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# Research

# Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux

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## Abstract

**Objective** To evaluate the efficacy of treatment for gastro-oesophageal reflux disease (GORD) on chronic cough in children and adults without an underlying respiratory disease.
**Design** Systematic review and meta-analysis.
**Data sources** Cochrane, Medline, and Embase databases, references from review articles.
**Included studies** Randomised controlled trials on GORD treatment for cough in children and adults without primary lung disease. Two reviewers independently selected studies and extracted paediatric and adult data on primary (clinical failure) and secondary outcomes.
**Results** 11 studies were included. Meta-analysis was limited to five studies in adults that compared proton pump inhibitors with placebo. All outcomes favoured proton pump inhibitors: the odds ratio for clinical failure (primary outcome) was 0.24 (95% confidence interval 0.04 to 1.27); number needed to treat (NNT) was 5 (harm 50 to ∞ to benefit 2.5). For secondary outcomes, the standardised mean difference between proton pump inhibitors and placebo was −0.51 (−1.02 to 0.01) for mean cough score at the end of the trial and −0.29 (−0.62 to 0.04) for change in cough score at the end of the trial. Subgroup analysis with generic inverse variance analysis showed a significant mean change in cough (−0.41 SD units, −0.75 to −0.07).
**Conclusion** Use of a proton pump inhibitor to treat cough associated with GORD has some effect in some adults. The effect, however, is less universal than suggested in consensus guidelines on chronic cough and its magnitude of effect is uncertain.

## Introduction

Cough is the most common symptom presenting to general practitioners.[1] Chronic cough considerably impairs quality of life in adults and worries parents of children with cough. Prolonged or chronic cough has been variously defined as a cough that persists for more than three to eight weeks and non-specific cough defined as non-productive cough in the absence of identifiable respiratory disease or known cause.[2]

Gastro-oesophageal reflux (GOR)—that is, reflux of gastric contents into the oesophagus—can be acid or non-acid. Reflux may be physiological and is associated with a range of gastrointestinal symptoms (abdominal pain, halitosis, etc) and extraoesophageal symptoms (cough, hoarseness, etc).[3] Cohort studies in adults suggest that GOR disease (GORD) related to acid causes 21-41% of chronic non-specific cough.[1] Guidelines on chronic cough suggest use of empirical treatment for GOR,[4 5] including a therapeutic trial of three to six months of treatment for GORD.[6] Although laboratory studies have shown a temporal relation between acid in the oesophagus and cough, some studies have shown that the cough resolves only after a mean of 169-179 days after treatment.[6] Other studies have shown that acid GORD is associated with, but is not the cause of, cough.[7]

Current treatments for GORD include conservative measures (diet, positioning, etc), pharmaceuticals (acid suppressants such as histamine $H_2$ receptor antagonists, and proton pump inhibitors; prokinetic agents such as domperidone, metoclopramide, and cisapride), and surgical approaches (fundoplication). These well established treatments for GOR, however, may not be beneficial for associated cough or may increase respiratory morbidity.[8] We examined the efficacy of treatments for GOR on non-specific chronic cough in adults and children in a systematic review. This review is based on a Cochrane systematic review.[9]

## Methods

We used QUOROM guidelines, Cochrane collaboration method, and software (RevMan 4.2) (see bmj.com). Studies in adults and children were eligible if they were randomised controlled trials of any GORD treatment for chronic cough (lasting more than three weeks) where cough was an outcome and not primarily related to an underlying respiratory disorder. We classified the evaluated treatment regimens by type: anti-reflux conservative measures (for example, positioning, diet), $H_2$ receptor antagonists, proton pump inhibitor, and surgical therapy. Our primary outcome was proportion of participants who were not cured at follow-up (failure to cure). Secondary outcomes were proportion of participants not substantially improved at follow-up, mean difference in cough indices (frequency of cough, scores, sensitivity), proportion who experienced adverse effects (such as rash, surgical morbidity, etc), and proportions who experienced complications (requirement for change in medication, repeat surgery, etc). We determined the proportions of participants who failed to improve on treatment using a hierarchy of assessment measures (see bmj.com).

