomes measured</td>
</tr>
<tr>
<td>Lojander 1996</td>
<td>Randomised study in 76 adults with OSA syndrome assessing the effectiveness and safety of nasal CPAP and that of surgery in comparison to conservative management. No cough outcomes measured</td>
</tr>
<tr>
<td>McLean 2005</td>
<td>Randomised, placebo-controlled, single blind, crossover study in 10 adults with nasal obstruction and OSA. No cough outcomes measured</td>
</tr>
</tbody>
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APPENDICES

Appendix 1. Database search strategies

CENTRAL search
#1 MeSH descriptor Cough explode all trees
#2 MeSH descriptor Bronchitis explode all trees
#3 cough* or bronchit*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Sleep Apnea Syndromes explode all trees
#6 (sleep near/3 (apnea* or apnoea*))
#7 (hypopnea* or hypopnoea*)
#8 OSA
#9 SHS
#10 OSAHS
#11 MeSH descriptor Snoring, this term only
#12 (Breath* near/3 disorder*)
#13 (breath* near/3 obstruct*)
#14 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 MeSH descriptor Pediatrics explode all trees
#16 MeSH descriptor Child explode all trees
#17 MeSH descriptor Infant explode all trees
#18 MeSH descriptor Adolescent explode all trees
#19 child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or "pre school*" or pre-school* or newborn* or "new born*" or new-born* or neo-nat* or neonat*
#20 (#15 OR #16 OR #17 OR #18 OR #19)
#21 (#4 AND #14 AND #20)

MEDLINE/OLD MEDLINE search
(Combined with RCT filter)
1 exp Cough/
2 exp BRONCHITIS/
3 (cough$ or bronchit$).mp.
4 or/1-3
5 exp Sleep Apnea Syndromes/
6 (sleep$ adj3 (apnea$ or apnoea$)).mp.
7 (hypopnea$ or hypopnoea$).mp.
8 OSA.mp.
9 SHS.mp.
10 OSAHS.mp.
11 Snoring/
12 ((disorder$ adj3 breath*) or (breath* adj3 disorder*)).mp.
13 ((obstruct* adj3 breath*) or (breath* adj3 obstruct*)).mp.
14 or/5-13
15 adolescent/ or exp child/ or exp infant/
EMBASE search
(Combined with RCT filter)
1 exp COUGHING/
2 exp BRONCHITIS/
3 (cough$ or bronchit$).mp.
4 or/1-3
5 exp sleep apnea syndrome/
6 exp sleep disordered breathing/
7 (sleep$ adj3 (apnea$ or apnoea$)).mp.
8 (hypopnea$ or hypopnoea$).mp.
9 OSA.mp.
10 SHS.mp.
11 OSAHS.mp.
12 Snoring/
13 ((disorder* adj3 breath*) or (breath* adj3 disorder*)).mp.
14 ((obstruct* adj3 breath*) or (breath* adj3 obstruct*)).mp.
15 or/5-14
16 exp adolescent/ or exp child/ or exp infant/ or exp newborn/
17 (child$ or paediat$ or pediat$ or adolesc$ or infant$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or new born$ or new born$ or neo-nat$ or neonat$).mp.
18 or/16-18
19 4 and 19 and 15

CONTRIBUTIONS OF AUTHORS

LT and AC wrote the protocol and review and independently reviewed potential abstracts and papers. All reviewed the submitted review.

DECLARATIONS OF INTEREST

None known.

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