

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

A B Chang, T J Lasserson, T O Kiljander, F L Connor, J T Gaffney, L A Garske

### 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  $\infty$  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

Cohort studies in adults suggest that gastro-oesophageal reflux disease (GORD) related to acid causes 21–41% of chronic non-specific cough.<sup>1</sup> Guidelines on chronic cough suggest use of empirical treatment for GORD,<sup>2–3</sup> including a therapeutic trial of three to six months of treatment for GORD.<sup>4</sup> 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.<sup>4</sup> Other studies have shown that acid GORD is associated with, but is not the cause of, cough.<sup>5</sup>

Current treatments for GORD include conservative measures (diet, positioning, etc), pharmaceuticals (acid suppressants such as histamine H<sub>2</sub> receptor antagonists, and proton pump inhibitors; prokinetic agents such as domperidone, metoclopramide, and cisapride), and surgical approaches (fundoplication). These treatments may not be beneficial for associated cough or may increase respiratory morbidity.<sup>6</sup> We examined the efficacy of treatments for GORD on non-specific chronic cough in adults and children in a systematic review. This review is based on a Cochrane systematic review.<sup>7</sup>

### Methods

We used QUOROM guidelines, Cochrane collaboration method, and software (see [bmj.com](http://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 treatment as anti-reflux conservative measures, H<sub>2</sub> receptor antagonists, proton pump inhibitors, and surgery. 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,

Department of Respiratory Medicine, Royal Children's Hospital, Herston, Brisbane, Qld 4029, Australia

A B Chang  
*consultant in paediatric respiratory medicine*

J T Gaffney  
*research nurse*

Cochrane Airways Group, St George's Hospital Medical School, London SW17 0RE

T J Lasserson  
*review group coordinator*

Medical Center Mehiläinen, Kauppiaskatu 8, FIN-20100 Turku, Finland

T O Kiljander  
*consultant in respiratory medicine*

Department of Gastroenterology, Royal Children's Hospital, Herston, Brisbane

F L Connor  
*consultant in paediatric gastroenterology*

Princess Alexandra Hospital, Brisbane, Woolloongabba, Qld 4102, Australia  
L A Garske  
*consultant in respiratory medicine*

Correspondence to: A Chang [annechang@ausdoctors.net](mailto:annechang@ausdoctors.net)

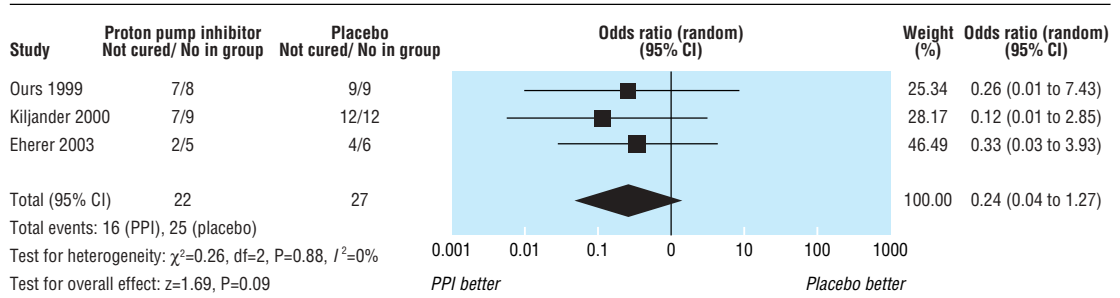
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Details on the search strategy, study selection and characteristics, and data extraction and quality assessment can be found on [bmj.com](http://bmj.com)



**Fig 1** 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)

etc). We determined the proportions of participants who failed to improve on treatment using a hierarchy of assessment measures (see [bmj.com](http://bmj.com)).

We used the Cochrane Airways Group search strategy, references in relevant publications, and written communication with the authors of papers. Two reviewers independently reviewed literature searches, selected articles, and extracted data. Details of other statistics including a priori subgroup, and sensitivity analyses are on [bmj.com](http://bmj.com).

**Results**

We identified 763 potentially relevant titles and reviewed 84 papers for inclusion. 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 (see [bmj.com](http://bmj.com)). All but one were single centre studies; the only multicentre study was also the only study supported by industry. All but two studies were in English. Additional data were sought from all authors of English articles, and two groups provided raw data. Jadad and quality assessment scores varied. Agreement for quality of studies was excellent; the weighted  $\kappa$  score was 0.71 for Jadad score and 0.89 for quality assessment.

