

Eradication of *Helicobacter pylori* for non-ulcer dyspepsia (Review)

Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A,
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ABSTRACT

Background

Helicobacter pylori (*H pylori*) is the main cause of peptic ulcer disease. The role of *H pylori* in non-ulcer dyspepsia is less clear.

Objectives

To determine the effect of *H pylori* eradication on dyspepsia symptoms in patients with non-ulcer dyspepsia.

Search strategy

Trials were identified through electronic searches of the Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE, CINAHL and SIGLE, using appropriate subject headings and keywords, searching bibliographies of retrieved articles, and through contacts with experts in the fields of dyspepsia and with pharmaceutical companies.

Selection criteria

All parallel group randomised controlled trials (RCTs) comparing drugs to eradicate *H pylori* with placebo or other drugs known not to eradicate *H pylori* for patients with non-ulcer dyspepsia.

Data collection and analysis

Data were collected on individual and global dyspeptic symptom scores, quality of life measures and adverse effects. Dyspepsia outcomes were dichotomised into minimal/resolved versus same/worse symptoms.

Main results

Twenty one randomised controlled trials were included in the systematic review. Eighteen trials compared antisecretory dual or triple therapy with placebo antibiotics +/- antisecretory therapy, and evaluated dyspepsia at 3-12 months. Seventeen of these trials gave results as dichotomous outcomes evaluating 3566 patients and there was no significant heterogeneity between the studies. There was a 10% relative risk reduction in the *H pylori* eradication group (95% CI = 6% to 14%) compared to placebo. The number needed to treat to cure one case of dyspepsia = 14 (95% CI = 10 to 25). A further three trials compared Bismuth based *H pylori* eradication with an alternative pharmacological agent. These trials were smaller and had a shorter follow-up but suggested *H pylori* eradication was more effective than either H2 receptor antagonists or sucralfate in treating non-ulcer dyspepsia.

Authors' conclusions

H pylori eradication therapy has a small but statistically significant effect in *H pylori* positive non-ulcer dyspepsia. An economic model suggests this modest benefit may still be cost-effective but more research is needed.

PLAIN LANGUAGE SUMMARY

Antibiotics to clear *H. pylori* infection may relieve indigestion that is not caused by ulcers, but more research is needed

Dyspepsia (indigestion or heartburn) is due to ulcers (stomach or duodenal) and acid in the gullet (oesophagus) but in many people the cause is uncertain. People without a cause for dyspepsia have non-ulcer dyspepsia. There is no clear evidence on the best treatment for this. *Helicobacter pylori* is a bacterium that infects the stomach. It is not cleared by the body and remains a life long infection unless treated with antibiotics. *Helicobacter pylori* causes most peptic ulcers but it is uncertain whether it has any role in non-ulcer dyspepsia. This review found that antibiotics for *H pylori* have a small benefit in treating non ulcer dyspepsia.

BACKGROUND

Dyspepsia is a very common problem (Morrell 1971; Jones 1990). In the past the prevalence rate has been found to be 25-30% (Weir 1968; Doll 1951). Recent surveys have shown a 6-month period prevalence of 38% in the community (Jones 1990; Penston 1996). Dyspepsia constitutes 2-3% of general practitioners' consultations (Jones 1990; Gear 1980) and 40% of gastroenterological consultations. However, around 60% of the patients presenting with dyspepsia would have negative investigations (Williams 1988) and belong to the group labeled as having non-ulcer dyspepsia (NUD).

Although the role of *Helicobacter pylori* (*H pylori*) in peptic ulcer disease is well established, its role in the pathogenesis of NUD remains controversial. Indeed, the prevalence rates of *H pylori* associated gastritis in NUD has varied from 39% to 87% (Loffeld 1989; Tytgat 1993). Some studies have shown no specific symptom profile associated with *H pylori* (Wyatt 1990) whereas other studies have shown that patients infected with *H pylori* have more symptoms of ulcer-like dyspepsia rather than dysmotility-like dyspepsia (Andersson 1994; Trespi 1994).

A review of randomised controlled trials evaluating the effect of *H pylori* eradication on NUD up to 1994 concluded they were poorly designed (Talley 1994). Trials did not use a validated dyspepsia questionnaire in the outcome assessment, follow-up was too short, inadequate *H pylori* eradication regimens were used and methods of randomisation were not stated. Two reviews of the literature have suggested that *H pylori* eradication may reduce NUD symptoms but their methodologies have been questioned and the results were based on poor quality studies (Laheij 1996; Jaakkimainen 1999). The results of other reviews that include more recent trials have been less certain (Danesh 1999; Laine 2001).

Well designed randomised controlled trials comparing *H pylori* eradication with placebo or alternative pharmacological therapies have recently been reported (Blum (OCAY) 1998; McColl 1998). These have given conflicting results and a systematic review of the literature is required to establish the role of *H pylori* in NUD.

OBJECTIVES

To assess whether *H pylori* eradication therapy improves individual or global dyspepsia symptom scores in patients with non-ulcer dyspepsia.

To assess whether *H pylori* eradication therapy alters quality of life scores in patients presenting with non-ulcer dyspepsia.

To assess whether *H pylori* eradication therapy improves the individual or global dyspepsia symptom scores in a subset of non-ulcer dyspepsia patients defined by their predominant dyspepsia symptoms.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only parallel group randomised controlled trials (RCTs) were eligible for inclusion in the review.

Types of participants

Adult patients presenting to secondary care with *H pylori* and dyspepsia, who have negative or insignificant findings on their endoscopy or barium studies, and have had other organic (pancreatobiliary disease, oesophagitis, peptic ulcer disease and neoplastic disease), drug-induced (non-steroidal anti-inflammatory drugs), and metabolic disorders excluded by appropriate investigations (such as blood tests, abdominal ultrasound or 24 hour oesophageal pH studies etc).

Definitions of dyspepsia include any gastrointestinal symptoms referable to the foregut or any of those suggested in the Working Group (Working Party 1988) and the Rome criteria (Talley 1991). Trials where participants present with only heartburn or reflux symptoms (symptoms suggestive of gastro-oesophageal reflux disease) were not included.

Types of intervention

Trials comparing *H pylori* eradication regimens with placebo, or with other drugs known not to eradicate *H pylori*. The earlier literature used regimens that were ineffective in treating *H pylori*. We have therefore predefined acceptable *H pylori* eradication regimens, and only considered those trials which used recognised eradication therapies in a modern clinical setting. The following were considered acceptable regimens:

- (1) Dual therapy with proton pump inhibitor in combination with either clarithromycin or amoxicillin.
- (2) Triple therapy with either proton pump inhibitor or Histamine H2 receptor antagonists in combination with either (i) amoxicillin

and nitroimidazole or (ii) amoxicillin and clarithromycin or (iii) clarithromycin and nitroimidazole.

(3) Bismuth based triple therapy with metronidazole and either amoxicillin or tetracycline.

(4) Quadruple therapy with proton pump inhibitor, bismuth, metronidazole, tetracycline or amoxicillin.

Types of outcome measures

The following outcomes were included in the review:

(1) Dyspeptic symptom assessments

a) Individual dyspepsia symptom scores (epigastric pain/discomfort, post-prandial fullness, early satiety, eructation, bloating, anorexia, nausea, vomiting, flatulence, belching, heartburn, acid regurgitation).

b) Global dyspepsia symptom scores (eg. Gastrointestinal Symptoms Rating Scales (GSRS), Glasgow Dyspepsia Severity Scores (GDSS))

(2) Quality of life (QoL) scores

a) QoL scores - Psychological Well Being (PGWB) index, Short Form 36 (SF36)

(3) Adverse effects

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Upper Gastrointestinal & Pancreatic Diseases Group methods used in reviews.

Trials were identified by searching the Cochrane Controlled Trials Register (Issue 2-2004), MEDLINE (1966-December 2005), EMBASE (1988-December 2005), CINAHL (1982-December 2005) and the database of grey literature and dissertations, SIGLE.

The following search strategies were constructed by using a combination of subject headings and textwords relating to the symptoms of dyspepsia and the relevant pharmacological interventions. The standard Cochrane search strategy filter for identifying randomised controlled trials was applied to all searches.

MEDLINE search strategy

randomized controlled trial.pt.

Randomized controlled trials/

Random Allocation/

Double-Blind Method/

Single-Blind Method/

1 or 2 or 3 or 4 or 5

Animal/

Human/

7 not (7 and 8)

6 not 9

clinical trial.pt.

exp Clinical trials/

(clin\$ adj3 trial\$).ab,ti.

((singl\$ or doubl\$ or treb\$ or trip\$) adj3 (blind\$ or mask\$)).ab,ti.

Placebos/

placebo\$.ab,ti.

random.ab,ti.

Research design/

11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

19 not 9

20 not 10

Comparative Study/

exp Evaluation Studies/

Follow-Up Studies/

Prospective Studies/

(control\$ or prospectiv\$ or volunteer\$).ab,ti.

22 or 23 or 24 or 25 or 26

27 not 9

28 not (10 or 21)

10 or 21 or 29

dyspepsia/

eructation/

flatulence/

heartburn/

gastroparesis/

gastric emptying/

gastritis/

atrophic gastritis/

Helicobacter pylori/

dyspep\$.tw.

(acid adj5 reflux).tw.

belch\$.tw.

bloat\$.tw.

burp\$.tw.

(early adj5 satiety).tw.

eructation.tw.

flatu\$.tw.

heartburn.tw.

indigestion.tw.

pyro\$.tw.

hiatus hernia.tw.

stomach paresis.tw.

gastritis.tw.

(gastric acid adj5 secretion).tw.

(stomach acid adj5 secretion).tw.

(gastric adj5 erosion\$).tw.

(stomach adj5 erosion\$).tw.

(gastric emptying adj5 disorder\$).tw.

(stomach emptying adj5 disorder\$).tw.

Gastroparesis.tw.

Helicobacter pylori.tw.

Campylobacter pylori.tw.

