Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults (Review)

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ABSTRACT

Background

Gastrooesophageal reflux disease (GORD) is said to be the causative factor in up to 41% of adults with chronic cough. However cough and GORD are common ailments and their co-existence by chance is high. Also cough can induce reflux episodes. Treatment for GORD includes conservative measures (diet manipulation), pharmaceutical therapy (motility or prokinetic agents, H\textsubscript{2}-antagonist and proton pump inhibitors (PPI)) and fundoplication.

Objectives

To evaluate the efficacy of GORD treatment on chronic cough in children and adults with GORD and prolonged cough that is not related to an underlying respiratory disease i.e. non-specific chronic cough.

Search strategy

We searched the Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Airways Group Specialised Register, MEDLINE and EMBASE databases, review articles and reference lists of relevant articles. The date of last search was 24th April 2009.

Selection criteria

All randomised controlled trials (RCTs) on GORD treatment for cough in children and adults without primary lung disease.

Data collection and analysis

Two review authors independently assessed trial quality and extracted. Study authors were contacted for further information.
Main results

Eighteen studies (5 paediatric, 13 adults) were included. None of the paediatric studies could be included in meta-analysis. In adults, analysis on use of H₂ antagonist, motility agents and conservative treatment for GORD were not possible (from lack of data) and there were no controlled studies on fundoplication as an intervention. Nine adult studies comparing PPI (two to three months) to placebo were analysed for various outcomes in the meta-analysis. Enrolment of participants subjects for two studies were primarily from medical clinics and another eight studies were otolaryngology clinic patients or patients with laryngeal symptoms. Using “intention to treat”, pooled data from studies resulted in no significant difference between treatment and placebo in total resolution of cough, Odds Ratio 0.46 (95% confidence interval (CI) 0.19 to 1.15). Pooled data revealed no overall significant improvement in cough outcomes (end of trial or change in cough scores). Significant differences were only found in sensitivity analyses. A significant improvement in change of cough scores was found in end of intervention (two to three months) in those receiving PPI with a standardised mean difference of -0.41 (95% CI -0.75 to -0.07) using generic inverse variance analysis on cross over trials. Two studies reported improvement in cough after five days to two weeks of treatment.

Authors’ conclusions

There is insufficient evidence to definitely conclude that GORD treatment with PPI is universally beneficial for cough associated with GORD in adults. The beneficial effect was only seen in sub-analysis. The optimal duration of such a trial of therapy to evaluate response could not be ascertained although two RCTs reported significant change by 2-weeks of therapy. Clinicians should be cognisant of a period (natural resolution with time) and placebo effect in studies that utilise cough as an outcome measure. Future paediatric and adult studies should be double blind, randomised controlled, parallel design, using treatments for at least two months, with validated subjective and objective cough outcomes and include ascertainment of time to respond as well as assessment of acid and/or non-acid reflux.

PLAIN LANGUAGE SUMMARY

Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

Cough in association with GORD is common in adults with chronic cough. The objective of this review was to evaluate the effectiveness of GORD treatment in children and adults with GORD and prolonged cough that is not related to an underlying respiratory disease i.e. non-specific chronic cough. Thirteen studies fulfilled predetermined criteria but only six could be used in various components of the meta-analysis including data obtained from trialists. Limited data on children prohibited any meta-analysis. In adults with cough and GORD, no significant difference was found in clinical cure using proton pump inhibitors (PPI) for cough and GORD. Using other outcomes, there was also no significant differences between PPI and placebo. This review also highlights the large placebo and time period effect of treatment for chronic cough. In adults GORD treatment with PPI for cough associated with GORD is inconsistent and its benefit variable. There was insufficient data to draw any conclusion from other therapies for cough associated with GORD. In children, the data is also inconclusive; thickened feeds had an inconsistent effect and no studies has examined PPI for cough and GORD.

BACKGROUND

Cough is the most common symptom presenting to general practitioners (Britt 2002). Worldwide, the desire to reduce the impact of the symptom of cough is reflected in the billions of dollars spent on the counter cough and cold medications (Mortice 2002). Non-specific cough has been defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology (Chang 2001). Prolonged or chronic cough has been variously defined as a cough which persists greater than three to eight weeks. Gastrooesophageal reflux (GOR) i.e. reflux of gastric contents into the oesophagus can be acid or non-acid (volume or alkaline reflux) and these occur physiologically, especially in the post-cibal state (AMA 1996). When reflux is 'excessive', GORD disease (GORD) is present. Symptoms attributed to GORD range from a variety of
When successfully treated, GORD associated cough is associated with a decrease in objective measurements of cough sensitivity (O’Connell 1994). In animals, potent acid instillation into the oesophagus causes airway neurogenic inflammation (Daoui 2002). In adult humans similar experimentation causes cough in a temporal manner (within 70 seconds) (Ing 1994). Although a temporal relationship has been shown in the laboratory, cough is reported in some earlier studies to only resolve after a mean time of 169 to 179 days following treatment for acid-GORD related cough (Irwin 2002a). It is thus not surprising that conflicting data have been reported and others have shown that acid GORD is associated with, but not the causative factor for, cough. Also, effective treatment of GORD that resolves gastrointestinal GORD symptoms may have no effect on objective pulmonary data (Ferrari 1995). Furthermore like asthma and GORD, both GORD and cough are common diseases, often coexist, and their association does not imply cause and effect (AMA 1996; Rudolph 2001; Rudolph 2003, Vakil 2006). Nevertheless, several reviews/guidelines suggest a therapeutic trial of three to six months of GORD treatment for non-specific chronic dry cough in both adults and children (Corrao 1996; Irwin 2002a; Kiljander 2003).

Current treatment for GORD include conservative anti-reflux measures (diet, positioning etc), pharmacological approaches [acid suppressing agents: histamine (H2) receptor antagonists, proton pump inhibitors (PPI) and prokinetic agents: domperidone, erythromycin, metoclopramide and previously cisapride] and surgical approaches (Nissen or Toupet fundoplication by laparoscopic or open procedures) (Rudolph 2001).

There are several definitions of GORD. Excessive distal oesophageal acidification is the most common clinical scenario of GORD and can be defined by the histological presence of reflux oesophagitis (on biopsy) or distal oesophageal pH metry (24 hour pH study) (AMA 1996). Distal pH metry is the most sensitive method for defining acid GORD and is a standard test recommended for evaluating chronic cough (Chung 1996; Irwin 1998). In children, acid GORD is present if distal pH metry shows a reflux index (% time pH < 4) of > 10% in infants, and > 4% in children aged over 12 months as suggested by GORD guidelines by the European (Vandenplas 1993) and American paediatric gastroenterology groups (Rudolph 2001). Dual channel (proximal and distal) oesophageal pH metry has also been used in assessing GORD with arguable clinical use even in the assessment of patients at risk for upper airway complications of GORD (Rudolph 2001). However there is variation in what constitutes an abnormal reflux index; in adults the definition of abnormal pH metry consistent with GORD varies from a reflux index of greater than 3.9 to 7.2% (AMA 1996).

A systematic review examining the efficacy of the various treatment modalities for prolonged non-specific cough in adults and children and GORD would help clarify the link (or otherwise) between cough and GORD.

**OBJECTIVES**

To evaluate the effectiveness of GORD treatment in adults and children with GORD and prolonged cough not related to an underlying respiratory disease i.e. non-specific chronic cough.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials of any GORD treatment with cough as an outcome, where cough is not primarily related to an underlying respiratory disorder (such as cystic fibrosis, asthma, chronic obstructive airway disease, suppurative lung disease etc) or medication use (ACE inhibitor).

**Types of participants**

Adults and/or children with chronic (three or more 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 (greater than two episodes), presence of other respiratory symptoms (productive cough, 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 therapies for GORD. Trials only comparing two or more medications without a placebo comparison group were not included. The following treatment regimes were evaluated:

1. Anti-reflux conservative measures
2. H₂ receptor antagonists
3. Proton pump inhibitors (PPI)
4. Surgical therapy

Trials that included the use of other medications or interventions was included if all participants had equal access to such medications or interventions.

**Types of outcome measures**
Attempts were made to obtain data on at least one of the following outcome measures.

**Primary outcomes**
Proportions of participants who were not cured or not substantially improved at follow up (failure to cure).

**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., rash, surgical morbidity etc).
5. Proportions experiencing complications e.g., requirement for medication change, repeat surgery 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 is listed first in the hierarchy was used).
1. Objective measurements of cough indices (cough frequency, cough receptor sensitivity).
2. Symptomatic (Quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the patient (adult or child).
3. Symptomatic (Quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the parents/carer.
4. Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by clinicians.
5. Relevant airway markers consistent with inflammation.

**Search methods for identification of studies**

The following topic search strategy was used to identify the relevant randomised controlled trials listed on the electronic databases:

- gastro-oesophageal reflux OR gastroesophageal reflux OR gastro-esophageal reflux OR reflux OR “ger” OR “gerd” OR “acid” OR “esophagus” OR “oesophagus”, all as [textword] or [MeSH] AND ("cough" as [textword] or [MeSH])

For the full strategies please see Appendix 2; Appendix 3 and Appendix 4.

We identified trials from the following sources:
1. The Cochrane Controlled Trials Register (CENTRAL) which includes the Airways Collaborative Review Group Specialised Trials Register.
2. MEDLINE 1966 to 2009. Topic search strategy combined with the MEDLINE randomised controlled trial search filter as outlined in the Airways Group module.
3. OLDMEDLINE 1951 to 1965. Topic search strategy combined with the Medline randomised controlled trial search filter as outlined in the Airways Group module.
4. EMBASE 1997 to 2009. Topic search strategy combined with the EMBASE randomised controlled trial search filter as outlined in the Airways Group module.
5. The list of references in relevant publications.
6. Written communication with the authors of trials included in the review when necessary.

Searches are current as of April 2009.

**Data collection and analysis**

**Selection of studies**

From the title, abstract or descriptions, two review authors (ABC, LAG) 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 review authors independently selected trials for inclusion. Agreement was measured using kappa statistics. Disagreement was resolved by consensus.

**Data extraction and management**

Trials that satisfied the inclusion criteria were reviewed and the following information recorded: study setting, year of study, source of funding, patient recruitment details (including number of eligible participants), inclusion and exclusion criteria, criteria used for GOR diagnosis, GOR symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of GORD therapy, 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 extracted data on the outcomes
described previously. Further information was requested from the authors if required.

Assessment of risk of bias in included studies

Two review authors independently performed quality assessment on studies included in the review. Four components of quality were assessed:

1. Allocation concealment. Trials will be scored as: Grade A: Adequate concealment, Grade B: Unclear, Grade C: Clearly inadequate concealment. (Grade A = high quality).
2. Blinding. Trials will be 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 will be scored as: Grade A: The progress of all randomised participants in each group described, Grade B: Unclear or no mention of withdrawals or dropouts, Grade C: The progress of all randomised participants in each group clearly not described. (Grade A = high quality).
4. Follow up. Trials will be 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 to 90%, Grade C: Unclear, Grade D: Outcomes measured in < 80%. (Grade A = high quality)

While only the allocation concealment quality assessment was displayed in the meta-analysis figures, all assessments were included in Characteristics of included studies. We measured Inter-review author reliability for the identification of high quality studies for each component using the Kappa statistic. Each study was also assessed using a 1 to 5 scale described by Jadad et al (Jadad 1996) and summarised as follows:

1. Was the study described as randomised? (1 = yes; 0 = no)
2. Was the study described as double blind? (1 = yes; 0 = no)
3. Was there a description of withdrawals and dropouts? (1 = yes; 0 = no)
4. Was the method of randomisation clearly described and appropriate? (1 = yes; 0 = no)
5. Was the method of double blinding well described and appropriate? (1 = yes; 0 = no)

When authors of papers gave additional data, quality assessments and Jadad scores were based on additional data supplied.

Data synthesis

An initial qualitative comparison of all the individually analysed studies examined whether pooling of results (meta-analysis) was reasonable. This took 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 were included in the subsequent meta-analyses. In cross-over trials (Eherer 2003; Kiljander 2000), when data was combined with parallel studies only data from the first arm was used as recommended (Elbourne 2002) There is methodological arguments of handling cross over data (Clarke 2003; Elbourne 2002) and we considered it was invalid to use second arm data given the known period effect of cough (i.e. cough tends to resolve with time (Chang 2001) and carry-on effect (studies had short wash time of two weeks compared to eight weeks of therapy in each arm).

For the dichotomous outcome variables of each individual study, relative and absolute risk reductions were calculated using a modified intention-to-treat analysis. This analysis assumes that participants not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). Numbers needed to treat (NNT) was calculated from pooled data with ‘intention to treat’ used as the denominator and calculated using the formula 1/risk difference (Clarke 2003). Event was defined as successful treatment defined by absence of cough by end of treatment period.

Imputed correlation coefficient for calculation of standard deviation of change from baseline (Clarke 2003) was derived from other studies in the review. The summary weighted risk ratio and 95% confidence interval (fixed-effect model) was calculated using the inverse of the variance of each study result for weighting (RevMan 2002). Data were pooled from similar studies, assuming cough indices were normally distributed continuous variables. For cross-over studies, mean treatment differences were calculated from raw data, extracted or imputed and entered as fixed-effect generic inverse variance (GIV) outcome was used to give a weighted SD unit difference and 95% confidence intervals (RevMan 2008) Heterogeneity between the study results was tested to see if it reached statistical significance using a chi-squared test. The 95% confidence interval estimated using a random-effects model was included whenever there were concerns about statistical heterogeneity.

Gastrointestinal symptoms were not included in the forest plots as it is not an objective of this review.

Subgroup analysis and investigation of heterogeneity

Sub-group Analysis:

An a priori sub-group analysis was planned
1. Age: adults or children (aged < 18 years and < 12 months)
2. Definition of GORD used: acid GORD defined by pH metry or oesophageal biopsy or non acid/volume (alkaline) reflux or ‘extraoesophageal reflux’.
3. Intervention type: medical or surgical intervention

Medical intervention further sub-grouped to:

a) H2 antagonists;
b) proton pump inhibitor (PPI);
c) conservative therapy.
Sensitivity analysis

We planned sensitivity analyses to assess the impact of the potentially important factors on the overall outcomes:

1. Study quality;
2. Study size;
3. Variation in the inclusion criteria;
4. Differences in the medications used in the intervention and comparison groups;
5. Differences in outcome measures;
6. Analysis using random effects model;
7. Analysis by "treatment received";
8. Analysis by "intention-to-treat"; and
9. Analysis by study design-parallel and cross over studies (added after protocol written).

We had planned to tested for publication bias using a funnel plot.

RESULTS

Description of studies

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

Results of the search

The 2008 search resulted in 432 potential titles. Of these 10 papers were retrieved, 6 papers were excluded and 4 new studies included. One of the included studies (Wo 2006) was identified from an excluded paper (Coron 2007) that was a generic review of the subject. All the 4 studies (Chao 2007; Moukarzel 2007; Pawar 2007; Wo 2006) were supported by the pharmaceutical industry involved in the product trialled in the study. This updated Cochrane review now has a total of 18 included studies (14 from previous version and 4 from current update). See Appendix 1 for details of results of previous searches. The 2009 search identified 457 potential titles; 15 papers were retrieved but none fulfilled inclusion criteria. Two studies were added to the excluded studies list.