We use the search strategy standardised by the Cochrane Airways Group as well as references in relevant publications and written communication with the authors of papers. Two reviewers independently reviewed literature searches, selected articles,

*Details on the search strategy, study selection and characteristics, and data extraction and quality assessment can be found on bmj.com*



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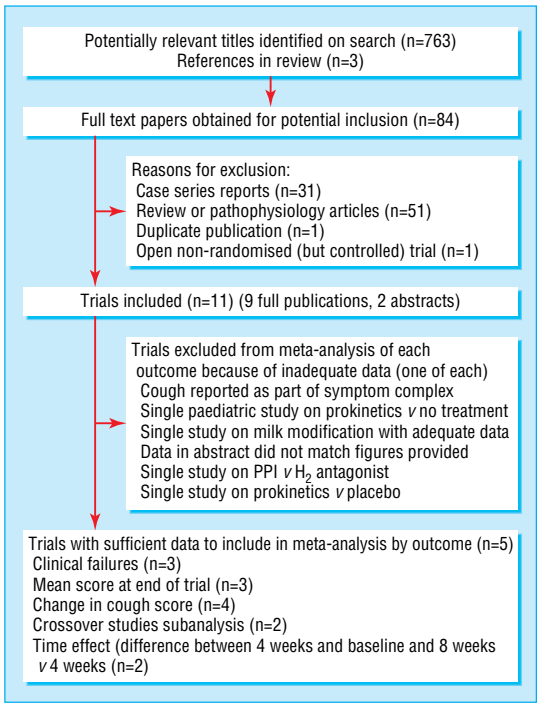



**Fig 1** Details of included and excluded trials

and extracted data. We used the κ statistic to assess agreement between reviewers. Details of other statistics including a priori, subgroup, and sensitivity analyses are on bmj.com. When we combined data with parallel studies we used only data from the first arm of crossover trials.

## Results

We identified 763 potentially relevant titles and reviewed 84 papers for inclusion (fig 1). There was 92% agreement for inclusion of the 11 studies (three in children, eight in adults, n = 383) that met criteria for the systematic review (table). All but one[10] were single centre studies; the only multicentre study was also the only study supported by industry.[10] All but two studies were in English.[11 12] Additional data were sought from all authors of English articles, and two groups provided raw data.[13 14] Jadad and quality assessment scores varied (table). Agreement for quality of studies was excellent; the weighted κ score was 0.71 for Jadad score and 0.89 for quality assessment.

### Paediatrics

Two studies in children found some improvement in GORD symptoms referring to the gastrointestinal system but data for the effect on cough were inconsistent.[10 15] One study found no significant effect of cisapride or domperidone on cough associated with GORD.[11] There were insufficient data in infants and children for meta-analysis and no randomised controlled trials on the use of proton pump inhibitors or surgery.

### Adults

Of the eight studies in adults, six were published full articles,[12–14 16–18] one was an abstract,[19] and one was duplicated in a conference report and abstract.[20] Five were parallel studies, and three were crossover studies. Five studies compared proton pump inhibitors with placebo but used varying doses and frequency (studies based in otolaryngology clinics[14 16 17] used higher doses of proton pump inhibitors, table). Although all studies included patients with cough that was presumed to be associated with GORD, criteria for entry into the studies varied. In three studies, participants enrolled through the otolaryngology department had "laryngitis" symptoms.[14 16 17] In these studies, the exclusion criterion of primary lung disease (for example, asthma defined by hyper-responsiveness) was not as stringently applied as in the studies that enrolled participants through medical outpatients.[12 13 18 20] In all but one study,[12] the presence of GORD was confirmed objectively. No studies used non-acidic reflux as an entry criterion.

Outcome measures for all studies were various subjective cough scales; none used objective monitoring of cough. One study compared proton pump inhibitors with ranitidine[12] and another was a 2×2 factorial design with cisapride and dietary intervention.[19] We could not extract data from the single study on $H_2$ receptor antagonists compared with placebo; trialists reported an improvement in cough scores with intervention in all participants and the effect was significant at two weeks.[20] In the six studies that compared proton pump inhibitors or cisapride with placebo, all but one study showed no difference in improvement in cough scores in the active and placebo arms.[12 14 16–19] Participants took proton pump inhibitors for two to three months, and only one study followed up patients after the trial.[18]

In the meta-analysis, the primary outcome (clinical failure) was the only outcome where we could use "intention to treat" data for all included studies displayed in the forest plot. The pooled odds ratio effect estimate was 0.24 (95% confidence interval 0.04 to 1.27 (fig 2; 49 participants)). Number needed to treat for benefit was 5 (harm 50 to ∞ to benefit 2.5).[21] Evaluation of the mean cough score at the end of the trial (secondary outcome), in a pooled (62 participants) analysis of three studies[13 14 16] showed a non-significant difference between groups (standardised mean difference −0.51, −1.02 to 0.01). When we restricted this pooled analysis to crossover studies,[13 14] the difference was also not significant (−0.29, −0.62 to 0.04). The outcome of change in cough scores at the end of the intervention pooled from four studies (77 participants)[13 14 16 17] was not significant (−0.29, −0.62 to 0.04 (fig 3)). Data from the two crossover trials[13 14] that assessed mean change in symptoms showed a significant difference (−0.41 SD units, −0.75 to −0.07 (fig 4, 35 subjects per arm)).