Campylobacter pyloridis.tw.
 (helicobacter pylori adj5 eradication).tw.
 omeprazole/
 drug combination/
 amoxicillin/
 bismuth/
 omeprazole.tw.
 lansoprazole.tw.
 pantoprazole.tw.
 Amox?cillin.tw.
 Azithromycin.tw.
 bismuth.tw.
 clarithromycin.tw.
 doxycycline.tw.
 erythromycin.tw.
 metronidazole.tw.
 oxytetracycline.tw.
 tetracycline.tw.
 tinidazole.tw.
 denol.tw.
 de-noltab.tw.
 ranitidine bismuth citrate.tw.
 pylorid.tw.
 tripotassium citrate.tw.
 or/31-45
 or/46-60
 or/61-75
 or/76-86
 or/87-90
 91 and (10 or 21 or 29)

Terms used for searching EMBASE

Dyspepsia
 Epigastric pain
 Stomach pain
 Flatulence
 Heartburn
 Indigestion
 Stomach emptying
 Stomach paresis
 Nausea
 Vomiting
 Gastritis
 Atrophic gastritis
 Chronic gastritis
 Erosive gastritis
 Stomach acid secretion
 Campylobacter Pyloridis
 Omeprazole
 Lansoprazole
 Pantoprazole
 Amoxicillin
 Azithromycin

Bismuth
 Bismuth citrate
 Bismuth compound
 Bismuth salicylate
 Colloidal bismuth compound
 Clarithromycin
 Doxycycline
 Erythromycin
 Metronidazole
 Oxytetracycline
 Ranitidine Bismuth Citrate
 Tetracycline
 Tinidazole
 Dyspep\$
 Epigastric adj5 pain\$
 Epigastric adj5 discomfort
 Stomach adj5 pain\$
 Stomach adj5 discomfort
 Regurgitation
 Flatu\$
 Acid adj5 reflux
 Belch\$
 Bloat\$
 Burp\$
 Heartburn
 Indigestion
 Flatu\$
 Postprandial adj5 fullness
 Early satiety
 Nausea
 Vomiting
 Hiatus hernia
 Stomach paresis
 Abdominal adj5 distension
 Stomach adj5 distension
 Stomach adj5 empty\$
 Gastroparesis
 Gastritis
 Gastric acid adj5 secretion
 Stomach acid adj5 secretion\$
 helicobacter pylori
 campylobacter pylori
 helicobacter pylori adj5 eradication
 campylobacter pylori adj5 eradication
 Amox?cillin
 Denol
 De-Noltab
 Pylorid
 Tripotassium bismuthate
 Tripotassium citrate
 Terms used for searching CINAHL
 Dyspepsia

Abdominal pain
 Flatulence
 Heartburn
 Nausea vomiting
 gastritis
 Helicobacter pylori
 Omeprazole
 Amoxicillin
 Azithromycin
 Clarithromycin
 Doxycycline
 Erythromycin
 Metronidazole
 Tetracycline
 Dyspep\$
 Abdom\$ adj5 pain\$
 Abdom\$ adj5 discomfort
 Epigastri\$ adj5 pain\$
 Epigastri\$ adj5 discomfort
 Stomach adj5 pain\$
 Regurgitation
 Flatulence reduction
 Flatu\$
 Heartburn
 Indigestion
 Acid adj5 reflux
 Belch\$
 Bloat\$
 Burp\$
 Early satiety
 Nausea
 Vomiting
 Pyrosis
 Hiatus hernia
 Flatu\$
 Stomach paresis
 Abdominal adj5 distension
 Stomach adj5 distension
 Postprandial adj5 fullness
 Early satiety
 Nausea
 Vomiting
 Abdom\$ adj5 distension\$
 Postprandial adj5 fullness
 Gastric emptying adj5 disorder\$
 Stomach emptying adj5 disorder\$
 Gastroparesis
 Gastritis
 Gastric acid adj5 secretion
 Helicobacter pylori
 Omeprazole
 Lansoprazole
 Amox?cillin

Azithromycin
 Bismuth
 Clarithromycin
 Doxycycline
 Erythromycin
 Metronidazole
 Oxytetracycline
 Tetracycline
 Tinidazole

Reference lists from trials selected by electronic searching were handsearched to identify further relevant trials.

In addition, experts in the field of dyspepsia and the following pharmaceutical companies - Astra-Zeneca, Wyeth Laboratories, Knoll, Yamanouchi Pharma, Abbott Laboratories, Pfizer Limited and Rhone-Poulenc Rorer were contacted and asked to supply details of any outstanding clinical trials and relevant unpublished materials.

The following experts in the field were contacted:

Dr. N. Ahluwalia, Stepping Hospital, Stockport, UK
 Dr. A. Andren-Sandberg, Lund University Hospital, Sweden
 Dr. M. Asante, Mayday University Hospital, Surrey, UK
 Professor A.T.R. Axon, Centre for Digestive Diseases, Leeds, UK
 Dr. C. Bardhan, Rotherham, UK
 Dr. C. Bassi, Borgo Roma University Hospital, Italy
 Ms. H. Bastian, Blackwood, Australia
 Professor A. Blum, Centre Hospitalier, Lausanne, Switzerland
 Dr. S. Boesby, Copenhagen, Denmark
 Dr. N. Broutet, Hopital Pellegrin, Bordeaux Cedex, France
 Ms. J. Bruce, University of Aberdeen, Aberdeen, UK
 Dr. P. Bytzer, Glostrup University Hospital, Glostrup, Denmark
 Dr. F. Carballo, Hospital General Universitario de Guadalajara, Guadalajara, Spain
 Dr. N. Chiba, Guelph, Canada
 Dr. A.R. Dar, London Regional Cancer Centre, London, Canada
 Dr. E. de Koster, Brugmann University Hospital, Brussels, Belgium
 Dr. M. Delvaux, CHU Rangueil, Toulouse, France
 Sister J. DeSilva, Endoscopy Unit, Rotherham, UK
 Dr. J. Dixon, Glaxo Wellcome plc, Middlesex, UK
 Dr. J.E. Dominguez-Munoz, Hospital de Conxo, Santaigo de Compostela, Spain
 Dr. C. Gluud, Copenhagen Trial Unit, Copenhagen, Denmark
 Professor C. Hawkey, Division of Gastroenterology, Nottingham, UK
 Dr. E. Hentschel, Vienna, Austria
 Professor R. Hunt, McMaster University Medical Centre, Hamilton, Canada
 Ms. E. Jonsson, Molndal, Sweden
 Mr. J.D. Kirby, Solihull, UK
 Dr. K. Krosgaard, Institute of Preventive Medicine, Copenhagen, Denmark

Dr. E. Kuipers, Free University Hospital, Amsterdam, Netherlands
Dr. R. Laheij, Dept. of Gastroenterology, Nijmegen, Netherlands
Professor L Laine, Los Angeles, USA
Dr. J. Lambert, Mornington Peninsula Hospital, Frankston, Australia
Professor M. Langman, Queen Elizabeth Hospital, Birmingham, UK
Dr. M. Larvin, Leeds General Infirmary, UK
Professor J. Lennard-Jones, London, UK
Dr. R. Logan, Nottingham, UK
Professor. J. Malagelada, Hospital Vall d'Hebron, Barcelona, Spain
Dr. R. Malthaner, London Health Sciences Centre, London, Canada
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Professor J. McDonald, University of Western Ontario, London, Canada
Professor F. Megraud, Hopital Pellegrin, Bordeaux Cedex, France
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Dr. J.E.M. Midgeley, Ilkley, UK
Dr. J.J. Misiewicz, Central Middlesex Hospital, Department of Gastroenterology, London, UK
Dr. H. Moller, The Danish National Research Foundation, Copenhagen, Denmark
Dr. M. Numans, Utrecht, Netherlands
Dr. O. Nyren, Uppsala Universitet, , Sweden
Dr. A. Oxman, National Institute of Public Health, Oslo, Norway
Dr. J. Penston, Dundee, Scotland
Dr. H. Persson, Stockholm, Sweden
Professor T. Poynard, Paris, France
Professor A. Price, Department of Clinical Oncology, Edinburgh, UK
Dr. E. Rauws, Academic Medical Centre, Amsterdam, Netherlands
Dr A. Rostom, Department of Medicine, Ottawa, Canada.
Dr. S. Rune, Glostrup University Hospital, Copenhagen, Denmark
Ms. D. Saddler, Society of Gastroenterology Nurses and Associates Inc, Chicago, USA
Dr. E. Saperas, Hospital Vall d'Hebron, Barcelona, Spain
Professor O. Schaffalitzky de Muckadell, Dept Medical Gastroenterology, Odense, Denmark
Dr. K. Shenoy, Medical College, Trivandrum, India
Dr. L. Stewart, MRC Cancer Trials Office, UK
Professor N. Talley, Clinical Sciences Building, Penrith, Australia
Dr. A. Thomson, Division of Gastroenterology, Edmonton, Canada
Dr. J. Tierney, MRC Cancer Trials Office, UK

Dr. P. Unge, Gävle, Sweden
Dr. S. Veldhuyzen van Zanten, Victoria General Hospital Site, Halifax, Canada
Dr. N. Waugh, Aberdeen, UK
Dr. P. Webb, University of Queensland Medical School, Herston, Australia
Professor S. Wessely, King's College School of Medicine and Institute of Psychiatry, London, UK
Dr. P. Wille Jorgensen, Cochrane Colorectal Cancer Group, Copenhagen NV, Denmark
Dr. C. Williams, Oxford, UK

METHODS OF THE REVIEW

Selection Of Studies

One reviewer excluded papers from the initial searches unrelated to dyspepsia in humans. These decisions were based on account of the title or abstract if available. A second reviewer independently checked a sample of this selection process.

Inclusion decisions were made independently by two reviewers according to the pre-stated eligibility criteria, and recorded on a specially developed form. Disagreements were reviewed, and a third reviewer was consulted if they could not be resolved.

Assessment of Study Quality

Only trials which described the word 'random, randomly, or randomised' in their trial were considered in this review and assessed for quality according to four characteristics:

Generation of the allocation schedule

(truly random, quasi-random, systematic, not stated/unclear)

Computer generated random numbers, coin toss, shuffles, etc are defined as truly random, allocation according to birth-date, patient number, etc are defined as quasi-random, whilst alternate allocation and deterministic methods are classified as systematic.

Concealment of the treatment allocation

(adequate, inadequate, unclear)

If trialists are unaware of each participant's allocation when they are recruited, the allocation is said to be adequately concealed. Methods such as central randomisation systems or serially numbered opaque envelopes fit this criteria. If the trialist may be aware of allocations at recruitment, as when the participant's birth-date or patient number is used for allocation, the allocation is inadequate.

Implementation of masking

(patient masked, clinician masked, outcome assessor masked)

When a placebo is used it is assumed that the participants are masked to their treatment allocation.