Included studies

Paediatrics

There were five studies in children; four in infants and one in children. Orenstein and colleagues' study described increased cough with thickened feeds as an intervention in a diverse group of infants with cough and GORD (Orenstein 1992). Although most in the group were otherwise well infants, some had primary respiratory disease (hence did not have non-specific cough). Four studies (Orenstein 1992; Vanderhoof 2003; Chao 2007; Moukarzel 2007) reported on the use of specific anti-regurgitation formula milk (as opposed to thickened formula) in infants with GORD that included cough as an outcome measure. However Moukarzel 2007 did not provide data specific to cough in the publication. Orenstein and colleagues' study described increased cough with thickened feeds as an intervention in a diverse group of infants with cough and GORD (Orenstein 1992). Although most in the group were otherwise well infants, some had primary respiratory disease (hence did not have non-specific cough). Three studies were supported (one in part) by the manufacturers of the milk utilised (Vanderhoof 2003; Chao 2007; Moukarzel 2007) and the other (Xinias 2003) was excluded because it was an open non-randomised (but controlled) trial. Outcome measures of the four studies on infants varied; in two he multi-centre studies (Vanderhoof 2003; Moukarzel 2007) cough was reported as part of a symptom complex (with gag or choke, etc) and although the authors provided further information, the data could not be used for analysis in this review. In one study only a small number of infants had cough (9 of 81) (Chao 2007) displayed in outcome 1.1 (no significant difference between groups).

The single study in children (Dordal 1994) included children with asthma; its exclusion criteria were insufficiently defined to allow classification of participants as having non-specific cough and it is unclear if the study was a randomised study. There were no controlled trials on the use of PPIs or surgery in infants or children.

Adults

In adults, thirteen studies were included; eleven were published articles, one in abstract form (Kopec 2001) and one in a conference report plus abstract (Ing 1997). Additional data were sought from all but one author(s), six responded but only three (Eherer 2003; Kiljander 2000; Vaizi 2006) were able to provide additional data that could be used for the meta-analysis. Although all studies included cough that was presumed associated with GOR, criteria for entry into the studies varied. In six studies, participants enrolled through the otolaryngology department had “laryngitis” symptoms (Eherer 2003; Havas 1999; Noordzij 2001; Steward 2004; Wo 2006). One study based in medical clinics also primarily enrolled participants with chronic “laryngitis” (Vaizi 2006). In these studies where subjects were recruited from otolaryngology clinics, primary lung disease (such as asthma defined by hyper-responsiveness) as an exclusion criteria were not as stringent as they were in the studies enrolled through medical outpatients (Ing 1997; Jaspersen 1999; Kiljander 2000; Ours 1999). Mean age of participants reported in studies was 46 to 58 years (range 18 to 80 years). Some studies had predominantly males (Eherer 2003; Ours 1999) whereas others had predominantly females (Kiljander 2000; Steward 2004; Wo 2006). Two One study had similar proportions of males to females (Vaizi 2006; Pawar 2007). In all but one study...
(Jaspersen 1999), presence of GOR (or extra-oesophageal reflux) were confirmed objectively. However in Vaedi and colleagues study, only 29% of participants had pHmetry characteristics of GORD (Vaedi 2006). In most the diagnosis of GOR was made with pHmetry, and some included dual channels. None of the studies used alkaline or volume reflux as an entry criteria although oesophageal manometry was also used in two studies.

There were ten parallel studies and three crossover studies, both with wash out periods of two weeks. Ten studies compared PPI to placebo but varying doses and frequency were used. Studies involving participants with 'laryngitis' (Eherer 2003; El Serag 2001; Havas 1999; Noordzij 2001; Vaedi 2006; Steward 2004; Pawar 2007) generally used higher doses of PPIs (twice daily regime). Three studies used omeprazole (Kiljander 2000; Noordzij 2001; Ours 1999), one used esomeprazole (Vaedi 2006) and the other three studies used a different PPI, pantoprazole (Eherer 2003; Wo 2006), rabeprazole (Steward 2004; Pawar 2007) and lansoprazole (Havas 1999; El Serag 2001). One study compared PPI to ranitidine (Jaspersen 1999) and another was a factorial design using cisapride and diet intervention (Kopec 2001). In one study (Steward 2004) all subjects (i.e. both controls and intervention groups) also received instructions to lifestyle modification. There was a single study on H2-antagonist versus placebo (Ing 1997), published only as a report on an oral presentation and abstract format. Data from this study was presented graphically (provided by the author) and could not be used as points on the graph were unclear (number in the study did not equate to the number of points on the graph). There were no randomised controlled studies on surgical intervention.

Length of intervention in the study on H2-antagonist versus placebo was two weeks each (Ing 1997). In the studies using PPI, length of intervention was two to three months (or 8 to 12 weeks) and two study had prolonged follow up post trial (Ours 1999). Outcome measures for all studies were subjective cough scales of varying types. Two studies had outcome assessments done mid way through trial (Havas 1999; Noordzij 2001), one had several evaluations during the trial (Vaedi 2006) but only one of these studies provided 'during trial' cough data in the paper (Noordzij 2001). Objective cough monitoring was not used in any study. In all but one study, gastrointestinal or "extra-oesophageal" symptoms of GORD were also outcome measures. Adverse events were specifically mentioned in six studies.

**Risk of bias in included studies**

Jadad score of the studies varied from 1 to 5; six studies had scores of 5 (Eherer 2003; Ours 1999; Vaedi 2006; Vanderhoof 2003; Steward 2004; Wo 2006), three studies scored 4 (El Serag 2001; Kiljander 2000; Noordzij 2001), three studies scored 3 points (Havas 1999; Ing 1997; Pawar 2007), three study scored 2 points (Orenstein 1992; Chao 2007; Moukarzel 2007), and three scored one point (Dordal 1994; Jaspersen 1999; Kopec 2001). The quality score also varied: One study scored ‘high quality’ in all four categories (Steward 2004). Five studies (Eherer 2003; El Serag 2001; Ours 1999; Vaedi 2006; Wo 2006) scored ‘high quality’ in three categories and four studies did have any high quality points for all four categories. Agreement between the two main reviewers (AC and LG) for quality of studies was excellent; weighted kappa score was 0.88 for Jadad score and 0.77 for quality assessment.

In the studies in infants, randomisation and blinding were clearly described in two studies (Orenstein 1992; Vanderhoof 2003). Randomisation method and blinding were not mentioned in the other 2 studies in infants (Chao 2007; Moukarzel 2007) or in the study in children (Dordal 1994). In the adult studies, the randomisation process was clearly described in four but allocation concealment was unclear in all but one study (Steward 2004, Figure 1). Method of blinding (i.e. appearance of placebo) was clearly described in five studies (Eherer 2003; Noordzij 2001; Ours 1999; Vaedi 2006; Wo 2006). There were only four studies with data (including data that were sought from authors) that could be utilised as ‘intention to treat’ for selected analysis (Eherer 2003; Kiljander 2000; Ours 1999; Vaedi 2006) without making any assumptions.

Figure 1. Methodological quality graph: review authors’ judgments about each methodological quality item presented as percentages across all included studies.
Effects of interventions

The 18 studies included 823 randomised participants (372 paediatrics, 476 adults) with 506 (317 paediatrics, 412 adults) completing the trials. Sixteen articles were published in English, one in German (Jaspersen 1999) and another in French (Dordal 1994). In the updated searches of 2005, 2006 and 2007 three studies (El Serag 2001; Vaezi 2006; Steward 2004) were found from recent review articles and the numbers above include these papers. Some of the trialists responded to requests for data. Although entry criteria were fulfilled in some participants, data on cough alone in these participants was not available on one study (El Serag 2001) but was available in the other two studies (Vaezi 2006; Steward 2004).

Paediatrics

There were insufficient data in infants and children to be displayed in the MetaView graphs as trials in infants were too dissimilar to be included in a meta-analysis. All four studies in infants found improvement in GORD symptoms referring to the GI system but data for effect on cough was inconsistent; the smaller study (Orenstein 1992) described significant increase in cough frequency post feeds when thickened feeds were given, Figure 2. The multicentre study described decrease in percentage of feeds associated with cough/gag/choke episodes in infants given pre-thickened milk (Vanderhoof 2003). Cough/gag/choke was grouped as a secondary outcome and scored in a binary manner in the study of Vanderhoof and colleagues (Vanderhoof 2003). Additional information was sought and provided but authors were unable to provide data on cough alone (cough was included in symptom complex with choke or gag or cough). In the Chao 2007 study, the number of children with cough was small (n=9 out of 81 infants who completed the study) and the difference between groups was not significant (outcome 1.1). In the Moukarzel 2007 study, although cough was an outcome measure, cough specific data were not presented in the paper. In the excluded study Xinas and colleagues found no effect of the anti-regurgitation formula milk on cough (Xinas 2003). Dordal and colleagues described no significant effect of cisapride or domperidone on cough presumably secondary to GORD (Dordal 1994). No adverse events were reported in any study.

Figure 2. Forest plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.1 Clinical failures (still coughing at end of trial or reporting period).

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<td>2.1.1 Medical clinics based enrolment</td>
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<td>Kojander 2000</td>
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<td>Test for overall effect: Z = 1.49 (P = 0.14)</td>
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2.1.2 Otolaryngology based enrolment

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<td>Total events</td>
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<tr>
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<thead>
<tr>
<th>Study or Subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>116</td>
<td>75</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>95</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hotston 2000</td>
<td>73</td>
<td>94</td>
<td>43</td>
<td>48</td>
</tr>
</tbody>
</table>

Adults

Cough outcomes

In the single study comparing PPI to H2-antagonist, 70% of those on PPI improved versus 30% of participants on H2-antagonist...
Data from the only study comparing H₂-antagonist to placebo was presented graphically and showed improvement in cough scores by intervention in all participants and the effect was significant by two weeks (Ing 1997).

In the ten studies comparing PPI or cisapride to placebo, all but two studies showed no difference between improvement of cough scores in the active versus placebo arms (Eherer 2003; Havas 1999; Kopec 2001; Noordzij 2001; Ours 1999; Steward 2004; Vaezi 2006; Wo 2006). Only two studies described a significant difference in favour of PPI (Kiljander 2000; Pawar 2007). In the meta-analysis the outcomes are described below:

**Primary outcome: Failure to cure (outcome 02.01)**

This was the only outcome where "intention to treat" data could be utilised in all included studies for this outcome (Eherer 2003; Kiljander 2000; Ours 1999; Vaezi 2006) displayed in the forest plot. Pooled OR effect estimate was 0.46 and non significant (95% CI 0.19 to 1.15, Figure 2). In Wo and colleagues study, the "% of subjects with adequate relief" was reported to be similar in both the PPI group and placebo group (40% and 42% respectively, p=0.89). As data specific for cough could not be obtained, this study was not included in the meta-analysis.

**Mean cough score at end of trial (outcome 02.02)**

In pooled analysis of four studies (Eherer 2003; Kiljander 2000; Noordzij 2001; Pawar 2007), the effect of active drug of borderline statistical significance (SMD -0.38, 95% CI -0.77 to 0, P = 0.05, Figure 3). A pooled analysis of data from crossover studies (Eherer 2003; Kiljander 2000) was also not significant (SMD -0.29, 95% CI -0.62 to 0.04,).

### Table 1. Forest plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.2 Mean cough score at end of trial (1st arm crossover/parallel group trials).

<table>
<thead>
<tr>
<th>Study</th>
<th>PPI Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Kiljander 2000</td>
<td>6.89 (5.01)</td>
<td>9.91 (4.1)</td>
<td>-0.80 (1.77, 0.05)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>9</td>
<td>12</td>
<td>17.8%</td>
<td></td>
</tr>
</tbody>
</table>

**Change in cough scores at end of intervention (parallel group/1st arm crossover data) (outcome 02.03 to 02.05)**

Pooled analysis for all six studies (Eherer 2003; Havas 1999; Kiljander 2000; Noordzij 2001; Steward 2004; Pawar 2007) was statistically significant (SMD -0.39, 95% CI -0.77 to -0.08, Figure 4), and there was a moderate level of heterogeneity (I²=12%). The two studies (Kiljander 2000; Noordzij 2001) which utilised omeprazole showed a significant benefit (SMD -0.71, 95% CI -1.29 to -0.41) and no significant heterogeneity. The studies that utilised other PPIs (lansoprazole, rabeprazole or pantoprazole) (Havas 1999; Eherer 2003; Steward 2004; Pawar 2007) showed no significant benefit of PPI over placebo. Within each subgroup, there was no significant heterogeneity, between group test for difference between omeprazole and the other PPIs was non significant (SMD -0.45, 95% CI -1.13 to 0.23). This subgroup analysis was post hoc. Kiljander 2000 and Noordzij 2001, the two studies that used omeprazole were also the studies that reported data at week four and whilst the study drugs may have an effect over a longer period than one month, the evidence from our analyses should be cautiously applied for several reasons. Firstly the sample sizes of the trials were small, and the sensitivity of the symptom scales is as yet unqualified. However, data from the two crossover trials (Eherer 2003; Kiljander 2000) assessing mean change in symp-
toms may confer some validity to the notion that there is an effect on symptom change. When these data were pooled using change from baseline scores, there was a significant difference of -0.41 standard deviation units (95% CI -0.75 to -0.07, Figure 5). The result with absolute scores was not statistically significant (Figure 6).