Few studies determined "time to response" and duration of treatment effect was limited; after four weeks of intervention change in cough score favoured proton pump inhibitors but was not significantly different (P = 0.09, standardised mean difference −0.51, −1.08 to 0.06, from two studies,[13 16] 51 participants). The effect at eight weeks compared with four weeks of intervention[13 16] was also not significant (−0.44, −1.04 to 0.16). The single study that specifically reported time to response[18] was also the only study that followed up participants after the trial (open study followed by randomised controlled trial), and the effect of treatment occurred within 5-14 days.[18]

None of the studies reported any relevant adverse events with the interventions, and it was not possible to look for an association between level of risk and benefit. Sensitivity analyses did not alter any results.

All studies that provided sufficient data reported significant improvement in gastrointestinal symptoms. In three studies, however, there was no difference in improvement between the intervention and placebo groups.[14 16 17] All three studies on otorhinolaryngological symptoms reported significant improvement in symptoms of laryngitis over time.[14 16 17] In two studies, the difference in subjective and semi-objective (laryngoscopy)



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**Table 1** Description of studies included in review

| Study | Setting (recruited/ followed up) | Mean age (SD or range*), sex | Methods, diagnosis | Participants | Interventions | Outcomes | Follow-up | High quality score; Jadad† |
|---|---|---|---|---|---|---|---|---|
| **Paediatric studies** | | | | | | | | |
| Dordal[11] 1994, Spain. Controlled parallel study | Outpatients clinic (65/55) | Cisapride group: 6.7 years (2.97), 15M:6F Domperidone group: 7.05 years (3.05), 10M:13F Control: 6.4 years (2.62), 5M:6F | Clinical exam, skin prick tests, spirometry, chest x ray, gastro-oesophageal imaging (graded 1-4, child eligible if grade ≥2) at baseline | 65 children (No screened not given) with predominant nocturnal cough (with or without asthma) and GORD symptoms; 15 of 55 who completed trial had cough without symptoms of asthma. Inclusion criteria: children with cough (with or without co-exiting asthma), predominantly nocturnal symptoms, reflux symptoms. Exclusions: none described | Cisapride (0.2 mg/kg 20 mins before each meal) with domperidone (0.2 mg/kg 15 mins before each meal) and no treatment (control) for 12 weeks. In all: no food two hours before bedtime, reduce intake of acidic foods, smaller more frequent meals, head of bed raised by 10 cm, sleeping on side | Cough; gastro-imaging | None after trial period | 0, 1 |
| Orenstein[15] 1992, US. Randomised single blind, crossover study | Gastro-enterology clinic (25/25) | Median postnatal age 7.5 weeks (2-26), corrected age 7 weeks (–6 to 26), sex not given | Assessor blinded but not care giver/nurse who fed infants. GORD diagnosed by pHmetry, barium swallow, or oesophageal biopsy | 25 infants randomised (No screened not given) from infants referred for GORD. Inclusion criteria: not defined. Exclusions: concurrent acute infectious respiratory illness, use of prokinetic or acid reducing medications | Thickened (with rice cereal) and unthickened feeds | Cough frequency during and after feeds per hour | None after trial period | 0, 1 |
| Vanderhoof[10] 2003, North America. Multi-centre randomised double blind, parallel study | Six paediatric centres (110/98) | Intervention group: 61 days (4), 27M:28F Control group: 58 days (4), 26M:23F | Infants with regurgitant reflux. Parents kept diary cards for two days. Eligible infants randomised. Infants reviewed after one week and pharmacological intervention started (ranitidine after day 7-8 and cisapride after day 14-15) | 110 infants randomised (No screened not given). Inclusion: ≥5 regurgitations/day for two baseline days, age 14-120 days, gestational age >37 weeks, birth weight ≥2500 g, maternal age ≥18 years. Exclusions: congenital abnormalities interfering with normal feeding or causing repeated regurgitation. Fever, infectious illness, clinical diagnosis of milk or soya protein allergy, complicated GORD (oesophagitis, haematemesis, recurrent respiratory symptoms, failure to thrive), previous treatment with thickened formula, or treatment with prokinetic medications five days before start of study | Prethickened formula (Enfamil AR) or placebo for 35/36 days, with equal access to additional pharmacological intervention | Regurgitation frequency and volume, on daily diary for first week and then two days/week. Percentage feeds followed by choke, gag, cough. Trouble sleeping. Measures at week one and end of participation | None after trial period | 2, 5 |
| **Adult studies** | | | | | | | | |
| Eherer[14] 2003, Austria. Randomised double blind, crossover study | Otolaryngology clinic (12 with cough/8) | 48 years (20-70), 16M:5F | Adults with "laryngitis" symptoms (includes cough) and GORD (defined on pHmetry). Video laryngo-stroboscopy performed and screened for exclusion criteria. Dual channel pHmetry performed and those with excessive reflux (>4.5% time pH<4) eligible and randomised | 21/22 adults randomised (62 screened), with GORD (diagnosed on pHmetry) and symptoms of laryngitis (cough, nocturnal cough, sore throat, hoarseness, sore dysphonic attacks, globus sensation). Inclusion: hoarseness for >2 months, laryngitis or other laryngeal symptoms which includes cough. Exclusions: smokers, other causes of laryngitis, prior operations on laryngeal area, laryngeal malignancy, COPD | Placebo or pantoprazole 40 mg bd for three months, two weeks washout followed by pantoprazole or placebo for three months | Laryngeal symptoms (0-72). Oesophageal symptoms (0-48). Laryngeal scoring. Raw data given by authors | None after trial period | 2, 5 Based on additional information given |
| Havas[17] 1999, Australia. Randomised double blind, parallel study | Oto-laryngology clinic (20/15) | 53.6 (32-76), 7M:8F | Adults with "posterior pharyngolaryngitis" symptoms (includes cough) with or without objective GORD. Video laryngoscopy, dual channel pHmetry, gastroscopy, and oesophageal manometry performed. Distal reflux defined as pH<4 for >4% of time, proximal = pH fall of ≥3 within nadir of ≤5 with oesophageal acidification | 20 adults randomised from 100 screened. Inclusion criteria: "posterior pharyngolaryngitis" assessed by video laryngoscopy and symptoms (see outcome measures). Exclusions: severe neurological disorders, chronic airflow limitation, pre-existing antisecretory medications, severe oesophagitis at endoscopy, singers | Lanoprazole 30 mg bd or placebo bd for 12 weeks | Laryngitis symptoms (cough, hoarseness, throat clearing, sore throat). Reflux symptoms (dysphagia, retrosternal burning pain, acid regurgitation, odynophagia). Laryngoscopy findings | None after trial period | 1,3 |