Completeness of follow-up and intention to treat analysis

(drop-outs and missing data rates by group)

Study quality was assessed by one reviewer and checked by a second.

Data Extraction

Data was extracted and recorded onto specially developed forms. Extraction was undertaken by one reviewer and checked by a second. Data entry into RevMan was also double-checked.

The following characteristics were recorded for each trial:

- (a) details of the participants including demographic characteristics, source of recruitment, criteria for diagnosis, and dyspeptic symptoms on presentation. Trials were categorised according to the most prevalent type of dyspepsia, whether ulcer-like, dysmotility-like, reflux-like or non-specific, if possible.
- (b) details of the experimental and control interventions including intervention type, names, dosages and schedules where appropriate.
- (c) the prevalence of individual dyspeptic symptoms before and after the intervention, dyspeptic symptom scores and global assessments of dyspeptic symptoms. Where measurement scales were used it was noted whether or not they were standard scales and whether they have been validated. Assessments of quality of life and adverse events were noted.

Data was extracted as intention to treat analyses.

Data Synthesis

For binary outcomes, such as the presence or absence of symptoms, the impact of the intervention were expressed as relative risks and relative risk reductions (RRR) (1-relative risk) together with 95% confidence intervals. The number needed to treat (NNT) was calculated using the formula $1/(BR \times RRR)$ where BR is the dyspepsia rate seen in the placebo group. The 95% confidence intervals of the NNT were calculated using the 95% confidence intervals for the RRR. For scale-based outcomes means and standard deviations were used to summarise the values in each group provided the scale took sufficient values (roughly more than 10). Such outcomes were analysed for the presence of skew.

Relative risks were combined for binary outcomes, standardised mean differences for continuous outcomes where we anticipated that a variety of scales have been used to assess the same concept. We intended to use a random effects analysis if there was significant ($P < 0.1$) heterogeneity detected in the data. Reasons for heterogeneity were explored and trials were categorised into the following predefined subgroups:

- (a) Trials specifically excluding patients with reflux predominant symptoms.
- (b) The length of follow-up
- (c) The actual *H pylori* eradication rates documented in the trials.
- (d) The method used to exclude organic upper gastrointestinal disease
- (e) The use of validated dyspepsia questionnaires

- (f) Multi-centre versus single centre trials

DESCRIPTION OF STUDIES

5,183 articles were identified by the search strategy. The titles and abstracts of these articles were reviewed and 63 trials were selected that attempted to evaluate *H pylori* eradication therapy in NUD. Forty two trials did not meet the eligibility criteria and thirteen trials were included in the systematic review. Eighteen trials (Blum (OCAY) 1998; McColl 1998; Talley (ORCHID) 1999; Talley (USA) 1999; Koelz 2003; Greenberg 1999; Miwa 2000; Malfertheiner 2003; Froehlich 2001; Varannes 2001; Hsu 2001; Koskenpato 2001; Gisbert 2004; van Zanten 2003; Gonzalez Carro 2004; Martinek 2005; Ruiz 2005; Mazzoleni 2006) compared *H pylori* eradication therapy with placebo antibiotics with or without anti-secretory therapy and followed up patients for 3-12 months. Three trials (Dhali 1999; Sheu 1996; Alizadeh-Naeni 2002) compared *H pylori* treatment with another, completely different, pharmacological agent and followed up patients on an intention to treat basis for three months or less. These trials were considered separately.

METHODOLOGICAL QUALITY

The seventeen trials included in the main analysis were generally well-designed and executed. The trials reported no evidence of imbalance in baseline characteristics apart from one study where more alcohol was consumed in the placebo group (Gonzalez Carro 2004). Outcomes were usually assessed using validated dyspepsia questionnaires, drop-out rates were low, and intention-to-treat analyses were reported for extended follow-up at 3-12 months. Eleven trials stated the method of randomisation and masking (Blum (OCAY) 1998; McColl 1998; Talley (ORCHID) 1999; Talley (USA) 1999; Malfertheiner 2003; Froehlich 2001; Hsu 2001; Varannes 2001; van Zanten 2003; Ruiz 2005; Mazzoleni 2006) but only four (McColl 1998; van Zanten 2003; Mazzoleni 2006; Ruiz 2005) reported the method of concealment. McColl 1998 included patients with reflux predominant symptoms whereas other studies excluded this group of patients.

The three trials comparing *H pylori* eradication with another pharmacological agent were smaller and the follow up period was three months. Alizadeh-Naeni 2002 et al. followed patients up for one year but the control group received *H pylori* eradication therapy if they had not responded to the initial intervention so randomisation was lost after three months. These trials used bismuth therapy which darkens the stool so patients were not masked. Patients were assessed with non-validated dyspepsia questionnaires. The three trials did not state the method of concealment and two (Sheu 1996; Alizadeh-Naeni 2002) did not state the method of randomisation.

RESULTS

Effect of H pylori eradication therapy on dyspepsia symptoms

One trial (Greenberg 1999) did not give results as dichotomous outcomes and this information could not be obtained from the authors. The remaining seventeen trials evaluated a total of 3566 patients. All trials used antisecretory dual or triple therapy and most defined dyspepsia cure as no symptoms or mild symptoms not interfering with daily activities. The mean placebo response rate at 3-12 months was 29% (range of 7-51%) and the mean *H. pylori* eradication therapy response rate was 36% (range 15-75%). An unusually high placebo response rate was observed in six trials (Talley (USA) 1999; Froehlich 2001; Varannes 2001; Hsu 2001; Gisbert 2004; Martinek 2005), another included some patients with predominant reflux symptoms (McColl 1998), and one trial reported a low eradication rate (Koelz 2003). There was, however, no statistically significant heterogeneity between the trial results (heterogeneity test [16 degrees of freedom] chi squared = 17.69, $p = 0.39$, $I^2 = 9.5\%$). There was also no evidence of funnel plot asymmetry. Overall there was a small but statistically significant benefit of *H. pylori* eradication therapy at 12 months (RRR = 10%; 95% CI = 6% to 14%). Fourteen patients (95% CI = 10 to 25) needed to be treated with *H. pylori* eradication therapy to cure one extra case of NUD. The point estimate of the relative risk reduction did not vary by more than 2% and remained statistically significant when any one trial was omitted from the analysis. Twelve trials (Blum (OCAY) 1998; McColl 1998; Talley (ORCHID) 1999; Greenberg 1999; Miwa 2000; Froehlich 2001; Koskenpato 2001; Hsu 2001; Malfertheiner 2003; van Zanten 2003; Gisbert 2004) reported dyspepsia as a continuous outcome in 2547 patients. There was a statistically significant reduction in dyspepsia score at one year (treatment versus placebo standardized mean difference -0.18; 95% CI = -0.26 to -0.1) in a fixed effects model. There was, however, statistically significant heterogeneity between studies (heterogeneity test [11 degrees of freedom] chi squared = 55.73, $p < 0.00001$, $I^2 = 80.3\%$) and in a random effects model there was no statistically significant difference between the two groups in continuous dyspepsia scores (treatment versus placebo standardized mean difference -0.18; 95% CI = -0.37 to 0.02).

Two trials (Koskenpato 2001; Gisbert 2004) formally evaluated individual dyspepsia symptoms but there were no differences in response rates between patients randomised to *H. pylori* eradication therapy or placebo. Three trials prospectively subdivided patients to ulcer-like and dysmotility-like dyspepsia categories (Talley (ORCHID) 1999; Talley (USA) 1999; Hsu 2001). A similar proportion of patients in these categories responded to *H. pylori* eradication therapy.

Seven trials (Blum (OCAY) 1998; Talley (ORCHID) 1999; Talley (USA) 1999; Varannes 2001; Koskenpato 2001; Hsu 2001; Maz-zoleni 2006) performed repeat endoscopy at 12 months to ensure patients remained free of peptic ulcer disease, although only four

trials (Blum (OCAY) 1998; Talley (USA) 1999; Hsu 2001; Maz-zoleni 2006) reported these results. 6/164 (4%), 7/143 (5%), 0/43 (0%) and 6/80 (7.5%) patients taking placebo developed peptic ulcer disease at the 12-month visit compared with 1/164 (0.6%), 3/150 (2%) 1/46 (2%) and 2/81 (2.5%) in the treatment group. A repeat endoscopy was not part of the protocol of the McColl 1998 trial although nine patients were endoscoped during follow-up due to persistent symptoms. All three patients in the treatment group had normal endoscopy whilst 4/6 in the placebo group had peptic ulcer disease.

The remaining three trials compared *H. pylori* eradication with another pharmacological therapy in NUD patients. Sheu 1996 et al. compared bismuth subcitrate, amoxicillin and metronidazole with H2 receptor antagonist prescription in 41 NUD patients. *H. pylori* eradication was associated with a significant reduction in symptoms at eight weeks compared with anti-secretory therapy (reduction in dyspepsia score = 0.98; 95% CI = 0.33 to 1.63). Dhali 1999 et al. compared bismuth subcitrate, tetracycline and metronidazole with sucralfate in 62 NUD patients. Symptom scores were significantly lower in patients allocated to *H. pylori* eradication therapy (mean decrease in score in the treated group = 1.8; 95% CI = 0.9 to 2.7). Alizadeh-Naeni 2002 et al. compared bismuth subnitrate, metronidazole and amoxicillin for two weeks with ranitidine and metoclopramide for four weeks in 157 patients. 23/84 (27.4%) of the *H. pylori* eradication group exhibited a complete or moderate resolution of symptoms compared with 14/73 (19.2%) of the control group, a difference that was not statistically significant (Fisher's exact test $p = 0.26$).

The effect of H pylori eradication on quality of life

Three trials (Blum (OCAY) 1998; Talley (ORCHID) 1999; McColl 1998) presented quality of life data at 12 months suitable for meta-analysis. Two trials used the psychological general well being index (Blum (OCAY) 1998; Talley (ORCHID) 1999) and one the SF-36 (McColl 1998). Overall there was no significant effect of *H. pylori* eradication on quality of life compared with placebo (standardised mean difference = 0.01; 95% CI = -0.12 to 0.15).

Adverse events associated with H pylori eradication therapy in NUD patients

Two trials reported adverse events associated with *H. pylori* eradication therapy (Varannes 2001; van Zanten 2003). 28% of *H. pylori* eradication patients and 10% of placebo patients experienced at least one adverse event in one trial (Varannes 2001) with the most common adverse events being diarrhoea and taste disorders. van Zanten 2003 et al reported diarrhoea in 14% of the eradication group compared with 9% of the control arm. Seven percent of the active therapy arm complained of a bitter/metallic taste in the mouth and this was not reported by the control group. Adverse events in both trials resolved once therapy was discontinued.