Figure 4. Forest plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.3 Change in cough scores (end-beginning of intervention - 1st arm crossover/parallel group trials).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>N, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.1 studies using omeprazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kliander 2000</td>
<td>-4.59</td>
<td>5.18</td>
<td>-0.41</td>
<td>-1.09 [-2.03, -0.01]</td>
</tr>
<tr>
<td>Nordest 2001</td>
<td>-11.29</td>
<td>165.68</td>
<td>-0.40</td>
<td>-1.03 [-1.21, 0.25]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td>27</td>
<td>30.4%</td>
<td>-0.71 [-1.29, 0.14]</td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 1.01, df = 1 (P = 0.32), I² = 1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.42 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3.2 studies using other PPI (lansoprazole, pantoprazole, rabeprazole)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>N, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewer 2003</td>
<td>-1.4</td>
<td>2.7</td>
<td>0.07</td>
<td>0.30 [-0.81, 1.50]</td>
</tr>
<tr>
<td>Hamza 1999</td>
<td>-0.9</td>
<td>3.37</td>
<td>0.98</td>
<td>-0.01 [-1.03, 1.00]</td>
</tr>
<tr>
<td>Fawar 2007</td>
<td>-0.52</td>
<td>1.23</td>
<td>0.776</td>
<td>-0.52 [-1.21, -0.03]</td>
</tr>
<tr>
<td>Steward 2004</td>
<td>-1.2</td>
<td>2.45</td>
<td>1.4</td>
<td>-0.11 [-0.75, 0.54]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>52</td>
<td>58</td>
<td>68.6%</td>
<td>-0.26 [-0.64, 0.12]</td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 3.01, df = 3 (P = 0.39); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.33 (P = 0.19)</td>
<td></td>
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</tbody>
</table>

Total (95% CI) 76 85 100% 0.39 [0.71, 0.00] 1 1 1

Favours PPI  Favours Placebo

Figure 5. Forest plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.4 Change in cough scores (crossover studies; standardised scale).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SD units</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
<th>SD units</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4.1 Sub-category</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewer 2003</td>
<td>-0.34</td>
<td>0.277</td>
<td>38.7%</td>
<td>-0.34 [0.00, 0.20]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kliander 2000</td>
<td>-0.45</td>
<td>0.22</td>
<td>61.3%</td>
<td>-0.45 [-0.88, -0.02]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>-0.41 [-0.75, -0.07]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.10, df = 1 (P = 0.76); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.37 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% -0.41 [-0.75, -0.07] 1 1 1

Favours PPI  Favours placebo

Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults (Review) 10
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Change in cough scores at week four of intervention (outcome 02.06)

Two studies (Kiljander 2000; Noordzij 2001) could be utilised for assessment of time effect i.e. after four weeks of intervention. The change in cough score was in favour of PPI use but was not significant ($P = 0.09$) with a standardised mean difference of $-0.51$ (95% CI -1.08 to 0.06, Figure 7).

Change in cough score between week eight (end of intervention) and week four (mid-intervention) (outcome 02.07)

Two studies (Kiljander 2000; Noordzij 2001) could be utilised for assessment of time effect from eight weeks (two months) to four weeks (one month) of intervention. There was no significant difference between change in cough score between week eight and week four (SMD of $-0.44$ (95% CI -1.04 to 0.16), Figure 8.
Determination of time to respond and duration of treatment effect was limited. The two studies that reported on scores midway through trial (at one month (Noordzij 2001) and at six weeks (Havas 1999)) found no difference in scores between midway scores versus end of trial scores. In the meta-analysis, whereby raw data was obtained from Kiljander 2000 (data from Havas 1999 could not be included), no significant effect was found between week eight and week four. In one crossover study, cough resolved while on omeprazole in two adults but recurred in the washout phase (Kiljander 2000). One study that reported time to response (Ours 1999) was also the only paper that had follow-up post trial (open non-RCT followed the double blind randomised placebo controlled parallel trial). The authors reported that cough totally resolved or showed a downward decline in cough scores in 5 to 14 days in coughers who responded to open label PPI (Ours 1999).

None of the studies reported any significant adverse events to interventions and hence ‘number needed to harm’ was not relevant in this review. Heterogeneity between studies included for meta-analysis was non-significant for all outcomes analysed. Funnel plot however looked asymmetrical but study numbers were small. Association between level of risk and benefit was not possible.

Gastrointestinal symptoms of GORD

All studies with sufficient data provided reported significant improvement in GI symptoms over time but treatment arm was no different from placebo arm in five studies (Eherer 2003; Havas 1999; Noordzij 2001; Pawar 2007; Wo 2006). In two studies, improvement in GORD symptoms could not be determined from lack of data or GORD symptoms were presumed absent (Ing 1997; Kopec 2001).

Laryngeal symptoms and scores

All eight studies that included this outcome measure reported significant improvement in other laryngitis symptoms over time (Eherer 2003; El Serag 2001; Havas 1999; Noordzij 2001; Steward 2004; Vaeezi 2006; Wo 2006). In six studies, the difference in total symptom improvement was similar in both the treatment arm and placebo arms (Eherer 2003; Havas 1999; Steward 2004; Vaeezi 2006; Pawar 2007; Wo 2006). One study found significant differences between PPI and placebo in hoarseness and throat clearing but not in throat pain (Noordzij 2001). Another study (El Serag 2001) described that a higher proportion of participants in the PPI group (86%) had a complete response when compared to the placebo group (40%) but no significant difference in laryngoscopy assessment. One study described no difference between PPI and placebo in total score but an improvement in cough score in favour of PPI, yet the objective score in reflux (by video laryngoscopy) significantly favoured the placebo group (Pawar 2007). Wo and colleagues described that at the 4 week follow up period post cessation of treatment, those on PPI had a significantly higher recurrence of laryngeal symptoms then those on placebo (Wo 2006).

When assessed by laryngoscopy, four studies described significant improvement in laryngoscopy-based scores but again the improvement in those receiving PPI was similar to those on placebo (Eherer 2003; Havas 1999; Steward 2004; Vaeezi 2006). However, Noordzij 2001 found no significant difference in laryngoscopy scores before and after treatment in both arms. Pawar 2007 and Wo 2006 described a significant difference between groups, both favouring the placebo group.

Sensitivity analyses

Limiting analysis to studies with Jadad score of 5 did not change the primary outcome (proportions not cured) with an effect estimate of 0.52 95% CI 0.20 to 1.35 (all-inclusive effect estimate 0.46, 95% CI 0.19 to 1.15). It was not possible to perform this on other outcomes. Varying inclusion criteria by removing studies of participants enrolled from otolaryngology clinics also did not change the primary outcome (effect estimate 0.17, 95% CI 0.02 to 1.73). Varying inclusion criteria by limiting studies to participants with ‘laryngitis’ also did not change the primary outcome (effect estimate 0.24, 95% CI 0.21 to 1.49). It was again not possible to test this effect on other outcomes in the MetaView. Varying inclusion criteria by removing studies of participants enrolled from medical clinics did not alter non-significance of results (altered ‘change in cough score’ outcome from all-inclusive SMD -0.4, 95% CI -0.86 to 0.06) to SMD -0.18, 95% CI -0.71 to 0.35). ‘Mean cough score at end of trial’ did not significantly change when medical clinic studies were omitted; SMD -0.34, 95% CI -0.97.
to 0.28 and analysis was not possible for the primary outcome. It was not possible to test for analysis for medication class type or study size because of all studies were small and only studies on PPI could be used in meta-analysis. Analysis by treatment received did not change the primary outcome i.e. proportions not cured; effect estimate 0.3 (95% CI 0.06 to 1.44). As for analysis for other outcomes were performed on “treatment received” (not possible on “intention to treat analysis”), this was not repeated for the other three outcomes. There was no difference in results when random effects model was used in all outcome measures shown in the MetaView. If however data from both arms of the cross-over studies were treated as parallel studies, a significant difference was found between week eight and week four (SMD -0.76 (95% CI -1.27 to -0.25) suggesting that the non significant effect is possibly related to a small sample size.

**Discussion**

This systematic review of 18 studies (five in infants/children and thirteen in adults) has shown the lack of high-level evidence that the treatment for GORD associated cough improves subjective cough in participants with non-specific cough universally. There was no effect in pooled analysis and the beneficial effect was seen only in the subgroup analysis. The OR for cough resolution pooled from four studies was insignificant and if calculated, the number to treat to achieve cough resolution was high at 14.9 and the 95% confidence interval around the NNT ranged from a negative number to a positive one which hence includes possible harm. Hence the CI was not given (Altman 1998) and this emphasises that treatment was not very different to placebo. This review also highlights the large placebo and time period effect of treatment for chronic cough.

In contrast to the low effect of GORD treatment on cough found in RCTs, in non-controlled trials (see Characteristics of excluded studies’ table) the improvement rate of cough by surgical intervention for GORD associated cough has been reported as high as 92% (Wright 2003) with cure rates as high as 81% (Brouwer 2003). For non-surgical intervention e.g. with PPI alone (Habermann 2002) or PPI with motility agents (Poe 2003), cough improvement rates of 86 to 100% have been reported (Habermann 2002; Poe 2003). The large difference between the effect of treatment of GORD on cough seen in RCT and uncontrolled trials is likely related to the period effect and/or placebo effect also reported in other treatments for cough (Chang 1999). The placebo effect of cough treatments has been reported to be as high as 85% (Eccles 2002). The high rate of placebo effect was specifically highlighted in two of the included studies (Eherer 2003; Noordzij 2001).

The beneficial effects of PPI for cough and GORD was inconsistent; significant only when cough outcomes were change in cough scores at end of trial of studies which used omeprazole (Kiljander 2000; Noordzij 2001) (both these studies also reported four weeks change) and in the GIV analysis on cross-over studies (Eherer 2003; Kiljander 2000). Non significant changes were found in the primary outcome measure of failure to cure, as well as in mean cough score at end of trial (borderline non-significant) and, when all studies were combined for change in cough score at end of trial analysis. While a possible contributor to this is the lack of power, another possible contributor to the inconsistent and small treatment effect is that, as cough and GORD are both common symptoms, the presumed GORD related cough was not caused by GORD. This explanation suggests that in a high proportion of cases of presumed GORD related cough, there is in fact an alternative cause for the persistent cough. Indeed cough is the most common symptom presenting to doctors (Britt 2002). Both GOR and cough are common diseases, often co-exist and its association does not imply cause and effect (Field 1999). Indeed both symptoms co-existing merely by chance is high and cough can induce reflux episodes as described in asthma and GORD literature (Field 1999; Zerbib 2002). However, our finding of an effect of therapy with PPI to improve cough does suggest that in a proportion of cases of chronic cough with associated GORD, GORD is a contributing cause of cough. There is no other biologically plausible explanation for the improvement in cough with PPI.

Other possible influences of the results of this review include the degree of acid inhibition achieved, the length of therapy, the outcomes of cough measured, and the type of GORD (acid versus non-acid/volume reflux). The degree of acid inhibition achieved in the treatment is probably a small factor, if any, given that in the majority of studies resolution of GORD symptoms (of the gastrointestinal system) was achieved. However it is also possible that different degrees of acid suppression are required to control the different manifestations of GORD. Subjective cough outcomes were variable between studies and in all studies, the diary systems used were non validated systems. Subjective cough monitoring is subjected to various influences (Chang 1998) and less reliable than objective cough monitoring in both adults (Hsu 1994) and children (Chang 2003; Chang 1998). In large RCTs, the influence of the outcome measures should be equal in both arms, but if one medication is more likely to improve symptoms other than cough, cough specific symptom reporting may be unequally influenced. This is relevant as in the majority of included studies, resolution of other GORD symptoms was achieved, which may have influenced cough specific reporting.

Some clinical heterogeneity was present in the participants of the studies included as the majority but not all participants enrolled from otolaryngology clinics had cough. However using separate analysis, the direction of change in favour of PPI use was the same in patients enrolled from medical or from otolaryngology clinics. Indeed excluding patients from otolaryngology clinics (or with laryngitis) did not alter the significance of the primary outcome. There was no significant statistical heterogeneity in studies
between omeprazole and other PPIs, but this data is limited by small sample size and different doses used by the different groups of trialists. The studies using omeprazole used either 40 mg daily (Kiljander 2000) or bd (Noordzij 2001) while the dosage for lansoprazole was 30 mg bd (Havas 1999), rabeprazole was 20 mg bd (Steward 2004) and pantoprazole was 40 mg bd (Eherer 2003). Other outcome analysis would not be possible without the studies based in otolaryngology clinics, which would have resulted in non significant changes in all the outcomes shown in the MetaView, with the exception of change in cough scores at the end of intervention which was significant in the single medical clinic study with data available. Another recent systematic review on laryngo-pharyngeal reflux (LPR) (where cough is often a dominant symptom), concluded that “high-dose proton pump inhibitor is no more effective than placebo in producing symptomatic improvement or resolution of laryngo-pharyngeal symptoms” (Gatta 2007).

Resolution of cough in response to effective treatment is the ideal outcome in these trials. However a clinically significant improvement, rather than total resolution of cough, may be relevant and acceptable to patients with poor quality of life. The magnitude of change in cough score that constitutes a clinically relevant improvement is unknown. The NNT for clinical significant improvement (as opposed to cough resolution) is unknown. The Cochrane Airway Group's policy is not to report on NNT (although arguably easily understood by clinicians) when the OR is not significant. Airway Group's policy is not to report on NNT (although arguably easily understood by clinicians) when the OR is not significant. Under these circumstances, (Altman 1998) clearly states that when CI for NNT should not be presented.

Data on length of therapy required to achieve a change in cough score are inconsistent. One study reported significant improvement after two weeks of H2-antagonist in all participants (Ing 1997), which is a less potent acid suppressing agent than PPI (Rudolph 2001). Ours 1999 made specific reference to the response time of 5-14 days in those whose cough was relieved by PPI in the open label phase. However, in the meta-analysis limited to two studies where week four outcomes were possible (Kiljander 2000; Noordzij 2001), a trend to improvement was seen at week four and again at eight weeks but this was not significant. If data from crossover trials were analysed as parallel trials (i.e. as first arm data), there was a significant difference between week eight and week four cough scores. While data on length of therapy is inconclusive, results from this review suggest that a trial of at least eight to nine weeks would be long enough to expect a significant improvement. This is also supported by a RCT comparing two doses of lansoprazole (30 mg bd to 30 mg daily). In participants whose cough responded to lansoprazole, the response was seen by four weeks and extended therapy (12 weeks) conferred no significant additional benefit (Baldi 2006). There is no RCT data to support recommendations of a six month therapy trial, in contrast to uncontrolled observations, that GORD associated cough takes a mean of a five to six months to take effect (Corraro 1996; Irwin 2002a).

PPIs are currently the most potent non surgical intervention for acid-GORD and no adverse events were reported in these studies. The use of these medications as a trial of therapy thus probably has little risk. However an epidemiology study reported that adults on PPI or H2 antagonist have an increased risk of having community acquired pneumonia, adjusted relative risk of 1.89 (95% CI 1.36 to 2.62) and 1.63 (95% CI 1.07 to 2.48) respectively (Lafeij 2004). This risk translates to "approximately one case of pneumonia for every 100 years of patient exposure" (Gregor 2004). Another study described increased risk of hip fractures associated with PPI use; the adjusted odds ratio for hip fracture associated with more than 1 year of PPI therapy was 1.44 (95%CI 1.30-1.59) (Yang 2006). Moreover, use of PPI has been reported to cause cough (Howaizi 2003) and the package insert for omeprazole includes cough as an adverse event in 1.1% of adults. In contrast to pharmaceutical interventions, there were no studies on surgical intervention, which carries a small but significant rate of serious adverse events.

Some authors suggest that cough in association with GORD related to acid reflux can occur with normal pH metry and indices (i.e. require reflux index of 0%), and that cough can take a prolonged time (a year) to settle post GORD intervention (Irwin 2002b). Such assertions are difficult to prove or disprove in the context of the difficulties with using cough as the primary outcome measure in studies and the feasibility of the required studies. The difficulties relating GORD to cough as causative (as opposed to an association) has been recently summarised (Eastburn 2007). However considerations of non acid reflux require further studies and perhaps multichannel intraluminal electrical impedance monitoring, said to be a more sensitive alternative technology for evaluating all types of GORD (acid and non-acid) (Shay 2004) may prove useful.