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| Study | Setting (recruited/ followed up) | Mean age (SD or range*), sex | Methods, diagnosis | Participants | Interventions | Outcomes | Follow-up | High quality score; Jadad† |
|---|---|---|---|---|---|---|---|---|
| Ing[20] 1997, Australia. Double blind crossover study | Medical outpatients (21/20) | 46.8 (SEM 3.3), 11M:14F | Chronic persistent cough (>2 months) with unknown aetiology after standard evaluation. pHmetry and histamine airway hyper-responsiveness. pHmetry repeated in seven, 4-6 weeks after ranitidine treatment. Significant GOR defined as presence of >12 reflux episodes/ 24 hours and time pH <4 was >0.7% | 25 patients randomised (No screened not given). All had PD20 to histamine >8 μmols. Inclusion criteria: chronic cough and significant GOR. Exclusions: asthma, chronic bronchitis, allergic rhinitis, sinusitis, postnasal drip, other respiratory and cardiac diseases, acute respiratory infections in preceding two months, smokers, or use of theophylline or ACE inhibitors | Placebo or ranitidine 150 mg bd for two weeks, two weeks wash out followed by ranitidine or placebo for two weeks | Cough scores (1-4) twice daily on diary cards. GORD symptoms | None after trial period | 1, 3 |
| Jaspersen[12] 1999, Germany. Randomised parallel study | Medical outpatients (20/20) | Omeprazole: 49.4 (16.3), 5M:5F Ranitidine: 46.5 (19.7); 6M:5F | Adults with chronic persistent cough (>8 weeks) with unknown aetiology. GORD symptoms or gastroscopy positive | 20 adults from 76 screened, with chronic cough, negative clinical and radiological findings. Inclusion criteria: persistent cough for eight weeks, negative findings from physical examination, negative radiological findings, with GORD and normal lung function. Exclusions: diagnosis of chronic asthma, COPD, chronic bronchitis, other oesophageal disease, ACE inhibitor use, ENT abnormalities, smokers | Omeprazole 10 mg/day or ranitidine 300 mg/day for eight weeks | Cough score. Oesophagitis score. Outcomes recorded for eight weeks | None after trial period | 0,1 |
| Kiljander[13] 2000, Finland. Randomised double-blind, crossover study | Pulmonary outpatients (29/21) | 49 (IQR 20-74), 10M:19F | Adults with chronic cough and GORD (defined on pHmetry) completed one week observation by diary cards, pHmetry then performed and those with excessive reflux randomised | 29 adults randomised from 48 patients screened, with GORD and chronic cough (≥2 months). Inclusion criteria: chronic persistent cough (≥2 months). Exclusions: abnormal chest or sinus radiology, positive methacholine test, rhinitis, nasal mucosa appearance of cobblestone or mucopurulent secretions, smokers, asthma, chronic bronchitis, use of ACE inhibitor | Omeprazole 40 mg per day or placebo for eight weeks, two weeks washout followed by omeprazole or placebo | Weekly daytime cough and night time cough. Weekly gastric symptoms | None after trial period. Raw data given by authors | 2, 3 |
| Kopec[19] 2001, US. Partial double blind parallel randomised placebo controlled trial (2×2 factorial design) | Medical outpatients (21/19) | 53.5 (12.9) | Unblind randomisation of diet. Double blind randomisation of cisapride. After standard diagnostic investigation for chronic cough, subjects who met criteria (authors assume that this predicts patients have approximate 92% chance of having chronic cough due to GORD diagnosed on pHmetry or on barium meal) randomised | 21 adults with chronic cough and GORD randomised from outpatients clinic (No of eligible patients not given). Inclusion criteria: adults with chronic cough (>8 weeks) and presumably GORD related cough. Exclusions: age <18 years, pregnancy, known contraindications to cisapride | 2×2 factorial design using usual care diet or antireflux diet and cisapride 10 mg qid or placebo for four months trial (four arm study) | Cough scores (visual analog score) | None after trial period | 0, 1 |
| Noordzij[16] 2001, US. Randomised double blind parallel study | Oto-laryngology clinic (30/28) | Omeprazole group: 51.7, 8M:7F Placebo group: 45.3, 8M:7F (SD of age NA) | Adults with "laryngitis" symptoms (includes cough) and GORD (defined on pHmetry). Video laryngostroboscopy performed and screened for exclusion criteria. Dual channel pHmetry then performed and those with reflux were eligible and randomised. Acid reflux defined as >4 episodes proximal pH <4 or 3 point drop in pH with simultaneous drop in distal pH of <4) | 30 randomised from 53 screened with GORD/laryngopharyngeal reflux and symptoms of laryngitis. Inclusion criteria: ≥1 symptom of laryngitis for >3 months (symptoms of chronic cough, hoarseness, excessive phlegm, throat clearing, throat pain, lump in throat and acid reflux). Exclusions: viral or bacterial laryngitis, benign vocal fold lesions, occupational exposures causing laryngitis, history of seasonal allergies or laryngeal malignancy | Omeprazole 40 mg bd or placebo bd for two months | Symptom scores of laryngitis (includes cough) and GOR Data on cough alone provided in paper | None after trial period | 2, 3 |





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| Study | Setting (recruited/ followed up) | Mean age (SD or range*), sex | Methods, diagnosis | Participants | Interventions | Outcomes | Follow-up | High quality score; Jadad† |
|---|---|---|---|---|---|---|---|---|
| Ours[18] 1999, US Randomised double blind parallel | Medical outpatients and community (17/17) | Age not given. Median age of 36 patients in study before results of pHmetry was 58 years with cough duration of five years (IQR 2-10) | Adults with chronic cough and GORD (defined on pHmetry). Potential subjects screened for exclusion criteria. Patients completed two week observation by diary cards. Those with score of ≥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 | 17 randomised from 71 screened. Patients with chronic cough enrolled from newspaper advertisements and outpatients (most were enrolled from community). Inclusion criteria: aged 18-80 years with chronic cough (≥6 weeks) with score of ≥2 and with excessive acid reflux distally or proximal. Exclusions: abnormal chest radiology, positive methacholine test, smokers, ex-smokers ≤3 months or ≥20 pack year history of smoking, upper respiratory infection within eight weeks of entry, use of ACE inhibitor or β blockers, unable to be weaned off some medications, history of pulmonary disease, malignancy, or any comorbid condition requiring treatment | Omeprazole 40 mg bd or placebo for 12 weeks | Cough severity and 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 night time cough of ≤1 for ≥2 weeks consecutively | After end of trial (12 weeks), open study performed with omeprazole (one month). Open trial results not used for analysis | 3, 5 |