**Paediatrics**

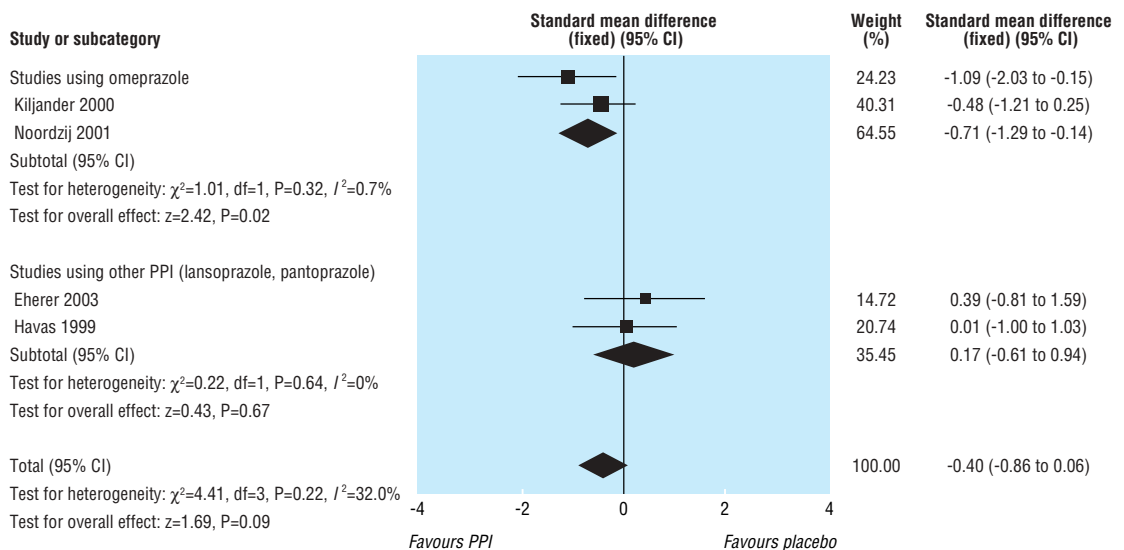
Two studies in children found some improvement in GORD symptoms referring to the gastrointestinal

system but data for the effect on cough were inconsistent. One study found no significant effect of cisapride or domperidone on cough associated with GORD. 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.

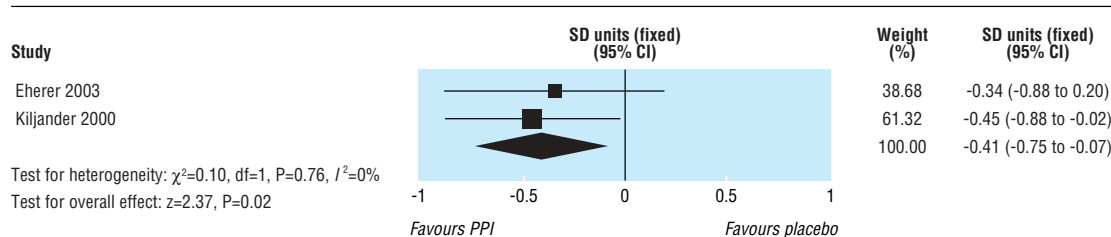
**Adults**

Of the eight studies in adults, six were published full articles, one was an abstract, and one was duplicated in a conference report and abstract. Five were parallel studies, and three were crossover studies. Five studies compared proton pump inhibitors with placebo but used varying doses and frequency (studies in otolaryngology clinics used higher doses of proton pump inhibitors). Although all studies included patients with cough that was presumed to be associated with GORD, criteria for entry varied. In three studies, participants enrolled through the otolaryngology department had “laryngitis” symptoms, and the exclusion criterion of primary lung disease was not as stringently applied as studies that enrolled through medical outpatients. In all but one study, 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 and another was a 2x2 facto-



**Fig 2** Meta-analysis of standardised cough scores at end of intervention (77 participants included in meta-analysis)



**Fig 3** Meta-analysis of data from the two crossover trials<sup>8,9</sup> assessing mean change in symptoms (subanalysis)

rial design with cisapride and dietary intervention. We could not extract data from the single study on H<sub>2</sub> 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. In the six studies that compared proton pump inhibitors or cisapride with placebo, all but one showed no difference in improvement in cough scores in the active and placebo arms. Participants took proton pump inhibitors for two to three months, and only one study followed up patients after the trial.