Limitations of review

The validity of this systematic review is hindered by the disparate nature of the interventions considered and the resulting small number studies, with only selected availability of unpublished data. Given the distribution of effects for the primary outcome, this may be a reason to suspect publication bias (Figure 9). Furthermore although 18 studies were identified, data could only be used for a subset of them. Our efforts to obtain numerical outcome data from a number of investigators have only been partially successful. This review is also limited by a lack of validated scales and objective data on cough as well as a lack of allocation concealment data and possibly by clinical heterogeneity of participants and medications. The review is primarily concerned with people who do not have primary lung disease but this as an exclusion factor could not be stringently applied in all studies. In all but four studies (Steward 2004; Vaezi 2006; Pawar 2007; Wo 2006), participants were selected for gastro-intestinal symptoms or objective evidence of GORD and most but not all participants had cough. GORD criteria also varied between studies which may influence
results. Most studies did not utilise GORD criteria specified by guidelines published by American and European Gastrointestinal Associations (AMA 1996; Rudolph 2001; Vandenplas 1993). There is also no data on non-acid reflux.

Figure 9. Funnel plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.1 Clinical failures (still coughing at end of trial or reporting period).

Authors’ Conclusions

Implications for practice

Cough and gastrointestinal symptoms of GORD are common ailments and presence of both symptoms by chance is high (in a cohort of patients with chronic cough, the chance occurrence maybe as high as 25%) (Eastburn 2007). There is insufficient evidence to definitely conclude that adults that GORD treatment with PPI for cough associated with GORD is beneficial. The beneficial effect was only seen in sub-analysis and its effect small. Given the significant morbidity of chronic cough in many patients, a trial of therapy with PPI in adults with chronic cough and GORD maybe considered but has to be balanced with the reported increased (but small) risk of pneumonia in adults on acid suppressant therapy. If a therapeutic or empiric trial of PPI is undertaken for treatment of cough, symptom improvement seems most likely to occur by two to eight weeks, although the optimal duration is uncertain. We would thus recommend that empiric trials not be abandoned before eight weeks until better evidence exist. However the period effect (natural resolution with time) of cough is significant. Clinicians should also be cognisant of the large influence of placebo intervention seen in studies that utilise cough as an outcome measure. It is probable that a proportion of adult patients with chronic cough are subjected to longer term PPI, because of an initial apparent response due to this placebo effect, when their cough is in fact not caused by their incidental GORD. There is insufficient data to support (or refute) common recommendations of diet ma-
treatment is prolonged care and the recommendation of surgical intervention is glaring. Respiratory illness and pharmacokinetics of medications (Sinaiko 2001) in children are sufficiently different to that in adults to warrant separate studies on children using child appropriate valid outcomes (Chang 2003).

**Implications for research**

Despite the widely advocated proposal that GORD associated cough is common and that prolonged treatment is required, there is paucity of RCT data on how effective GORD management is, in treating cough associated with GORD. Sufficiently powered RCTs examining time for improvement and resolution of cough as well as optimal duration of therapy using valid cough outcomes are required. These cough outcomes should include objective tools (e.g. ambulatory cough monitors) and validated subjective cough instruments such as cough specific QoL instruments (Birring 2003; French 2002) and cough diaries (Chang 1997; Hsu 1994). Studies on prediction of response to treatment would also be useful for clinical practice. The significant time period effect and placebo influences on cough as a symptom would render non-controlled studies difficult to interpret. Design of future RCTs should be parallel and placebo controlled and have sufficient follow-up time post trial to evaluate possible carry-on effect or recurrence of cough post cessation of therapy. All three cross-over studies reported a significant carry-on effect (Eherer 2003; Ing 1997; Kiljander 2003); cross-over designed studies should therefore not be repeated. Objective measurement of reflux (acid and non-acid) whilst on therapy would also be beneficial. Given the possible significant harm of surgical intervention and the recommendation of surgical intervention if cough does not resolve with non-surgical intervention for cough presumed associated with GORD symptoms (Irwin 1998), the need for a randomised controlled study of surgical intervention is glaring. Respiratory illness and pharmacokinetics of medications (Sinaiko 2001) in children are sufficiently different to that in adults to warrant separate studies on children using child appropriate valid outcomes (Chang 2003).

**Acknowledgements**

We thank Michael McKean and Chris Cates for their advice, supportive role and comments to the protocol and review. We are also grateful to Elizabeth Arnold for performing the relevant searches and obtaining the articles, and Toby Lasserson for translation of German and French papers, Charlotte Pisinger for Czechoslovakian translation and Gianni Ferrara for Italian translation. We also thank Drs. Eherer, Ing, Kiljander, Kopec, Orenstein, El Serag, Omari, Steward and Vanderhoof for responding and/or provision of additional data. For the 2007 update, we thank Susan Hansen for performing the search as well as obtaining the relevant articles.

**References**

**References to studies included in this review**

Chao 2007 *(published and unpublished data)*

Dordal 1994 *(published data only)*

Eherer 2003 *(published and unpublished data)*

Eherer 2003 *(published data only)*

El Serag 2001 *(published data only (unpublished sought but not used))*

Havas 1999 *(published data only (unpublished sought but not used))*

Ing 1997 *(published and unpublished data)*

Jaspersen 1999 *(published data only)*
References to studies excluded from this review

Ahmad 2004 [published data only]

Allen 1998 [published data only]

Allen 2002 [published data only]

Allen 2004 [published data only]

Baldi 2006 [published data only]

Baldi 2006a [published data only]

Belafsky 2008 [published data only]

Brouwer 2003 [published data only]

Chandra 2007 [published data only]

Chen 2000 [published data only]
Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults (Review)

Coron 2007  [published data only]

Dalby-Payne 2003  [published data only]

DeMeester 1990  [published data only]

Dore 2007  [published data only]

Ekstrom 2000  [published data only]

El Hennawi 2004  [published data only]

Eubanks 2001  [published data only]

Farrell 2001  [published data only]

Fock 2008  [published data only]

Fraser 2000  [published data only]

Gatta 2007  [published data only]

Greason 2002  [published data only]

Grill 1985  [published data only]

Habermann 1999  [published data only]

Habermann 2002  [published data only]

Hui 2000  [published data only]

Hunter 1996  [published data only]

Irwin 1993  [published data only]

Irwin 2002  [published data only]

Issing 2004  [published data only]
Katzka 1996 [published data only]

Leeder 2002 [published data only]

Monini 2006 [published data only]

Murray 2006 [published data only]

Novitsky 2002 [published data only]

Omari 2006 [published data only]

Oridate 2008 [published data only]

Poe 2003 [published data only]

Songur 2008 [published data only]

Swoger 2006 [published data only]

Thoman 2002 [published data only]

Tibbling 1993 [published data only]

Tibbling 1995 [published data only]

van Zanten 2006 [published data only]

Waring 1995 [published data only]

Wo 1997 [published data only]

Wright 2003 [published data only]

Xinias 2003 [published data only]

Yang J 2006 [published data only]

References to studies awaiting assessment

Morice 2008 [published data only]

Additional references

Eastburn 2007


Eccles 2002


Elbourne 2002


Ferrari 1995


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Field SK, Sutherland LR. Gastroesophageal reflux and asthma: are they related?: *Journal of Asthma* 1999;36(8):631–44.

French 2002


Gregor 2004


Howazi 2003


Hsu 1994


Ing 1994


Irwin 1990


Irwin 1998


Irwin 2002a

Irwin RS, Madison JM. Diagnosis and treatment of chronic cough due to gastro-esophageal reflux disease and postnasal

**Irwin 2002b**

**Kiljander 2003**
Kiljander TO. The role of proton pump inhibitors in the management of gastroesophageal reflux disease-related asthma and chronic cough. *American Journal of Medicine* 2003;115(Suppl 3A):65S–71S.

**Laheij 2004**

**O’Connell 1994**

**RevMan 2008**

**Rudolph 2001**

**Rudolph 2003**

**Shay 2004**

**Sinaiko 2001**

**Vakil 2006**

**Vandenplas 1993**

**Yang 2006**

**Zerbib 2002**

* Indicates the major publication for the study
### Characteristics of included studies  
ordered by study ID

#### Chao 2007

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single centre, double-blinded, randomised placebo-controlled trial that compared a commercial corn-starched milk anti-reflux (AR) formula to a regular 1.25% strength formula. Infants given regular milk at baseline and scintigraphy performed. Diaries collected and repeat scintigraphy performed using the intervention formula. Randomisation method not well described. Allocation by envelope. Jadad score: 2. High quality score: B, C, A, B. Study was financially supported by a pharmaceutical industry.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>100 included infants, 81 completed the 2-month clinical follow-up. Intervention group (n=41): mean age-90.2 (SD 26.8) days, 21 males, 20 females. Placebo group (n=40): mean age-90.5 (SD 27.4) days, 21 males, 19 females. Only total of 9 children had cough as a symptom. Inclusion criteria: Non breast-fed infants (age 2-4 months) presenting with frequent regurgitation/vomiting (&gt; 3 times/day). Exclusion criteria: Infants with atopic symptoms such as eczema, watery rhinorrhea or diarrhoea suspecting cow’s milk allergy, presence of mechanical obstruction such as infantile hypertrophic pyloric stenosis and malrotation (excluded with an upper gastrointestinal barium study).</td>
</tr>
<tr>
<td>Interventions</td>
<td>A cornstarch thickened anti reflux formula compared to 1.25% strength regular formula for 2 months.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Diary: mean frequency of episodes of regurgitation, and/or vomiting, mean feeding volume tolerated as well as associated symptoms (irritability, cough, choking, crying) during the 3 days prior to a visit, and weight gain. 90-min milk scintigraphy with 500 μCl technecium to quantify gastric emptying.</td>
</tr>
<tr>
<td>Notes</td>
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### Risk of bias

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<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Envelope drawing system, no further information described</td>
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</table>
Methods

Controlled parallel study comparing cisapride with domperidone and no treatment (as control). At baseline, patients were examined clinically. They underwent skin prick tests, spirometry, chest X-ray and gastro-oesophageal imaging (bolus liquid was administered and a computer generated image traced the path of the liquid through the oesophagus). Gastroesophageal imaging graded from 1-4. 1 = normal, 2 = partial retention of bolus (5 to 10 secs), 3 = retention of bolus (10 to 20 secs), 4 = prolonged retention of bolus (> 20 seconds). If gastroesophageal imaging of child >= 2, child eligible

Dropouts: n = 10, 15.4% of those recruited. 4 dropouts from cisapride group (2 from adverse events, 2 lost), 2 from domperidone (lost) and 4 from no treatment group (lost)

Randomisation not mentioned, blinding not described and allocation method not described

Participants

65 children (number screened not given) from outpatients with predominant nocturnal cough (with or without asthma) and GORD symptoms. 15 of the 55 participants who completed trial had cough without symptoms of asthma

Median age of groups: cisapride- 6.7 years, SD 2.97 (n = 21, 15 males 6 females); domperidone - 7.05 years, SD 3.05 (n = 23, 10 males 13 females); control - 6.4 years, SD 2.62 (n = 11, 5 males 6 females)

Inclusion criteria: Children with cough (with or without co-existing asthma), predominantly nocturnal symptoms, reflux symptoms

Exclusion: none described.

Interventions

Cisapride (0.2mg/kg 20mins before each meal) with domperidone (0.2mg/kg 15mins before each meal) and no treatment (as control) for 12 weeks.

All also received the following: Withhold food 2 hours before bedtime, reduce intake of acidic foods, lower size of meals, but increase frequency, raise height of the head of the bed by 10 cm and, sleeping on one's side.

Outcomes

1. Symptoms of cough
2. Gastro-imaging

Notes

Data on children without asthma were not provided. No significant difference found between the groups

Risk of bias

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</table>
Eherer 2003

**Methods**
Randomised double blind, crossover study comparing pantoprazole vs placebo in adults with ‘laryngitis’ symptoms (includes cough) and GORD (defined on pHmetry). Patients with inclusion criteria enrolled from outpatients clinic, telescopic video laryngo-stroboscopy performed and screened for exclusion criteria. Dual channel pHmetry performed and those with excessive reflux (> 4.5% time pH < 4) were eligible and randomised
Randomisation by blocks of 4 performed by pharmaceutical supplier. Allocation method not described. Compliance monitoring not described
Dropouts (30% of those randomised) were not described and were not included as treatment failures in paper. But analysis by ‘intention to treat’ was possible with additional data provided by authors

**Participants**
21 adults (mean age 48 years, range 20-70, 16 males, 5 females) randomised from eligible 22 patients; (62 patients screened) with GORD (diagnosed on pHmetry) and symptoms of laryngitis (cough, nocturnal cough, sore throat, hoarseness, sore dysphonic attacks, globus sensation) attending otolaryngeal clinic in a tertiary institution (Karl-Franzens University, Austria). 12 of the 21 had chronic cough, 7 were initially commenced on placebo, and 5 on pantoprazole. 4 of those with cough (25%) did not complete trial; 2 in each arm
Inclusion: hoarseness for > 2 months, laryngitis or other laryngeal symptoms which includes cough
Exclusion: smokers, other causes of laryngitis, prior operations on laryngeal area, laryngeal malignancy, COPD

**Interventions**
Placebo or pantoprazole 40mg bd for 3 months, 2 weeks wash out followed by pantoprazole or placebo for 3 months

**Outcomes**
1. Laryngeal symptoms (0-72) = sum of frequency of each symptom by intensity of symptom.
2. Oesophageal symptoms (0-48) = sum of frequency of each symptom by intensity of symptom.
3. Laryngeal scoring.
All scored at 2 weeks after completion of treatment phase.