NA=not available in publication. GORD=gastro-oesophageal reflux disease; ACE=angiotensin converting enzyme; ENT=otorhinolaryngology; bd=twice a day; qid=four times/day.
*Unless stated otherwise.
†See bmj.com for explanation of quality assessment.

improvement was similar in treatment and placebo groups.[14 17] One study found significant differences between proton pump inhibitors and placebo in hoarseness and throat clearing but not in throat pain.[16]

## Discussion

In this systematic review of the effects of treatment for GOR for cough associated with GORD, we identified 11 randomised controlled trials. In the meta-analysis of five studies, subgroup analysis indicated that treatment of cough associated with GORD improves subjective cough in participants with non-specific cough. There was no effect in the pooled analysis of the main outcomes, although all favoured proton pump inhibitors. The NNT to achieve cough resolution was 5 (the confidence interval included infinity). This review also highlights the large placebo and time period effect of treatment for chronic cough.

### Differences between trial types

European[5] and American guidelines[4] on the management of chronic cough recommends the use of GORD therapy (including as empirical therapy). The meta-analyses for main outcomes were not significant but all favoured treatment with proton pump inhibitors and subanalyses yielded significant results. Thus, proton pump inhibitors are probably effective in this population. Nevertheless, the small effect (considering other meta-analyses on cough[22] and large confidence intervals) of GORD treatment on cough that we found contrasts with results of non-controlled trials, which almost invariably report high rates of improvement: 100% with proton pump inhibitors alone, 86% with proton pump inhibitors with motility agents, and cure rates of 81% by surgical intervention.[9] The difference between the effect of treatment of GORD on cough seen in randomised controlled trials and uncontrolled trials may be related to the period or placebo effect, which is as high as 85%.[23]

Other possible contributors are selection of patients, the degree of acid inhibition, length of therapy, outcomes of cough measured, role of non-acid reflux, and the presumed GORD related cough which in fact may not have been caused by GORD. Both GOR and cough are common and often coexist, but an association does not imply cause and effect.[7] Our finding of an effect of treatment with proton pump inhibitors to improve cough in subgroup analysis, however, does suggest that in a proportion of adults with chronic cough and GORD, GORD is a contributing cause. The degree of acid inhibition achieved with treatment is probably a small factor, if any, given that most studies achieved a resolution of GORD gastrointestinal symptoms. It is possible, however, that different degrees of acid suppression are required to control the different manifestations of GORD. Results from the meta-analysis on length of therapy were inconclusive.

### Limitations of this review

The validity of this systematic review is also hindered by the disparate nature of the interventions. In all studies participants were selected for gastrointestinal symptoms or objective evidence of

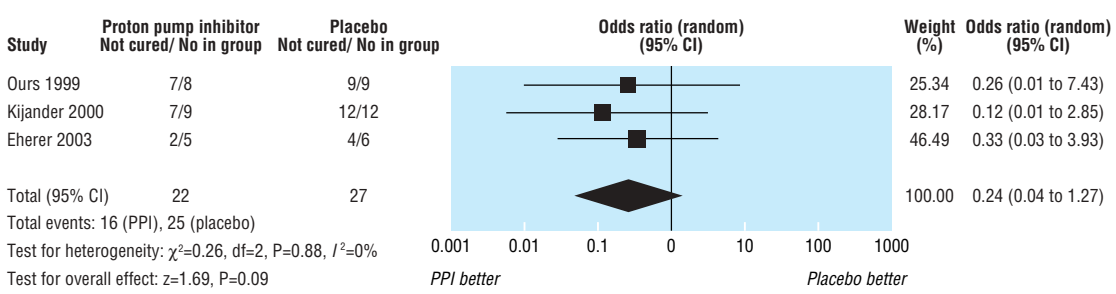



**Fig 2** Meta-analysis of primary outcome (clinical failures—that is, patients still had cough at the end of the trial or reporting period), analyses by intention to treat (49 participants included in meta-analysis)



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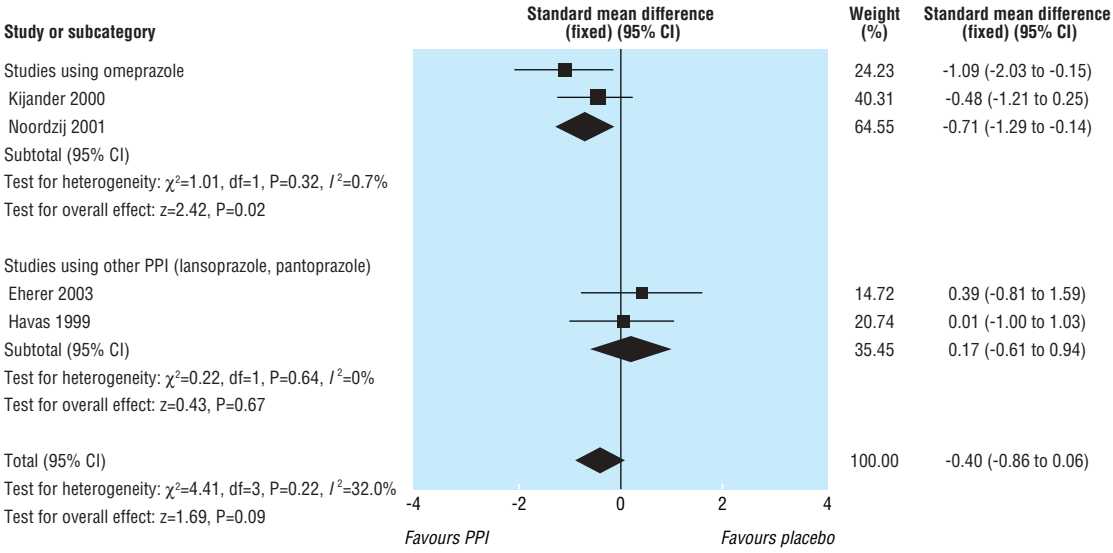



**Fig 3** Meta-analysis of standardised cough scores at end of intervention (77 participants included in meta-analysis)

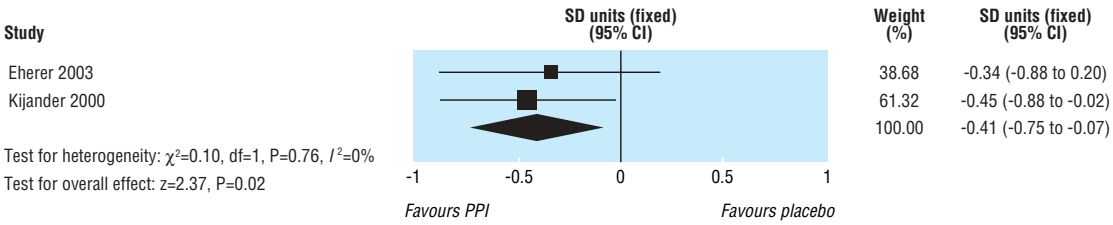



**Fig 4** Meta-analysis of data from the two crossover trials[13 14] assessing mean change in symptoms (subanalysis). Using generic inverse variance for crossover studies, use of proton pump inhibitors was significantly more likely than placebo to reduce cough scores at end of intervention, –0.41 SD units (–0.75 to –0.07)

GORD, and most, but not all, had cough. GORD criteria also varied between studies, which may have influenced results. Most studies did not use criteria for GORD specified by international guidelines.[3 24] There are no data from randomised controlled trials on the efficacy of GORD treatment for chronic cough in the absence of GORD symptoms. In view of the possibility of period or placebo effect leading to misdiagnosis of chronic non-specific cough as due to GORD, we believe that objective confirmation of GORD is preferable to empirical therapy in patients with chronic non-specific cough and no gastrointestinal symptoms. In those with gastrointestinal symptoms, however, an empirical trial of proton pump inhibitors may be justified.

Proton pump inhibitors are currently the most potent non-surgical intervention for acid-GORD, and no adverse events were reported in these studies. The use of these drugs as a trial of therapy is probably low risk but rational prescription is required.[8] Proton pump inhibitors may also cause cough and the package insert for omeprazole includes cough as an adverse event (1.1%).[9] In contrast with pharmaceutical interventions, we found no studies on surgical intervention, which is associated with a small but measurable rate of serious adverse events.

### Conclusion and future research

From this systematic review and meta-analysis we conclude that proton pump inhibitors for cough associated with GORD probably have some effect in some adults, though the effect is less universal than reported in cohort studies. There are insufficient data to support or refute common recommendations to change the diet or use motility agents either as a single agent or in conjunction with proton pump inhibitors. In children, the absence of data makes specific recommendations impossible, and other causes of cough should be considered in children before any empirical treatment with a prolonged course of GORD medications or interventions. Sufficiently powered parallel placebo controlled randomised controlled trials that include an examination of "time to response," optimal duration of treatment, effects after treatment, and valid cough outcomes (objective and validated subjective scales) are required to justify international guidelines.[4 5] Examinations of different treatments for acid and non-acid GOR are also required.