DISCUSSION

Twelve out of seventeen trials evaluating dyspepsia outcome at three months to one year did not demonstrate any statistically significant benefit of *H pylori* eradication over placebo in NUD patients. Five of the remaining trials showed a significant effect of *H pylori* eradication on the proportion of patients cured of dyspepsia (McColl 1998; Varannes 2001; Ruiz 2005; Martinek 2005; Gonzalez Carro 2004) whilst one (Malfertheiner 2003) showed a significant impact of *H pylori* eradication on the continuous dyspepsai symptom score. The reason for six trials (McColl 1998; Malfertheiner 2003; Varannes 2001; Gonzalez Carro 2004; Martinek 2005; Ruiz 2005) giving a positive result whilst the others have been negative has been the subject of lively debate (McColl 1999). *H pylori* treatment has only a small effect on dyspepsia at 12 months and none of the trials have sufficient power to detect this difference. The 10% relative risk reduction in NUD for patients treated with *H pylori* eradication therapy is however statistically significant and is robust when individual trials are omitted. The results are also supported by two small trials that showed a benefit for *H pylori* therapy at 2-3 months over H2- receptor antagonists or sucralfate in NUD patients.

Another well conducted systematic review did not find any benefit of *H pylori* eradication in NUD patients (Laine 2001). We have systematically evaluated the discrepancies between our review and that of Laine 2001 et al. and found six differences in methodology between the two papers (Moayyedi 2003). Differences in outcomes assessed and methods of analysis had a small impact on the conclusions reached by the review (Moayyedi 2003). The main difference however, was the date of the search as Laine 2001 et al. completed their search in December 1999. They therefore only included 7 studies involving 1544 NUD patients. Their systematic review therefore did not have the power to detect the small effect of *H pylori* eradication on NUD symptoms and more data has emerged since their rigorous and well conducted review was submitted (Moayyedi 2003).

Data from an observational study suggested that *H pylori* eradication therapy may increase the incidence of reflux disease (Labenz 1993) but this finding could be due to bias or confounding factors. Two trials reported endoscopy findings (Blum (OCAY) 1998; Talley (USA) 1999) and oesophagitis was rare at 12 months in both the *H pylori* eradication and placebo arms. Oesophagitis was found in 17/297 (6%) of the treatment group and 9/306 (3%) of the placebo group and this difference was not statistically significant (relative risk = 2.07; 95% CI = 0.94 to 4.56). Furthermore, two randomised controlled trials specifically designed to evaluate this issue have failed to show any effect of *H pylori* eradication on the exacerbation of reflux disease (Moayyedi 2001; Schwizer 2001)

Only two of the trials (Varannes 2001; van Zanten 2003) reported the frequency of adverse events in patients allocated *H pylori* erad-

ication therapy. This also needs to be considered although other trials evaluating the efficacy of regimens in eradicating *H pylori* suggest adverse events are usually mild and self limiting (Unge 1989).

The mechanism by which *H pylori* causes a reduction in dyspepsia symptoms in NUD patients is unclear (Talley 1995). *H pylori* infection is often associated with increased gastric acid output (El-Omar 1995) but investigators have not found a relationship between low pH and NUD symptoms (Mearin 1995; Pieramico 1993). Studies evaluating the effects of *H pylori* infection on gastric motility are also conflicting (Rees 1980; Pieramico 1993). *H pylori* is the cause of most gastric and duodenal ulcers and it is possible that the therapeutic effect noted in this meta-analysis is due to the treatment of undiagnosed peptic ulcer disease. Patients all had an endoscopy before entry into the trials to exclude peptic ulcer disease but this is a relapsing and remitting disorder and patients with an ulcer diathesis do not always have an ulcer associated with their dyspepsia (Gibinski 1983; Isenberg 1983). This is emphasised by the observation that 4% of patients enrolled in the NUD trials developed peptic ulcer disease during follow-up in the placebo group. *H pylori* therapy may therefore only be treating the small subset of patients with peptic ulcer disease that has been misclassified as NUD. This possibility does not invalidate the conclusion of the review. Pragmatically, patients with dyspepsia and a normal endoscopy gain a modest benefit from *H pylori* eradication therapy, and this is useful information in clinical practice.

Dyspepsia is associated with a reduced quality of life (Wiklund 1998), yet this review showed only a small, non-significant, trend for *H pylori* therapy to improve quality of life. The questionnaires used in the trials to evaluating quality of life were not disease specific and were relatively insensitive to changes in dyspepsia status. A larger sample size would therefore be required to detect a change and it is doubtful whether such a small effect on quality of life would be clinically meaningful. There was no statistically significant difference between the two groups when the dyspepsia scores were measured on a continuous scale in a random effects model. There were fewer trials available for this analysis and a change in dyspepsia score has less clinical meaning than the proportion of patients cured.

The benefit of *H pylori* eradication therapy on NUD is relatively small and this is reflected in 14 patients needing treatment to cure one case. We have constructed a health economic model to determine whether this modest effect is likely to be cost-effective (Moayyedi 2000). The base case scenario suggested *H pylori* eradication therapy costs an extra £56 (\$84) per extra month free of dyspepsia compared with antacid therapy. A cost-effectiveness acceptability curve indicated that *H pylori* eradication therapy is likely to be cost effective in the base case scenario provided the policy maker is willing to pay £75 (\$112.50) per month free of dyspepsia and willing to accept a 20% chance of being incorrect. The acceptability of this needs further study.

AUTHORS' CONCLUSIONS

Implications for practice

The review suggests that *H pylori* eradication therapy reduces symptoms in patients with non-ulcer dyspepsia. The impact on symptoms was statistically significant but the effect size was small and most *H pylori* positive patients with non-ulcer dyspepsia will still have symptoms after eradication therapy. *H pylori* eradication therapy may still be cost-effective depending on the willingness to pay to cure dyspepsia.

Implications for research

The findings of this review are robust and unlikely to change with the result of further trials. The main area of uncertainty is the willingness to pay for cure of dyspepsia and more research is needed in this area.

POTENTIAL CONFLICT OF INTEREST

Paul Moayyedi, David Forman and Brendan Delaney have received honoraria for talks from pharmaceutical companies making proton pump inhibitors. The Chair Paul Moayyedi holds is in part funded by an endowment from AstraZeneca.

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- *Indicates the major publication for the study

TABLES

Characteristics of included studies

| Study | Alizadeh-Naeeni 2002 |
|------------------------|---|
| Methods | Two centre RCT unblinded |
| Participants | Iran 157 patients with H pylori infection and normal endoscopy and upper abdominal pain not responding to antacid therapy |
| Interventions | Bismuth subnitrate 500mg, metronidazole 250mg and amoxicillin 500mg all twice daily for two weeks versus ranitidine 150 mg bd and metoclopramide 10 mg tds for four weeks |
| Outcomes | Total symptom score presented as mean and complete response (no symptoms or <20% of original dyspepsia score) |
| Notes | H p eradication = 53% (evaluable patients) |
| Allocation concealment | B – Unclear |

| Study | Blum (OCAY) 1998 |
|------------------------|---|
| Methods | Multicentre (OCAY) RCT, double-blind |
| Participants | Switzerland 348 patients with Hp infection and dyspeptic symptoms. Reflux excluded. |
| Interventions | 1 week Omeprazole 20mg bid, amoxicillin 1g bid and clarithromycin 500mg bid vs Omeprazole 20mg bid |
| Outcomes | Global symptom score GSRS(dyspepsia symptom score) QoL (PGWB) Follow-up of 12 months |
| Notes | Hp erad = 79% (ITT) Hp erad = 87% (per-protocol analysis) |
| Allocation concealment | A – Adequate |

| Study | Dhali 1999 |
|------------------------|--|
| Methods | Single centre RCT Double-blind |
| Participants | Asian Indians 62 patients with Hp infection and > 4 weeks dyspepsia. Reflux excluded |
| Interventions | Bismuth subcitrate 120 mg qds, tetracycline 500 mg qds, metronidazole 400 mg tds for 2 weeks versus sucralfate 1g qds for 4 weeks. |
| Outcomes | Patient's subjective improvement in dyspepsia symptoms. Changes in dyspepsia questionnaire score. Follow-up 3 months. |
| Notes | Hp erad = 88% (ITT) |
| Allocation concealment | A – Adequate |

Characteristics of included studies (Continued)

| Study | Froehlich 2001 |
|------------------------|---|
| Methods | RCT double blind multi-centre |
| Participants | Switzerland 158 patients with normal endoscopy and hp +ve. Dyspepsia > 3 months. Reflux excluded |
| Interventions | One week of lansoprazole 30 mg bid, clarithromycin 500 mg bid, amoxicillin 1g bid or lansoprazole 30 mg bid plus matching placebos. |
| Outcomes | Success defined as a dyspepsia score of less than 10 using a validated dyspepsia questionnaire (van Zanten et al.) Quality of life using SF-12 Length of follow-up: 12 months |
| Notes | hp erad = 72% |
| Allocation concealment | A – Adequate |

| Study | Gisbert 2004 |
|------------------------|--|
| Methods | RCT No blinding Single centre |
| Participants | Spain 50 H pylori infected patients Rome II criteria NUD |
| Interventions | Ten days of omeprazole 20 mg bd, amoxicillin 1g bd, versus ten days of ranitidine 150 mg bd. clarithromycin 500mg bd |
| Outcomes | Overall treatment success defined as >three point improvement on global dyspepsia score (Likert scale) |
| Notes | hp erad = 76% |
| Allocation concealment | C – Inadequate |

| Study | Gonzalez Carro 2004 |
|------------------------|---|
| Methods | RCT Double blind Single centre |
| Participants | Spain 93 H pylori infected patients Rome II criteria |
| Interventions | 1 week Omeprazole 20mg bid, amoxicillin 1g bid and clarithromycin 500mg bid vs placebo PPI and antibiotics |
| Outcomes | Success defined as symptom improvement at 9 months using a questionnaire adapted from Sheu et al. 1996 |
| Notes | hp erad = 66% |
| Allocation concealment | B – Unclear |

| Study | Greenberg 1999 |
|--------------|---------------------------------------|
| Methods | RCT, double blind single centre |
| Participants | USA |