**Notes**
Raw cough scores were scores provided by Dr. Eherer.

**Risk of bias**

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El Serag 2001

**Methods**
Randomised double blind, parallel study comparing lansoprazole vs placebo in adults with ‘laryngitis’ symptoms (includes cough) with or without GORD (defined on pHmetry). Patients with inclusion criteria enrolled from otolaryngology outpatients clinic. Video laryngoscopy, dual channel pHmetry, gastroscopy (some also had oesophageal manometry) performed
Allocation method not described. Compliance monitoring by pill counting
Dropouts (n = 2, 9% of those randomised), one from each arm

**Participants**
22 adults randomised from 27 patients screened, with laryngitis with or without GORD (diagnosed on pHmetry) and symptoms of laryngitis attending otolaryngeal clinic in a tertiary institution (Houston, Michigan). 14 (64%) of participants had chronic cough. Distal reflux defined as DeMeester score > 14.
7. 21 males, 1 female in study, mean age 59 (SD 12) years in lansoprazole group, 65 (SD 12) years in...
placebo group
Inclusion: has (a) 'laryngitis' symptoms as described in outcome measures, (b) posterior laryngitis as assessed by video laryngoscopy and (c) absence of concurrent infections or allergic causes of laryngitis
Exclusion: aerodigestive malignancies, radiation therapy, or previous GI surgery

Interventions
Lansoprazole 30mg bd or placebo bd for 3 months

Outcomes
1. Symptoms of hoarseness, frequent clearing of throat, dry cough, globus or persistent sore throat for > 3 weeks.
2. Laryngoscopy findings. (no scale used for either)

Notes
Authors contacted for further information but no data were provided

Risk of bias
Item Authors’ judgement Description
Allocation concealment? Unclear Information not available

Havas 1999

Methods
Randomised double blind, parallel study comparing lansoprazole vs placebo in adults with 'posterior pharyngolaryngitis' symptoms (includes cough) with or without GORD (defined on pHmetry). Patients with inclusion criteria enrolled from otolaryngology outpatients clinic. Video laryngoscopy, dual channel pHmetry, gastroscopy and oesophageal manometry performed
Randomisation and allocation method not described. Compliance monitoring not described
Dropouts (n = 5, 25% of those randomised) data on which group was not given and not included in paper's analysis or described as treatment failures

Participants
20 adults randomised from 100 patients screened, with laryngopharyngeal reflux with or without GORD (diagnosed on pHmetry) and symptoms of laryngitis attending otolaryngeal clinic in a tertiary institution (Prince of Wales Hospital, Sydney). Distal reflux defined as pH< 4 for > 4% of time, proximal = pH fall of >= 3 within nadir of <= 5 with oesophageal acidification. Of the 15 (7 males, 8 females, mean age 52.9 years) who completed the trial, 8 received lansoprazole and 7 placebo
Inclusion: has 'posterior pharyngolaryngitis' assessed by video laryngoscopy and symptoms (described in outcome measures)
Exclusion: severe neurological disorders, chronic airflow limitation, pre-existing anti-secretory medications, severe oesophagitis seen at endoscopy, professional voice users (singers)

Interventions
Lansoprazole 30mg bd or placebo bd for 12 weeks

Outcomes
1. Symptom scores (addition of scores for severity [0-3] to scores for frequency [0-4]) for each of 4 symptoms of laryngitis (chronic cough, hoarseness, throat clearing, sore throat pain).
2. Reflux symptoms scored as above for dysphagia, retrosternal burning pain, acid regurgitation and odynophagia.
3. Laryngoscopy findings (0-4)
4. Adverse events.
Scores obtained at 6 and 12 weeks and data on cough alone was provided in paper
Havas 1999  (Continued)

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<th>Notes</th>
<th>Authors contacted for further information but no data were provided</th>
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</table>

Ing 1997

**Methods**

Double blind cross over study comparing ranitidine with placebo. Patients with chronic persistent cough (> 2 months) with unknown aetiology after a standard diagnostic evaluation were evaluated. They underwent pHmetry and histamine airway hyper responsiveness. pHmetry was repeated in 7 participants, 4-6 weeks after the ranitidine treatment period. Dropouts (n = 1, 4% of those recruited).

**Participants**

25 patients randomised (number screened not given) from medical outpatients of a tertiary hospital. All patients had PD20 to histamine > 8 umols. 13 participants had placebo medication in the first treatment period, and the 11 patients who had ranitidine in the first treatment period (1 dropout described). Mean age was 46.8 (SEM 3.3) yrs, 11 male, 14 female. Inclusion: chronic cough and significant gastro-oesophageal reflux (presence of > 12 reflux episodes per 24 hours and time pH < 4 was > 0.7%). Exclusion: patients with bronchial asthma, chronic bronchitis, allergic rhinitis, sinusitis, post nasal drip, other respiratory and cardiac diseases, acute respiratory infections occurring within 2 months of the study, smokers, or using theophylline or angiotensin converting enzyme inhibitors.

**Interventions**

Placebo or ranitidine 150mg bd for 2 weeks, 2 weeks wash out followed by ranitidine or placebo for 2 weeks.

**Outcomes**

1. Cough scores (1-4) on a twice daily on diary cards recorded basis
2. Presence of symptoms of GORD.

**Notes**

Study not published other than in abstract and conference report

**Risk of bias**

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</table>
Jaspersen 1999

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, parallel study comparison of omeprazole versus ranitidine. Method of allocation not described. Study was not double blinded. Compliance monitoring not mentioned. No withdrawals reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>20 adults from outpatients department, with chronic cough, with otherwise normal lung function and negative clinical and radiological findings. 10 participants in omeprazole group (5 males, 5 females, mean age 49.4 years SD 16.3) and 10 in ranitidine group (6 males, 5 females, mean age 46.5 SD 19.7) Inclusion: persistent cough for 8 weeks, negative findings from physical examination, negative radiological findings, with either symptoms of GORD or positive investigation of GORD (diagnosed by gastroscopy), and normal lung function Exclusion: Diagnosis of chronic asthma, COPD, chronic bronchitis, other oesophageal disease, ACE inhibitor therapy, ENT abnormalities, or smokers</td>
</tr>
<tr>
<td>Interventions</td>
<td>Omeprazole 10mg/day or ranitidine 300mg/day for 8 weeks.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>1. Cough score (range 0-4) 2. Oesophagitis score (range 0-4) 3. Adverse events. Outcomes recorded for 8 weeks.</td>
</tr>
</tbody>
</table>

Kiljander 2000

| Methods | Randomised double-blind, crossover study comparing omeprazole vs placebo in adults with chronic cough and GORD (defined on pHmetry). Patients with chronic cough enrolled from pulmonary outpatients clinic were screened for exclusion criteria. Patients completed one-week observation by diary cards, pHmetry then performed and those with excessive reflux were randomised Randomisation and allocation method not described. Compliance monitored by pill counts after treatment period. 8 did not complete trial (27% of those randomised) were not further described and were not included as treatment failures. Analysis by intention to treat for primary outcome only |
| Participants | 29 adults (median age 49, IQR 20-74, 10 males, 19 females) randomised from 48 patients screened, with GORD (diagnosed on pHmetry) and chronic (≥ 2 months) cough attending pulmonary clinic in a tertiary institution (Turku University, Finland). 12 initially randomised to placebo and 9 to omeprazole Inclusion: chronic persistent cough (≥ 2 months) Exclusion: Abnormal chest or sinus radiology, positive methacholine test, rhinitis, nasal mucosa appearance of cobblestone or muco-purulent secretions, smokers, asthma, chronic bronchitis, use of angiotensin converting enzyme inhibitor |
### Kiljander 2000 (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Omeprazole 40mg per day or placebo for 8 weeks, 2 weeks washout followed by omeprazole or placebo</th>
</tr>
</thead>
</table>
| Outcomes      | 1. Weekly daytime cough and night time cough (cough disturbing sleep) scores = sum of daily 4 point (0 to 3) scale of symptoms (both has range of 0-21)  
2. Weekly gastric symptoms (heartburn, regurgitation, chest pain) = sum of daily 4 point (0 to 3) scale of symptoms (range 0-63). Average of last 3 weeks at end of each treatment period (8 weeks) |
| Notes         | Cough scores obtained from primary author.                                                                      |

### Risk of bias

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</table>

### Kopec 2001

| Methods | Partial double-blind parallel randomised placebo controlled trial comparing diet and/or cisapride (2 factorial design). Randomisation of the diet was not blinded, randomisation of cisapride was double-blinded  
After standard diagnostic work-up for chronic cough, participants who met criteria (authors assume that this predicts patients have an approximate 92% chance of having chronic cough due to GERD) were randomised and pHmetry performed  
Randomisation and allocation method not described.  
Dropouts (n = 2, 9.5% of those randomised) were not described and were not included as treatment failures. Analysis by intention to treat not possible  
Compliance monitoring not described. |
|----------|---------------------|--------------|
| Participants | 21 adults (mean age 53.5 years, SD 12.9) with chronic cough and GORD randomised from outpatients clinic. (number of eligible patients not given). GORD diagnosed on pHmetry or on barium meal  
Inclusion: Adults with chronic cough (> 8 weeks) and presumably GORD related cough  
Exclusion: age < 18 years, pregnancy, known contraindications to receiving cisapride, such as known allergy to the medication, or prolonged QT interval on EKG or concurrent use of medications that might interact with cisapride to place the patients at risk of a potentially life-threatening cardiovascular complication |
| Interventions | 2 factorial design using usual care diet or anti-reflux diet and cisapride 10mg qid or placebo for 4 months trial ie 4 arm study |
| Outcomes | Cough scores measured by visual analogue score (VAS) from 0 to 100 |
| Notes | No difference found in VAS between groups  
Further data provided by author was insufficient for inclusion into meta-analysis |

### Risk of bias

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### Moukarzel 2007

#### Methods

Single centre, double-blinded, randomised placebo-controlled trial that compared a commercial pre-thickened anti-reflux (AR) formula to a regular formula. Medical history was obtained and complete physical examination was performed at entry. All infants underwent a 24-hour oesophageal pH monitoring while receiving alternating normal and anti-reflux milk. Weekly monitoring of episodes of regurgitation, vomiting, coughing, crying, and stool frequency and consistency. The volume of each feeding during a 24 hours period once weekly was also recorded. Randomisation and allocation method not well described. Jadad score: 2, High quality score: B, C, A, B Study was financially supported by a pharmaceutical industry.

#### Participants

74 included infants, 60 completed the 1-month clinical follow-up. Mean age of group was 3.24 (SD 1.28) months, 40 males, 34 females. Intervention group n=28, Placebo group n=32. Mean age of infants within each group was not described.

Inclusion criteria: Non breast-fed infants (aged <6 months) with GER (determined using Orenstein criteria).

Exclusion criteria: Breast-fed and premature infants, infants with history of wheezing, aspiration pneumonia, apnoea, failure to thrive, anaemia, bleeding, laryngitis, and apparent life threatening events. Infants already receiving AR or medications that could affect the motility of the gastrointestinal tract. Parents who subjected infants to overfeeding, dilution errors, and inadequate feeding technique.

#### Interventions

A pre-thickened anti reflux formula compared to regular formula for 1 month.

#### Outcomes

Diary: episodes of regurgitation, vomiting, coughing, crying, and stool frequency and consistency.

Data relating to pH monitoring (reflux index, oesophageal clearance, etc), electrogastrography (a cutaneous recording of gastric myoelectrical activity).

#### Notes

Wrote to authors 31st May 2008.

### Risk of bias

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</table>
Noordzij 2001

Methods
Randomised double blind, parallel study comparing omeprazole vs placebo in adults with 'laryngitis' symptoms (includes cough) and GORD (defined on pHmetry).
Patients with inclusion criteria enrolled from outpatients clinic. Video-laryngo-stroboscopy performed and screened for exclusion criteria. Dual channel pHmetry then performed and those with reflux were eligible and randomised.
Randomisation and allocation method not described.
Compliance monitoring not described.
Dropouts (6.7% of those randomised) were included in analysis but not described as treatment failures. Analysis by intention to treat not possible.

Participants
30 adults randomised from 53 patients screened) with GORD/laryngopharyngeal reflux (diagnosed on pHmetry) and symptoms of laryngitis attending otolaryngeal clinic in a tertiary institution (University of Virginia). 15 participants in omeprazole group (8 males, 7 females, mean age 51.7 years) and 15 in placebo group (8 males, 7 females, mean age 45.3). 2 (6.7 %) did not complete trial, one from placebo group and the other unknown.
Inclusion: one or more symptoms of laryngitis for > 3 months ie symptoms of chronic cough, hoarseness, excessive phlegm, throat clearing, throat pain, lump in throat and acid reflux (> 4 episodes proximal pH < 4 or 3 point drop in pH with simultaneous drop in distal pH of < 4)
Exclusion: viral or bacterial laryngitis (undefined), benign vocal fold lesions, occupational exposures causing laryngitis, history of seasonal allergies or laryngeal malignancy

Interventions
Omeprazole 40mg bd or placebo bd for 2 months.

Outcomes
1. Symptom scores (multiplication of severity [0-100] of symptom by frequency [number of days over last 2 weeks] for each of 6 symptoms of laryngitis (chronic cough, hoarseness, excessive phlegm, throat clearing, throat pain, lump in throat) and 3 symptoms of GOR (dysphagia, odynophagia and heartburn 2. Adverse events.
Scores obtained at 1 and 2 months and data on cough alone was provided in paper

Notes
Authors contacted for further information but no data were provided

Risk of bias

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<td>Allocation concealment?</td>
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</table>

Orenstein 1992

Methods
Randomised single blind, cross over study comparing thickened and unthickened feeds on cough associated with feeds, related to GORD diagnosed by pHmetry, barium swallow or oesophageal biopsy. Assessor was blinded but not care-giver/nurse who fed infants.
Randomisation well described (lottery) but allocation method not described.
No dropouts mentioned. Uncertain if analysis was by intention to treat.

Participants
25 infants randomised (number screened not given) from outpatients of a tertiary gastroenterology centre (Children’s Hospital of Pittsburg) referred for GORD.
Median post natal age 7.5 weeks (range 2-26), corrected age 7 weeks (-6 to 26), gender not given. Symptoms
**Orenstein 1992** (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Thickened (with rice cereal) and unthickened feeds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Cough frequency during feeds and post prandial per hour.</td>
</tr>
<tr>
<td>Notes</td>
<td>Results showed that cough frequency when on thickened feeds (3.9) was significantly higher than when on unthickened feeds (2.2); ( P = 0.006 )</td>
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<td>Information not available</td>
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**Ours 1999**

**Methods**

- Randomised double blind, parallel comparison of omeprazole vs placebo in adults with chronic cough and GORD (defined on pHmetry). Potential participants screened for exclusion criteria. Patients completed 2 weeks observation by diary cards. Those with score of at least 3 were treated with antihistamine and nasal corticosteroids. If persistent cough remained (score >= 2) oesophageal manometry and pHmetry were undertaken. Those with GORD were randomised. No withdrawals. After end of trial (12 weeks), open study performed using omeprazole (one month)
- Randomisation by computer but allocation method not described. Compliance monitored by pill counts after treatment period
- All completed trial. Analysis by intention to treat possible

**Participants**

- 17 participants randomised from 71 patients screened. Patients with chronic cough enrolled from newspaper advertisements and outpatients (most were enrolled from community). Mean age and duration of cough in those randomised were not given. Median age of 36 patients in study prior to results of pHmetry was 58 years with cough duration of 5 years (interquartile range 2-10)
- Inclusion: Aged 18-80 years with chronic cough (>= 6 weeks) with score of >= 2 and with excessive acid reflux distally or proximal (defined by pHmetry)
- Exclusion: Abnormal chest radiology, positive methacholine test, smokers, ex-smokers <= 3 months or == 20 pack-yr history of smoking, upper respiratory infection within 8 weeks of entry, use of angiotensin converting enzyme inhibitor or beta blockers, unable to be weaned off some medications (corticosteroids, methylxanthines, cough suppressants, beta agonist, anti-cholinergics, or anti-inflammatory agents), history of pulmonary disease, malignancy, or any co-morbid condition requiring treatment

**Interventions**

- Omeprazole 40 mg bd or identical appearing placebo for 12 weeks

**Outcomes**

- Cough severity and cough frequency scale (0-8), day and night, measured daily by diary cards for 12 weeks
- Response to treatment defined as weekly cough frequency combined with severity score for daytime or nighttime cough of <= 1 for >= 2 weeks consecutively
Ours 1999  (Continued)