### What is already known on this topic

Gastroesophageal reflux disease (GORD) is common in adults with chronic cough

International guidelines on cough recommend empirical treatment for GORD in those with chronic cough, though evidence for an effect is conflicting

### What this study adds

Drugs to reduce the effect of gastric acid in GORD are beneficial in some adults with cough associated with GORD

The effect is less universal than suggested in cohort studies and international guidelines on chronic cough, and the magnitude of the clinical effect is uncertain





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Contributors: ABC was responsible for initiation, design and direction of review, wrote the protocol and review, selected studies, extracted data, analysed and interpreted results, and is guarantor. LAG selected studies and extracted data, wrote the primary protocol and review, and is guarantor. TJL extracted and analysed data, interpreted results, and wrote the review. TOK wrote the review. JTG extracted data. FLC reviewed the manuscript.

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Ethical approval: Not required.

1 Morice AH. Epidemiology of cough. *Pulm Pharmacol Ther* 2002;15:253-9.
2 Chang AB, Asher MI. A review of cough in children. *J Asthma* 2001;38:299-309.
3 American Gastroenterological Association medical position statement: guidelines on the use of esophageal pH recording. *Gastroenterology* 1996;110:1981-96.
4 Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest* 1998;114:133-81S.
5 Morice AH, Fontana GA, Sovijarvi AR, Pistolesi M, Chung KF, Widdicombe J, et al. The diagnosis and management of chronic cough. *Eur Respir J* 2004;24:481-92.
6 Irwin RS, Madison JM. Diagnosis and treatment of chronic cough due to gastro-esophageal reflux disease and postnasal drip syndrome. *Pulm Pharmacol Ther* 2002;15:261-6.
7 Laukka MA, Cameron AJ, Schei AJ. Gastroesophageal reflux and chronic cough: which comes first? *J Clin Gastroenterol* 1994;19:100-4.
8 Gregor JC. Acid suppression and pneumonia: a clinical indication for rational prescribing. *JAMA* 2004;292:2012-3.
9 Chang AB, Lasserson T, Gaffney J, Connor FC, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev* 2005;(2):CD004823.
10 Vanderhoof JA, Moran JR, Harris CL, Merkel KL, Orenstein SR. Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux. *Clin Pediatr (Phila)* 2003;42:483-95.
11 Dordal MT, Baltazar MA, Roca I, Marques L, Server MT, Botoy J. [Nocturnal spasmodic cough in the infant. Evolution after antireflux treatment.] *Allerg Immunol (Paris)* 1994;26:53-8.
12 Jaspersen D, Diehl KL, Geyer P, Martens E. Omeprazole in reflux-associated chronic persistent cough. *Endoskopie Heute* 1999;12:12-4.
13 Kiljander TO, Salomaa ER, Hietanen EK, Terho EO. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. *Eur Respir J* 2000;16:633-8.
14 Eherer AJ, Habermann W, Hammer HF, Kiesler K, Friedrich G, Krejs GJ. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled double-blind crossover study. *Scand J Gastroenterol* 2003;38:462-7.
15 Orenstein SR, Shalaby TM, Putnam PE. Thickened feedings as a cause of increased coughing when used as therapy for gastroesophageal reflux in infants. *J Pediatr* 1992;121:913-5.
16 Noordzij JP, Khidr A, Evans BA, Desper E, Mittal RK, Reibel JF, et al. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. *Laryngoscope* 2001;111:2147-51.
17 Havas T, Huang S, Levy M, Abi-Hanna D, Truskett P, Priestly J, et al. Posterior pharyngolaryngitis: double-blind randomised placebo-controlled trial of proton pump inhibitor therapy. *Austr J Otolaryngol* 1999;3:243-6.
18 Ours TM, Kavuru MS, Schilz RJ, Richter JE. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999;94:3131-8.
19 Kopec SE, Irwin RS, French CL, Wilson MM, Bol S. Treatment of cough due to gastroesophageal reflux disease (GERD): a double-blind randomized placebo-controlled trial comparing diet and/or cicaprode. *Am J Respir Crit Care Med* 2001;163(5 suppl):A64.
20 Ing A. Chronic cough. *Respirology* 1997;2:309-16.
21 Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317:1309-12.
22 Marchant JM, Morris P, Gaffney J, Chang AB. Antibiotics for prolonged moist cough in children. *Cochrane Database Syst Rev* 2005;(4):CD004822.
23 Eccles R. The powerful placebo in cough studies? *Pulm Pharmacol Ther* 2002;15:303-8.
24 Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 2001;32(suppl 2):S1-31.

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