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 1; 49 participants)). Number needed to treat for benefit was 5 (harm 50 to  $\infty$  to benefit 2.5). Evaluation of the mean cough score at the end of the trial (secondary outcome), in a pooled (62 participants) analysis of three studies 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, 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) was not significant ( $-0.29$ ,  $-0.62$  to  $0.04$  (fig 2)). Data from the two crossover trials that assessed mean change in symptoms showed a significant difference ( $-0.41$  SD units,  $-0.75$  to  $-0.07$  (fig 3, 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, 51 participants). The effect at eight weeks compared with four weeks of intervention was also not significant ( $-0.44$ ,  $-1.04$  to  $0.16$ ). The single study that specifically reported time to response 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.

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. All three studies on otorhinolaryngological

symptoms reported significant improvement in symptoms of laryngitis over time. In two studies, the difference in subjective and semi-objective (laryngoscopy) improvement was similar in treatment and placebo groups. One study found significant differences between proton pump inhibitors and placebo in hoarseness and throat clearing but not in throat pain.

## Discussion

In this systematic review, 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.

The small effect of GORD treatment on cough we found contrasts with non-controlled trials that almost invariably report high rates of improvement. This may be related to the period or placebo effect, which is as high as 85%,<sup>10</sup> 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. Our finding of an effect of treatment with proton pump inhibitors in subgroup analysis does suggest that in a proportion of adults with chronic cough and GORD, GORD is a contributing cause. It is possible, however, that different degrees of acid suppression are required to control the different manifestations of GORD.

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 GORD, and most, but not all, had cough. GORD criteria also varied between studies. Most studies did not use criteria for GORD specified by international guidelines. 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. The use of these drugs as a trial of therapy is probably low risk but rational prescription is required.<sup>6</sup> Proton pump inhibitors may also cause cough as an adverse event.<sup>7</sup>

We conclude that proton pump inhibitors for cough associated with GORD probably have some

**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

effect in some adults, though the effect is less universal than reported in cohort studies. In children, the absence of data makes specific recommendations impossible, and other causes of cough should be considered first. Sufficiently powered parallel placebo controlled randomised controlled trials are required to justify international guidelines.<sup>2,3</sup> Examinations of different treatments for acid and non-acid GOR are also required.

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Ethical approval: Not required.

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## Partner notification of chlamydia infection in primary care: randomised controlled trial and analysis of resource use

Nicola Low, Anne McCarthy, Tracy E Roberts, Mia Huengsberg, Emma Sanford, Jonathan A C Sterne, John Macleod, Chris Salisbury, Karl Pye, Aisha Holloway, Andrea Morcom, Rita Patel, Suzanne M Robinson, Paddy Horner, Pelham M Barton, and Matthias Egger for the Chlamydia Screening Studies (ClASS) Project Group

### Abstract

**Objective** To evaluate the effectiveness of a practice nurse led strategy to improve the notification and treatment of partners of people with chlamydia infection.

**Design** Randomised controlled trial.

**Setting** 27 general practices in the Bristol and Birmingham areas.

**Participants** 140 men and women with chlamydia (index cases) diagnosed by screening of home collected urine sample or vulval swab specimen.

**Interventions** Partner notification at the general practice immediately after diagnosis by trained practice nurses, with telephone follow-up by a health adviser; or referral to a specialist health adviser at a genitourinary medicine clinic.

**Main outcome measures** Primary outcome was the proportion of index cases with at least one treated sexual partner. Specified secondary outcomes

included the number of sexual contacts elicited during a sexual history, positive test result for chlamydia six weeks after treatment, and the cost of each strategy in 2003 pounds sterling prices.

**Results** 65.3% (47/72) of participants receiving practice nurse led partner notification had at least one partner treated compared with 52.9% (39/68) of those referred to a genitourinary medicine clinic (risk difference 12.4%, 95% confidence interval -1.8% to 26.5%). Of 68 participants referred to the clinic, 21 (31%) did not attend. The costs per index case were £32.55 for the practice nurse led strategy and £32.62 for the referral strategy.

**Conclusion** Practice based partner notification by trained nurses with telephone follow-up by health advisers is at least as effective as referral to a specialist

Department of Social Medicine, University of Bristol, Bristol, BSS 2PR

Nicola Low senior lecturer in epidemiology and public health

Anne McCarthy research fellow

Emma Sanford research associate

Jonathan A C Sterne reader in medical statistics and epidemiology

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