Notes

Paper provided failure and success rates but no details on cough scores that can be entered for other meta-analysis
Open trial results not used for analysis

Risk of bias

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<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Information not available</td>
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Pawar 2007

Methods
Single centre, double-blinded, randomised placebo-controlled trial that compared twice-daily rabeprazole with placebo for 90 days in adults with "post nasal drip (PND), throat clearing or excessive throat mucus"
Subjects were recruited from otolaryngology clinic at Medical College of Wisconsin or through newspaper advertisements. Rigid nasal endoscopy, two-site 24-hour pharyngeal pH probe monitoring (pH threshold =5) and video laryngoscopy performed before Rx. Video laryngoscopy and other 2 outcomes below repeated on day 90
Non prescription antacids (including H2 antagonists and other PPIs), anti-histamines, decongestants disallowed to be used concomitantly
Randomisation method and allocation method not described. Jadad score: 3, High quality score B, A, B, B (no intention to treat analysis)
Study was financially supported in part by a pharmaceutical company

Participants
180 people screened. Of these 53 subjects enrolled, 47 (89%) completed study
Rabeprazol group: n=21 (11 males, 10 female), mean age= 55.6 years (range 40-75). Placebo group: n= 26 (12 males, 14 female), mean age=54.3 years (range 24-76)
Inclusion: Aged 18-80 with main complain of PND, throat clearing or excessive throat mucous
Exclusion: Acute or chronic sinus disease (using nasal endoscopy and/or coronal sinus CT scan), acute rhino sinusitis, nasal polyps or neoplasms, subjects with vasomotor rhinitis or GER treated in preceding 2 months, smoking, oesophageal or gastric surgery, cardiovascular disease, allergies or pregnancy

Interventions
Rabeprazole (20 mg, orally twice daily) or placebo for 90 days

Outcomes
Visual analogue scales for PND symptoms, reflux symptom index (higher score = worse), and reflux finding score (RFS) (higher score = worse)

Notes
Symptomatic score significantly improved in intervention arm but the objective score (RFS) was significantly worse. Wrote to authors 30th May 2008

Risk of bias

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<tr>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Information not available</td>
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<tr>
<td><strong>Methods</strong></td>
<td>Single centre randomised double blind, parallel comparison of rabeprazole vs placebo in adults with chronic cough and GORD (defined on pHmetry). Potential participants screened for exclusion criteria. Patients completed underwent video strobo-laryngoscopy and undertook questionnaire. 24-hour dual probe pHmetry was initially part of protocol but was later optional (as patients poorly tolerated it) Randomisation by computer generated random number table and allocation concealed (using sealed envelopes). Compliance to PPI/placebo not described. Analysis available for 30 of the 42 (71.4%) subjects randomised. Intention to treat data not available.</td>
<td></td>
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<tr>
<td><strong>Participants</strong></td>
<td>194 patients screened, 42 randomised. Patients enrolled from an academic otolaryngology practice at the University of Cincinnati, USA and from poster and newspaper advertisements. Rabeprazole group (n = 21): mean age (SD) = 52.8 (11.5), 23% males. Placebo group (n = 21): mean age (SD) = 45.8 (11.2), 33.3% males. Inclusion criteria: 1) age &gt; 18 years; 2) history of hoarseness, throat clearing, non-productive cough, globus sensation, or sore throat &gt;4 weeks; and 3) physical examination consistent with diagnosis of laryngopharyngeal reflux (ie, edema, erythema, and/or pachydermia). Exclusion criteria included: 1) previous surgery for gastroesophageal reflux disease, or current gastrostomy tube; 2) history of hypersecretory disorder (ie, Zollinger Ellison); 3) current tracheotomy tube; 4) current or recent (within 1 month) use of a proton pump inhibitor; 5) current or recent (within 1 month) use of a histamine-2 receptor blocker (except over-the-counter use on an as-needed basis &lt;3 times per week); 6) allergy to proton pump inhibitors; 7) current systemic steroid therapy; 8) previous laryngeal or hypopharyngeal neoplasm; 9) previous radiation therapy to neck; 10) endotracheal tube intubation within past 2 months; 11) diagnosis of vocal cord paralysis; 12) diagnosis of active granulomatous disease (laryngeal or pulmonary, including sarcoid, Wegener’s, tuberculosis, histoplasmosis, blastomycosis) requiring systemic therapy; and 13) suspicion for laryngeal neoplasm requiring biopsy for diagnosis.</td>
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<tr>
<td><strong>Interventions</strong></td>
<td>Rabeprazole 20 mg twice-daily or placebo (identical appearance) for 2 months. All also received lifestyle modification instructions minimize acid reflux (avoidance of fatty meals, caffeine, alcohol, smoking, and oral intake within 2 hours of lying down or bedtime, as well as the addition of extra pillows to raise the head or bedpost blocks to elevate the head of the bed 6 inches).</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>The primary outcome measures: change in total reflux symptom scores and proportion of subjects noting significant global improvement. The reflux symptom scores were modification of a previously validated GERD outcome questionnaire that included laryngo-pharyngeal symptoms. The questionnaire included 9 items (heartburn, acid regurgitation, dysphagia, globus, throat clearing, hoarseness, sinus drainage or phlegm, sore throat, and dry cough). Patients responded to frequency of symptoms (never, monthly, weekly, several times per week, or daily) and severity of symptoms (none, mild, moderate, severe, very severe), both scored 0 to 4 on a Likert scale. The total reflux symptom score included sum of frequency and severity scores for all items. The secondary outcome measures were change in SF36, change in laryngeal grading of videostrobolaryngoscopy, and changes in component reflux symptoms scores (frequency, severity, “typical,” “laryngeal,” “pharyngeal,” and individual symptoms). The component reflux symptom scores were defined as follows: frequency = sum of all reflux symptom frequency scores; severity = sum of all reflux symptom severity scores; “typical” = sum of frequency and severity scores for symptoms of heartburn and acid regurgitation; “laryngeal” = sum of frequency and severity scores for symptoms of hoarseness, dry cough, and throat clearing; and “pharyngeal” = sum of frequency and severity scores for symptoms of throat clearing, globus sensation, and phlegm. The tertiary outcome measures were changes in frequency of lifestyle factors related to reflux derived from the lifestyle questionnaire. The lifestyle questionnaire included 9 items (smoking, alcohol use, caffeine use, head of bed elevation with blocks, use of 2 pillows to raise head, oral intake within 2 hours of bedtime, physical activity, and weight loss).</td>
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oral intake within 2 hours of lying down, antacid use, and histamine-2 receptor blocker use). Response choices included: never, monthly, weekly, several times per week, and daily (0-4 Likert scale).

Notes

Cough reported separately in paper. Authors contacted for further data.

Risk of bias

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<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Sealed envelopes concealed randomisation process from study investigators</td>
</tr>
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</table>

Vaezi 2006

Methods

Multicenter, randomized, placebo controlled parallel group trial that compared twice-daily esomeprazole 40 mg with placebo for 16 weeks in adults with suspected chronic laryngeal symptoms and signs from GOR (but those with significant GI manifestations of GOR were excluded—see exclusion criteria)

Screening laryngoscopy and screening period were performed. Eligible patients then underwent a 7- to 14-day screening period without treatment, during which they completed a daily diary card on which they assessed each of 5 symptoms (throat clearing, cough, globus, sore throat, and hoarseness) over the past 24 hrs on a 7-point Likert scale (0 = none to 6 = very severe). At the end of this period, patients each identified their single most bothersome symptom as the primary symptom. Patients eligible for randomization must have completed at least 80% of diary entries, had a cumulative primary symptom score of >= 9, and had >= 3 days with moderately severe symptoms (>= 3 points) over any 7 consecutive days of the 7 to 14 days

Participants randomized in a 2:1 ratio (esomeprazole:placebo) at each center by blocks of six.

After randomization and before receipt of study medication, patients had for ambulatory pharyngoeosophageal pH monitoring (APEM). Patients who refused APEM were allowed top participate. APEM consisted of two-catheter, three-probe 24-hr study with probe placement in the hypopharynx, proximal esophagus, and distal esophagus. APEM was assessed by a single, independent investigator at a central laboratory, blinded to patient-identifying data.

Patients used daily diary card used to assess symptoms each day throughout the 16-week trial. At weeks 0, 4, 8, 12, and 16, the investigator assessed the same symptoms that the patients assessed in their diary cards using a four-point Likert scale (0 = none to 3 = severe). At the final visit, the investigator also provided an overall evaluation of improvement

Allocation method not described. Compliance monitored by pill counting. Analysis was by intention to treat not relevant. Total of 17 (11.7%) withdrawals

Participants

146 participants randomised but one dropped out prior to any Rx (number screened not given). Patients enrolled from 7 US centres. Esomeprazole group (n = 95): mean age (SD) = 51.5 (15.2), 48 males and 47 females. Placebo group (n = 50): mean age (SD) = 50.5 (14.5), 23 males and 27 females

Inclusion criteria: aged > 18 y and had one or more of the following symptoms for 3 or more consecutive months before screening: throat clearing, cough, globus, sore throat, or hoarseness; and laryngoscopic signs consistent with reflux (assessed by a panel via consensus)

Exclusion: clinically significant conditions that might, in the judgment of the investigator, put the patient at risk, influence the results, affect the patient’s ability to participate in the study, or necessitate surgery

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during the study. Patients who had experienced moderate-to-severe heartburn 3 or more days per week over a 3-month period before screening; history of respiratory or gastro-intestinal malignancy; radiation therapy to the head and neck, lung, or gastrointestinal tract; gastroesophageal surgery; chronic sinusitis or rhinitis in the last year; an allergic cause of laryngitis; an acute traumatic event near the larynx in the last year; tracheostomy or other significant laryngeal or tracheal surgery; and substance or alcohol abuse in the past year; other malignancy (except superficial basal cell carcinoma) within the previous 5 years; presence of an infectious cause of laryngitis in the past 3 months; need for continuous therapy within 1 week of randomisation with diazepam, phenytoin, mephenytoin, warfarin, anticholinergics, antineoplastics, prostaglandin analogs, H2-receptor antagonists, steroids (inhaled, oral, or intravenous), promotility drugs, and sucralfate; use of tobacco products in the past year, any PPI in the last 2 weeks, theophylline, or any other investigational compound or participation in another investigational drug study in the past 30 days; and any contraindication to esomeprazole, such as known or suspected allergy or sensitivity to any PPI; or pregnancy and lactating women.

### Interventions

Esomeprazole 40 mg twice-daily or placebo (identical appearance) for 16 weeks

### Outcomes

Patients used daily diary card used to assess symptoms each day throughout the 16-week trial. At weeks 0, 4, 8, 12, and 16, the investigator assessed the same symptoms that the patients assessed in their diary cards using a 4-point Likert scale (0 = none to 3 = severe). At the final visit, the investigator also provided an overall evaluation of improvement for each symptom as follows: 0 = resolved, 1 = improved, 2 = same, 3 = worse.

Laryngoscopic scoring performed at week 8 and 16.

The primary outcome was % patients who had resolution of the primary symptom according to patient diary card assessment at the final visit. Symptom resolution was defined as a primary symptom severity score of 0 (none) during the last 7 days of the study, but allowing a score of 1 (minimal severity) for up to 3 days.

Secondary efficacy variables included relief of the primary symptom (by patient), % symptom-free days, and % of symptom-free patients, symptom severity change from baseline, and the investigator's assessment of symptom-free patients. Relief of the primary symptom was defined as a greater than 50% reduction from baseline in the primary symptom score during the final week.

### Notes

Authors provided additional cough specific data.

### Risk of bias

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<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Information not available</td>
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</table>
**Vanderhoof 2003**

| **Methods** | Multi-centre randomised double blind, parallel study comparing a pre-thickened formula with placebo in infants with regurgitant reflux. Parents of infants kept diary cards for 2 days and if eligible randomised. After one week, infants were reviewed and commenced on pharmacological intervention (ranitidine after day 7/8 and cisapride after day 14/15). Further follow up till day 35/36. Randomisation well described based on site but allocation method not described. Compliance monitoring done. Dropouts (n = 12, 10.9% of those randomised. Dropouts included in some analysis but not described as treatment failures. Analysis by intention to treat not possible. |
| **Participants** | 110 infants randomised (number screened not given) from 6 North American paediatric centres. 7 drop outs and of remaining 103, mean age of 55 (27males, 28 females) intervention group was 61 days (SD 4) and that of control group (26males, 23 females) was 58 days (SD 4). Inclusion: >= 5 regurgitations per day for 2 baseline days, age 14-120 days, gestational age > 37 weeks, birth weight >= 2.5kg, maternal age >= 18 years. Exclusion: congenital abnormalities interfering with normal feeding or causing repeated regurgitation. Fever, infectious illness, clinical diagnosis of milk or soy protein allergy, complicated GORD (oesophagitis, haematemesis, recurrent respiratory symptoms, failure to thrive), previous treatment with thickened formula, or treatment with prokinetic medications 5 days before start of study. |
| **Interventions** | A pre-thickened formula (Enfamil AR) with placebo for 35/36 days, with equal access to additional pharmacological intervention. |
| **Outcomes** | 1. Regurgitation frequency, regurgitation volume, as documented on daily diary sheets for the first week and then 2 days/week subsequently. 2. Percentage feeds followed by choke/gag/cough. 3. Trouble sleeping 4. Adverse events Measures at week 1 and end of participation. |
| **Notes** | Authors replied but were unable to provide information on cough alone as an outcome measure. |

### Risk of bias

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<td>Information not available</td>
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</table>
### Methods

Single centre, double-blinded, randomised placebo-controlled trial that compared once daily pantoprazole with placebo for 12 weeks in adults.

Protocol was 2-wk run-in, 12-wk randomised treatment, and 4-wk off-treatment follow-up periods. During the run-in period, subjects filled out weekly diaries. Subjects were seen mid protocol. Nasopharyngoscopy, oesophageal manometry and triple sensor pH monitoring performed performed before Rx. Naso-pharyngoscopy, laryngoscopy and triple sensor pH monitoring performed repeated on end of week 12. Diaries collected till 4 weeks post Rx.

Randomisation method and allocation method clearly described.

Jadad score: 5, High quality score: A, A, A, A

Study was financially supported by a pharmaceutical research grant.

### Participants

42 of 51 who had pH monitoring qualified for study. Of these 42 adults, 39 were randomised and all completed study.

Pantoprazole group: n=20 (7 males, 13 female), mean age= 39 years (range 23-59). Placebo group: n=19 (6 males, 13 female), mean age=37 years (range 23-61).

Subjects were recruited from otolaryngology clinic at University of Louisville or through newspaper advertisements.

Inclusion criteria: Subjects with the main complaint of hoarseness, sore throat, throat burning/pain, throat clearing, voice loss, cough, excessive throat mucus, globus, or choking for >3 days per wk in the past 2 months. The diagnosis of LPR was confirmed by laryngeal exam and a positive pH test of the hypopharynx or distal oesophagus (defined as total number of hypopharyngeal reflux episodes >=3 or distal oesophageal total time pH< 4 was >=4.2%).