Characteristics of included studies (Continued)

| | |
|------------------------|--|
| | 84 patients with dyspepsia > 4 weeks resistant to H2RA. Reflux excluded |
| Interventions | 2 weeks of omeprazole 20 mg bid, clarithromycin 500 mg bid and amoxycillin 1g bid or omeprazole 20 bid and identical antibiotic placebos |
| Outcomes | Change in dyspepsia score on a continuous scale at 12 months |
| Notes | Hp erad = 90% (ITT) |
| Allocation concealment | D – Not used |

| | |
|------------------------|--|
| Study | Hsu 2001 |
| Methods | RCT double blind single centre |
| Participants | China 161 hp positive patients. Rome II criteria for NUD |
| Interventions | One week of lansoprazole 30mg bd, metronidazole 250mg qds, tetracycline 500 mg qds versus lansoprazole 30 mg bd and placebo antibiotics for one week |
| Outcomes | Absence of dyspepsia symptoms at 12 months |
| Notes | hp erad = 78% |
| Allocation concealment | B – Unclear |

| | |
|------------------------|---|
| Study | Koelz 2003 |
| Methods | RCT, double-blind, Multicentre trial |
| Participants | Germany 181 patients with chronic therapy resistant functional dyspepsia. Reflux excluded. |
| Interventions | 2 weeks of Omeprazole 40mg bid plus amoxycillin or Omeprazole 20mg/day |
| Outcomes | Global symptom scores Follow-up 6 months |
| Notes | Hp erad = 52% (ITT) |
| Allocation concealment | A – Adequate |

| | |
|------------------------|---|
| Study | Koskenpato 2001 |
| Methods | RCT double blind Single centre |
| Participants | Finland 151 hp positive patients with dyspepsia. Normal OGD, normal ultrasound, predominant reflux excluded |
| Interventions | 2 weeks omeprazole 20 mg bd, amoxycillin 500mg qds, metronidazole 400 mg tds followed by omeprazole 20 mg od for 3 months, placebo for the next 9 months versus same regimen but placebo antibiotics over the first 2 weeks |
| Outcomes | dyspepsia responders (at least 50% improvement in dyspepsia score) |
| Notes | hp erad = 81% |
| Allocation concealment | C – Inadequate |

Characteristics of included studies (Continued)

| Study | Malfertheiner 2003 |
|------------------------|--|
| Methods | RCT double blind multi-centre |
| Participants | Germany 860 patients. Normal endoscopy, hp +ve. Dyspepsia fo > 4 weeks. Unclear if reflux excluded |
| Interventions | One week of Lansoprazole 30/15mg bid, clarithromycin 500 mg bid and amoxycillin 1g bid for 7 days or Lansoprazole 15 mg od and matching placebos |
| Outcomes | Success defined as no or minimal symptoms in previous week using validated German dyspepsia questionnaire at 12 months |
| Notes | hp erad = 80% |
| Allocation concealment | A – Adequate |

| Study | Martinek 2005 |
|------------------------|---|
| Methods | RCT double blind multi-centre |
| Participants | Czech Republic 40 patients Normal endoscopy, hp positive, upper GI symptoms |
| Interventions | 1 week Omeprazole 20mg bid, amoxycillin 1g bid and clarithromycin 500mg bid vs Omeprazole 20mg bid + placebo antibiotics |
| Outcomes | Success defined as improvement in dyspepsia symptoms |
| Notes | hp erad = 89% |
| Allocation concealment | B – Unclear |

| Study | Mazzoleni 2006 |
|------------------------|---|
| Methods | RCT double blind single centre |
| Participants | Brazil 89 patients, normal endoscopy, hp positive, Rome II criteria for NUD |
| Interventions | 10 days lansoprazole 30 mg bid, amoxycillin 1 g bid and clarithromycin 500 mg bid vs lansoprazole 30 mg bid and placebo antibiotics |
| Outcomes | Resolution of dyspepsia symptoms at 12 months |
| Notes | hp erad = 91% |
| Allocation concealment | A – Adequate |

| Study | McColl 1998 |
|---------------|---|
| Methods | RCT, double-blind single centre |
| Participants | UK 330 patients with Hp infection and dyspepsia. Reflux included |
| Interventions | 2 weeks |

Characteristics of included studies (Continued)

| | |
|------------------------|---|
| | Omeprazole 20mg bid, amoxicillin 500mg tid (or tetracycline 500mg tid) and metronidazole 400mg tid Omeprazole 20mg bid |
| Outcomes | Global symptom score Glasgow Dyspepsia Severity Scores GDSS Follow-up of 12 months. Hp erad = 88% (ITT). Hp erad = % (per protocol analysis) |
| Notes | |
| Allocation concealment | A – Adequate |

Study Miwa 2000

| | |
|------------------------|--|
| Methods | RCT double blind single centre |
| Participants | Japan 90 patients with NUD (normal endoscopy and Hp +ve) Reflux excluded |
| Interventions | One week of omeprazole 20 mg bid, amoxicillin 500 mg tds, clarithromycin 200 mg bid or placebos |
| Outcomes | No or minimal symptoms on GSRS at 3 months |
| Notes | hp erad = 85% |
| Allocation concealment | A – Adequate |

Study Ruiz 2005

| | |
|------------------------|---|
| Methods | RCT double blind single centre |
| Participants | Spain 158 patients with normal endoscopy, hp infection and Rome II criteria for NUD |
| Interventions | 1 week Omeprazole 20mg bid, amoxicillin 1g bid and clarithromycin 500mg bid vs placebo drugs |
| Outcomes | Improvement in dyspepsia symptoms at 12 months (at least two points on a five point Likert scale) |
| Notes | hp erad = 81% |
| Allocation concealment | A – Adequate |

Study Sheu 1996

| | |
|------------------------|---|
| Methods | RCT Taiwan Patients not masked |
| Participants | 41 patients NUD and HP. Reflux excluded. |
| Interventions | 4 weeks of Bismuth subcitrate 120mg tid and 2 weeks of metronidazole 500mg tid and moxycillin 500mg tid vs 2 months of H2RA |
| Outcomes | Mean symptom scores |
| Notes | |
| Allocation concealment | C – Inadequate |

Characteristics of included studies (Continued)

| Study | Talley (ORCHID) 1999 |
|------------------------|--|
| Methods | ORCHID, multicentre RCT, double-blind |
| Participants | Australia Primary and secondary care patients. Reflux excluded 287 patients with functional dyspepsia and Hp infection |
| Interventions | 1 week Omeprazole 20mg bid, amoxicillin 1g bid and clarithromycin 500mg bid Placebo |
| Outcomes | Global symptom scores GSRS(dyspepsia symptom score) QoL (PGWB) Follow-up of 12 months. Hp erad = 85%. ITT. |
| Notes | |
| Allocation concealment | A – Adequate |

| Study | Talley (USA) 1999 |
|------------------------|--|
| Methods | Multicentre, RCT Double blind |
| Participants | USA trial, 293 H pylori positive patients with NUD. Reflux excluded. |
| Interventions | 2 weeks omeprazole 20 mg bd, amoxicillin 1g bd and clarithromycin 500 mg bd |
| Outcomes | Global symptom score GSRS QoL (SF-36) Follow up 12 months Eradication rate 90% |
| Notes | |
| Allocation concealment | A – Adequate |

| Study | Varannes 2001 |
|------------------------|--|
| Methods | RCT double blind multi-centre |
| Participants | France 253 patients with normal endoscopy and hp +ve. Dyspepsia > 3 months. Reflux excluded |
| Interventions | One week of ranitidine 300 mg bid, amoxicillin 1g bid, clarithromycin 500 mg bid or matching placebos. |
| Outcomes | No epigastric pain on Likert scale in previous week at 12 months |
| Notes | hp erad = 70% |
| Allocation concealment | A – Adequate |

| Study | van Zanten 2003 |
|---------------|---|
| Methods | Multicentre RCT double blind |
| Participants | Canadian trial, 157 H pylori positive patients with Rome criteria for NUD (> 3months epigastric pain) |
| Interventions | lansoprazole 30 mg, clarithromycin 500 mg and amoxicillin 1000mg all twice a day for one week versus identical placebos |

| | |
|------------------------|---|
| Outcomes | Mean dyspepsia summary score. Classified as responders if had a decrease of 4 points or greater |
| Notes | hp erad = 82% evaluable patients |
| Allocation concealment | A – Adequate |

Characteristics of excluded studies

| Study | Reason for exclusion |
|------------------|---|
| Berstad 1988 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. Dyspepsia or quality of life not measured as an outcome. |
| Catalano 1999 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| David 1996 | Abstract only with no extra information available from author. |
| Florent 2000 | Abstract only with no extra information available from author. |
| Frazzoni 1993 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Gad 1989a | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Gad 1989b | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. Study not a randomised controlled trial. |
| Gilvarry 1997 | RCT comparing bismuth triple therapy with bismuth + placebo. Patients and investigators aware of H pylori status at follow-up visits and main outcomes compared H pylori -ve versus +ve rather than the randomised groups. |
| Glupczynski 1988 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Goh 1991 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Hazell 1997 | Dyspepsia or quality of life not measured as an outcome. |
| Holcombe 1992 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Hsu 1999 | Abstract but extra data available from the authors. RCT suggested H pylori eradication was statistically superior to placebo but unclear whether patients and investigators were adequately masked. Main analysis compared H pylori -ve versus +ve rather than the randomised groups. |
| Humphreys 1988 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. Peptic ulcer disease not excluded by endoscopy or barium meal. Dyspepsia or quality of life not an outcome measure. |
| Kamada 2003 | RCT but reported results by H pylori status rather than randomized groups. |
| Kang 1990 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Kazi 1990 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Kumar 1996 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Kyzekova 1999 | Assessed histological improvement in gastritis only. No dyspepsia symptoms assessed |
| Labenz 1993 | Dyspepsia or quality of life not measured as an outcome. The study was not a randomised controlled trial. |
| Lambert 1989 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Lanza 1989 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. Dyspepsia or quality of life not measured as an outcome. |
| Loffeld 1989 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Marshall 1993 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| McNulty 1986 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. Peptic ulcer disease not excluded by endoscopy or barium meal. |
| McNulty 1990 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. Peptic ulcer disease not excluded by endoscopy or barium meal. |
| Mitty 1997 | Abstract only. No extra data from authors. |

Characteristics of excluded studies (Continued)

| | |
|-----------------|--|
| Morgan 1988 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Nafeeza 1992 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Parente 1998 | Dyspepsia or quality of life not measured as an outcome. |
| Passos 1998 | Abstract only. No extra data available from the authors. |
| Patchett 1991 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. Study not a randomised controlled trial. |
| Rokkas 1988 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Sheu 2001 | Not a randomised study |
| Testoni 2000 | Patients selected to show absence of gastric phase III of the migrating motor complex. Dyspepsia outcome presented as median and range so data could not be extracted. |
| Tham 1996 | Peptic ulcer disease not excluded at endoscopy or barium meal. Dyspepsia or quality of life not measured as an outcome. |
| Unge 1989 | Peptic ulcer disease not excluded by endoscopy or barium meal. Dyspepsia or quality of life not measured as an outcome. Study not a randomised controlled trial. |
| Vaira 1992 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| Xia 2003 | Report of subgroups of patients that are from a publication already included in this systematic review (Talley et al. Orchid). |
| Xiao 1990 | Did not use an adequate H pylori eradication regimen according to pre-defined criteria. |
| van Zanten 1995 | Abstract only. No extra data available from the authors. |
| van Zanten 2000 | Patients with and without history of peptic ulcer disease included. Dyspepsia outcome not assessed. |

ANALYSES

Comparison 01. Helicobacter pylori (HP) eradication and NUD

No outcomes currently reported

Comparison 02. At end of treatment

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|--|----------------|---------------------|---|---------------------|
| 01 Global symptom scores (dichotomous) | 1 | 275 | Peto Odds Ratio 95% CI | 0.32 [0.13, 0.79] |
| 02 Global symptom scores (continuous) (high is poor) | 2 | 599 | Weighted Mean Difference (Fixed) 95% CI | -0.08 [-0.22, 0.06] |
| 03 Quality of life scales- disease specific | 2 | 592 | Weighted Mean Difference (Fixed) 95% CI | 0.19 [0.03, 0.35] |
| 04 Quality of life scales- generic scales | 2 | 531 | Weighted Mean Difference (Fixed) 95% CI | -1.28 [-4.51, 1.96] |

Comparison 03. Follow-up at < 3 months

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|--|-----------------------|----------------------------|---|---------------------|
| 01 Global symptom scores (dichotomous) | 1 | 275 | Peto Odds Ratio 95% CI | 1.60 [0.88, 2.90] |
| 02 Global symptom scores (continuous) (high is poor) | 3 | 627 | Weighted Mean Difference (Fixed) 95% CI | -0.04 [-0.18, 0.10] |
| 04 Quality of life scales - generic | 0 | 0 | Weighted Mean Difference (Fixed) 95% CI | Not estimable |

Comparison 04. Follow-up between 3-12 months

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|-----------------------|----------------------------|--|----------------------|
| 01 Global symptom scores (dichotomous) | 17 | 3566 | Relative Risk (Fixed) 95% CI | 0.90 [0.86, 0.94] |
| 02 Global dyspepsia score - continuous variable | 12 | 2547 | Standardised Mean Difference (Fixed) 95% CI | -0.18 [-0.26, -0.10] |
| 03 Quality of life scales - generic | 3 | 839 | Standardised Mean Difference (Random) 95% CI | 0.01 [-0.12, 0.15] |

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Drug Therapy, Combination; Dyspepsia [*drug therapy; microbiology]; Gastrointestinal Agents [*therapeutic use]; Helicobacter Infections [*drug therapy]; *Helicobacter pylori; Randomized Controlled Trials

MeSH check words

Adult; Humans

COVER SHEET

| | |
|--|--|
| Title | Eradication of Helicobacter pylori for non-ulcer dyspepsia |
| Authors | Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A, Bennett C, Forman D |
| Contribution of author(s) | S Soo performed the main search strategy, assessed eligibility and extracted the data. P Moayyedi was involved in developing the protocol, checked eligibility and data extraction and wrote the manuscript. J Deeks was involved in developing the protocol, checked eligibility and data extraction and performed the statistical analyses. B Delaney and A Harris were involved in developing the protocol and checked eligibility. M Innes, R Oakes, S Wilson, A Roalfe helped search for articles and/or provided secretarial support. D Forman was involved in developing the protocol and provided senior support in overseeing the project. |
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| | |
|---|--|
| What's New | This update has identified 5 new randomized controlled trials evaluating H. pylori eradication versus placebo in non-ulcer dyspepsia. These new trials have not altered the conclusion of the previous review but have increased the precision of the estimate of effect. |
| Date new studies sought but none found | Information not supplied by author |
| Date new studies found but not yet included/excluded | Information not supplied by author |
| Date new studies found and included/excluded | Information not supplied by author |
| Date authors' conclusions section amended | Information not supplied by author |
| Contact address | Prof Paul Moayyedi Professor of Gastroenterology Department of Medicine, Gastroenterology Division McMaster University HSC-3N51d 1200 Main Street West Hamilton Ontario L8N 3Z5 CANADA E-mail: moayyep@mcmaster.ca Tel: +1 905 525 7140 Fax: +1 905 522 3454 |
| DOI | 10.1002/14651858.CD002096.pub4 |
| Cochrane Library number | CD002096 |
| Editorial group | Cochrane Upper Gastrointestinal and Pancreatic Diseases Group |
| Editorial group code | HM-UPPERGI |



GRAPHS AND OTHER TABLES

Analysis 02.01. Comparison 02 At end of treatment, Outcome 01 Global symptom scores (dichotomous)

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

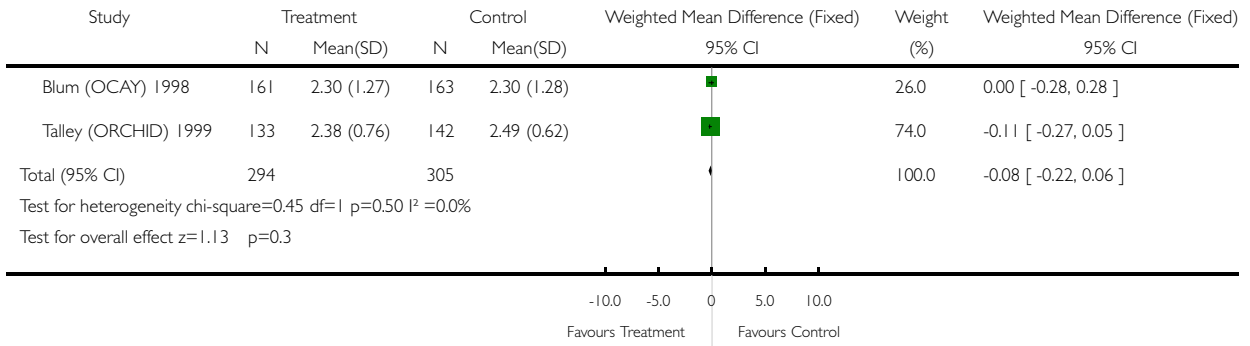
Comparison: 02 At end of treatment

Outcome: 01 Global symptom scores (dichotomous)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|--|------------------|----------------|---|-----------------|---------------------------|
| Talley (ORCHID) 1999 | 118/133 | 137/142 |  | 100.0 | 0.32 [0.13, 0.79] |
| Total (95% CI) | 133 | 142 |  | 100.0 | 0.32 [0.13, 0.79] |
| Total events: 118 (Treatment), 137 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=2.47 p=0.01 | | | | | |
| | | | 0.1 0.2 0.5 2 5 10 | | |
| | | | Favours Treatment | Favours Control | |

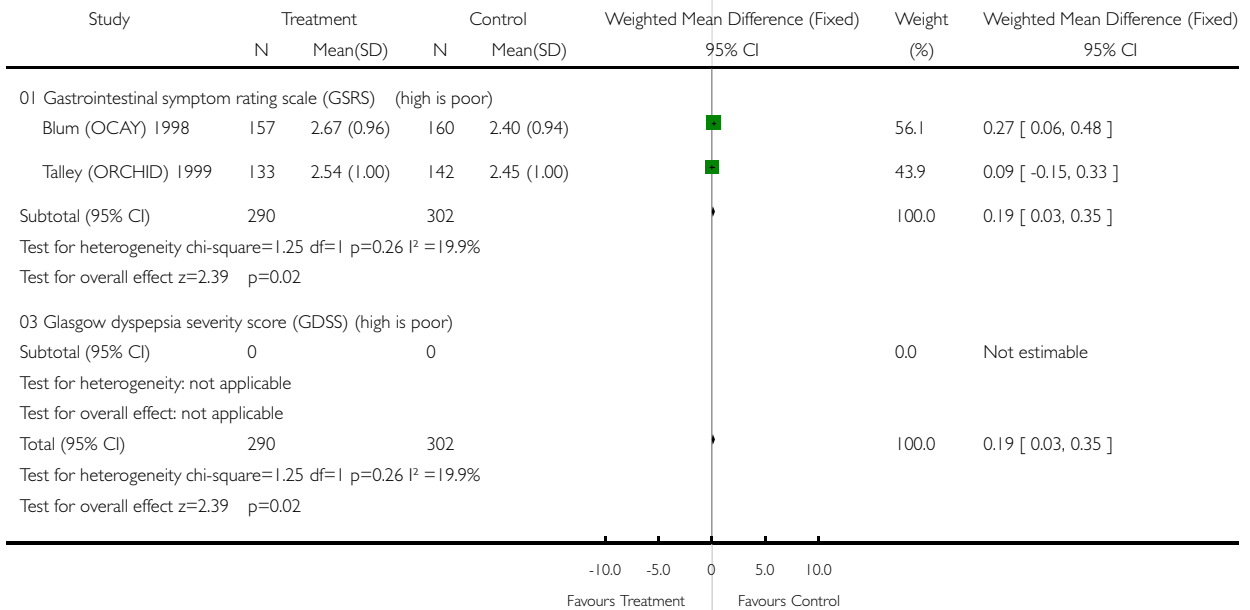
Analysis 02.02. Comparison 02 At end of treatment, Outcome 02 Global symptom scores (continuous) (high is poor)

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia
 Comparison: 02 At end of treatment
 Outcome: 02 Global symptom scores (continuous) (high is poor)



Analysis 02.03. Comparison 02 At end of treatment, Outcome 03 Quality of life scales- disease specific

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia
 Comparison: 02 At end of treatment
 Outcome: 03 Quality of life scales- disease specific

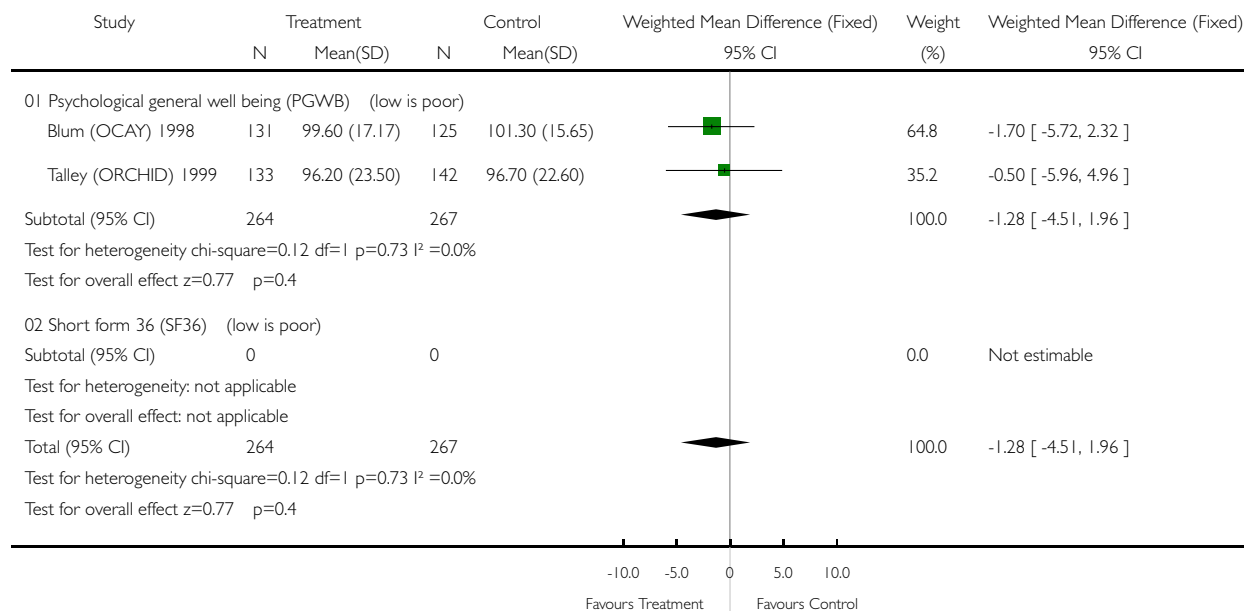


Analysis 02.04. Comparison 02 At end of treatment, Outcome 04 Quality of life scales- generic scales

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

Comparison: 02 At end of treatment

Outcome: 04 Quality of life scales- generic scales

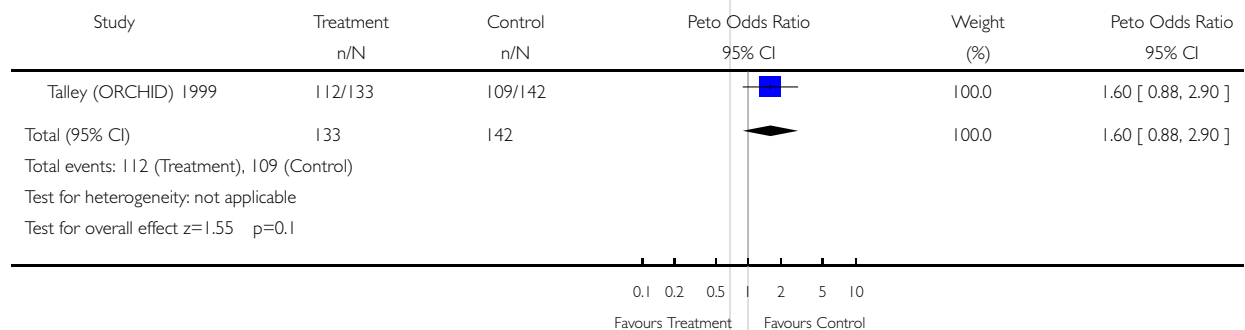


Analysis 03.01. Comparison 03 Follow-up at < 3 months, Outcome 01 Global symptom scores (dichotomous)

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

Comparison: 03 Follow-up at < 3 months

Outcome: 01 Global symptom scores (dichotomous)

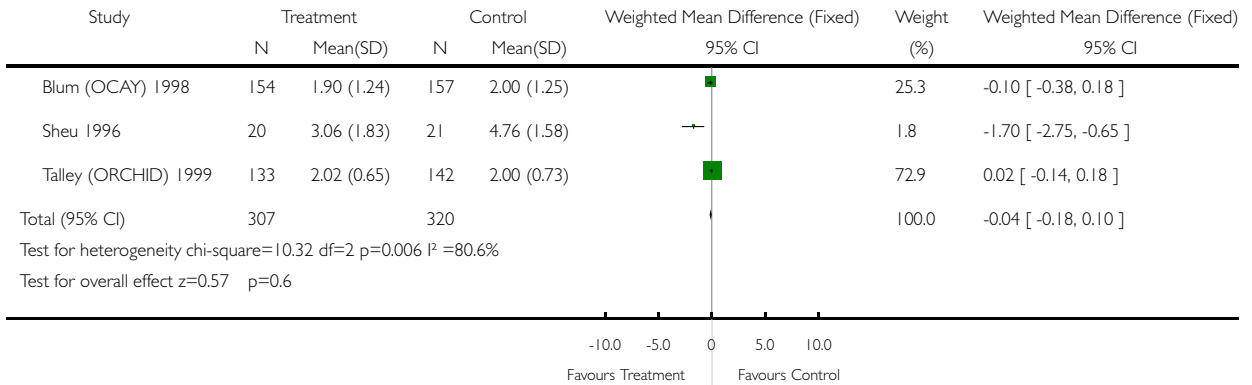


Analysis 03.02. Comparison 03 Follow-up at < 3 months, Outcome 02 Global symptom scores (continuous) (high is poor)

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

Comparison: 03 Follow-up at < 3 months

Outcome: 02 Global symptom scores (continuous) (high is poor)

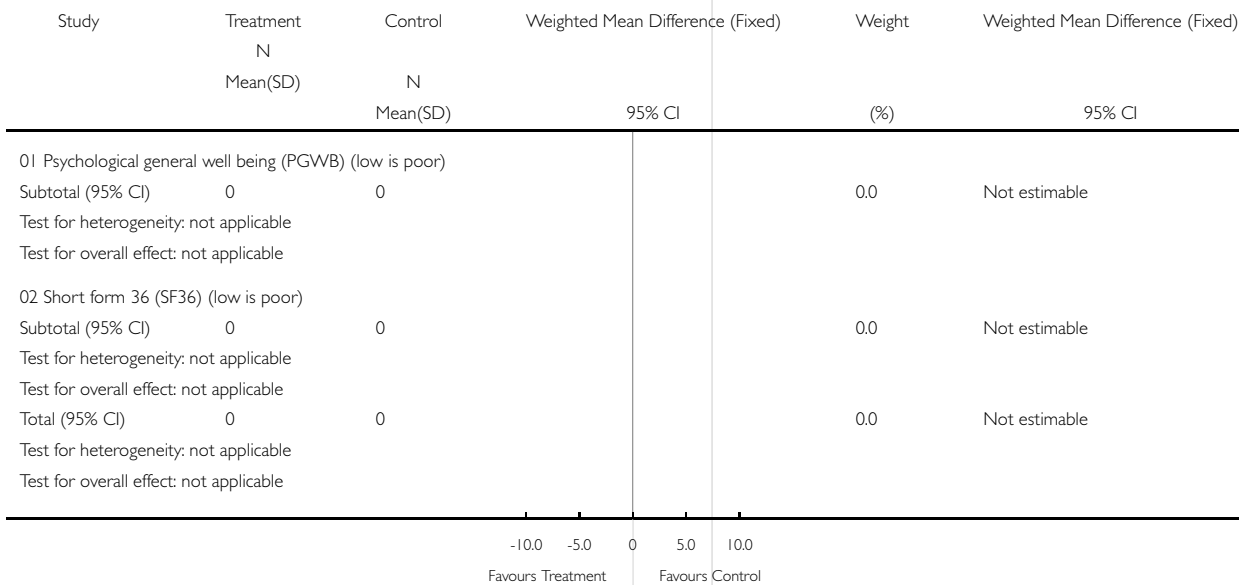


Analysis 03.04. Comparison 03 Follow-up at < 3 months, Outcome 04 Quality of life scales - generic

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

Comparison: 03 Follow-up at < 3 months

Outcome: 04 Quality of life scales - generic

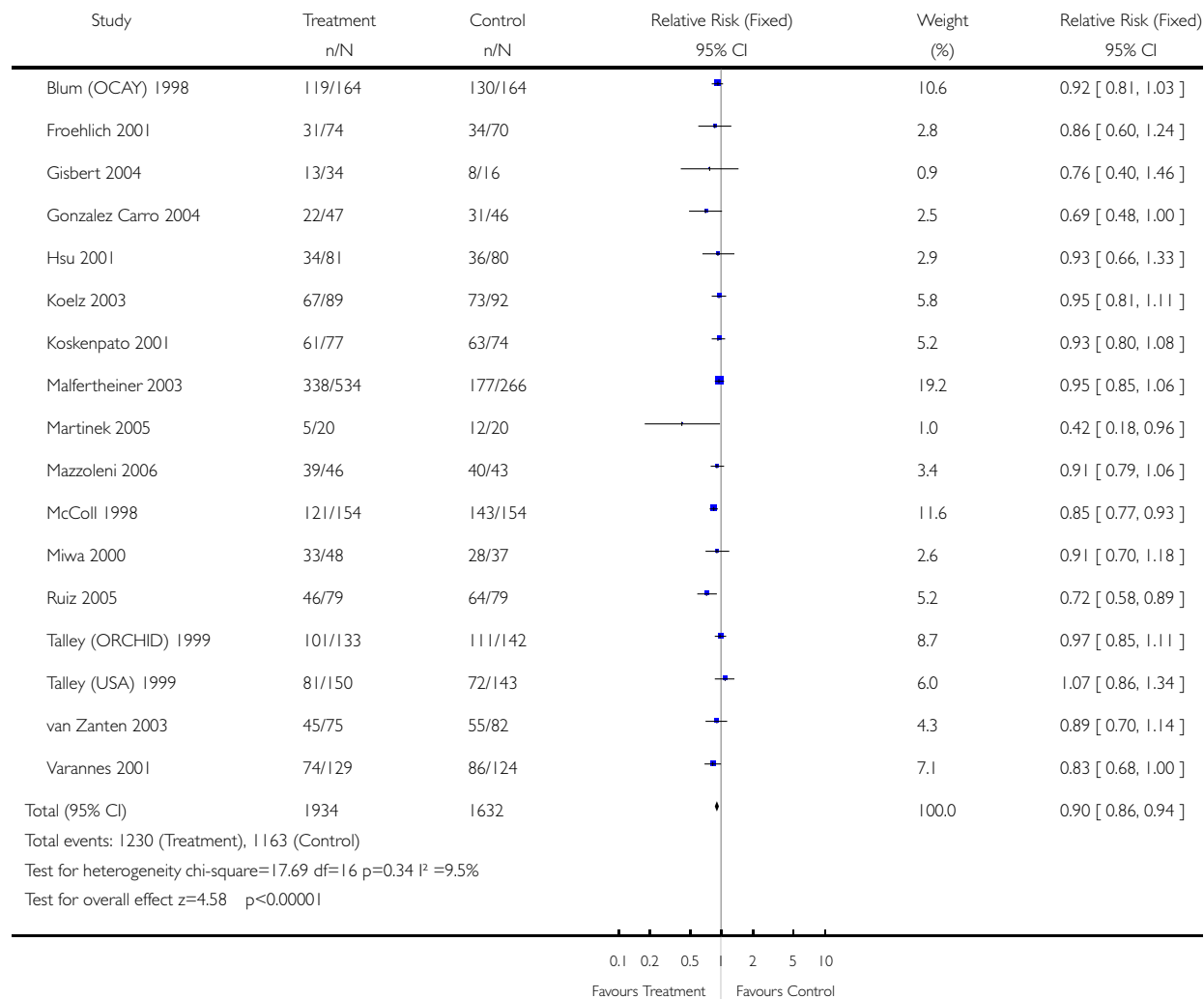


Analysis 04.01. Comparison 04 Follow-up between 3-12 months, Outcome 01 Global symptom scores (dichotomous)

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

Comparison: 04 Follow-up between 3-12 months

Outcome: 01 Global symptom scores (dichotomous)

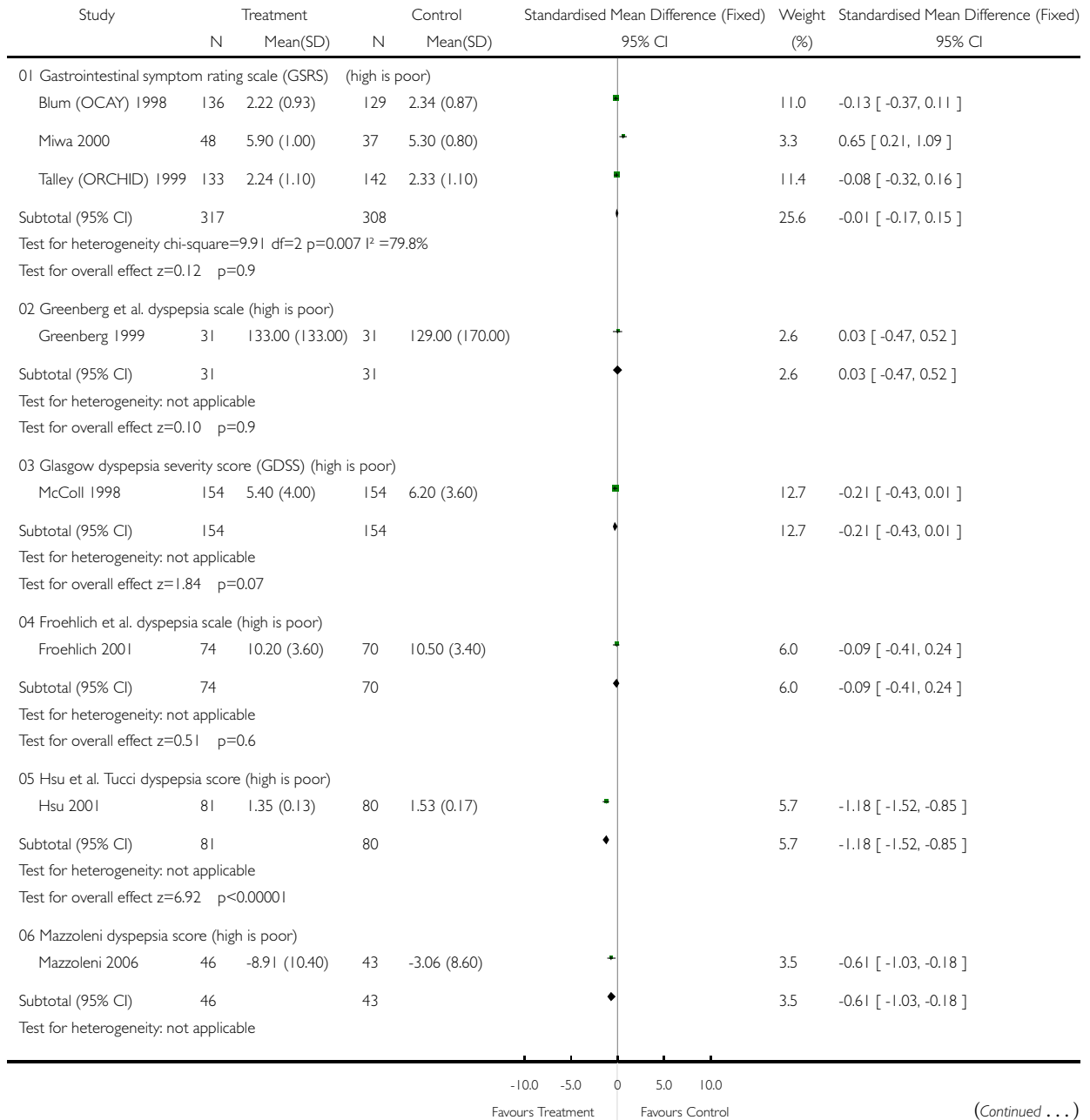


Analysis 04.02. Comparison 04 Follow-up between 3-12 months, Outcome 02 Global dyspepsia score - continuous variable

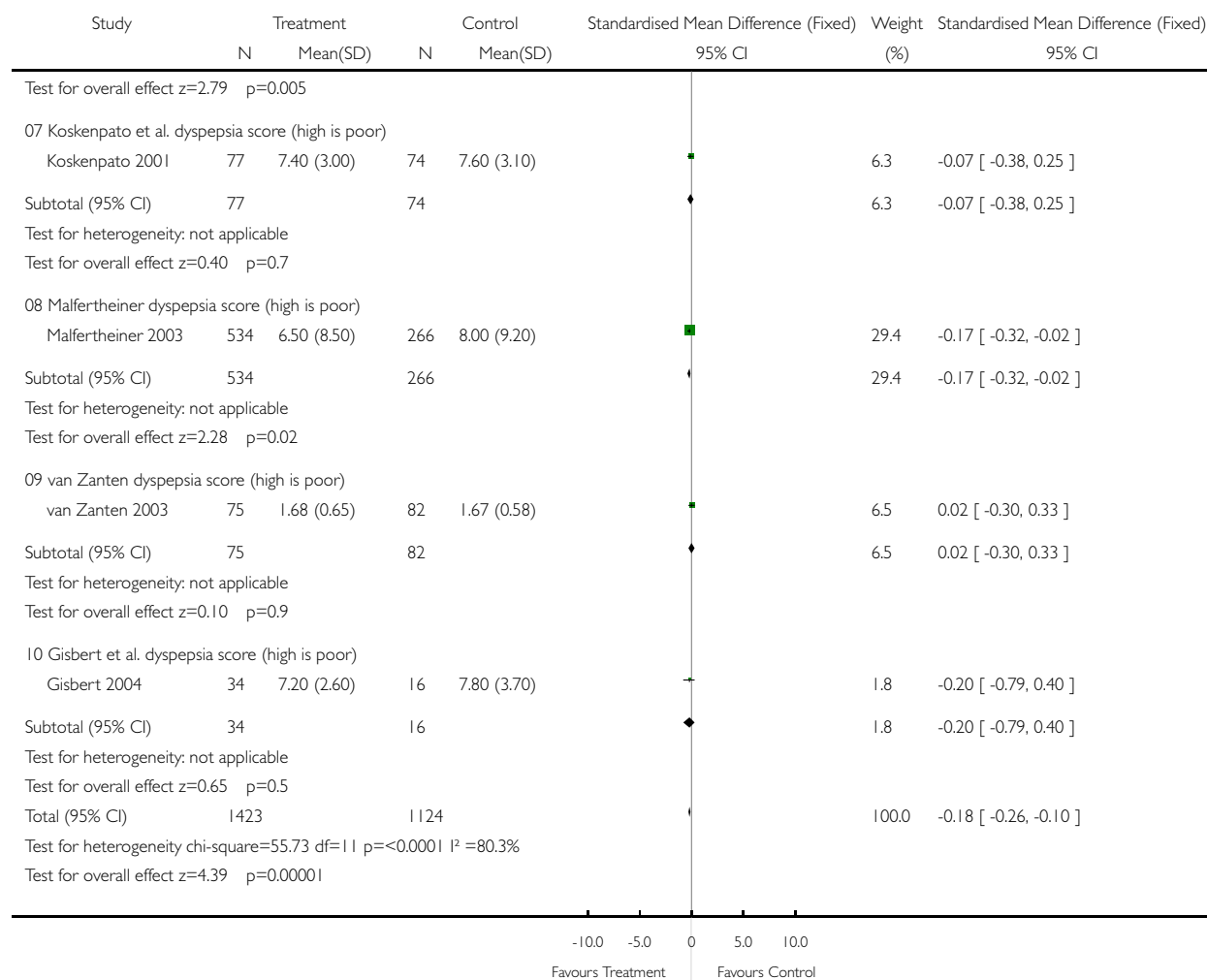
Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

Comparison: 04 Follow-up between 3-12 months

Outcome: 02 Global dyspepsia score - continuous variable



(... Continued)



Analysis 04.03. Comparison 04 Follow-up between 3-12 months, Outcome 03 Quality of life scales - generic

Review: Eradication of Helicobacter pylori for non-ulcer dyspepsia

Comparison: 04 Follow-up between 3-12 months

Outcome: 03 Quality of life scales - generic