Exclusion criteria: Previous treatment of LPR or GORD, known gastroparesis, connective tissue disorder, previous endoscopic or surgical antireflux procedure, or gastric surgery. Also those with vocal cord ulcer, vocal cord granuloma, or laryngeal malignancy seen on naso-pharyngoscopic examination were excluded.

### Interventions

Pantoprazole (40 mg once daily) or placebo for 12 weeks.

### Outcomes

Symptom assessment: weekly diaries of visual analogue scales (0: none to 20: severe) for six laryngeal symptoms: globus, cough, sore throat, hoarseness, throat clearing, and excessive throat mucus. A total laryngeal symptom score (0-120) was defined as the sum of the laryngeal symptoms. A similar visual analogue scale (0-20) was obtained for daytime and nighttime heartburn.

Nasopharyngoscopy: Reflux finding score (RFS) (higher=worse).

### Risk of bias

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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Randomisation assignment generated by third party in blocks of 4 with sequential numbering but insufficient details to be certain if allocation concealment occurred</td>
</tr>
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</table>

APEM: ambulatory pharyngoesophageal pH monitoring; bd: twice daily; GOR: Gastroesophageal reflux; GORD: Gastroesophageal reflux disease; SD: Standard deviation; vs: versus
### Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td><strong>Ahmad 2004</strong></td>
<td>Non RCT. Prospective follow up study of 303 adults with otolaryngeal manifestations of GORD. 86% had cough and choking events presumed secondary to GORD (diagnosed on gastroscopy) were treated with antireflux therapy (PPI’s in 90%, ranitidine in 3%, Gaviscon in 11%). Complete response to therapy occurred in 25.7%, no response in 23.1% and the rest had variable response. Adverse events not mentioned</td>
</tr>
<tr>
<td><strong>Allen 1998</strong></td>
<td>Non RCT. Prospective follow up study of 195 adults with GORD (diagnosed objectively by combination of gastroscopy, pHmetry, manometry) treated with Nissen fundoplication. Cough was primary reason for surgery in 42 (21.5%) patients. Cough scores significant reduced post surgery - 51% were cough free and 31% improved. Cough scores correlated to dysphagia score ($r = 0.233$, $P = 0.004$) but did not relate to scores for heartburn, pain or regurgitation. Adverse events not mentioned</td>
</tr>
<tr>
<td><strong>Allen 2002</strong></td>
<td>Non RCT. Prospective study on predictors for response of cough to laparoscopic fundoplication in 354 adults (sub group of total 657 fundoplication). Cough was eliminated in 54% of the 82% (287) followed-up and improved in further 31%. Strongest predictor for response of cough was preoperative cough score ($r = 0.62$). Change in cough score on and off PPI ie positive response to PPI ($r = 0.296$) was a weak predictor. Time scale of response of PPI was not provided. Those with positive Bernstein test were more likely ($P = 0.024$) to respond but predictive value not given. Adverse events not reported</td>
</tr>
<tr>
<td><strong>Allen 2004</strong></td>
<td>Non RCT. Follow up of 209 with respiratory symptoms, mainly cough who underwent laparoscopic Nissen fundoplication. 81% were followed at 6 months, 73% at 2 years, and 60% at 5 years. Cough improved in 83% at 6 months, 74% at 2 years, and 71% at 5 years</td>
</tr>
<tr>
<td><strong>Baldi 2006</strong></td>
<td>Placebo not used. RCT comparing 30 mg bd of lansoprazole to 30 mg daily for 12 weeks. Authors suggest a positive response at 4 weeks of PPI is an effective criteria for assessing response to PPI treatment</td>
</tr>
<tr>
<td><strong>Baldi 2006a</strong></td>
<td>Non RCT. Observational prospective study.</td>
</tr>
<tr>
<td><strong>Belafsky 2008</strong></td>
<td>Retrospective study on LPR</td>
</tr>
<tr>
<td><strong>Brouwer 2003</strong></td>
<td>Non RCT. Prospective study of 29 adults with GORD (diagnosed on gastroscopy) and respiratory symptoms including cough ($n = 19$) following laparoscopic Nissen fundoplication. 14 months follow up; 3 required conversion to open procedure, 4 with major complications. Cough (assessed by subjective score) reported to resolve completely in 81% and improved in 13%. pHmetry findings in those with respiratory symptoms similar to those with gastrointestinal symptoms</td>
</tr>
<tr>
<td><strong>Chandra 2007</strong></td>
<td>Review paper. No additional references identified.</td>
</tr>
<tr>
<td><strong>Chen 2000</strong></td>
<td>Non RCT. Retrospective and prospective study of 90 adults undergoing laparoscopic Nissen fundoplication, 97% with typical GI symptoms, 56% with concurrent non-GI symptoms including cough in 17%. Post surgery patients with non-GI symptoms improved in 54% but reflux symptoms in 95%. New symptoms of flatulence, belching, dysphagia, chest and abdominal pain were reported but not measured. Surgical complications not mentioned</td>
</tr>
<tr>
<td><strong>Coron 2007</strong></td>
<td>Review paper. One additional paper identified from references</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
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<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Dalby-Payne 2003</td>
<td>Meta-analysis of cisapride for treatment of GORD in children. Cough was not an outcome measure in meta-analysis</td>
</tr>
<tr>
<td>DeMeester 1990</td>
<td>Non RCT. Prospective study evaluating the effect of fundoplication in 17 adults with chronic/persistent respiratory symptoms (including cough) and GORD in-patients with or without chest radiograph abnormality. Surgery was not beneficial only on those whose respiratory symptoms occurred pre reflux event. Those whose respiratory symptoms occurred during or within 3 mins following or were unrelated to reflux episodes and had pre surgical normal motility were more likely to benefit</td>
</tr>
<tr>
<td>Dore 2007</td>
<td>None placebo controlled RCT. Study used different PPIs (rabeprazole, pantoprazole, esomeprazole and lansoprazole) and placebo was not used</td>
</tr>
<tr>
<td>Duffy 2003</td>
<td>Non RCT. Prospective study of 148 adults with GORD (diagnosed on gastroscopy, pHmetry or manometry) undergoing laparoscopic Nissen fundoplication. Of these 31% had cough pre surgery. Modified Gastrointestinal Quality of Life Index used and no cough specific scores utilised. Improved QOL post surgery reported, surgical complications not reported</td>
</tr>
<tr>
<td>Ekstrom 2000</td>
<td>Non RCT. Prospective study evaluating the effect of fundoplication on 24 patients with severe GORD) and concomitant asthma (n = 13) or chronic cough (n = 11). In non-asthmatic patients, daytime cough reduced by 47% and night cough by 80% 12 months after surgery</td>
</tr>
<tr>
<td>El Hennawi 2004</td>
<td>Non RCT. 64 of 80 adults treated with 'anti-reflux Rx'. Before and after Rx effect described</td>
</tr>
<tr>
<td>Eubanks 2001</td>
<td>Non RCT. Before and after PPI study for 3 months relating symptoms of cough, hoarseness and throat clearing with proximal pHmetry in 14 adults, 7 of whom had cough. 5 of the 7 who improved with PPI had reduction of &gt; 70% of pharyngeal acid reflux ie 2 of 7 improved without significant reduction. PPI well tolerated, no side effects reported</td>
</tr>
<tr>
<td>Farrell 2001</td>
<td>Prospective non RCT. Symptoms measured pre and post fundoplication (at 6 weeks) in 324 adults of which 67 had cough. Post surgery, cough resolved in 67%, those with atypical symptoms of GORD were more likely to have had less severe pHmetry indices than those with classical GORD symptoms</td>
</tr>
<tr>
<td>Fock 2008</td>
<td>Consensus guidelines. No additional references identified.</td>
</tr>
<tr>
<td>Fraser 2000</td>
<td>Prospective non RCT. Symptoms measured pre and post PPI treatment (20 mg daily and if no response by 3 months increased to 40 mg daily) in 87 adults (25 had cough as primary symptom). After 6 weeks, 52% had good response (undefined)</td>
</tr>
<tr>
<td>Gatta 2007</td>
<td>Meta-analysis assessing the effectiveness of medical or surgical therapy for reflux disease in adult patients with laryngeal or pharyngeal symptoms presumed to be due to gastro-oesophageal reflux disease. The authors concluded that “Therapy with a high-dose proton pump inhibitor is no more effective than placebo in producing symptomatic improvement or resolution of laryngo-pharyngeal symptoms”</td>
</tr>
<tr>
<td>Greason 2002</td>
<td>Retrospective non RCT in adults with primary respiratory symptoms. Most had abnormal pulmonary function test</td>
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<tr>
<td>Author</td>
<td>Study Type</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Grill 1985</td>
<td>Non RCT</td>
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<tr>
<td>Habermann 1999</td>
<td>Non RCT</td>
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<td>Habermann 2002</td>
<td>Non RCT</td>
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<tr>
<td>Hui 2000</td>
<td>Retrospective non RCT</td>
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<tr>
<td>Hunter 1996</td>
<td>Non RCT</td>
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<td>Irwin 1993</td>
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<td>Issing 2004</td>
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<td>Katzka 1996</td>
<td>Non RCT</td>
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<td>Leeder 2002</td>
<td>Non RCT</td>
</tr>
<tr>
<td>Monini 2006</td>
<td>Non placebo controlled trial</td>
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<td>Author Year</td>
<td>Study Type</td>
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<td>Murray 2006</td>
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<td>Swoger 2006</td>
<td>Prospective controlled non-randomised trial</td>
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<td>Thoman 2002</td>
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<td>Non RCT</td>
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<tr>
<td>Tibbling 1995</td>
<td>Similar data set</td>
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<tr>
<td>van Zanten 2006</td>
<td>RCT</td>
</tr>
<tr>
<td>Waring 1995</td>
<td>Non RCT</td>
</tr>
<tr>
<td>Wo 1997</td>
<td>Non RCT</td>
</tr>
</tbody>
</table>
Wright 2003  
Non RCT. Prospective study on effect of laparoscopic fundoplication in 145 adults with hiatus hernia and symptoms suggestive of GORD and laryngopharyngeal reflux. 55% had abnormal pHmetry. 41% of cohort had cough pre-surgery of which 92% reported improvement. 5 (1.4%) had significant complications (2nd surgery for bleeding, oesophageal perforation, severe odynophagia required in 3 and pulmonary embolus in 2)

Xinias 2003  
Open placebo controlled but non-randomised trial using modified milk for GORD in 56 infants. After 4 weeks of therapy, there was no change in cough scores although significant reduction in reflux index, vomiting and regurgitation episodes were found in treatment arm compared to placebo arm

Yang J 2006  
Non RCT. Subjects with chronic treated with 8 weeks of PPI.

ENT: Ear nose throat  
GI:  
GORD: Gastroesophageal reflux disease  
PI:  
PPI:  
qid:  
QOL: Quality of life  
RCT: Randomised controlled trial  
Rx: Treatment

Characteristics of studies awaiting assessment  [ordered by study ID]

Morice 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT on proscriptive or standard anti-reflux advice with brief dietary weight loss intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Obese adults with presumed cough associated with reflux</td>
</tr>
<tr>
<td>Interventions</td>
<td>Dietary</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Cough QOL</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>
### DATA AND ANALYSES

**Comparison 1. Thickened versus unthickened feeds (infants)**

<table>
<thead>
<tr>
<th>Outcome or subgroup 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>Subjects cured (of cough) at end of study</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>Cough frequency</td>
<td>1</td>
<td></td>
<td>Coughs/hr (Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

**Comparison 2. PPI versus placebo (> 18 years)**

<table>
<thead>
<tr>
<th>Outcome or subgroup 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>Clinical failures (still coughing at end of trial or reporting period)</td>
<td>4</td>
<td>191</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.46 [0.19, 1.15]</td>
</tr>
<tr>
<td>1.1 Medical clinics based enrolment</td>
<td>2</td>
<td>38</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.17 [0.02, 1.73]</td>
</tr>
<tr>
<td>1.2 Otolaryngology based enrolment</td>
<td>2</td>
<td>153</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.56 [0.21, 1.49]</td>
</tr>
<tr>
<td>Mean cough score at end of trial (1st arm crossover/parallel group trials)</td>
<td>4</td>
<td>109</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.38 [-0.77, 0.00]</td>
</tr>
<tr>
<td>2.1 Medical clinic based enrolments</td>
<td>1</td>
<td>21</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.86 [-1.77, 0.05]</td>
</tr>
<tr>
<td>2.2 Otolaryngology based enrolments</td>
<td>3</td>
<td>88</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.28 [-0.70, 0.14]</td>
</tr>
<tr>
<td>Change in cough scores (end-beginning of intervention - 1st arm crossover/parallel group trials)</td>
<td>6</td>
<td>161</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.39 [-0.71, -0.08]</td>
</tr>
<tr>
<td>3.1 studies using omeprazole</td>
<td>2</td>
<td>51</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.71 [-1.29, -0.14]</td>
</tr>
<tr>
<td>3.2 studies using other PPI (lansoprazole, pantoprazole, rabeprazole)</td>
<td>4</td>
<td>110</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.26 [-0.64, 0.12]</td>
</tr>
<tr>
<td>Change in cough scores (crossover studies; standardised scale)</td>
<td>2</td>
<td></td>
<td>SD units (Fixed, 95% CI)</td>
<td>-0.41 [-0.75, -0.07]</td>
</tr>
<tr>
<td>4.1 Sub-category</td>
<td>2</td>
<td></td>
<td>SD units (Fixed, 95% CI)</td>
<td>-0.41 [-0.75, -0.07]</td>
</tr>
<tr>
<td>Absolute cough scores (crossover studies, standardised scale)</td>
<td>2</td>
<td></td>
<td>SD units (Fixed, 95% CI)</td>
<td>-0.29 [-0.62, 0.04]</td>
</tr>
<tr>
<td>Change in cough score after 4 weeks treatment (1st arm crossover/parallel group trials)</td>
<td>2</td>
<td>51</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.51 [-1.08, 0.06]</td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison 1 Thickened versus unthickened feeds (infants), Outcome 1 Subjects cured (of cough) at end of study.

Review: Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

Comparison: 1 Thickened versus unthickened feeds (infants)

Outcome: 1 Subjects cured (of cough) at end of study

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thickened feeds</th>
<th>Unthickened feeds</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao 2007</td>
<td>0/5</td>
<td>2/4</td>
<td>0.09 [0.00, 2.68]</td>
</tr>
</tbody>
</table>

Analysis 1.2. Comparison 1 Thickened versus unthickened feeds (infants), Outcome 2 Cough frequency.

Review: Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

Comparison: 1 Thickened versus unthickened feeds (infants)

Outcome: 2 Cough frequency

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Coughs/hr (SE)</th>
<th>Coughs/hr M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orenstein 1992</td>
<td>1.1 (0.89)</td>
<td>1.10 [-0.64, 2.84]</td>
</tr>
</tbody>
</table>
## Analysis 2.1. Comparison 2 PPI versus placebo (> 18 years), Outcome 1 Clinical failures (still coughing at end of trial or reporting period).

**Review:** Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

**Comparison:** 2 PPI versus placebo (> 18 years)

**Outcome:** 1 Clinical failures (still coughing at end of trial or reporting period)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Medical clinics based enrolment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiljander 2000</td>
<td>7/9</td>
<td>12/12</td>
<td></td>
<td>8.2 %</td>
<td>0.12 [0.01, 2.85]</td>
</tr>
<tr>
<td>Ours 1999</td>
<td>7/8</td>
<td>9/9</td>
<td></td>
<td>7.4 %</td>
<td>0.26 [0.01, 7.43]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>17</td>
<td>21</td>
<td></td>
<td>15.6 %</td>
<td>0.17 [0.02, 1.73]</td>
</tr>
</tbody>
</table>

Total events: 14 (PPI), 21 (Placebo)

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 1 (P = 0.74); I^2 = 0.0$

Test for overall effect: $Z = 1.49 (P = 0.14)$

2 Otolaryngology based enrolment

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>n/N</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eherer 2003</td>
<td>2/5</td>
<td>4/6</td>
<td></td>
<td>13.5 %</td>
<td>0.33 [0.03, 3.93]</td>
</tr>
<tr>
<td>Vaezi 2006</td>
<td>79/94</td>
<td>43/48</td>
<td></td>
<td>70.9 %</td>
<td>0.61 [0.21, 1.80]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>99</td>
<td>54</td>
<td></td>
<td>84.4 %</td>
<td>0.56 [0.21, 1.49]</td>
</tr>
</tbody>
</table>

Total events: 81 (PPI), 47 (Placebo)

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.20; df = 1 (P = 0.66); I^2 = 0.0$

Test for overall effect: $Z = 1.17 (P = 0.24)$

**Total (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>n/N</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>116</td>
<td>75</td>
<td></td>
<td>100.0 %</td>
<td>0.46 [0.19, 1.15]</td>
</tr>
</tbody>
</table>

Total events: 95 (PPI), 68 (Placebo)

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 1.14; df = 3 (P = 0.77); I^2 = 0.0$

Test for overall effect: $Z = 1.66 (P = 0.097)$
Analysis 2.2. Comparison 2 PPI versus placebo (> 18 years), Outcome 2 Mean cough score at end of trial (1st arm crossover/parallel group trials).

Review: Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

Comparison: 2 PPI versus placebo (> 18 years)

Outcome: 2 Mean cough score at end of trial (1st arm crossover/parallel group trials)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Medical clinic based enrolments</td>
<td>9</td>
<td>5.89 (5.01)</td>
<td>12</td>
<td>9.91 (4.1)</td>
<td>17.8 % -0.86 [ -1.77, 0.05 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>9</td>
<td></td>
<td>12</td>
<td></td>
<td>17.8 % -0.86 [ -1.77, 0.05 ]</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.84 (P = 0.065)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Otolaryngology based enrolments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eherer 2003</td>
<td>5</td>
<td>0.4 (0.55)</td>
<td>6</td>
<td>1.5 (1.64)</td>
<td>9.3 % -0.79 [ -2.04, 0.47 ]</td>
</tr>
<tr>
<td>Noordzij 2001</td>
<td>15</td>
<td>243.3 (346.62)</td>
<td>15</td>
<td>328.2 (473.67)</td>
<td>28.6 % -0.20 [ -0.92, 0.52 ]</td>
</tr>
<tr>
<td>Pawar 2007</td>
<td>21</td>
<td>0.29 (0.64)</td>
<td>26</td>
<td>0.5 (1.1)</td>
<td>44.3 % -0.22 [ -0.80, 0.35 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>41</td>
<td></td>
<td>47</td>
<td></td>
<td>82.2 % -0.28 [ -0.70, 0.14 ]</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.71, df = 2 (P = 0.70); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.29 (P = 0.20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>50</td>
<td></td>
<td>59</td>
<td></td>
<td>100.0 % -0.38 [ -0.77, 0.00 ]</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.98, df = 3 (P = 0.58); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.95 (P = 0.051)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 1.27, df = 1 (P = 0.26), I² =21%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Analysis 2.3. Comparison 2 PPI versus placebo (> 18 years), Outcome 3 Change in cough scores (end-beginning of intervention - 1st arm crossover/parallel group trials).

Review: Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

Comparison: 2 PPI versus placebo (> 18 years)

Outcome: 3 Change in cough scores (end-beginning of intervention - 1st arm crossover/parallel group trials)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Kiljander 2000</td>
<td>9 -4.55 (5.18)</td>
<td>12 1.33 (5.18)</td>
<td>11.4 % -1.09 [-2.03, -0.15]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noordzij 2001</td>
<td>15 -112.9 (165.68)</td>
<td>15 -20 (207.16)</td>
<td>19.0 % -0.48 [-1.21, 0.25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>24</strong></td>
<td><strong>27</strong></td>
<td><strong>30.4 % -0.71 [-1.29, -0.14]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 studies using omeprazole

Heterogeneity: Chi² = 1.01, df = 1 (P = 0.32); I² =1%
Test for overall effect: Z = 2.42 (P = 0.015)

2 studies using other PPI (lansoprazole, pantoprazole, rabeprazole)

- Eherer 2003 5 -1.4 (2.7) 6 -2.66 (3.14) 6.9 % 0.39 [-0.81, 1.59]
- Havas 1999 8 -0.9 (3.37) 7 -0.86 (3.33) 9.8 % -0.01 [-1.03, 1.00]
- Pawar 2007 21 -0.52 (1.123) 26 0.08 (0.775) 28.9 % -0.62 [-1.21, -0.03]
- Steward 2004 18 -1.2 (2.48) 19 -0.9 (3.02) 24.1 % 0.11 [-0.75, 0.54]

**Subtotal (95% CI)** | **52** | **58** | **69.6 % -0.26 [-0.64, 0.12]** | |

2 studies using other PPI (lansoprazole, pantoprazole, rabeprazole)

Heterogeneity: Chi² = 3.01, df = 3 (P = 0.32); I² =1%
Test for overall effect: Z = 1.33 (P = 0.19)

**Total (95% CI)** | **76** | **85** | **100.0 % -0.39 [-0.71, -0.08]** |

Heterogeneity: Chi² = 5.68, df = 5 (P = 0.34); I² =12%
Test for overall effect: Z = 2.44 (P = 0.015)
Test for subgroup differences: Chi² = 1.66, df = 1 (P = 0.20), I² =40%
### Analysis 2.4. Comparison 2 PPI versus placebo (> 18 years), Outcome 4 Change in cough scores (crossover studies; standardised scale).

**Review:** Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

**Comparison:** 2 PPI versus placebo (> 18 years)

**Outcome:** 4 Change in cough scores (crossover studies; standardised scale)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>SD units (SE)</th>
<th>SD units (SE)</th>
<th>Weight</th>
<th>SD units (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Sub-category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eherer 2003</td>
<td>-0.34 (0.277)</td>
<td></td>
<td>38.7 %</td>
<td>-0.34 [-0.88, 0.20]</td>
</tr>
<tr>
<td>Kiljander 2000</td>
<td>-0.45 (0.22)</td>
<td></td>
<td>61.3 %</td>
<td>-0.45 [-0.88, -0.02]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>-0.41 [-0.75, -0.07]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.10$, df = 1 ($P = 0.76$); $I^2 = 0.0$

Test for overall effect: $Z = 2.37$ ($P = 0.018$)

Test for subgroup differences: Not applicable

### Analysis 2.5. Comparison 2 PPI versus placebo (> 18 years), Outcome 5 Absolute cough scores (crossover studies, standardised scale).

**Review:** Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

**Comparison:** 2 PPI versus placebo (> 18 years)

**Outcome:** 5 Absolute cough scores (crossover studies, standardised scale)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>SD units (SE)</th>
<th>SD units (SE)</th>
<th>Weight</th>
<th>SD units (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Eherer 2003</td>
<td>-0.161 (0.27)</td>
<td></td>
<td>39.9 %</td>
<td>-0.16 [-0.69, 0.37]</td>
</tr>
<tr>
<td>Kiljander 2000</td>
<td>-0.375 (0.22)</td>
<td></td>
<td>60.1 %</td>
<td>-0.38 [-0.81, 0.06]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>-0.29 [-0.62, 0.04]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.38$, df = 1 ($P = 0.54$); $I^2 = 0.0$

Test for overall effect: $Z = 1.70$ ($P = 0.089$)

Test for subgroup differences: Not applicable
### Analysis 2.6. Comparison 2 PPI versus placebo (> 18 years), Outcome 6 Change in cough score after 4 weeks treatment (1st arm cross over/parallel group trials).

Review: Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

Comparison: 2 PPI versus placebo (> 18 years)

Outcome: 6 Change in cough score after 4 weeks treatment (1st arm cross over/parallel group trials)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiljander 2000</td>
<td>9</td>
<td>-1.78 (4.47)</td>
<td>-1.58 (3.78)</td>
<td>43.1 %</td>
<td>-0.05 [-0.91, 0.82]</td>
</tr>
<tr>
<td>Noordzij 2001</td>
<td>15</td>
<td>-166.8 (197.17)</td>
<td>9.4 (199.98)</td>
<td>56.9 %</td>
<td>-0.86 [-1.62, -0.11]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>24</strong></td>
<td><strong>27</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>-0.51 [-1.08, 0.06]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.95, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 1.76 (P = 0.078)
Test for subgroup differences: Not applicable
Analysis 2.7. Comparison 2 PPI versus placebo (> 18 years), Outcome 7 Difference in cough scores at week 8 - week 4 (1st arm cross over/parallel group trials).

Review: Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults

Comparison: 2 PPI versus placebo (> 18 years)

Outcome: 7 Difference in cough scores at week 8 - week 4 (1st arm cross over/parallel group trials)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPI</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiljander 2000</td>
<td>9</td>
<td>-4.67 (2.17)</td>
<td></td>
<td>30.1 %</td>
</tr>
<tr>
<td>Noordzij 2001</td>
<td>15</td>
<td>53.9 (161.51)</td>
<td></td>
<td>69.9 %</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>27</td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 11.09, df = 1 (P = 0.00087); I² =91%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable

APPENDICES
Appendix 1. Archive of search results (All years to April 2007)
The Airways Group specialised register/search identified 763 potentially relevant titles in the original search in 2004. After assessing the abstracts, 84 papers were obtained for considered for inclusion into review. The main reason for non-eligibility of studies for review criteria was the non-controlled non-randomised nature of the respective studies (see table ‘Characteristics of excluded studies’). One controlled but non-randomised study was also excluded (Xinias 2003). Eleven studies were included in the original version of the review (see ‘Characteristics of included studies’), and all but one (Vanderhoof 2003) were single centre studies. The multi-centre study (Vanderhoof 2003) also the only study supported by commercial interest then. In the 2005 update a further 11 articles were retrieved; one study was included (El Serag 2001) and the rest were excluded, with two described in the excluded table (El Hennawi 2004; Issing 2004). Following the 2006 search update, eight papers were retrieved. One RCT in adults (Vaezi 2006) was included and another RCT was excluded (Baldi 2006) as a placebo was not used. The excluded study compared two doses of lansoprazole for adults with chronic cough (Baldi 2006). Following the 2007 search update, 407 abstracts were reviewed, 12 papers were retrieved; none fulfilled eligibility criteria. One study that was excluded but should be highlighted was that of a controlled (but non randomised) trial on fundoplication for laryngopharyngeal reflux (LPR) of which 30-31% of the subjects had chronic cough, the 2nd or 3rd most common symptom (Swoger 2006). Swoger 2006 described no difference between groups at one year, despite technical success of the fundoplication. A systematic review on the efficacy of PPIs for LPR was also excluded (Gatta 2007). The paper (Gatta 2007) however revealed a relevant study that was not found in previous searches; this study (Steward 2004) is now included in this update.
Appendix 2. CENTRAL search strategy

#1 MeSH descriptor Gastroesophageal Reflux explode all trees in MeSH products
#2 ((gastro-oesophageal next reflux) or (gastroesophageal next reflux) or (gastro-esophageal next reflux) or reflux or ger or gerd or acid or esophagus or oesophagus)
#3 MeSH descriptor Esophagus explode all trees in MeSH products
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Cough explode all trees in MeSH products
#6 MeSH descriptor Bronchitis explode all trees in MeSH products
#7 cough*
#8 bronchiti*
#9 (#5 OR #6 OR #7 OR #8)
#10 (#4 AND #9)

Appendix 3. MEDLINE search strategy

1. exp COUGH/
2. exp Bronchitis/
3. (cough$ or bronchit$).mp.
4. 1 or 2 or 3
5. exp GASTROESOPHAGEAL REFLUX/
6. exp Esophagus/
7. (gastro-oesophageal reflux or gastroesophageal reflux or gastro-esophageal reflux or reflux or ger or gerd or acid or esophagus or oesophagus).mp.
8. 5 or 6 or 7
9. 4 and 8

Appendix 4. EMBASE search strategy

1. exp Coughing/
2. exp Bronchitis/
3. (cough$ or bronchit$).mp.
4. 1 or 2 or 3
5. exp Gastroesophageal Reflux/
6. exp esophagus/
7. (gastro-oesophageal reflux or gastroesophageal reflux or gastro-esophageal reflux or reflux or ger or gerd or acid or esophagus or oesophagus).mp.
8. 5 or 6 or 7
9. 4 and 8

WHAT’S NEW

Last assessed as up-to-date: 9 June 2009.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 April 2009</td>
<td>New search has been performed</td>
<td>Literature search re-run; no new studies were identified.</td>
</tr>
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HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 2, 2005

<table>
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<tr>
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<th>Event</th>
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<tr>
<td>11 April 2008</td>
<td>New search has been performed</td>
<td>Literature search re-run; four new studies were identified which met the eligibility criteria of the review. The conclusions were not altered on the basis of the new trial evidence</td>
</tr>
<tr>
<td>5 April 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>1 August 2007</td>
<td>New citation required but conclusions have not changed</td>
<td>One new study met the entry criteria of the review (Steward 2004). This study was identified from a systematic review on laryngopharyngeal reflux and cough (Gatta 2007). It contributed data to a secondary outcome (change in cough scores at end of intervention), but did not alter the conclusions of the review</td>
</tr>
<tr>
<td>6 September 2006</td>
<td>New citation required but conclusions have not changed</td>
<td>One new study met the entry criteria of the review (Vaezi 2006). This study contributed data to the primary outcome (still coughing at end of trial), but did not alter the conclusions of the review</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

A Chang: initiation, design and direction of review, writing of protocol and review, selection of studies, data extraction, performed analysis and interpretation of results. LG: selection of studies and data extraction, writing of primary protocol and review. JG: data extraction; FC: review of manuscript. TJL: data extraction and analysis, interpretation of results and writing of review. The on-line editor for this review was Dr. M McKean.

DECLARATIONS OF INTEREST

Nil.
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- Queensland Government Smart State Funds, Australia.

Salary Support for AC

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Cough [complications; *therapy]; Gastroesophageal Reflux [complications; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans