Health Technology Assessment 2000; Vol. 4: No. 39

Review

The management of dyspepsia: a systematic review

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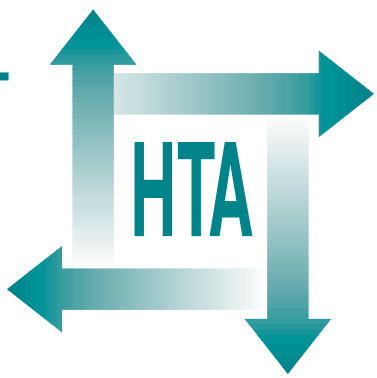
Health Technology Assessment
NHS R&D HTA Programme



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The management of dyspepsia: a systematic review

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Competing interests: R Hobbs is a board member of the European Society of Primary Care Gastroenterology, and has received sponsorship for travel and honoraria from a number of biotechnology and pharmaceutical companies for plenary talks and attendance at major scientific congresses and conferences.

Published end of 2000

This report should be referenced as follows:

Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*. The management of dyspepsia: a systematic review. *Health Technol Assess* 2000;**4**(39).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

The research reported in this monograph was funded as project number 96/37/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

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ISSN 1366-5278

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Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

Contents

List of abbreviations

AMED	Allied and Complementary Medicine Database
b.d.	*bis die* (twice daily)*
BIDS	Bath Information & Data Service
CI	confidence interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CT	computed tomography
DES	discrete events simulation
df	degrees of freedom
ELISA	enzyme-linked immunosorbent assay*
ENRD	endoscope-negative reflux disease
GI	gastrointestinal*
GORD	gastro-oesophageal reflux disease
GP	general practitioner
GSRS	Gastrointestinal Symptom Rating Scale
HetQ	test of heterogeneity, Q*
i.m.	intramuscularly*
i.v.	intravenously*
ICER	incremental cost-effectiveness ratio
ISCI	Integrated Sciences Citation Index
ITT	intention-to-treat*
LR	likelihood ratio*
NICE	National Institute for Clinical Excellence
NNH	number-needed-to-harm
NNT	number-needed-to-treat
NPV	negative predictive value*
NSAID	non-steroidal anti-inflammatory drug
NUD	non-ulcer dyspepsia
o.d.	once daily*
OGD	oesophageal-gastro-duodenoscopy*
OR	odds ratio
OTC	over-the-counter
PGWB	Psychological General Well-Being [scale]
PPI	proton pump inhibitor
PPV	positive predictive value*
PUD	peptic ulcer disease
q.d.s.	*quater die sumendum* (four times daily)*
QALY	quality-adjusted life-year*
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SF-36	Short Form 36
SIGLE	System for Information on Grey Literature in Europe
SIP	Sickness Impact Profile
SMD	standardised mean difference*
t.d.s.	*ter die sumendum* (three times daily)*

* Used only in tables and figures

Executive summary

Background

Managing dyspepsia costs the NHS in excess of £500 million per year; 2% of the population consult their general practitioner (GP) with dyspepsia each year, and 450,000 endoscopies are performed at a cost of £90 million. Most patients undergoing endoscopy have no significant abnormality and are termed as having non-ulcer dyspepsia (NUD). The initial management of uninvestigated dyspepsia in primary care is considered in this review together with treatments for proven NUD. The study linked systematic reviews with simulation modelling to provide the best available evidence for managing patients with dyspepsia.

Questions addressed

The management of uninvestigated dyspepsia in primary care

1. How effective is initial pharmacological therapy?
2. How effective is early endoscopy?
3. How effective is *Helicobacter pylori* screening before endoscopy in patients with dyspepsia?
4. How effective is *H. pylori* screening before eradication therapy in patients with dyspepsia?
5. Does subdividing dyspepsia on the basis of symptom patterns predict response to particular therapies?
6. What are the most cost-effective combinations of initial investigation strategy and prescribing for patients?
7. What are the most important strategies to compare in future trials?

Therapy for proven NUD

1. How effective is pharmacological therapy?
2. How effective is *H. pylori* eradication?
3. What is the most cost-effective therapy?
4. What are the most important therapies to compare in the treatment of NUD?

Methods

Data sources

The Cochrane Collaboration Controlled Trials Register and Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, SIGLE and ISCI were searched up until January 1999. Experts in the field of dyspepsia, major pharmaceutical companies and journal editors were also contacted. Authors of publications only available as abstracts were contacted for full trial results.

Study selection

Dyspepsia was defined following the 1988 Rome Working Party definition as any symptom referable to the upper gastrointestinal tract lasting for more than 4 weeks. Two reviewers independently selected eligible trials, according to the following criteria.

Dyspepsia in primary care

- Population: patients presenting to primary care with dyspeptic symptoms but not selected on the basis of any previous investigative results.
- Intervention: empirical acid suppression therapy; early endoscopy (with or without a screening questionnaire); *H. pylori* screening followed by endoscopy of patients with positive results; *H. pylori* screening followed by eradication therapy for patients with positive results.
- Comparison: placebo/antacid; other medication; other strategy.
- Outcomes: quality of life; individual dyspepsia symptoms or symptom scores; patient acceptability; consultation and referral rates for upper gastrointestinal symptoms; prescribing; diagnostic findings; costs.

Pharmacological treatment for NUD

Patients with NUD were defined as those with dyspepsia and insignificant findings at endoscopy or barium meal, who were not required to have had 24-hour oesophageal pH studies, upper abdominal ultrasound or computed tomography scans. Patients with hiatus hernia, less than five gastric erosions or mild duodenitis were included, as these lesions correlate poorly with dyspepsia symptoms.

- Population: adult patients (aged 16–80 years) presenting in secondary care with diagnosis of NUD; all patients to have had either an endoscopic or barium meal examination to exclude peptic ulcer disease.

- Intervention: antacids; H_2-receptor antagonists, including cimetidine, famotidine, nizatidine and ranitidine; proton pump inhibitors (PPIs); prokinetics, including cisapride, domperidone and metoclopramide; mucosal protecting agents, including colloidal bismuth compounds, misoprostol, and sucralfate; antimuscarinics, including pirenzepine; pre-defined effective *H. pylori* eradication therapy versus placebo or acid suppression.
- Outcomes: individual dyspepsia symptom scores; global symptom scores expressed in dichotomous format; quality of life.

Data extraction
Data from eligible trials were collected for analysis.

Data synthesis
Data from ordinal outcomes, such as dyspepsia rating scales, were combined by transforming to a binary scale. Fixed effect models (Mantel–Haenszel) were used for pooling data to obtain a pooled relative risk (RR) unless significant heterogeneity was present, when the random effects model (DerSimonian and Laird) was adopted. For continuous outcomes, the inverse variance (Woolf's method) model was used as the fixed effect method and the DerSimonian and Laird method for random effects. Egger's test of asymmetry was used to detect publication bias. Numbers-needed-to-treat (NNTs) and their confidence intervals (CIs) were calculated. For continuous measures, Hedges' adjusted *g* was used to calculate standardised mean differences, expressing the treatment effect in units of standard deviation.

RRs, mean differences and standardised mean differences were pooled. Additional analyses investigating heterogeneity and publication bias were undertaken.

Modelling
All health economics modelling adopted an NHS perspective. Effects of treatment were obtained from the systematic reviews where possible; other necessary data, including test performance, prevalence and outcome data were obtained systematically from papers collected alongside the reviews, but not relating directly to the study questions. Cost data were obtained from the Drug Tariff and NHS 1998 Reference Costs. Markov cost-effectiveness models of therapy for proven NUD were constructed. The discrete event simulation model of the management of dyspepsia in primary care was programmed directly in Visual Basic©. Costs were discounted at 6% and benefits at 3%. Cost-effectiveness ratios and incremental cost-effectiveness ratios (ICERs) for comparisons of strategies were obtained and a wide sensitivity analysis of variation in both costs and effectiveness was performed.

Results

Interventions for uninvestigated dyspepsia in primary care
In all, 12 papers reporting 14 comparisons were found, with a further four trials being available as abstracts. Meta-analysis of trials comparing PPIs with antacids and H_2-receptor antagonists, and of early endoscopy compared with initial acid suppression was possible. PPIs were very significantly more effective than both H_2-receptor antagonists and antacids. RR reductions with 95% CIs were: for PPIs versus antacids, 29% (36 to 21); for PPIs versus H_2-receptor antagonists 37% (53 to 15). Results for other drug comparisons were either absent or inconclusive. Early endoscopy may be more effective than initial prescribing but the effect size was small and non-significant (RR reduction, 11% (1 to 22)). Although economic data are not yet available, cost-effectiveness is likely to be low. *H. pylori* test-and-endoscope was associated with no significant difference in effectiveness compared with selective endoscopy at the GP's discretion, and no reduction in costs. *H. pylori* test-and-treat has been shown to be as effective as early endoscopy and to reduce costs in patients referred for investigation, but uncertainty remains as to its cost-effectiveness in primary care compared with empirical acid suppression.

The model indicated that strategies involving initial prescribing, or *H. pylori* eradication (test-and-treat) were more cost-effective than strategies involving endoscopy. Prescribing H_2-receptor antagonists was more effective than antacid (ICER, £15.88 per additional month symptom-free over 5 years). PPIs were more effective than antacids (ICER, £21.76 per month) and H_2-receptor antagonists (ICER, £41.64 per month). The results were sensitive to the costs and effectiveness of the medications. A mean saving of 3 weeks' dyspeptic symptoms over 5 years was obtained by *H. pylori* test-and-treat rather than prescribing, with an ICER of £62.77 per month saved. The result was sensitive to the cost of ongoing dyspepsia treatment and the prevalence of *H. pylori*.

Interventions for NUD
The one eligible trial suggested that antacids were no more effective than placebo in NUD.

Meta-analysis was possible for prokinetics, H_2-receptor antagonists, PPIs, bismuth, pirenzepine, sucralfate, and *H. pylori* eradication against placebo. Prokinetics and H_2-receptor antagonists were more effective than placebo (prokinetics: RR reduction, 50% (95% CI, 30 to 70); H_2-receptor antagonists, 29% (47 to 4)) but trials were often of poor quality with significant heterogeneity between studies. A funnel plot revealed that the results of the prokinetic meta-analysis could be due to publication bias or related quality issues. PPIs and bismuth tended to be more effective than placebo but this did not reach statistical significance. There was no evidence that sucralfate was superior to placebo. Pirenzepine showed a significant benefit (RR reduction, 4 (95% CI, 3 to 10) but this was based on only two trials and the drug is no longer available in the UK. *H. pylori* eradication was associated with a 9% RR reduction (95% CI, 14 to 4); an NNT of 15 (10 to 1) was calculated based on a control event rate of 72%.

Economic modelling based on these data, assuming a threshold ICER of £100 per month, and a wide sensitivity analysis indicated that PPIs and cisapride were unlikely to be cost-effective treatments for NUD. If cheaper prokinetics (domperidone or metoclopramide) were sufficiently effective to give an NNT of at most 55, or H_2-receptor antagonists to give an NNT of 14, these treatments may represent cost-effective choices. *H. pylori* eradication was cost-effective with an ICER against antacid alone of £56 per month.

Conclusions

Implications for healthcare

There is still much uncertainty around the management of dyspepsia, both uninvestigated dyspepsia and proven NUD. This review indicates that the treatment for NUD, for which the evidence is most reliable, is *H. pylori* eradication. The effect is small but cost-effective as the treatment is potentially curative rather than just suppressive. Whether the effect is due to treating latent peptic ulcer disease or some other mechanism, the implication is that patients diagnosed on the basis of a negative endoscopy will benefit from *H. pylori* eradication.

In primary care, the conclusions are much less robust. PPIs are the most effective treatment for undiagnosed dyspepsia and reasonably cost-effective. This is because the case-mix includes patients with peptic ulcer disease and gastro-oesophageal reflux disease, for which PPIs are effective treatments. The relative efficacy of H_2-receptor antagonists is uncertain, because of a lack of trials comparing antacids and H_2-receptor antagonists and a lack of trials in patients without reflux as a dominant symptom. Although management based on early endoscopy may lead to a small reduction in dyspeptic symptoms, the cost-effectiveness of endoscopy is uncertain. Modelling suggests that, for most patients, endoscopy-based management is not cost-effective as there is little gain in symptom relief and considerable additional cost. Of the empirical strategies, *H. pylori* test-and-treat is likely to be more cost-effective than endoscopy but well-designed, primary care based trials are needed to compare cost-effectiveness and effects on quality of life with empirical acid suppression.

Recommendations for research

Primary research

In the treatment of NUD:

(i) long-term effectiveness of H_2-receptor antagonists and 'cheaper' prokinetics compared with placebo in proven NUD
(ii) patient's views on the value of *H. pylori* eradication therapy
(iii) new therapies.

For the initial management of dyspepsia:

(i) cost-effectiveness of *H. pylori* test-and-treat compared with acid suppression for uninvestigated dyspepsia in primary care
(ii) cost-effectiveness of H_2-receptor antagonists compared with PPIs in primary care
(iii) effectiveness of the Rome II criteria for determining therapy in primary care.

Secondary research

These reviews (in their Cochrane format) should be kept up-to-date, as research in this field is extremely fast moving. Given the number of new trials and the potential for important subgroup analysis based on age or symptoms, there is potential for an individual patient data meta-analysis. The Cochrane Upper Gastrointestinal and Pancreatic Disease Review Group is actively planning such a review.

Chapter 1

Background

The initial management of dyspepsia in primary care and treatments for proven non-ulcer dyspepsia (NUD) are considered in this study. The majority of dyspeptic patients have no endoscopic abnormality and there is uncertainty among clinicians both as to the role of diagnostic tests, including endoscopy, and the most effective treatments for patients without clear pathology. Thus, in this study systematic reviews of primary care management and therapy for NUD are linked with simulation modelling to provide the best available evidence to assist general practitioners (GPs) and specialists in managing patients with dyspepsia.

NUD has been defined as dyspepsia occurring in a patient with no significant abnormality on endoscopy or upper abdominal ultrasound (gastritis alone is not considered a significant abnormality).[1] Although studies from both primary and secondary care have established the cost-effectiveness of *Helicobacter pylori* eradication in peptic ulcer disease (PUD), NUD remains an area in which trial results have been conflicting. One explanation for this is that NUD encompasses a number of symptom clusters which may be clinically important and respond to different treatments.[2] Reports suggest that drug therapies may be effective in only some of these subgroups of NUD.[3,4] There are a number of different definitions of these NUD subgroups.[5,6]

A diagnosis of NUD requires that the patient has been fully investigated. However, most dyspeptic patients are managed within primary care and, in spite of consensus statements and guidelines, the most effective strategy for managing dyspepsia in this setting remains to be determined.

The principal questions to be answered are what management strategies in primary care are the most cost-effective, what therapies are effective in treating proven NUD, and whether some types of NUD respond better to some therapies than others. The management of both the uninvestigated dyspeptic patient in primary care and the known NUD patient are addressed in this review.

The uninvestigated dyspeptic patient in primary care

Investigative strategies for dyspepsia

Currently, only about 40% of dyspeptic patients are investigated by endoscopy, the remainder being treated on a symptomatic basis.[7] Resources for healthcare are always limited and it is too expensive to investigate every patient who presents with dyspepsia. Strategies have therefore been proposed that will adequately determine which patients should receive what therapy, while reducing unnecessary endoscopy workload.[8,9] These include:

- empirical anti-secretory therapy/ treat-and-endoscope
- early endoscopy
- dyspepsia questionnaires
- screening for *H. pylori*
- empirical *H. pylori* eradication therapy for all dyspetic patients.

Empirical anti-secretory therapy/ treat and endoscope

Treating young (under the age of 45 years) dyspeptic patients with antacids, histamine (H_2)-receptor antagonists or proton pump inhibitors (PPIs) and only investigating those that fail to respond has been a popular method of reducing endoscopy workload.[10] This strategy reserves costly investigations for those patients who are consuming more medication and, hence, might recover the cost of investigation by decreased prescribing. The finding that patients are prescribed less anti-secretory medication and have reduced consultation rates after a negative endoscopy suggests that this assumption may be false.[11,12] In addition, persistent symptoms might be positively associated with serious pathology, although there is little evidence to support this. A further criticism of this strategy is that patients with PUD may receive intermittent anti-secretory drugs, responding promptly at each recurrence, even though *H. pylori* eradication is now the treatment of choice for this group. Nevertheless, empirical anti-secretory therapy or early endoscopy is the usual approach taken by GPs when initially investigating patients with dyspepsia.

Early endoscopy

An alternative strategy has been to investigate all patients with symptoms that are significant enough to warrant prescribing before initiating a prescription. A prospective randomised study has indicated that early endoscopy may be more cost-effective than empirical antacid therapy.[13] Were such a policy applied nationally, there would be considerable resource implications, as the number of endoscopies performed would have to rise.

Dyspepsia questionnaires

Selection protocols aim at raising the prior probability of pathology in those investigated; the scoring system of Holdstock and Mann has been the most widely used.[14] Most systems rely on a combination of age, length of history and response to initial therapy. Data suggest that administering these questionnaires to young dyspeptic patients and not investigating those with a low probability of significant pathology could halve the number of endoscopies performed.[15] However, many of the questionnaires proposed are too unwieldy for use in general practice and evidence is lacking as to whether results of a questionnaire would sufficiently reassure patients on the absence of significant disease. Such concerns appear justified, as the sensitivity of this strategy is only 80–90% – a proportion of peptic ulcers being missed by symptom questionnaires in prospective studies.[15] Symptom questionnaires can therefore enhance the diagnostic accuracy of the clinical history but are probably unsuitable as screening tools to reduce endoscopy workload; they are not considered further in this review.

Screening for H. pylori

Test-and-endoscope *H. pylori* is associated with nearly all peptic ulcers in patients not taking non-steroidal anti-inflammatory drugs (NSAIDs).[16] A strategy of screening patients for *H. pylori* with serology or urea breath tests and only investigating those infected has been suggested by several groups. This could reduce endoscopies in young dyspeptic patients by 23–66%, while detecting almost 100% of peptic ulcers in those not taking NSAIDs.[17–19] It is possible that this strategy may not reassure patients adequately and may simply transfer the cost of managing dyspepsia from hospital to primary care. A decision-analytic model comparing empirical anti-secretory therapy with *H. pylori* screening found that it would take 5–18 years for savings to accrue if the latter strategy did not influence patient behaviour.[20] However, some recent evidence suggests that knowledge of *H. pylori* status can reassure patients and may be a cost-effective strategy.[21]

Test-and-treat PUD is cured by *H. pylori* eradication, and there are now safe and relatively inexpensive regimens that effectively treat this organism.[22] A logical extension of *H. pylori* screening is therefore to simply treat the infection if it is present, as recommended by a recent European *Helicobacter pylori* Study Group consensus statement, rather than referring this group of patients for endoscopy.[23] This would cure almost all peptic ulcers while avoiding endoscopy in all young dyspeptic patients. At present there has been very little published on the efficacy of this approach but it is possible that it may reduce both endoscopy workload and patients' utilisation of healthcare resources.[24]

Empirical H. pylori *eradication therapy for all dyspeptic patients*

The simplest *H. pylori* management strategy of all would be to prescribe empirical *H. pylori* eradication therapy to all young dyspeptic patients. This would avoid the inconvenience and cost of testing for *H. pylori*, and a published model has suggested this may be the most cost-effective strategy for managing dyspepsia.[25] Empirical treatment was only slightly cheaper than the screening and treatment strategy, and resulted in 50–70% of young dyspeptic patients who were *H. pylori*-negative receiving antibiotics unnecessarily. Whether the increase in antibiotic exposure is worth this small cost saving needs to be addressed by prospective studies. Too few data are currently available to justify a review in this area but a comparative model will still be applied to highlight the crucial uncertainties.

Prescribing for dyspepsia

Antacids

Antacids have been used for centuries to treat dyspepsia and are still the most popular over-the-counter (OTC) medication for upper gastrointestinal symptoms.[26] The popularity of antacids in clinical practice has waned since the introduction of the H_2-receptor antagonists, and it is easy to overlook the fact that antacids are safe, cheap and effective drugs.[27] Antacids are usually salts of aluminium and/or magnesium that are designed to neutralise acid. Randomised controlled trials (RCTs) have shown that antacids are significantly better than placebo[28] at healing PUD and have a potency similar to H_2-receptor antagonists.[29] The mechanism of action probably relates to the ability to reduce gastric acid damage, as intensive therapy with antacids can neutralise

1008 mmol of hydrogen ions per day.[30] Antacids also chelate conjugated bile and could therefore protect against the noxious effects of bile acids on the gastric mucosa if this was important in the pathogenesis of NUD.[31] Aluminium salts may have an additional cytoprotective action as they stimulate the production of prostaglandins in the gastric mucosa.[32]

The main disadvantage of antacids is the frequency with which they need to be taken. The original studies gave antacids 1 and 3 hours after breakfast, lunch and supper, as well as a nocturnal dose.[30] This 'seven times daily' regimen is complicated and patient compliance is likely to be poor outside the context of a clinical trial. Simpler regimens have been proposed[33] but these still cannot compete with H_2-receptor antagonists that only need to be taken once or twice daily.

H_2-receptor antagonists

The development of H_2-receptor antagonists in the 1970s revolutionised the treatment of PUD.[34] These drugs reduce pentagastrin-stimulated acid output by 30–50%.[35] They are particularly effective at reducing nocturnal acid secretion, although their effect on meal-stimulated acid output is more modest.[36] RCTs have shown that H_2-receptor antagonists are significantly superior to placebo in treating duodenal ulcer disease, with 80% of lesions healed at 4 weeks.[37] H_2-receptor antagonists are less effective in patients with gastro-oesophageal reflux disease (GORD) but are still superior to placebo.[38] Cimetidine was the first H_2-receptor antagonist to be developed and is the cheapest drug in this class.[39] The main disadvantage of cimetidine is that it competitively displaces dihydrotestosterone from androgen binding sites, occasionally leading to gynaecomastia in men.[40] The newer H_2-receptor antagonists, ranitidine, nizatidine and famotidine, are more potent inhibitors of acid secretion on a weight basis and do not have anti-androgenic side-effects.[41] They are, however, more expensive than cimetidine.

PPIs

PPIs were another landmark development in gastroenterology.[42] These drugs irreversibly inhibit the gastric H^+, K^+ ATPase pump,[43] and reduce both basal and stimulated gastric acid output more effectively than H_2-receptor antagonists.[44] Clinical trials have consistently shown that PPIs are more effective than H_2-receptor antagonists in healing peptic ulcers. PPIs are the most potent therapy for GORD and are the treatment of choice for oesophagitis.[45] Evidence for their efficacy in NUD is limited; few trials have addressed this issue and there has been no systematic review of the literature. This is important because these drugs are commonly used to treat NUD. PPIs are more expensive than H_2-receptor antagonists and cost the UK NHS over £500 million each year.[46]

Prokinetics

Metoclopramide was the first prokinetic to be developed in the 1960s, from a programme that was evaluating local anaesthetics.[47] It is structurally related to procainamide but has negligible local anaesthetic and cardiac effects, while having clinically significant effects on gastrointestinal motility.[47] Metoclopramide has antidopaminergic activity and increases motility by enhancing the release of acetylcholine from postganglionic nerve endings of the myenteric plexus of gastrointestinal smooth muscle.[48] This leads to an increase in lower oesophageal sphincter pressure, improved gastric peristalsis, enhanced pyloric activity and accelerated transit through the jejunum.[49] There is no demonstrable effect on colonic motility.[50] Metoclopramide reduces nausea and vomiting, and is more effective than placebo in healing oesophagitis.[51] The drug is cheap and is generally well tolerated; however, it does cross the blood–brain barrier and extrapyramidal side-effects occasionally occur, particularly when large doses are given to elderly subjects.[52] Domperidone has a similar efficacy to metoclopramide[53] but, as it does not cross the blood–brain barrier, there is a much lower propensity to cause extrapyramidal side-effects.[54] It is more expensive than metoclopramide but is still relatively cheap compared with other dyspepsia drugs.

Cisapride is chemically related to metoclopramide but has no anti-dopaminergic activity.[55] The drug has recently been withdrawn on the advice of the Committeee on Safety of Medicines because of the risk of rare but often fatal arrthymias. This decision may be rescinded after further investigation. However, cisapride has been used extensively and was a major focus of researchers in the past; hence, it is important to consider it in this review. The drug has a similar or superior efficacy to metoclopramide in improving gastric emptying.[56] Cisapride enhances motility of the colon as well as the upper gastrointestinal tract and has been used in constipation.[57] It is generally well tolerated although it can prolong the Q-T interval and is not recommended in patients with co-existing ischaemic heart disease.[58] In terms of cost-effectiveness, cisapride is more expensive than PPIs and has not been shown

to be more effective than the other prokinetics,[59] although information in this area is sparse.

Cytoprotective agents

Bismuth preparations have been used for centuries to treat abdominal pain and dyspepsia.[60] A number of trivalent bismuth compounds have been marketed; tri-potassium di-citrato bismuthate (De-Nol®: Yamanouchi Pharma Ltd) is the most available product in the UK. This stimulates gastric prostaglandin synthesis and may form complexes with gastric glycoproteins to enhance the mucosal barrier to hydrogen ion diffusion.[61]

Combination strategies

In order to limit the prescribing of more expensive and more powerful acid suppression therapy to patients who seem to need them most to control their symptoms, a number of possible strategies have been proposed. These fall into 'step-up' regimes from antacids via H_2-receptor antagonists to PPIs, only those patients remaining symptomatic receiving more powerful therapy, or 'step-down' from PPI to antacid via H_2-receptor antagonists, with the aim of obtaining good symptom control at the first outset. The role of prokinetics is less clear, being much less commonly used in the UK than in other European countries. Possible strategies include using them first-line in patients with 'dysmotility-like' dyspepsia (predominant nausea, bloating and belching), or trying them after acid suppression had failed.

Established NUD

Whatever the most appropriate strategy for managing dyspepsia, a majority of patients with persistent symptoms will eventually undergo either upper gastrointestinal endoscopy or a barium meal examination. The result will be normal in over 50% of patients[8] and, in the presence of a normal ultrasound scan, these patients will be classified as having NUD.[62] The pathophysiology of this condition is, unfortunately, poorly understood and its treatment uncertain.[63] There are a number of reasons why the evidence for the effectiveness of NUD therapies is somewhat conflicting. There is a large placebo response in patients with NUD and the length of follow-up required to establish an effect (especially in patients receiving *H. pylori* eradication) is uncertain. Furthermore, few studies have used rigorously validated outcome measures.[64] It is important to perform a systematic review of the effectiveness of NUD therapies in order to highlight areas of uncertainty and to establish the most appropriate treatments. Reviews on the use of prokinetics,[65] H_2-receptor antagonists[66] and *H. pylori* eradication therapy[67] have been published but not all have used rigorous search strategies or clearly outlined methods for the assessment of studies.

In addition, NUD encompasses a number of symptom clusters which may be clinically important and respond to different treatments. Some patients describe symptoms suggestive of PUD although no ulcer is present (ulcer-like dyspepsia), while others have symptoms consistent with GORD (reflux-like dyspepsia). Other patients may have symptoms suggestive of gastric stasis (dysmotility-like dyspepsia), while yet others do not fall into any of these classifications (unspecified dyspepsia). Reports suggest that drug therapies may be effective in only some of these subgroups of NUD.[3] Unfortunately, there are a number of different definitions of these NUD subgroups.[4,68] Moreover, these symptom complexes overlap with each other in 30–100% of cases and individuals may change between these subgroups over time.

Possible pathophysiology of NUD

There have been a variety of putative pathophysiological mechanisms that could contribute to dyspeptic symptoms. Factors that have been studied include gastric acid secretion, gastroduodenal motility and visceral hypersensitivity.

Evidence for gastric acid secretion abnormalities

Symptoms of patients with NUD can be remarkably similar to those with PUD. Patients with duodenal ulcer have increased gastric acid secretion so it is logical to suggest that this may also be an important factor in NUD. Studies evaluating this have consistently reported that basal and peak acid output in NUD patients is similar to controls,[69] and symptoms have not been reproduced by acid infusion at endoscopy.[70] The evidence that gastric acid has an important role in NUD is therefore weak, yet drugs aimed at reducing gastric acid secretion are commonly prescribed for this condition. Antacids have usually been no more effective than placebo in controlled trials,[71] while a large number of trials investigating H_2-receptor antagonist therapies have given discordant results.[72,73] PPIs have been less well evaluated but preliminary evidence suggests they may be beneficial.[74] Mucosal protecting agents such as misoprostol, sucralfate and bismuth salts have been used in NUD.[75] Evidence from randomised trials has again been conflicting and, in the case of bismuth salts, has been

compounded by the possibility that their effect may be due to suppression of *H. pylori*.[76,77]

Evidence for disorders of gastroduodenal motility

Patients with NUD often complain of abdominal distension, early satiety, belching and nausea. Such symptoms are consistent with delayed gastric emptying and several techniques have been used to evaluate the association between NUD and disorders of upper gastrointestinal motility.[78] Gastric emptying of a radio-labelled meal is delayed in 30–80% of patients with NUD.[79] This wide variation reflects the lack of a gold standard for measuring gastric emptying, although most studies report that it is abnormal in at least some patients with NUD.[78] This is supported by gastrointestinal manometric studies in which antral hypomotility is present in 25–70% of patients, which correlates with the degree of gastroparesis.[80] Emptying of solids is affected to a greater extent than liquids. However, NUD is often subdivided into 'ulcer-like', 'reflux-like' and 'dysmotility-like' dyspepsia based on symptom patterns. Delayed gastric emptying would be expected to predominate in the dysmotility-like group but the data do not support this hypothesis. Indeed, no motor abnormality is found in 30–50% of patients with dysmotility-like NUD.[81] A number of double-blind, placebo-controlled trials have suggested that prokinetic agents are beneficial[71,82] but this was not a universal finding.[83] One report suggested that cisapride was more effective than metoclopramide in treating NUD[84] but evidence for this is conflicting.[85]

Evidence for abnormal visceral hypersensitivity

Visceral hypersensitivity was proposed as a putative mechanism that might explain the significant number of patients with NUD with no evidence of dysmotility.[86] The pain threshold for gradual intragastric balloon distension is lower in NUD patients compared with normal controls, with 50% of dyspeptic patients describing pain at physiological balloon volumes.[86] This is similar to findings in irritable bowel syndrome and, indeed, the two disorders can coexist, which suggests that there may be a subset of individuals with abnormal visceral perception.[86] In case–control studies it has been reported that patients with NUD are more anxious and depressed compared with healthy controls or patients with ulcers, and also have less mature stress-coping mechanisms.[87] Non-pharmacological therapies such as behavioural therapy and psychotherapy have therefore been tried in NUD but there are few controlled trials in this area.[88]

Evidence for the role of H. pylori *in NUD*

There is unequivocal evidence that *H. pylori* is the main cause of both gastric and duodenal ulceration. The organism is present in 85–95% of patients with PUD compared with a prevalence of 30–40% in the normal population.[89] Treatment of the infection is as effective as acid suppression in healing peptic ulcers and results in permanent cure of the disease, whereas 60–80% of patients relapse within 1 year if treated with anti-secretory therapy alone.[90] The evidence for an association between *H. pylori* and NUD is less clear.[91] *H. pylori* induces chronic inflammation in gastric mucosa and this is likely to be associated with disturbed gastric physiology. Fasting and meal-stimulated gastric acid output is increased in *H. pylori*-positive patients with duodenal ulcer compared with uninfected normal controls.[92] Studies assessing the effect of *H. pylori* on gastric dysmotility are conflicting, and any difference between infected and uninfected patients is likely to be small.[93] There is also no evidence that *H. pylori*-infected NUD patients have altered gastric visceral perception compared with uninfected NUD controls.[94]

Studies have suggested that *H. pylori* infection is more common in NUD patients compared with asymptomatic controls, but this is not a universal finding. A review of the literature and meta-analysis suggested *H. pylori* was a risk factor for NUD (odds ratio (OR), 2.3; 95% confidence interval (CI), 1.9 to 2.7),[67] but the choice of control groups in some of the studies included in the review were inappropriate.[95] *H. pylori* prevalence increases with age, and is more common in patients from developing countries and of lower socio-economic status. Most studies did not control for these factors in the analysis, which could have accounted for the apparent association between *H. pylori* and NUD. An Italian study reported that spouses of infected ulcer patients had an increased prevalence of *H. pylori*. Dyspepsia was more common in *H. pylori*-positive spouses compared with an *H. pylori*-negative control group but these findings could be due to confounding factors.[96]

Initial therapy for *H. pylori* infection consisted of one antibiotic or bismuth salts. This temporarily reduced infection load so that the organism was difficult to detect, but this 'clearance' rarely led to cure as *H. pylori* was usually found again within 1 month of treatment. Early trials using these suboptimal therapies were therefore unlikely to demonstrate a benefit for *H. pylori* eradication therapy in NUD. *H. pylori* eradication is more

consistently achieved with a combination of either anti-secretory therapy or bismuth salts with any two of the following antibiotics: clarithromycin, amoxycillin and 5-nitroimidazole.[97] Such regimens usually achieve eradication rates in excess of 85% in clinical trials[97] and are therefore more appropriate treatments for evaluation in RCTs evaluating the role of *H. pylori* in NUD.

Chapter 2

Questions addressed by this review

Questions addressed by systematic review

The questions addressed by this review fall into two areas.

The management of uninvestigated dyspepsia in primary care

1. How effective is the initial pharmacological therapy?
2. How effective is early endoscopy?
3. How effective is *H. pylori* screening before endoscopy in patients with dyspepsia?
4. How effective is *H. pylori* screening before eradication therapy in patients with dyspepsia?
5. Does subdividing dyspepsia on the basis of symptom patterns, predict response to particular therapies?

Therapy for proven NUD

1. How effective is pharmacological therapy?
2. How effective is *H. pylori* eradication?

Questions addressed by modelling

Cost-effectiveness of management strategies for dyspepsia in primary care and therapies for NUD were examined using modelling. The following questions were addressed.

1. What are the most cost-effective combinations of initial investigation strategy and prescribing for the management of uninvestigated dyspeptic patients in primary care?
2. What is the most cost-effective therapy for established NUD?
3. What are the most important strategies for managing dyspepsia in primary care to compare in future trials?
4. What are the most important therapies to compare in the treatment of NUD?

Chapter 3

Review methods

In line with accepted systematic review methodology formalised by the Cochrane Collaboration,[98] searches for relevant papers and the subsequent assessments of their value were systematic and comprehensive. A decision was taken early on to include unpublished data, if possible, in order to reduce publication bias. Although there has been some debate about this,[99] there is good reason for including unpublished data when available.[100] The reviews of management strategies for undiagnosed dyspepsia (hereafter referred to as the primary care review) and *H. pylori* eradication and pharmacological therapy for NUD (hereafter referred to as the NUD reviews) were conducted separately. The underlying principles of a standardised and reproducible process were maintained throughout, although the nature of dyspepsia as well as the particular interests of the review necessitated some variations. Standardised methodologies were tailored as described below. A summary of the eligibility criteria is presented in *Table 1*.

Definition of dyspepsia

Many definitions have been used over the years but the two most important are the following.

1. Working Party criteria (1988)[2]

Dyspepsia was defined as any symptom referable to the upper gastrointestinal tract lasting for more than 4 weeks. Symptoms could also be pooled into subgroups that reflected the most likely underlying pathophysiology and these subgroups could guide therapy. The subgroups were:

(I) reflux-like (heartburn and acid regurgitation predominant)
(II) ulcer-like (epigastric pain predominant)
(III) dysmotility-like (nausea, belching and early satiety predominant)
(IV) non-specific dyspepsia.

TABLE 1 *Summary of eligibility criteria for inclusion in the specified reviews*

Review	Population	Intervention and comparison	Study type	Outcomes
Primary care management of dyspepsia	Any uninvestigated patient presenting to a centre of primary care	Any form of: empirical acid suppression therapy; early endoscopy (with or without screening questionnaire); *H. pylori* screening followed by endoscopy of patients with positive results; *H. pylori* screening followed by eradication therapy for patients with positive results **Comparison**: placebo, another therapy, another investigative strategy	RCT and controlled cohort	Any one of: quality of life; individual dyspepsia symptoms or symptom scores; patient acceptability; consultation rates for upper GI tract; referral rates for upper GI tract; prescribing of PPI or H_2-receptor antagonist; diagnostic findings; costs
Pharmacological treatment for NUD	Patients with dyspepsia and negative investigations	Any one of the following six classes of drugs in the management of NUD: antacids; H_2-receptor antagonists; PPIs; prokinetics; mucosal protecting agents; antimuscarinics **Comparison**: placebo, another drug	RCTs	Any one of: individual dyspepsia symptom scores; global symptom scores; quality-of-life measurement
H. pylori eradication therapy for NUD	Patients with dyspepsia and negative investigations	Treatment recognised as one of: dual therapy; triple therapy; bismuth-based triple therapy; quadruple therapy **Comparison**: placebo, another drug	RCTs	Any one of: individual dyspepsia symptom scores; global symptom scores; quality-of-life measurement

2. Rome criteria (1991), updated (1999)*
This definition is similar to that above, but patients with predominant reflux symptoms (heartburn and acid regurgitation) were excluded. The rationale was that reports suggested that the majority of patients with reflux symptoms had evidence of GORD. Patients should only be defined as having chronic dyspepsia if symptoms persisted for more than 12 weeks and were present for at least 25% of the time.

The Rome criteria are very useful for research purposes but do not coincide with the conceptual framework that GPs follow; hence, this review included all studies meeting the Working Party definition. However, trials using the Rome criteria were not excluded because patients meeting these criteria would also meet those of the Working Party.[2]

Dyspepsia in primary care

Population

Patients presenting to a centre for primary care with dyspeptic symptoms that fulfilled one of the four following criteria:

- either of the published consensus definitions for dyspepsia detailed above
- a number of symptoms from a list of symptoms relating to the upper abdomen
- any dyspeptic symptom clearly pre-specified by the authors
- not selected on the basis of previous investigations.

Intervention

Although the aim of the review was to identify as many interventions as possible, in order to avoid selection bias it was necessary to be clear about which interventions were to be evaluated prior to inclusion in the analysis. These were therefore outlined in the eligibility assessment. Interventions to be included were identified from preliminary searches as follows:

- empirical acid suppression therapy
- early endoscopy (with or without a screening questionnaire)
- *H. pylori* screening followed by endoscopy of patients with positive results
- *H. pylori* screening followed by eradication therapy for patients with positive results.

Control group

Studies, including randomised trials and controlled cohort studies, were eligible for inclusion if any type of control group was used as a comparison to the intervention.

Outcomes

The difference between the intervention and control groups in terms of outcomes was assessed under the following headings:

- **quality of life –** any instrument that was designed to assess quality of life was included
- **individual dyspepsia symptoms or symptom scores –** any measure that assessed symptoms or assigned a score based on symptoms was included
- **patient acceptability –** any assessment that examined the satisfaction of patients was included
- **consultation rates for upper gastrointestinal tract –** comparisons of consultation statistics (e.g. frequency, rates, or total numbers of consultations) were identified for inclusion
- **referral rates for upper gastrointestinal tract –** trials that assessed the difference in rates of referral between intervention and control were deemed eligible
- **prescribing of PPIs or H_2-receptor antagonists –** any outcome that assessed the differential rates of prescribing for symptom control over and above the intervention (if it included a prescription) was selected
- **diagnostic findings –** trials with comparisons of the variation in diagnoses before and after the trial were included in the analysis
- **costs –** if costs were analysed, the trial was accepted as eligible; this was to ensure that there was sufficient data for the modelling section of the review, as well as to allow cost-effectiveness assessments to be made.

Pharmacological treatment for NUD

Definition of NUD

Patients with dyspepsia and negative investigations were defined as having NUD (functional, essential, idiopathic or flatulent dyspepsia are synonymous terms for the condition). The definition requires further clarification of the terms ‘dyspepsia’ and ‘negative investigation’.

* Rome II. The functional gastrointestinal disorders (2nd edition). Drossman DA, editor. US Library of Congress, 1999.

Definition of negative investigation

NUD excludes patients with organic pathology. A barium meal investigation or upper gastrointestinal endoscopy can exclude PUD. Endoscopy can also diagnose oesophagitis but acid reflux can occur without any evidence of mucosal damage and the majority of patients with GORD will have a normal endoscopic examination (endoscopy-negative reflux disease). Oesophageal pH studies over 24 hours are more accurate but are not freely available, and few NUD trials have used them to exclude patients.

Gallstones and pancreatic pathology can cause upper gastrointestinal symptoms and NUD patients should ideally have a normal upper abdominal ultrasound and computed tomography (CT) scan. Pharmacological therapies for NUD do not improve symptoms of gallstones or pancreatic disease. Trials in which these investigations were not undertaken would therefore remain valid although less precise because a few patients with pancreatic or biliary disease could be included.

Thus, NUD was defined as dyspepsia with insignificant findings at endoscopy or barium meal, that did not require patients to have 24-hour oesophageal pH studies, upper abdominal ultrasound or CT scans. Patients with hiatus hernia, less than five gastric erosions or mild duodenitis could be included, as these lesions do not correlate with dyspepsia symptoms.

Population

Adult patients (aged 16–80 years) presenting in secondary care with a diagnosis of NUD. All patients must have had either an endoscopic or barium meal examination to exclude PUD.

Intervention

The effectiveness of the six different classes of drugs was reviewed, compared with (a) placebo and (b) any one of the other six classes of drugs in the management of NUD. The drugs included are as follows:

- antacids (details of the search for antacids included a large number of brand names: see search strategies (appendix 1)
- H_2-receptor antagonists including: cimetidine, famotidine, nizatidine and ranitidine
- PPIs including: omeprazole, lansoprazole and pantoprazole
- prokinetics including: cisapride, domperidone and metoclopramide
- mucosal protecting agents including: colloidal bismuth compounds, misoprostol and sucralfate
- antimuscarinics including: pirenzepine.

The effectiveness of psychological interventions compared with placebo in the management of NUD was also considered.

Outcomes

The clinical benefits and efficacy of six different drugs in the management of NUD included assessment of the following parameters.

Individual dyspepsia symptom scores

Individual dyspepsia symptom scores were assessed, including: epigastric pain/discomfort, postprandial fullness, early satiety, anorexia, vomiting, bloating, flatulence, belching, eructation, heartburn and acid regurgitation. To allow synthesis of the results, data were dichotomised into 'improved' or 'not improved' according to the criteria outlined in *Table 2*.

TABLE 2 *Split of outcomes for dichotomous data in the review*

Dyspepsia symptom scores grading found in different trials				
	Good outcome		**Poor outcome**	
	No	Mild	Moderate	Severe
	Excellent	Good	Fair	Poor
Marked improvement	Moderate improvement	Minimal improvement	Unchanged	Deteriorated
Very good	Good	Very bad changes to bad	Bad	Very bad
	Resolved	Improved	Unchanged	Worse
	Symptom free	Improved	No change	Worse
	Improved		Not improved	
	Asymptomatic		Symptomatic	

Global symptom scores

These data were expressed in dichotomous format, as shown in *Table 2*.

Quality-of-life measurement

Any validated quality-of-life instrument, including psychological general well-being (PGWB), gastrointestinal symptoms rating scale (GSRS), Short Form 36 (SF-36), Glasgow severity dyspepsia score, and others if relevant.

H. pylori eradication therapy for NUD

Population

Adult patients (aged 16–80 years) presenting in secondary care with diagnosis of NUD. All patients must have had either an endoscopic or barium meal examination to exclude PUD.

Intervention

Effective *H. pylori* eradication therapy (as defined in *Table 3*) versus placebo or acid suppression.

Outcomes

Dyspeptic symptoms or quality of life as an outcome, using a previously validated measure, as for the pharmacological therapy review.

Search methods

Electronic searches

Databases

Although the literature to support the practice of multiple database searching is relatively sparse, it is generally accepted that several databases must be searched for maximal sensitivity.[101–106] A total of nine electronic databases were searched, as follows.

Primary care management of dyspepsia – Cochrane Controlled Trials Register; Cochrane Database of Systematic Reviews; MEDLINE; EMBASE; CINAHL (Cumulative Index of Nursing and Allied Health); SIGLE (System for Information on Grey Literature in Europe); Integrated Science Citation Index (via Bath Information and Data Services (BIDS)).

Treatment of NUD – Cochrane Controlled Trials Register; Cochrane Database of Systematic Reviews; MEDLINE; EMBASE; CINAHL; AMED (Allied and Complementary Medicine database); SIGLE; PsycLIT.

Terms and strategy

Indexing terms differ between databases, so the exact terms used differed for each database searched, as well as for the two reviews. A generic model of the search (*Figure 1*) was developed to provide uniformity for the separate reviews. Specific search strategies were developed from this generic model by selecting the most appropriate equivalent terms from the thesaurus of each database.

Because of both the quality of research found on preliminary searches and the different questions addressed by the reviews, the strategies between the reviews had to differ quite considerably. In the primary care review of dyspepsia management, RCTs were uncommon while other study designs were frequently used. In the NUD reviews, research was extensive with many RCTs. Following an initial broad search identifying all dyspepsia research, different filters were applied to limit the search set. In the primary care review, this focused on primary care investigation and economic terms. For NUD, the limiting strategy was that designed by the Cochrane Collaboration to select RCTs only.

More details of the terms included within each of the larger groups for primary care and NUD are presented in *Tables 4* and *5*.

The specific search terms for MEDLINE, EMBASE, CINAHL and PsycLIT in each of the reviews, including their limiting strategies, are set out in appendix 1.

TABLE 3 H. pylori *eradication regimens judged as effective for the review*

Type of regimen	Definition
PPI dual therapy	PPI + either amoxycillin or clarithromycin for 2 weeks
New triple therapy	PPI, H_2-receptor antagonist or ranitidine bismuth citrate with two out of three of: amoxycillin, clarithromycin, 5-nitroimidazole, for at least 1 week
Standard triple therapy	Bismuth salt with two out of three of: tetracycline, amoxycillin, metronidazole, for at least 1 week
Quadruple therapy	PPI + standard triple therapy

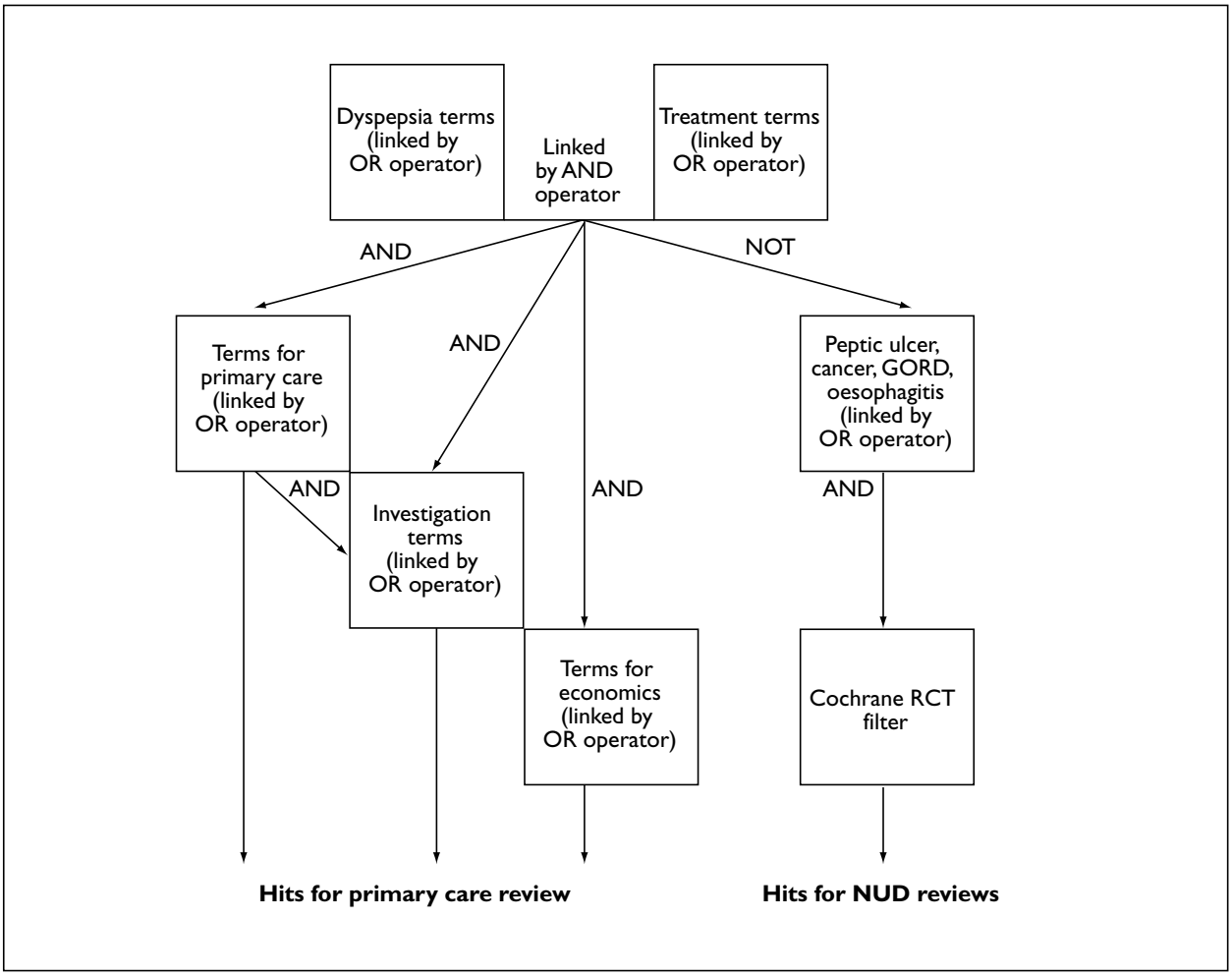


FIGURE 1 *Generic search strategy for database searches*

TABLE 4 *Categories within different search groups for the dyspepsia in primary care search*

Dyspepsia terms	Treatment terms	Investigation terms	Economics terms
Symptoms of dyspepsia	Therapeutic group names	Indexed endoscopy and *H. pylori* tests	Decision support techniques
Signs of dyspepsia	Individual drug names	Text word for endoscopy, serology and *H. pylori* tests with 'wild characters'	Economic indexed terms
Differential diagnoses	Combination therapy	Text word combinations	Text word equivalents with 'wild characters'
Text word equivalents with 'wild characters'	Text word equivalents with 'wild characters' Text word combinations	Text word combinations	Text word combinations

All searches were run from the earliest date available (1966 for MEDLINE, 1988 for EMBASE and 1982 for CINAHL) until the present date of the search. Because of variations in the speed at which different databases are updated, the dates of the most recent papers available for searching varied by 1 or 2 months between databases. This is a universal problem for systematic reviews and means that some very recent papers will be missed even though they are in print.

All languages and indexed journals were included. Each search was run twice (August 1998 and January 1999). All retrieved citations were downloaded electronically into a Reference Manager™ (v. 8.5) file, as detailed below.

TABLE 5 *Categories within different search groups for the NUD search*

Dyspepsia terms	Treatment terms
Symptoms of dyspepsia	Therapeutic group names including *H. pylori* eradication
Signs of dyspepsia	Individual drug names
Differential diagnoses including *H. pylori*	Combination therapy
Text word equivalents with 'wild characters'	Text word equivalents with 'wild characters'
Text word combinations	Text word combinations

Citations

Following the general searches in the primary care review, specific searches were made in Integrated Sciences Citation Index. These citation searches were for specific authors and major papers identified in the previous searches. Details are given in *Table 6*.[20,21,28,107–134]

TABLE 6 *References of citations searched with Integrated Science Citation Index*

Bodger, *et al.*, 1996[107]	Heikkinen, *et al.*, 1996[134]
Briggs, *et al.*, 1996[20]	Hungin, 1995[109]
Brun, 1996[110]	Hungin, *et al.*, 1994[113]
Bytzer, 1996[114]	Hungin, *et al.*, 1995[111]
Bytzer, *et al.*, 1994[116]	Jonsson, 1994[115]
Bytzer, *et al.*, 1995[112]	Mucklow, *et al.*, 1996[117]
Campbell, 1994[118]	Muris, *et al.*, 1994[119]
Cromwell & Pasricha, 1996[120]	Numas, *et al.*, 1994[121]
Fendrick, *et al.*, 1995[25]	Patel, *et al.*, 1995[21]
Fennerty, 1995[122]	Roberts & Bateman, 1995[123]
Fraser, *et al.*, 1996[124]	Sena, *et al.*, 1994[125]
Freston, 1994[126]	Silverstein, *et al.*, 1996[127]
Halter, 1996[128]	Sonnenberg, 1996[129]
Heading, *et al.*, 1995[130]	Talley, 1996[131]
Heatley, 1994[132]	Thompson, 1995[133]
Heikkinen, *et al.*, 1995[108]	

Expert contacts

Experts in the field of dyspepsia known to the review team via the Cochrane Upper Digestive and Pancreatic Group and the Dyspepsia Trials Collaborators Group were also contacted. The group has maintained a prospective register of primary-care dyspepsia trials for the past 5 years by contact with presenters, funders and searching national trial databases. They were asked for any information on trials or papers of which they had any knowledge. Furthermore, these experts were also asked for any information on trials relating to dyspepsia in which they were currently involved. With respect to the confidentiality of the replies, an assurance was given that further use of any data supplied would only occur with the permission of the supplier. A full list of expert contacts is given in appendix 1.

In an attempt to be comprehensive, the editors of several major journals (*Table 7*) were contacted and asked for information on any papers in print or undergoing peer review.

Pharmaceutical companies

All the major pharmaceutical companies (see *Table 8*) with products in the gastroenterological field were contacted for any data on trials, published or unpublished. As with the expert contacts, an assurance was given about the confidentiality of the data received.

Reference management

For each review, all citations retrieved from all sources were saved and downloaded into the Reference Manager file. The software was set to check automatically for duplicate entries, based on the journal title, date, start and end pages, and volume number, when importing citations from the source. Any citations retrieved from sources that did not provide electronic downloading were entered by hand in the same format as the electronic citations. The completed file was further checked by hand, analysing by date, author, journal and title to exclude any duplicated references.

Once the database was loaded with all the references from the different sources, it was refined by hand. A manual search by one reviewer was made of all the references to exclude any irrelevant papers. Papers were judged to be irrelevant when they did not focus on the area of review. For example, despite all the filters for tests, many papers covering colposcopy were identified in

TABLE 7 *Journals contacted for unpublished papers*

Alimentary Pharmacology and Therapeutics
American Journal of Gastroenterology
American Journal of Medicine
Annals of Internal Medicine
British Journal of Clinical Practice
British Journal of General Practice
BMJ
Canadian Journal of Gastroenterology
Current Therapeutic Research
Digestion
Digestive Diseases and Sciences
Digestive Endoscopy
European Journal of Gastroenterology and Hepatology
European Journal of General Practice
Family Practice
Gastroenterology
Gastroenterology International
Gut
Helicobacter
International Journal of Gastroenterology
Italian Journal of Gastroenterology
JAMA
Journal of Clinical Gastroenterology
Journal of Gastroenterology
Journal of Gastroenterology and Hepatology
Lancet
New England Journal of Medicine
Scandinavian Journal of Gastroenterology

TABLE 8 *Pharmaceutical companies contacted for information*

Pharmaceutical company	Product
Abbot Laboratories	Klaricid®
Antigen Pharmaceuticals (UK)	Metoclopramide
Ashbourne Pharmaceuticals	Gastroflux®
AstraZeneca Pharmaceuticals	Losec®
Chugai Pharma UK	Antepsin®
Cox Pharmaceuticals	Metoclopramide
CP Pharmaceuticals	Metoclopramide
Eli Lily & Co	Axid®
Glaxo Wellcome UK	Zantac®
Hansam Healthcare	Pro-Banthine®
Janssen-Cilag	Prepulsid®
Knoll	Protium®
Lagap Pharmaceuticals	Parmid®
Merck Sharp & Dohme	Pepcid®
Monmouth Pharmaceuticals	Maxalon®
Norton Healthcare	Metoclopramide
Pfizer	Fasigyn®
Reckitt & Colman Products	Gaviscon®
Rhone-Poulenc Rorer	Flagyl®
Sanofi Winthrop	Motilium®
Searle	Cytotec®
Seton Healthcare Group	Gastrocote®
SmithKline Beecham Pharmaceuticals	Tagamet®
Wyeth Laboratories	Zoton®
Yamanouchi Pharma	De-Nol®

the primary-care searches. These were excluded by hand. A second reviewer cross-checked by repeating the process for a number of original citations and comparing the results. The resulting list of citations was deemed to be the set of included papers for further processing.

Assessment of eligibility

Prior to selection of any studies for inclusion in the review, definite criteria were established to limit selection bias. These were set out in the form of eligibility criteria for identified potential papers. The criteria consisted of acceptable features relating to areas of trial design as follows: setting of the study (primary or secondary care); source of the patients (primary or secondary care); type of intervention; outcomes measured; comparison group used. These were standardised into eligibility forms that were applied to each of the included papers based on the agreed criteria. Two reviewers independently completed forms for each paper. As there is still some debate about blinding of assessors to the identity of the authors of each trial,[135–137] and in view of the estimated time and resources that such blinding would take,[135] assessors were not blinded when filling out eligibility forms. The results were then compared. If there was disagreement, a third reviewer completed a form and then the three decided jointly whether to accept or reject the paper. A kappa score was calculated to test assessor agreement.

Only those papers that passed the eligibility criteria were included for assessment of quality and data extraction.

Assessment of quality and data collection

Quality (validity) testing

Once a decision had been made to include a paper for data extraction, a test was made of the paper's quality with reference to the aims of the review. To standardise this and avoid bias, the test was pre-specified. It considered elements of the design and publication of the trial as described below. Because the primary care review was designed to include trials with any control group, it was not possible to design any scoring system for this test of quality that allowed for all the possibilities. However, the NUD review did score the trials on quality as detailed in *Table 1*.

Duplication of publication – the results of some trials may have been published several times but in different formats. This test aimed at avoiding the inclusion of trial results more than once in the review.

Randomisation – the process of randomisation was tested to clarify the quality by looking at the following: allocation truly random (random numbers, coin toss, shuffle, etc); allocation quasi-random (e.g. patient number, date of birth); allocation systematic (alternate); method of randomisation not stated or unclear.

Concealment – the quality of the concealment of allocation of treatment category to the patient was tested as a measure of avoidance of allocation bias. The following were considered: concealment adequate (central allocation at trials office or pharmacy, sequentially numbered or coded vials or other method by which the trialist allocating treatment could not be aware of the treatment); concealment inadequate (allocation was alternate – by patient, day of the week, admission ward, or based on information, such as date of birth, already known to the trialist); concealment unclear (inadequate information given).

Masking – the degree of masking of the outcome assessor to the patients' treatment allocation was tested as a test of assessment bias by considering the following: trial described as 'double-blind' treatment allocation masked from participants (either stated explicitly or an identical placebo used); treatment allocation masked from clinicians; treatment allocation masked at outcome assessment.

Completeness of the trial – account was taken of the completeness of the trial in terms of the number of drop-outs and the handling of data relating to these individuals. Intention-to-treat trials, in which the outcomes from drop-outs were included in the final analysis, were considered to be the best in quality.

Data collection

Authors of publications available only as abstracts and of those in which the data were unclear were contacted by mail for detailed results or clarification. Data from eligible trials were collected on a set extraction sheet. This included: trial details, such as which interventions were being tested; data relating to the quality tests, trial demographics and baseline measurements; and any of the prespecified outcome scores. All data collected from the eligible papers were entered into RevMan© software (v. 3.1 followed by v. 4.0.1, supplied by the Cochrane Collaboration) for analysis.

Statistical methods

Categorisation of outcome measures

Meta-analysis methods are widely available for two types of data: binary and continuous. However, many of the outcomes encountered in this review were ordinal outcomes, such as dyspepsia rating scales, quality-of-life scales, Likert scales indicating degree of recovery, and symptom scores. To combine these outcomes, they were either transformed to binary scales or were assumed to have numerical properties similar to continuous data and treated as such. The shorter ordinal scales (generally with less than ten categories) were dichotomised, reducing the categories to 'good' and 'bad' outcomes. This was only possible when the numbers in each category were reported in the original publication. Longer scales, such as quality-of-life assessments, were combined as if they were continuous data. This involved consideration of differences in the mean values between the two groups, which was unlikely to be misleading providing the distributions of the observations were not seriously skewed.

Direct and indirect comparisons

For clinical problems with several treatment options, it is common to find that many pairwise comparisons between treatments have not been evaluated in randomised trials, as it is not possible

to conclude which treatments are the most effective solely on the basis of the randomised comparisons. However, if all the treatments have been compared in randomised trials with a standard alternative (typically a placebo), indirect estimates of relative effectiveness can be derived by comparing summary treatment effects estimated from the pooled randomised comparisons between each drug and the common comparator. Estimates of indirect effects and their CIs are best obtained from meta-regression analyses. Interpretation of indirect comparisons must be undertaken with caution, as it is possible that apparent differences between treatments reflect variation in other known and unknown factors, which vary between trials. Possible sources of confounding include variation in the mode of treatment delivery, patient case-mix, duration of therapy, method of outcome assessment and the degree of rigor with which the trial is conducted.

Methods of pooling binary outcomes

Fixed effect models were used for pooling data to obtain a pooled relative risk (RR) unless significant heterogeneity was present when the random effects model was adopted. Binary data were pooled using Mantel–Haenszel fixed effect methods and the DerSimonian and Laird random effects model. For continuous outcomes, the inverse variance (Woolf's method) model was used as the fixed effect method, and the DerSimonian and Laird method for the random effects.

Calculation of numbers-needed-to-treat

The number-needed-to-treat (NNT) was calculated using the RR reduction. For a given baseline event rate (*BR*), and RR reduction (*RR reduction* = 1 – RR × 100), the number of patients needed to be treated to prevent one event is given by:

$$\text{NNT} = 1/(\textit{RR reduction} \times \textit{BR})$$

The 95% CIs for the NNT were calculated by substituting the RR reduction with its lower and upper confidence limits in the above equation. It should also be noted that the uncertainty in these CIs ignores uncertainty in the estimate of baseline risk, assuming that this value to be fixed and known. To ensure that comparisons of NNTs can be made on a level footing, they have been calculated assuming the same baseline event rate within each section of the review. A 'typical' baseline event rate has been estimated from the observed control group event rate across all treatments considered. The number-needed-to-harm (NNH) refers to NNTs calculated from absolute risk reductions when the CI crosses zero, that is, the potential for an adverse effect cannot be excluded. NNTs from these reviews should be considered as aids to interpretation of the size of treatment effects, the analysis of differences in RR (see direct and indirect comparisons below) being preferable for formal analysis of the significance of differences between treatments.

Methods for pooling continuous outcomes

If the outcome was a continuous measure, the number of patients, the mean response and its standard deviation (SD), were required for both intervention and control groups. Hedges' adjusted *g* has been used to calculate standardised mean differences, expressing the treatment effect in units of SD. Some authors have proposed guides that suggest that changes of the order of 0.5 SD are large enough to be of clinical interest. Alternatively, a standardised mean difference can be back-transformed to the original measurement scales by multiplying by the mean observed SD in the trials for each scale. Once converted into traditional units, judgements of clinical significance can be made.

Methods for investigating heterogeneity

Meta-regression is a statistical technique that investigates patterns in the summary statistics from the trials according to trial-specific covariates. The covariates can be categorical (such as the type of drug) or continuous measurements (such as the percentage of the sample with specific symptoms at baseline). Meta-regression will also estimate linear trends across ordered categories. Like the methods of meta-analysis described above, meta-regression weights studies according to measures of the quantity of information that they contain, so that larger studies are generally more influential than smaller studies. Meta-regression was used for two purposes in this review. First, indirect comparisons between treatments have been estimated by pooling all placebo-controlled trials, and using a meta-regression model to estimate the differences between one treatment (the baseline treatment) and every other treatment. The baseline treatment was chosen as being the treatment with the clearest evidence of an effect (judged according to treatment effect and the number of trials available). The meta-regression model included standard zero–one dummy variables for each of the other treatments.

Second, one hypothesis to be tested in this review was that the effectiveness of the treatments

depends on the symptom patterns of the dyspeptic patients included in the trials. Four key symptoms were selected (epigastric pain, heartburn, nausea and early satiety) and data extracted from each study (if possible) on the proportions of patients with each of these symptoms before treatment commenced. This hypothesis was tested by including the percentage, with each of the key symptoms as a covariate, in meta-regression models. Each covariate and drug was considered separately. If there was a relationship between efficacy and symptoms, this model should demonstrate a trend. This approach to investigating the effects of patient characteristics is less powerful than consideration of treatment efficacy in specific subgroups of patients; however, this would require individual patient data to be available for all trials. Undertaking an individual patient data analysis was not feasible, because (a) it was highly unlikely that the data would be available for many of the older trials which had not had continuing follow-up and (b) the trials used different approaches to the baseline assessment and categorisation of patients, so universally accepted subgroups will not exist.

Avoiding multiple inclusion of trial participants

An essential rule in all meta-analysis is to ensure that data from each participant contributes to each meta-analysis only once. This is an important consideration in multi-arm trials and in trials where several patients have undergone multiple measurements. Duplicate publication of results, whether as complete duplication of a trial or as publication of results from single centres involved in a multicentre trial, also contravenes this principle.

Multi-arm trials typically have one control group and several intervention groups, which may, for example, receive different doses of the same drug, or different drugs. Two unsatisfactory methods for including all arms of these trials in the meta-analyses are (i) to combine the treatment arms into a single pooled group and (ii) to enter the trial separately for each treatment arm. The first approach masks the presence of heterogeneity between the treatment arms; the second includes the members of the control group more than once in the analysis. In this review, an adaptation of the second method has been used, in which the events and participants in the control group are divided equally between each of the treatment arms, so that the totals from the meta-analysis tally with the actual number of patients included in the trials. When exact division of events and participants between the groups has not been possible, the remaining one or two events or participants have been allocated to the group that will give the more conservative result.

The problem of multiple measurements can occur when more than one measurement tool has been used within a trial to record a generic outcome. For example, dyspepsia trials may have two measurements of quality of life, one made using a generic quality-of-life tool, and one with a disease-specific quality-of-life tool. Including data on both measurements from that trial in the same analysis will result in inappropriately excessive weight being given to that trial. Throughout this review, to avoid encountering this problem, either one outcome measurement has been selected or results from different scales have been pooled separately.

Methods for investigating bias

In the absence of many forms of bias, a funnel plot of the effect size for each trial against its precision (or sample size) will reveal that the points fall within a 'funnel shape', with trials of low precision (low sample size) displaying more variability around the pooled effect line than those with high precision (high sample size). If systematic biases do exist, for example, publication bias based upon the significance and direction of benefit, the funnel plot will have asymmetry, typically with an absence of small non-significant studies. Egger has proposed a simple test of asymmetry that has been applied in this review. If asymmetry is detected, it can still be difficult to ascertain the mechanism of the bias. One explanation is a standard publication bias, a second is a relationship between study quality and effect size – studies of poorer quality tending to exaggerate treatment effects and to have smaller sample sizes.

Software

RRs, mean differences and standardised mean differences were pooled using the MetaView 3.0 programme distributed with the RevMan 3.01 software (Update Software and the Cochrane Collaboration). Additional analyses investigating heterogeneity and publication bias were undertaken using STATA v. 6.0, using the commands METAREG and METABIAS.

Chapter 4

Interventions for dyspepsia in primary care

Introduction

A number of strategies have been proposed for managing dyspepsia in primary care. These can be broken down into investigative strategies and prescribing strategies, as described in the background. The following initial investigative strategies are considered in this review.

1. None: initial pharmacological therapy and empirical *H. pylori* eradication therapy.
2. Endoscopy: early endoscopy.
3. *H. pylori* test: *H. pylori* screening before endoscopy and *H. pylori* screening before eradication therapy.
4. Treatment with H_2-receptor antagonists, PPIs, antacids and prokinetics are also considered.

The results of the search and hence the available comparisons considered are shown later.

Results of the search

The combined searches yielded 2290 unique references that were registered as potentially eligible for inclusion in the review. As expected, an initial review of these citations revealed that many papers were not relevant to the review. The very wide search strategy for the review ensured that as many references as possible were found; however, it generated large numbers of references at this initial stage. The articles had been published in 119 different journals. From these possible references, 485 were identified as being potentially relevant to the subject by their title or abstract alone. These references were retrieved and subjected to the standardised test for eligibility. Exclusion at this stage was either because they were not primary care papers or they had nothing to do with dyspepsia, or both. Kappa scores were generated from the eligibility forms of the two main assessors according to the treatment regime, as in *Table 9*.

Although it is a useful exercise to check on agreement between assessors in a systematic review, these kappa scores have limited value. The figures are low not because there was poor agreement overall but because there were so few trials included from such a large number that any disagreement at all had a large effect on the figure. This is reflected to some degree by the large CIs. It would be very unusual to have no disagreement but in this situation kappa scores, by virtue of the methods for their generation, cannot give a true picture of the degree of this disagreement.

Studies included in the review

A total of 12 papers were included in the review (see appendix 2 for details), reporting 14 interventions (*Table 10*). Eight were concerned with initial pharmacological interventions, four with early investigation and one each were 'test-and-endoscopy' and 'test-and-treat'. There were 11 RCTs and two controlled cohort studies. In all but two studies, recruitment and randomisation took place in the primary care setting. In the other two trials, patients were recruited in primary care but treatment allocated in a secondary care setting after referral. Studies in which recruitment and randomisation took place among patients already referred for

TABLE 9 *Kappa scores for the two assessors in primary care*

Intervention addressed	Kappa score BD vs. MI (95% CI)
Early investigation in primary care	0.43 (0.03 to 0.84)
Empirical acid suppression in primary care	0.70 (0.44 to 0.95)
H. pylori test-and-endoscope in primary care	0.67 (0.05 to 1.00)
H. pylori test-and-treat in primary care	0.57 (0.12 to 1.00)

BD, B Delaney; MI, M Innes

TABLE 10 *Numbers of comparisons found between the different investigation strategies*

	Prescribe	Endoscope	Test-and-endoscope	Test-and-treat
Prescribe	8			
Endoscope	4 (+ 2 abstracts)	0		
Test-and-endoscope	0 (+ 2 abstracts)	1	0	
Test-and-treat	0 (+ 2 abstract)	1 (+ 1 abstract)	0	0

TABLE 11 *Number of comparisons found between different therapies*

	Antacid/placebo	H_2-receptor antagonist	PPI	Prokinetic
Antacid/placebo				
H_2-receptor antagonist	1	0		
PPI	2	3	1	
Prokinetic	0	0	1	0

investigation were not included, as these patients would not be the same as unselected dyspeptic patients and the results of such secondary care studies could be misleading for primary care. A brief summary of each trial is provided in appendix 2. A further four studies with six comparisons, currently available only as abstracts, are also included in *Table 10*.

There are two types of comparisons – between strategies and of different variations within strategies. Prescribing strategies (i.e. the effectiveness of therapies for dyspepsia) can be considered as one of the latter types. The possible comparisons and the number of studies found are shown in *Table 11*.

It can be seen that there was a lack of studies comparing test-and-endoscope with initial prescribing and test-and-treat with all strategies. Considering possible 'within strategy' comparisons, the largest number of studies compared one medication with another. All placebo-controlled trials allowed open use of antacids. There was a lack of comparison of H_2-receptor antagonists with antacids and only one very recent trial had studied prokinetic agents at all. Trials of cisapride compared with domperidone or metoclopramide in primary care were also notable by their absence. Other possible comparisons might have included endoscopy in different settings, different diagnostic tests for *H. pylori* and different eradication regimes; none were found.

Studies excluded from the review

A total of 30 studies were considered to be eligible for the review, in that they described studies of the management of dyspepsia in unselected patients in primary care, but they were excluded; one paper was a duplicate publication in Danish and 29 were uncontrolled cohort studies. All excluded papers are referenced in appendix 3. The large number of review-style articles, in relation to the few trials with an intervention that exist, is surprising, in that there seemed to be little data on which to base the reviews.

Ongoing studies

There are currently seven ongoing trials of dyspepsia management in primary care. Six of these are due to report during 2000. Data from abstracts for four of these studies, presented at the British Society of Gastroenterology 2000 and Digestive Diseases Week 2000, augmented by additional data from the authors, have now been included in this review.[138–141] As they have not yet been published, detailed comparison is not possible, particularly with respect to the economics data. The effect on dyspeptic symptoms

TABLE 12 *Primary care dyspepsia trials in progress*

Trial name or title	Participants	Interventions	Outcomes	Starting date	Contact information	Notes
ETHER	1000 patients with chronic dyspepsia in primary care	*H. pylori* eradication (omeprazole + clarithromycin + amoxycillin) or omeprazole plus placebo antibiotic	Dyspepsia symptom score. Use of medication for dyspepsia	1997	Dr J Danesh Dept Public Health & Primary Care, University of Oxford, UK	Due to report during 2001
Birmingham Open Access Endoscopy study – early endoscopy in the over-50s	443 patients with dyspepsia aged 50 years and over	Early open access endoscopy vs. empirical acid suppression with selective endoscopy	Dyspepsia symptom score, quality of life, resource utilisation, patient satisfaction	1995	Dr BC Delaney Dept Primary Care & General Practice, University of Birmingham, UK	Awaiting publication
Birmingham Open Access Endoscopy study – *H. pylori* test-and-endoscope in the under-50s	477 patients with more than 4 weeks of dyspeptic symptoms, aged < 50 years	*H. pylori* test (Helisal® near-patient test) and endoscopy if positive, vs. empirical acid suppression	Dyspepsia symptom score, quality of life, resource utilisation, patient satisfaction	1995		Awaiting publication
Trial of endoscopy, *H. pylori* testing or empirical treatment for dyspepsia	762 patients with dyspeptic symptoms, aged 18 years and over; alarm symptoms and NSAID use excluded	1. Early endoscopy 2. *H. pylori* test-and-endoscope 3. *H. pylori* test-and-treat 4. PPI	Dyspepsia symptom score, quality of life, resource utilisation, patient satisfaction	1995	Prof RFA Logan Dept Public Health & Epidemiology, University of Nottingham, UK	Awaiting publication
H. pylori test-and-treat or prompt endoscopy for dyspeptic patients in primary care	Patients consulting GP with dyspepsia of sufficient severity to warrant acid suppression therapy	*H. pylori* test-and-treat and endoscopy if not improved vs. early endoscopy	Symptom diaries, resource utilisation, sick leave days	1996	Dr AT Lassen Odense University Hospital, Denmark	Awaiting publication
Welsh Helicobacter and Endoscopy in Dyspepsia trial (WHENDY)	Patients consulting GP with dyspepsia, aged 18–45 years and testing positive on serology for *H. pylori*	Early endoscopy vs. usual management	Dyspepsia symptom score, quality of life, resource utilisation	1998	Dr P Myres Dept General Practice, UWCM, Wrexham, Wales	Closed due to slow recruitment
Torbay Helicobacter Research Project	Consulting with GP for dyspepsia, aged 18–50 years, acid-related dyspepsia, no previous investigations	1. Empirical acid suppression 2. Early endoscopy 3. *H. pylori* test-and-treat 4. *H. pylori* test-and-endoscope if positive	Symptom scores, symptom-free days, quality of life	1998	Dr J Roberts Royal Devon and Exeter NHS Trust, Torbay, UK	Closed due to slow recruitment

TABLE 13 *Numbers of comparisons between the different investigation strategies for ongoing studies*

	Prescribe	Endoscope	Test-and-endoscope	Test-and-treat
Prescribe	8			
Endoscope	4	0		
Test-and-endoscope	3	2	0	
Test-and-treat	2	3	2	0

is available from the abstract for each of these trials. Two further studies have closed prematurely due to slow recruitment. Limited information, when available from the abstract, has been included in each of the relevant sections. Details of the ongoing studies are shown in *Table 12*. A table of comparisons for the ongoing studies is shown in *Table 13*.

Results of the review

Pharmacological interventions for dyspepsia

Description of studies

Two studies, of similar design,[142,143] have compared a PPI with either open label Gaviscon or Gaviscon and ranitidine. Goves and colleagues[142] recruited 670 patients from 100 UK practices, and Mason and colleagues[143] 703 patients from 131 practices. In Goves and colleagues' study, patients had to have had at least 1 month of acid-related dyspeptic symptoms (defined as heartburn and/or epigastric pain and 'evidence of some benefit' from antacids) and at least 2 days symptoms in the week prior to study entry. Apart from the expected exclusions (pregnancy, NSAIDs, suggestion of malignancy), patients with previously proven 'structural lesions' (peptic ulcer only given as an example) were excluded. Patients were randomised to either omeprazole, 10–20 mg once daily with dose titration at 2 weeks, or Gaviscon, 10 ml four times daily. At 2 weeks, patients in either group could be 'stepped up' to omeprazole, 20 mg once daily. Assessments were made at 2 and 4 weeks. On account of the intervention only being maintained for 2 weeks, only the 2-week assessment was included in the analysis. Outcomes assessed were global relief of symptoms over past 7 days, frequency of individual symptoms in the previous 7 days, PGWB scale and the GSRS.

Mason and colleagues[143] used the same inclusion and exclusion criteria but specified oesophagitis as well as peptic ulcer as exclusions. Patients with symptoms suggestive of irritable bowel syndrome were also excluded. Patients were randomised to omeprazole, 10–40 mg once daily, or Gaviscon, 10 ml four times daily, with or without ranitidine, 150 mg 2–4 times daily. Dose titration was carried out on the basis of symptom response at clinic visits (at 2, 4, 8, 12, and 16 weeks). Outcome measures were self-rated global response, antacid use, and heartburn and epigastric pain at 4 and 16 weeks.

Meineche-Schmidt & Krag[144] recruited 1017 patients aged 18–65 years from 63 practices in Denmark. Dyspepsia was defined using a symptom chart based on the 1998 Working Party criteria;[2] only patients with predominantly reflux-like or ulcer-like symptoms were recruited. Exclusions were pregnancy, risk of malignancy and NSAID ingestion. The patients were divided into two groups on the basis of their history. Group A, those with a history of proven PUD or oesophagitis, were randomised to either omeprazole, 20 mg once daily, or cimetidine, 400 mg twice daily. Group B, patients with no proven diagnosis or non-ulcer, non-reflux dyspepsia, were randomised to omeprazole, 20 mg once daily, or placebo. The assessments at 15 days consisted of a global assessment of symptom improvement and relief of specific symptoms.

Paton[145] randomised 255 patients from 42 UK practices to either ranitidine, 300 mg daily, or Gaviscon, 10–20 ml four times daily. All patients had symptoms of reflux-like dyspepsia; predominant ulcer-like dyspepsia or symptoms suggestive of malignancy led to exclusion. Outcomes – heartburn, overall improvement and quality of life – were assessed at 24 weeks.

Jones and Baxter[146] randomised 450 patients from 32 UK practices to either lansoprazole, 30 mg once daily, or ranitidine, 150 mg twice daily, for 4 weeks. Patients were aged 18–80 years, with either reflux-like or ulcer-like dyspepsia, including proven PUD or oesophagitis. Outcomes, measured at 2 and 4 weeks, were heartburn and epigastric pain, divided into daytime and nocturnal, global improvement and use of antacids. Jones and Crouch[147] also compared lansoprazole, 15 mg daily, with omeprazole, 10 mg daily, over 4 weeks in 562 patients from 52 UK practices. In this study, patients had mild epigastric pain of heartburn only and no previously documented oesophagitis or PUD. The outcome measures were the same as for Jones and Baxter.[146]

Lewin-van den Broek[148] recruited 263 patients aged 18–80 years, consulting 95 Dutch GPs with dyspeptic symptoms. These were randomised into one of three prescribing strategies: omeprazole, 20 mg once daily, cisapride, 20 mg three times daily, or treatment based on symptom patterns in which patients with ulcer-like and reflux-like symptoms received an H_2-receptor antagonist (of the GP's choice) and patients with 'non-specific' (meaning dysmotility-like) dyspepsia were to receive either cisapride or domperidone. The latter strategy is the current guideline of the Dutch College of General Practitioners.

Methodological quality of included studies

All the studies were RCTs but they differed with respect to case definition, blinding and the concealment of allocation.

Definitions and diagnostic criteria These seven papers included data on eight interventions. In only two papers[144,148] was reference made to agreed

definitions of dyspepsia (Working Party 1988;[2] Rome criteria 1991); all other papers used vague terms such as 'ulcer-like' without any evidence of objective diagnostic criteria. Although the aim of several of the studies was to recruit a pragmatic sample of patients presenting to their GPs, the combination of vague case definitions and specific exclusion criteria meant that case-mix might vary considerably between studies.

Case-mix Most of the studies included a mixture of uninvestigated patients, patients with normal endoscopies and predominant epigastric or mixed symptoms (NUD) and patients with normal endoscopies and predominant reflux-like symptoms (endoscopy-negative reflux disease, ENRD) (see *Table 14*). Three studies had a different case-mix. Jones and Baxter[146] included patients with all possible diagnoses, except serious disease, thus including oesophagitis and PUD. In Meineche-Schmidt and Krag's group A,[144] only patients with PUD and oesophagitis were recruited, and Paton[145] recruited only patients with predominant reflux-like symptoms, with and without oesophagitis. In only one study[146] was the frequency of previous diagnoses given: 27 duodenal ulcers and 58 cases of oesophagitis out of 283 patients. Mason and colleagues[143] and Jones and Crouch[147] detailed case-mix by predominant symptom (93%, 75% and 85% had some reflux symptoms, respectively).

Randomisation and concealment of allocation All seven trials were RCTs, but only five[142,144,146–148] reported their method of allocation, and only three of these[144,146,147] the mechanism of sequence generation. One study used a centralised telephone randomisation service.[148] Unless otherwise stated, the sequence generation was by random number and concealment of allocation by a sealed pack with placebo or study drug.

TABLE 14 *Acid suppression in primary care: case-mix*

Study	Included	Excluded	Likely case-mix	Details given
Goves, *et al.*, 1998[142]	Heartburn, epigastric pain	Any organic diagnosis	Uninvestigated, NUD, ENRD	95% had some reflux symptoms
Mason, *et al.*, 1998[143]	Heartburn, epigastric pain	Any organic diagnosis	Uninvestigated, NUD, ENRD	93% had heartburn
Meineche-Schmidt & Krag, 1997[144]	Reflux-like, ulcer-like by symptom pattern scoring	Group A: not investigated or no abnormality on endoscopy; Group B: proven peptic ulcer or oesophagitis	Group A: peptic ulcer, oesophagitis; Group B: uninvestigated, NUD, ENRD	Nil
Paton, 1995[145]	Reflux-like	Ulcer-like only, peptic ulcer or oesophageal stricture/Barratt's	ENRD, oesophagitis	Nil
Jones & Baxter, 1997[146]	Reflux-like, ulcer-like	None	All causes	Ulcer-like alone 25%; reflux-like alone 61%; both 14%. Duodenal ulcer 27; proven oesophagitis 58
Jones & Crouch, 1999[147]	Mild reflux- or ulcer-like symptoms	Peptic ulcer, oesophagitis	NUD, ENRD, uninvestigated	Ulcer-like alone 15%; reflux-like alone 28%; both 57%
Lewin-van den Broek, 1999[148]	Dyspepsia – defined as epigastric pain or discomfort with or without nausea, vomiting, heartburn, regurgitation, early satiety, or post-prandial fullness originating from the upper abdomen	Symptoms suggestive of malignancy, pregnancy, use of medication for dyspepsia in previous 2 weeks	All causes	Reflux-like 57%; ulcer-like 25%; non-specific 18%

Co-interventions Trials also differed with respect to the use of concurrent antacid medication and whether or not dose titration was permitted. While four studies[142,143,146,147] provided top-up antacid and assessed its use during the trial, Meineche-Schmidt and Krag[144] and Lewin-van den Broek[148] allowed the use of OTC antacids and Paton[145] did not mention antacid use. Mason and colleagues[143] and Goves and colleagues[142] allowed dose titration. Goves and colleagues[142] allowed the introduction of omeprazole, 20 mg, in both groups (30% of the alginate group had omeprazole added). Mason and colleagues[143] titrated the omeprazole group, up to 40 mg daily, and allowed the introduction of ranitidine, up to 150 mg four times daily, in the alginate group; in fact, by 16 weeks only 8% of the initial alginate group were not taking ranitidine.

Outcome measures Only three trials were double-blind.[144,146,147] The remainder were open both to patients and assessors of outcomes.

Most trials used short-term follow-up, four at up to 1 month only. In all analyses, the final end-point was used if possible. In one study,[142] only the data at 2 weeks could be used; after this both groups could receive PPIs. The study by Meineche-Schmidt and Krag[144] ran for only 15 days, those by Jones and Baxter[146] and Jones and Crouch[147] for 4 weeks; the study by Mason and colleagues[143] ran for 16 weeks, those by Paton[145] and Lewin-van den Broek[148] for 24 and 52 weeks, respectively. The principal outcome from each trial was 'absence of symptoms' but this differed in how many consecutive days without symptoms were classed as 'complete relief'. For example, it was 7 days in Goves and colleagues' study[142] and 15 days in Meineche-Schmidt and Krag's study.[144]

Drop-outs None of the trials analysed on an intention-to-treat basis. In only two (Jones & Baxter;[146] Paton[145]) was follow-up less than 70%. Lewin-van den Broek followed 94%,[148] Meineche-Schmidt and Krag 98%,[144] Goves and colleagues 89%,[142] Mason and colleagues 79%,[143] and Jones and Crouch 73%.[147] Jones and Baxter followed up only 63%,[146] although drop-outs were similar in each group. Paton's trial[145] was subject to the loss of 97 of 255 (62%) patients recruited during the trial by the 24-week end-point, although the drop-out rate was equal in both groups. The loss to follow-up and the reduction in sample sizes leaves these last two trials at serious risk of bias.

Results

Comparisons were made between:

(i) PPI and alginate/antacid
(ii) PPI and H_2-receptor antagonist
(iii) H_2-receptor antagonist and alginate/antacid
(iv) PPI and cisapride
(v) omeprazole, 10 mg, and lansoprazole, 15 mg.

PPI versus antacid/alginate Two trials could be pooled with 1186 patients (*Figure 2*). Although in one study[144] patients began treatment with a placebo control, they were also allowed to use any antacids purchased from pharmacies, so were pooled with the study by Goves and colleagues.[142]

This meta-analysis showed that PPIs were more effective in reducing dyspeptic symptoms than antacids. The pooled RR reduction for global assessment of PPI versus antacid/alginate was 28% (95% CI, 36 to 20; Z = –6.18; $p < 0.0000001$; heterogeneity test, Q = 1.4, degrees of freedom (df) = 1, $p = 0.2$). For heartburn the effect was greater, RR reduction 48% (95% CI, 40 to 55; Z = –8.93; $p < 0.0000001$; heterogeneity test, Q = 0.002, df = 1, $p = 0.96$), but for epigastric pain there was significant heterogeneity and a random effects model gave a non-significant RR reduction of 16% (95% CI, –37 to 13; Z = –0.96; $p = 0.33$; heterogeneity test, Q = 4.5, df = 1, $p = 0.03$).

PPI versus H_2-receptor antagonist Three RCTs with a total of 1267 patients randomised compared PPI with H_2-receptor antagonist (*Figure 3*). In one study,[143] patients in the control group initially started antacid/alginate but by 16 weeks all but 8% had been stepped up to an H_2-receptor antagonist. This data was therefore pooled with the other studies of H_2-receptor antagonists.

For global improvement, PPIs were more effective than H_2-receptor antagonists in reducing dyspeptic symptoms in patients with dyspepsia but no serious disease. The analysis showed significant heterogeneity (Q = 10.1; df = 2; $p = 0.006$). A random effects model was employed, giving an RR reduction of 36% (95% CI, 51 to 18). PPIs appeared more effective for heart-burn than for epigastric pain. In these cases there was no significant heterogeneity and a fixed effects model was employed giving an RR reduction of 31% (95% CI, 42 to 19; Z = –4.3; $p < 0.0005$; heterogeneity test Q = 2.2, df = 2, $p = 0.34$) for heartburn, and a RR reduction of 54% (95% CI, 43 to 63; Z = –7.38; $p < 0.0000001$; heterogeneity test, Q = 0.25, df = 2, $p = 0.98$) for epigastric pain.

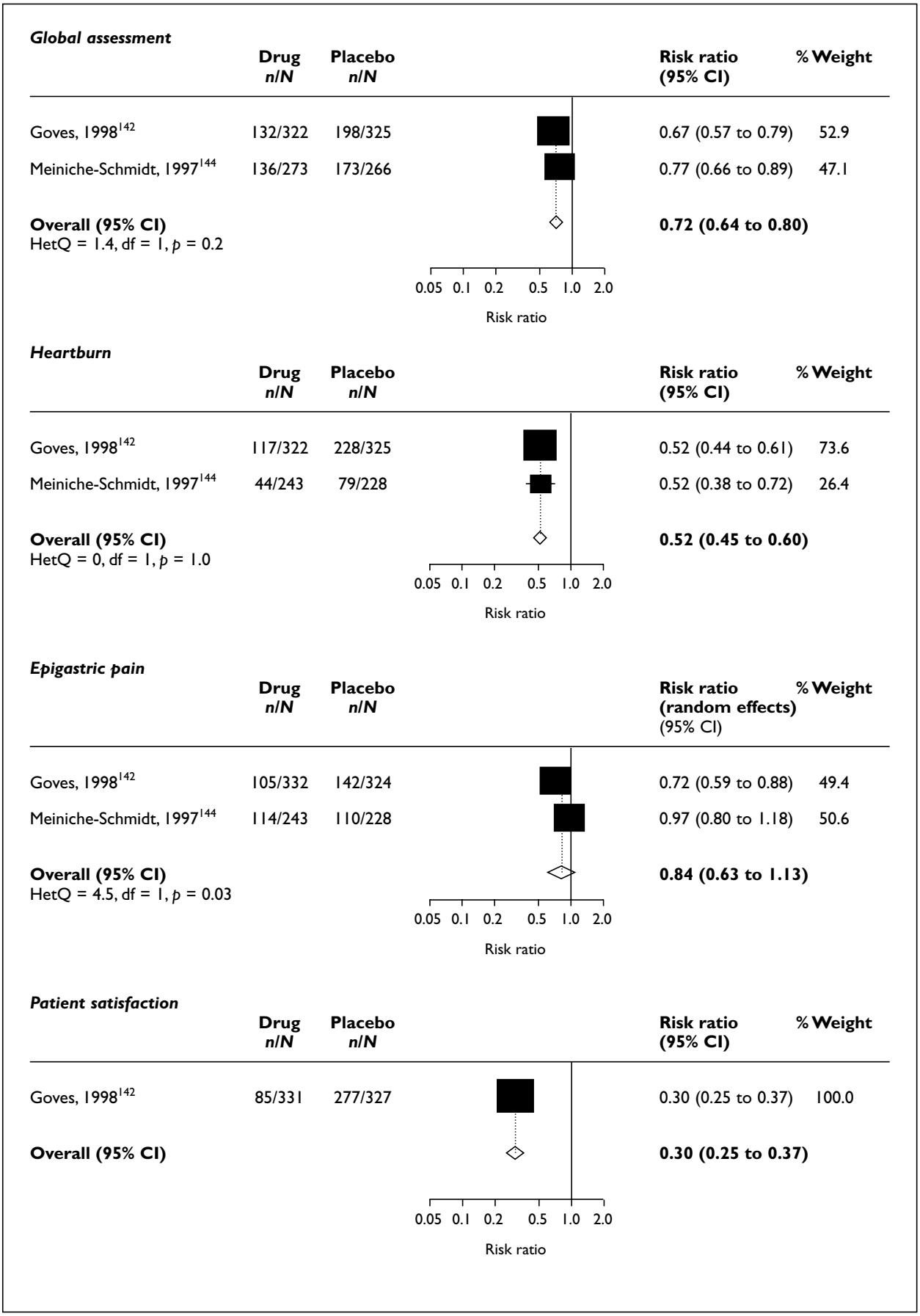


FIGURE 2 *Acid suppression in primary care: meta-analysis of PPI (drug) vs. alginate/antacid (placebo)*

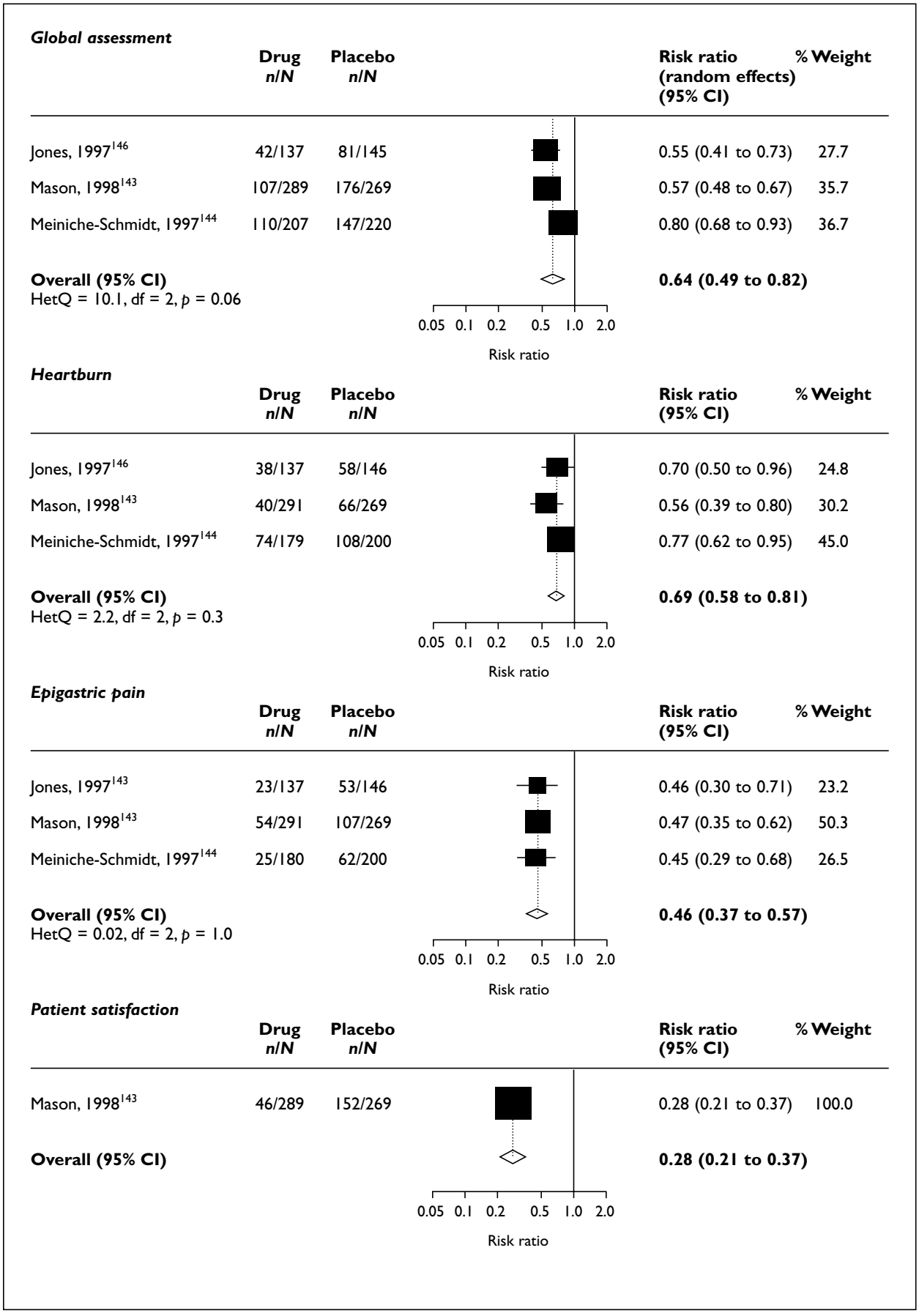


FIGURE 3 *Acid suppression in primary care: meta-analysis of PPI (drug) vs. H_2-receptor antagonist (placebo)*

H_2-receptor antagonists versus alginate/antacid
Only one trial[145] compared H_2-receptor antagonists with antacids. Paton's study included data on heartburn and global improvement alone, as patients with predominant epigastric pain were not included; no significant difference was observed between H_2-receptor antagonists and antacid/alginate. The RR reduction was 14% (95% CI, 65% reduction to 111% increase) for heartburn and 2% (95% CI, 22% reduction to 24% increase) for global improvement. It is possible that the study was underpowered to detect a difference in heartburn symptoms. The control event rate was 47%; with only 80 patients in the study group, the trial would only have been able to detect a 50% RR reduction with 80% power and 95% significance.

PPI versus cisapride Lewin-van den Broek[148] found no difference in the proportion of patients symptom-free at 52 weeks between those treated with omeprazole or cisapride (62/84 versus 62/80); the RR reduction was 5% (95% CI, –13 to 20). Treatment was for 8 weeks and assessments were made at 8, 14 and 52 weeks. None of the assessments showed a significant difference. Symptom scores were also compared, again no difference was observed.

Omeprazole, 10 mg, versus lansoprazole, 15 mg
Jones and Crouch[147] failed to show any difference between lansoprazole, 15 mg, and omeprazole, 10 mg, at 4 weeks. The RR reductions were: heartburn 14% (95% CI, 32% reduction to 10% increase); epigastric pain 16% (95% CI, 31 to 0); global improvement 16% (95% CI, 32 to 0).

Clinical heterogeneity

With respect to clinical heterogeneity, all the studies included patients with a mixture of ulcer-like and reflux-like symptoms (*Table 14*), most excluding oesophagitis or PUD where known. The exceptions were two of the PPI versus H_2-receptor antagonist studies, which either included all patients[146] or only those with proven PUD or oesophagitis,[144] and Paton[145] in which suspected reflux disease was an essential criterion for inclusion (as the patients were uninvestigated, this met the eligibility criteria).

Discussion

This review shows that for treating patients with dyspepsia in the primary care setting, without an initial diagnosis or where no significant abnormality has been found on endoscopy, PPIs were significantly more effective than both antacids and H_2-receptor antagonists. With H_2-receptor antagonists or antacid, approximately 40% of patients improved and with a PPI an additional 20% improved. The NNTs for global improvement, calculated from the pooled RR reduction and using a control event rate of 60%, were 4.5 (95% CI, 3.1 to 11.1) for PPI versus H_2-receptor antagonists and 5.7 (95% CI, 4.6 to 7.9) for PPI versus antacid. For relief of epigastric pain, the NNT for PPI versus H_2-receptor antagonist was 5.6 (95% CI, 4.1 to 11.1), there being no significant benefit over antacids (NNT, 10.42; 95% CI, 4.1 (benefiting) to 8.8 (harmed)). For heartburn symptoms, the NNTs were 3.5 (95% CI, 3.0 to 4.2) for PPI over antacids and 3.1 (95% CI, 2.7 to 3.9) for PPI versus H_2-receptor antagonists.

Differences between PPIs and antacids and PPIs and H_2-receptor antagonists were similar and, with a similar control event rate, the effect was seen for global symptoms, heartburn and epigastric pain (with the exception of PPI versus antacids). In support of the biological plausibility of the effect, the effect on heartburn was greater than that for epigastric pain alone.

How robust are these findings? Are H_2-receptor antagonists no more effective than alginates? The only study directly comparing them with alginate/antacid in primary care was an open randomised trial, owing to the inability to blind for liquid alginate. The trial showed no difference (RR 0.98; 95% CI, 0.78 to 1.24) and would have been only adequately powered to detect a 20% difference in treatments with a control event rate of 40%. In addition, this trial was of longer duration, 24 weeks, rather than the 2–16 weeks of the other trials. In a systematic review it is always possible that the results are biased by selective publication. Exhaustive search methods were used to identify all relevant literature, including contacting pharmaceutical companies. Although a number of studies of the efficacy of H_2-receptor antagonists versus placebo in selected patients with GORD or PUD were identified, no other primary care trials were found. Open trials are likely to exaggerate treatment differences rather than reduce them but a clinically significant difference between antacid and H_2-receptor antagonists cannot be excluded. This is clearly of importance, as H_2-receptor antagonists are cheaper than PPIs and more convenient than taking antacid six times daily.

In the absence of true placebo-controlled trials, it is only possible to conclude that, in terms of

short-term symptom relief, PPIs are more effective than antacids and more acceptable to patients but more costly. There are no long-term treatment trials, which is important as dyspepsia is a chronic, relapsing condition, and it is possible that intermittent use of a PPI may be effective but at less cost than continuous therapy. The cost-effectiveness of PPI treatment compared with antacid or an H_2-receptor antagonist is considered in chapter 7.

In keeping with the typical case-mix of patients seen in primary care, the majority of the patients in these trials had ulcer-like or reflux-like symptoms. Tighter definition of dyspepsia, excluding any patient with predominantly reflux symptoms, would be likely to show less marked benefit of acid suppression therapies. In addition, none of the studies are directly comparable with the analysis of NUD trials described later. The missing group from these primary care trials are the smaller number of primary care patients with predominantly bloating or dysmotility symptoms. Although symptom pattern does not predict pathology, and only poorly predicts response to treatment, the exclusion of these patients from most of these trials may result in an exaggerated treatment effect for PPIs.

Early investigation versus acid suppression

The results of studies that compared early investigation (meaning investigation prior to deciding on therapy) with empirical acid suppression or prokinetic therapy are described. Empirical *H. pylori* eradication is considered later.

Description of studies

Four studies were found that evaluated the effectiveness of early investigation rather than initial pharmacological treatment in the management of dyspepsia. A controlled cohort study[149] and two RCTs[116,148] compared early endoscopy with cisapride, ranitidine and a range of treatments, respectively. A further RCT examined the effectiveness of early barium studies versus regular antacid.[150] Two further RCTs were available as abstracts.[138,140]

Goodson and colleagues' study was set in primary care clinics and emergency rooms in the USA.[151] Patients had to have had more than 4 days of upper abdominal pain but not symptoms suggestive of malignancy or be using an H_2-receptor antagonist. Patients with a history of proven ulcer in the past 2 years, as well as drug or alcohol abuse, were also excluded. In all, 101 patients were recruited to the trial and randomised to either an early barium meal examination, with treatment based on the findings, or treatment with regular antacid (Maalox, 15–30 ml, seven times daily). Either group could receive H_2-receptor antagonists, and the antacid group could be investigated after randomisation at the physician's discretion. Patients were followed-up for 26 weeks using a dyspepsia symptom score and the Sickness Impact Profile (SIP).

The Omega project[149] recruited patients from Swiss primary care with upper gastrointestinal symptoms for more than a month, based on the 1988 Working Party criteria. Patients with alarm symptoms were excluded. Patients received either early endoscopy or cisapride, 30–40 mg per day. Patients in the cisapride group over the age of 50 years, or who had at least two of the following, nocturnal symptoms, reflux-type pain, weight loss and food relieving pain, were also endoscoped. This was a controlled cohort study, as GPs could choose whether to recruit for the early endoscopy arm or the cisapride arm. In all, 172 patients underwent early endoscopy and 656 were managed empirically (of whom 203 had an endoscopy).

Bytzer and colleagues conducted an RCT in Denmark, where GPs identified patients with dyspeptic symptoms, of sufficient severity to warrant prescription of acid suppression therapy.[116] Patients with alarm symptoms, or use of acid suppression in the previous 2 months were excluded. A total of 414 patients were randomised at the endoscopy unit to either early endoscopy or 4 weeks' treatment with ranitidine, 150 mg twice daily.

Lewin-van den Broek recruited 176 patients aged 18–80 years, consulting 95 GPs with dyspepsia defined by the 1988 Working Party definition and 'needing treatment' in the opinion of the GP.[148] Patients were randomised to either empirical treatment of the GP's choice or early endoscopy.

The Nottingham dyspepsia study randomised patients age 18 and over, consulting their GP with dyspepsia to either early endoscopy, *H. pylori* test-and-endoscope, *H. pylori* test-and-eradicate (using serology (FlexSure®) in both cases), or to 4 weeks of lansoprazole, 30 mg once daily.[138] In all, 762 patients were recruited, of whom 187 had early endoscopy and 179 PPI. Data are currently only available on the percentage with improved symptoms and mean total cost.

The Birmingham study randomised 442 patients, aged 50 years and over, consulting with dyspepsia to early endoscopy or empirical acid suppression with outpatient referral at the GPs' discretion.[140] Data are currently available for mean effect on symptoms.

Methodological quality of included studies

Case-mix All six studies recruited patients with dyspeptic symptoms in primary care. However, as the GPs in the Omega trial knew which protocol they were following, it is likely that considerable bias could exist in both the mix of cases entering and the response to the intervention.[149] In Bytzer and colleagues' study,[116] the patients were randomised in secondary care after GPs had referred suitable patients. The authors do include data that show that the study patients were similar in final diagnostic category to non-trial patients undergoing open-access endoscopy. This does not exclude the possibility that GPs were referring a selected group of dyspeptic patients to either the trial or endoscopy and not referring every patient with eligible dyspepsia. This is a problem with all trials but whether the Bytzer trial can genuinely be said to be primary care-based, hence reflecting a primary care case-mix, remains an issue for debate. Both the Nottingham and Birmingham trials recruited and randomised patients in primary care.[138]

Randomisation and concealment of allocation The Omega project was non-randomised, as the GPs in the study proved unwilling to randomise to early endoscopy.[149] In Bytzer and colleagues' RCT,[116] although patients were randomised in blocks of 25, it was not clear how the randomisation schedule was generated, nor is there any evidence that the randomisation was concealed, introducing the possibility of bias. Goodson and colleagues[151] did not report the method of randomisation or treatment allocation. Both Lewin-van den Broek[148] and the Nottingham trialists[138] used a computerised schedule and central telephone randomisation. The Birmingham trialists used sealed sequentially numbered opaque envelopes.[140]

Co-interventions The principal weakness with three of these trials[116,149,151] is that none of the patients found on investigation to have PUD received *H. pylori* eradication therapy. A major part of the effectiveness of any diagnostic strategy concerns the action taken in response to investigation. In two trials[116,149] this was both pre-specified (acid suppression therapy for both reflux disease and PUD) and included as a trial outcome. In the barium trial,[150] all patients could receive acid suppression, the amount taken being one of the study outcomes. Lewin-van den Broek[148] specified that, after endoscopy, patients with Grade I oesophagitis would receive an H_2-receptor antagonist, and those with Grade II and higher a PPI. Peptic ulcer patients were treated with *H. pylori* eradication therapy. In Birmingham and Nottingham, patients were treated according to locally active protocols that specified *H. pylori* eradication therapy for peptic ulcer.

Outcome measures All six studies recorded a global symptom score but in only three trials[138,140,148] was this a previously validated measure. Bytzer and colleagues[116] also recorded individual symptom scores for epigastric pain, vomiting, daytime and nocturnal heartburn. Bytzer and colleagues and Goodson and colleagues[151] measured use of medication using symptom diaries. Economic data was collected by all five RCTs; Bytzer and colleagues[116] recorded resource use in primary and secondary care, as well as measuring patient satisfaction using a simple score. All three trials measured sick days, while Goodson and colleagues used a quality-of-life measure, the SIP. None of the trials could be adequately blinded because of the nature of the intervention.

Drop-outs All of the RCTs were analysed on an intention-to-treat basis but were subject to a degree of attrition. Goodson and colleagues' trial[151] recruited only 101 patients from 405 assessed as eligible, and only 78 completed the study. The other trials all followed-up more than 75% of patients recruited.

Results

Effectiveness The early barium meal trial[150] showed no difference in symptom scores between the early investigative strategies (called traditional care) and the control strategy involving initial empirical treatment and selective investigation in treatment failures alone. The effect of early investigation on quality of life (SIP), disability days and patient satisfaction was measured at 6 months post randomisation. There was no difference in quality of life, sick days or patient satisfaction; SIP differences were: sleep/rest 1.7 (–3.1 to 6.5); physical 1.1 (0 to 2.3); psychosocial 1.7 (–0.7 to 4.1).

Bytzer and colleagues' study[116] showed no differences in global improvement or individual symptoms scores after 1 year (number asymptomatic, 40/187 early endoscopy versus 41/186 controls). This is supported by the Omega study,[149] in which there was again no difference in dyspepsia symptom scores between the two groups (mean 1.6/39 versus 1.5/39, not significant). Lewin-van

den Broek[148] found no difference in symptom scores at 14 weeks (0.39/1 versus 0.45/1, not significant); a poor response rate (59%) to the questionnaires limited the analysis. At 52 weeks there was a statistically non-significant reduction in 'strategy failure' in the early oesophageal-gastroduodenoscopy (OGD) group (31/74 symptom-free versus 45/81, RR reduction 25% (95% CI, –5 to 48; $p = 0.09$). Duggan and colleagues[138] found no significant difference in symptoms, although more patients undergoing endoscopy were 'improved' than those receiving empirical PPI (66% versus 60%). The Birmingham study[140] found a significant improvement in symptom score for dyspepsia with early endoscopy.

Data on global improvement from four trials[116,138,140,148] were pooled (*Figure 4*), as the Omega study was non-randomised[149] and the early barium meal study[150] was not considered to be an equivalent intervention to early endoscopy. The four RCTs of early endoscopy and empirical prescribing included 1127 patients and showed a non-statistically significant pooled RR reduction of 11% (95% CI, 22% reduction to 1% increase), Z = –1.77, $p = 0.15$; heterogeneity test Q = 1.43, df = 3, $p = 0.70$.

Costs

As far as economics data were concerned, for endoscopy, Bytzer and colleagues[116] found that there were more endoscopies in the early endoscopy group (241/187 versus 193/186), and more use of H_2-receptor antagonists (6636 versus 11,208 defined daily doses) and more GP consultations (47/187 versus 114/186) in the control group. As the protocol demanded endoscopy in control group patients with persisting symptoms at 8 weeks, a majority of these patients (66%) had had an endoscopy by follow-up at 1 year. No formal economic analysis was performed on this data, although the author comments that the costs of the additional prescribing 'balanced out' the costs of the additional endoscopies. There were both fewer dyspepsia-related and other sick leave days in the early investigation group. Patient satisfaction as measured by a simple 4-point Likert scale was higher in patients in the early investigation group ($p < 0.0001$).

In the Omega study[149] there were 67% fewer endoscopies in the 'selective endoscopy' arm (1.02/patient versus 0.34/patient, $p < 0.001$) without significantly more consultations (19% more were non-significant). Use of H_2-receptor antagonists was not reported separately but an economic analysis, conducted as part of this study, indicated a mean reduction in costs of SFr 300 (£118) over 3 months by the selective strategy (SFr 960 (£378) versus SFr 660 (£260); $p < 0.001$). No sensitivity analysis was conducted.

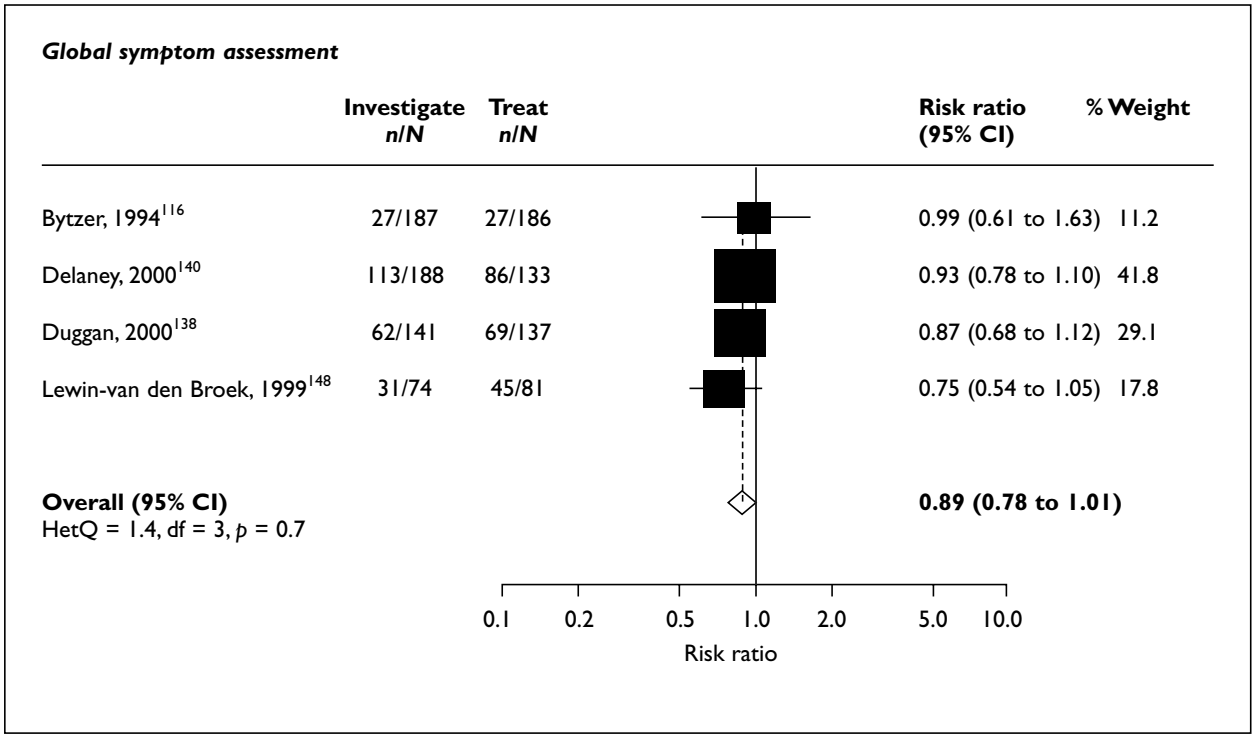


FIGURE 4 *Meta-analysis of early investigation vs. empirical treatment in primary care*

Goodson and colleagues[151] found that more patients in the early barium study group were prescribed H_2-receptor antagonists than in the antacid and reassurance group (27/50 (54%) versus 8/51 (16%); $p < 0.001$). Overall, 15% of the antacid group were investigated at 27 weeks compared with 94% of the early investigation group. There was no difference in symptom score or quality of life. Economic analysis indicated a mean cost of $287 (£179) for early investigation and $116 (£72) for antacid therapy ($p < 0.0001$).

Economic data from the Nottingham and Birmingham trials have not yet been published.

Discussion

The data on barium meal investigation can be largely discounted, on the basis that only a small number of eligible patients agreed to be randomised and that it would be difficult to extrapolate from the use of a barium meal to upper gastrointestinal endoscopy. This leaves five studies: four RCTs – one conducted in secondary care, two in primary care but in abstract only, one primary care-based – and a controlled cohort study. Although Bytzer and colleagues[116] attempted to recruit patients that GPs felt 'needed prescription of acid suppression therapy' and not just those that had been referred for investigation, it is not possible to conclude that the same results would have been obtained in primary care. In particular, Bytzer and colleagues and Lewin-van den Broek[148] differ markedly in the number of endoscopies conducted in the control–selective endoscopy arms (66% versus 31%). In addition to Bytzer and colleagues' study requiring endoscopy if symptoms persisted after 8 weeks, it is possible that more patients were subsequently investigated than would have been the case if they had not been taking part in a trial. This is supported by Lewin-van den Broek's trial, in which only 43% of patients in the control group, managed in the primary care setting, were referred for endoscopy in spite of the protocol specifying endoscopy if symptoms had not settled at 8 weeks' follow-up. With respect to patient satisfaction, Bytzer and colleagues' data are probably not generalisable to the primary care setting. The effect of attending the hospital and then not receiving an investigation would be expected to be less satisfying for patients than remaining in GP care.

The handling of the economics data from the available three trials leaves much to be desired. In only two trials was there any statistical examination of the uncertainty related to sampling of the cost data (p-values, CIs) and neither study used modelling to perform sensitivity analysis or extrapolate from the trial data. In conclusion, it is unlikely that early endoscopy would result in a reduction in overall economic costs of managing dyspepsia at 1-year follow-up. It is more likely that an initial excess cost would be incurred that may be recouped in some prescribing and consultation reductions in subsequent years. The point at which early endoscopy might become cost-neutral, if at all, cannot be determined from these trials. As the result of the meta-analysis includes no effect within the CI for effectiveness, calculation of a cost-effectiveness ratio is not possible at this stage.

The second question that needs to be addressed is whether the lack of *H. pylori* eradication therapy for patients with proven peptic ulcers in Bytzer and colleagues' trial[116] reduced the effectiveness of early investigation in symptom relief. Both trials show a reduction in the number of peptic ulcers detected from that expected in patients endoscoped in the control group.[116,149] Peptic ulcers are healed and do not recur in significant numbers in the time-scale of the studies but reflux and non-ulcer symptoms persist. If the effect of *H. pylori* eradication on decreasing the recurrence of ulcers were to have a significant impact on dyspepsia recurrence rates, this might favour early endoscopy (with *H. pylori* eradication for proven ulcers) over no investigation/no eradication. In Bytzer and colleagues' study,[116] 21% of patients in the study group had a peptic ulcer compared with only 7.6% in the Omega study;[149] these data for Lewin-van den Broek's study are not yet available. This may account for some of the differences between the studies. These studies cannot answer the question of whether early endoscopy combined with *H. pylori* eradication for proven ulcers, as would be current practice, might be more cost-effective than empirical acid suppression alone. The answer would, however, be expected to depend at least partly on the prevalence of PUD.

A further difference between the studies is the choice of initial empirical treatment. In the study by Bytzer and colleagues,[116] this consisted of H_2-receptor antagonists, with PPIs only used subsequently for patients with oesophagitis on investigation. Similarly, in Lewin-van den Broek's study,[148] 70% of the patients were initially prescribed an H_2-receptor antagonist, 25% a prokinetic and only 5% a PPI. The first section of this review indicates that H_2-receptor antagonists may be no more efficacious than antacid in primary care patients with uninvestigated dyspepsia. However, the results of these two trials may not

accurately reflect what may be expected in current UK practice. The effectiveness of prokinetic agents for treating dyspeptic symptoms in primary care is uncertain but the one trial reported earlier[148] failed to show a significant difference between omeprazole and cisapride.

At present there are insufficient trial data to form firm conclusions about the value of early endoscopy, as the CIs around the RR are too wide and insufficient patient-based economic data are available. Full publication of the economics data from the Birmingham and Nottingham trials may help to resolve this issue.

H. pylori test-and-endoscopy versus unselected endoscopy or empirical prescribing

Studies included here are those that compared selective early endoscopy based on the result of a non-invasive test for *H. pylori*, with either unselected early endoscopy or empirical acid suppression therapy.

Description of studies

Only one published study with any comparative data was found. Patel and colleagues[21] conducted a prospective cohort study with historical controls, in which 183 patients, aged under 45 years, were recruited via an open access endoscopy clinic; 70 tested positive for *H. pylori* using the *Helico G*® serology test with a cut-off of 6.3 U/ml. These 70 patients were compared with 70 referred for endoscopy who tested negative for *H. pylori* but had been endoscoped in the previous months.

Two RCTs were available in abstract form. In the Nottingham trial, described earlier, 199 patients were randomised to test-and-endoscope, 187 to early endoscopy and 178 to PPI.[138] In the Birmingham trial,[140] 478 patients under the age of 50 years were randomised to either test-and-endoscope (using the *Helisal*® point-of-care test) or empirical acid suppression with outpatient referral at the GP's discretion.

Methodological quality of included studies

Unfortunately Patel and colleagues[21] did not follow-up the whole screened cohort; only those patients who tested negative for *H. pylori* were included in a 6-month follow-up. The historical control group was used to compare symptom severity, interference with life events and use of medication at 6 months between endoscoped (historical controls) and screened-and-not-endoscoped patients. The exclusion of the *H. pylori*-positive patients from the follow-up seriously weakens this study.

Both the Nottingham and Birmingham trials were primary care based RCTs, conducted as described above under early endoscopy.

Case-mix In the study by Patel and colleagues,[21] patients were all referred for investigation by GPs. This study was unable to address the question of whether GPs should apply the strategy to all dyspeptic patients, as this was a selected group.

Concealment of allocation As Patel and colleagues study was an open one,[21] not only were the patients and staff aware of whether or not a patient was to be endoscoped, but they were also aware of the patient's *H. pylori* status at the time of endoscopy. This may have influenced the findings on endoscopy. The Nottingham and Birmingham studies were adequately concealed.[138,140]

Co-interventions No information was given by Patel and colleagues.[21] The Nottingham and Birmingham studies specified *H. pylori* eradication for peptic ulcer and PPI to heal oesophagitis.

Outcome measures In the study by Patel and colleagues,[21] endoscopic findings in the 70 *H. pylori*-positive patients endoscoped and the 26 *H. pylori*-negative patients endoscoped for other reasons (sinister symptoms, 14; NSAID use, 9; re-referred, 3) were compared. Symptom severity, interference with life events, days off work, consultations with the GP and use of medication were assessed using an unvalidated questionnaire posted to patients. Use of medication was assessed according to a scale: antacids–H_2-receptor antagonists/prokinetics–PPIs; details are not given fully in the paper.

Data for symptomatic improvement and mean cost are available for the Nottingham and Birmingham studies.

Drop-outs Follow-up in both groups was 80% in the study by Patel and colleagues.[21] No data are available for the Nottingham or Birmingham studies.

Results

In the study by Patel and colleagues, the prevalence of PUD in the *H. pylori*-positive group who were endoscoped was 29% of those endoscoped, or 19% of the total population.[21] Symptom severity, interference with life events and use of medication all decreased after either endoscopy or serology alone. There were no differences between the two groups, except that the reduction

in medication use was greater in the serology alone group than in the endoscoped group.

In the Birmingham study, 39% of the study group were *H. pylori*-positive, 44% were endoscoped and 7.4% overall were found to have PUD.[141] Only 26% of patients in the control group were endoscoped and the incidence of peptic ulcer detected was only 2.1%. In spite of this, there was no significant difference in dyspeptic symptoms between the two groups. Costs were higher in the test-and-endoscope group (£376 versus £247).

In the Nottingham study, there was no difference in the proportion of patients improved (59% test-and-endoscope versus 60% PPI) and costs were similar (£127 versus £123).[138]

Discussion

Great caution should be exercised in drawing conclusions from the small cohort study.[21] The most that can be said is that in patients referred for investigation, serology testing alone rather than endoscopy in those testing *H. pylori*-negative appears to be equally effective. However, these results need to be confirmed both by an RCT and in less selected groups of patients recruited from primary care. This caution is borne out by the two primary care RCTs, in which the incidence of PUD detected was much lower and no significant differences were found in symptoms. One trial was associated with a marked increase in endoscopy and therefore costs.[141] Detailed evaluation of the full reports of these two trials is needed to determine why this was the case. However, there is sufficient evidence from the two abstracts to indicate that *H. pylori* testing and endoscopy is neither more effective nor cheaper than selective endoscopy at the GP's discretion.

Although an alternative policy of *H. pylori* eradication therapy in *H. pylori*-positive patients, combined with endoscopy in *H. pylori*-negative patients has been suggested in North America, no trials of this policy were found.

H. pylori test-and-eradicate versus other strategies

Studies that compared the initial management strategy of *H. pylori* eradication therapy, based on the results of a non-invasive *H. pylori* test, compared with any other strategy are described here.

Description of studies

One controlled trial of *H. pylori* test-and-eradicate[152] compared with endoscopy (probably with no direction that this should be early) was found. One study is currently only available in abstract form but communication with the authors yielded additional material.[138] Duggan and colleagues randomised 198 patients with dyspepsia who consulted their GP to *H. pylori* testing using the Flexure test and eradication therapy; 187 patients were randomised to early endoscopy and 178 to empirical lansoprazole. A further study randomised patients to either prompt endoscopy or to ^{13}C urea breath testing and *H. pylori* eradication.[139]

Methodological quality of included studies

The London study was a cluster randomised trial, treatments being allocated by randomising the 15 practices.[152] However, this aspect of the design was ignored in the analysis, which will have led to an overestimate of the significance of the results. There were six study practices and nine control practices but no details were given about the method of selection and randomisation of the practices. The Nottingham study[138] was randomised and analysed by individual patient.

Case-mix In the London study,[152] the patients in the control group were those referred for open access endoscopy, with subsequent negative findings, whereas the study patients were those under the age of 45 years with more than 4 weeks of 'ulcer-like' dyspepsia, for whom the GP 'considered further investigation appropriate'. Patients with PUD and oesophagitis, the two conditions that may be most affected by eradication therapy, were thus excluded from the control cohort. This may have biased the study in favour of the intervention.

The Danish study[139] aimed to recruit all dyspeptic patients consulting with local GPs but, as patients were recruited at the endoscopy unit, it is possible that some degree of selection could have taken place. The Nottingham study[138] recruited and randomised in primary care.

Randomisation and concealment of allocation

As allocation is open using the cluster design, GPs may have been able to enter patients selectively, knowing that they would receive either an endoscopy or an *H. pylori* test and treatment. Studies in which allocation is not concealed have been shown to overestimate the effect of an intervention. Both the Nottingham and Danish studies were adequately concealed.

Co-interventions In the London study,[152] the choice of *H. pylori* eradication therapy was left

to the investigator; although 50/58 patients were given a triple therapy, PPI-based regime, the effectiveness of the treatment given was not assessed.

Outcome measures In the London study,[152] the principal outcome was cost. Resource utilisation, in terms of prescribing, consultations, and investigations were collected from GP records at 12 months. No patient-orientated data (symptoms, quality of life or satisfaction) were collected. In Denmark[139] and Nottingham,[138] the studies assessed both costs and effects.

Drop-outs Follow-up data were available on 141 (85%) of the 165 study patients in the London study[152] and on all 92 patients in the control group. No data are available for the Danish or Nottingham studies.

Results

In the London study,[152] there were 97 endoscopies over the year in the 92 patients in the control group compared with 17 in the 141 in the study group. There were more non-endoscopy secondary-care referrals in the study group (16/92 versus 43/141; $p < 0.05$). No differences were observed in GP consultation rates, prescribing or investigation costs. The mean annual cost per patient with dyspepsia was estimated at £205.67 for study patients and £404.31 for control group patients.

In Nottingham,[138] there were no significant differences in the proportions of patients with improved symptoms, 53% with test-and-treat, 66% with early endoscopy, 60% with empirical PPI. There were 72% fewer endoscopies in the test-and-treat group compared with early endoscopy, with a reduction in mean cost per patient from £145 to £127 over 12 months.

In the Danish study,[139] 250 patients were randomised to each group; there was no difference in the median number of dyspeptic 'symptom days' and endoscopies were 60% less than in the early endoscopy control arm of the study.

Discussion

There are major problems with drawing conclusions from the London study.[152] Although considerable cost savings are shown, the design of the study would be such as to seriously bias the study in favour of the intervention group. Furthermore, no patient specific data were collected and no information was available on the sample size for detecting differences in resource utilisation.

A recent RCT[153] suggests that *H. pylori* test-and-treat is an effective strategy for managing patients under the age of 45 years with ulcer-like symptoms in secondary care. The London trial did not distinguish between patients referred to open-access gastroscopy by GPs and those sent for gastroscopy by hospital clinics. Therefore, it is not possible to extrapolate from this study to primary care.

The Nottingham[138] and Danish[139] studies found that endoscopy and test-and-treat were equally effective but that test-and-treat was cheaper, although the apparent difference in cost was much less than in the London study. This may relate as much to study design and costs applied as to genuine differences, and a detailed examination of the full paper is needed. The Nottingham study also found little difference in either costs or effects between empirical PPI and test-and-treat but the study was probably underpowered for this comparison.

Considerable gaps exist in our knowledge of how to best to manage the patient with dyspepsia in primary care. There is insufficient published trial data to determine the most cost-effective strategy for investigating these patients. Although this is largely due to a lack of trials in the primary care setting, it is also due to the poor quality of several existing studies. Additional information may come from two sources, robust modelling studies and trials already in progress. Later in chapter 7, a model to address the unanswered questions from this review is described. In addition, the review is being maintained as a Cochrane review and, as data becomes available from trials, it will be updated.

Role of symptom patterns in diagnosing dyspepsia

Results of the search

A subgroup of 8 papers was selected from the main search results, on the basis that they contained data relating to the performance of individual symptoms or symptom clusters in predicting diagnosis. A further set of criteria, relating to quality measurement in diagnostic test papers (see below), were then applied. This left four papers (Talley, *et al.*,[154] Edenholm, *et al.*[156] Adang, *et al.*,[157] and Muller-Hansen, *et al.*[158]).

Inclusion criteria

- Spectrum of cases: consecutive, unselected patients presenting for upper gastrointestinal endoscopy, having been referred from primary care.

- Reference standard: finding at endoscopy of peptic ulcer (not including duodenitis) or oesophagitis.
- Avoidance of verification bias: all patients had symptom classification and endoscopy.
- Blinding of endoscopists to symptom classification.
- Avoidance of work-up bias: prompt endoscopy prior to any treatment.
- Papers report data enabling 2 × 2 table of number of patients with symptom (cluster) by presence/absence of ulcer/oesophagitis.

Included studies are presented in *Table 15*,[154,156–158] and excluded studies in *Table 16*.[112,159–161]

Results

Data was extracted from the papers by dichotomising on the basis of 'any symptom' versus 'no symptom' for clusters and 'lesion present at OGD (oesophageal-gastro-duodenoscopy)' versus 'no lesion present' (for peptic ulcer, normal endoscopy and oesophagitis, respectively) (*Table 17*).

In general, the performance of both individual symptoms and symptom clusters in predicting endoscopic diagnosis is poor. Specificity tends to be better than sensitivity. As the prevalence of significant endoscopic disease is quite low, the effect of this for individual patients is that patients with 'classic' symptoms tend to have a no-better-than-evens chance of having a specific lesion but, for those without symptoms, the chances of being disease-free are reasonable, often 80–90%.

To take a specific example, before taking a history, the chance of having oesophagitis is about 17%; if reflux-like symptoms are present this figure rises to 24% but if they are not it falls to only 10%. Although the power of the symptoms to change diagnosis is weak, it does shift the chances around the critical 80–90% area, where the initial treatment choices may be made by clinicians. Away from the trial setting, and among primary care patients not yet referred for endoscopy,

TABLE 15 *Role of symptom patterns in diagnosing dyspepsia: included papers*

	Edenholm, et *al.*, 1985[156]	**Talley, et *al.*, 1993[154]**	**Adang, et *al.*, 1996[157]**	**Muller-Hansen, et *al.*, 1998[158]**
Spectrum	Yes	Yes	Yes	Yes
Reference standard	Yes	Yes	Yes	Yes
Verification	No – 15 incomplete OGD	Yes	Yes	Yes
Blinding	No	Yes	Unclear	No
Work up	Yes	Yes	Yes	Yes
'Symptoms' studied	Yes – individual symptoms of peptic ulcer alone	Yes – extractable for symptom clusters	Yes	Yes

TABLE 16 *Role of symptom patterns in diagnosing dyspepsia: excluded papers*

	Bytzer, et *al.*, 1995[112]	**Warndorf, et *al.*, 1989[159]**	**Mansi, et *al.*, 1990[160]**	**Heikkinen, et *al.*, 1996[161]**
Spectrum	Yes	Yes	No – NUD patients only	Yes
Reference standard	Yes	No – 'final overall diagnosis'	Yes	No – final diagnosis
Verification	Yes	No	Yes	Yes
Blinding	Not in all cases	No	No	No
Work up	Yes	No	No – diagnosis at end if investigation pathway	No – diagnosis at end if investigation pathway
'Symptoms' studied	No – clinical judgement	No – initial clinical impression	Yes	No – performance of OGD in predicting 'final diagnosis'

TABLE 17 *Role of symptom patterns in diagnosing dyspepsia: results*

Symptom	Edenholm, *et al.*, 1985[156]	Talley, *et al.*, 1993[154]	Adang, *et al.*, 1996[157]	Muller-Hansen, *et al.*, 1998[158]
Peptic ulcer				
Pain before meals or relieved by food	Sensitivity 86%; specificity 46%; prevalence 25%; PPV 36%; NPV 91%; LR + 1.59; LR – 0.30		Sensitivity 38%; specificity 73%; prevalence 13%; PPV 28%; NPV 91%; LR + 1.41; LR – 0.85	
Day or nocturnal epigastric pain	Sensitivity 90%; specificity 49%; prevalence 25%; PPV39 %; NPV 94%; LR + 1.76; LR – 0.20		Sensitivity 83%; specificity 46%; prevalence 17%; PPV 23%; NPV 93%; LR + 1.54; LR – 0.37	
Ulcer-like symptom cluster		Sensitivity 31%; specificity 71%; prevalence 22%; PPV 24%; NPV 78%; LR + 1.07; LR – 0.97		Sensitivity 62%; specificity 81%; prevalence 16%; PPV 40%; NPV 92%; LR + 3.3; LR – 0.47
Oesophagitis				
Heartburn			Sensitivity 71%; specificity 59%; prevalence 27%; PPV 38%; NPV 85%; LR + 1.73; LR – 0.49	
Retrosternal pain			Sensitivity 41%; specificity 83%; prevalence 27%; PPV 46%; NPV 80%; LR + 2.4; LR – 0.71	
Reflux-like symptom cluster		Sensitivity 58%; specificity 70%; prevalence 14%; PPV 24%; NPV 90%; LR + 1.9; LR – 0.6		Sensitivity 62%; specificity 82%; prevalence 23%; PPV 51%; NPV 87%; LR + 3.4; LR – 0.46
Functional dyspepsia				
Dysmotility-like symptom cluster		Sensitivity 16%; specificity 87%; prevalence 19%; PPV 21%; NPV 80%; LR + 1.23; LR – 0.96		Sensitivity 36%; specificity 87%; prevalence 54%; PPV 80%; NPV 52%; LR + 1.3; LR – 0.73

the prevalence of disease is lower and the negative predictive value of symptoms is likely to be more significant. It is not possible to calculate likely predictive values as there is a considerable risk of spectrum bias in these studies, making application of test performance in another setting risky.

Discussion

In general, although the relationship between symptoms and disease is weak, the low prevalence of disease means that although positive diagnoses cannot be made on the basis of symptoms, treatment choices may be influenced by their absence. Further work is needed in this area.

Chapter 5

Pharmacological interventions for NUD

Introduction

Patients with dyspepsia are often referred for endoscopy or barium studies to exclude organic pathology. This can reveal PUD or oesophagitis and these conditions usually respond well to treatment.[45] Investigation is normal in over 50% of cases[8] and, although some patients will be reassured by this knowledge, many will request further therapy to cure their symptoms. These patients are labelled as having NUD and the treatment of this group is more problematic. The pathophysiology of this condition is poorly characterised[162] and the trials of drug therapies have given conflicting results. There has been no recent systematic review of pharmacological therapies for NUD and the most effective treatment is unclear.

The aim of this review was to determine the effectiveness of pharmacological therapy for patients with NUD. Definitions of NUD, the search strategy and eligibility criteria were outlined in chapter 3.

Results of the search

Details of the search strategies for the various electronic databases are given in appendix 1. A total of 11,775 citations were retrieved. The majority were identified from MEDLINE, EMBASE and the Cochrane controlled trial register. Requests to 29 pharmaceutical companies yielded a further 38 articles (*Table 18*).

Eligibility assessment

The eligibility of all papers was assessed by one reviewer and then checked by at least one of four further reviewers. The kappa scores for the four reviews were 0.8, 0.87, 0.93 and 1.0. The discrepancies have arisen from: uncertainty of inclusion of patients with chronic gastritis; uncertainty of inclusion of patients with gastroparesis; and inclusion of papers in which patients with diagnoses other than NUD were included and subgroup analysis was not reported. The disagreements were resolved by discussion and a majority decision was reached.

TABLE 18 *Citations retrieved from each database: pharmacological interventions for NUD*

Databases	Number of citations retrieved
MEDLINE	5,180
EMBASE	4,438
Cochrane Controlled Trials Register	2,029
CINAHL	29
Bibliographies of retrieved papers	45
Pharmaceutical companies (29)	38
Experts/editors (70)	0
SIGLE	1
Abstracts	15
Total	**11,775**

Data extraction

Data were extracted from the 57 included trials. They included:

(a) the definition and duration of dyspepsia
(b) any subgrouping of dyspepsia
(c) details of the participants, including number and the source of recruitment, that is, primary or secondary care
(d) details of intervention in terms of dosage and duration of treatment
(e) outcome measurements in terms of individual and global dyspepsia symptom scores and quality-of-life scores
(f) number of drop-outs
(g) duration of follow-up
(h) adverse events.

Quality of studies

In order to look at the validity and quality of the RCTs, the following were considered in each trial.

- **Method of randomisation** A trial was defined as randomised if any words such as random, randomisation or randomly was used in the paper. If a trial was described as randomised, then it was assessed to see if it was truly randomised, quasi-randomised, or not stated. Trials with systematic (quasi-

randomised) allocation were not included in this review.
- **Method of concealment of treatment allocation** If there was a central allocation where the trialist could not be aware of the treatment, the method was described as 'adequate'. If the allocation was 'alternate' (for example, by patient, day of the week, admission ward, based on information already known to the trialist), then the method was deemed 'inadequate'. If not stated, then it was 'unclear'.
- **Implementation of masking** The adequacy of masking was evaluated by assessing if the word 'double-blind' was used in the paper, if identical placebos were used, and if clinicians and final outcome assessors were unaware of treatment allocation.
- **Drop-out rates** The number and the reasons for drop-outs in each group were clearly stated. The percentage of patients completing each trial was also recorded.
- **Intention-to-treat analysis** Use of intention-to-treat analysis in trials evaluating outcomes was recorded.

The overall quality of each paper was subjectively assessed according to these criteria but a 'quality score' was not assigned to the trial. There is evidence that poorer quality trials exaggerate the treatment effect but others have criticised the use of quality scoring.[163] It was considered that formally assigning a score to this quality would attempt to quantify what was a subjective judgement.

Exploring heterogeneity between studies

As NUD is a multifactorial disease, including patients with different potential causes as well as symptom patterns, between-study heterogeneity and prospectively listed factors were expected that might explain this. If different drugs might work in different subgroups of patients and trials contain differing case-mixes, the effectiveness of the drugs might be expected to vary more than by chance alone. Both pre- and post-hoc criteria were defined, as follows.

- ***Pre-hoc* criteria** Study quality (blinding, concealment, masking, length of follow-up, completeness of follow-up), case-mix (proportion of patients with duodenitis at endoscopy, endoscopy rather than barium meal used as screening investigation, primary versus secondary care studies).
- ***Post-hoc* criteria** The country in which the trial was conducted and year of publication of results.

Studies included in the review

A total of 57 trials were finally included in the meta-analysis. A brief summary of the details of each trial is given in appendix 2. The majority of papers compared either prokinetics, bismuth salts or H_2-receptor antagonists with placebo (*Table 19*).

TABLE 19 *Summary of the intervention arms in included studies: pharmacological interventions for NUD*

Drug intervention	Number of RCTs
Antacids vs. placebo	1
H_2-receptor antagonists vs. placebo	8
H_2-receptor antagonists vs. antacids	2
H_2-receptor antagonists vs. prokinetics	2
H_2-receptor antagonists vs. sucralfate	1
H_2-receptor antagonists vs. antimuscarinics	2
PPI vs. placebo	4
Prokinetics vs. placebo	17
Prokinetics vs. prokinetics	3
Sucralfate vs. placebo	3
Sucralfate vs. bismuth	1
Misoprostol vs. placebo	2
Bismuth vs. placebo	9
Antimuscarinics vs. placebo	2
Total	**57**

Studies excluded from the review

In all, 87 controlled clinical trials were excluded from the review. Of these, 50 trials were excluded on eligibility criteria; the majority were comparing prokinetic therapy with placebo (*Table 20*). The commonest reasons were that the trial was not an RCT ($n = 22$), PUD was not excluded ($n = 17$) or patients were included with mixed diagnoses and subgroup analysis was not possible ($n = 15$) (see *Table 3*). A detailed listing of the reasons for exclusion can be found in appendix 3.

A total of 37 comparisons (published in 34 papers) were excluded from the review because data could not be extracted in a format that could be analysed. The majority of these again compared prokinetic therapy with placebo (*Table 21*). The most common reason for trials to be excluded at this stage was presentation of the results in a

TABLE 20 *Summary of interventions in studies not meeting eligibility criteria: pharmacological interventions for NUD*

Drug intervention	Number
Antacids vs. placebo or others	2
H_2-receptor antagonists vs. placebo or others	6
Prokinetics vs. placebo or others	35
Bismuth vs. placebo or others	5
Antimuscarinics vs. placebo or others	2
Total	**50**

format that could not be analysed; this particularly applied to crossover trials. Further details of reasons for exclusion, together with summaries of the papers, are given in appendix 3. A summary of interventions studied in the excluded trials is presented in *Table 21*.

TABLE 21 *Summary of interventions in studies from which data extraction was not possible: pharmacological interventions for NUD*

Drug intervention	Number of RCTs
Antacids vs. placebo or others	5
H_2-receptor antagonists vs. placebo or others	9
Prokinetics vs. placebo or others	15
Mucosal protecting agents:	
• bismuth vs. placebo or others	3
• sucralfate vs. placebo or others	2
Antimuscarinics vs. placebo or others	3
Total	**37**

Results

There were 57 trials included in the review with 50 comparisons of global measures of dyspepsia, 20 comparisons evaluating individual symptom scores, and four (all PPI versus placebo) evaluations of quality of life. The case-mix of patients was varied (see appendix 4).

Effects of pharmacological therapies on global dyspepsia

Randomised comparisons of each of the eight therapies with placebo were found, from which evidence of their effectiveness could be assessed. Direct evidence of relative effectiveness of the therapies was limited, with data being available for only five of the possible 28 comparisons. Additional evidence of relative effectiveness could be estimated by making indirect comparisons based on the placebo-controlled trials.

Comparisons with placebo

The overall placebo response rate for pharmacological therapies in NUD was high and variable in the randomised trials. On average, 56% of control group participants showed some degree of improvement in dyspepsia symptoms, with a range of 5–90% between trials.

Prokinetic therapy

A total of 17 trials of prokinetic therapy versus placebo were eligible for meta-analysis;[82,164–178] cisapride was investigated in 15 trials;[82,164,165,167–172,174–178] two studies evaluated domperidone,[166,173] and there were no eligible trials that assessed metoclopramide. A dichotomous global dyspepsia outcome was reported in 12 trials (in 11 papers) evaluating 829 patients.[82,164–173] The meta-analysis suggested that patients treated with prokinetics were more than twice as likely to have an improvement in dyspepsia symptoms compared with patients receiving placebo (RR reduction 55%; 95% CI, 36 to 78) (*Figure 5*). However, there was substantial inconsistency between the trials (test for heterogeneity, $Q = 37.7$, $df = 11$, $p < 0.0001$) and there was evidence of asymmetry in a funnel plot of the trial results (*Figure 6*) with larger trials showing smaller treatment benefits. The heterogeneity could not be explained by any of the *a priori* explanations based on case-mix but further analysis indicated that the heterogeneity could be explained by two factors: year of publication; and reported degree of completeness of follow-up. More recent trials have tended to be larger and have smaller effects but also report lower rates of completeness of follow-up. The combined estimate of effectiveness from the four most recent trials (1996–98) gave an RR reduction of 10% (95% CI, –11 to 27), which is significantly different from the estimate of effect from the earlier trials (1979–95) (RR reduction, 69%; 95% CI, 59 to 77); within each period there is no evidence of heterogeneity.

Three further trials evaluating a total of 120 patients reported a continuous dyspepsia outcome (one trial gave both dichotomous and continuous outcomes for improvement in dyspepsia). Changes in continuous outcomes were in the same direction but were statistically non-significant (*Figure 7*).

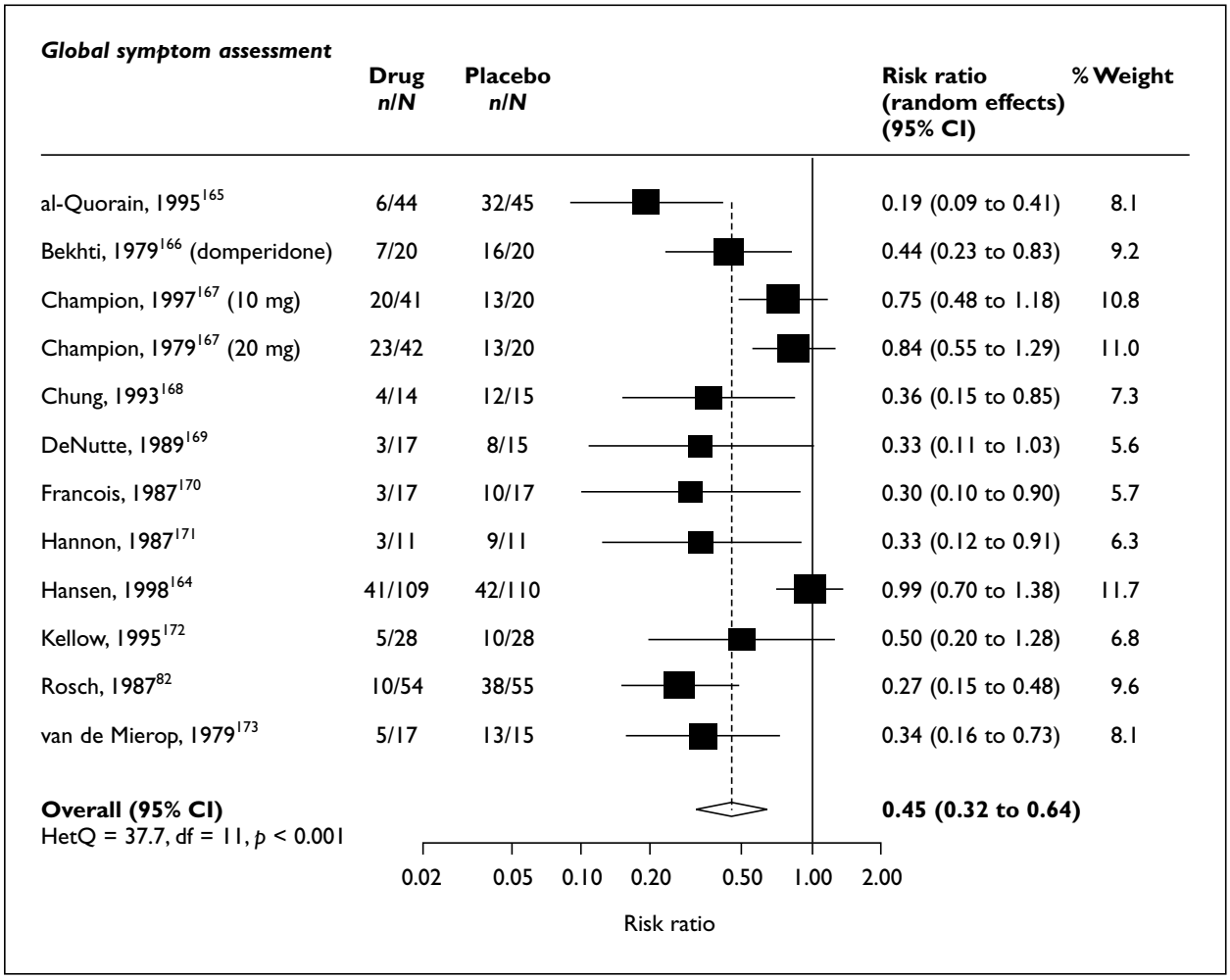


FIGURE 5 *Meta-analysis of efficacy of prokinetic therapy (drug) vs. placebo on global dyspepsia symptoms (dichotomous outcome trials)*

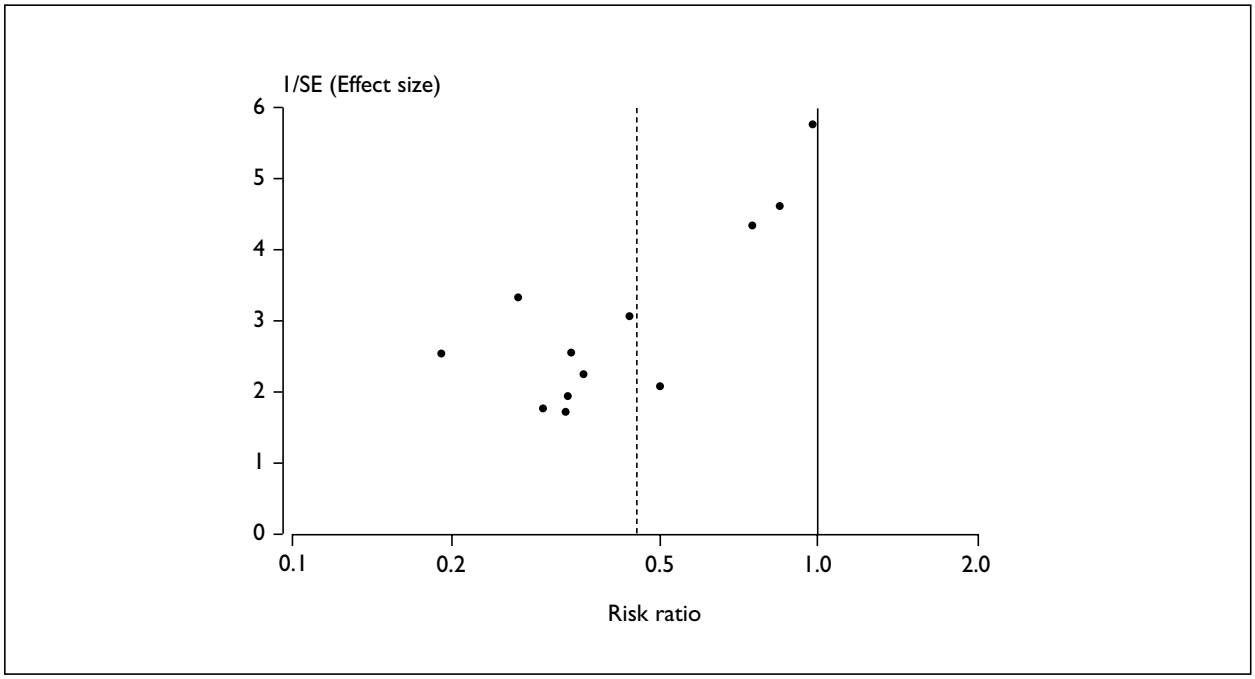


FIGURE 6 *Funnel plot of prokinetic therapy trials*

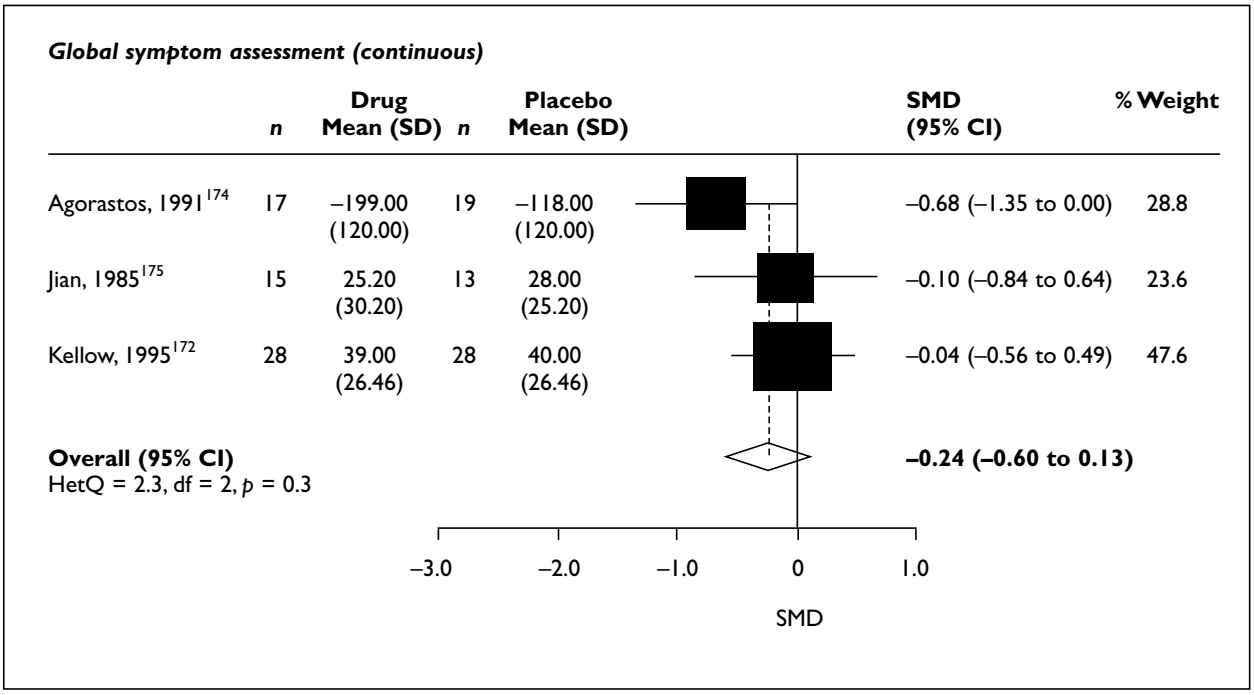


FIGURE 7 *Meta-analysis of efficacy of prokinetic therapy (drug) vs. placebo on global dyspepsia symptoms (continuous outcome trials)*

H_2-receptor antagonist therapy

In the nine trials in which H_2-receptor antagonists were compared with placebo, a total of 1330 patients were evaluated.[72,73,164,179–184] Eight studies showed overall improvement in dyspepsia as a dichotomous variable, which suggested a significant benefit of H_2-receptor antagonists over placebo (RR reduction, 30%; 95% CI, 4 to 48) (*Figure 8*). Again, there was significant heterogeneity between trial results (Q = 27.85; df = 7; $p < 0.0001$) but no evidence of funnel plot asymmetry. Exclusion of one trial with an extreme result[180] did not completely remove the heterogeneity. Again, *a priori* explanations of treatment effects relating to case-mix were not supported by meta-regression. Further analysis identified two factors correlated with treatment effects: year of publication and duration of treatment. More recent trials have shown smaller treatment benefits and have also had shorter follow-up times.

PPI therapy

Four trials that compared omeprazole, 10 mg or 20 mg, with placebo were reported in a single paper; 1248 patients were evaluated.[185] There was a modest benefit in the omeprazole-treated patients compared with placebo; however, this was of marginal statistical significance (RR reduction, 12%; 95% CI, –1 to 24) (*Figure 9*) and the results were also heterogeneous (Q = 9.60; df = 3; $p = 0.02$). The heterogeneity could not be explained by the differences in dosage between the 10 mg/day and 20 mg/day arms.

Bismuth salts

Bismuth salts were compared with placebo in nine trials (reported in seven papers), in which a total of 415 patients were assessed.[186–192] All reported global dyspepsia symptom scores. The majority of the trials evaluating bismuth assessed the role of *H. pylori* eradication in NUD. Trials were, therefore, predominantly in *H. pylori*-positive patients but, as bismuth rarely successfully treats the infection, these were classified as trials evaluating the efficacy of bismuth in NUD. Two trials included both *H. pylori*-positive and -negative individuals and these groups were entered separately to evaluate any difference in outcome according to infection status.[191,192] Six trials reported global dyspepsia improvement as a dichotomous outcome[187–190,192] and there was a trend towards bismuth salts being more effective than placebo, although this was of marginal statistical significance (RR reduction, 40%; 95% CI, –3 to 65) (*Figure 10*). Again, significant heterogeneity was noted in the analysis (Q = 18.31; df = 5; $p = 0.003$), due to the inclusion of one trial[190] with a very low placebo response rate (5%) and a correspondingly large treatment effect (RR reduction, 79%). The estimate of effectiveness when this trial was excluded was an RR reduction of 26% (95% CI, 0 to 45). Three trials reported dyspepsia improvement as a continuous

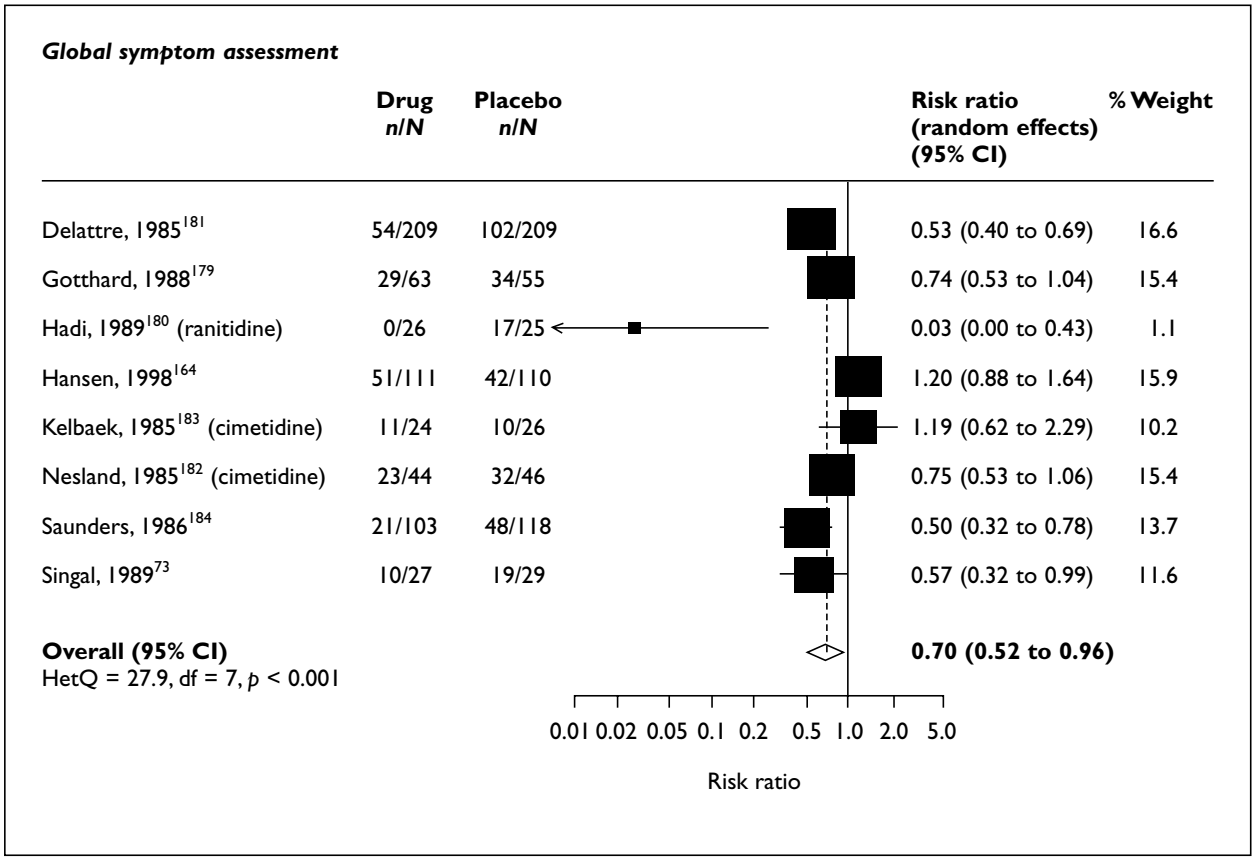


FIGURE 8 *Meta-analysis of efficacy of H_2-receptor antagonists (drug) vs. placebo on global dyspepsia symptoms*

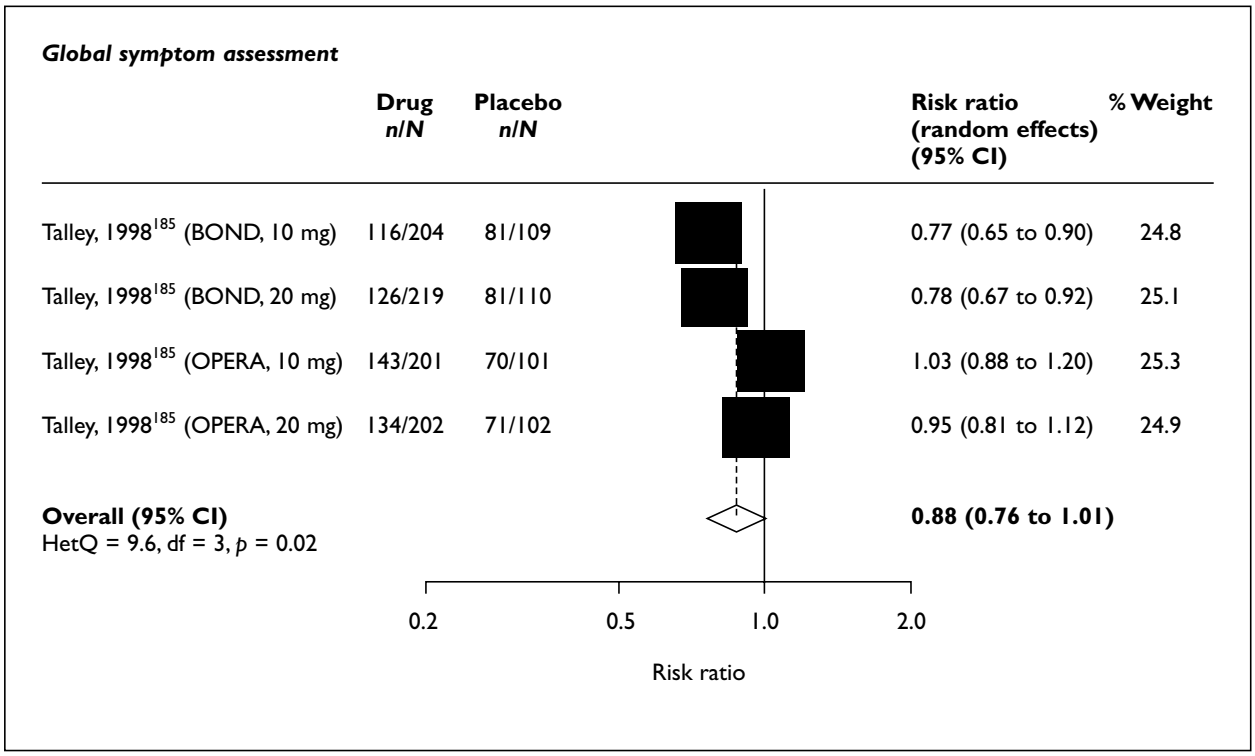


FIGURE 9 *Meta-analysis of efficacy of PPIs (drug) vs. placebo on global dyspepsia symptoms*

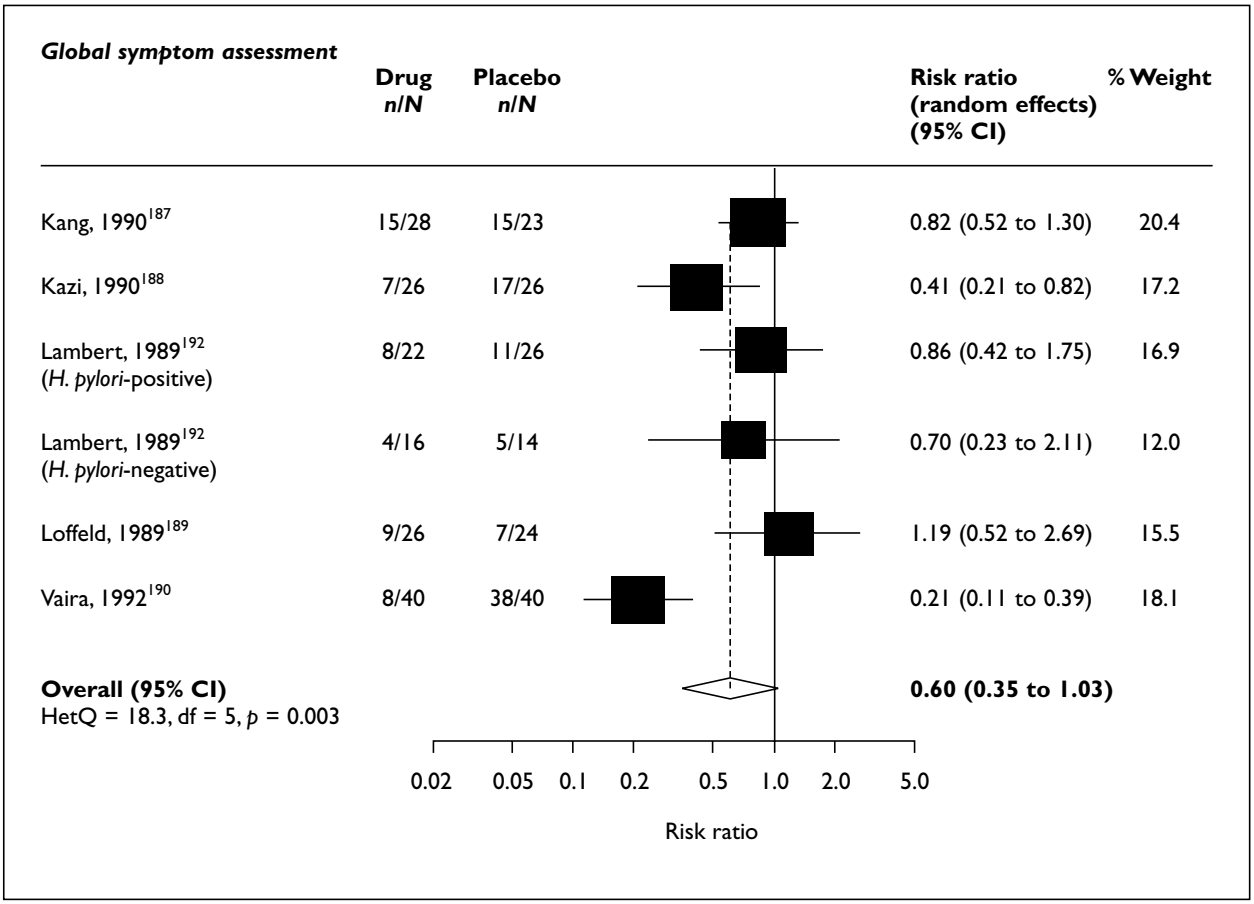


FIGURE 10 *Meta-analysis of bismuth salts (drug) vs. placebo for global dyspepsia symptoms (dichotomous outcome trials)*

variable[186,186,191] and, again, there was a non-significant trend towards a benefit for bismuth salts (*Figure 11*). There was no obvious relationship between *H. pylori* status and effectiveness.[191,192]

Other pharmacological agents

There were two trials in which the antimuscarinic, pirenzepine, was compared with placebo in a total of 163 patients.[193,194] Both reported improvements in global dyspepsia symptoms as a dichotomous variable. There was a significant reduction in dyspepsia in treated patients (RR reduction, 51%; 95% CI, 20 to 70) (*Figure 12*). In two trials, misoprostol was compared with placebo in a total of 177 NUD patients.[195,196] In one (40 patients),[196] improvement in dyspepsia symptoms were evaluated as a dichotomous variable and a significant reduction in dyspepsia was reported for the misoprostol-treated group (RR reduction, 68%; 95% CI, 21 to 87). In the other, larger trial (137 patients), dyspepsia symptoms were reported as a continuous variable and it was suggested that there was a small non-significant improvement with treatment (mean improvement in score, 4.2; 95% CI, 12.7 to –4.3).[195] In this trial, two individual symptoms (epigastric pain and nausea) were also evaluated and the authors suggested that there was a significant increase in epigastric pain in patients treated with misoprostol.

Antacids were not found to be significantly better than placebo[72] (RR, 1.02; 95% CI, 0.76 to 1.36) in the one trial (109 patients) that evaluated this intervention. There was also no evidence that sucralfate was superior to placebo from a meta-analysis of two trials (*Figure 13*).[76,197] A further trial (28 patients), in which global symptoms were reported as a continuous outcome measure, also found no difference between sucralfate and placebo (symptom score improved by a mean of 0.8 in the placebo group compared with the sucralfate group; 95% CI, –0.83 to 2.43).[186]

Direct comparisons between interventions

The trials in which therapies were compared directly were all too severely underpowered to detect any likely differences between therapies, having sample sizes ranging from 23 to 220 patients. A trial would require about 1100 participants to have an 80% power of detecting an absolute change of 10% in improvement rates, assuming an average improve-

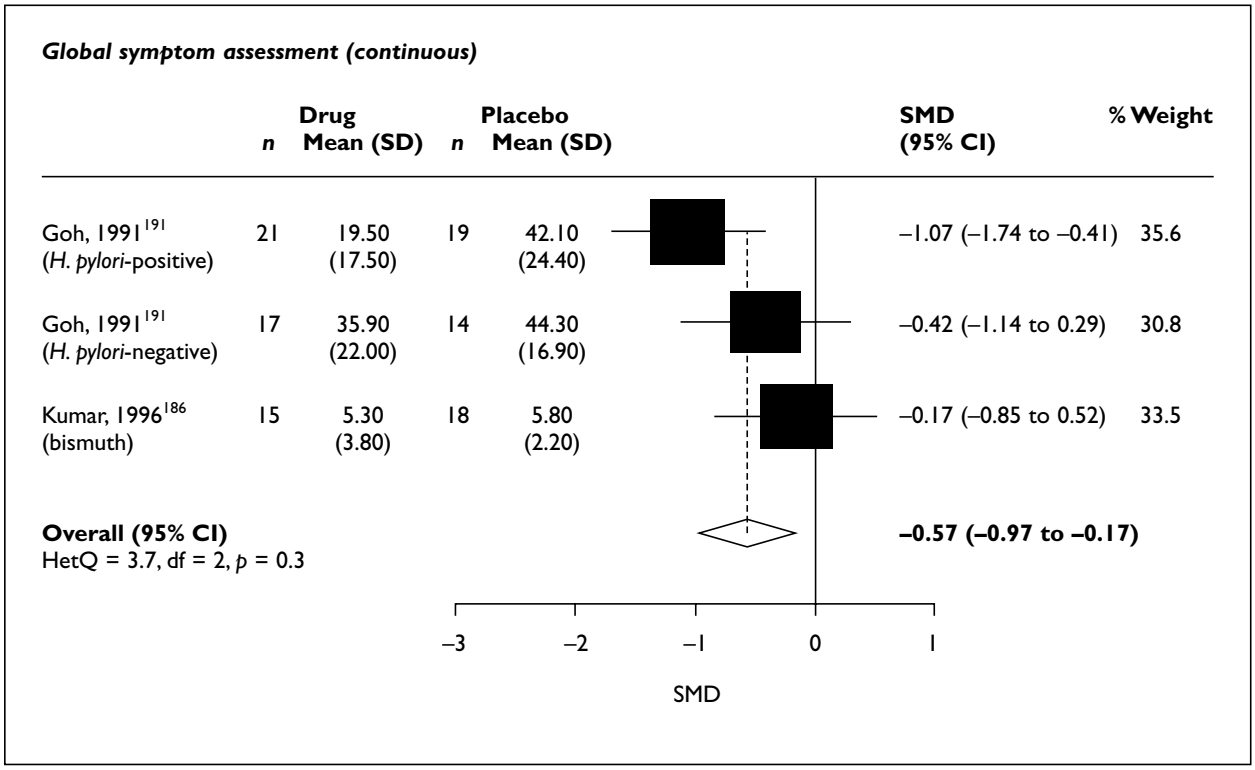


FIGURE 11 *Meta-analysis of bismuth salts (drug) vs. placebo for global dyspepsia symptoms (continuous outcome trials)*

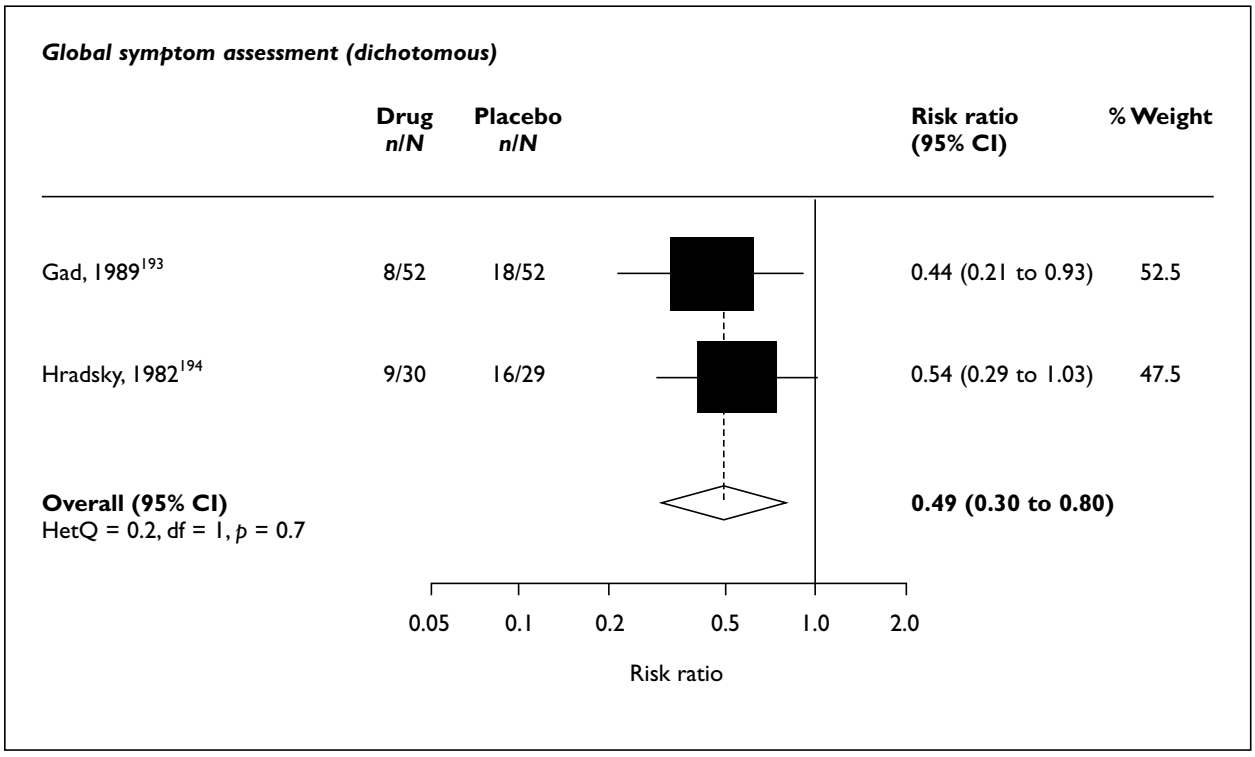


FIGURE 12 *Meta-analysis of pirenzepine (drug) vs. placebo for global dyspepsia symptoms*

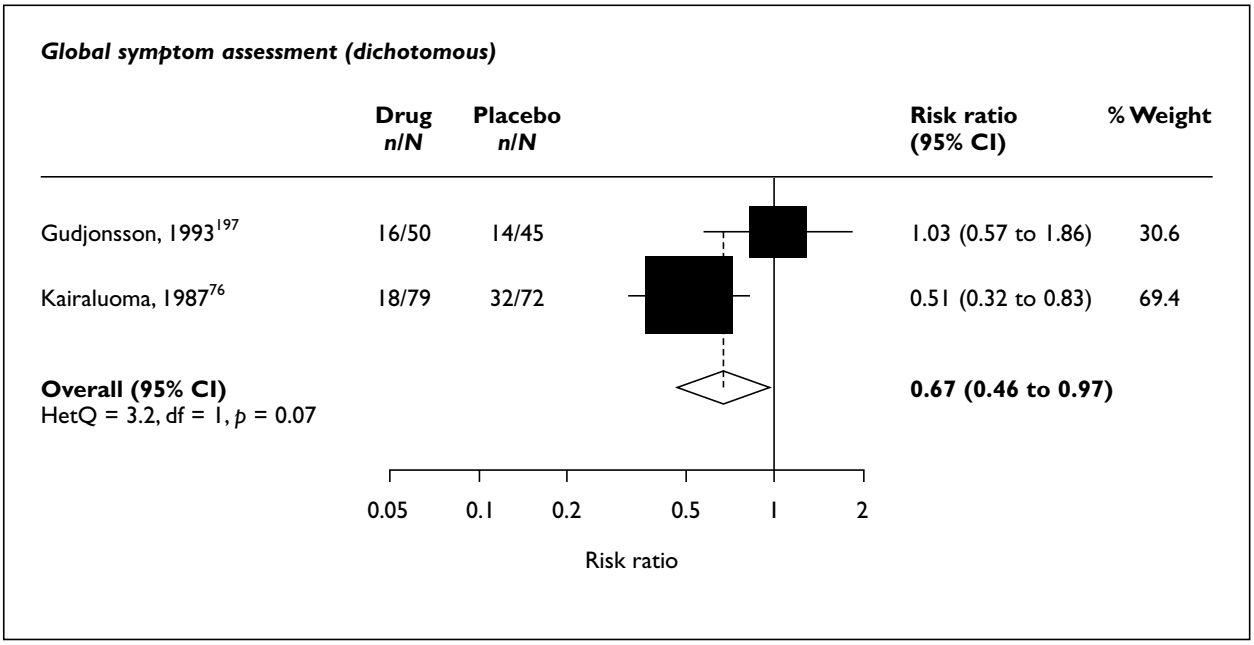


FIGURE 13 *Meta-analysis of sucralfate (drug) vs. placebo for global dyspepsia symptoms*

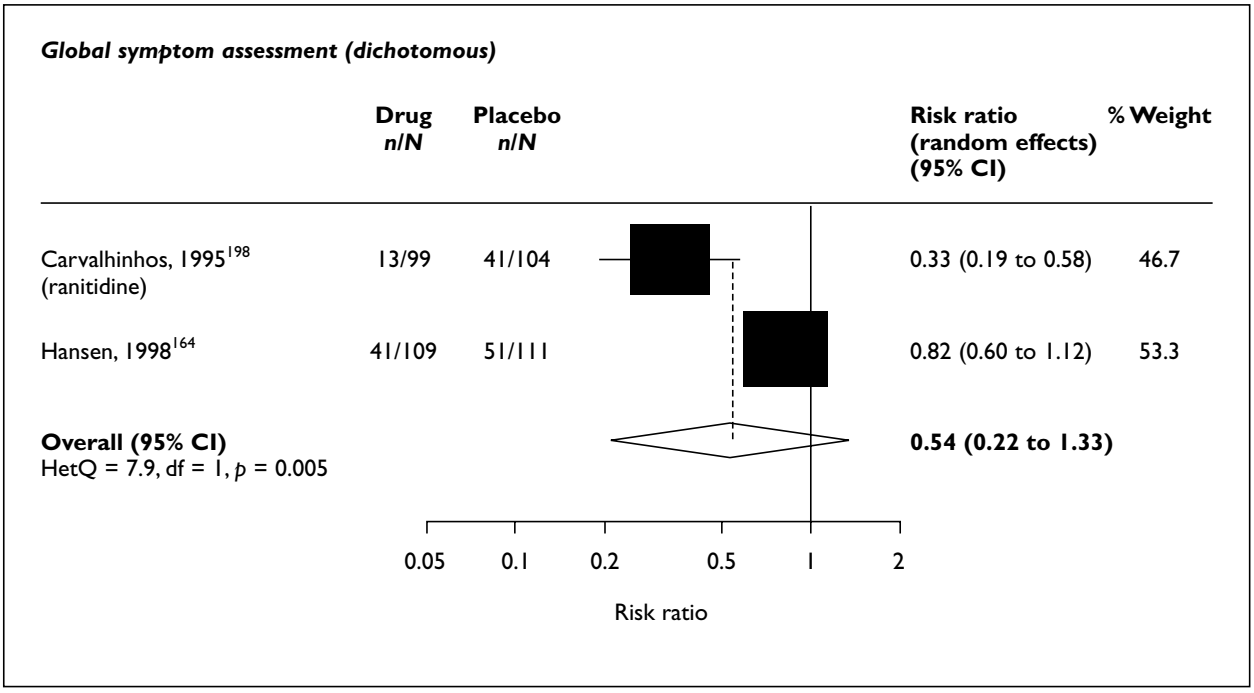


FIGURE 14 *Meta-analysis of prokinetics (drug) vs. H_2-receptor antagonists (placebo) for global dyspepsia symptoms*

ment rate of about 50%. Despite this, three trials showed significant benefits of one treatment over another.

Two trials in which prokinetics were compared with H_2-receptor antagonists used global dyspepsia improvement as a dichotomous variable.[164,198] The results favoured prokinetics, although the difference was not statistically significant (RR of remaining dyspeptic following prokinetics compared with H_2-receptor antagonists, 0.54; 95% CI, 0.22 to 1.33) and the trial results were not consistent (test for heterogeneity: Q = 7.9; df = 1; $p = 0.005$) (*Figure 14*).

In one trial, antacids were compared with H_2-receptor antagonists in 104 patients with NUD.[199] The outcome, dyspepsia improvement,

was measured as a dichotomous variable and there was a 33% RR reduction in favour of antacids, although the CIs were wide (95% CI, 80 to –123).

There was no significant difference between H_2-receptor antagonists and pirenzepine in a trial evaluating dyspepsia improvement as a dichotomous outcome (114 patients) (RR reduction, 7% in favour of H_2-receptor antagonists; 95% CI, –51 to 42),[200] although in a small trial of 23 patients, in which the two drugs were compared with global dyspepsia score as a continuous outcome, a significant benefit was shown for pirenzepine.

One trial compared an H_2-receptor antagonist with sucralfate and reported that those receiving antisecretory therapy were 2.7 times (95% CI, 1.3 to 6.0) more likely to have moderate or severe dyspepsia at the end of the trial than those allocated to sucralfate.[201]

Bismuth salts and sucralfate were compared in one trial of 29 patients; no significant difference was found between the two drugs.[186]

Indirect comparisons between interventions

This results of this systematic review suggest that there are four interventions for which comparisons are of importance based on the placebo-controlled estimates of effectiveness: prokinetics, PPIs, bismuth salts and H_2-receptor antagonists. Indirect comparisons of effectiveness can be made between these agents by comparing the results of the placebo-controlled trials, effectively ranking their RR reductions. The significance of these differences can be tested in a random effects meta-regression. In this instance, all of the comparisons are made between PPIs and other groups (*Table 22*).

Although all therapies other than antacids showed a trend towards being more effective than PPIs, the indirect analysis showed only prokinetics to be statistically significantly better than PPIs (RR reduction, 41%; 95% CI, 6 to 63; $p = 0.03$). However, when the prokinetic trials are stratified as before 1996 or after 1995, this difference remains only for the earlier trials (RR reduction, 55%; $p < 0.001$), not for the more recent trials (RR reduction, 1%; $p = 0.98$).

TABLE 22 *Summary of RR reductions and NNTs for placebo-controlled trials: pharmacological interventions for NUD*

Drug group	Trials and subgroups	RR reduction (95% CI)	NNT (95% CI) assuming 50% placebo recovery	Statistical between-study heterogeneity
Prokinetics	12 trials	50% (30 to 70)	4 NNT (benefit) (3 (benefit) to 7(benefit))	Q = 37.7 (df = 11); $p < 0.001$
	Post-1995 trials only	10% (–11 to 27)	20 NNT (benefit) (7 (benefit) to 18 (harm))	Q = 0.99 (df = 3); $p = 0.80$
	Pre-1996 trials only	69% (59 to 77)	3 NNT (benefit) (3 (benefit) to 3 (benefit))	Q = 4.06 (df = 7); $p = 0.77$
H_2-receptor antagonists	8 trials	29% (4 to 47)	7 NNT (benefit) (4 (benefit) to 50 (benefit))	Q = 27.9 (df = 7); $p < 0.0001$
Bismuth	6 trials	40% (–3 to 65)	5 NNT (benefit) (3 (benefit) to 67 (harm))	Q = 18.3 (df = 5); $p < 0.001$
	Excluding Vaira	26% (0 to 45)	8 NNT (benefit) (4 (benefit) to ∞)	Q = 4.4 (df = 4); $p = 0.35$
PPIs	4 trials	12% (–1 to 24)	17 NNT (benefit) (8 (benefit) to 200 (harm))	Q = 9.6 (df = 3); $p = 0.02$
Pirenzepine	2 trials	51% (20 to 70)	4 NNT (benefit) (3 (benefit) to 10 (benefit))	Q = 0.17 (df = 1); $p = 0.68$
Sucralfate	2 trials	29% (–40 to 64)	7 NNT (benefit) (3 (benefit) to 5 (harm))	Q = 3.19 (df = 1); $p = 0.07$
Misoprostol	1 trial	68% (21 to 87)	3 NNT (benefit) (2 (benefit) to 10 (benefit))	N/A
Antacids	1 trial	–2% (–36 to 24)	100 NNT (harm)	N/A

Summary of placebo comparisons

The most notable feature of the placebo-controlled trials is the high degree of heterogeneity observed for all therapies. This hinders easy interpretation of effects in the observed trials, the manner in which it is dealt with affecting both the size and significance of the effects. In an analysis considering the most conservative estimates (based on prokinetic trials from 1996 onwards and excluding the trial by Vaira and colleagues[190]), H_2-receptor antagonists and bismuth showed significant RR reductions of more than 25%, while PPIs and prokinetics demonstrate RR reductions of about 10% which just fail to reach significance, there being no significant differences between any of the treatments (*Table 22*).

Comparisons of different brands of the same class of drug

There have been few direct comparisons of the efficacy of different brands of the same class of drug. Trials have not compared different brands of H_2-receptor antagonists with each other in patients with NUD, although evidence would suggest that the efficacy of these drugs is similar in treating PUD. PPIs have also not been compared in patients with NUD, although they have a similar efficacy in treating oesophagitis. There is only one type of bismuth salt available in the UK.

There is some evidence for cisapride being more effective than domperidone or metoclopramide in improving gastric emptying; direct comparisons between cisapride, domperidone and metoclopramide in patients with NUD were made in three trials:

- cisapride versus metoclopramide (60 patients)[84]
- cisapride versus domperidone (84 patients)[202]
- metoclopramide versus domperidone (138 patients).[85]

There were no significant differences within any of these trials, although cisapride tended to be the most effective. The RR reduction for cisapride compared with domperidone was 48% (95% CI, –72 to 84), while compared to metoclopramide it was 43% (95% CI, –75 to 81). There was no difference between domperidone and metoclopramide (RR, 1.01; 95% CI, 0.70 to 1.45).

The effects of pharmacological therapies on individual symptoms

This analysis of individual symptoms should be interpreted with caution, and comparisons should not be made between drugs. This is because symptoms at baseline differed between trials and, therefore, the effect of treatments on symptoms might be expected to vary.

Comparison with placebo

Eleven trials evaluated the effect of prokinetic therapy on individual symptoms, including three trials in which this was the only outcome measured.[176–178] For epigastric pain, there was a 60% reduction in the risk of symptoms remaining at the end of treatment. This was similar for some other outcomes: early satiety (RR reduction, 56%), eructation (78%) and nausea (67%); but smaller for others: post-prandial fullness (RR reduction, 30%) and bloating (RR reduction, 45%) (*Figure 15*).

The effect of H_2-receptor antagonists on individual dyspepsia symptoms was assessed in five trials.[164,179,181–183] Epigastric pain (RR reduction, 18%; 95% CI, 0 to 32) and postprandial fullness (RR reduction, 28%; 95% CI, 0 to 49) were improved by H_2-receptor antagonist therapy compared with placebo with no significant improvement in other individual symptoms (*Figure 16*).

The study in which PPI therapy in NUD was evaluated did not report the response of individual symptoms. However, patients were prospectively divided into ulcer-like (predominant epigastric pain), dysmotility-like (predominant postprandial fullness, early satiety or belching), or reflux-like (predominant heartburn or acid regurgitation) dyspepsia subgroups. Reflux-like dyspepsia responded most successfully to therapy, with 54% of patients reporting complete symptom relief with omeprazole, 20 mg once daily, compared with 23% with placebo ($p = 0.002$). Ulcer-like dyspepsia also responded to omeprazole, 20 mg once daily (40% complete relief versus 27% with placebo; $p = 0.006$), but active treatment was not significantly better than placebo for dysmotility-like dyspepsia (32% of patients' symptoms completely responded to omeprazole, 20 mg, 31% responded to placebo; $p = 0.92$).

A significant reduction in flatulence was noted in patients treated with bismuth salts (RR reduction 97%) but that result came from the trial with the most extreme global result. In two other trials that evaluated individual dyspepsia symptoms, the efficacy of bismuth salts was found to be no better than placebo for epigastric pain, bloating, nausea, flatulence, belching and heartburn.

The effect of antacids on epigastric pain was evaluated in two trials,[72,179] one of which also reported bloating and nausea.[179] There was no

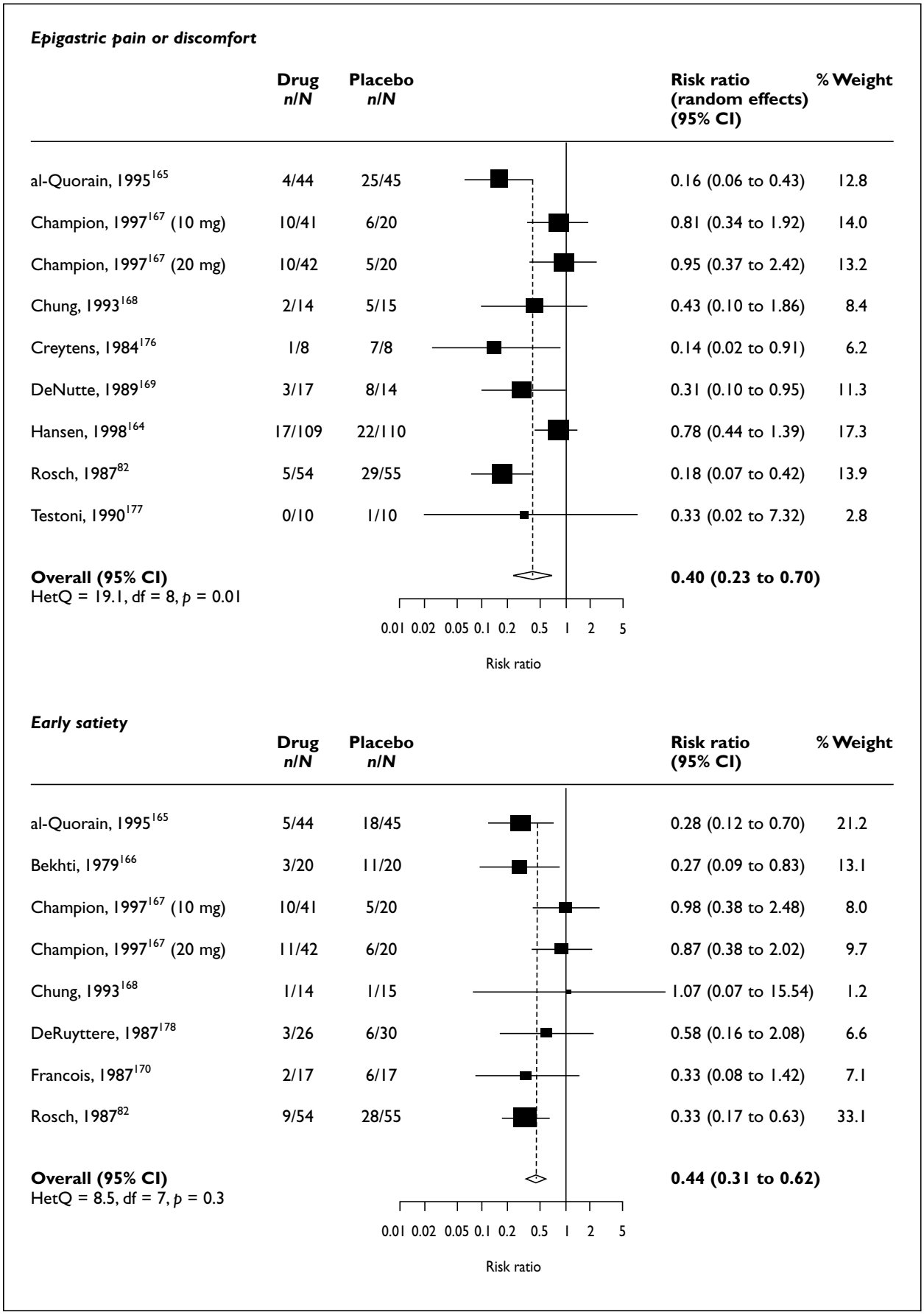
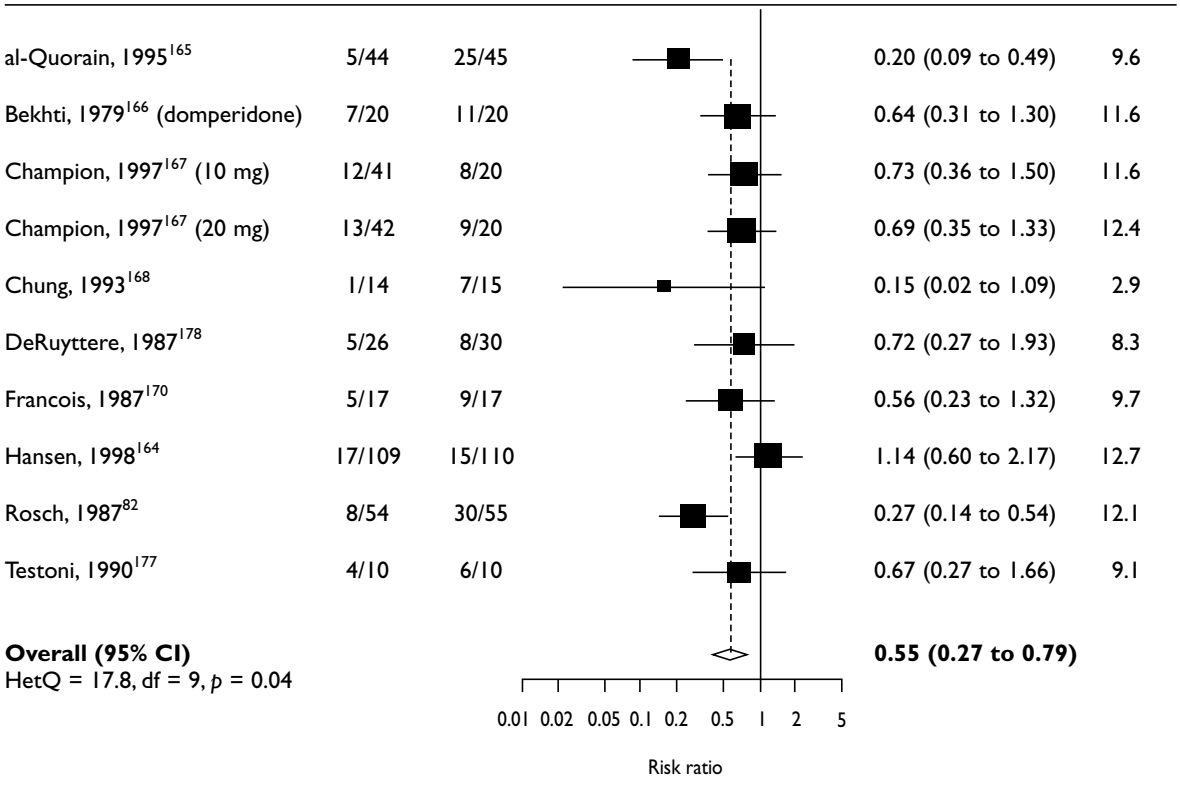


FIGURE 15 *Meta-analysis of prokinetic therapy (drug) vs. placebo on individual dyspepsia symptoms*

Bloating



Nausea

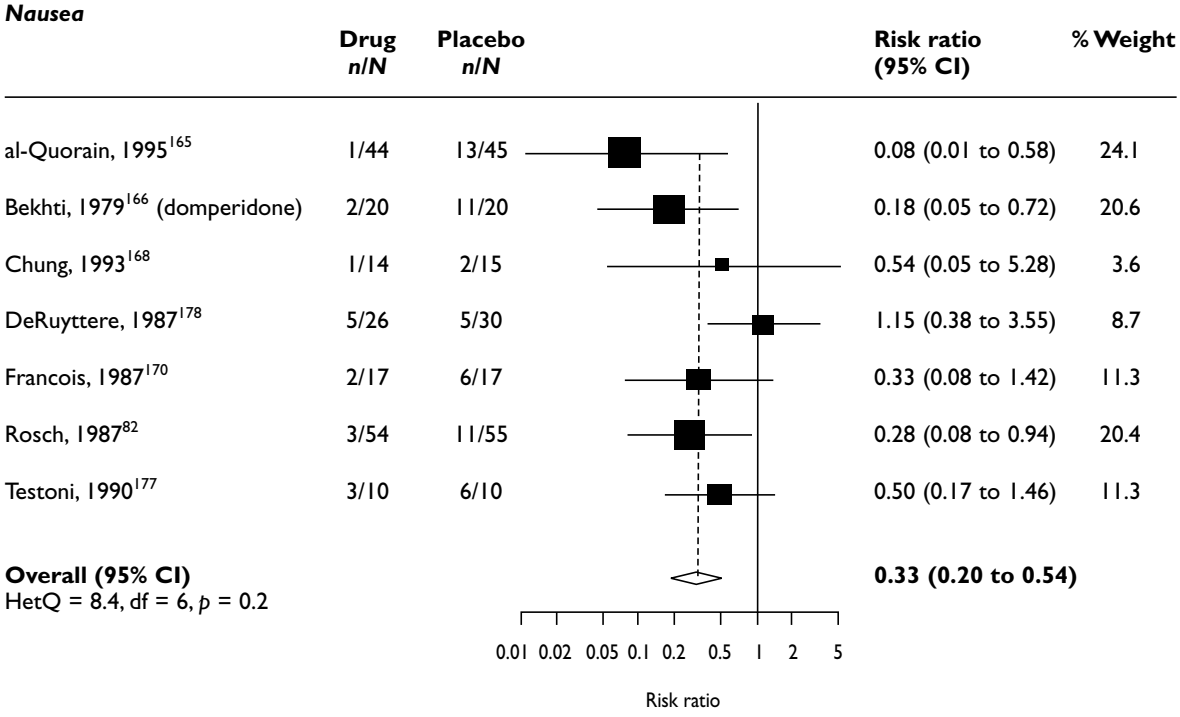


FIGURE 15 contd *Meta-analysis of prokinetic therapy (drug) vs. placebo on individual dyspepsia symptoms*

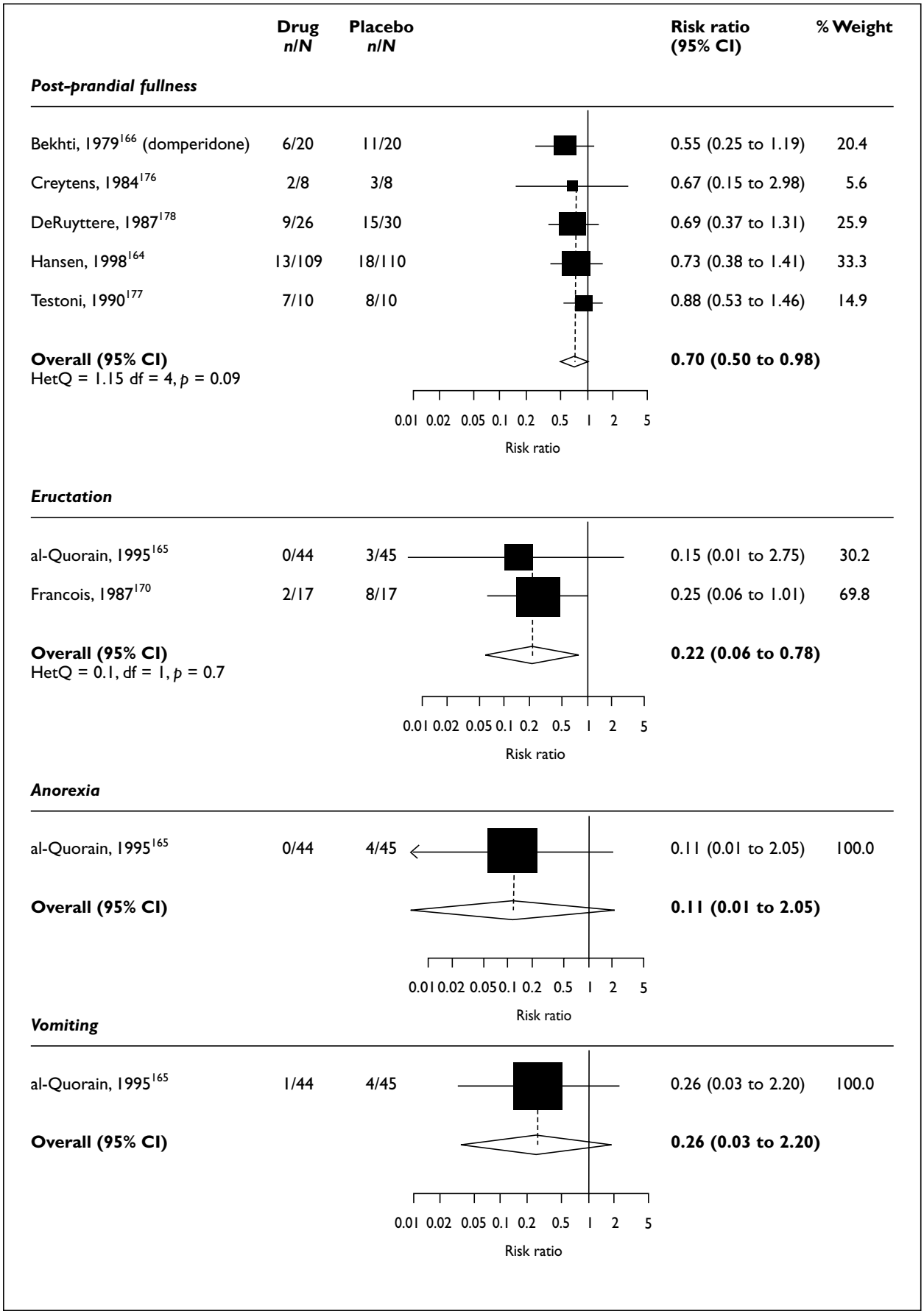


FIGURE 15 contd *Meta-analysis of prokinetic therapy (drug) vs. placebo on individual dyspepsia symptoms*

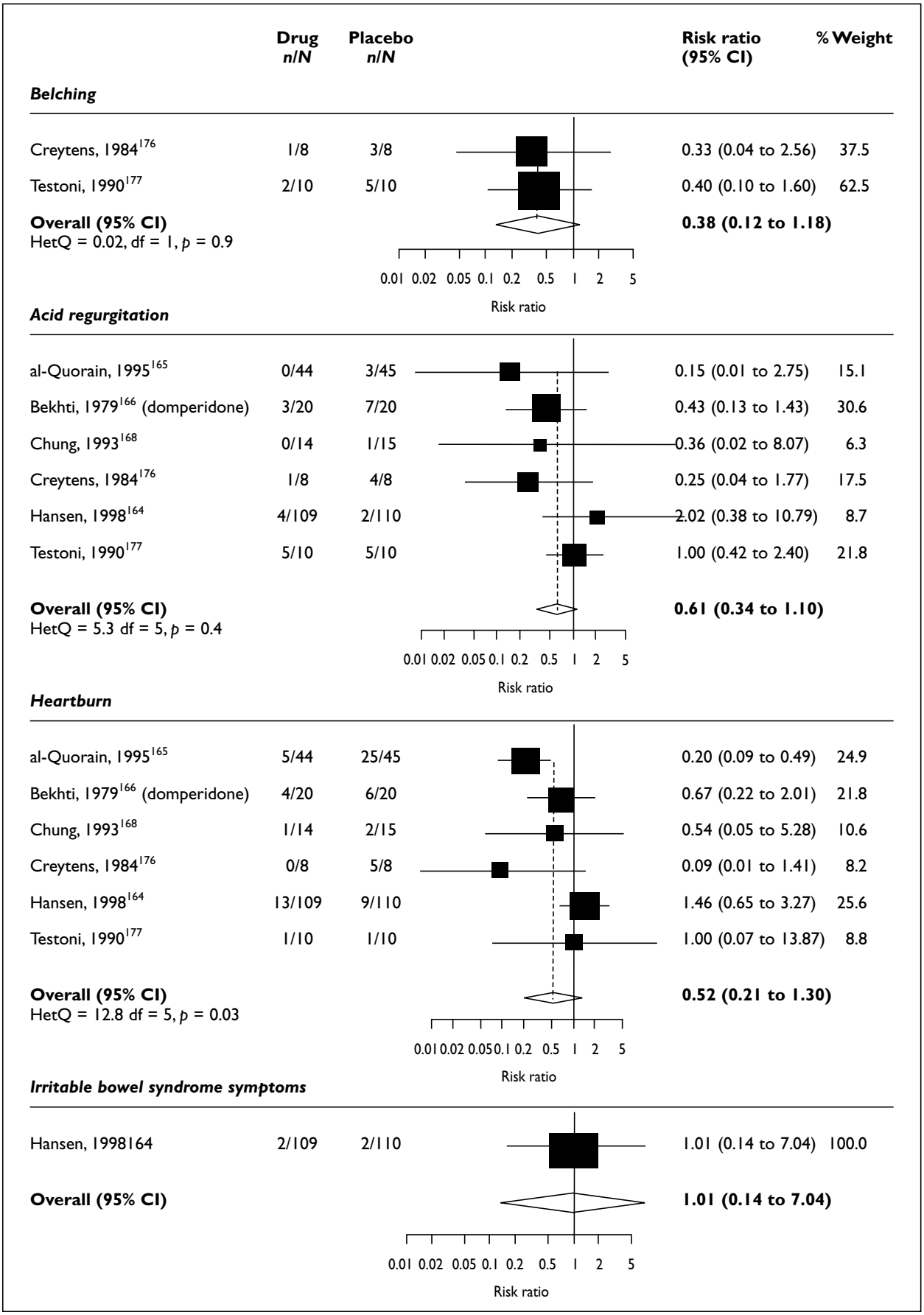


FIGURE 15 contd *Meta-analysis of prokinetic therapy (drug) vs. placebo on individual dyspepsia symptoms*

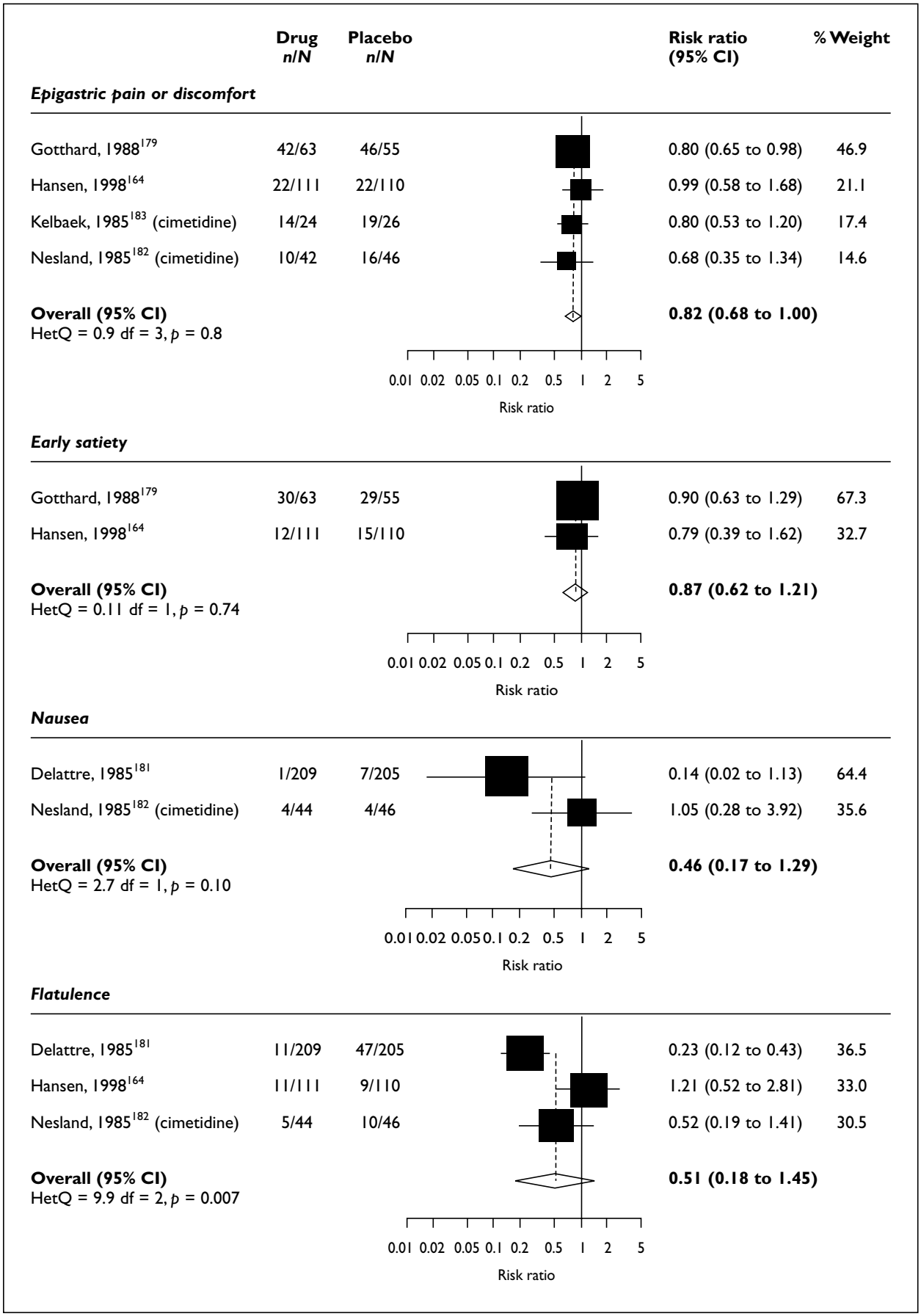


FIGURE 16 *Meta-analysis of H_2-receptor antagonist therapy (drug) vs. placebo on individual dyspepsia symptoms*

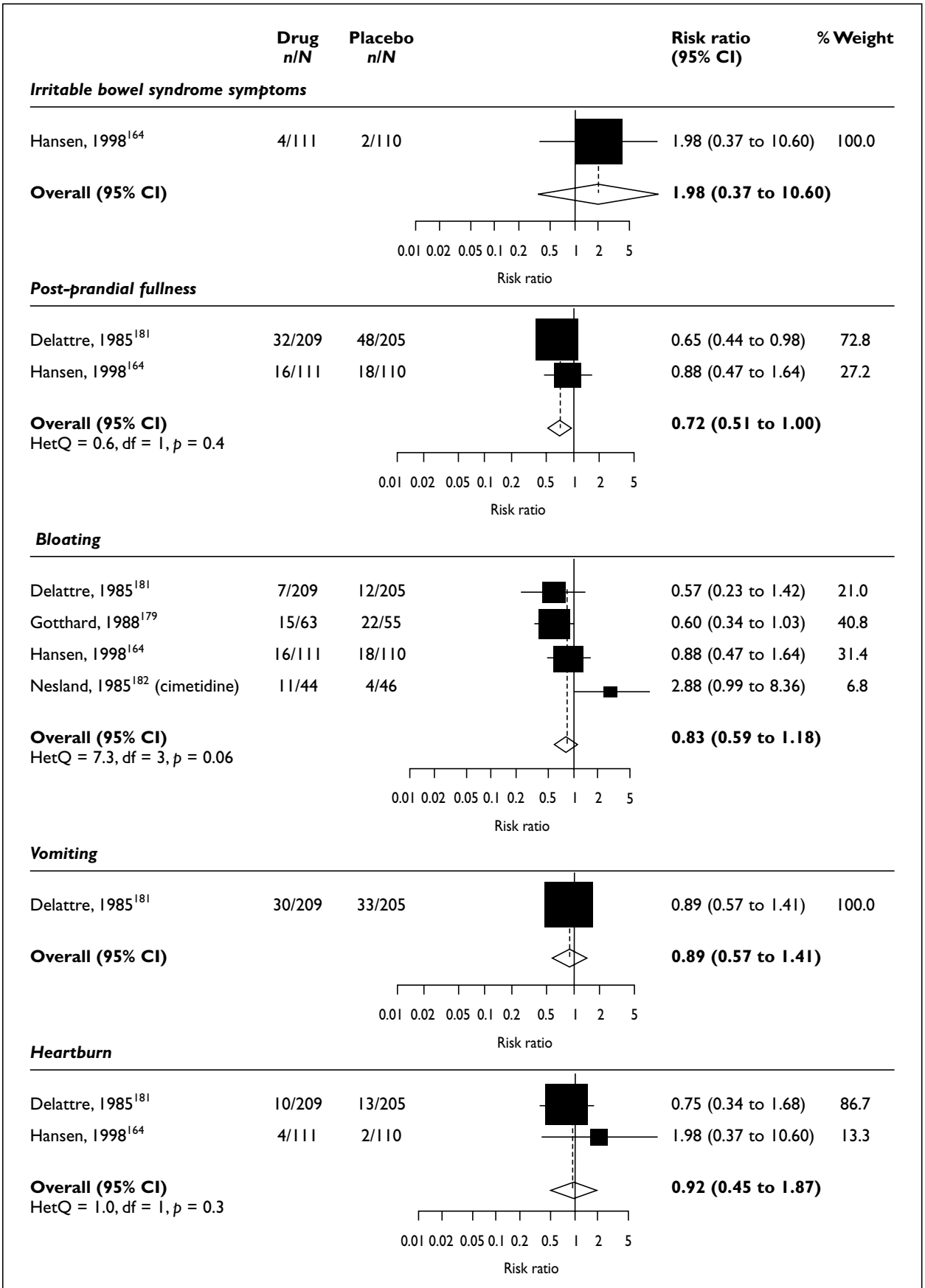


FIGURE 16 contd *Meta-analysis of H_2-receptor antagonist therapy (drug) vs. placebo on individual dyspepsia symptoms*

evidence that antacids were superior to placebo for any of these symptoms apart from bloating, which was marginally improved in patients with NUD taking antacids (RR, 0.60; 95% CI, 0.37 to 0.95).

Direct comparison between interventions

One trial compared H_2-receptor antagonists with prokinetics using individual dyspepsia symptoms as an outcome.[164] Prokinetics were superior in reducing nausea (RR reduction, 87%; 95% CI, 46 to 97), showed a trend to reductions in epigastric pain, postprandial fullness and symptoms of irritable bowel syndrome, and no difference for acid regurgitation, heart-burn and bloating. The difference for nausea was the only one to reach statistical significance (*Figure 17*). A further trial compared H_2-receptor antagonists and antacids using individual symptoms of epigastric pain, nausea, postprandial fullness, bloating and early satiety as outcomes but showed no significant differences between the treatments.[179]

Sensitivity analyses

Quality of the trials

The quality of trials evaluating pharmacological therapies in NUD that were included was evaluated using predefined criteria. Trials were mainly conducted in secondary care and patients needed to have dyspepsia for between zero and 6 months before being included in the trial (appendix 4).

Overall, the quality of trial reporting was poor, with most not specifying the method of randomisation or concealment or that the investigator assessing the outcome was masked. The exception to this was the study evaluating PPI therapy in NUD. This did state the method of randomisation, concealment and masking. There was also a 97% follow-up rate in this study, which generated four trials for the review.

Reasons for heterogeneity

Trials comparing prokinetics with placebo exhibited significant heterogeneity (Q = 37.68; df = 11; $p < 0.001$). Clear asymmetry is evident in the funnel plot for prokinetic trials (looking at the outcome of global response). The Egger test of funnel plot asymmetry was statistically significant for the prokinetic trials (see *Figure 13*; $p = 0.002$). There was an excess of small beneficial trials and an absence of small trials with no effect, or harmful effects. The larger trials showed an almost complete absence of effect. The superiority of prokinetics observed in the other analyses could be explained by publication bias or related quality issues and, in reality, may not exist.

There was also significant heterogeneity in H_2-receptor antagonist trials (Q = 27.9; $p < 0.0001$). There was little asymmetry in the Egger test of funnel plot ($p = 0.5$) suggesting publication bias did not explain the superiority of H_2-receptor antagonists over placebo. There was one very small and very positive trial with six from eight studies reporting a result in favour of H_2-receptor antagonists.

The four trials generated from one PPI study also exhibited heterogeneity (Q = 9.60; df = 3; $p = 0.02$) as acknowledged by the authors. There were different doses of PPI used and different proportions of patients were recruited from primary care, but this did not explain the heterogeneity between trials.

Bismuth trials also demonstrated significant between-study heterogeneity (Q = 18.31; df = 5; $p < 0.001$) but there was no evidence that individuals uninfected with *H. pylori* were different from infected patients.[191,192,203] There was no asymmetry in the Egger plot ($p = 0.8$), all the trials being about the same size.

Prokinetics, H_2-receptor antagonists and PPIs have effects on GORD, which can be present despite a normal endoscopy. A proportion of patients with NUD may have GORD, and reduction in heartburn symptoms may explain the results observed. To investigate this hypothesis, the efficacy of therapy was evaluated according to the proportion of patients with NUD with symptoms of heartburn at the start of the trial. There was no evidence that any of these drugs was more effective with increasing proportions of patients with heartburn at baseline. Other than for prokinetics, H_2-receptor antagonists and bismuth, there were insufficient trials to investigate the potential sources of heterogeneity in any meaningful or robust manner.

Discussion

Prokinetic therapy

The existing data suggest that prokinetic drugs are the most effective agents in patients with NUD. This is consistent with reports that gastric dysmotility is more frequently seen in patients with NUD compared with asymptomatic controls. This conclusion should be interpreted with caution as there was statistically significant heterogeneity, accounted for by publication year, with

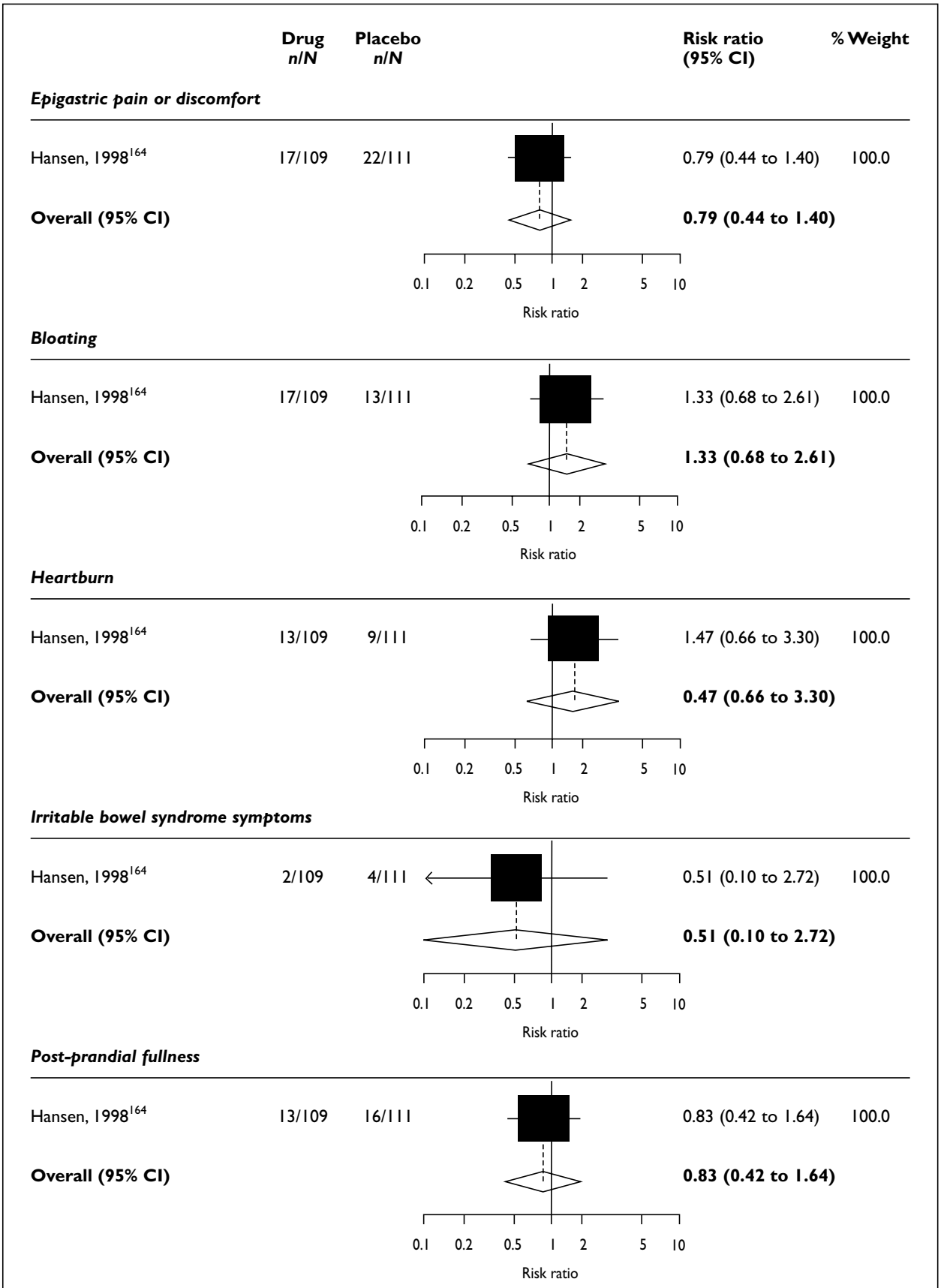


FIGURE 17 *Meta-analysis of prokinetics (drug) vs. H_2-receptor antagonists (placebo) for individual dyspepsia symptoms*

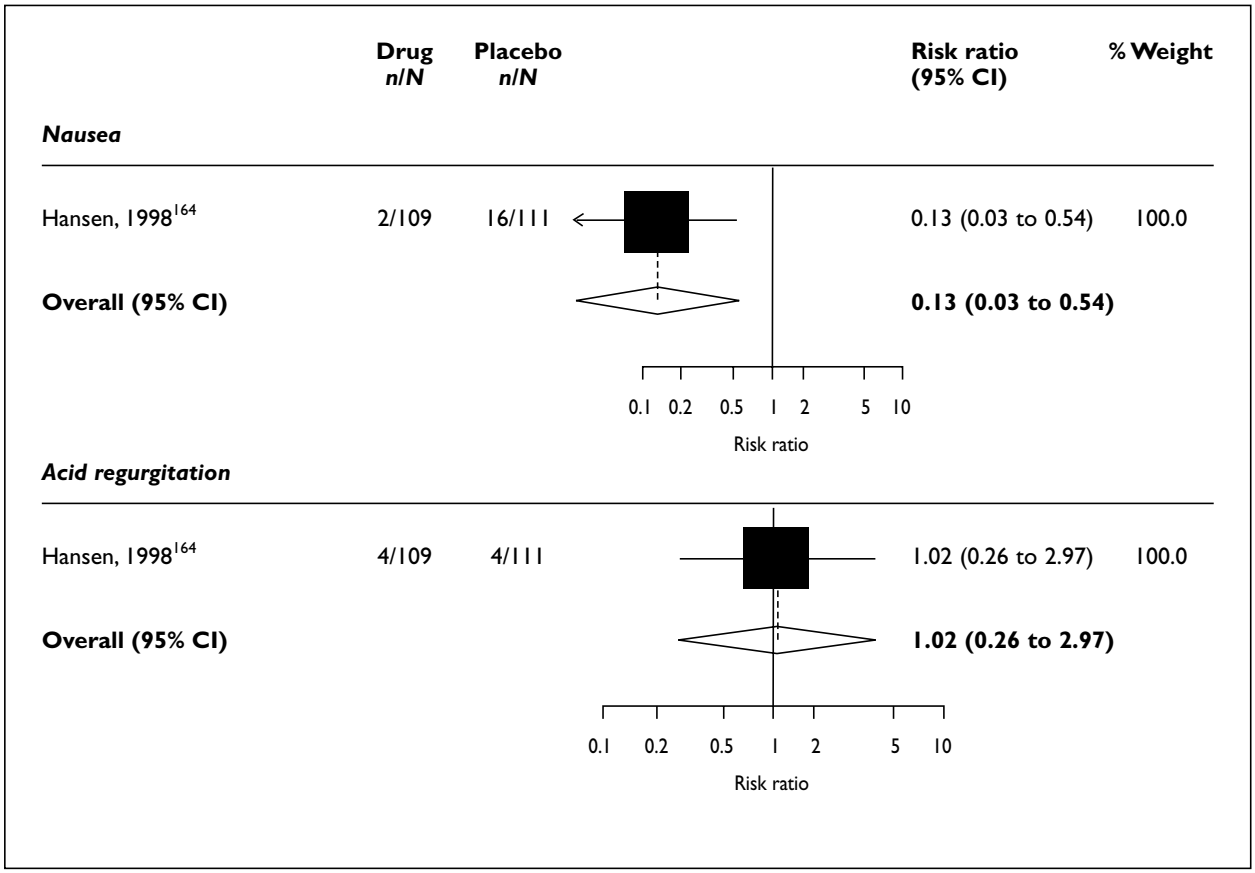


FIGURE 17 contd *Meta-analysis of prokinetics (drug) vs. H_2-receptor antagonists (placebo) for individual dyspepsia symptoms*

more recent studies showing no significant effect. Moreover, the funnel plot indicated that this could be due to publication bias or to inclusion of poor quality studies.

The majority of NUD trials have methodological problems;[64] this was supported by an assessment of the quality of papers comparing prokinetic drugs with placebo before synthesis of the results. Most of the trials evaluating prokinetic therapy were small. The 11 prokinetic papers included in the meta-analysis of dichotomous global dyspepsia outcomes studied fewer patients with NUD than the one paper that evaluated PPI therapy. Only one prokinetic trial recruited more than 100 patients into each arm of the study; it was one of only two trials that reported the method of randomisation and concealment. The study reported the RR nearest to unity in the prokinetic meta-analysis; this is consistent with reports that trials with 'inadequate' randomisation and concealment have exaggerated estimates of RR.[204] There was a trend for prokinetic therapy to be superior to H_2-receptor antagonists in NUD but this finding was influenced by one trial not reporting methods of concealment or randomisation, and was not confirmed by a larger study reporting an adequate method of randomisation.

There are also concerns about the type of patients with NUD included in the prokinetic studies. Trials only including patients with gastroparesis were excluded from the review but those that evaluated all patients attending for gastric emptying studies were included. This group of patients may be different from those with NUD normally seen in clinic and the results should be generalised with caution. Large, well-designed, RCTs comparing prokinetic therapy with placebo in unselected patients with NUD are still required in order to be confident that this approach is effective.

The choice of prokinetic drug is also uncertain. The majority of prokinetic trials evaluated cisapride. These trials were small and it is not possible to be certain that cisapride is more effective than either domperidone or metoclopramide in patients with NUD. More importantly, since it has been withdrawn from the market, possible evidence in its favour is unhelpful. It was also the most expensive dyspepsia drug. Only two placebo-controlled trials have assessed the alternative

treatment, domperidone, in patients with NUD. Metoclopramide is cheaper still and in one trial that evaluated 138 patients a similar efficacy to domperidone in NUD was reported. Metoclopramide is, however, associated with occulogyric crises in a small number of patients and no placebo-controlled trial that evaluated this drug was eligible for this review. Trials that have suggested that cisapride is more effective than either domperidone or metoclopramide in patients with NUD have been small and inconclusive. In the light of the withdrawal of cisapride, further evidence is required on the efficacy of domperidone and metoclopramide compared with placebo in patients with NUD.

Anti-secretory therapy

Anti-secretory drugs have been the most evaluated therapy in NUD, despite there being little evidence that acid is involved in the aetiology of this condition. H_2-receptor antagonist therapy was superior to placebo (RR, 0.7; 95% CI, 0.52 to 0.96) with 1225 patients evaluated in the meta-analysis. The efficacy of H_2-receptor antagonists appears more pronounced than PPI therapy (RR, 0.88; 95% CI, 0.76 to 1.01). This is unexpected as PPIs are more potent acid inhibitors and more effective in PUD and oesophagitis. This probably relates to methodological issues, particularly as a large trial, so far only reported in abstract form, suggests anti-secretory therapy is superior to placebo, with PPIs being more effective than H_2-receptor antagonists. There was no evidence of publication bias from the funnel plot of H_2-receptor antagonist therapy trials but the overall quality of the trials was inferior to the one study that investigated PPIs in NUD. This study evaluated more patients (1248) than all of the other eight H_2-receptor antagonist studies and adequately stated the method of randomisation and concealment. It is likely that if the eight H_2-receptor antagonist trials had been as rigorous as the PPI studies then the efficacy in NUD would be less pronounced. Nevertheless, there is currently no evidence that PPIs are more effective than H_2-receptor antagonist therapy and, overall, there is some evidence that acid inhibition is effective in NUD. H_2-receptor antagonists may therefore be the drugs of choice as they are cheaper than PPI therapies. Comparative trials of these two agents are lacking, although it was suggested in one abstract that PPI therapy may be slightly more effective than H_2-receptor antagonist therapy.

The efficacy of anti-secretory therapy in NUD may relate to the treatment of ENRD. GORD is more common in patients reporting predominant heartburn and acid reflux, although the sensitivity of these symptoms is not ideal. There is no evidence that the effect size of H_2-receptor antagonist trials, with a higher proportion of patients complaining of heartburn, was greater than trials excluding these patients. Heartburn was, however, relieved more effectively than epigastric pain or nausea and it was reported in the PPI paper that the active drug was most effective in patients with reflux-like dyspepsia. It is possible that the efficacy of anti-secretory therapy relates to the effects on atypical ENRD. Nevertheless, this review indicates that patients diagnosed as having NUD by their clinician are more likely to respond to anti-secretory therapy than placebo. This pragmatic finding is important as it suggests that GPs and gastroenterologists should use these agents even if the explanation for their effectiveness lies in the treatment of atypical GORD.

Bismuth salts

Bismuth salts were also more effective than placebo in NUD (RR, 0.6; 95% CI, 0.35 to 1.03), although this was of marginal statistical significance. In the meta-analysis of dichotomous global dyspepsia improvement, 311 patients were evaluated, which was far fewer than those assessed in the prokinetic and anti-secretory sections of the review. The effect of bismuth salts on NUD is therefore uncertain and this is compounded by the quality of the trials. Three trials recorded evidence of adequate randomisation and concealment but only one stated that the outcome assessor was masked. This is particularly important as bismuth salts darken the stools, which could reveal the treatment group to both the patient and the clinician. The two studies with a statistically significant result investigated bismuth salts as a method of eradicating *H. pylori*. Hence, these studies only recruited *H. pylori*-positive individuals; however, they were included in this part of the review as bismuth salts alone rarely cure the infection. The findings of these trials, however, may not be generalisable to all patients with NUD. Bismuth salts are associated with neurotoxicity when prescribed long-term and NUD is a chronic disorder. Hence, bismuth salts cannot be recommended for first-line therapy for NUD on the present evidence but they may be useful second-line agents.

Other agents

Antacids, sucralfate and misoprostol have been evaluated in a small number of patients with NUD and there is no evidence that these drugs are superior to placebo. The anti-muscarinic,

pirenzepine, improved dyspeptic symptoms more effectively than placebo (RR, 0.5; 95% CI, 0.31 to 0.81); however, the evidence for this is derived from two old trials that evaluated only 164 patients. This relevance of this finding is therefore uncertain and this drug is no longer available in the UK health service.

Lessons for future trial methodology

NUD is a chronic relapsing-and-remitting disorder. Trials should therefore evaluate symptoms over a time frame that reflects this, such as 6 months or 1 year. The median length of follow-up in the trials in this review was 4 weeks, with the maximum evaluation time being 12 weeks. The quality of most trials was poor and in the future papers should state the method of randomisation, concealment and masking. Patients with predominant heartburn and acid regurgitation will be more likely to have GORD than patients without these symptoms and should be excluded from NUD studies. Trials did not use validated dyspepsia questionnaires and an outcome of minimal or no dyspepsia is preferable to dyspepsia 'improvement', as the latter is less clinically meaningful. Crossover trials should be avoided, as uncertainty over washout periods can be a problem. The majority of NUD studies have evaluated patients attending specialist clinics. NUD is a problem in both primary and secondary care and, hence, future trials need to recruit patients from both settings. The population from which the trial patients have been recruited should be stated and the characteristics of patients that refused to participate recorded. Trials should measure compliance, attempt to maximise the number of patients followed-up and analyse the results on an intention-to-treat basis.

Chapter 6

H. pylori eradication therapy for NUD

Introduction

Trials evaluating *H. pylori* eradication in NUD have been criticised for being methodologically inadequate.[205] A 1994 review identified 16 trials evaluating *H. pylori* therapy in NUD and all had one or more serious flaws in their design. The main concerns included lack of masking, ineffective *H. pylori* eradication therapies, inadequate outcome measures, small sample sizes and an insufficient length of follow-up.[205] This latter point is a criticism of all NUD trials but is particularly pertinent to *H. pylori* eradication therapies, as the chronic gastritis the infection causes can take up to 1 year to resolve. The need for long-term follow-up in NUD trials was highlighted by a study of 84 patients receiving eradication therapy followed-up for 1 year.[206] *H. pylori* was eradicated in 49% of patients and, initially, there was no difference in dyspepsia symptoms between infected and uninfected cases. There was, however, a significant improvement in dyspepsia scores in *H. pylori*-eradicated patients compared with those remaining infected at 1 year. Patients and investigators were aware of the success of treatment and, as there was no placebo group, this study is difficult to interpret. Nevertheless, it emphasises the need for long-term follow-up in trials assessing *H. pylori* eradication in NUD.[206]

Recently, a number of large, well-designed, placebo-controlled trials evaluating *H. pylori* therapy in NUD have been conducted.[207,208] These have avoided the criticisms of earlier studies but have still given conflicting results. A synthesis of the data is therefore required to evaluate the efficacy of *H. pylori* eradication in NUD.

Eligibility criteria and outcome measurements

Inclusion criteria

Eligibility criteria for studies included the following:

(i) patients must be adult (aged 16–80 years) presenting in secondary care with a diagnosis of NUD
(ii) all patients must have had either an endoscopic or barium meal examination to exclude PUD
(iii) it must include one of the outcome measurements defined below
(iv) it must be an RCT
(v) it must fulfil pre-defined *H. pylori* eradication regimens as specified below.

Pre-defined *H. pylori* eradication criteria

Trials compared *H. pylori* eradication regimen with placebo or with other drugs known not to eradicate *H. pylori*. The *H. pylori* eradication regimens were, therefore, predefined and only trials that used regimens which might potentially offer more than 80% (intention-to-treat) eradication rates according to the published literature were considered.[209] The following were considered acceptable regimens:

(i) dual therapy with PPI in combination with either clarithromycin or amoxycillin
(ii) triple therapy with either a PPI or H_2-receptor antagonist in combination with either (a) amoxycillin and nitroimidazole or (b) amoxycillin and clarithromycin or (c) clarithromycin and nitroimidazole
(iii) bismuth-based triple therapy with metronidazole and either amoxycillin or tetracycline
(iv) quadruple therapy with PPI, bismuth, metronidazole, tetracycline or amoxycillin.

Outcomes assessment

The clinical benefits and efficacy of *H. pylori* eradication in the management of NUD included assessment of the following parameters.

Individual dyspepsia symptom scores Twelve individual dyspepsia symptom scores including epigastric pain/discomfort, post-prandial fullness, early satiety, anorexia, vomiting, bloating, flatulence, belching, eructation, heartburn and acid regurgitation were assessed.

Global symptom scores These assessed the global improvement of the patients' dyspeptic symptoms following intervention. These data were split into two categories, either symptomatic

or asymptomatic or, alternatively, either responders or non-responders. Validated dyspepsia questionnaires include the GSRS, and the Glasgow Dyspepsia Severity Score. Few studies recorded dyspepsia symptoms as continuous data and the means and SDs were recorded.

Quality-of-life measurement The alteration in quality of life, if any, that was achieved by the intervention was considered. Assessment could be by any of the following: PGWB, SF-36, others if relevant.

Results of the search

Details of the search strategies for the various electronic databases are shown in appendix 1. MEDLINE and EMBASE searches were updated in June 2000 and relevant journals were reviewed to obtain more up-to-date information in this rapidly moving field. A total of 5146 citations were retrieved through searching six electronic databases, bibliographies of retrieved articles, and making enquiries of experts and pharmaceutical companies. Abstracts and letters were not included in the meta-analysis as the results were not detailed enough for data extraction. However, every attempt was made to trace any manuscripts from the authors concerned. A summary of the citations received from each source is presented in *Table 23*.

TABLE 23 *Citations identified from each data source:* H. pylori *eradication therapy for NUD*

Databases	Number of citations retrieved
MEDLINE	3996
EMBASE	983
Cochrane Controlled Trials Register	133
CINAHL	2
Bibliography	5
Pharmaceutical companies (29)	16
Experts/editors (70)	2
SIGLE	1
Abstracts	19
Total	**5146**

In all, 47 trials were identified that appeared to evaluate *H. pylori* eradication therapy in NUD.

Studies excluded from the review

A total of 35 trials were not included in the review, as they did not fulfil the predefined eligibility criteria (see appendix 3). The commonest reasons for exclusion were that the trial did not use a regimen recognised as having an eradication rate of > 80% ($n = 24$) or did not assess dyspepsia symptoms as an outcome ($n = 8$). One trial stated that dyspepsia scores were obtained but did not show the relevant data in the published article. Although an attempt was made to contact the first author, no reply was received. Five trials did not exclude PUD or oesophagitis using barium meal or endoscopy, and four studies were not randomised.

Studies included in the review

A total of 12 trials met the eligibility criteria and were included in the systematic review (details are given in appendix 2).[207,208,210–219] Ten trials[207,208,210,212,214–219] compared *H. pylori* eradication therapy with placebo or a PPI plus placebo antibiotics, with follow-up of 3–12 months. The other two trials[211,213] are considered separately as they compared *H. pylori* treatment with an alternative pharmacological agent and only followed patients for 3 months or less.

Results of the review

The effect of *H. pylori* eradication on global dyspepsia symptoms

One trial[215] did not present results as dichotomous outcomes and this information could not be obtained from the authors. This trial evaluated 84 patients and reported no change in mean dyspepsia score between those randomised to *H. pylori* eradication therapy and placebo. Nine trials,[207,208,210,212,214,216–219] evaluating a total of 2541 patients, reported dyspepsia as a dichotomous outcome at 6 months or 1 year (*Figure 18*). Three trials[207,208,212] reported continuous data for 848 patients at 1 year (*Figure 19*). All trials used PPI dual or triple therapy, and dyspepsia cure was defined as no symptoms or as mild symptoms not interfering with daily activities. The mean placebo response rate at 1 year was 28% (range 7–51%) and the mean *H. pylori* eradication therapy response rate was 29% (range 21–46%). There was no statistically significant heterogeneity between trial results (heterogeneity test, df = 8; $\chi^2 = 7.09$; $p = 0.53$). There was no evidence of funnel plot asymmetry. There was a small but significant reduction in risk of dyspepsia for patients allocated to *H. pylori*

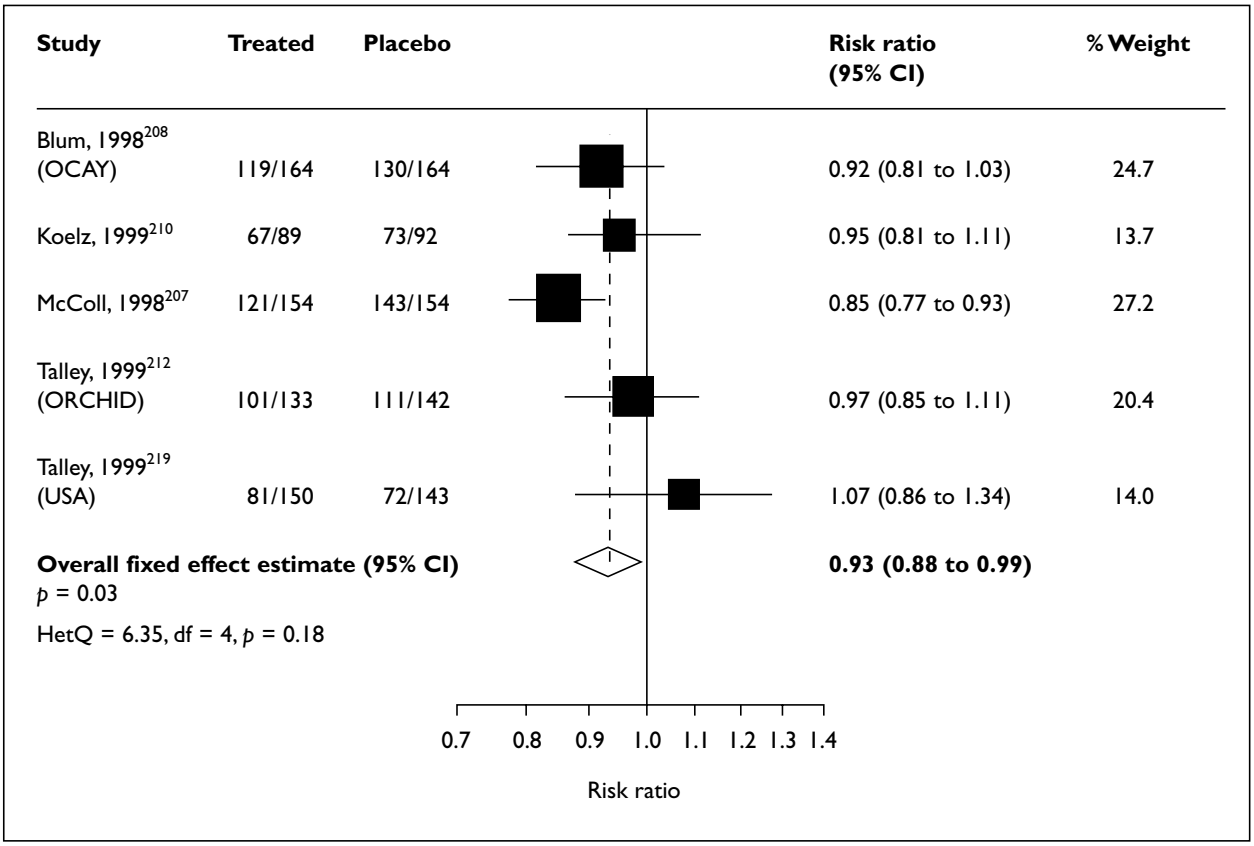


FIGURE 18 *Effect of* H. pylori *eradication therapy on NUD symptoms (dichotomous outcome – no or minimal vs. continued dyspepsia)*

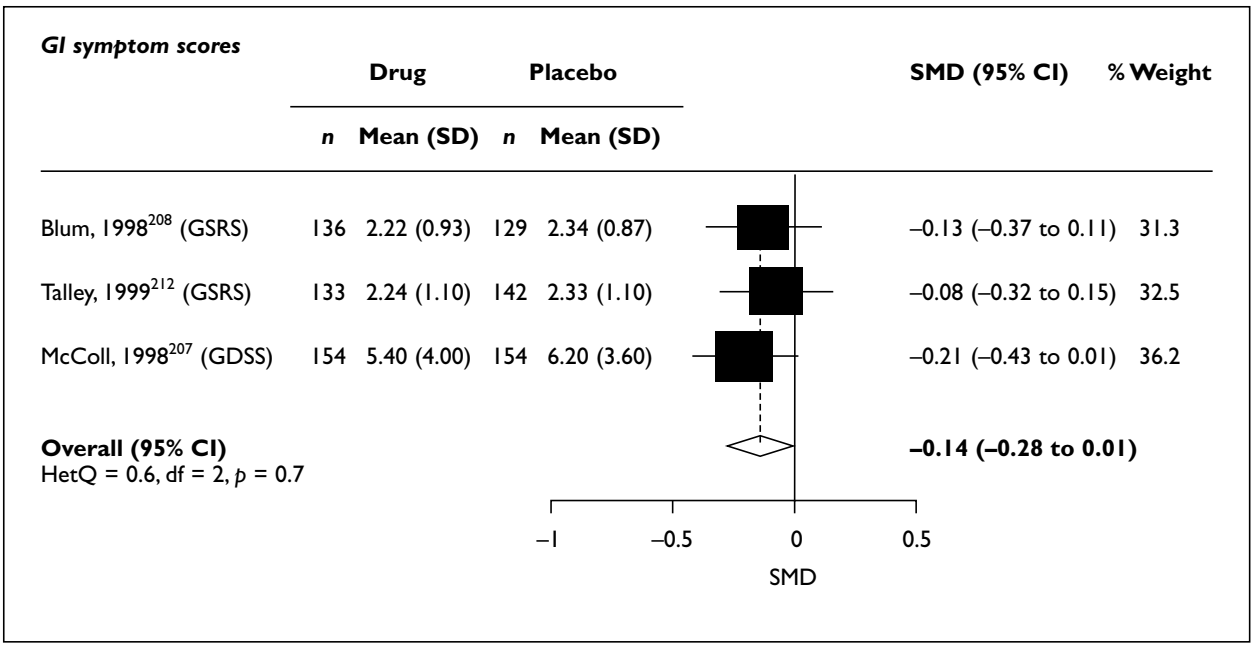


FIGURE 19 *Effect of* H. pylori *eradication therapy on NUD symptoms (continuous outcome – dyspepsia score) (GDSS, Glasgow Dyspepsia Severity Score)*

eradication therapy (RR reduction 9% (95% CI, 4 to 14)). Given the observed placebo response of 28%, 15 patients with NUD (95% CI, 10 to 35) need to be treated with *H. pylori* eradication therapy to cure one extra case of NUD. The point estimate of the RR reduction did not vary by more than 1% and remained statistically significant when any one trial was omitted from the analysis. The meta-analysis included several studies that were available in abstract form and for which there was no full

paper to review. These were excluded in a sensitivity analysis and the effect of *H. pylori* eradication therapy on NUD symptoms remained (RR reduction, 7%; 95% CI, 1 to 12) (*Figure 18*).

Two trials compared *H. pylori* eradication with another pharmacological therapy in NUD. Sheu and colleagues[211] compared bismuth subcitrate, amoxycillin and metronidazole with H_2-receptor antagonist prescription in 41 patients with NUD. *H. pylori* eradication was associated with a significant reduction in symptoms at 8 weeks compared with antisecretory therapy (reduction in dyspepsia score, 0.98; 95% CI, 0.33 to 1.63). Dhali and colleagues[213] compared bismuth subcitrate, tetracycline and metronidazole with sucralfate in 62 patients with NUD. The symptom score was significantly lower in patients allocated to *H. pylori* eradication therapy, with a mean decrease in score in the treated group of 1.8 (95% CI, 0.9 to 2.7).

None of the trials formally evaluated individual dyspepsia symptoms, although two trials[212,214] prospectively subdivided patients to ulcer-like and dysmotility-like dyspepsia categories. A similar proportion of patients in these categories responded to *H. pylori* eradication therapy.

The effect of *H. pylori* eradication on quality of life

Three trials evaluated quality of life as an outcome measure at 12 months that could be incorporated in the meta-analysis (*Figure 20*). Two trials used the PGWB index[208,212] and one the SF-36.[207] 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).

Quality of trials included in the review

All the trials that compared *H. pylori* eradication with placebo antibiotics were double-blind and placebo-controlled, with follow-up of at least 6 months. Four of these[207,208,212,214] gave details of the population from which patients with NUD were recruited and stated the method of randomisation. These trials also used a validated dyspepsia questionnaire. All trials excluded patients with confirmed PUD and/or oesophagitis before enrolment.

Endoscopy was repeated at 12 months in three trials[208,212,214] to ensure that patients remained free of PUD, although only two[208,214] reported their results. These trials found 6/164 and 7/143 (4%) of patients taking placebo had developed PUD at the 12-month visit compared with 1/164 and 3/150 (1%) in the treatment groups. McColl and colleagues[207] did not have a repeat endoscopy as part of the trial protocol, although nine patients were referred for endoscopy during follow-up because of persistent symptoms. Three patients in the treatment group had a normal endoscopy and 4/6 in the placebo group had PUD.

Two trials[208,217] reported endoscopic oesophagitis as an outcome measure at 12 months, showing a

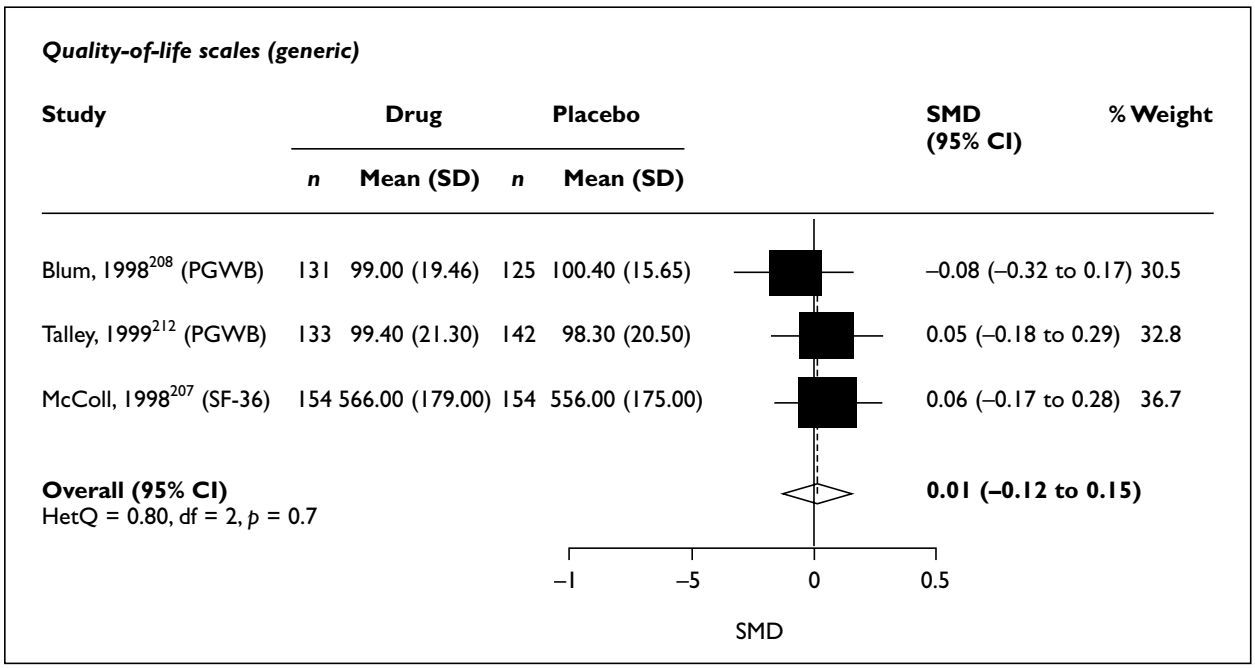


FIGURE 20 *Effect of* H. pylori *eradication therapy on quality of life in NUD patients*

trend towards oesophagitis to be more frequent in patients allocated to *H. pylori* eradication therapy. However, these events were rare (17/297 (6%) in the treatment group and 9/306 (3%) in the placebo group) and the difference between the groups was not statistically significant (RR, 2.07; 95% CI, 0.94 to 4.56).

Discussion

The trials evaluating *H. pylori* eradication therapy were generally of good quality. Trials usually reported methods of randomisation but methods of concealment were not stated. The trials were large and there was no evidence of imbalance in baseline characteristics. All trials evaluating *H. pylori* eradication therapy with placebo antibiotics reported intention-to-treat outcome at 6 months or 1 year and used validated dyspepsia questionnaires.

Seven out of eight trials[208,212,214,215,217–219] evaluating dyspepsia outcome at 1 year did not demonstrate any statistically significant benefit of *H. pylori* eradication over placebo in patients with NUD. The reasons for one trial[207] giving a positive result while the others have been negative has been the subject of lively debate.[222] One reason for the discrepancy is that *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 7% RR reduction in NUD for patients treated with *H. pylori* eradication therapy is, however, statistically significant in both random and fixed effects models. The results are supported by two small trials that showed a benefit for *H. pylori* therapy at 2–3 months over H_2-receptor antagonists[211] or sucralfate[213] in patients with NUD. Data from observational studies have suggested that *H. pylori* eradication therapy may increase the incidence of reflux disease[223] but these are open to bias or confounding factors. These RCTs did not report an increase in reflux symptoms or oesophagitis in patients allocated to receive eradication therapy. Oesophagitis was present in 8/133 (6%) patients given *H. pylori* eradication therapy and in 6/142 (4%) *H. pylori*-positive patients at 12 months after randomisation ($p = 0.59$).[224]

The mechanism by which *H. pylori* causes a reduction in dyspepsia symptoms in patients with NUD is unclear.[91] *H. pylori* infection is often associated with increased gastric acid output[92] but investigators have not found a relationship between low pH and NUD symptoms.[69] Studies evaluating the effects of *H. pylori* infection on gastric motility are also conflicting.[78] *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 PUD. All patients had an endoscopy before entry into the trials to exclude PUD but this is a relapsing-and-remitting disorder and patients with an ulcer diathesis do not always have an ulcer associated with their dyspepsia.[29,225,226] This is emphasised by the observation that 4% of patients enrolled in the NUD trials developed PUD during follow-up in the placebo group. *H. pylori* therapy may therefore only be treating the small subset of patients with PUD that had 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; this is useful information in clinical practice.

Dyspepsia is associated with a reduced quality of life,[227] 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 evaluate 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.

The benefit of *H. pylori* eradication therapy on NUD is relatively small and this is reflected in the figure of 15 patients needing treatment to cure one case. This figure is higher than for prokinetic or H_2-receptor antagonist therapy, although *H. pylori* eradication therapy is only required once while other drugs would need to be given more long term. Trials evaluating *H. pylori* eradication therapy have been better designed and are of better quality than those assessing H_2-receptor antagonist and prokinetic therapy. Nevertheless, the cost-effectiveness of *H. pylori* eradication compared with prokinetic therapy or acid suppression needs to be modelled to determine whether this small effect is likely to be clinically useful.

Chapter 7

Management strategies for dyspepsia in primary care: a discrete event simulation model

Background

In the absence of direct trial evidence to support the number of suggested management strategies for dyspepsia in primary care, there have been a number of published models of the cost-effectiveness of different approaches. There are several benefits of such modelling. Firstly, clinical trials of the effectiveness of managing chronic disease such as dyspepsia take some years and cost large amounts of money. Modelling not only helps to guide practice in the meantime but also ensures that trials concentrate on strategies that are most likely to be effective and assess the most important outcomes.

Managing dyspepsia is challenging to model, as there are a number of competing strategies for investigation and a large number of different therapeutic approaches. We estimated that there are at least 70 different combinations. In addition, 'dyspepsia' represents a complex of conditions ranging from definable pathological states, such as peptic ulcers, oesophagitis and malignancy, to symptom complexes where no organic disease can be found (NUD and ENRD). Although it has been proposed that reflux disease can be distinguished from dyspepsia and defined separately, at the primary care level there is considerable overlap between these symptom complexes and they have not proved a satisfactory means of predicting disease. Further dyspeptic symptoms recur over many years and models need to consider the effect of strategies over at least medium-term scales, such as 5 years.

Modelling healthcare can take the form of simple cost flows over time, cost minimisation or include the different effects of treatments in cost-effectiveness analyses. Simple decision models consider effects over fixed periods, averaging costs and probabilities over a year for example. More sophisticated models, such as Markov processes, allow for patients to flow between states, and are more suitable for modelling chronic conditions over time. When faced with many alternatives, Markov models become too complex to represent and simulation modelling needs to be used.

The systematic review of dyspepsia in primary care found 11 reports of economic modelling relating to strategies for the management of the uninvestigated dyspeptic patient (see appendix 5). There are no established criteria for the synthesis of economic studies, and the heterogeneity of assumptions, strategies, costs and geographical differences in these 11 studies would make this task impossible. However, some general comments can be made. All the models found that strategies involving early endoscopy in most or all patients were more costly and no more effective than selective endoscopy.[20,127,228,229] Six studies (in five papers) compared *H. pylori* test-and-treat with other strategies,[230–234] although only Ebell and colleagues[231] considered differences in effectiveness as well as costs. All six studies found test-and-treat to be the most cost-effective strategy.

A number of weaknesses were found in all the reported models:

(i) benefits are usually limited to a 'avoided costs'and assumptions about effectiveness of different treatments are limited
(ii) case-mix is poorly considered; most studies are limited to effects engendered by *H. pylori* eradication on recurrent PUD alone
(iii) modelling approaches are usually limited to one or two strategies with no analysis of different prescribing choices
(iv) most studies exclude any high-cost serious outcomes, such as bleeding ulcers or cancers
(v) international comparisons, especially with those high USA healthcare costs, are difficult and potentially misleading
(vi) most studies are limited to 1-year fixed period; there were only two Markov models[20,229] and no simulation approaches.

There is a need to examine the cost-effectiveness of different approaches to managing dyspepsia using a simulation model, examining effectiveness as well as costs, and comparing all the possible investigation and prescribing approaches. The model used in this study was a form of the simulation modelling known as 'discrete event simulation' (DES).

Methods

Structure of the model

In any DES model, individual entities move through the model, passing through events, which are assumed to take no time, and activities, which may have a fixed or variable duration. Entities may also join queues, which they can only leave when a space occurs elsewhere in the model. For example, consultation with a GP can be considered as an event, taking a course of prescribed medicine is an activity with a fixed duration, self-treating 'until cured' is an activity of variable duration, as is waiting for the next onset of dyspepsia.

The principal benefit of using DES is that individuals can be given attributes that determine the distribution of time taken in any particular state and the probability of transition to other states. In the dyspepsia model, an individual at any time may or may not be infected with *H. pylori* and may or may not have any combination of duodenal ulcer, gastric ulcer, NUD and reflux dyspepsia. Separate attributes are used for each of these conditions; the patient is assumed to be suffering from dyspepsia if any of them is positive. The probability of having these conditions may also be affected by the *H. pylori* status of the individual and this factor is also included in the model. The various states through which the patient can pass are shown in *Figure 21*.

The structure of the model was established by a series of discussions between the authors, including extensive examination of outputs at different stages and an iterative development cycle based on responses to draft outputs. The model was set up using Microsoft Visual Basic© programming language by one author (PB).

By running the model for a large number of individuals, comparisons were made between strategies. The model could be set to run either for the full lifetime of each individual or for a fixed maximum time after first consultation. Each individual was run through the model for the desired length of time but only summary statistics were maintained. These included total cost and benefit in dyspepsia-free months, expressed as

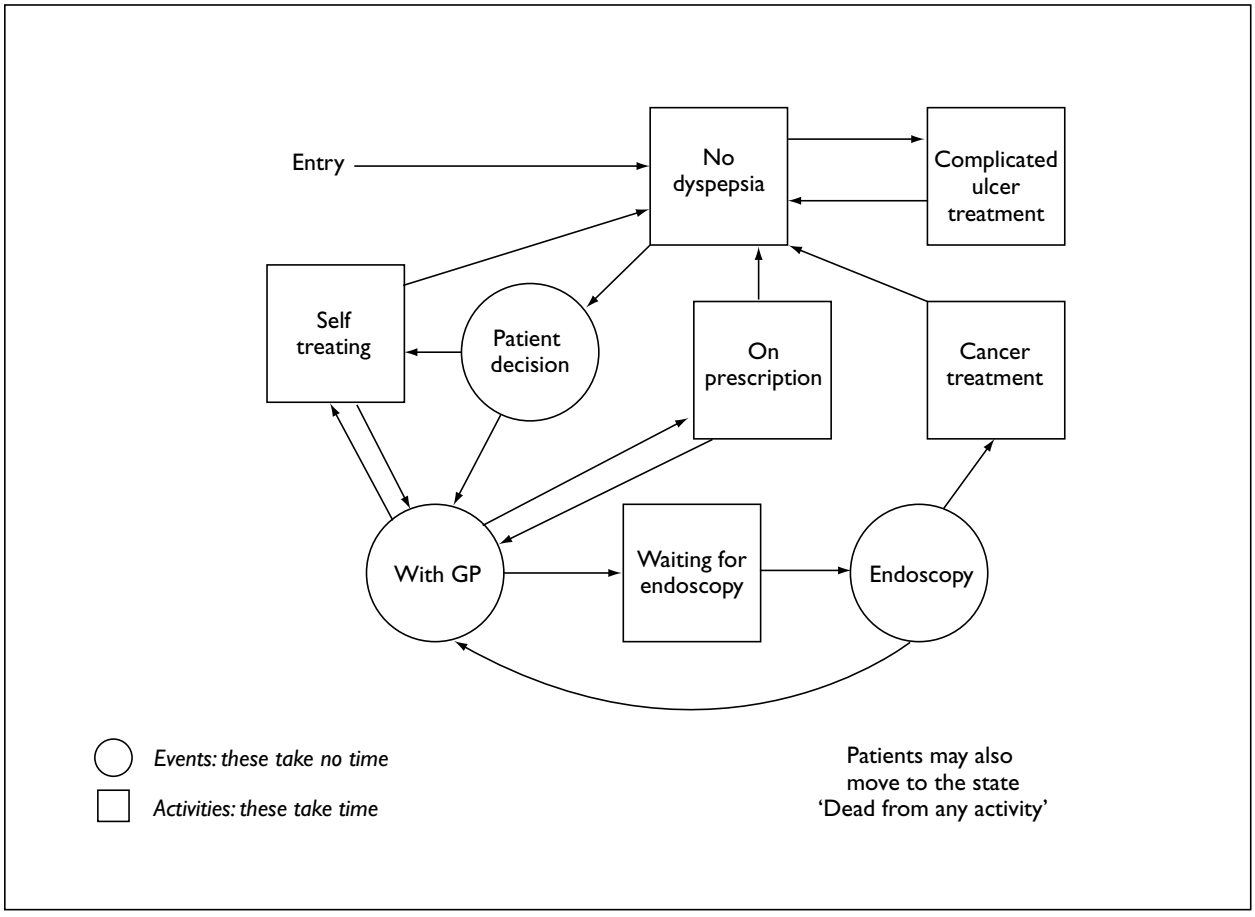


FIGURE 21 *States in the DES model*

averages per patient consulting, together with standard errors for each of these estimates.

Uncertainty in modelling can be termed first order or second order. First order uncertainty reflects variation between individuals and can be reduced by increasing simulation size. Second order uncertainty reflects lack of precise knowledge of the model parameters and can be explored by sensitivity analysis. In simple decision-analytic models, first order uncertainty is not considered. In simulation models, standard errors relate to first order uncertainty. The meaningful measure here is the standard error rather than the SD, since the aim is to compare the costs and benefits of strategies as applied to populations rather than to individuals. The purpose of reporting standard errors is to demonstrate that a sufficient number of replications have been made.

In general, enough replications were made to ensure that differences in costs and benefits between different strategies were statistically significant, allowing exploration of second order uncertainty by sensitivity analysis. Clinical significance depends on the acceptability of the incremental cost-effectiveness ratio (ICER).

Investigation strategies

When a patient consults a GP for the first time, the GP will follow one of the possible initial management strategies, referred to hereafter as 'investigation strategies'. Five strategies were programmed into the model:

(i) *H. pylori* eradication for all patients
(ii) endoscopy for all patients
(iii) *H. pylori* test, followed by endoscopy if positive
(iv) *H. pylori* test, followed by *H. pylori* eradication therapy if positive
(v) initial empirical pharmacological therapy.

In investigation strategy (i), all patients were given *H. pylori* eradication therapy at first consultation. If the patient remained symptomatic after the first attempt at eradication, then a ^{13}C-urea breath test was performed. A negative result meant that the patient joined the same prescribing strategy (see later) as for investigation strategy (v), while a positive test resulted in a second attempt at *H. pylori* eradication. Patients remaining *H. pylori*-positive after two courses of eradication therapy were prescribed long-term maintenance with a low-dose H_2-receptor antagonist.

Strategy (iv) started with an *H. pylori* test. If positive, the patient was given eradication therapy and the possibilities were as for strategy (i). If the test was negative, then the patient proceeded as for strategy (v).

Strategy (iii) also started with an *H. pylori* test. Again, a negative result converted to strategy (v) but, in this case, a positive result led to endoscopy.

Finally in strategy (ii), all patients were referred to endoscopy at first consultation.

Strictly, waiting for endoscopy should be treated as a queue. However, this requires a large number of patients to be considered at the same time. When a DES model is run using a large number of entities, the largest part of the computational effort goes into determining which patient is to be dealt with next. To avoid unnecessary computational effort, it was decided to model waiting for endoscopy as an activity of variable duration. The model could then be run for a single patient lifetime, replicated as many times as necessary to produce estimates of population outcomes within reasonable CIs.

Prescribing strategies

In addition to investigation, the effect of prescribing was also modelled. Either initially (strategy (v) above) or, in the case of an endoscopy, not showing a peptic ulcer, the following specified prescribing strategies could be applied:

(1) prescription antacid only
(2) H_2-receptor antagonist only
(3) prokinetics only
(4) PPI only
(5) antacid, H_2-receptor antagonist, PPI, prokinetics and stay
(6) antacid, H_2-receptor antagonist/prokinetics, PPI and stay
(7) antacid, H_2-receptor antagonist, PPI and stay
(8) antacid, H_2-receptor antagonist, PPI, prokinetics and down
(9) antacid, H_2-receptor antagonist/prokinetics, PPI and down
(10) antacid, H_2-receptor antagonist, PPI and down
(11) prokinetics, PPI, H_2-receptor antagonist, antacid and stay
(12) PPI, H_2-receptor antagonist/prokinetics, antacid and stay
(13) PPI, H_2-receptor antagonist, antacid and stay
(14) PPI or prokinetics tried until one of them works.

In the case of prescribing strategies (6), (9) and (12), either of H_2-receptor antagonists and prokinetics may be given first, followed by the other. On first consultation, the patient joins the prescribing strategy with the first type of medication. In the cases of strategies (5)–(10) inclusive, antacid will mean self-treating but, if the patient has already been self-treating, then the next item on the list is used. If the patient becomes asymptomatic after a single prescription, then he/she returns to the state of 'no dyspepsia'. Otherwise, up to two repeat prescriptions may be given without further consultation.

The prescribing strategies were modelled in such a way as to allow for repeat prescribing for up to 3 months if treatment was not immediately successful. The patient would next consult the GP either on a recurrence of symptoms or after failure of the third prescription. In the case of strategies (5)–(10) inclusive, which are 'step-up' approaches, if the patient returned within 4 months of the previous consultation, the GP would move the patient onto the next type of medication on the list. In the case of the 'step-up-and-down' strategies (8)–(10), if the time since the last consultation were greater than 1 year, then the GP would move one place back on the list. In the case of 'step-down' strategies (11)–(13), if the time since the last consultation were greater than 1 year, then the GP would move one place forward on the list.

To allow for a 'treat-and-endoscope' strategy, patients being referred if initial management failed, a further strategy switch allowed endoscopy at the top of a prescribing strategy. When this switch was on, in the case of prescribing strategies (1)–(10) inclusive, if the patient returned within 4 months of reaching the last type of medication on the list, and had not yet been endoscoped, then he/she was referred for endoscopy. The switch had no effect on the 'step-down-and-stay' strategies (11)–(13). Finally, if the patient had been on the treatment ladder for over 5 years without other investigation, then referral for endoscopy applied at the next consultation. The periods, 4 months, 1 year and 5 years, referred to above were parameters of the model and may be adjusted in strategic analysis.

Prescribing strategy (14) worked in a somewhat different way. In this case, a patient was initially given a 2-month prescription for a PPI and asked to return to the GP at the end of the prescription period. If at that time the patient was free of dyspepsia, then the GP noted that PPI had proved effective and used intermittent PPI treatment for all future recurrences. Otherwise, the patient was given a 2-month prescription for a prokinetic and again asked to return. This time, if the patient was free of dyspepsia, the GP noted that prokinetics had proved effective, and used intermittent prokinetic treatment for recurrences. If the patient was still symptomatic after both types of medication have been tried, then endoscopy was used if the switch mentioned in the previous paragraph was on; otherwise, the patient was given long-term maintenance therapy, which is taken to be half-dose H_2-receptor antagonist.

Modelling assumptions

Dyspepsia categories and risk

1. Dyspepsia was divided into four categories, duodenal ulcer, gastric ulcer, NUD and reflux disease, represented by on/off switches.
2. Dyspepsia was either present or absent, severity not being considered at the individual level.
3. Risk of onset of a given type of dyspepsia was constant from age 20 years, except that:
   - risk of onset of either type of ulcer depended on *H. pylori* status: successful *H. pylori* eradication immediately reduced the risk of ulcer to that for an *H. pylori*-negative individual
   - having either duodenal or gastric ulcer halved the risk of onset of the other.
4. For an individual, once a type of dyspepsia was acquired, recurrence of that type was more likely than others in the future, but declined with time.
5. Risk of recurrence was independent of age or type of medication last taken.

Consulting behaviour

1. On each occurrence of uncomplicated dyspepsia, an individual could either self-treat until cured, self-treat for 1 month and then consult a GP if not cured, or consult a GP immediately.
2. Patients had an initial policy, almost all self-treating until cured, and a fixed probability of changing policy at each new occurrence.
3. The parameters used in the base case were calibrated so that approximately 20% of onsets led to consultation at age 30 years and 50% at age 70 years, following available data on the proportion of patients consulting with dyspepsia at different ages.[7]

Diagnostic interventions

1. It is was not possible to distinguish reliably between dyspepsia types other than by

endoscopy. Even then, ENRD could not be distinguished from NUD.
2. Endoscopy was assumed to be 100% sensitive and specific at detecting duodenal and gastric ulcers, *H. pylori* infection and oesophagitis.
3. Some 30% of cases of reflux dyspepsia would be reported as oesophagitis.
4. *H. pylori* infection could also be detected by non-invasive diagnostic tests that have known sensitivity and specificity.
5. For the rare case of *H. pylori*-negative patients with a peptic ulcer, a PPI was prescribed, followed by a further endoscopy booked in 6 weeks' time. For simplicity in the model, it is assumed here that the treatment was always successful but that long-term maintenance with half-dose H_2-receptor antagonist was needed.

Therapeutic interventions

1. *H. pylori* eradication therapy had a fixed probability of success at first attempt, and a fixed (lower) probability of success at a second attempt.
2. Patients for whom a third course of eradication therapy was indicated were put on long-term maintenance therapy.
3. Each type of dyspepsia treatment had a fixed probability of clearing a given dyspepsia type in 1 month's course of treatment, regardless of age, number of times previously given and *H. pylori* status.
4. If an individual had two types of dyspepsia simultaneously, the separate types are handled independently.
5. It was assumed that eradication therapy was capable of causing reflux disease in a patient who did not previously have it.

Serious events

1. A fixed proportion of ulcers were complicated (bleeding or perforated).
2. Complicated ulcers required immediate hospital treatment.
3. The risk of gastric cancer was assumed to increase with age from 25 years and distal gastric cancer to be six times as high in *H. pylori*-positive individuals as in *H. pylori*-negative individuals, and twice as high in males as in females.
4. Gastric cancer was assumed to pass through a treatable stage; once it reached the untreatable stage the patient was assumed to die quickly.
5. Cancer in the treatable stage may be detected only by endoscopy.
6. Figures for all the parameters used in the model are listed in *Tables 24–27*.[45,54,90,97,235–262]

Validation

Validation involves comparing the model output with behaviour predicted from the literature that had not been used in the construction of the model. Outputs used for validation included the proportion of the population having some form of dyspepsia in a given 6-month period, which did not vary significantly with age, and the distribution of age at first consultation. Outputs from the model were obtained for: the proportion of the total population incurring each combination of dyspepsia types, the distribution of ages at first onset and first consultation, and the proportion of onsets which lead to consultation classified by age.

A further validation exercise involved comparing the case-mix at endoscopy with known data from 35 published cohorts of patients undergoing open access endoscopy (*Table 28*).[8,12,113,149,263–277] As the yield from endoscopy varied widely with case-mix in these studies, a range only was used for comparison. As later studies have shown lower rates of PUD and cancer, the aim for these was at the lower end of this range, and at the upper end of the range for oesophagitis.

The model was run to represent 'typical practice' using the strategy of initial medication with PPI only but allowing endoscopy after treatment failure, and reinvestigation when a patient reappeared after 5 years without endoscopy. The results were totalled separately for endoscopies when the patient was under or over the age of 50 years. Two separate runs were made, one with an *H. pylori* prevalence of 30% and one with a prevalence of 60%. *Table 29* shows the results for under-50s from the first run and over-50s from the second run.

Results

Base-case analysis

Using the base-case values of the parameters, and considering the effect on each patient for up to 5 years from first consultation, all combinations of strategies were compared. Results were obtained both with and without discounting. Discounting made no difference to the list of non-dominated strategies; for convenience of interpretation, the undiscounted results are given. *Figure 22* shows the costs and benefits in the base case for each initial investigation strategy combined with the prescribing strategy of PPI only. There was very little difference in benefits but the strategies involving endoscopy were more expensive.

TABLE 24 *Parameters used in the DES model as probabilities*

Parameter	Base-case value	Low value	High value	Source
Probability of being female	0.5	0.5	0.5	N/A
Probability of acquiring *H. pylori* in childhood	0.3	0.1	0.6	Drumm, *et al.*, 1990[235]; Neale & Logan, 1995[236]
Probability that individual will initially self-treat	0.97	0.9	0.99	Jones, *et al.*, 1990[237]
Probability that a particular instance of reflux disease is oesophagitis	0.1	0.05	0.2	Armstrong, *et al.*, 1996[238]
Sensitivity of near patient test	0.8	0.2	0.99	Duggan, *et al.*, 1998[239]
Specificity of near patient test	0.8	0.5	0.99	Duggan, *et al.*, 1998[239]
Sensitivity of ELISA	0.9	0.6	0.99	Wilcox, *et al.*, 1996[240]
Specificity of ELISA	0.9	0.8	0.99	Wilcox, *et al.*, 1996[240]
Sensitivity of urea breath test	0.95	0.9	1	Atherton & Spiller, 1994[241]
Specificity of urea breath test	0.99	0.9	1	Atherton & Spiller, 1994[241]
H. pylori *eradication*				
Success rate at first attempt	0.85	0.8	0.95	Unge, 1997[97]
Second attempt ratio	0.67	0.6	0.75	Moayyedi, *et al.*, 1995[242]
Probability of clearing duodenal ulcer	0.95	0.85	0.99	Hosking, *et al.*, 1994[90]
Probability of clearing gastric ulcer	0.85	0.8	0.95	Sung, *et al.*, 1995[243]
Probability of clearing NUD	0.3	0.2	0.4	From review
Probability of causing reflux	0.15	0	0.3	Labenz, *et al.*, 1997[223]; Talley, *et al.*, 1998[224]
Prokinetics				
Probability of clearing duodenal ulcer	0.2	0	0.4	Brogden, *et al.*, 1982[54]
Probability of clearing gastric ulcer	0.2	0	0.4	Brogden, *et al.*, 1982[54]
Probability of clearing NUD	0.3	0.2	0.7	From review
Probability of clearing reflux	0.45	0.4	0.5	Chiba, *et al.*, 1997[45]
PPIs				
Probability of clearing duodenal ulcer	0.85	0.7	0.9	Poynard, *et al.*, 1995[244]; Eriksson, *et al.*, 1995[245]
Probability of clearing gastric ulcer	0.85	0.7	0.9	Eriksson, *et al.*, 1995[245]
Probability of clearing NUD	0.3	0.2	0.4	From review
Probability of clearing reflux	0.8	0.6	0.9	Chiba, *et al.*, 1997[45]
H_2-receptor antagonists				
Probability of clearing duodenal ulcer	0.8	0.7	0.9	Poynard, *et al.*, 1995[244]; Eriksson, *et al.*, 1995[245]; Burget, *et al.*, 1990[246]
Probability of clearing gastric ulcer	0.8	0.7	0.9	Eriksson, *et al.*, 1995[245]; Burget, *et al.*, 1990[246]
Probability of clearing NUD	0.3	0.2	0.5	From review
Probability of clearing reflux	0.5	0.2	0.7	Chiba, *et al.*, 1997[45]

continued

TABLE 24 contd *Parameters used in the DES model as probabilities*

Parameter	Base-case value	Low value	High value	Source
Antacids				
Probability of clearing duodenal ulcer	0.3	0.2	0.5	Poynard, *et al*., 1995[244]; Eriksson, *et al*., 1995[245]; Burget, *et al*., 1990[246]
Probability of clearing gastric ulcer	0.3	0.2	0.5	Eriksson, *et al*., 1995[245]; Burget, *et al*., 1990[246]
Probability of clearing NUD	0.25	0.1	0.3	From review
Probability of clearing reflux	0.2	0.1	0.5	Chiba, *et al*., 1997[45]
Probability that an ulcer is complicated	0.001	0.0005	0.002	Bardhan, *et al*., 1989[247]; Gustavsson, *et al*., 1990[248]; Christensen, *et al.,* 1988[249]; Bardhan, 1987[250]
Probability of death during complicated ulcer treatment	0.05	0.03	0.07	Coggon, *et al*., 1981[251]; Bonnevie, 1978[252]
Probability of death during cancer treatment	0.01	0.005	0.02	Sue-Ling, *et al*., 1993[253]
Eradication efficacy for cancer	0.6	0.2	1	Forman, 1996[254]
Endoscopy waiting time, minimum (months)	0.5	0.5	0.5	
Endoscopy waiting time, range (months)	1.5	1	4	
Discount rate for costs (annual %)	6	6	6	
Discount rate for benefits (annual %)	3	3	3	

TABLE 25 *Lifetime and annual recurrence risks for dyspepsia categories*

Description	Risk (%)	Source
Lifetime risk		
Duodenal ulcer (*H. pylori*-positive)	15	Cullen, *et al*., 1993[255]; Sipponen, *et al*., 1990[256]; Kuipers, *et al*., 1995[257]
Gastric ulcer (*H. pylori*-positive)	5	Sipponen, *et al*., 1990[256]; Kuipers, *et al*., 1995[257]
NUD (overall)*	50	Jones, *et al*., 1990[237]
Duodenal ulcer (*H. pylori*-negative)	1	Sipponen, *et al*., 1990[256]
Gastric ulcer (*H. pylori*-negative)	1	Sipponen, *et al*., 1990[256]
Reflux (overall)	50	Jones, *et al*., 1990[237]
Annual recurrence risk		
Duodenal ulcer (*H. pylori*-positive)	80	Hentschel, *et al*., 1993[258]; Hopkins, *et al*., 1996[259]
Gastric ulcer (*H. pylori*-positive)	60	Hopkins, *et al*., 1996[259]; Axon, *et al*., 1997[260]
Duodenal ulcer (*H. pylori*-negative)	5	Hentschel, *et al*., 1993[258]; Hopkins, *et al*., 1996[259]
Gastric ulcer (*H. pylori*-negative)	5	Hopkins, *et al*., 1996[259]; Axon, *et al.,* 1997[260]
NUD (*H. pylori*-positive)	50	From review
NUD (*H. pylori*-negative)	48	From review
Reflux	80	Hetzel, *et al*., 1988[261]

* *NUD risk ratio (*H. pylori-*positive:* H. pylori-*negative) of 1.6 applied to the instantaneous risk to achieve increased risk if* H. pylori-*positive*[262]

TABLE 26 *DES model: table of costs*

Parameter	Base-case value (£)	Low value (£)	High value (£)	Source
Endoscopy	246	186	299	NHS 1998 reference costs R
Near patient test	17.77	7	25	Cortecs Diagnostics, Clwyd
Urea breath test	30.80	15	40	Bureau of Stable Isotope Analysis, Brentford
ELISA	10	5	15	Public Health Laboratory Service
GP consultation	17	14	20	Talley, *et al.,* 1994[220]
Treatment for complicated ulcer	1000	500	2000	NHS 1998 reference costs
Cancer treatment	10000	5000	15000	NHS 1998 reference costs
Cost applied for death from untreatable cancer	2000	1000	10000	NHS 1998 reference costs
H. pylori eradication therapy	27.15	15	38.64	Drug Tariff, 1999
Prokinetics	35.09	1.13	35.09	
PPI	30.13	23.75	30.13	
H_2-receptor antagonist	16.11	5.69	26.60	
Prescription antacid	2.10	1.68	12.10	
Antacid self-treating	4.20	3.94	5.40	
Maintenance (half-dose, H_2-receptor antagonist or PPI)	8.06	2.85	15.07	

TABLE 27 *Choices of drugs for medication*

	Base	Low	High
H. pylori eradication	Omeprazole, 20 mg b.d. Clarithromycin, 250 mg b.d. Metronidazole, 400 mg t.d.s.	As base	Heliclear®
Prokinetics	Cisapride, 20 mg bd	Metoclopramide NP, 10 mg t.d.s.	As base
PPI	Omeprazole, 20 mg o.d.	Rabeprazole, 20 mg o.d.	As base
H_2-receptor antagonist	Ranitidine NP, 300 mg o.d.	Cimetidine NP, 800 mg b.d.	Famotidine, 40 mg o.d.
Prescribed antacid	As base	Aluminium hydroxide NP	Gaviscon Advance®
Antacid self-treat	–	–	–
Maintenance	Half-dose H_2-receptor antagonist	Half-dose H_2-receptor antagonist	Half-dose PPI

NP, non-proprietary

One strategy is said to be 'simply dominated' by another if it is both more costly and less effective. Of the seventy possible combinations of investigation and prescribing strategies, all but nine were eliminated by simple dominance. *Table 30* shows the list of non-dominated options, also shown in *Figure 23*.

The results show that all strategies involving endoscopy or the initial use of prokinetic agents are dominated. Strategies involving medication only are invariably cheaper but slightly less effective than those equivalent strategies using an initial *H. pylori* test with the same prescribing strategy. Four combinations involving 'mixed prescribing strategies are not actually dominated but the extra cost is very small compared with the extra benefit of moving to PPI only.

Antacids are the cheapest but least effective option. Switching to an H_2-receptor antagonist would result in a mean of 6.7 months less dyspepsia at an additional cost of £105.68 over 5 years (ICER, £15.88 per additional month

TABLE 28 *Cohorts of patients undergoing open access endoscopy*

Study/ country	Source of sample	Exclusion or selection criteria	No.	Spectrum	Duodenal ulcer, *n* (%)	Benign gastric ulcer, *n* (%)	Oesophagitis, *n* (%)	Upper GI cancer, *n* (%)
Holdstock, *et al.*, 1979[263] UK	(1) Open access	Nil	1077		176 (16.3)		108 + 62	14 (1.3)
Holdstock, *et al.*, 1979[263] UK	(2) Via OPD	Nil	728		80 (11)		51 + 39	23 (3.2)
Mann, *et al.*, 1983[264] UK	(Scoring paper – totals reported)	Aged < 55 years	126		11 (8.7)	3 (2.4)		
Gear & Wilkinson, 1989[265] UK	Open access	Nil, but no dysphagia	8781		759 (8.6)	382 (4.4)	1258 (14.3)	Gastric 102 (1.2); oesophageal 84 (1.0)
Williams, *et al.*, 1988[8] UK	Open access	(1) Aged < 45 years	271		24 (9)	18 (7)	23 (9)	0
Williams, *et al.*, 1988[8] UK	Open access	(2) Aged > 45 years			59 (14)	36 (9)	74 (18)	Oesophageal 6 (1.5); gastric 11 (3)
Gear & Barnes, 1980[266] UK	Open access (single practice)		346		42 (12.1)	22 (6.4)		6 (1.7)
Goy, *et al.*, 1986[267] Australia	(1) Open access clinic	Nil	1409	4931 men, 3339 women	238 (17)	108 (7.7)	95 (6.7)	8 (0.6)
Goy, *et al.*, 1986[267] Australia	(2) Via specialist referral	Nil	5935		650 (11)	421 (7.1)	427 (7.2)	54 (0.9)
Jones, 1986[268] UK	Open access GP clinic (20 practices)	Nil	354	185 men; 169 women; mean age 49 years	35 (10)	21 (6)	52 (15)	7(2)
Hungin, 1987[12] UK	Open access (single practice)	Nil	102	68 men; 34 women; mean age 46 years	14 (14.9)	2 (2.1)	11 (11.7)	0
MacIntyre, 1988[269] Scotland	Open access clinic (65 GPs)	Nil	382		49 (12.8)	44 (11.5)	18 (4.7)	7 (1.8); 11 (2.8)
Kageri, et al., 1989[361] Sweden	All dyspeptic patients (single clinic)	Symptoms referable to upper GI tract, excluding history of GI bleeding	185	1 week to OGD; 92 men; 93 women; mean age 43 years	16 (9)	3 (2)	11 (6)	2 (1)

continued

TABLE 28 contd *Cohorts of patients undergoing open access endoscopy*

Study/ country	Source of sample	Exclusion or selection criteria	No.	Spectrum	Duodenal ulcer, *n* (%)	Benign gastric ulcer, *n* (%)	Oesophagitis, *n* (%)	Upper GI cancer, *n* (%)
Graham, 1989[270] Australia	Open access (GP clinic)	Nil	646		69 (10.7)	43 (6.6)	75 (11.6)	5 (0.8)
Kerrigan, *et al.*, 1990[271] UK	(1) Open access clinic	Nil	1091	510 women	207 (19)		251 (23)* including hiatus hernia	22 (2)
Kerrigan, *et al.*, 1990[271] UK	(2) referral by specialist	Nil	454	193 men	177 (39)		109 (24)* including hiatus hernia	23 (5)
Schroeder, 1990[271] Finland	Open access (GP clinic)	Nil	605	Students, aged < 35 years; 63% men; 37% women	14 (2.3)	0	52 (8.6)	0
Adang, *et al.*, 1994[361] The Netherlands	(1) Open access		1205	Mean age 51.8 years; 55.7% men	109 (9.3)	80 (6.8)	144 (12.2)	20 (1.7)
Adang, *et al.*, 1994[361] The Netherlands	(2) Via specialist		1695		125 (7.6)	141 (8.5)	253 (15.1)	35 (2.1)
Mansi, *et al.*, 1993[273] Italy	(1) Open access clinic	Alarm symptoms; history of surgery	1392	Average delay 10 days; no medication; mean age 53 years; men: women 0.96; non-smokers: smokers 0.67 (33% smokers)	79 (5.7)	22 (1.6)	81 (5.8)	19 (1.4)
Mansi, *et al.*, 1993[273] Italy	(2) Referral by specialists	Alarm symptoms; history of surgery	861		31 (3.6)	13 (1.5)	48 (5.6)	25 (2.9)
Bytzer, *et al.*, 1994[116] Denmark (RCT)	(1) Early OGD study group		208 (ITT)		31 (14.9)	14 (6.7)	21 (10.1)	Gastric 2 (1.0); oesophageal 0
Bytzer, *et al.*, 1994[116] Denmark (RCT)	(2) Initial empirical treatment control group, subsequently endoscoped by 1 year		136 (per protocol)		11 (8.1)	17 (12.5)	16 (11.7)	Gastric 0; oesophageal 2 (1.5)

continued

TABLE 28 contd *Cohorts of patients undergoing open access endoscopy*

Study/ country	Source of sample	Exclusion or selection criteria	No.	Spectrum	Duodenal ulcer, *n* (%)	Benign gastric ulcer, *n* (%)	Oesophagitis, *n* (%)	Upper GI cancer, *n* (%)
Hungin, *et al.*, 1994[113] UK	Open access		715	Mean age 45 years	(17.8)	(3.5)	(14.4)	(0.3)
Quine, *et al.*, 1994[274] UK	Not classified		342	< 40	16 (4.7)	3 (0.9)	37 (10.8)	0
Quine, *et al.*, 1994[274] UK	Not classified		691	> 50	44 (6.4)	29 (4.2)	111 (16.1)	7 (1)
Quine, *et al.*, 1994[274] UK	Not classified		964	< 40	89 (9.2)	28 (2.9)	98 (10.2)	0
Quine, *et al.*, 1994[274] UK	Not classified		1766	> 50	200 (11)	80 (4.5)	246 (14)	19 (1)
Patel, 1995[275] UK	Open access clinic	Age < 45 years, *H. pylori*-positive or NSAIDs/ alarm symptoms	115	< 45 selected group	30 (26)	4 (3.4)	9 (7.8)	0
Fraser, *et al.*, 1996[276] New Zealand	All		436		43 (9.9)	18 (4.1)	56 (12.8) moderate/ severe, 65 (14.9) mild	1 (0.2)
Martin, *et al.*, 1997[277] UK	(1) Private open access	Unclear, probably nil	327		20 (6.1)			4 (1.2)
Martin, *et al.*, 1997[277] UK	(2) NHS open access	Unclear, probably nil	150		9 (6)			3 (2)
Brignoli, *et al.*, 1997[149] Switzerland	(1) Primary care cohort, early OGD	Concurrent	172		12 (7.0)	1 (0.6)	13 (7.6)	1 (0.6); not specified
Brignoli, *et al.*, 1997[149] Switzerland	(2) Primary care cohort, selective OGD	Concurrent	203		7 (3.4)	1 (0.3)	7 (3.4)	1 (0.3); not specified
O'Neill, et al., 1998[362] Ireland	Open access		891		118 (13)	41 (5)	105 (12) (mild oesophagitis 180 (20))	9 (1)

TABLE 29 *Endoscopy case-mix results*

	Aged under 50 years: *H. pylori* prevalence 30%			Aged over 50 years: *H. pylori* prevalence 60%			All ages		
	n	**%**	**Target range (%)**	***n***	**%**	**Target range (%)**	***n***	**(%)**	**Target range (%)**
Total endoscopies	60,806	100		147,028			207,834		
Gastric cancer	1	0.0	0	134	0.1	0.3–2	135	0.1	0.15–0.1
Duodenal ulcer	1,529	2.5	2–10	5,824	4.0	5–15	7,353	3.5	2–15
Gastric ulcer	342	0.6	0.5–5	1,524	1.0	1–14	1,866	0.9	1–14
Oesophagitis	8,681	14.3	4–16	20,063	13.6	4–16	28,744	13.8	4–16

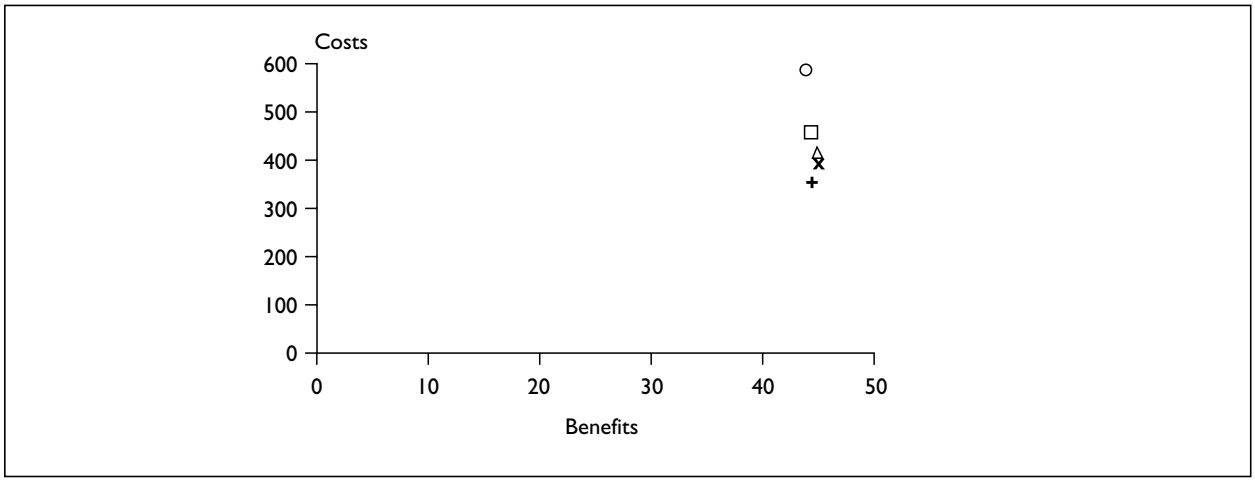


FIGURE 22 *The DES model: comparison of initial strategies (○, endoscope all; □, test-and-endoscope; △, eradicate all; ×, test-and-eradicate; +, medication only)*

TABLE 30 *Non-dominated strategies in the base case*

Point	Investigation strategy	Prescription strategy	Cost over 5 years (£)	Standard error†	Dyspepsia-free months in 5 years	Standard error†	Extra cost for 1 month's extra benefit compared with:	
							Previous (£)	Cheapest (£)
A	Medication only	Antacid only	169.05	0.43	35.59	0.056		
B	Test-and-eradicate	Antacid only	221.60	0.55	36.42	0.058	62.77	62.77
C	Medication only	H_2-receptor antagonist	274.73	0.67	42.25	0.047	9.12	15.86
D*	Medication only	Antacid, H_2-receptor antagonist, PPI, and down	319.63	0.27	43.12	0.014	51.36	19.98
E*	Medication only	PPI, H_2-receptor antagonist, antacid, and stay	324.57	0.26	43.17	0.015	105.98	20.51
F	Medication only	Antacid, H_2-receptor antagonist, PPI, and stay	328.56	0.88	43.49	0.046	12.57	20.19
G	Medication only	PPI only	357.17	0.89	44.23	0.046	38.41	21.76
H	Test-and-eradicate	PPI only	395.08	0.93	44.88	0.046	58.73	24.32
I	Test-and-eradicate	PPI or prokinetic if effective	479.37	1.16	45.13	0.047	329.04	32.50

* *For points D and E, the number of replications was increased to ensure a statistically significant difference*

† *Standard errors reported rather than SDs as comparison of costs and benefits relates to populations not individuals (see page 67)*

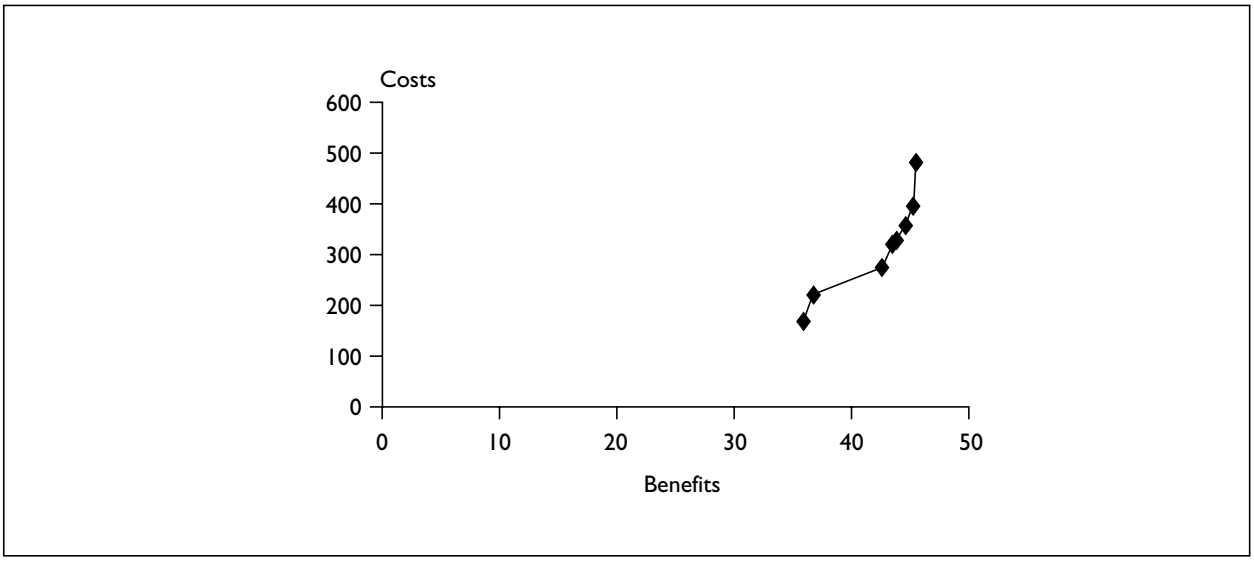


FIGURE 23 *The DES model: non-dominated strategies in the base case*

symptom-free). Switching from H_2-receptor antagonist to PPI alone would reduce the mean time with dyspepsia over 5 years by just 2 months at an additional cost of £82.44 (ICER, £41.64 per additional month symptom-free).

The additional cost of the 'test-and-eradicate' strategies includes the immediate cost of the *H. pylori* test and subsequent eradication therapy for patients testing positive. Against this is offset the cost saving in terms of recurrent ulcers prevented. The additional costs and benefits are both greater in the case where the prescribing strategy is to use antacids, as is the ratio between them (ICER).

Table 31 summarises the cost-effectiveness ratios that might be obtained over 5 years of using a particular prescribing strategy, that is the cost per month symptom-free.

Sensitivity analysis

It is important to test the robustness of any model output to possible variation in the model parameters. Sensitivity analyses were conducted using the high and low values of the parameters. These reflected both uncertainty in the underlying assumptions of the model and possible variations in practice. A summary is set out in appendix 5.

Variation in H. pylori *prevalence*

There is a substantial birth cohort effect in *H. pylori* prevalence that causes it to reduce by approximately 1% per year.[236] The model samples *H. pylori* status for each individual using a fixed probability. Thus any output is, strictly speaking, valid only for a particular birth cohort. On the other hand, the individuals first consulting for dyspepsia in any one year will vary widely in age and, thus, differ in the probability of being infected with *H. pylori*. To test the importance of this difference, the model was re-run with *H. pylori* prevalence set first to 10% and then to 605. All the strategies that had been non-dominated in the base case remained non-dominated but some additional strategies also appeared. In the case of 60% prevalence, some combinations involving the investigation strategy 'eradicate all' were slightly more effective but

TABLE 31 *Cost-effectiveness ratios for prescribing in primary care*

Prescribing	Cost-effectiveness ratio (£/month)
Antacid	4.75
H_2-receptor antagonist	6.50
PPI	8.07
H. pylori eradication then antacid	6.08
H. pylori eradication then H_2-receptor antagonist	Dominated by step-up and step-down strategies
H. pylori eradication then PPI	8.80

appreciably more expensive than 'test-and-eradicate' with the same prescribing strategy. The ICERs between the strategies varied with prevalence. As expected, the higher the prevalence of *H. pylori*, the higher the differences, in both costs and benefits, for the 'test-and-eradicate' investigation strategy compared with the 'medication only' investigation strategy with the same prescribing strategy. The variation is shown in *Figures 24* and *25*.

Relationship of H. pylori *to reflux disease*

Two issues relating to reflux disease were tested in sensitivity analysis. First, there has been a suggestion that individuals who are *H. pylori*-negative may have a greater risk of reflux disease than those who are *H. pylori*-positive.[223] To test the importance of this suggestion, the parameter for reflux onset risk (see *Table 7*) was replaced by separate parameters according to *H. pylori* status. The model was re-run with the same average risk as for the base case but changed so that individuals who were *H. pylori*-negative had double the risk of reflux disease compared with those who were *H. pylori*-positive. The results were not significantly different from the base case. Second, there is the question of the proportion of NUD to reflux disease. In the base case, the risks of these were

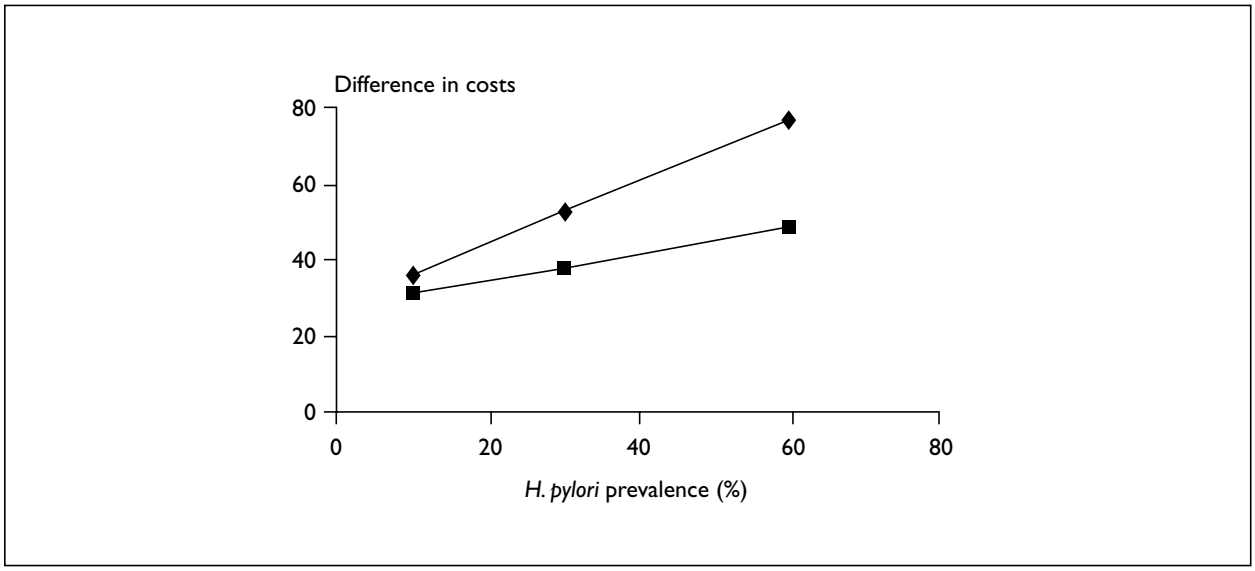


FIGURE 24 *Effect of variation in* H. pylori *prevalence on difference in costs for 'test-and-eradicate' compared with 'medication only' (♦–♦, antacid; ■–■, PPI)*

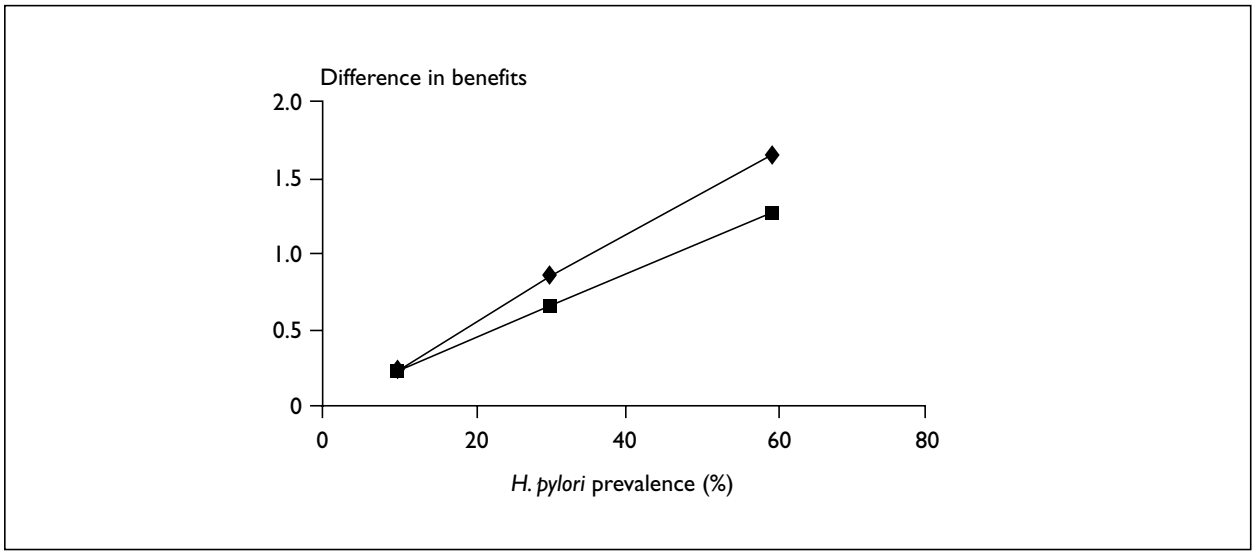


FIGURE 25 *Effect of variation in* H. pylori *prevalence on difference in benefits for 'test-and-eradicate' compared with 'medication only' (♦–♦, antacid; ■–■, PPI)*

taken as equal. The parameters for NUD onset risk and reflux disease onset risk were altered so that the risk for reflux disease was nine times that for NUD, maintaining the same total risk. With those values, the strategy involving 'PPI or prokinetic if effective' was now dominated. The ICERs were somewhat lower than those for the base case.

Varying effectiveness of medication

For each type of medication in turn, the effectiveness for all four types of dyspepsia was simultaneously changed, first to the low value, then to the high. Making the H_2-receptor antagonists less effective removed the 'step-up/down' prescribing strategies and H_2-receptor antagonists alone from the list of non-dominated options. Making H_2-receptor antagonists more effective had a profound effect, resulting in only three non-dominated strategies, antacid alone, H_2-receptor antagonists alone and *H. pylori* eradication followed by H_2-receptor antagonists. The cost-effectiveness ratio for H_2-receptor antagonists fell to £4.77 per month, with 10 months less dyspepsia over 5 years at an ICER of £5.36 over antacid alone over 5 years.

Making prokinetics less effective had no effect on the non-dominated strategies. Making prokinetics more effective allowed some strategies involving prokinetics to become non-dominated. Making PPIs more effective made the strategies involving PPI both more effective and cheaper (because of fewer repeat prescriptions). The strategy involving 'PPI or prokinetic if effective' became dominated. Making PPIs less effective meant that the only non-dominated strategies were combinations of 'medication only' and 'test-and-eradicate' with 'antacid only', 'H_2-receptor antagonists only' and 'PPI or prokinetic if effective'.

Changing the effectiveness of antacid required some care, as the calibration of the self-treating parameters may be affected. In practice, an adjustment was only necessary when antacids are made more effective. When the effectiveness of antacid was set to its lowest value, one of the step prescribing strategies was removed from the list of non-dominated options; the options involving antacid only became both less effective and more expensive, so that the ICER in switching from antacid to H_2-receptor antagonist was reduced to £2.77. 'Test-and-eradicate' followed by antacid only became dominated but 'test-and-eradicate' followed by 'H_2-receptor antagonists only' became non-dominated. Making antacids more effective (and adjusting the self-treating parameters) removed 'H_2-receptor antagonists only' from the list of non-dominated options and replaced one combination with a mixed prescribing strategy by another. This time, the strategies involving antacid only became somewhat cheaper and much more effective.

A further analysis in changing the effectiveness of medication was to adopt a set of parameters designed to reflect the limits of effectiveness in different directions for NUD and reflux disease. Prokinetics were set to the maximum effectiveness for NUD but the minimum for reflux disease, and H_2-receptor antagonists and PPI were set to the minimum effectiveness for NUD, also setting PPI to the maximum for reflux disease. This made a considerable difference to the list of non-dominated options (*Table 32*).

Varying cost of medication

In the next group of sensitivity analyses, one type of medication was replaced by a different type from the same class. In general, it was assumed that the effectiveness data in *Table 25* applied to all medication in a given class; thus the change made here was simply in the price of a given class of medication. Some exceptions are noted below.

Considering antacids first: using the cheapest antacid made no difference to the list of non-dominated options but meant that the strategies using antacid became slightly cheaper and, hence, the ICERs of the other strategies compared with antacid alone were increased slightly. Using Gaviscon instead caused a considerable increase in the price of antacid and meant that the strategies using antacid only were now dominated. It has been suggested that Gaviscon is more effective than non-alginate antacids for reflux disease. A threshold analysis revealed that the effectiveness for reflux disease would need to increase from 20% success in 1 month to over 38% before a strategy involving Gaviscon alone became non-dominated.

Turning to H_2-receptor antagonists, using the most expensive H_2-receptor antagonist simply removed the mixed prescribing strategies and H_2-receptor antagonists from the list of non-dominated options compared with the base case. Using the cheapest made a substantial change to the list of non-dominated options, as shown in *Table 33*. The H_2-receptor antagonist only strategies, alone or with test-and-treat, now dominated antacid alone. However, although the PPI strategies were still more effective, all the ICERs were at least £100 per additional month symptom-free. It has been suggested

TABLE 32 *Varying treatment effectiveness to opposite extremes for NUD and reflux*

Investigation strategy	Prescription strategy	Costs, absolute (£)	Standard error†	Benefits, absolute	Standard error†	ICER	Compared with cheapest
Medication only	Antacid only	171.03	1.57	35.66	0.18		
Test-and-eradicate	Antacid only	222.71	1.86	36.54	0.18	58.83	6.10
Medication only	H_2-receptor antagonist only	306.67	2.48	41.00	0.15	18.83	7.48
Test-and-eradicate	H_2-receptor antagonist only	350.42	2.62	41.70	0.16	61.97	8.40
Medication only	PPI, H_2-receptor antagonist, antacid, and stay	358.60	0.31	42.19	0.01	16.76	8.50
Medication only	Antacid, H_2-receptor antagonist/ prokinetics, PPI, and stay	367.47	0.31	43.19	0.01	8.83	8.51
Medication only	PPI only	394.86	0.34	43.33	0.01	204.48	9.11
Test-and-eradicate	Antacid, H_2-receptor antagonist/ prokinetics, PPI, and stay	405.99	0.31	43.85	0.02	21.25	9.26
Medication only	Try PPI or prokinetics until one of them works	406.38	0.33	44.19	0.01	1.18	9.20
Test-and-eradicate	Try PPI or prokinetics until one of them works	441.23	0.33	44.83	0.01	54.11	9.84

† *Standard errors reported rather than SDs as comparison of costs and benefits relates to populations not individuals (see page 67)*

TABLE 33 *Using the cheapest H_2-receptor antagonist*

Investigation strategy	Prescription strategy	Cost over 5 years (£)	Standard error†	Dyspepsia-free months in 5 years	Standard error†	Extra cost for 1 month's extra benefit compared with:	
						Previous (£)	Cheapest (£)
Medication only	H_2-receptor antagonist only	161.06	1.33	42.50	0.15		
Test-and-eradicate	H_2-receptor antagonist only	214.07	0.53	42.88	0.05	139.22	139.22
Medication only	Antacid, H_2-receptor antagonist, PPI, and down	270.11	0.83	43.16	0.05	201.61	165.54
Medication only	PPI, H_2-receptor antagonist, antacid, and stay	288.91	0.78	43.21	0.05	352.58	179.55
Medication only	Antacid, H_2-receptor antagonist, PPI, and stay	289.76	0.88	43.50	0.05	2.92	128.52
Test-and-eradicate	Antacid, H_2-receptor antagonist, PPI, and down	313.29	0.86	43.76	0.05	88.74	120.19
Test-and-eradicate	Antacid, H_2-receptor antagonist, PPI, and stay	333.21	0.91	44.06	0.05	68.05	110.40
Medication only	PPI only	354.25	2.82	44.47	0.14	51.45	98.15
Test-and-eradicate	PPI only	394.59	0.93	44.87	0.05	99.67	98.41
Test-and-eradicate	PPI or prokinetic if effective	483.36	1.17	45.19	0.05	279.27	119.78

† *Standard errors reported rather than SDs as comparison of costs and benefits relates to populations not individuals (see page 67)*

that cimetidine is less effective than other H_2-receptor antagonists in treating dyspepsia. When the effectiveness was reduced to equal that for antacid, the strategies involving H_2-receptor antagonists alone became somewhat more expensive and less effective, but were still non-dominated. The strategy of test-and-eradicate, followed by stepping down through H_2-receptor antagonists to antacid became non-dominated. Using the cheapest PPI had the effect of reducing the cost of the strategies involving PPI alone (see *Table 34*).

The choice of prokinetics was important in the model. The huge difference in price between cisapride and the cheapest available, metoclopramide, would be expected to have a dramatic effect and this is indeed the case. The new list of non-dominated strategies appears in *Table 35*. The strategies involving antacid or H_2-receptor antagonists alone were now dominated. However, this result needs to be treated with caution because metoclopramide and cisapride are not directly equivalent. Cisapride has been shown to be more effective than metoclopramide in improving gastric motility. Furthermore, an RCT comparing the two drugs in patients with NUD suggested that cisapride might be more effective, although this trend was not statistically significant. Metoclopramide should not be given to young patients because of the risk of occulogyric side-effects and there is also a risk of tardive dyskinesia, particularly in the elderly.

A complete list of all the results of the base-case analysis, with a summary of the sensitivity analyses conducted, is given in appendix 5. In each row, the non-dominated strategies are numbered in order from cheapest and least effective to most expensive and most effective. Unnumbered strategies are dominated under the assumptions used for that row.

Discussion

Limitations of the model

While the model described here is considerably more detailed than any previous model concerned with dyspepsia, it still has several limitations, which must be recognised. There are a number of homogeneity assumptions, including the effectiveness of medication (other than *H. pylori* eradication therapy), which is assumed to be independent of age and previous history, both of disease and of taking medication. Similarly, the risk of recurrence after clearing of symptoms is taken to be independent of the medication taken. The shape of the risk function for recurrence is based on data for 1 year only after medication.

TABLE 34 *Using the cheapest PPI*

Investigation strategy	Prescription strategy	Cost over 5 years (£)	Standard error†	Benefits: dyspepsia-free months in 5 years	Standard error†	Extra cost for 1 month's extra benefit compared with:	
						Previous (£)	Cheapest (£)
Medication only	Antacid only	167.73	167.73	35.86	0.18		
Test and eradicate	Antacid only	219.11	219.11	36.74	0.18	58.71	5.96
Medication only	H_2-receptor antagonist only	272.65	272.65	42.50	0.15	9.30	6.42
Medication only	Antacid, H_2-receptor antagonist, PPI, and down	290.45	290.45	43.12	0.01	28.41	6.74
Medication only	PPI, H_2-receptor antagonist, antacid, and stay	291.23	291.23	43.17	0.01	16.83	6.75
Medication only	Antacid, H_2-receptor antagonist, PPI, and stay	293.62	293.62	43.49	0.05	7.56	6.75
Medication only	PPI only	299.66	299.66	44.47	0.14	6.17	6.74
Test and eradicate	PPI only	344.79	344.79	44.93	0.05	97.45	7.67
Test and eradicate	PPI or prokinetic if effective	436.66	436.66	45.11	0.05	514.77	9.68

† *Standard errors reported rather than SDs as comparison of costs and benefits relates to populations not individuals (see page 67)*

TABLE 35 *Using the cheapest prokinetic*

Investigation strategy	Prescription strategy	Cost over 5 years (£)	Standard error†	Benefits: dyspepsia-free months in 5 years	Standard error†	Extra cost for 1 month's extra benefit compared with:	
						Previous (£)	Cheapest (£)
Medication only	Prokinetic only	118.03	1.06	41.29	0.15		
Test and eradicate	Prokinetic only	170.59	0.15	42.20	0.02	57.84	4.04
Medication only	Antacid, H_2-receptor antagonist, PPI, prokinetic, and stay	233.07	0.15	42.34	0.02	443.61	5.50
Medication only	Prokinetic, PPI, H_2-receptor antagonist, antacid, and stay	250.50	0.68	43.01	0.05	25.91	5.82
Medication only	Antacid, H_2-receptor antagonist, PPI, prokinetic, and stay	280.70	0.18	43.16	0.02	209.07	6.50
Medication only	PPI, prokinetic, H_2-receptor antagonist, antacid, and stay	293.71	0.25	43.27	0.01	112.70	6.79
Medication only	Antacid, H_2-receptor antagonist, prokinetic, PPI and stay	310.79	0.86	43.42	0.05	116.00	7.16
Test and eradicate	PPI, prokinetic, H_2-receptor antagonist, antacid, and stay	337.64	0.85	43.99	0.05	47.30	7.68
Test and eradicate	PPI only	354.25	2.82	44.47	0.14	34.77	7.97
	PPI only	394.71	0.92	44.90	0.05	92.91	8.79
	PPI or prokinetic, whichever works	445.07	1.10	45.15	0.05	201.51	9.86

† *Standard errors reported rather than SDs as comparison of costs and benefits relates to populations not individuals* (see page 67)

The preference for 'medication only' and 'test-and-eradicate' as investigation strategies is highly robust; by comparison, the choice of prescribing strategy is by no means clear-cut and there is scope for considerable further research into the long-term effects of different types of medication.

The outcome, symptom-free months, was chosen for the model, as it could be taken as a proxy for both symptom response and quality of life. Studies have shown a close relationship between recurrent dyspeptic symptoms and reduced quality of life.[278] The model could be adjusted to provide an output equivalent to the risk ratio for a clinical trial, by determining the proportion of symptom recurrences in a given time. The outcome, symptom-free months, was kept as it is considered to be more informative to clinicians.

Principal findings

This DES model suggests that over a 5-year period, the choice of prescribing strategy primarily affects benefits and the choice of initial investigation strategy overall costs. This is logical because, although less effective medications will lead to more frequent consultation, the effect of the high initial costs of endoscopy and, to a lesser extent, *H. pylori* eradication add considerably to overall costs and are not significantly recouped by later prescribing savings. The model indicates that strategies involving endoscopy are not cost-effective, as prescribing alone or 'test-and-eradicate' are both as effective and cheaper. This effect was robust to all the sensitivity analyses conducted.

There are two main areas for discussion, the role of *H. pylori* eradication and the choice of medication and prescribing strategy. The question of the cost-effectiveness of screening for early gastric cancer at this age and above, using endoscopy in symptomatic patients with dyspepsia, is a separate question that overlaps with the effect of *H. pylori* eradication on the development of distal gastric cancer, and will be the subject of future development of the model.

It is known that as *H. pylori* prevalence and the prevalence of PUD and distal gastric cancer has been declining, the prevalence of oesophageal

disease has been rising. In addition, several studies have shown a negative relationship between *H. pylori* gastritis and oesophagitis. Although there may be many other explanations for this trend, including behaviour, diet and reporting of disease, it has been postulated that the rise in oesophageal disease is directly related to the decline in *H. pylori* infection. If true this would have two possible effects: first, reflux disease would be more common in *H. pylori*-negative individuals and, second, that *H. pylori* eradication may lead to the development of reflux symptoms in susceptible individuals. There is currently no consensus on this issue, although the only RCT that assessed this showed that *H. pylori* eradication had no effect on gastro-oesophageal reflux symptoms or oesophagitis. It is nevertheless important to examine how robust the model would be to *H. pylori* eradication exacerbating reflux disease. The effect of this was examined by both altering the ratio of NUD to reflux disease in patients without ulcers and by doubling the risk of reflux disease after *H. pylori* eradication; neither of these had significant effects on the analysis.

Sensitivity analysis indicates that the benefit of the 'test-and-treat' strategy over prescribing alone is largely lost when the prevalence of *H. pylori* is decreased to 10%; at this level the benefit for the small numbers of patients detected is outweighed by the costs. Above this level, *H. pylori* test-and-treat provides, on average, 1 month less of dyspepsia over 5 years for between £66 and £83, depending on the prescribing strategy. Although this may seem small, the effect hides the fact that for individuals with an 'ulcer diathesis', and there is no means of defining this in the absence of a previous history, the effect will be very much greater.

Turning to choice of medication, the analysis is sensitive to variation in a number of parameters and choices will need to be made depending on the availability of resources. First, for single medication strategies the choice is between antacids alone, H_2-receptor antagonists alone or PPIs alone. The uncertainty around the effectiveness of H_2-receptor antagonists in NUD allows their use in preference to antacids, or in stepwise strategies between antacids and PPIs. The step strategies (antacid–H_2-receptor antagonist–PPI, either 'step-up and maintain' or 'step-up and down') are only marginally cheaper than intermittent PPI alone, a difference that may not be realised in clinical practice. A 'do nothing' strategy was not included in the model as the minimum treatment that any patient would be prepared to accept would be antacid alone. None of the trials in the review prevented patients from taking either open label or OTC antacid.

The other major area of uncertainty relates to the role of prokinetic agents in dyspepsia. Generic metoclopramide is cheaper than antacids and might represent the most cost-effective choice for some patients. Much more research is required in the effectiveness of metoclopramide in NUD before clear recommendations can be made. Further analysis of this model is in progress to examine the cost-effectiveness of early endoscopy at different age cut-off points for the diagnosis of treatable gastric cancer.

Chapter 8

Cost-effectiveness of treatments for NUD

H. pylori eradication therapy in NUD

The systematic review suggests that *H. pylori* eradication is effective in NUD. The finding is robust, as it is derived from five large well-designed trials with no significant between-study heterogeneity. The overall effect size is small, however, and so the cost-effectiveness of *H. pylori* eradication therapy in NUD is uncertain. The cost of per month of dyspepsia cured was therefore evaluated in an economic model (*Figure 26*).

Strategies compared in the model

In the model, *H. pylori* eradication was compared with 1 month of antacid therapy in patients with NUD. Antacid therapy was assumed to act as an inexpensive placebo and the impact of these interventions was assessed over 1 year. Patients with continuing symptoms despite these interventions were given lifestyle advice and reassurance by their GP. The model did not compare *H. pylori* eradication therapy with a 'do nothing' strategy, as clinicians feel obliged to give some form of therapy to patients with NUD.

Costs and benefits identified in the model

The model evaluated the impact of *H. pylori* eradication from a health service perspective. The cost of medication and visits to the GP were assessed (*Table 36*). The main uncertainty in the model was the number of times a patient with continuing dyspepsia would visit their GP. It was arbitrarily assumed that patients would visit their GP three times in 1 year but this assumption was evaluated over a wide range of values in a sensitivity analysis.

The benefit of therapy was measured in terms of the number of months of minimal or no dyspeptic symptoms over 1 year. The response rate at 1 year for those receiving antacids was estimated from the placebo group in the systematic review and converted into a monthly probability of recurrent dyspepsia. The RR reduction from the review was applied to estimate the response rate for those receiving *H. pylori* eradication. Robustness of the results was explored in one-way sensitivity analyses. The main areas of uncertainty in the model are the estimate of the RR reduction and the maximum willingness-to-pay for 1 month free of dyspepsia. The RR of dyspepsia in patients treated with *H. pylori* eradication therapy was assumed to have a log normal distribution with a mean and SD derived from the pooled estimate from the meta-analysis. A probabilistic sensitivity analysis was then conducted using a Monte Carlo simulation of 1000.[279] This analysis was repeated for high- and low-cost eradication regimens.

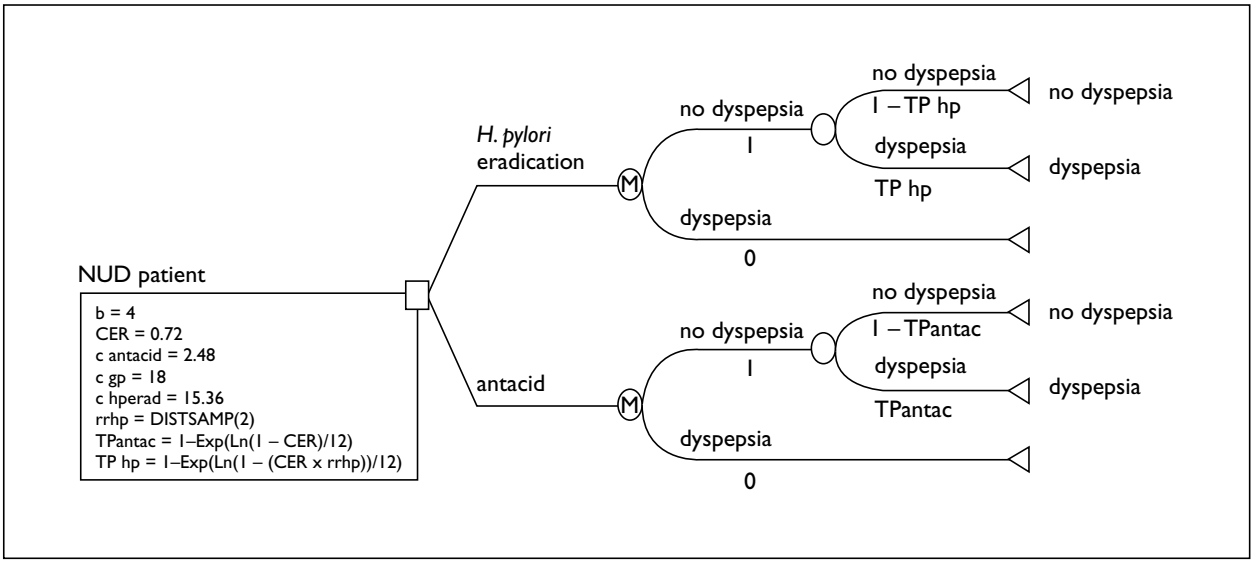


FIGURE 26 *Markov model comparing* H. pylori *eradication therapy with antacid therapy for NUD (CER, cost-effectiveness ratio)*

TABLE 36 *Costs and parameters used in the models evaluating the cost effectiveness of pharmacological interventions and* H. pylori *eradication therapy*

Variable	Base case	Range used in sensitivity analyses
Cost of GP visit	£18[a]	£9–20
Number of GP visits/year if dyspeptic	3	1–12
Cost of antacid	£2.48[b]	£1.68[c]–12.50[d]
Cost of *H. pylori* eradication	£37.94[e]	£15.36[f]–39.32[g]
Cost of PPI	£30.13[h]	£23.75[i]–30.13[h]
Cost of H_2-receptor antagonist	£18.63[j]	£5.89[k]–26.60[l]
Cost of prokinetic	£7.56[m]	£1.17[n]–37.60[o]
Placebo response rate	0.28	[p]
RR of dyspepsia in patients treated with *H. pylori* eradication therapy	0.91[p]	0.86–0.96[q]

[a] *Netten A, Dennett J, Knight J. Unit costs of health and social care. Canterbury: University of Kent; 1998*
[b] *Cost of magnesium trisilicate, 10 ml q.d.s., for 30 days*[*]
[c] *Cost of magnesium carbonate, 10 ml q.d.s., for 30 days*[*]
[d] *Cost of Gaviscon Advance, 10 ml q.d.s., for 30 days*[*]
[e] *Cost of lansoprazole, 30 mg b.d., clarithromycin. 500 mg b.d., and amoxycillin, 1000 mg b.d., for 7 days*[*]
[f] *Cost of ranitidine bismuth citrate, 400 mg b.d., amoxycillin, 1000 mg b.d., metronidazole, 400 mg b.d., for 7 days*[*]
[g] *Cost of omeprazole, 20 mg b.d., clarithromycin, 500 mg b.d., and amoxycillin, 1000 mg b.d., for 7 days*[*]
[h] *Cost of omeprazole, 20 mg b.d., for 28 days*[*]
[i] *Cost of rabeprazole, 20 mg b.d., for 28 days*[*]
[j] *Cost of ranitidine, 150 mg b.d., (non-proprietary) for 30 days*
[k] *Cost of cimetidine, 400 mg b.d., (non-proprietary) for 30 days*
[l] *Cost of famotidine, 20 mg b.d., for 30 days*
[m] *Cost of domperidone, 10 mg t.d.s., for 30 days*
[n] *Cost of metoclopramide, 10 mg t.d.s., for 30 days*
[o] *Cost of cisapride, 20 mg b.d., for 30 days*
[p] *Mean placebo response rate at 1 year in the systematic review*
[q] *From systematic review of* H. pylori *eradication in NUD*
[*] *British National Formulary, British Medical Association 1999*

A set of cost-effectiveness acceptability curves was constructed to reflect uncertainty in both effects and the maximum willingness-to-pay using an Excel© 97 (Microsoft Corporation) spreadsheet.[280]

The value of each month free from dyspepsia is uncertain in patients with NUD and this has to be indirectly estimated from implicit willingness-to-pay for cure of other upper gastrointestinal diseases. GORD is reliably treated with acid suppression and it has been estimated that this costs £64–100 per patient cured at 1 month.[281,282] The upper limit for the value of each month free from dyspepsia was therefore taken as £100 in patients with NUD.

Results of the model

The cost-effectiveness analysis estimated that *H. pylori* eradication would be £31.76 more expensive per patient per year than the antacid strategy (cost of antacid strategy, £55.25; cost of *H. pylori* eradication strategy, £87.01), but that those receiving *H. pylori* eradication therapy would benefit by, on average, 0.56 months extra free from dyspepsia than those on antacid. This yielded an ICER of £56 per extra month free from dyspepsia. This finding was robust to all one-way sensitivity analyses except for the magnitude of RR reduction (*Table 37*).

The decision as to whether *H. pylori* eradication therapy is cost-effective in NUD depends on the maximum willingness-to-pay for each month free of dyspepsia and the uncertainty that the decision maker is willing to tolerate. This is shown in the cost-effectiveness acceptability curve (*Figure 27*). If a decision maker is willing to accept a 20% chance of the policy being incorrect then, for a maximum willingness-to-pay of £75 per month free of dyspepsia, the 'base-case scenario' would be acceptable. If the maximum acceptable were only £25 then only cheaper eradication regimens would be cost-effective. The equivalent 95% CI

TABLE 37 *One-way sensitivity analyses for the cost-effectiveness of* H. pylori *eradication therapy in NUD*

Variable altered	Incremental cost of *H. pylori* eradication compared with antacid strategy (£/month free from dyspepsia)	
	Worst case	Best case
Cost of GP visit	60	56
Number of visits to GP	59	43
Cost of antacid	58	39
Cost of eradication therapy	59	16
RR of dyspepsia	132	35

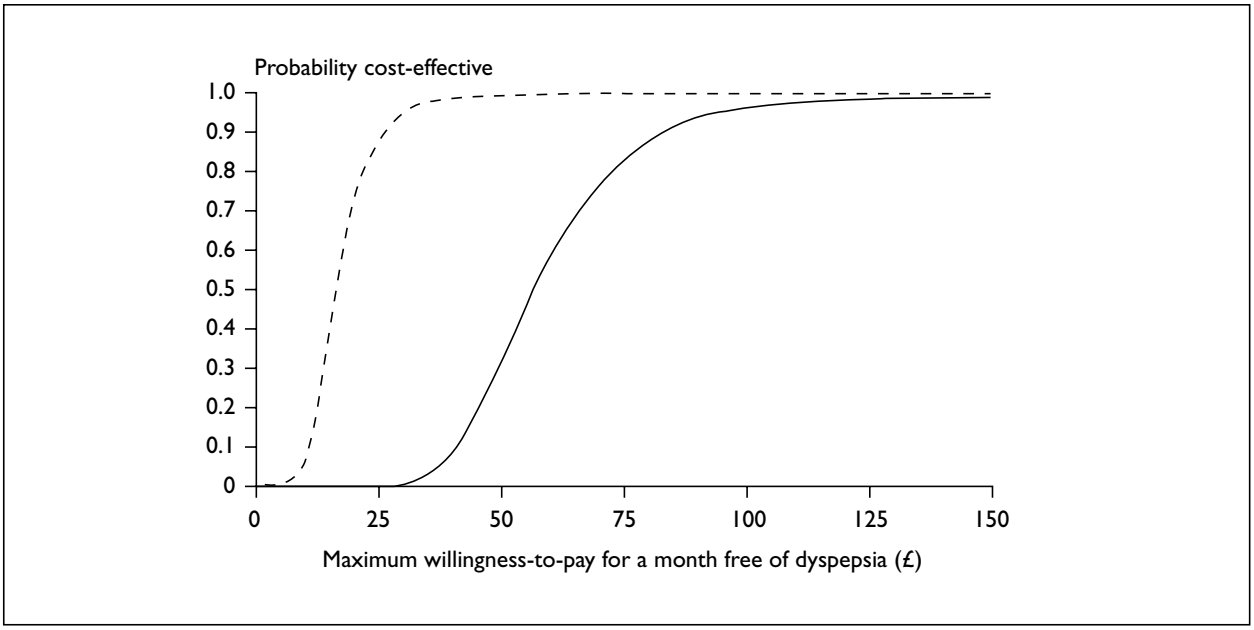


FIGURE 27 *Cost-effectiveness acceptability curve of* H. pylori *eradication in NUD patients with varying cost of eradication regimens (– – –, base case; ——, cheapest eradication)*

of the ICER from the cost-effectiveness acceptability curve is £36 to £118 per patient for the base case.

Discussion

H. pylori eradication

This Markov model is an oversimplification of the treatment of NUD. Patients not responding to initial therapy would be prescribed anti-secretory or prokinetic therapy in clinical practice. The efficacy of this approach is uncertain, so was not evaluated in the model. Including the use of these drugs in the model is likely to make *H. pylori* eradication therapy more cost-effective, as fewer patients have dyspepsia in this group. Furthermore, the benefits are likely to continue to accrue beyond 1 year in patients receiving *H. pylori* eradication therapy. Hence, the Markov model provides a conservative estimate of the cost-effectiveness of *H. pylori* eradication. The costs and benefits were not discounted as assessments were being made over 1 year.

In conclusion, *H. pylori* eradication therapy appears to be a cost-effective treatment for NUD and this is robust to most sensitivity analyses exploring uncertainty in the data.

Pharmacological therapies in NUD

The effectiveness of antisecretory and prokinetic therapy in NUD remains uncertain. Trials evaluating PPIs have been large and well designed, so the meta-analysis of this data is likely to be the most accurate. This indicated that PPI therapy is likely to be effective (RR, 0.88; 95% CI, 0.76 to 1.01), although this was of marginal statistical

significance. Trials evaluating H_2-receptor antagonists and prokinetics were of variable quality and it is not possible to draw firm conclusions on the efficacy of these drugs in NUD.

A Markov model was employed to evaluate the sample size that future trials need in order to establish whether these drugs would be cost-effective treatments in NUD. Trials evaluating pharmacological therapies have usually assessed patients after 4 weeks and no trial has evaluated patients for longer than 12 weeks. NUD is a chronic disorder and patients should be followed-up for a year to accurately establish the long-term efficacy of pharmacological intervention. The model compared placebo (a 'do nothing' strategy) with either PPI, H_2-receptor antagonist or prokinetic therapy over 1 year (*Figure 28*). The economic analysis was in the context of an RCT with predefined return visits, so only drug costs were considered. The maximum cost-effectiveness that would be considered acceptable was £100/month free from dyspepsia.[281,282]

PPI therapy

The Markov model was used to establish whether PPIs were cost-effective in treating NUD. The systematic review suggested that patients with NUD had an RR of 0.88 (95% CI, 0.76 to 1.01) of having dyspepsia after treatment. It was assumed this RR would continue over 1 year. Omeprazole cost £170/month free from dyspepsia and using the cheapest PPI (rabeprazole) would only reduce this to £132/month free from dyspepsia. Taking the greatest possible efficacy of PPIs from the 95% CIs of the data only reduced the cost-effectiveness to £100/month free of dyspepsia. PPIs are therefore unlikely to be a cost-effective therapy for NUD in the long term and further trials evaluating these drugs are not warranted.

H_2-receptor antagonist therapy

The finding that PPI therapy is not cost-effective in NUD emphasised the need for inexpensive drugs to treat this condition. Cimetidine is the cheapest H_2-receptor antagonist but is prescribed less frequently than ranitidine. Non-proprietary ranitidine is cheaper than PPI therapy and may therefore still be a cost-effective treatment of NUD. A threshold analysis using a Markov model (*Figure 28*) suggests that this therapy would be cost-effective, provided the RR for dyspepsia on treatment was ≤ 0.88. A trial with approximately 400 patients in each arm would detect this risk difference at the 80% power and 5% significance level.

Prokinetic therapy

Domperidone is a cheap prokinetic that has a better adverse event profile than metoclopramide (*Table 37*). The use of this drug in the treatment of NUD was evaluated in the model (*Figure 28*) and domperidone would be cost-effective provided

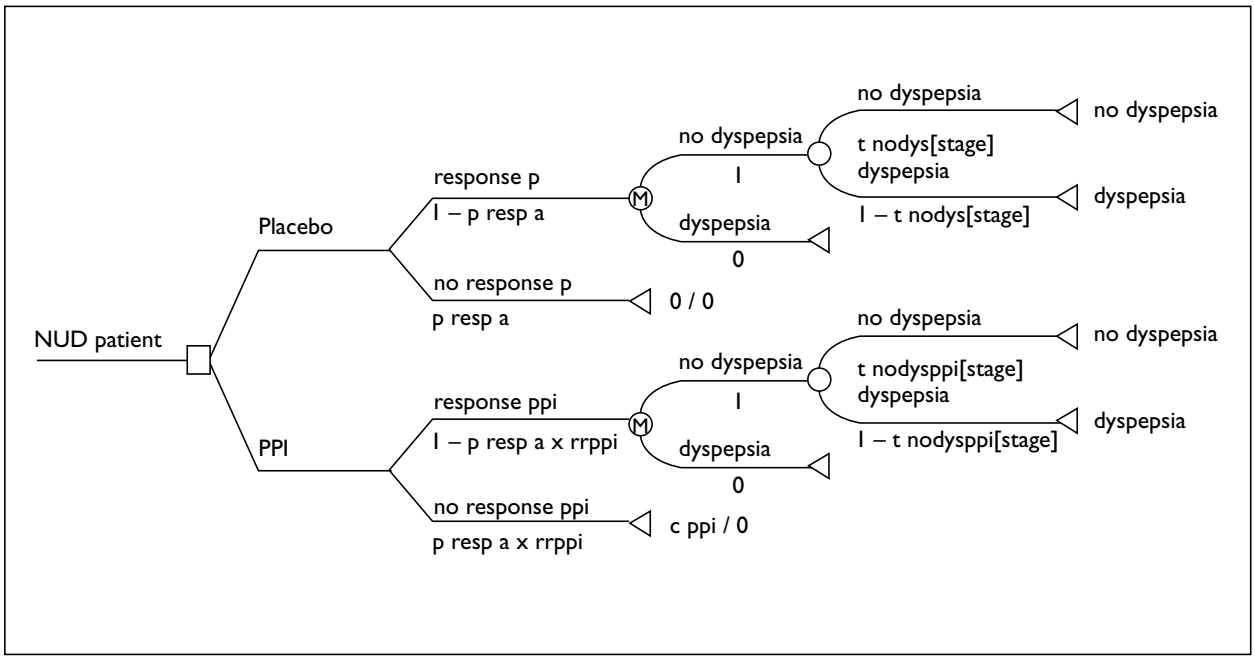


FIGURE 28 *Markov model comparing pharmacological therapy with placebo in an RCT in NUD patients (model shows PPI but relevant values for H_2-receptor antagonists and prokinetics can be substituted)*

that the RR for dyspepsia on treatment was ≤ 0.97. A trial with over 5500 patients in each arm would detect this risk difference at the 80% power and 5% significance level. A trial of this size is impractical so, even if future studies do not confirm the efficacy of domperidone, this does not preclude this from being a cost-effective strategy.

Chapter 9
Conclusions

The principal objectives of the review were to determine the cost-effectiveness of therapies for patients with NUD and of primary care-based approaches to the management of the uninvestigated patient with dyspepsia. Although these are linked, uninvestigated patients with dyspepsia do not necessarily have NUD. The link arises because of the lack of direct primary care-based trial evidence to address the role of *H. pylori* testing and either eradication therapy or endoscopy.

This lack of direct data is addressed in this review, using a DES model in which the results of the NUD reviews provide modelling parameters for the effect of investigative strategies and treatments on patients with NUD in the model. The decision to prescribe or follow a particular path of investigation depends on where particular choices lie on the cost-effectiveness plane. Cheap and effective strategies will be chosen in preference to strategies that are more expensive with the same or inferior outcomes. For more effective/more costly and less effective/less costly interventions there will be an ICER. A choice needs to be made as to the point at which the ICER becomes too costly for the intervention to be deemed cost-effective. This is clearly a matter of policy and judgement, although, as we have indicated previously, interventions of the order of £100/month symptom-free are in widespread use in this clinical field. A summary of the overall findings of the review relating to effectiveness, cost-effectiveness and the level of evidence found is shown in *Table 38*.

Cost-effectiveness of treatments for NUD

Considering first those patients with dyspepsia who have had an endoscopy with normal findings and are labelled as having NUD, the review indicates that PPIs are not a cost-effective treatment for this group of patients. This is in contrast to patients with uninvestigated dyspepsia, as those with GORD and PUD have been excluded.

There is some evidence that H_2-receptor antagonist therapy may be effective in NUD. The trials evaluating prokinetic therapy are difficult to interpret, as the meta-analysis result could have been due to publication bias. Further research using prokinetics and anti-secretory therapy is required before any firm conclusions can be reached. The effect of these drugs is likely to be small and many patients will need to take them on a long-term basis, so the therapies assessed need to be inexpensive and well tolerated. These trials also need to assess patients over 12 months, as dyspepsia is a chronic disorder with a persistent placebo effect and long-term trials are lacking.

There is a small but statistically significant benefit of *H. pylori* eradication therapy in NUD. A Markov model suggests that *H. pylori* eradication is a cost-effective strategy compared with antacid therapy in patients with NUD. This result is robust to the removal of any one trial. If reports of trials currently available in abstract form only, but to which there was access to a draft paper, were removed, the effect is still significant, but smaller (RR reduction, 7%; 95% CI, 1 to 12). Although there has been lively debate as to potential differences between the trials, there is no statistically significant heterogeneity. None were designed with enough power to detect a difference as small as 9% in RR. A trial with a sample size to detect this difference is unlikely to be performed and *H. pylori* eradication may be considered cost-effective in NUD on the available evidence. As dyspepsia is a chronic relapsing condition, associated with a significant reduction in quality of life, it is likely that patients would value this small benefit. However, this remains to be determined.

Trials need to evaluate the efficacy of inexpensive anti-secretory and prokinetic therapy in *H. pylori*-negative patients with NUD and in *H. pylori*-positive patients with NUD who remain symptomatic 6–12 months after successful eradication therapy. These trials should evaluate patients over at least 6 months, as the long-term efficacy of acid supression or prokinetic therapy in NUD is uncertain.

Cost-effectiveness of interventions for uninvestigated dyspepsia in primary care

The systematic review of therapies for the uninvestigated dyspeptic patient in primary care

TABLE 38 *Summary table*

Comparison	RR ratio and NNT[a] (with 95% CIs)	Level of evidence[b]	Cost-effectiveness (level of evidence)[b]
Pharmacological interventions for NUD			
Prokinetics vs. placebo	RR ratio 50% (30 to 70) NNT 4 (3 to 7)	1a (–) Funnel plot asymmetry	Cisapride now suspended from UK and N. American markets. Sensitivity analysis suggests an NNT of 55 would be cost-effective, with a threshold of £100/month if domperidone used (4)
H_2-receptor antagonist vs. placebo	RR ratio 29% (4 to 47) NNT 7 (4 to 50)	1a (–) Only short-term trials	Sensitivity analysis suggests an NNT of 14 would be cost-effective with a threshold of £100/month if generic ranitidine used (4)
PPI vs. placebo	RR ratio 12% (–1 to 24) NNT 17 (8 to 200 (NNH))	1a (–)	ICER, £170 per extra month symptom-free. Reduces to minimum of £132 on sensitivity analysis. Unlikely to be cost-effective (4)
Bismuth vs. placebo	RR ratio 40% (–3 to 65) NNT 5 (3 to 67 (NNH))	1b (–)	
Antimuscarinics	RR ratio 51% (20 to 70) NNT 4 (3 to 10)	1a	No longer available in UK due to adverse side-effect profile
Sucralfate	RR ratio 29% (–64 to 40) NNT 7 (3 to 5 (NNH))	1a	
Misoprostol	RR ratio 68% (21 to 87) NNT 3 (2 to 10)	1b	
Antacids	Ineffective	One inconclusive trial	
H. pylori *eradication for NUD*			
H. pylori eradication vs. placebo	RR ratio 9% (4 to 14) NNT 15 (10 to 31)	1a	ICER in favour of H. pylori eradication, £56 per extra month symptom-free over 1 year (4)
Pharmacological therapy for uninvestigated dyspepsia			
PPI vs. antacids	RR ratio 29% (21 to 36) NNT 6 (5 to 8)	1a	ICER, £21.76 per extra month symptom-free over 5 years. Sensitive to costs and effectiveness of PPI and antacids (4)
PPI vs. H_2-receptor antagonist	RR ratio 37% (15 to 53) NNT 5 (3 to 11)	1a	ICER, £41.64 per extra month symptom-free over 5 years. Sensitive to costs and effectiveness of PPI and antacids (4)
PPI vs. prokinetics	RR ratio 5% (–20 to 30) NNT 33 (8 to 1.1 (NNH))	Inconclusive single trial	Dominated but sensitive to cost and effectiveness of prokinetics (4)
H_2-receptor antagonist vs. prokinetics	No trials	–	Model sensitive to NUD efficacy (4)
H_2-receptor antagonist vs. antacids	RR ratio 2% (–22 to 24) NNT 12 (3 to 1.5 (NNH))	Inconclusive single trial	ICER, £15.88 per extra month symptom-free over 5 years. Model sensitive to NUD efficacy (4)
Antacids vs. prokinetics	No trials	–	Model sensitive to NUD efficacy (4)
Early endoscopy			
Early endoscopy vs. initial prescribing	RR ratio 15% (–8 to 38) NNT 9 (4 to 20 (NNH))	1a	Dominated by initial treatment strategies; robust to sensitivity analysis (4)
Early endoscopy vs. test-and-treat	Not calculable	Inconclusive	
Early endoscopy vs. test-and-endoscope	Not calculable	Inconclusive cohort study	

continued

TABLE 38 contd *Summary table*

Comparison	RR ratio and NNT[a] (with 95% CIs)	Level of evidence[b]	Cost-effectiveness (level of evidence)[b]
Test-and-endoscope			
Test-and-endoscope vs. initial prescribing	No trial data	–	Dominated by initial treatment strategies; robust to sensitivity analysis (4)
Test-and-endoscope vs. test-and-treat	No trial data	–	
Test-and-treat			
Test-and-treat vs. initial prescribing	No trial data	–	ICER in favour of test-and-treat, £62.77 per month over 5 years; sensitive to medication and *H. pylori* prevalence (4)

[a] Calculated using baseline event rates appropriate for each intervention
[b] From Centre for Evidence-based Medicine, University of Oxford: 1a, meta-analysis with no significant heterogeneity; 1b, single well-designed, significant trial; 2a, meta-analysis of cohort studies; 2b, cohort study; 3, case–control studies; 4, case series and modelling studies; 5, expert opinion without critical appraisal. – indicates significant heterogeneity exists in the meta-analysis or a single trial is of poor quality and results should be interpreted with caution (available at http://cebm.jr2.ox.ac.uk/docs/levels.html)

presents somewhat different results. It is important to note that this group of patients will include a much wider spectrum of disease, including undiagnosed PUD and GORD. Furthermore, the Rome and Rome II Working Parties have recommended that patients with predominant reflux-type symptoms be excluded from the definition of dyspepsia and, instead, be diagnosed with GORD. The original Rome criteria based on symptom patterns did not prove to have adequate predictive value. The revised Rome II criteria, based on 'predominant' symptoms have yet to be tested, especially in primary care populations. For this reason primary care trials also include patients with both overt GORD, based on a previous diagnosis of oesophagitis or predominant heartburn, or reflux-like dyspepsia.

The review of treatments for dyspepsia in primary care indicated that, in this group of unselected patients, PPIs were the most effective treatment overall and were particularly effective in reducing heartburn when compared with both antacid/placebo or H_2-receptor antagonists. There was a lack of studies comparing H_2-receptor antagonists with antacid/placebo and prokinetic agents, particularly cheaper agents, with antacid/placebo.

There were few trials comparing investigative strategies for dyspepsia in primary care and only two RCTs of adequate quality. It is possible that early endoscopy may prove to be more effective than empirical treatment but the result of the pooled studies does not achieve significance and must await publication of further studies. During 2000, the results of several large primary care-based RCTs, currently only available in abstract, will be published. This review could be quickly updated to include these trial data; this particularly applies to two 'early endoscopy' studies (at Birmingham and Nottingham).

In the absence of trial data, particularly relating to the *H. pylori* test-and-treat strategy for which no trials are in progress, the best source of information is the DES model developed in this study. The model indicates that strategies based on either initial prescribing or *H. pylori* test-and-treat are likely to be cost-effective. Antacids, H_2-receptor antagonists and PPIs are all cost-effective with an increasing cost and with increasing effectiveness, in that order. Treating patients with a PPI rather than an antacid resulted in 8 months less dyspepsia over 5 years at a cost of £21.76 per month gained. *H. pylori* eradication resulted in a mean additional 0.83 months free of dyspepsia at a mean cost of £62.77 per month gained.

The model supports the principal uncertainties identified in the review, being particularly sensitive to the cost and effectiveness of H_2-receptor antagonists and the prevalence of *H. pylori*. Well-designed, primary care based, cost-effectiveness RCTs comparing *H. pylori* test-and-treat with empirical therapy or early endoscopy and PPIs with H_2-receptor antagonists will be required, even when results of trials in progress are available. In addition, the further development of the Rome criteria require that the proposal to diagnose GORD on the basis of 'predominant' symptoms is formally tested in primary care, using symptom response to PPI as the principal outcome. All

the reviews conducted in this study will be maintained and updated as Cochrane reviews, as more trial evidence becomes available.

Recommendations for further research

Primary research

In the treatment of NUD

1. Long-term effectiveness of H_2-receptor antagonists and 'cheaper' prokinetics compared with placebo in proven NUD The review indicates that the majority of patients with NUD will need to be maintained on some form of effective therapy. None of the existing acid suppression therapies could be termed effective given current evidence, both because of the quality of trials and lack of precision of the estimate. The modelling suggests that PPIs would not be cost-effective, as existing evidence excludes an effect that would justify their cost. Cisapride has now been suspended from the market both in the UK and North America. Research is needed to determine whether H_2-receptor antagonists or domperidone are effective in more than short-term trials. This should take the form of well-designed RCTs with patient satisfaction and quality of life measured using robust methods, as well as symptom response.

2. Patient's views on *H. pylori* eradication therapy for NUD Although *H. pylori* eradication has been shown to be effective, and probably cost-effective, there is no information as to patient's views. As the treatment effect is small, acceptability is particularly important. Research should focus on acceptability, both through interview assessment methods (such as willingness-to-pay) and measurement of the effect of treatment on quality of life.

3. New therapies for NUD None of the existing treatments will benefit more than 10% of patients. The development of new compounds in this area by the pharmaceutical industry will be of importance. Large-scale clinical trials of emerging treatments will be important so that efficacy and cost-effectiveness can be established prior to uptake, rather than after, as in the treatments studied here.

For the initial management of dyspepsia

1. Cost-effectiveness of *H. pylori* test-and-treat compared to acid suppression for uninvestigated dyspepsia in primary care Modelling shows that the cost of endoscopy is not justified by its effectiveness in guiding appropriate therapy in patients under the age of 50 years with dyspepsia. The question is whether the additional cost of testing and treating for *H. pylori* is justified in the majority of patients. Trials based in secondary care now indicate that test-and-treat is more cost-effective than endoscopy for patients referred for investigation by their GP.[139] The key question is whether test-and-treat is cost-effective as a strategy for use in primary care. The 1994 British Society of Gastroenterology guidelines recommended 'test-and-endoscopy' for patients under the age of 45 years, on the basis of studies in secondary care,[17,21] but RCTs conducted by this group have shown that this strategy is not cost-effective in primary care.[141] Pilot studies and modelling have suggested that 'test-and-treat' may be cost-effective and the National Institute for Clinical Excellence (NICE) has concluded that patients should not receive long-term treatment with PPIs without investigation. A full primary care based RCT is required to determine the cost-effectiveness of the test-and-treat strategy compared with empirical acid suppression for the initial management of dyspepsia in primary care.

2. Cost-effectiveness of H_2-receptor antagonists compared with PPI in primary care The modelling indicates that PPIs are likely to be more effective than H_2-receptor antagonists for both initial empirical acid suppression and for intermittent treatment (possibly after *H. pylori* eradication). PPIs are more costly, so there is a cost-effectiveness case to address. There is insufficient certainty as to the cost-effectiveness of PPIs and H_2-receptor antagonists in direct comparison in both these indications. Although the cost of PPIs is falling, there is still guidance from NICE to limit their use. An RCT with adequate length of follow-up, of at least several years, and measurement of patient preference and quality of life is required.

3. Effectiveness of the Rome II criteria for determining therapy in primary care The Rome II consensus panel have revised their definition of dyspepsia to exclude patients with predominant heartburn (diagnosed as GORD) or bloating symptoms (diagnosed as irritable bowel syndrome). All the trials in the initial management strategies include patients with reflux-type symptoms; indeed, there is no consensus among GPs that such criteria have any validity in primary care. Research is needed as to the effect of applying the Rome II diagnostic criteria to management. Studies should be pragmatic RCTs, in which the outcome is response to therapy rather than diagnostic accuracy. This question could be

addressed by appropriate symptom questionnaires and pre-specified subgroup analysis of the two questions above.

Secondary research

This is required to keep these reviews (in their Cochrane format) up-to-date, as this is an extremely fast-moving field. Given the number of new trials and the potential for important subgroup analysis based on age or symptoms, there is potential for an individual patient data meta-analysis. The Cochrane Upper Gastrointestinal and Pancreatic Disease Review Group is actively planning such a review.

Acknowledgements

This study was commissioned by the NHS HTA programme.

Dr Cathy Bennett, formerly Coordinator of the Cochrane Upper Gastrointestinal and Pancreatic Disease Review Group, was of invaluable help throughout the review, and we are most grateful to her for her advice and support.

The authors would like to thank Andrea Roalfe for her statistical support of the primary care review.

We are grateful for the support and advice provided by James Mason, Centre for Health Economics, University of York, especially at the start of the review.

We would like to thank all authors, experts and pharmaceutical companies who we contacted, and who took the time to reply. We are particularly indebted to those authors who provided extra data and information from their studies; in particular: Professor R Jones, Wolfson Professor, Guy's, Kings and St Thomas's Hospital Trust, London; Drs M Numans and NT Lewin-van den Broek, from the Department of Primary Care and General Practice, University of Utrecht, The Netherlands.

We are also grateful to J Rayworth, Librarian at Leeds University Medical Library for her invaluable help with retrieving citations.

The views expressed in this report are those of the authors, who are also responsible for any errors.

The authors are indebted to the referees for their perseverance in reading the report and the quality of their comments.

Individual funding

Dr Brendan Delaney is funded by an NHS R&D Primary Care Career Scientist Award and Dr Paul Moayyedi by an MRC Health Services Research Training Fellowship.

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Appendix 1

Search terms and contacts

Throughout this appendix the following conventions are used:

- upper case denotes controlled vocabulary
- lower case denotes free-text terms
- $ = any text character or characters, number or numbers
- ADJ = adjacent to (maximum number of words specified by the number).

Terms for dyspepsia searches

MEDLINE MeSH terms

Dyspepsia-related

DYSPEPSIA
HEARTBURN
ERUCTATION
PEPTIC ULCER
GASTRITIS
ACHLORHYDRIA
GASTROESOPHAGEAL REFLUX
ESOPHAGITIS
BARRETT ESOPHAGUS
ESOPHAGEAL SPASM, DIFFUSE
DEGLUTITION DISORDERS
GASTROPARESIS
STOMACH NEOPLASMS
DUODENOGASTRIC REFLUX
HELICOBACTER PYLORI
ESOPHAGEAL ACHALASIA

Therapy-related

ANTI-ULCER AGENTS
HISTAMINE H2 ANTAGONISTS
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
OMEPRAZOLE
DOMPERIDONE
METOCLOPRAMIDE
ANTACIDS
ALUMINUM HYDROXIDE
CALCIUM CARBONATE
MAGNESIUM HYDROXIDE
MAGNESIUM OXIDE
AMOXICILLIN
METRONIDAZOLE
CLARITHROMYCIN

MEDLINE text terms

Dyspepsia-related

Dyspep$
Heartburn
Eructation
Peptic ADJ5 Ulcer$
Gastritis
Achlorhydri$
Gastro?esophageal ADJ5 reflux
Esophagitis
Oesophagitis
Barrett$ ADJ5 esophagus
Barrett$ ADJ5 oesophagus
Esophageal ADJ5 spasm ADJ5 diffuse
Oesophageal ADJ5 spasm ADJ5 diffuse
Gastroparesis
Deglutition ADJ5 disorder$
Stomach ADJ5 neoplasm$
Duodenogastric ADJ5 reflux
Helicobacter ADJ5 pylori$
Esophag$ ADJ5 achalasia
Oesophag$ ADJ5 achalasia
Pyro$
Acid ADJ5 reflux
Duodenal ADJ5 ulcer$
Stomach ADJ5 ulcer$
Gastric ADJ5 ulcer$
Indigestion
Stomach ADJ5 pain$
Epigastric ADJ5 pain$
Hiat$ ADJ5 hernia$
Earl$ ADJ5 satiety
Dysphagi$
Belch$
Burp$
Stomach ADJ5 ache$

Therapy-related

Anti?ulcer
Histamine ADJ5 H2 ADJ5 antagonist$
Cimetidine
Famotidine
Nizatidine
Ranitidine
Omeprazole
Domperidone
Metoclopramide
Antacid$
Alumin?um ADJ5 hydroxide
Calcium ADJ5 carbonate

Magnesium ADJ5 hydroxide
Magnesium ADJ5 oxide
Amox?cillin
Metronidazole
Clarithromycin
Prokinetic
Proton ADJ5 pump$ ADJ5 inhibitor$
H2 ADJ5 receptor$ ADJ5 antagonist$
Gastrointestinal ADJ5 mucosa
Protective ADJ5 agent$
Stomach ADJ5 secretion$ ADJ5 inhibitor$
Antibiotic ADJ5 therap$
Lansoprazole
Pantoprazole

EMBASE MeSH terms

Dyspepsia-related

DYSPEPSIA
HEARTBURN
INDIGESTION
STOMACH PAIN
PEPTIC ULCER
GASTRITIS
STOMACH EROSION
STOMACH ACID SECRETION
GASTROINTESTINAL REFLUX
ESOPHAGUS MOTILITY
ESOPHAGUS FUNCTION DISORDER
DUODENOGASTRIC REFLUX
CAMPYLOBACTER PYLORIDIS
STOMACH TUMOR
BARRETT ESOPHAGUS
GASTROESOPHAGEAL REFLUX
STOMACH CANCER
EPIGASTRIC PAIN
HIATUS HERNIA
DYSPHAGIA

Therapy-related

PROTON PUMP INHIBITOR
ANTIULCER AGENT
HISTAMINE H_2 RECEPTOR ANTAGONIST
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
OMEPRAZOLE
PROKINETIC AGENT
CISAPRIDE
DOMPERIDONE
METOCLOPRAMIDE
ERYTHROMYCIN
ANTACID AGENT
ALUMINUM HYDROXIDE
CALCIUM CARBONATE
MAGNESIUM HYDROXIDE
AMOXICILLIN
METRONIDAZOLE
COMBINED ANTIULCER AGENT
GASTROINTESTINAL MUCOSA PROTECTIVE AGENT
STOMACH SECRETION INHIBITOR
ANTIBIOTIC THERAPY
ANTIMICROBIAL THERAPY
DRUG COMBINATION
DRUG MIXTURE
STOMACH EMPTYING ACCELERATOR
DRUG CHOICE

EMBASE text terms

Dyspepsia-related

Dyspep$
Heartburn
Indigestion
Stomach ADJ5 pain$
Peptic ADJ5 ulcer$
Gastritis
Stomach ADJ5 erosion$
Stomach ADJ5 acid ADJ5 secretion$
Gastrointestinal ADJ5 reflux
Esophagus ADJ5 motility
Oesophagus ADJ5 motility
Stomach ADJ5 function$ ADJ5 disorder$
Duodenogastric ADJ5 reflux
Campylobacter ADJ5 pylori$
Eructation
Stomach ADJ5 tumo?r$
Barrett$ ADJ5 esophagus
Barrett$ ADJ5 oesophagus
Gastro?esophageal ADJ5 reflux
Stomach ADJ5 cancer$
Hiat$ ADJ5 hernia$
Dysphagi$
Pyro$
Acid ADJ5 reflux
Duodenal ADJ5 ulcer$
Stomach ADJ5 ulcer$
Gastric ADJ5 ulcer$
Earl$ ADJ5 satiety
Belch$
Burp$
Helicobacter ADJ5 pylor$
Epigastric ADJ5 pain$

Therapy-related

Proton ADJ5 pump$ ADJ5 inhibitor$
Anti?ulcer
H2 ADJ5 receptor$ ADJ5 antagonist$
Cimetidine
Famotidine
Nizatidine
Ranitidine
Omeprazole
Prokinetic

Cisapride
Domperidone
Metoclopramide
Erythromycin
Antacid$
Alumin?um ADJ5 hydroxide
Calcium ADJ5 carbonate
Magnesium ADJ5 hydroxide
Amox?cillin
Metronidazole
Combined ADJ5 anti?ulcer ADJ5 agent$
Gastrointestinal ADJ5 mucosa
Protective ADJ5 agent$
Stomach ADJ5 secretion$ ADJ5 inhibitor$
Antibiotic ADJ5 therap$
Antimicrobial ADJ5 therap$
Drug ADJ5 combination$
Drug ADJ5 mixture$
Stomach ADJ5 emptying ADJ5 accelerator$
Drug ADJ5 choice$
Pontoprazole
Lansoprazole

CINAHL MeSH terms

Dyspepsia-related

DYSPEPSIA
HEARTBURN
ABDOMINAL PAIN
PEPTIC ULCER
GASTRITIS
GASTROESOPHAGEAL REFLUX
HELICOBACTER PYLORI
STOMACH NEOPLASMS

Therapy-related

ANTIULCER AGENTS
HISTAMINE ANTAGONISTS
CIMETIDINE
FAMOTIDINE
RANITIDINE
OMEPRAZOLE
ANTACIDS
ALUMINUM HYDROXIDE
AMOXICILLIN
CLARITHROMYCIN
METRONIDAZOLE
DRUG COMBINATIONS
DRUG THERAPY, COMBINATION
METOCLOPRAMIDE

CINAHL text terms

Dyspepsia-related

Dyspep$
Heartburn
Abdominal ADJ5 pain$
Peptic ADJ5 ulcer$
Gastritis
Gastro?esophageal ADJ5 reflux
Esophagitis
Oesophagitis
Barrett$ ADJ5 esophagus
Barrett$ ADJ5 oesophagus
Helicobacter ADJ5 pylori$
Gastroparesis
Stomach ADJ5 neoplasm$
Pyro$
Acid ADJ5 reflux
Duodenal ADJ5 ulcer$
Stomach ADJ5 ulcer$
Gastric ADJ5 ulcer$
Indigestion
Stomach ADJ5 pain$
Epigastric ADJ5 pain$
Hiat$ ADJ5 hernia$
Earl$ ADJ5 satiety
Dysphagia
Belch$

Therapy-related

Anti?ulcer
Histamine ADJ5 antagonist$
Cimetidine
Famotidine
Nizatidine
Ranitidine
Omeprazole
Prokinetic
Domperidone
Metoclopramide
Antacid$
Alumin?um ADJ5 hydroxide
Amox?cillin
Clarithromycin
Metronidazole
Drug ADJ5 combination$
Drug ADJ5 therap$ ADJ5 combination$
Proton ADJ5 pump$ ADJ5 inhibitor$
H2 ADJ5 receptor ADJ5 antagonist$
Cisapride
Pantoprazole
Lansoprazole

Stomach ADJ5 ache$
Burp$

Terms for NUD pharmacological intervention searches

Cochrane Controlled Trials Register MeSH terms

Dyspepsia-related

DYSPEPSIA
ERUCTATION

FLATULENCE
HEARTBURN
NAUSEA
VOMITING
BELCHING
BLOATING
PYROSIS
INDIGESTION
HIATUS HERNIA
REGURGITATION
EARLY SATIETY
ACID REFLUX
STOMACH PARESIS
POSTPRANDIAL FULLNESS
GASTROPARESIS
GASTRITIS

Therapy-related
HISTAMINE H2 ANTAGONISTS
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
PROTON PUMP
OMEPRAZOLE
PROKINETICS
DOMPERIDONE
METOCLOPRAMIDE
ANTACIDS
ALGINATES
ALUMINIUM HYDROXIDE
ALUMINIUM OXIDE
ALUMINIUM SILICATES
HYDROXIDES
CALCIUM CARBONATES
BICARBONATES
BISMUTH
CARBENOXOLONE
MISOPROSTOL
SUCRALFATE
ANTIMUSCARINIS
MUSCARINIC ANTAGONISTS
PIRENZEPINE
PROPANTHELINE

Cochrane Controlled Trials Register text terms

Dyspepsia-related
Dyspep*
Epigastr* near pain*
Epigastr* near discomfort*
Stomach near pain*
Stomach near paresis
Stomach near distension*
Gastric acid near secretion*
Gastric erosion*
Stomach erosion*
Stomach acid near secretion*
Stomach emptying near disorder*

Therapy-related
Cimetidine
Famotidine
Nizatidine
Ranitidine
Lansoprazole
Pantoprazole
Prokinetics
Metoclopramide
Domperidone
Cisapride
Algicon
Alginates
Aluminium hydroxide
Aluminium bicarbonate
Aluminium glycinate
Aluminium hydroxycarbonate
Amalgel
Asilone
Altacite
Hydrotalcite
Calcium carbonate
Gaviscon
Gastrocote
Hydrotalcite
Maalox
Magnesium trisilicate
Magnesium oxide
Magnesium trisilicate
Sodium bicarbonate
Sodium carbonate
Rennie
Mucaine
Bismuth citrate
Bismuth subsalicylate
Bismuth subnitrate
Ranitidine bismuth citrate
Denol
De-Noltab
Pylorid
Tripotassium bismuthate
Tripotassium citrate
Carbenoxolone
Misoprostol
Sucralfate
Antimuscarinics
Muscarinic receptor blocking agents
Muscarinic antagonists
Pirenzepine
Propantheline
Propantheline bromide

MEDLINE MeSH terms

Dyspepsia-related

DYSPEPSIA
ERUCTATION
FLATULENCE
HEARTBURN
GASTROPARESIS
GASTRIC EMPTYING
GASTRITIS/ATROPHIC GASTRITIS

Therapy-related

ANTI-ULCER AGENTS
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
PROTON PUMP
OMEPRAZOLE
DOMPERIDONE
ERYTHROMYCIN
METOCLOPRAMIDE
ANTACIDS
ALGINATES
ALUMINIUM HYDROXIDE
MAGNESIUM HYDROXIDE
MAGNESIUM OXIDE
CALCIUM CARBONATE
HYDROTALCITE
MAGNESIUM CARBONATE
MAGNESIUM HYDROXIDE
MAGNESIUM OXIDE
MAGNESIUM TRISILICATE OR RENNIE
BISMUTH
CARBENOXOLONE
MISOPROSTOL
SUCRALFATE
MUSCARINIC ANTAGONISTS
DICYCLOMINE
PIRENZEPINE
PROPANTHELINE

MEDLINE text terms

Dyspepsia-related

Dyspep$
Acid ADJ5 reflux
Belch$
Bloat$
Burp$
Early ADJ5 satiety
Eructation
Flatu$
Heartburn
Indigestion
Pyro$
Hiatus hernia
Stomach paresis
Gastritis
Gastric acid ADJ5 secretion
Stomach acid ADJ5 secretion
Gastric ADJ5 erosion$
Stomach ADJ5 erosion$
Gastric emptying ADJ5 disorder$
Stomach emptying ADJ5 disorder$
Gastroparesis
Symptom$ ADJ5 score$

Therapy-related

Histamine H2 antagonist$
Antiulcer ADJ5 agent$
H2 ADJ5 receptor ADJ5 antagonist$
Cimetidine
Famotidine
Nizatidine
Ranitidine
Proton pump ADJ5 inhibitor$
Omeprazole
Lansoprazole
Pantoprazole
Prokinetic ADJ5 agent$
Metoclopramide
Domperidone
Cisapride
Algicon
Alginates
Altacite plus
Alumin?um ADJ5 hydroxide
Asilone
Calcium ADJ5 carbonate
Gastrocote
Gaviscon
Hydrotalcite
Maalox
Magnesium ADJ5 hydroxide
Magnesium ADJ5 oxide
Magnesium ADJ5 trisilicate
Mucaine
Sodium ADJ5 bicarbonate
Sodium ADJ5 carbonate
Mucosal ADJ5 protecting ADJ5 agent$
Carbenoxolone
Misoprostol
Sucralfate
Antimuscarinic$
Muscarinic receptor ADJ5 antogonist$
Dicyclomine
Pirenzepine
Propantheline
Propantheline bromide

EMBASE MeSH terms

Dyspepsia-related

DYSPEPSIA
EPIGASTRIC PAIN
STOMACH PAIN
FLATULENCE
HEARTBURN
INDIGESTION
STOMACH EMPTYING
STOMACH PARESIS
NAUSEA
VOMITING
GASTRITIS
ATROPHIC GASTRITIS
CHRONIC GASTRITIS
EROSIVE GASTRITIS
STOMACH ACID SECRETION

Therapy-related

HISTAMINE H2 RECEPTOR ANTAGONIST
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
PROTON PUMP INHIBITOR
STOMACH SECRETION INHIBITOR
LANSOPRAZOLE
OMEPRAZOLE
PANTOPRAZOLE
PROKINETIC AGENT
STOMACH EMPTYING ACCELERATOR
CISAPRIDE
DOMPERIDONE
METOCLOPRAMIDE
GASTROINTESTINAL MUCOSA PROTECTIVE AGENT
CARBENOXOLONE
SUCRALFATE
MISOPROSTOL
ANTACID AGENT
ALGICON
ALMAGATE
ALMAGEL
ALUMINIUM GLYCINATE
ALUMINIUM HYDROXIDE
ALUMINIUM HYDROXIDE PLUS CALCIUM CARBONATE PLUS MAGNESIUM HYDROXIDE
ALUMINIUM HYDROXIDE PLUS MAGNESIUM TRISILICATE
ALUMINIUM HYDROXYCARBONATE
ALUMINIUM MAGNESIUM HYDROXIDE
ALUMINIUM MAGNESIUM SODIUM SILICATE
ALUMINIUM OXIDE
ALUMINIUM PHOSPHATE
BICARBONATE
CALCIUM CARBONATE
DIHYDROXYALUMINUM SODIUM CARBONATE
GAVISCON
HYDROTALCITE
MAGNESIUM CARBONATE
MAGNESIUM HYDROXIDE
MAGNESIUM OXIDE
MAGNESIUM TRISILICATE
RENNIE
MUSCARINIC ANTAGONISTS
PIRENZEPINE
PROPANTHELINE BROMIDE

EMBASE text terms

Dyspepsia-related

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$

Therapy-related

Histamine H2 adj5 antagonist$
Proton pump adj5 inhibitor$
Prokinetic adj5 agent$
Stomach emptying accelerator$
Muscarinic receptor adj5 antogonist$
Antimuscarinics
Dicyclomine

CINAHL MeSH terms

Dyspepsia-related

DYSPEPSIA
ABDOMINAL PAIN
FLATULENCE
HEARTBURN

NAUSEA VOMITING
GASTRITIS

Therapy-related
HISTAMINE H2 RECEPTOR ANTAGONIST
CIMETIDINE
FAMOTIDINE
RANITIDINE
OMEPRAZOLE
METOCLOPRAMIDE
ANTACIDS
ALUMINIUM HYDROXIDE
SUCRALFATE
MISOPROSTOL

CINAHL text terms
Dyspepsia-related
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

Therapy-related
Nizatidine
Proton pump adj5 inhibitor$
Lansoprazole
Prokinetic adj5 agent$
Metoclopramide
Domperidone
Cisapride
Domperidone
Antacids
Alginates
Alumin?um adj5 hydroxide
Calcium carbonate
Maalox
Magnesium adj5 oxide
Sodium bicarbonate
Sodium adj5 carbonate
Mucosal protect$ adj5 agent$
Misoprostol
Sucralfate
Antimuscarinic$
Dicyclomine
Pirenzepine
Propantheline

Terms for NUD *H. pylori* searches

Cochrane Controlled Trials Register MeSH terms
Dyspepsia-related
DYSPEPSIA
ERUCTATION
FLATULENCE
HEARTBURN
NAUSEA
VOMITING
BELCHING
BLOATING
PYROSIS
INDIGESTION
HIATUS HERNIA
REGURGITATION
EARLY SATIETY
ACID REFLUX
STOMACH PARESIS
POSTPRANDIAL FULLNESS
GASTROPARESIS
GASTRITIS
HELICOBACTER PYLORI

Therapy-related
HISTAMINE H2 ANTAGONISTS
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
PROTON PUMP
OMEPRAZOLE
ERYTHROMYCIN
TETRACYCLINE

OXYTETRACYCLINE
BISMUTH
METRONIDAZOLE

Cochrane Controlled Trials Register text terms

Dyspepsia-related

Dyspep*
Epigastr* near pain*
Epigastr* near discomfort*
Stomach near pain*
Stomach near paresis
Stomach near distension*
Gastric acid near secretion*
Gastric erosion*
Stomach erosion*
Stomach acid near secretion*
Stomach emptying near disorder*

Therapy-related

Cimetidine
Famotidine
Nizatidine
Ranitidine
Omeprazole
Lansoprazole
Pantoprazole
Azithromycin
Erythromycin
Clarithromycin
Oxytetracycline
Bismuth citrate
Bismuth subsalicylate
Bismuth subnitrate
Ranitidine bismuth citrate
Denol
De-Noltab
Pylorid
Tripotassium bismuthate
Tripotassium citrate

MEDLINE MeSH terms

Dyspepsia-related

DYSPEPSIA
ERUCTATION
FLATULENCE
HEARTBURN
GASTROPARESIS
GASTRIC EMPTYING
GASTRITIS
GASTRITIS, ATROPHIC
HELICOBACTER PYLORI

Therapy-related

OMEPRAZOLE
DRUG COMBINATIONS
AMOXICILLIN
BISMUTH

MEDLINE text terms

Dyspepsia-related

Dyspep$
Acid ADJ5 reflux
Belch$
Bloat$
Burp$
Early ADJ5 satiety
Eructation
Flatu$
Heartburn
Indigestion
Pyro$
Hiatus hernia
Stomach paresis
Gastritis
Gastric acid ADJ5 secretion
Stomach acid ADJ5 secretion
Gastric ADJ5 erosion$
Stomach ADJ5 erosion$
Gastric emptying ADJ5 disorder$
Stomach emptying ADJ5 disorder$
Gastroparesis
Helicobacter pylori
Campylobacter pylori
Campylobacter pyloridis
Helicobacter pylori ADJ5 eradication

Therapy-related

Omeprazole
Lansoprazole
Pantoprazole
Amox?cillin
Azithromycin
Bismuth
Clarithromycin
Doxycycline
Erythromycin
Metronidazole
Oxytetracycline
Tetracycline
Tinidazole
Denol
De-Noltab
Ranitidine bismuth citrate
Pylorid
Tripotassium citrate

EMBASE MeSH terms

Dyspepsia-related

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

Therapy-related
OMEPRAZOLE
LANSOPRAZOLE
PANTOPRAZOLE
AMOXYCILLIN
AZITHROMYCIN
BISMUTH
BISMUTH CITRATE
BISMUTH COMPOUND
BISMUTH SALICYLATE
COLLOIDAL BISMUTH COMPOUND
CLARITHROMYCIN
DOXYCYCLINE
ERYTHROMYCIN
METRONIDAZOLE
OXYTETRACYCLINE
RANITIDINE BISMUTH CITRATE
TETRACYCLINE
TINIDAZOLE

EMBASE text terms

Dyspepsia-related
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

Therapy-related
Amox?cillin
Denol
De-Noltab
Pylorid
Tripotassium bismuthate
Tripotassium citrate

CINAHL MeSH terms

Dyspepsia-related
DYSPEPSIA
ABDOMINAL PAIN
FLATULENCE
HEARTBURN
NAUSEA VOMITING
GASTRITIS

Therapy-related
HISTAMINE H2 RECEPTOR ANTAGONIST
CIMETIDINE
FAMOTIDINE
RANITIDINE
OMEPRAZOLE
METOCLOPRAMIDE
ANTACIDS
ALUMINIUM HYDROXIDE
SUCRALFATE
MISOPROSTOL

CINAHL text terms

Dyspepsia-related
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

Therapy-related

Nizatidine
Proton pump ADJ5 inhibitor$
Lansoprazole
Prokinetic ADJ5 agent$
Metoclopramide
Domperidone
Cisapride
Domperidone
Antacids
Alginates
Alumin?um ADJ5 hydroxide
Calcium carbonate
Maalox
Magnesium ADJ5 oxide
Sodium bicarbonate
Sodium ADJ5 carbonate
Mucosal protect$ ADJ5 agent$
Misoprostol
Sucralfate
Antimuscarinic$
Dicyclomine
Pirenzepine
Propantheline

Dyspepsia limiting strategy for management of dyspepsia in primary care

Primary care MeSH and text headings

MEDLINE

PRIMARY HEALTH CARE
FAMILY PRACTICE
PHYSICIANS, FAMILY
Primary ADJ5 health ADJ5 care
Family ADJ5 practi$
Physician$ ADJ5 family
Family ADJ5 medic$
Daily ADJ5 practi$
General ADJ5 practi$

EMBASE

PRIMARY HEALTH CARE
GENERAL PRACTICE
FAMILY MEDICINE
GENERAL PRACTITIONER
Primary ADJ5 health ADJ5 care
General ADJ5 practi$
Family ADJ5 medic$
Family ADJ5 practi$
Daily ADJ5 practi$
Physician$ ADJ5 family

CINAHL

PRIMARY HEALTH CARE
FAMILY PRACTICE
PHYSICIANS, FAMILY
Primary ADJ5 health ADJ5 care
Family ADJ5 practi$
Physician$ ADJ5 family
Family ADJ5 medic$
Daily ADJ5 practi$
General ADJ5 practi$

Tests/investigations MeSH and text headings

MEDLINE

BREATH TESTS
GASTROSCOPY
DUODENOSCOPY
HELICOBACTER PYLORI
ENDOSCOPY
SEROLOGY
Breath ADJ5 test$
Gastroscopy
Duodenoscopy
Helicobacter ADJ5 pylori$
Endoscopy
Serology
Near ADJ5 patient$ ADJ5 test$

EMBASE

BREATH ANALYSIS
SERODIAGNOSIS
GASTROSCOPY
DUODENOSCOPY
ENDOSCOPY
SEROLOGY
Breath$ ADJ5 test$
Serodiagnosis
Gastroscopy
Duodenoscopy
Endoscopy
Serology
Helicobacter ADJ5 pylori$
Near ADJ5 patient$ ADJ5 test$

CINAHL
BREATH TESTS
ENDOSCOPY, DIGESTIVE SYSTEM
HELICOBACTER PYLORI
SEROLOGY
GASTROSCOPY
SERODIAGNOSIS
Breath$ ADJ5 test$
Endoscopy
Helicobacter ADJ5 pylori$
Serology
Gastroscopy
Serodiagnosis
Near ADJ5 patient$ ADJ5 test$
Duodenoscopy

Economics MeSH and text headings

MEDLINE
DECISION SUPPORT TECHNIQUES
ECONOMICS
COST BENEFIT ANALYSIS
MODELS, STATISTICAL
Cost ADJ5 utilit$
Cost ADJ5 benefit$
Cost ADJ5 minimisation$
Cost ADJ5 effectiv$
Decision ADJ5 support ADJ5 technique$
Economic$
Cost ADJ5 benefit ADJ5 analy$
Statistical ADJ5 model$
Markov ADJ5 model$
Decision ADJ5 analy$

EMBASE
COMPUTER ANALYSIS
ECONOMICS
COST BENEFIT ANALYSIS
STATISTICAL MODEL
COST EFFECTIVENESS
Cost ADJ5 utilit$
Cost ADJ5 benefit$
Cost ADJ5 minimi?ation$
Cost ADJ5 effectiv$
Decision ADJ5 support ADJ5 technique$
Economic$
Cost ADJ5 benefit ADJ5 analysis
Statistical ADJ5 model$
Markov ADJ5 model$
Decision ADJ5 analysis

CINAHL
DECISION MAKING
ECONOMICS
COST BENEFIT ANALYSIS
MODELS, STATISTICAL
DATA ANALYSIS
Cost ADJ5 utilit$
Cost ADJ5 benefit$
Cost ADJ5 minimi?ation$
Cost ADJ5 effectiv$
Decision ADJ5 support ADJ5 technique$
Economic$
Cost ADJ5 benefit ADJ5 analysis
Statistical ADJ5 model$
Markov ADJ5 model$
Decision ADJ5 analysis

Cochrane RCT filters for NUD searches

Cochrane RCT filter for MEDLINE

1 RANDOMIZED CONTROLLED TRIAL.pt
2 CONTROLLED CLINICAL TRIAL.pt
3 RANDOMIZED CONTROLLED TRIALS.sh
4 RANDOM ALLOCATION.sh
5 DOUBLE-BLIND METHOD.sh
6 SINGLE-BLIND METHOD.sh
7 or/1-6
8 ANIMAL.sh not HUMAN.sh
9 7 not 8
10 CLINICAL TRIAL.pt
11 exp CLINICAL TRIALS
12 (clin$ ADJ25 trial$).ti, ab
13 ((singl$ or doubl$ or trebl$ or tripl$) ADJ5 (blind$ or mask$)).ti, ab
14 PLACEBOS.sh
15 placebo$.ti, ab
16 random$.ti, ab
17 RESEARCH DESIGN.sh
18 or/10-17
19 18 not 8
20 19 not 9
21 COMPARATIVE STUDY.sh
22 exp EVALUATION STUDIES
23 FOLLOW UP STUDIES.sh
24 PROSPECTIVE STUDIES.sh
25 (control$ or prospectiv$ or volunteer$).ti, ab
26 or/21-25
27 26 not 8
28 27 not (9 or 20)
29 9 or 20 or 28

Cochrane RCT filter for EMBASE

1 random$.ti, ab, hw, tn, mf
2 exp CONTROLLED STUDY
3 exp MAJOR CLINICAL STUDY
4 RANDOMIZED CONTROLLED TRIAL.sh
5 Trial$.ti, ab, hw, tn, mf
6 Blind$.ti, ab, hw, tn, mf
7 Doubl$.ti, ab, hw, tn, mf
8 exp CLINICAL TRIAL
9 allocat$.ti, ab, hw, tn, mf
10 exp DOUBLE BLIND PROCEDURE

11 (crossover$ or cross-over$).ti, ab, hw, tn, mf
12 (assign$ or cross-over$).ti, ab, hw, tn, mf
13 placebo$.mp
14 control.mp
15 study.mp
16 versus.mp
17 factorial.mp
18 or/1-17
19 limit 18 to human

mp = title, abstract, heading word, trade name, manufacturer name

Cochrane RCT filter for CINAHL

1 Random?sed.ti, sh, ab, it.
2 (random$ ADJ (allocat$ or allot$ or assign$ or basis or divid$ or order$)). ti, sh, ab, it.
3 Random$.ti, sh, ab, it.
4 ((singl$ or doubl$ or trebl$ or tripl$) ADJ (blind$ or mask$)).ti, sh, ab, it.
5 ((compar$ or control$ or experiment$ or intervention$ or therap$ or treatment$) ADJ group).ti, sh, ab, it.
6 (allocat$ or allot$ or assign$ or divid$ or order$).ti, sh, ab, it.
7 5 and 6
8 (crossover$ or cross-over$).ti, sh, ab, it.
9 ((clinic$ or control$) ADJ (trials$ or study$ or studies$)).ti, sh, ab, it.
10 Placebo$.ti, sh, ab, it.
11 Or/1-10
12 Exp ANIMAL STUDIES
13 11 not 12
14 exp CLINICAL TRIALS
15 exp CROSSOVER DESIGN
16 exp PLACEBOS
17 Versus.ti, sh, ab, it.
18 or/5-17
19 18 not 13
20 exp COMPARATIVE STUDIES
21 exp PROSPECTIVE STUDIES
22 20 or 21
23 22 not 13
24 13 or 19 or 23

Non-electronic database searches

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Journals publishing primary-care dyspepsia papers

Full journal title	Number of papers found
Acta Endoscopica	1
Acta Endoscopica Polona	1
Acta Gastro-Enterologica Belgica	3
Advances in Therapy	1
Alimentary Pharmacology & Therapeutics	25
American Family Physician	3
American Journal of Gastroenterology	8
American Journal of Hospital Pharmacy	1
American Journal of Medicine	2
American Journal of Roentgenology	1
American Journal of Health-System Pharmacy	1
American Journal of Managed Care	3
American Journal of Therapeutics	1
Anales de Medicina Interna	1
Annals of Internal Medicine	5
Annals of Surgery	1
Annual Review of Medicine	1
Arbeitsmedizin Sozialmedizin Umweltmedizin	1
Archives of Family Medicine	1
Archives of Gastroenterohepatology	1
Archives of Internal Medicine	8
Archives Francaises de Pediatrie	1
Asian Journal of Surgery	1
ASTRA conference abstracts	7
Australian Family Physician	2
Australian & New Zealand Journal of Surgery	1
Baillieres Clinical Gastroenterology	2
BMJ	39
British Journal of Clinical Practice	6
British Journal of General Practice	9
British Journal of Hospital Medicine	2
British Journal of Medical Economics	7
British Journal of Surgery	1
British Medical Bulletin	1
Canadian Family Physician	3
Canadian Journal of Gastroenterology	8
Canadian Medical Association Journal	3
Chirurgia Italiana	1
Cleveland Clinic Journal of Medicine	1
Clinical Therapeutics	1
Comprehensive Therapy	1
Current Medical Research & Opinion	2
Danish Medical Bulletin	1
Deutsche Apotheker Zeitung	2
Digestive Diseases	2
Digestive Diseases & Sciences	4
Digestion	3
Digestive Endoscopy	1
Drug Information Journal	1
Drugs	2
Drugs & Aging	1

Full journal title	Number of papers found
Drugs & Therapy Perspectives	1
Dysphagia	1
Endoscopy	3
Epidemiology & Infection	1
European Journal of Cancer & Clinical Oncology	1
European Journal of Epidemiology	1
European Journal of Gastroenterology & Hepatology	21
European Journal of General Practice	1
Expert Opinion on Investigational Drugs	1
Family Practice	5
Family Medicine	1
Fortschritte der Medizin	7
Gastroenterology International	4
Gastroenterologia Polska	1
Gastroenterologie Clinique et Biologique	1
Gastroenterologist	1
Gastroenterology	25
Gastrointestinal Endoscopy	3
Giornale Italiano di Endoscopia Digestiva	1
Gut	18
Health Bulletin	1
Helicobacter	2
Hospital Pharmacy	1
Hospital Practice (Office Edition)	1
Huisarts en Wetenschap	1
Indian Journal of Gastroenterology	1
International Journal of Clinical Practice	3
International Journal of Pharmacy Practice	1
Irish Journal of Medical Science	2
Israel Journal of Medical Sciences	1
Italian Journal of Gastroenterology	1
Italian Journal of Gastroenterology and Hepatology	2
JAMA	1
Journal of Antimicrobial Chemotherapy	1
Journal of Chronic Diseases	1
Journal of Clinical Epidemiology	1
Journal of Clinical Gastroenterology	5
Journal of Clinical Research	1
Journal of Drug Development & Clinical Practice	1
Journal of Epidemiology & Community Health	1
Journal of Family Practice	6
Journal of Gastroenterology	1
Journal of Gastroenterology & Hepatology	6
Journal of General Internal Medicine	4
Journal of Infectious Diseases	1
Journal of International Medical Research	1
Journal of Medical Screening	1
Journal of Nurse-Midwifery	1
Journal of Palliative Care	1
Journal of Physiology and Pharmacology	4
Journal of Psychosomatic Research	2
Journal of Public Health Medicine	1
Journal of the American Board of Family Practice	1
Journal of the Royal College of General Practitioners	4
Journal of the Royal Society of Medicine	1
Lakartidningen	1
Lancet	8
Leber, Magen, Darm	2
Medical Care	1
Medical Decision Making	1
Medical Journal of Australia	6
Medizinische Welt	1
New England Journal of Medicine	1
Nederlands Tijdschrift voor Geneeskunde	6
New Zealand Medical Journal	3
Nordisk Medicin	1
Pharmacoeconomics	9
Thesis	5
Physician Assistant	1
Postgraduate Medical Journal	4
Postgraduate Medicine	2
Practical Gastroenterology	1
Practitioner	5
Praxis Magazin Med	1
Primary Care Update for Ob/Gyns	1
Primary Care; Clinics in Office Practice	1
Psychotherapy and Psychosomatics	1
Quality of Life Research	2
Revista Espanola de Enfermedades Digestivas	4
Scandinavian Journal of Gastroenterology	14
Scandinavian Journal of Gastroenterology Supplement	21
Scandinavian Journal of Primary Health Care	4
Schweizerische Medizinische Wochenschrift	2
Schweizerische Rundschau fur Medizin Praxis	1
Semaine des Hopitaux	1
Seminars in Gastrointestinal Disease	1
Southern Medical Journal	1
Tijdschrift voor Therapie Geneesmiddel en Onderzoek	1
Therapiewoche	2
Tidsskrift for Den Norske Laegeforening	1
Tropical Gastroenterology	1
Tumori	1
Ugeskrift for Laeger	9
Yale Journal of Biology and Medicine	3
Zeitschrift für Allgemeinmedizin	3
Zeitschrift für Gastroenterologie	1
Zeitschrift für Gastroenterologie – Verhandlungsband	1

Appendix 2

Studies included in the review

The management of dyspepsia in primary care

Study/Country	Method	Participants	Interventions	Outcomes	Results	Notes
Brignoli, *et al.*, 1997[149] Switzerland	Concurrent cohort study	828 patients fulfilling 1988 Rome working party criteria with symptoms of more than 1 month's duration Exclusions: symptoms suggestive of malignancy	Early endoscopy vs. selective endoscopy (age: 50 + years; with two nocturnal symptoms from: reflux, weight loss, food relieving pain). All patient with no or negative endoscopy received cisapride, 30–40 mg daily; patients with positive diagnoses on endoscopy received acid suppression	Dyspepsia symptom score (not validated); diagnostic yield; % absent from work in week before assessment at 12 weeks	Dyspepsia score: early endoscopy 1.6/3; selective endoscopy 1.5/3 Diagnostic findings: 67% fewer endoscopies and 19% more GP consultations in selective vs. early endoscopy group. Reduction in costs for selective strategy: SFr 960–660 over 3 months ($p < 0.001$)	Primary care physicians chose to follow either intervention or control protocol No randomisation, no *H. pylori* eradication in PUD
Goodson, *et al.*, 1989[150] USA	Multicentre, RCT	101 patients presenting in primary care clinics and emergency rooms with 4 days of symptoms fitting 1998 Rome working party criteria. Exclusions: using H_2-receptor antagonists, ulcer in past 2 years, tetracycline therapy, drug or alcohol abuse, symptoms suggestive of malignancy, GI bleeding, lack of cooperation or fluent English	Early barium meal vs. Maalox® (Rhone-Poulenc Rorer), 15–30 ml 7 times daily. Treatment of breakthrough dyspepsia with H_2-receptor antagonist	Dyspepsia score (unvalidated), use of H_2-receptor antagonist at 26 weeks, SIP. Mean costs as resources over 6 months	Over 6 months 48 (94%) had barium investigation in study group vs. 8 (15.4%) in control group. Dyspepsia score decreased in both groups at 8 weeks (mean at entry, study 5.6/10; control 5.5/10; after intervention, both groups 2.0/10). Use of H_2-receptor antagonists, study 27/50 vs. control 8/51 at 26 weeks. SIP improved equally in both groups at 4 weeks. Mean cost/patient/6 months, early barium group $286.80, control group $116.10 ($p < 0.0001$)	Only 101 recruited of 405 eligible (mainly refusals), only 78 completed trial. Per protocol analysis only
Bytzer, *et al.*, 1994[116] Denmark	RCT	414 patients aged 18 years and over; symptoms of upper GI disease and no previous history of PUD or oesophagitis of sufficient severity for GP to prescribe acid suppression. Patients recruited in primary care, randomised in secondary care. Exclusions: H_2-receptor antagonists or PPI in past 2 months, symptoms suggestive of malignancy, pregnancy, serious intercurrent illness, lack of cooperation	Endoscopy without prior treatment vs. empirical treatment with 4 weeks of ranitidine, 150 mg b.d. Patients endoscoped given treatment on basis of findings; duodenal ulcer, ranitidine, two courses then maintenance at 150 mg o.d. Oesophagitis, ranitidine then omeprazole, 20–40 mg o.d., according to response. Gastric ulcers, healing with ranitidine and endoscopy check at 6 weeks. Control patients endoscoped if symptoms persisted after 8 weeks	Individual symptom score for epigastric pain, vomiting, daytime and nighttime heartburn at 1 year. Patient self-report of improvement on 4-point scale, satisfaction on 4-point scale. Resource use: GP visits, sick days, endoscopies, prescribing costs	No difference in individual symptom scores, global improvement or quality of life. Patients more 'satisfied' with early endoscopy. More endoscopies in early endoscopy group (241 vs. 193). More GP consultations and H_2-receptor antagonist prescribing in control group (47 vs. 119 consultations; 6636 vs. 11,208 defined daily doses)	66% of control patients had endoscopy at 1-year follow-up Per protocol analysis only No formal economic evaluation No *H. pylori* eradication for PUD, likely to minimise effect of intervention as no definitive treatment given

continued

The management of dyspepsia in primary care *contd*

Study/Country	Method	Participants	Interventions	Outcomes	Results	Notes
Goves, *et al.*, 1998[142] UK	Multicentre, RCT	670 primary care patients from 100 UK practices. Symptoms fitting 1988 Rome working party of at least 1 month's duration on at least 2 days in week prior to starting study. Exclusions: previous organic diagnosis on barium or endoscopy, use of acid suppression in month prior to study, symptoms suggestive of malignancy or GI bleeding	Omeprazole, 10–20 mg for 4 weeks; open label Gaviscon, 10 ml q.d.s. for 4 weeks. Both groups: omeprazole, 20 mg, available if symptoms not improved at 2 week assessment	Assessments at 2 weeks and 4 weeks. Epigastric pain, heartburn, belching. Dyspepsia symptom score (unvalidated). Global assessment of 'complete and sufficient' relief of symptoms, antacid consumption, PGWB and GSRS, side-effects	Only 2-week data included Epigastric pain, 137/331 vs. 152/331 still had mild or severe pain. Heartburn, 155/331 vs. 239/332 still had some symptoms. No data for global score but 94/325 vs. 22/322 had no relief of symptoms. No data extractable for PGWB or GSRS. 85/331 omeprazole patients dissatisfied vs. 277/327 Gaviscon	Only 2 week data could be used as trial essentially ended when a significant number of Gaviscon patients started taking omeprazole
Jones & Baxter, 1997[146]	Multicentre, RCT, double-blind, placebo-controlled	450 patients from 32 general practices, fitting 1988 Rome working party criteria (acid-related groups I & II only), with symptoms for at least 2 weeks and in 4/7 days of week preceding study entry	Lansoprazole, 30 mg o.d., + placebo o.d. for 4 weeks; ranitidine, 150 mg b.d., for 4 weeks. Identical formulation	Symptoms of day and night epigastric pain and heartburn, global improvement, mean use of antacid top-up at 2 and 4 weeks	All data extracted at 4-week endpoint. Daytime epigastric pain, 38/137 (28%) vs. 58/146 (40%); night heartburn, 23/137 (17%) vs. 53/146 (36%). Global assessment symptoms improved in 95/137 PPI vs. 64/145 H_2-receptor antagonist. Mean use of antacids, 6.5 vs. 12.9 tablets over 2 weeks	
Jones & Crouch, 1999[147] UK	Multicentre, RCT, double-blind, placebo-controlled	562 patients from 52 UK practices with dyspepsia meeting 1988 Rome working party criteria but excluding confirmed oesophagitis, PUD and non-acid-related dyspepsia in diagnostic criteria. Symptoms 'persistent', for more than 4 days duration in week preceding entry	Lansoprazole, 15 mg o.d., vs. omeprazole, 10 mg o.d., for 4 weeks	Daytime and nocturnal epigastric pain and heartburn at 4 weeks. Global dyspepsia score, global assessment of symptoms. Consumption of open-label antacids	Daytime epigastric pain, 103/385 vs. 151/279 not improved; nocturnal epigastric pain, 111/285 vs. 137/279 not improved; daytime heartburn, 86/285 vs. 117/279; night-time heartburn, 88/285 vs. 100/279. All at 4 weeks. Global dyspepsia score not extractable. Global assessment of symptoms, 139/235 (59%) symptom-free vs. 117/229 (51%). Consumption of open-label antacids, 138/235 vs. 161/229	

continued

The management of dyspepsia in primary care *contd*

Study/Country	Method	Participants	Interventions	Outcomes	Results	Notes
Jones, *et al.*, 1999[152] UK	Cluster RCT	165 dyspeptic patients from six study practices; more than 4-weeks' 'ulcer-like' dyspepsia, no symptoms suggestive of malignancy and GP considered further investigation 'appropriate'. 92 patients referred for endoscopy from nine control practices and not found to have PUD or oesophagitis All practices in SE London	*H. pylori* test with Helisal Rapid Blood Near Patient Test and eradication therapy (unspecified regimens at GP's discretion) if positive	Endoscopy rates; GP consultations; secondary care referrals and total costs	Endoscopies, 17/165 from test-&-treat practices vs. 97/92 for controls (five follow-up investigations). No difference in consultations (mean of 6 in both groups). Referrals (excluding for breath tests), 15/165 vs. 32/92. Total costs over 1 year, £205.67 (test-&-treat) vs. £404.31 (endoscopy)	Randomisation by practice but method not clear. In control group, not all patients referred, only those investigated and found not to have ulcer or oesophagitis. Probably unacceptable control group (should be all patients intended to refer, whether attended or not, irrespective of final diagnosis). Removal of PUD patients from control group will decrease effectiveness of control treatment
Mason, *et al.*, 1998[143] UK	RCT, (open)	703 patients with dyspepsia from 131 practices. Patients with definite previous diagnosis of PUD or oesophagitis excluded	Omeprazole, 10–40 mg, vs. Gaviscon, 10 ml q.d.s., + ranitidine, 150 mg as required. Treatment for 16 weeks	Epigastric pain and heartburn at 4 and 16 weeks. Global assessment of improvement	16-week outcomes extracted. Epigastric pain, 40/291 vs. 66/269 some symptoms; heartburn, 54/291 vs. 107/269. Global assessment of improvement, 187/289 vs. 93/269 symptom-free	
Meineche-Schmidt & Krag, 1997[144] Denmark	Multicentre, RCT, double-blind, double-dummy, placebo-controlled	1017 patients with dyspepsia, defined by1988 Rome working party excluding categories III and IV, from 63 practices. Divided into (A) patients with proven PUD or oesophagitis (469), (B) uninvestigated dyspepsia (548)	(A) Omeprazole, 20 mg o.d., vs. cimetidine, 400 mg b.d., for 2 weeks (B) Omeprazole, 20 mg o.d., vs. placebo o.d., for 2 weeks	Epigastric pain at 15 days. Dyspepsia symptom score (visual analogue scale 0–100), total symptom relief at 15 days	(A) Daytime epigastric pain, 74/179 vs. 108/200; nighttime epigastric pain, 48/180 vs. 71/200 still had symptoms. Heartburn, 25/180 vs. 62/200. No difference in improvement in dyspepsia symptom score. Total symptom relief in 97/207 (47%) vs. 73/220 (33%). (B) Daytime epigastric pain, 114/243 vs. 110/228; nighttime epigastric pain, 56/243 vs. 56/228 still had symptoms. Heartburn, 44/243 vs. 79/228. No difference in improvement in dyspepsia symptom score. Total symptom relief in 137/273 (50%) vs. 93/266 (35%)	Group (B) patients also allowed to self-treat with antacids.

continued

The management of dyspepsia in primary care *contd*

Study/Country	Method	Participants	Interventions	Outcomes	Results	Notes
Patel, *et al.*, 1995[21] UK	Prospective cohort study with historical controls	70 patients referred for open-access endoscopy. 183 patients referred for endoscopy, of whom 70 tested *H. pylori*-positive and were endoscoped	Routine endoscopy in all patients vs. *H. pylori* serology test-&-endoscope in positive only	Dyspepsia score, global improvement, quality of life, use of medication	No differences detected in symptoms or quality of life after investigation between serology or endoscopy cohorts	Outcomes for *H. pylori*-negative test-&-endoscope patients not reported
Paton, 1995[145] UK	Multicentre, RCT (open)	255 patients with heartburn only, recruited from 42 UK general practices	Gaviscon, 10–20 ml q.d.s., vs. ranitidine, 300 mg o.d. Treatment for 24 weeks	Heartburn, symptom scores, global assessment and quality of life (Nottingham Health Profile)	Symptom score not extractable. At endpoint, 8/83 Gaviscon patients vs. 9/80 ranitidine patients had symptoms (no difference). Also no difference in global improvement, 52% vs. 53% being symptom-free in each group	Quality-of-life data not reported
Lewin-van den Broek, 1999[148] The Netherlands	RCT	263 patients, aged 18–80 years; recruited by 95 Dutch GPs	Treatment based on symptom pattern (ulcer-like and reflux-like given ranitidine or cimetidine; non-specific given cisapride or domperidone) Omeprazole, 20 mg o.d. Cisapride, 20 mg t.d.s.	Re-attendance after 8 weeks up to 1 year Symptom score (Utrecht score) at 8 and 14 weeks	No difference in symptom scores at 14 weeks. No difference in re-attendance rates at 1 year Per protocol analysis	Only 130/263 patients available for symptom score at 14 weeks. 247/263 available for re-attendance
Lewin-van den Broek, 1999[148] The Netherlands	RCT	176 patients, aged 18–80 years; recruited by 95 Dutch GPs	Empirical treatment; (70% had H_2-receptor antagonists, 25% prokinetics, 5% PPI) Early endoscopy	Re-attendance after 8 weeks up to 1 year Symptom score (Utrecht score) at 8 and 14 weeks	No difference in symptom scores at 14 weeks. No difference in re-attendance rates at 1 year	43% of empirical treatment group went on to endoscopy. 162/176 available for analysis

Pharmacological interventions for NUD (trials included in the meta-analysis)

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
Antacids vs. placebo (1 trial)						
Gotthard, *et al.*, 1988[179] Sweden	RCT, double-blind, placebo-controlled. 210 patients: cimetidine 73, antacid 74, placebo 75. Dyspepsia of unknown origin 3 months. Acid output studies performed. Duodenitis 16%	6-week comparisons of three drugs: cimetidine, 400 mg b.d., vs. placebo vs. antacid, 10 ml q.d.s.	Yes	No	No	Cimetidine superior to both placebo and antacid in relieving pain and nausea but not bloating
Cisapride vs. placebo (17 trials)						
Agorastos, *et al.*, 1991[174] Greece	RCT, single-blind. 36 patients with NUD; cisapride 17, placebo 19. 2-week placebo run-in period	4 weeks: cisapride, 5 mg t.d.s., vs. placebo	Yes	No	No	Symptomatic response was better for cisapride
Al-Quorain, *et al.*, 1995[165] Saudi Arabia	RCT, double-blind, placebo-controlled. 89 patients: cisapride 44, placebo 45. Three subgroups: ulcer-like, reflux-like, dysmotility-like. 2-week placebo run-in period. 91% completed trial	4 weeks: cisapride, 5 mg t.d.s., vs. placebo	Yes	Yes	No	Cisapride significantly superior to placebo in improving heartburn, postprandial bloating, epigastric pain, early satiety, epigastric burning and nausea
Champion, *et al.*, 1997[167] Canada (2 trials)	RCT, double-blind, placebo-controlled. 123 patients with NUD: cisapride, 10 mg, 42, cisapride, 20 mg, 41, placebo 40. 2-week placebo run-in period. OGD. 78% completed trial	6 weeks: cisapride, 10 mg t.d.s., vs. cisapride, 20 mg t.d.s., vs. placebo	Yes	Yes	No	Cisapride at either dose not effective compared with placebo in improving symptoms in NUD patients. Side-effects profile comparable to that of placebo
Chung, 1993[168] Korea	RCT, double-blind, placebo-controlled. 29 patients with chronic dyspepsia: cisapride 14, placebo 15. 97% completed trial	4 weeks: cisapride, 10 mg t.d.s., vs. placebo	Yes	Yes	No	Bloating and epigastric discomfort significantly reduced compared with placebo. Good or excellent global response in 71.4%. No significant side-effects noted
Creytens, 1984[176] Belgium	RCT, double-blind, placebo-controlled, crossover. 32 patients with chronic dyspepsia, 16 in each arm. Included reflux symptoms. 2-week drug-free period. Either OGD or barium studies undertaken. No drop-outs	3 weeks: cisapride, 4–8 mg t.d.s. (doubling the dose after 10 days if needed), vs. placebo	Yes	No	No	Cisapride significantly superior to placebo. Markedly improved nausea; good response for epigastric discomfort and reflux symptoms. No adverse events noted

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
***Cisapride vs. placebo (17 trials)* contd**						
De Nutte, *et al.*, 1989[169] Belgium	RCT, double-blind, placebo-controlled. 32 patients predominantly with epigastric pain: cisapride 17, placebo 15. No drop-outs. NSAIDs withdrawn at start of treatment in four patients. 2-week placebo run-in period. No drop-outs	4 weeks: cisapride, 5 mg t.d.s., vs. placebo	Yes	Yes	No	Cisapride effective in reducing epigastric pain
Deruyttere, *et al.*, 1987[178] Belgium	RCT, double-blind, placebo-controlled. 56 patients with chronic functional dyspepsia: cisapride, 26, placebo, 30. 93% completed trial	3 weeks: cisapride, 4 mg t.d.s., vs. placebo	Yes	No	No	Cisapride particularly superior to placebo in improvement of cluster of symptoms typical of postprandial discomfort, including early satiety and nausea. Side-effects minimal
Francois & De Nutte, 1987[170] Belgium	RCT, double-blind, placebo-controlled. 36 patients with dyspepsia (3/12); 18 in each arm; 64% with either gastritis and/or bulbitis. 2-week drug withdrawal. 94.4% completed trial	3 weeks: cisapride, 5 mg t.d.s., vs. placebo	Yes	Yes	No	Cisapride significantly superior to placebo in relieving epigastric burning or pain, heartburn, regurgitation, and abdominal distension
Hannon, 1987[171] Belgium	RCT, double-blind, placebo-controlled, crossover. 22 patients with NUD, 11 in each arm. 2-week wash-out period. No drop-outs	3 weeks: cisapride, 5 mg t.d.s., vs. placebo	No	Yes	No	Cisapride superior to placebo in relieving cluster of dyspeptic symptoms, in particular, epigastric burning and early satiety. Global therapeutic effect good or excellent in treatment group (64%) compared with control group (27%)
Hansen, *et al.*, 1998[164] Denmark	RCT, double-blind, placebo-controlled. Primary care recruitment. 330 patients: cisapride 109, ranitidine 111, placebo 110. Mean duration of dyspeptic symptoms 88 months. Four subgroups: ulcer-like (13%), reflux-like (23%), dysmotility-like (46%), unclassified (18%). Included superficial erosions on OGD. 85% completed trial	2 weeks: cisapride, 10 mg t.d.s., vs. nizatidine, 300 mg nocte, vs. placebo	Yes	Yes	No	Effects of 2-week course of cisapride or nizatidine recruited from primary care not superior to those of placebo. Symptom subgrouping not predictive of response to treatment

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
***Cisapride vs. placebo (17 trials)* contd**						
Jian, *et al.*, 1989[283] France	RCT, double-blind, placebo-controlled. 28 patients with chronic idiopathic dyspepsia suggestive of gastroparesis: cisapride 15, placebo 13. Gastric emptying test (59% positive) and OGD. 82% completed trial	6 weeks: cisapride, 10 mg t.d.s., vs. placebo	No	Yes	No	Cisapride significantly improved gastric emptying for liquids and individual dyspeptic scores. Best symptomatic response to cisapride in patients with gastroparesis
Kellow, *et al.*, 1994[172] Australia	RCT, double-blind, placebo-controlled. 61 patients with NUD: cisapride 30, placebo 31. 2-week placebo run-in period. Two subgroups: reflux-like, dysmotility-like. Gastric emptying tests. 91.8% completed trial	4 weeks: cisapride, 10 mg t.d.s., vs. placebo	No	Yes	No	Major differences in short-term efficacy of cisapride and placebo. Indications of beneficial effects of cisapride over placebo in those with reflux-like dyspepsia and in those without gastroparesis
Rosch, 1987[82] Germany	RCT, double-blind, placebo-controlled. 118 patients with NUD: cisapride 54, placebo 55. Duration of dyspepsia unclear. Two subgroups: reflux-like, dysmotility-like. OGD	4 weeks: cisapride, 10 mg t.d.s., vs. placebo	Yes	Yes	No	Significant improvement with cisapride compared with placebo in both frequency and severity of symptoms
Testoni, *et al.*, 1990[177] Italy	RCT, single-blind, placebo-controlled. 20 patients, 10 in each arm. Dyspepsia and delayed antroduodenal motility on manometry, 6 months. OGD. No drop-outs	15 days: cisapride, 10 mg q.d.s., vs. placebo	Yes	No	No	Symptomatic improvement in both groups, hardly significant ($p = 0.049$). Cisapride improved interdigestive antroduodenal motor activity
Yeoh, *et al.*, 1997[284] Singapore	RCT, double-blind, placebo-controlled. 104 patients with functional dyspepsia, 38 in each arm: one group with gastritis, one without. 2 weeks antacid run-in period. 73% completed trial	4 weeks: cisapride, 10 mg t.d.s., vs. placebo	No	Yes	No	Cisapride good or better global response in 58% with gastritis and 53% without gastritis compared with 47% and 52%, respectively, patients on placebo. No significant difference between groups
Domperidone vs. placebo (1 trial)						
Bekhti & Rutgeerts, 1979[166] Belgium	RCT, double-blind, placebo-controlled. 40 patients, 20 in each arm. Chronic dyspepsia, weak antral contractions and delayed gastric emptying tests. Radiological examination only. 15% radiological reflux. No drop-outs	4 weeks: domperidone, 10 mg t.d.s., vs. placebo	No	Yes	No	Global evaluation significantly in favour of domperidone. Few side-effects

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
Prokinetics vs. prokinetics (3 trials)						
Fumagali & Hammell, 1994[84] Switzerland	RCT, double-blind, placebo-controlled. 60 patients, 30 in each arm. 1-month dyspepsia, included reflux symptoms. Two subgroups: reflux-like, typical dyspepsia. OGD. 95% completed trial. 2-week follow-up	4 weeks: cisapride, 10 mg t.d.s., vs. metoclopramide, 10 mg t.d.s.	No	Yes	No	Significant improvement in both groups (no significant intergroup difference). At 2-week follow-up, response rate significantly better with cisapride (73%) than with metoclopramide (47%)
Halter, *et al.*, 1997[202] Switzerland	RCT, double-blind, placebo-controlled. 127 patients, cisapride 68, domperidone 59. 1 month of dyspepsia. Two subgroups: reflux-like, dyspepsia. OGD. 2-month follow-up. 88.9% completed trial	4 weeks: cisapride, 10 mg q.d.s., vs. domperidone, 20 mg q.d.s.	No	Yes	No	Cisapride more effective than domperidone in reflux group. Domperidone more effective against nausea in reflux group
van Outryve, *et al.*, 1993[85] Belgium	RCT, double-blind placebo-controlled trial. 147 patients: metoclopramide 77, domperidone 70. 2.8 months mean duration of chronic dyspepsia. Included reflux symptoms. OGD within 3 months before trial. 18% clinical diagnoses of GORD	2 weeks Phase I study: metoclopramide, 10 mg t.d.s., vs. domperidone, 10 mg t.d.s. Phase II study: cisapride, 10 mg t.d.s., vs. placebo	No	Yes	No	Metoclopramide and domperidone produced comparable alleviation of epigastric symptoms. Global efficacy good or excellent in 62% and 57% of patients, respectively. In refractory patients, cisapride efficacy significant compared with placebo
H2-receptor antagonists vs. placebo (8 trials)						
Delattre, *et al.*, 1985[181] USA	RCT, double-blind, placebo-controlled. 414 patients: treatment 63, placebo 62. 3 months of predominantly epigastric pain. Gastroduodenitis in 22% of patients	4 weeks: cimetidine, 200 mg q.d.s., vs. placebo	Yes	Yes	No	Cimetidine significantly better in providing symptomatic relief in patients who had previously responded favourably to antacids
Gotthard, *et al.*, 1988[179] Sweden	RCT, double-blind, placebo-controlled. 210 patients: cimetidine 73, antacid 74, placebo 75. 3/12 dyspepsia of unknown origin. Seen by gastroenterologist. Acid output studies performed. Duodenitis 16%	6 weeks: cimetidine, 400 mg b.d., vs. placebo vs. antacid, 10 ml q.d.s.	Yes	No	No	Cimetidine superior to both placebo and antacid in relieving pain and nausea but not bloating
Hadi, 1989[180] Indonesia	RCT, double-blind, placebo-controlled. 52 patients: ranitidine 26, placebo 26. Duration of dyspepsia unclear. Gastritis on all OGDs. Drop-out rate: placebo 23%, ranitidine 4%	4 weeks: ranitidine, 300 mg daily, vs. placebo	No	Yes	No	Ranitidine effective as short-term treatment for patients with endoscopically proven gastritis.

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
***H_2-receptor antagonists vs. placebo (8 trials)* contd**						
Hansen, *et al.*, 1998[164] Denmark	RCT, double-blind, placebo-controlled. Primary care recruitment of 330 patients: cisapride 109, ranitidine 111, placebo 110. Mean duration of dyspeptic symptom 88 months. Four subgroups: ulcer-like (13%), reflux-like (23%), dysmotility-like (46%), unclassified (18%). Included superficial erosions on OGD. 85% completed trial	2 weeks: cisapride, 10 mg t.d.s., vs. nizatidine, 300 mg nocte, vs. placebo	Yes	Yes	No	Effects of 2-week course of cisapride or nizatidine recruited from primary care not superior to those of placebo. Symptom subgrouping not predictive of response to treatment
Kelbaek, *et al.*, 1985[183] Denmark	RCT, double-blind, placebo-controlled. 52 patients: cimetidine 24, placebo 26. 1 month epigastric pain. Acid output studies performed. OGD. 14 patients, symptom-free at end of treatment, had 3 months' follow-up. 96% completed trial	3 weeks: cimetidine, 200 mg t.d.s. + 400 mg nocte, vs. placebo	No	Yes	No	Cimetidine does not appear to be superior to placebo in NUD
Nesland & Berstad, 1985[182] Norway	RCT, double-blind, placebo-controlled. 100 patients: cimetidine 44, placebo 46. 6 months of predominantly ulcer-like pain, with erosive prepyloric changes. Acid output studies performed. 90% completed trial	4 weeks: cimetidine, 400 mg b.d., vs. placebo	Yes	Yes	No	Patients with NUD and erosive prepyloric changes who have epigastric pain/ discomfort as a prominent symptom appear to profit from treatment with cimetidine
Singal, *et al.*, 1989[73] India	RCT, double-blind, placebo-controlled. 67 patients: cimetidine 33, placebo 34. 1 month of primary symptom of upper abdominal discomfort. Irritable bowel syndrome excluded	4 weeks: cimetidine, 400 mg b.d., vs. placebo	No	Yes	No	Abdominal pain and other secondary dyspeptic symptoms relieved in higher proportions in cimetidine-treated group, though difference not significant
Saunders, *et al.*, 1986[184] UK	RCT, double-blind, placebo-controlled, multicentre. Primary care recruitment, 251 patients with NUD: ranitidine 115, placebo 136. 88% completed trial. 1-year follow-up, but results included other peptic disease	6 weeks: ranitidine, 150 mg b.d., vs. placebo	No	Yes	No	Significantly more NUD patients became symptom-free with ranitidine compared with placebo

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
H_2-receptor antagonists vs. others (7 trials)						
Carvalhinhos, *et al.*, 1995[198] Belgium	RCT, double-blind, placebo-controlled. 203 patients: cisapride 99, ranitidine 104. 1 month of dyspepsia. 93% completed trial	8 weeks: cisapride, 30 mg daily, vs. ranitidine, 300 mg daily	No	Yes	No	Both cisapride and ranitidine improved individual symptoms of NUD. Cisapride superior to ranitidine particularly on combined evaluation of response to treatment and recurrence of symptoms
Casiraghi, *et al.*, 1986[199] Italy	RCT, double-blind, placebo-controlled. 104 patients, 52 in each arm. 1 month of predominantly epigastric pain or heartburn as primary symptoms; list of other secondary symptoms. OGD. 83% completed trial	2 weeks: cimetidine, 200 mg q.d.s., vs. antacid, 1 tablet q.d.s.	No	Yes	No	Cimetidine significantly more effective than antacids in reducing numbers of pain or heartburn episodes. Confirms efficacy of cimetidine in providing symptomatic relief in patients with NUD, particularly when pain is major complaint
Dal Monte, *et al.*, 1989[200] Italy	RCT, double-blind, placebo-controlled. 114 patients: pirenzepine 59, cimetidine 55. Dyspepsia definition and duration not stated. All had chronic erosive gastritis on OGD. 95% completed trial	6 weeks: pirenzepine, 50 mg b.d., vs. cimetidine, 400 mg b.d.	No	Yes	No	64% pirenzepine group and 62% cimetidine group free of symptoms. Endoscopy revealed healing of lesions in 78% and 80%, respectively. Differences between groups not significant
Fedeli, *et al.*, 1982[285] Italy	RCT, double-blind, placebo-controlled. 23 patients: pirenzepine 12, cimetidine 11. NUD with erosive or congestive gastritis	4 weeks: pirenzepine, 100 mg daily, vs. cimetidine, 1000 mg daily	No	Yes	No	Pirenzepine significantly reduces symptom scores
Gotthard, *et al.*, 1988[179] Sweden	RCT, double-blind, placebo-controlled. 222 patients, cimetidine 73, antacid 74, placebo 75. Dyspepsia of unknown origin 3/12. Acid output studies. Duodenitis 16%	6 weeks: cimetidine, 400 mg b.d., vs. placebo vs. antacid, 10 ml q.d.s.	Yes	No	No	Cimetidine superior to both placebo and antacid in relieving pain and nausea but not bloating
Hansen, *et al.*, 1998[164] Denmark	RCT, double-blind, placebo-controlled. 330 patients, primary care recruitment: cisapride 109, ranitidine 111, placebo 110. Mean duration of dyspeptic symptom 88 months. Four subgroups: ulcer-like (13%), reflux-like (23%), dysmotility-like (46%), unclassified (18%). Included superficial erosions on OGD. 85% completed trial	2 weeks: cisapride, 10 mg t.d.s., vs. nizatidine, 300 mg nocte, vs. placebo	Yes	Yes	No	2-week course of cisapride or nizatidine not superior to placebo in patients recruited from primary care. Symptom subgrouping not predictive of response to treatment

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
***H_2-receptor antagonists vs. others (7 trials)* contd**						
Misra, *et al.*, 1992[201] India	Open RCT. 100 patients: ranitidine 47, sucralfate 53. 1 month of abdominal symptoms referable to upper GI tract. GORD and irritable bowel syndrome excluded. 87% completed trial	4 weeks: ranitidine, 150 mg b.d., vs. sucralfate, 1000 mg q.d.s.	No	Yes	No	Global relief in symptoms significantly more frequent in sucralfate group than in ranitidine group. Sucralfate superior to ranitidine
Sucralfate vs. placebo (3 trials)						
Gudjonsson, *et al.*, 1993[197] Iceland	RCT, double-blind, placebo-controlled. 104 patients, private practice recruitment: cisapride 56, placebo 48. 1 month of dyspepsia. OGD. 91% completed trial	3 weeks: sucralfate, 1000 mg q.d.s., vs. placebo	No	Yes	No	No significant difference with individual symptom and global symptom scores between sucralfate and placebo
Kairaluoma, *et al.*, 1987[76] Finland	RCT, double-blind, placebo-controlled. 151 patients: sucralfate 79, placebo 72. 3 months of dyspepsia. OGD. Duodenitis 6%. 86% completed trial	4 weeks: sucralfate, 1000 mg t.d.s., vs. placebo	No	Yes	No	Significant difference between sucralfate and placebo in global response. Best response achieved in patients with mild or moderate symptoms
Kumar, *et al.*, 1996[186] India	RCT, double-blind, placebo-controlled. 63 patients: colloidal bismuth subcitrate 18, placebo I 15, sucralfate 15, placebo II 15. NUD and *H. pylori* infection. 78% completed trial	4 weeks: colloidal bismuth subcitrate, 240 mg b.d., vs. placebo I vs. sucralfate, 2000 mg b.d., vs. placebo II	No	Yes	No	Colloidal bismuth subcitrate more effective that sucralfate in inducing endoscopic and histologic healing of *H. pylori*-related gastritis among NUD patients
Sucralfate vs. bismuth (1 trial)						
Kumar, *et al.*, 1996[186] India	RCT, double-blind, placebo-controlled. 45 patients: colloidal bismuth subcitrate 18, placebo I 15, sucralfate 15, placebo II 15. NUD and *H. pylori* infection. 78% completed trial	4 weeks: colloidal bismuth subcitrate, 240 mg b.d., vs. placebo I vs. sucralfate, 2000 mg b.d., vs. placebo II	No	Yes	No	Colloidal bismuth subcitrate more effective that sucralfate in inducing endoscopic and histologic healing of *H. pylori*-related gastritis among NUD patients
Misoprostol vs. placebo (2 trials)						
Hausken, *et al.*, 1990[195] Norway	RCT, double-blind, placebo-controlled. 137 patients: misoprostol 68, placebo 69. 3 months dyspepsia in patients with NUD with erosive prepyloric changes. 84% completed trial	4 weeks: misoprostol, 400 µg b.d., vs. placebo	No	Yes	No	Misoprostol had significant worsening effect on epigastric pain, nausea, lower abdominal pain (15% vs. 1%), meteorism and diarrhoea (29% vs. 4%) compared with placebo

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
***Misoprostol vs. placebo (2 trials)* contd**						
Pazzi, *et al.*, 1994[196] Italy	RCT, double-blind, placebo-controlled. 48 patients, 24 in each arm. Duration of dyspepsia not stated. OGD showed chronic erosive gastritis. 83% completed trial	2 months: misoprostol, 200 µg b.d., vs. placebo	No	Yes	No	Significant improvement in symptom scores, endoscopic and histological appearance of gastric mucosa with misoprostol
Bismuth vs. placebo (9 trials)						
Goh, *et al.*, 1991[191] Malaysia (2 trials)	RCT, double-blind, placebo-controlled. 71 NUD patients. 40 *H. pylori*-positive: treatment 21, placebo 19. 31 *H. pylori*-negative: treatment 17, placebo 14. Non-erosive duodenitis included. 84.5% completed trial.	4 weeks: colloidal bismuth subcitrate, 2 tablets b.d., vs. placebo	No	Yes	No	All groups reported improvement in symptom scores. *H. pylori*-positive group: colloidal bismuth subcitrate group recorded significantly higher improvement than other groups. 12/16 patients relapsed 1 month after withdrawal of colloidal bismuth subcitrate
Kang, *et al.*, 1990[187] Singapore	RCT, double-blind, placebo-controlled. 51 patients: treatment 28, placebo 23. Dyspepsia with food-related abdominal pain and *H. pylori* gastritis. 70% completed trial	8 weeks: colloidal bismuth subcitrate, 1 tablet q.d.s., vs. placebo	No	Yes	No	Colloidal vismuth subcitrate benefited those with gastritis but not those without
Kazi, *et al.*, 1990[188] India	RCT, not specified whether double-blind. 52 patients, 26 in each arm. Dyspepsia and *H. pylori* gastritis. No drop-outs	3 weeks: bismuth salicylate, 500 mg t.d.s., vs. placebo	No	Yes	No	Resolution of gastritis and improvement of symptoms significantly greater in patients in whom *H. pylori* cleared compared with those in whom it persisted
Kumar, *et al.*, 1996[186] India	RCT, double-blind, placebo-controlled. 63 patients: colloidal bismuth subcitrate 18, placebo I 15, sucralfate 15, placebo II 15. NUD and *H. pylori* infection. 78% completed trial	4 weeks: colloidal bismuth subcitrate, 240 mg b.d., vs. placebo I vs. sucralfate, 2000 mg b.d., vs. placebo II	No	Yes	No	Colloidal bismuth subcitrate more effective that sucralfate in inducing endoscopic and histologic healing of *H. pylori*-related gastritis in NUD patients
Lambert, *et al.*, 1989[192] Australia (2 trials)	RCT, double-blind, placebo-controlled. 82 patients with NUD, some with *C. pylori* infection. 48 *C. pylori*-positive: treatment 22, placebo 26. 30 *C. pylori*-negative: treatment 16, placebo 14. 95% completed trial	4 weeks: bismuth subcitrate, 4 tablets daily, vs. placebo	No	Yes	No	Clearance of *C. pylori* and histological improvement was associated with significant decrease in symptoms. In *C. pylori*-negative patients, improvement occurred in both placebo and treatment groups

continued

Pharmacological interventions for NUD (trials included in the meta-analysis) *contd*

Study/country	Design/participants	Intervention	Outcomes			Results
			Individual symptom score	Global symptom score	Quality of life	
***Bismuth vs. placebo (9 trials)* contd**						
Loffeld, *et al.*, 1989[189] The Netherlands	RCT, double-blind, placebo-controlled. 57 patients: treatment 26, placebo 24. NUD with *C. pylori* gastritis. 88% completed trial	4 weeks: colloidal bismuth subcitrate, 240 mg daily, vs. placebo	No	Yes	No	Improvement in subjective complaints in both groups, except nausea and meteorism that improved more in colloidal bismuth subcitrate group. Significant reduction in *C. pylori* colonisation and gastritis score
Vaira, *et al.*, 1992[190] Italy	RCT, double-blind, placebo-controlled. 80 patients, 40 in each arm. *H. pylori*-associated NUD. Follow-up 4 weeks post-treatment 97.5%. *H. pylori* eradication rate 54%	4 weeks: colloidal bismuth subcitrate, 240 mg b.d., vs. placebo	Yes	Yes	No	Colloidal bismuth subcitrate effective treatment for *H. pylori*-associated NUD, with improved gastric antral histological appearances and beneficial effect on symptoms
Pirenzepine vs. placebo (2 trials)						
Gad & Dobrillon, 1989[193] Italy	RCT, double-blind, placebo-controlled, multicentre. 128 patients with NUD and *C. pylori* infection: pirenzepine 66, placebo 62. 84% completed trial	4 weeks: pirenzepine, 50 mg b.d., vs. placebo	No	Yes	No	Improvement in endoscopic and clinical findings but no change in degree of mucosal inflammation or extent of colonisation by *C. pylori*
Hradsky & Wikander, 1982[194] Sweden	RCT, double-blind, placebo-controlled. 59 patients with NUD: pirenzepine 30, placebo 29. 82% completed trial	4 weeks: pirenzepine, 25 mg b.d., vs. placebo	No	Yes	No	Pirenzepine very effective and significantly more effective than placebo in treatment of NUD
PPI vs. placebo (4 trials)						
Talley, *et al.*, 1998[185] Australia (4 trials: BOND & OPERA trials)	Two identically designed RCTs, double-blind, placebo-controlled, at two doses of omeprazole. 1262 patients with functional dyspepsia, some with *H. pylori* gastritis. 96.6% completed trials	4 weeks. Bond trial: omeprazole, 10 mg daily (204), vs. omeprazole, 20 mg daily (219), vs. placebo Opera trial: omeprazole, 10 mg daily (201), vs. omeprazole, 20 mg daily (202), vs. placebo	No	Yes	No	Omeprazole modestly superior to placebo in functional dyspepsia at both 20 mg and 10 mg doses, particularly in those with ulcer-like and reflux-like dyspepsia, but not in those with dysmotility-like dyspepsia. Significant improvement in GSRS between omeprazole, 20 mg, and placebo but not 10 mg and placebo. PGWB improved in all groups, results not significant between three treatment arms

H. pylori eradication for NUD

Study/location	Methods	Participants	Intervention	Outcomes
Sheu, *et al.*, 1996[211] Taiwan	Blinding: patients not masked. Outcome assessments masked but no method stated. No description of randomisation method or of concealment. Drop-outs: full follow-up until 2 months when those still *H. pylori*-positive in treatment arm (25%) received additional eradication therapy and were not followed further	Single centre: 41 patients. Patient selection: consecutive referrals for dyspepsia with normal endoscopy and *H. pylori*-positive on urea breath test, serology and histology. Dyspepsia score > 2/10. Reflux-like disease: patients with symptoms of heartburn, acid regurgitation and vomiting excluded	Duration: mixed. Eradication arm: 4 weeks of colloidal bismuth subcitrate, 120 mg t.d.s., and 2 weeks of metronidazole, 500 mg t.d.s., + amoxycillin, 500 mg t.d.s. Control arm: 2 months of H_2-receptor antagonist. Concomitant treatments: short courses of antisecretory agents permitted. *H. pylori* eradication rates: eradication arm 75%, control arm not stated	(a) Mean symptom score (own scale based on assessment of five symptom groups) (b) mean serological titres of *H. pylori* (c) grade of gastritis Length of follow-up: 2 months in randomised groups, 6 months in total
Blum, *et al.*, 1998[208] (OCAY study) Austria, Canada, Germany, Iceland, Ireland, South Africa, Sweden	Blinding: patients and investigators masked by use of matching placebos. Random allocation used but no method of concealment stated. Drop-outs: 6% of participants excluded from ITT analysis	Multicentre: 348 patients. Patient selection: > 6-month history of dyspepsia with normal endoscopic findings and *H. pylori*-positive on rapid urease test. Moderate to very severe dyspepsia for > 3 days in previous week. Reflux-like disease: excluded by definition of dypepsia and previous history	Duration: 1 week. Eradication arm: omeprazole, 20 mg b.d. + amoxycillin, 1000 mg b.d., + clarithromycin, 500 mg b.d. Control arm: omeprazole, 20 mg b.d., + matching placebos. Concomitant treatments: not stated. *H. pylori* eradication rates: eradication arm 79%, control arm 2%	(a) Treatment success defined as no symptoms or only minimal pain in previous 7 days (b) symptoms rated according to GSRS (c) quality of life measured with PGWB (d) healing of gastritis Length of follow-up: 12 months
McColl, *et al.*, 1998[207] Scotland	Blinding: patients and investigators masked by use of matching placebos. Concealed random allocation used. Drop-outs: 4% of participants excluded from ITT analysis	Single centre: 318 patients. Patient selection: > 4-month history of dyspepsia with normal endoscopy and *H. pylori*-positive on urea breath test. All dyspepsia patients referred from primary care eligible. Reflux-like disease: included	Duration: 2 weeks. Eradication arm: omeprazole, 20 mg b.d., + amoxycillin, 500 mg t.d.s. (or tetracycline, 500 mg t.d.s.), + metronidazole, 400 mg, t.d.s. Control arm: omeprazole, 20 mg b.d. + matching placebos. Concomitant treatments: antisecretory agents permitted. *H. pylori* eradication rates: eradication arm 88%, control arm 5%	(a) Treatment success defined as a Glasgow Dyspepsia Severity Score (GDSS) rating of zero in previous 6 months (b) mean GDSS scores (c) quality of life measured using SF-36 (d) use of H_2-receptor antagonist and PPI medication Length of follow-up: 12 months
Talley, *et al.*, 1999[212] (ORCHID study) Australia, Denmark, Finland, France, Hungary, New Zealand, Norway, Spain, The Netherlands, UK	Blinding: patients and investigators masked by use of matching placebos. Random allocation used but no method of concealment stated. Drop-outs: 25% excluded as *H. pylori*-positive (by urea breath test) at randomisation. Additional 1% excluded from ITT analysis	Multicentre: 370 patients. Patient selection: > 3-month history of dyspepsia with normal endoscopy and *H. pylori*-positive on serology. Moderate to very severe dyspepsia for > 3 days in previous week. Reflux-like disease: excluded by definition of dypepsia and previous history	Duration: 1 week. Eradication arm: omeprazole, 20 mg b.d., + amoxycillin, 1000 mg b.d. + clarithromycin, 500 mg b.d. Control arm: omeprazole, 20 mg b.d. + matching placebos. Concomitant treatments: use of weak antacid permitted. *H. pylori* eradication rates: eradication arm 85%, control arm 4%	(a) Treatment success defined as no symptoms or only minimal pain in previous 7 days (b) symptoms rated according to GSRS (c) quality of life measured with PGWB (d) healing of gastritis Length of follow-up: 12 months

continued

H. pylori eradication for NUD

Study/location	Methods	Participants	Intervention	Outcomes
Talley, *et al.,* 1999[214] USA	Blinding: patients and investigators masked by use of matching placebos. Random allocation used but no method of concealment stated. Drop-outs: 13% excluded from ITT analysis.	Multicentre: 337 patients. Patient selection: > 3-month history of dyspepsia with normal endoscopy and *H. pylori*-positive on urea breath test. Moderate to very severe dyspepsia for >3 days in previous week. Reflux-like disease: patients with predominant heartburn excluded	Duration: 2 weeks. Eradication arm: omeprazole, 20 mg b.d., + amoxycillin, 1000 mg b.d., + clarithromycin, 500 mg b.d. Control arm: omeprazole, 20 mg b.d., + matching placebos. Concomitant treatments: use of weak antacid permitted. *H. pylori* eradication rates: eradication arm 90%, control arm 2%	(a) Treatment success defined as no symptoms or only minimal pain in previous 7 days, and no use of medication other than antacids in the previous 30 days (b) symptoms rated according to GSRS (c) quality of life measured with SF-36 (d) healing of gastritis Length of follow-up: 12 months
Dhali, *et al*., 1999[213] India	Blinding: patients and investigators not masked. Random allocation used but no method of concealment stated. Drop-outs: unclear	62 patients. Patient selection: > 4-week history of dyspepsia with normal endoscopy and *H. pylori*-positive on biopsy or rapid urease test. Reflux-like disease: patients with predominant heartburn excluded.	Duration: mixed. Eradication arm: bismuth subcitrate, 120 mg q.d.s., + tetracycline, 500 mg q.d.s., + metronidazole, 400 mg t.d.s., for 2 weeks. Control arm: sucralfate, 1000 mg q.d.s. for 4 weeks. Concomitant treatments: antacids. *H. pylori* eradication rates: eradication arm 88%, control arm	Patients subjective improvement in dyspepsia symptoms. Changes in dyspepsia questionnaire score. Length of follow-up: 3 months
Greenburg & Cello, 1999[215] USA	Blinding: patients and investigators masked using identical placebos. Method of randomisation and concealment not stated. Drop-outs: 16% of patients excluded from ITT analysis	Single centre: 84 patients. Patient selection: > 4-week history of epigastric pain not responsive to H_2-receptor antagonists with normal endoscopy and *H. pylori*-positive on biopsy. Reflux-like disease: patients with predominant heartburn excluded	Duration: 2 weeks. Eradication arm: omeprazole, 20 mg b.d., + clarithromycin, 500 mg t.d.s. Control arm: identical placebos. Concomitant treatments: patients allowed any dyspepsia medication. *H. pylori* eradication rates: eradication arm 71%, placebo arm 8%	Change in dyspepsia score. Questionnaire evaluated five symptoms using visual analogue scale (possible scores 0–500). Unclear whether this questionnaire validated. Length of follow-up: 12 months
Miwa, *et al*., 2000[216] Japan	Blinding: study described as double-blind. The use of identical placebos not explicitly stated. Method of randomisation and concealment not stated.	Single centre: 85 patients. Patient selection: > 4-week history of dyspepsia with normal endoscopy and *H. pylori*-positive on biopsy or rapid urease test. Reflux-like disease: patients with predominant heartburn excluded	Duration: 1 week. Eradication arm: omeprazole, 20 mg b.i.d., + amoxycillin, 500 mg t.d.s., + clarithromycin, 200 mg b.d. Control arm: placebos. Concomitant treatments: antacids and H_2-receptor antagonists. *H. pylori* eradication rate: eradication arm 85%	Treatment success defined as none or minimal symptoms (score 0 or 1) in the previous 7 days. Symptoms rated according GSRS. Length of follow-up: 3 months

continued

H. pylori eradication for NUD *contd*

Study/location	Methods	Participants	Intervention	Outcomes
Malfertheiner, *et al.*, 2000[217] [abstract] Germany	Blinding: patients and investigators matched using identical placebos. Adequate randomisation and concealment. Drop outs: 22% of participants excluded from ITT analysis	Multicentre: 674 patients. Patient selection: > 4-week history of dyspepsia with normal endoscopy and *H. pylori*-positive on biopsy or rapid urease test. Reflux-like disease: unclear whether patients with predominant heartburn excluded	Duration: 1 week. Eradication arm: lansoprazole, 30/15 mg b.d., + clarithromycin, 500 mg b.d., + amoxycillin, 1000 mg b.d., for 7 days. Control arm: lansoprazole, 15 mg o.d. + matching placebos. Concomitant treatments: antacids and H_2-receptor antagonists. *H. pylori* eradication rates: eradication arm 80%, placebo arm 7%	Treatment success defined as no or minimal epigastric pain in previous week. Validated German dyspepsia questionnaire evaluating nine dyspeptic symptoms. Length of follow-up: 12 months
Bruley des Varannes, *et al.*, 2000[218] [abstract] France	Blinding: patients and investigators matched using identical placebos. Adequate randomisation, method of concealment not stated. Drop-outs: all enrolled patients included in ITT analysis	Multicentre: 253 patients. Patient selection: > 3 months of epigastric pain with normal endoscopy and *H. pylori*-positive on biopsy or rapid urease test. Reflux-like disease: excluded by the definition of dyspepsia	Duration: 1 week. Eradication arm: ranitidine, 300 mg b.d., + amoxycillin, 1000 mg b.d., + clarithromycin, 500 mg b.d. Control arm: matching placebos. Concomitant treatments: unclear. *H. pylori* eradication rates: eradication arm 69%, placebo arm 9%	Treatment success defined as no epigastric pain in previous week (score = 0). Likert scale used, unclear whether dyspepsia questionnaire validated. Length of follow-up: 12 months
Froehlich, *et al.*, 2000[219] [abstract] Switzerland	Blinding: patients and investigators matched using identical placebos. Adequate randomisation and concealment. Drop-outs: 9% of patients excluded from ITT analysis	Multicentre: 144 patients. Patient selection: > 3 months of epigastric pain with normal endoscopy and *H. pylori*-positive on biopsy or rapid urease test. Reflux-like disease: excluded by the definition of dyspepsia	Duration: 1 week. Eradication arm: lansoprazole, 30 mg b.d., + clarithromycin, 500 mg b.d., + amoxycillin, 1000 mg b.d. Control arm: matching placebos. Concomitant treatments: any dyspepsia medication allowed during follow-up. *H. pylori* eradication rates: eradication group 72%, placebo arm 2%	Outcome was change in dyspepsia score (defined as a sum of five dyspeptic symptoms). Validated dyspepsia questionnaire used (Veldhuyzen van Zanten, *et al.*[364]). Quality of life using SF-12. Length of follow-up: 12 months
Koelz, *et al.*, 1999[210] Germany	Blinding: patients and investigators masked by use of matching placebos. No description of method of randomisation or concealment. Drop-outs: all participants included in ITT analysis	Multicentre: 181 patients. Patient selection: > 1-month history of dyspepsia with normal endoscopy and *H. pylori*-positive on rapid urease test and urea breath test. Patients were all resistant to PPI or H_2-receptor antagonist (ascertained in previous trial). Dyspepsia was severe enough to require treatment. Reflux-like disease: specifically excluded	Duration: 2 weeks. Eradication arm: omeprazole, 40 mg b.d. + amoxycillin, 1000 mg b.d. Control arm: omeprazole, 20 mg daily, + matching placebos. Concomitant treatments: occasional use of antacid. *H. pylori* eradication rates: eradication arm 52%, control arm 10%	(a) Treatment success defined as no dyspepsia symptoms in previous week (b) subjective grading of individual symptoms and overall symptoms in previous week (c) quality of life measured using a German lifestyle questionnaire (results not available) (d) time off work/in hospital Length of follow-up: 6 months

Appendix 3

Excluded studies

Interventions for dyspepsia in primary care

Asante MA, Patel P, Mendall M, Jazrawi R, Northfield TC. The impact of direct access endoscopy, Helicobacter pylori near patient testing and acid suppressants on the management of dyspepsia in general practice. *Int J Clin Pract* 1997;**51**:497–9.

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Pharmacological interventions for NUD

Trials excluded on eligibility criteria (Group A)

Study	Participants	Intervention	Outcomes
Antacids vs. placebo or others			
Kerkar, *et al.*, 1988[286] India	Not RCT 15 NUD patients	4 weeks Aluminium hydroxide and magnesium trisilicate, 30 ml, at 1 and 3 hours after each meal. No placebo	High-dose liquid antacids result in definite and impressive relief in dyspeptic symptoms as well as the gastroduodenal histological changes in NUD
Parr, 1989[287] UK	RCT, double-blind, multicentre 80 patients with persistent dyspepsia	Single dose of 1 tablet of chewable cimetidine, 200 mg, or chewable antacid tablet	Time for improvement and for total disappearance of pain noted. No statistically significant difference noted between the two treatments
Cisapride vs. placebo or others			
Abell, *et al.*, 1991[288] USA	Open trial, not RCT 21 patients with gastric stasis and gastroparesis or chronic intestinal pseudo-obstruction; no OGD	12 months Cisapride, 10 mg t.d.s.; no placebo	Cisapride effective in improving gastric emptying and symptoms in those with gastroparesis
Abell, *et al.*, 1993[289] USA	Not RCT 8 patients with GI symptoms including four with diabetes	12 months Cisapride, 10 mg t.d.s.; no placebo	Significant improvement in total symptom score, overall patient assessment and quality of life as measured by Minnesota Multiphasic Personality inventory and physical function (SIP)
Brummer, *et al.*, 1997[290] The Netherlands	RCT, double-blind, placebo-controlled, crossover 32 patients with demonstrated delayed gastric emptying	A single dose of suppositories, cisapride, 60 mg, or placebo	Cisapride significantly accelerated gastric emptying of the solid meal and radio-opaque markers in gastroparesis
Camilleri, *et al.*, 1989[291] USA	RCT, double-blind, placebo-controlled 26 patients with gastroparesis and chronic intestinal pseudo-obstruction	6 weeks Cisapride, 10 mg t.d.s., vs. placebo	Both cisapride and placebo showed improvement in total symptom scores. No significant difference in overall symptom scores
Cutts, *et al.*, 1996[292] USA	Not RCT 27 patients with 6 months severe dyspepsia; 22 received cisapride and five domperidone	12 months Cisapride, 10 mg t.d.s., vs. placebo	12 months of prokinetic therapy improved clinical symptoms and quality of life
Degryse, *et al.*, 1993[293] Belgium	?RCT, double-blind, placebo-controlled 28 patients with functional dyspepsia and hypomotility stomach as shown on barium meal	Single bolus intravenous injection of cisapride or placebo	Significant increase in deep peristaltic waves in the cisapride group
Fraser, *et al.*, 1994[294] Australia	Not RCT 12 patients with gastroparesis and 9 healthy patients	Single dose of cisapride injection of 5 mg. No placebo	Disturbance of the relationship between antral, pyloric and duodenal pressure waves was major abnormality of postprandial gastric motor function in gastroparesis
Frazzoni, *et al.*, 1993[295] Italy	RCT, double-blind, placebo-controlled 53 patients with dyspepsia; treatment regimen depends on *H. pylori* status	For *H. pylori*-positive group: colloidal bismuth subcitrate, 240 mg b.d., for 28 days + metronidazole, 500 mg t.d.s., for 10 days vs. placebo For *H. pylori*-negative group: cisapride, 10 mg t.d.s., for 28 days vs. placebo	Symptomatic remission rates assessed after 1-month washout period, not at end of treatment (excluded). No significant difference in either treatment or control group. Bulbar and antral biopsies not useful in clinical management

continued

Trials excluded on eligibility criteria (Group A) *contd*

Study	Participants	Intervention	Outcomes
***Cisapride vs. placebo or others* contd**			
Hausken & Berstad, 1992[296] Norway	?RCT, double-blind, placebo-controlled 106 patients with NUD and erosive prepyloric changes, and 40 healthy individuals	2 weeks Cisapride, 10 mg t.d.s., vs. placebo	The wide antral area tended to decrease with cisapride. Bloating was only symptom significantly associated with wide antral area
Inoue, *et al.*, 1993[297] Japan	Multicentre, not RCT 240 patients with dyspepsia	4 weeks Cisapride, 2.5 mg t.d.s. No placebo	Cisapride resulted in moderate or marked improvement in 79.1% of patients, dysmotility-like (85.2%), reflux-like (81%) and non-specific dyspepsia (76.1%)
Jian, *et al.*, 1985[175] France	RCT, double-blind, placebo-controlled, crossover 60 patients with postprandial dyspeptic symptoms: idiopathic dyspepsia, postvagotomy and secondary to medical disorders. OGD performed	Single dose Cisapride, 8 mg i.v., vs. placebo in only 10 of 60 selected patients	A significant increase of solid and liquid emptying rates was found in patients with initial delayed gastric emptying
Kendall, *et al.*, 1997[298] USA	Open-label, not RCT 30 patients with gastroparesis, idiopathic and diabetic. Gastric emptying tests performed	2 years Cisapride, 20 mg t.d.s. No placebo	Long-term cisapride treatment produced long-term symptomatic improvement in 42% of patients with severe gastroparesis, with a sustained acceleration of gastric emptying for up to 2 years
Milo, 1984[299] Belgium	RCT, open and double-blind, placebo-controlled, crossover 59 patients with moderate or severe upper GI symptoms and/or constipation	3 weeks Cisapride, 5 mg t.d.s., on 43 patients in the open trial Cisapride, 4 mg t.d.s., vs. placebo on 16 remainding patients in double-blind placebo-controlled crossover	Three-quarters of patients showed a good to excellent response. Marked relief of upper abdominal complaints including postprandial fullness, gastro-oesophageal reflux symptoms and nausea or vomiting, even when associated with irritable bowel syndrome
Mittal, *et al.*, 1997[300] India	Not RCT 20 patients with NUD, nine with delayed gastric emptying vs. 30 healthy individuals as controls	Cisapride, 10 mg t.d.s.; duration of treatment unclear No placebo	All nine patients with delayed gastric emptying showed marked improvement in upper GI symptoms; majority of patients with normal gastric emptying showed no improvement in symptoms
Rezende-Filho, *et al.*, 1989[301] USA	RCT, double-blind, placebo-controlled Seven patients with dyspepsia and increased biliary reflux	Single dose Cisapride, 10 mg i.v., vs. placebo	Cisapride stimulates antral motility and decreases biliary reflux in patients with dyspepsia and increased duodenogastric reflux
Richards, *et al.*, 1993[302] USA	RCT, double-blind, placebo-controlled 43 patients with idiopathic and diabetic gastroparesis	6 weeks Cisapride, 20 mg t.d.s., vs. placebo	Cisapride significantly improved gastric emptying of solids but not significantly improved any symptoms of gastroparesis compared with placebo
Rothstein, *et al.*, 1993[303] USA	Not RCT, no placebo 14 patients with idiopathic or diabetic gastroparesis. Gastric emptying tests performed	6 months Cisapride, 10 mg t.d.s.	Patients with gastroparesis had increase in gastric emptying. Patients with diabetes had similar improvement. Patients who had normalisation of the electrogastrogram had greater gastric emptying rate than patients with continued dysrhythmias. Thus, dysrhythmias are important in the aetiology of gastroparesis

continued

Trials excluded on eligibility criteria (Group A) *contd*

Study	Participants	Intervention	Outcomes
***Cisapride vs. placebo or others* contd**			
Tatsuta, *et al.*, 1989[304] Japan	Not RCT 31 patients with dyspepsia vs. six healthy individuals. Study of delayed gastric emptying tests between six controls and six patients (how six patients selected was unclear)	Single dose of domperidone, 20 mg orally, vs. placebo	Single dose of domperidone significantly increased gastric emptying
Urbain, *et al.*, 1988[305] USA	Not RCT, no placebo 17 patients with dyspepsia; idiopathic dyspepsia 8, post-surgical dyspepsia 9 Gastric emptying tests performed	Single intravenous bolus of cisapride, 10 mg, followed by 2 weeks of cisapride, 10 mg q.d.s.	Cisapride significantly shortened gastric emptying in both groups
Domperidone vs. placebo or others			
Agorastos, *et al.*, 1981[306] Greece	RCT, double-blind, placebo-controlled (1), and crossover (2) (1) 24 patients with acute vomiting (anti-emetic trial) (2) 18 patients with dyspepsia	(1) Single dose domperidone, 10 mg i.m., or placebo (2) 6-week crossover trial, domperidone, 10 mg t.d.s., or placebo	(1) Therapeutic results better with domperidone than placebo (2) Total score of dyspepsia symptoms decreased significantly in both groups during first 3 weeks and compared with pre-trial period. During second phase, significant decrease of total symptom scores observed only in group treated with domperidone last
Bradette, *et al.*, 1991[307] Canada	RCT, double-blind, placebo-controlled, crossover Ten patients with functional dyspepsia and 10 healthy individuals as controls. Study of symptomatic responses on pressure variations during progressive gastric distensions	Single dose, domperidone, 20 mg, or placebo Study repeated 4–6 weeks later with alternate medication	Patients with functional dyspepsia have lower threshold both to initial symptomatic recognition and to perception of pain during gastric distension; domperidone may have an effect on threshold of these conscious visceral sensations
Davis, *et al.*, 1988[308] USA	RCT, double-blind, placebo-controlled 16 NUD patients with idiopathic gastric stasis and altered gastro-duodenal motility. Gastric emptying tests performed	6 weeks Domperidone, 20 mg b.d., vs. placebo	Domperidone significantly improved symptom scores of NUD but not gastroduodenal motor activity
Englert & Schlich, 1979[309] Germany	RCT, double-blind, placebo-controlled, crossover 48 patients with postprandial upper GI distress	8 weeks Domperidone, 10 mg t.d.s., vs. placebo	Domperidone significantly improved symptom scores. Side-effects were rare and mild
Eyre-Brook, *et al.*, 1984[310] UK	RCT, double-blind, placebo-controlled 30 patients with dyspepsia. Monitoring of antroduodenal motility	Single dose, domperidone, 20 mg i.v., vs. placebo	Domperidone significantly increased number of antral contractions. When spontaneous duodenal activity present, domperidone reduced number of isolated duodenal contractions without detectable alteration in behaviour of pylorus
Haarman, *et al.*, 1979[311] Germany	RCT, double-blind, placebo-controlled 41 patients with chronic dyspepsia with mixed aetiologies	4 weeks Domperidone, 30 mg daily, vs. placebo	Dyspeptic symptoms except reflux significantly improved on domperidone. No side-effects seen
Lienard, *et al.*, 1978[312] Belgium	Not RCT 202 patients with chronic dyspepsia (mixed aetiologies) with delayed gastric emptying tests	4 weeks Domperidone, 10 mg t.d.s., doubled if no improvement after 1 week. No placebo	78% had good to excellent improvement. Mild side-effects seen

continued

Trials excluded on eligibility criteria (Group A) *contd*

Study	Participants	Intervention	Outcomes
***Domperidone vs. placebo or others* contd**			
Madangopalan, *et al*., 1981[313] India	Open pilot study, no placebo 25 patients with dyspepsia or reflux oesophagitis on OGD	4 weeks Domperidone, 10 mg t.d.s.	Domperidone safe and effective for symptomatic relief of NUD and reflux oesophagitis. Retching, heartburn and bloated feeling relieved in almost all patients while symptomatic relief for nausea and epigastric discomfort was 80% and 87%, respectively
Nagler & Miskovitz, 1981[314] USA	RCT, double-blind, placebo-controlled 11 patients with chronic post-prandial idiopathic upper GI distress with mixed aetiologies	4 weeks Domperidone, 10 mg q.d.s., vs. placebo	No superiority of domperidone over placebo. Side-effects consisted of gas pain (1) and skin rash (1)
Roy, *et al*., 1991[315] UK	RCT, double-blind placebo-controlled; primary care recruitment 95 patients with nausea and vomiting from variety of causes	1 week Controlled release metoclopramide, 15 mg t.d.s., vs. domperidone, 10 mg t.d.s., or domperidone, 20 mg t.d.s.	All three treatments significantly reduce symptoms of belching, flatulence, distension, heartburn, regurgitation, reflux, nausea and vomiting. No significant differences in treatment efficacy or in number or severity of side-effects
Soykan, *et al*., 1997[316] USA	Not RCT, no placebo 17 patients with gastroparesis with various aetiologies	6–48 months Domperidone, 20 mg q.d.s.	Chronic domperidone treatment significantly reduced gastroparesis symptoms and hospitalisations. Domperidone enhanced quality of life in 88% of patients and accelerated gastric emptying of a solid meal to normal rate. It successfully treated gastroparesis on long-term outcome basis and had excellent safety profile
Van Ganse, *et al*., 1979[317] Belgium	RCT, double-blind, placebo-controlled, multicentre 71 patients with chronic dyspepsia of mixed aetiologies	2 weeks Domperidone, 10 mg t.d.s. vs. placebo	Good and excellent improvement obtained in 88.5% of domperidone-treated patients against only 25% of placebo-treated patients. No side-effects reported
Van Outryve, *et al*., 1979[318] Belgium	RCT, double-blind. placebo-controlled 40 patients with nausea and vomiting from a variety of underlying causes	2 weeks Domperidone, 20 mg t.d.s., vs. placebo	Nausea and vomiting reduced in those treated with domperidone. Results recorded as excellent for 62% in domperidone group and 18% of control group
Metoclopramide			
O'Shea, *et al*., 1980[319] Republic of Ireland	RCT, double-blind, placebo-controlled 40 patients with chronic postprandial dyspepsia	4 weeks Domperidone, 20 mg t.d.s., vs. metoclopramide, 20 mg t.d.s.	Reduction of abdominal distension, epigastric burning, belching and nausea significantly reduced after only 2 weeks treatment with either drug. However, domperidone offered advantage over metoclopramide in absence of extrapyramidal side-effects
Cisapride vs. cimetidine			
Halter, *et al*., 1994[320] Switzerland	Multicentre RCT, double-blind, placebo-controlled 137 patients with functional dyspepsia, divided into five subgroups. Only 73% had OGD	4 weeks Cisapride, 5 mg q.d.s., vs. cimetidine, 200 mg q.d.s.	Small but significant difference in favour of cisapride found only in 'dysmotility subgroup' but not in others
Domperidone vs. antacids			
Mwakyusa, 1987[321] Tanzania	Not RCT 48 patients with dyspepsia	4 weeks Domperidone, 10 mg t.d.s., vs. magnesium trisilicate	Domperidone safe and effective in dyspepsia

continued

Trials excluded on eligibility criteria (Group A) *contd*

Study	Participants	Intervention	Outcomes
H_2-receptor antagonists vs. placebo or others			
Bortolotti, *et al.*, 1992[322] Italy	Not RCT 16 patients with ulcer-like dyspepsia due to hypersecretory gastroduodenitis and six healthy individuals as controls	Single dose, ranitidine, 100 mg i.v., with or without pre-treatment with cimetidine, 200 mg i.v.	Ranitidine induced premature and prolonged activity fronts in all patients without antisecretory pre-treatment and in majority of patients in whom acid secretion was previously blocked
Johannessen, *et al.*, 1991[365] Norway	RCT, double-blind, placebo-controlled, single subject multi-crossover 409 patients with dyspepsia	6 treatment days Cimetidine, 400 mg t.d.s., and placebo organised in six pairs with no interposed washout periods	Overall symptomatic effect of cimetidine in dyspepsia and identified individual responders among patients with NUD with a clinically reasonable profile
Miwa & Miyoshi, 1987[323] Japan	Not RCT, multicentre, double-blind, comparative 102 patients with endoscopic gastritis and haemorrhage and/or erosions	2 weeks Three different doses of famotidine, at 5 mg, 10 mg or 20 mg b.d.	Improvement of epigastric pain, heartburn, and discomfort were found with all three doses. Differences not significant. Famotidine, 10 mg and 20 mg, more effective in healing erosions and haemorrhages than 5 mg dose
La Brooy & Misiewicz, 1978[324] UK	RCT 41 patients with ulcer-like dyspepsia. Patients divided according to histology of duodenal biopsies	4 weeks Cimetidine, 200 mg t.d.s. and 400 mg nocte, vs. placebo	Cimetidine provided no more effective symptoms of relief than placebo. Results in number of days of pain and visual analogue scores. Trial consisted of 68% patients with duodenitis, hence excluded
Zuberi, *et al.*, 1988[325] Pakistan	RCT status unclear, placebo-controlled 30 patients with upper abdominal pain	4 weeks Cimetidine, 200 mg t.d.s., vs. placebo	Reported pain intensity scores. Cimetidine offered no significant therapeutic advantage over placebo. Result cannot be extracted even if this is an RCT
Lance, *et al.*, 1989[326] UK	RCT status unclear; prospective, double-blind, placebo-controlled 60 NUD patients	4 weeks Cimetidine, 200 mg t.d.s. plus 400 mg nocte, vs. placebo	Results presented in 'success' and 'failures' groups. No statistical difference found between cimetidine and placebo. Success defined as improvement of symptoms by at least one grade at 1 month (unclear which exact category). Data extraction impossible even if it was RCT
Pirenzepine vs. placebo or others			
Smith, *et al.*, 1990[327] Republic of Ireland	RCT, double-blind, placebo-controlled, multicentre 71 NUD patients with mixed aetiologies	4 weeks Pirenzepine, 50 mg b.d., vs. placebo	No significant differences found between two groups in total symptom scores. Adverse events found in 37% of pirenzepine group and 17% in placebo group
Gasbarrini, *et al.*, 1979[328] Italy	RCT, double-blind, placebo-controlled 112 patients with gastro-duodenitis or PUD	Pirenzepine, 25 mg t.d.s. for 10 days followed by 25 mg b.d. for 20 days, vs. carbenoxolone, 100 mg t.d.s. for 10 days followed by 100 mg b.d. for 20 days, vs. placebo	Pirenzepine is effective in acute treatment for gastroduodenitis and PUD. Also significantly more active than placebo in relieving symptoms of both the above
Bismuth vs. placebo or others			
Hailey & Newsom, 1984[329] USA	RCT, double-blind, placebo-controlled, multi-crossover 48 patients with episodic acute indigestion. No endoscopic or radiological examination	Bismuth subsalicylate, 30 ml every 30 minutes as needed for a total of 8 doses, vs. placebo	Bismuth subsalicylate provided greater and faster relief than placebo for nausea, sense of fullness, heartburn, feeling of abdominal distension and flatulence but not for upper abdominal pain

continued

Trials excluded on eligibility criteria (Group A) *contd*

Study	Participants	Intervention	Outcomes
***Bismuth vs. placebo or others* contd**			
Lanza, *et al*., 1989[330] USA	RCT, blinding not mentioned 20 patients with variety of upper GI complaints and *C. pylori* gastritis	3 weeks Bismuth subsalicylate, 525 mg q.d.s., vs. placebo	Bismuth subsalicylate provided short-term clearance of *C. pylori* in antral mucosa; this clearance associated with an improvement in histological diagnosis
Malfertheiner, *et al*., 1988[331] Germany	Not RCT, open controlled therapeutic 37 patients with chronic erosive gastritis	3 weeks of bismuth subsalicylate liquid, 314 mg q.d.s., vs. 2 weeks of bismuth subsalicylate tablet, 300 mg t.d.s.	Significant reductions found in symptom scores and endoscopic erosions achieved in both groups
McNulty, *et al*., 1986[332] UK (see below)	RCT, single-blind, placebo-controlled 50 patients with *C. pylori* associated gastritis with various aetiologies	3 weeks Bismuth subsalicylate, 30 ml q.d.s., vs. placebo I vs. erythromycin ethylsuccinate, 10 ml q.d.s., vs. placebo II	Significantly greater improvement in endoscopic appearances in patients cleared of *C. pylori* compared with those with persistent infection. Symptoms improved with clearance though not statistically significant
McNulty, 1990[333] UK (see above)	RCT, single-blind, placebo-controlled 50 patients with GI symptoms with *C. pylori* gastritis	3 weeks Bismuth subsalicylate, 30 ml q.d.s. for 3 weeks vs. placebo I vs. erythromycin ethylsuccinate, 10 ml q.d.s., vs. placebo II	Significantly greater improvement in endoscopic appearances in patients cleared of *C. pylori* compared with those with persistent infection. Heartburn improved in 50% with bismuth subsalicylate and 17% with placebo

Summary of features of trials excluded on eligibility criteria (Group A)

Study	Endoscopy performed and either PUD or GORD excluded	Mixed diagnoses; subgroup analysis not possible	Comparative intervention	Dyspepsia or quality-of-life scores	RCT
Antacids vs. placebo/others					
Kerkar, *et al.*, 1988[286]			No		No
Parr, 1989[287]	No				
Prokinetics vs. placebo/others					
Cisapride					
Abell, *et al.*, 1991[288]	No	Yes	No		No
Abell, *et al.*, 1993[289]	No	Yes	No		No
Brummer, *et al.*, 1997[290]	No	Yes		No	
Camilleri, *et al.*, 1989[291]		Yes			
Cutts, *et al.*, 1996[292]	No	Yes			No
Degryse, *et al.*, 1993[293]		Yes		No	Unclear
Fraser, *et al.*, 1994[294]		Yes	No	No	No
Frazonni, *et al.*, 1993[295]				Not at end of treatment	
Hausken & Berstad, 1992[296]				No	Unclear
Inoue, *et al.*, 1993[297]			No		No
Jian, *et al.*, 1985[175]		Yes		No	
Kendall, *et al.*, 1997[298]		Yes	No		No
Milo, 1984[199]	No	Yes			
Mittal, *et al.*, 1997[300]			No		No
Rezende-Filho, *et al.*, 1989[301]				No	
Richards, *et al.*, 1993[302]		Yes			
Rothstein, *et al.*, 1993[303]		Yes	No		No
Tatsua, *et al.*, 1989[304]					No
Urbain, *et al.*, 1988[305]	No		No	No	No
Domperidone					
Agorastos, *et al.*, 1981[306]	No				
Bradette, *et al.*, 1991[307]				No	
Davis, *et al.*, 1988[308]	No				
Englert & Schlich, 1979[309]	No	Yes			
Eyre-Brook, *et al.*, 1984[310]				No	
Haarmann, *et al.*, 1979[311]		Yes			
Lienard, *et al.*, 1978[312]	No	Yes	No		No
Mandangopalan, *et al.*, 1981[313]	No		No		No
Nagler & Miskovitz, 1981[314]	No	Yes			
Roy, *et al.*, 1991[315]	No	Yes			
Soykan, *et al.*, 1997[316]	No	Yes	No		No
Van Ganse, *et al.*, 1978[317]	No	Yes			
Van Outryve, *et al.*, 1979[318]	No	Yes			
Metoclopramide					
O'Shea, *et al.*, 1980[319]	No	Yes			
Cisapride vs. antacids					
Mwakyusa, 1987[321]					No
Cisapride vs. H_2-receptor antagonists					
Halter, *et al.*, 1994[320]	No	Yes			

continued

Summary of features of trials excluded on eligibility criteria (Group A) *contd*

Study	Endoscopy performed and either PUD or GORD excluded	Mixed diagnoses; subgroup analysis not possible	Comparative intervention	Dyspepsia or quality-of-life scores	RCT
H_2-receptor antagonists vs. placebo/others					
Bortolotti, *et al.,* 1992[322]			No	No	No
Johannessen, 1991[365]	No				
Miwa & Miyoshi, 1987[323]			No		No
La Brooy & Misiewicz, 1978[324]		Duodenitis 68%			
Zuberi, *et al.,* 1988[325]					Unclear
Lance, *et al*., 1986[326]					Unclear
Antimuscarinics (pirenzepine) vs. placebo/others					
Gasbarrini, *et al.,* 1979[328]	No	Yes			
Smith, *et al*., 1990[327]	No	Yes			
Bismuth vs. placebo/others					
Hailey & Newsom, 1984[329]	No				
Lanza, *et al*., 1989[330]				No	
Malfertheiner, *et al*., 1988[331]			No	No	No
McNulty, *et al*., 1986[332]	No	Yes			
McNulty, 1990[333]	No				

Trials excluded on data extraction grounds* (Group B)

Study/country	Participants	Methods	Outcomes
Antacids vs. placebo/others			
Nyren, *et al.*, 1986[72] Sweden (Counts as two trials here)	RCT, double-blind, placebo-controlled 159 patients with NUD: 54 on antacids, 51 on cimetidine and 54 on placebo	3 weeks Antacid suspensions post meals vs. cimetidine, 400 mg b.d., vs. placebo	Neutralisation or suppression of gastric acid of no clinical value in patients with NUD. Recorded pain intensity and pain index scores, also number of days with symptom
Panijel, 1985[334] Germany	RCT, single-blind 60 patients with NUD: 30 in each arm	1 week Cimetidine suspension, 200 mg q.d.s., vs. Maalox™	Cimetidine very effective in acute dyspepsia
Weberg & Berstad, 1988[335] Norway (Counts as two trials here)	RCT, double-blind, placebo-controlled 100 patients with NUD and erosive prepyloric changes	4 weeks Antacids, 1 tablet q.d.s., vs. placebo I vs. pirenzepine, 50 mg b.d., vs. placebo II	Neither pirenzepine nor antacid was significantly superior to placebo. No serious side-effects noted
Prokinetics vs. placebo or others **Cisapride vs. placebo**			
Arts, *et al.*, 1979[336] Belgium	RCT, double-blind, crossover 14 patients with chronic dyspepsia	2 weeks Domperidone, 10 mg t.d.s., vs. placebo	Domperidone significantly reduced dyspepsia
Corinaldesi, *et al.*, 1987[337] Italy	RCT, double-blind, placebo-controlled, crossover 12 patients with 1 year of chronic idiopathic dyspepsia and gastro-paresis (proven delayed gastric emptying)	2 weeks Cisapride, 10 mg t.d.s., vs. placebo	Cisapride significantly shortened gastric emptying. No significant difference in symptom improvement. No side-effects reported
Dworkin, *et al.*, 1994[338] USA	RCT, double-blind, placebo-controlled 11 patients with idiopathic gastroparesis. OGD within 6/12 of trial. Randomisation number unclear	8 weeks Cisapride, 10 mg t.d.s. (double dose if needed), vs. placebo	Cisapride significantly reduced GI symptoms and associated with improvement in solid gastric emptying
Goethals & van de Mierop, 1987[339] Belgium	RCT, double-blind, placebo-controlled, crossover 24 patients with functional dyspepsia	2 successive 4-week periods Cisapride, 4 or 8 mg, vs. placebo	First period, no significant inter-group differences in symptoms Second period favoured cisapride for symptoms of postprandial discomfort, GORD and total symptom score
Hveem, *et al.*, 1996[340] Norway	RCT, double-blind, placebo-controlled, crossover 19 patients with functional dyspepsia and erosive prepyloric changes. Randomisation number unclear	3 days Cisapride, 10 mg t.d.s., vs. placebo	Cisapride reduced postprandial and antral area but had no effect on amplitudes of antral contractions or symptoms in functional dyspepsia
Tatsuta, *et al.*, 1992[341] Japan	RCT, double-blind, placebo-controlled 25 patients with chronic idiopathic dyspepsia	1 week Cisapride, 2.5 mg t.d.s., vs. placebo	Cisapride significantly improved gastric emptying and reduced symptom scores
Testoni, *et al.*, 1990[342] Italy	RCT, double-blind, placebo-controlled 36 patients with chronic antral reflux gastritis	8 weeks Cisapride, 10 mg q.d.s., vs. placebo	No significant difference in symptom scores found but cisapride improved endoscopic gastritis
Van de Mierop, *et al.*, 1979[173] Belgium	RCT, double-blind, placebo-controlled 32 patients with chronic dyspepsia and normal radiological examination	4 weeks Domperidone, 20 mg t.d.s., vs. placebo	Domperidone has beneficial effect on chronic postprandial dyspepsia

continued

Trials excluded on data extraction grounds* (Group B) *contd*

Study/country	Participants	Methods	Outcomes
Domperidone vs. placebo			
Sarin, *et al.*, 1986[343] India	RCT, double-blind, placebo-controlled 44 patients with NUD	2 weeks Domperidone, 10 mg t.d.s., vs. placebo	Domperidone resulted in significant symptom improvement (84%) and to significant shortening of gastric emptying time (by 28%)
Metoclopramide vs. placebo			
Johnson, 1971[344] UK	RCT, double-blind, placebo-controlled, crossover 29 patients with flatulent dyspepsia. Number in each arm unclear	2 weeks Metoclopramide, 10 mg t.d.s., vs. placebo	Metoclopramide effective
Perkel, *et al.*, 1980[345] USA	RCT, double-blind, placebo-controlled 55 patients with delayed gastric emptying and nausea with mixed aetiologies	3 weeks Metoclopramide, 10 mg q.d.s., vs. placebo	Metoclopramide significantly better than placebo in symptomatic improvement
Domperidone vs. metoclopramide			
Moriga, 1980[346] Japan	RCT, double-blind comparison 484 patients with acute gastritis, chronic gastritis (dyspepsia), nervous gastritis and others. Number in each arm unclear	2 weeks Domperidone, 10 mg t.d.s., vs. metoclopramide, 10 mg t.d.s.	Diagnoses and histological grouping of patients unclear in trial Domperidone significantly superior to metoclopramide
Cisapride vs. metoclopramide			
Corinaldesi, *et al.*, 198[759] Italy	RCT, double-blind, crossover 16 patients with NUD and gastroparesis	2 weeks Cisapride, 10 mg t.d.s., vs. metoclopramide, 10 mg t.d.s.	Both significantly improved dyspeptic symptoms and acceleration of gastric emptying rates. No significant differences between the two
Archimandritis, *et al.*, 1992[347] Greece	RCT, double-blind, comparative 60 patients with severe dyspepsia, 20 in each arm	4 weeks Cisapride, 5 mg t.d.s., vs. metoclopramide, 10 mg t.d.s., vs. ranitidine 150 mg b.d.	Prokinetic drugs, especially cisapride, significantly better than ranitidine in controlling symptoms, especially reflux
Cisapride vs. H_2-receptor antagonists			
Archimandritis, *et al.*, 1992[347] Greece	RCT, double-blind, comparative 60 patients with severe dyspepsia	4 weeks Cisapride, 5 mg t.d.s., vs. metoclopramide, 10 mg t.d.s., vs. ranitidine, 150 mg b.d.	Cisapride significantly better than ranitidine in controlling symptoms, especially reflux
H_2-receptor antagonists vs. placebo/others			
Farup, *et al.*, 1991[348] (Larsen, *et al.*, 1991[349]) Norway	RCT, multicentre, multicrossover, double-blind, placebo-controlled 115 patients with NUD	6 weeks Alternating weekly ranitidine, 150 mg b.d., vs. placebo	Impressive symptomatic effect in cimetidine responders. Non-responders had significantly unfavourable effect of ranitidine compared with placebo
Farup, *et al.*, 1997[350] Norway	RCT, multicentre, multicrossover, double-blind, placebo-controlled 226 patients with functional dyspepsia	6 weeks Alternating weekly ranitidine, 150 mg b.d., vs. placebo	Clinical improvement significantly in favour of ranitidine responders compared with non-responders. Ranitidine clinically significant effect in subset of patients with functional dyspepsia
Johannessen, *et al.*, 1988[3] Norway	RCT, multicrossover, double-blind, placebo-controlled 123 patients with NUD	12 days of multicrossover of 6 treatment periods, each lasting 2 days Cimetidine, 400 mg t.d.s., vs. placebo	End of crossover result showed symptoms compatible with GORD significantly more frequent in cimetidine responders than in non-responders

continued

Trials excluded on data extraction grounds* (Group B) *contd*

Study/country	Participants	Methods	Outcomes
***H_2-receptor antagonists vs. placebo/others* contd**			
Kleveland, *et al.*, 1985[351] Norway	RCT, multicrossover, double-blind, placebo-controlled 27 patients with NUD	Multicrossover with treatment periods lasted 2–4 days Cimetidine, 800–1000 mg daily, vs. placebo	This multicrossover model may identify individual cimetidine responders in patients with NUD
Larsen, *et al.*, 1991[349] (Farup, *et al.*, 1991[348]) Norway	RCT, multicentre, multicrossover, double-blind, placebo-controlled 115 patients with NUD	6 weeks with multicrossover alternating weekly Ranitidine, 150 mg b.d., vs. placebo	Large response and relapse rates in group of multicrossover responders verify that this model is reliable method for correctly classifying responders to treatment
Nyren, *et al.*, 1986[72] Sweden	RCT, double-blind, placebo-controlled 159 patients with NUD: antacids 54, cimetidine 51, placebo 54	3 weeks Antacids suspensions after meals vs. cimetidine, 400 mg b.d., vs. placebo	Neutralisation or suppression of gastric acid of no clinical value in patients with NUD. Recorded pain intensity and pain index scores and also number of days with symptoms
Talley, *et al.*, 1986[352] Australia (Counts as two trials here)	RCT, double-blind, crossover, comparison 62 patients with NUD and GORD	4 weeks Cimetidine, 200 mg q.d.s., vs. placebo I vs. pirenzepine, 50 mg b.d., vs. placebo II	Cimetidine superior to placebo but not pirenzepine in decreasing abdominal symptoms. Results at end of crossover period
Olubuyide, *et al.*, 1986[353] Nigeria	RCT, double-blind, placebo-controlled 45 NUD patients compared with 20 patients with duodenal ulcer. Only NUD patients were randomised to either ranitidine (23) or placebo (22)	4 weeks Ranitidine, 150 mg b.d., vs. placebo	No significant difference in symptomatic improvement between treatment and the control groups. Significant difference in acid output studies between NUD and duodenal ulcer patients
Mucosal protecting agents vs. placebo/others			
Sucralfate vs. placebo/others			
Funch-Jensen, *et al.*, 1987[354] Denmark	Prospective RCT but difficult to tell if it was a true RCT. Only 15 of 100 patients with gastritis enrolled in trial. Number of patients in each group unclear	6 weeks Sucralfate, 2000 mg b.d., vs. placebo	Symptomatic and endoscopic improvement seemed promising but too sparse to draw any conclusion
Skoubo-Kristensen, *et al.*, 1989[77] Denmark	RCT, double-blind, placebo-controlled 70 patients with dyspepsia and macroscopic gastritis	6 weeks Sucralfate, 2000 mg b.d., vs. placebo	No significant difference between sucralfate and placebo. Excluded as 37% of patients were on NSAIDs
Bismuth vs. placebo/others			
Humphreys, *et al.*, 1988[355] Republic of Ireland	RCT 135 patients with peptic disease of mixed aetiologies and *C. pylori* gastritis	6 weeks Cimetidine, 400 mg b.d., vs. colloidal bismuth subcitrate, 5 ml q.d.s.	*C. pylori* strongly associated with presence of histological gastritis, which was decreased by colloidal bismuth subcitrate
Marshall, *et al.*, 1993[356] USA	RCT, double-blind, placebo-controlled 50 patients with severe dyspepsia and *H. pylori* gastritis	3 weeks Bismuth subsalicylate, 512 mg q.d.s., vs. placebo	No significant change in level of dyspeptic symptoms. Bismuth subsalicylate suppresses but does not eradicate *H. pylori*. Results reported as number of days in week with symptoms
Rokkas, *et al.*, 1988[357] UK	RCT, double-blind, placebo-controlled 66 patients with NUD; included some patients with *C. pylori* infection	8 weeks De-Nol, two tablets b.d.. vs. placebo	De-Nol group: gastritis improved and symptomatic response better than placebo group. *C. pylori* clearance 83.3%; none in placebo group

continued

Trials excluded on data extraction grounds* (Group B) *contd*

Study/country	Participants	Methods	Outcomes
Antimuscarinics (pirenzepine) vs. placebo/others			
Talley, *et al.*, 1986[352] Australia	RCT, double-blind, crossover, comparison 62 patients with NUD and GORD	4 weeks Cimetidine, 200 mg q.d.s., vs. placebo I vs. pirenzepine, 50 mg b.d., vs. placebo II	Cimetidine superior to placebo but not pirenzepine in decreasing abdominal symptoms. Results at end of crossover period
Dal Monte, *et al.*, 1989[358] Italy	RCT, double-blind, placebo-controlled 50 patients with NUD	4 weeks Pirenzepine, 25 mg b.d. + 50 mg nocte, vs. placebo	Pirenzepine significantly relieved symptoms of dyspepsia and also endoscopic appearance
Weberg & Berstad, 1988[335] Norway	RCT, double-blind, placebo-controlled 100 patients with NUD and erosive prepyloric changes	4 weeks Antacids, 1 tablet q.d.s., vs. placebo I vs. pirenzepine, 50 mg b.d., vs. placebo II	Neither pirenzepine nor antacid significantly superior to placebo. No serious side-effects noted

* ***Reasons for exclusion on data extraction grounds***
Data extraction not possible because:

- *crossover or multicrossover trials in which results were given at the end of the crossover period rather than at the end of the first crossover period*
- *data presentation was unclear, because*
  - *required outcome data not presented.*
  - *results presented in the form of graphs or* p*-values rather than actual patient numbers*
- *data ambiguous when*
  - *number of randomisations unclear*
  - *subgroup analysis not possible in RCTs in which there were mixed aetiologies*
- *symptom scores were presented in short scales (non-parametric data)*
- *trial outcomes considered were in different formats; some trials recorded improvement of dyspepsia symptoms in terms of*
  - *reduction in pain intensity*
  - *number of days in a week with such symptoms*
  - *before-and-after treatment symptom scores*

H. pylori eradication in NUD

Study/country	Participants	Intervention	Outcomes and results
McNulty, 1986 UK	RCT, single-blind, placebo-controlled 50 patients with *C. pylori* associated gastritis with various aetiologies	3 weeks Bismuth subsalicylate, 30 ml q.d.s., vs. placebo I vs. erythromycin ethylsuccinate, 10 ml q.d.s., vs. placebo II	Significantly greater improvement in endoscopic appearances in patients cleared of *C. pylori* compared with those with persistent infection. Symptoms improved with *C. pylori* clearance although not statistically significant
Berstad, 1988 Norway	RCT, double-blind, placebo-controlled 100 patients with NUD and erosive prepyloric changes. *C. pylori* found in 25% of patients	4 weeks Antacids (aluminium–magnesium), 1 tablet q.d.s., vs placebo I; pirenzepine, 50 mg b.d., vs. placebo II	Neither NUD nor erosive prepyloric changes are strongly associated with antral *C. pylori* changes. Aluminium–magnesium antacids may suppress antral *C. pylori* infection without healing gastritis or relieving symptoms
Glupczynski, 1988 Belgium	RCT, double-blind, placebo-controlled 45 patients with *C. pylori* gastritis	8 days Amoxycillin, 1000 mg b.d., vs. placebo	No significant improvement observed in gastritis and clinical symptoms. Reappearance of *C. pylori* and significant worsening of gastritis seen after 2 weeks in all patients
Humphreys, 1988 Republic of Ireland	RCT 135 patients with PUD and *C. pylori* gastritis	6 weeks Cimetidine, 400 mg b.d., vs. colloidal bismuth subcitrate, 5 ml q.d.s.	*C. pylori* strongly associated with presence of histological gastritis, which was decreased by colloidal bismuth subcitrate
Morgan, 1988 Peru	RCT, double-blind, placebo-controlled 106 patients with upper GI symptoms and *C. pylori* gastritis	2 weeks Furazolidone, 400 mg q.d.s., vs. nitrofurantoin, 400 mg q.d.s., vs. placebo	No significant difference in relief in symptoms found between three treatments
Rokkas, 1988 UK	RCT, double-blind, placebo-controlled 66 patients: De-Nol 25, placebo 27. NUD including some patients with *C. pylori* infection	8 weeks De-Nol, two tablets b.d., vs. placebo	De-Nol group: gastritis improved and symptomatic response better than in placebo group. *C. pylori* clearance: De-Nol group 83.3%, placebo group 0
Gad, 1989 Sweden	Uncontrolled pilot trial 186 patients with NUD and *C. pylori*	10 days Erythromycin, 500 mg b.d. vs. Cavedess (bismuth subnitrate and antacids combination)	Combination of antibiotic and bismuth/antacid compound resulted in improvement in histological picture, disappearance of *C. pylori* and amelioration of symptoms
Gad, 1989 Italy	RCT, double-blind, placebo-controlled, multicentre 128 patients with NUD and *C. pylori* gastritis: pirenzepine 66, placebo 62. 84% completed trial	4 weeks Pirenzepine, 50 mg b.d., vs. placebo	Improvement in endoscopic and clinical findings but no change of degree of mucosal inflammation or extent of colonisation by *C. pylori*
Lambert, 1989 Australia	RCT, double-blind, placebo-controlled 82 with NUD +/– *C. pylori* infection: 48 *C. pylori*-positive: treatment 22, placebo 26. 30 *C. pylori*-negative: treatment 16, placebo 14	4 weeks Bismuth subcitrate, 4 tablets daily, vs. placebo	Clearance of *C. pylori* and histological improvement associated with significant decrease in symptoms. In *C. pylori*-negative patients, improvement occurred in both placebo and treatment groups
Lanza, 1989 USA	RCT, blinding not mentioned 20 patients with variety of upper GI complaints and *C. pylori* gastritis	3 weeks Bismuth subsalicylate, 525 mg q.d.s., vs. placebo	Bismuth subsalicylate provides short-term clearance of *C. pylori* in antral mucosa which is associated with an improvement in histological diagnosis
Loffeld, 1989 The Netherlands	RCT, double-blind, placebo-controlled 57 patients: treatment 26, placebo 24 NUD with *C. pylori* gastritis	4 weeks Colloidal bismuth subcitrate, 240 mg daily, vs. placebo	Subjective complaints improved in both groups except for nausea and meteorism that improved more in colloidal bismuth subcitrate group. Significant reduction in *C. pylori* colonisation and gastritis score

continued

H. pylori eradication in NUD *contd*

Study/country	Participants	Intervention	Outcomes and results
Unge, 1989 Sweden	Randomised, double-blind, pilot study 24 *C. pylori*-positive patients	2 weeks Omeprazole, 40 mg daily, + amoxycillin, 750 mg b.d., vs. omeprazole, 40 mg daily, vs. amoxycillin, 750 mg b.d.	Omeprazole, as a powerful inhibitor of gastric acid secretion, has been identified as a promising therapeutic means of combating *C. pylori* infection
Kang, 1990 Singapore	RCT, double-blind, placebo-controlled 73 patients with food-related abdominal pain: treatment 21, placebo, 19	8 weeks Colloidal bismuth subcitrate, 1 tablet q.d.s. versus placebo	Colloidal bismuth subcitrate benefited those with gastritis but not those without
Kazi, 1990 India	RCT 52 patients, 26 in each arm. Dyspepsia and *H. pylori* gastritis	3 weeks Bismuth salicylate, 500 mg t.d.s., vs. placebo	Resolution of gastritis and improvement of symptoms were significantly better in patients in whom *H. pylori* cleared compared with those in whom it persisted
McNulty, 1990 UK	RCT, single-blind, placebo-controlled 50 patients; upper GI symptoms with *C. pylori* gastritis	3 weeks Bismuth subsalicylate, 30 ml q.d.s., vs. placebo I vs. erythromycin ethylsuccinate, 10 ml q.d.s., vs. placebo II	Significantly greater improvement in endoscopic appearances in patients cleared of *C. pylori* compared with those with persistent infection. Heartburn improved: bismuth subsalicylate 50%, placebo 17%
Xiao, 1990 Republic of China	RCT 72 patients with dyspepsia and *H. pylori* gastritis	3 weeks Furazolidone, 500 mg t.d.s., vs. metronidazole, 200 mg t.d.s., vs. placebo	Furazolidone effective in clearance of *H. pylori* and provided marked improvement in inflammatory infiltration in gastric mucosa and in symptoms
Goh, 1991 Malaysia	RCT, double-blind, placebo-controlled 71 patients with NUD +/– *H. pylori* infection: 40 H. pylori-positive, treatment 21, placebo 19; 31 *H. pylori*-negative, treatment 17, placebo 14. Non-erosive duodenitis included. 84.5% completed trial	4 weeks Colloidal bismuth subcitrate, 2 tablets b.d., vs. placebo	All groups reported improvement in symptom scores. In *H. pylori*-positive group, colloidal bismuth subcitrate-treated group recorded significantly greater improvement than other groups. 12/16 patients relapsed 1 month after withdrawal of treatment
Patchett, 1991 Republic of Ireland	Not RCT 90 patients with NUD and *H. pylori* gastritis	Colloidal bismuth subcitrate, 120 mg q.d.s., for 4 weeks vs. metronidazole, 400 mg t.d.s., + amoxycillin, 500 mg t.d.s., for 1 week vs. colloidal bismuth subcitrate, 120 mg q.d.s., for 4 weeks + metronidazole, 400 mg t.d.s., for 1 week	Gastritis score improved with *H. pylori* eradication. However, mean symptom scores improved whether or not gastritis improved. Antral infection with *H. pylori* does not have an important aetiological role in NUD
Holcome, 1992 UK	RCT 130 patients with NUD and *H. pylori* infection	4 weeks *Gelusil*®, 1 tablet q.d.s., vs. De-Noltab, 240 mg q.d.s., for 28 days together with amoxycillin, 500 mg q.d.s., for first 14 days	Bismuth and amoxycillin significantly better at achieving symptom resolution than antacid but symptomatic improvement did not relate to *H. pylori* clearance
Nafeeza, 1992 Malaysia	RCT, double-blind, controlled 48 patients with NUD and *H. pylori* gastritis	Colloidal bismuth subcitrate, 480 mg b.d., for 28 days + ampicillin, 500 mg q.d.s., for first 10 days vs. colloidal bismuth subcitrate for 28 days + placebo matched to ampicillin vs. ampicillin, 500 mg q.d.s., for first 10 days + placebo matched to colloidal bismuth subcitrate for 28 days	Suppression of *H. pylori* on combined therapy but none in single therapy. Suppression of *H. pylori* associated with both histological and symptomatic improvement

continued

H. pylori eradication in NUD *contd*

Study/country	Participants	Intervention	Outcomes and results
Vaira, 1992 Italy	RCT, double-blind, placebo-controlled 80 patients, 40 in each arm. *H. pylori*-associated NUD. Follow-up at 4 weeks post-treatment 97.5%. Eradication rate 54%	4 weeks Colloidal bismuth subcitrate 240 mg b.d., vs. placebo	Colloidal bismuth subcitrate is effective treatment for *H. pylori* associated NUD with improved gastric antral histological appearances and has a beneficial effect on symptoms
Frazzoni, 1993 Italy	Two RCTs, double-blind, placebo-controlled 53 patients with dyspepsia. Treatment regimen depends on *H. pylori* status	*H. pylori*-positive group: colloidal bismuth subcitrate, 240 mg b.d., for 28 days + metronidazole, 500 mg t.d.s., for 10 days vs. placebo *H. pylori*-negative group: cisapride, 10 mg t.d.s., for 28 days vs. placebo	Symptomatic remission rates following 1-month wash-out period in both treatment groups no higher than in controls. Bulbar and antral biopsies are not useful in clinical management
Labenz, 1993 Germany	Open clinical trial 180 patients with *H. pylori*-associated NUD or PUD. Only 17 patients had NUD	5 groups: 4 groups with various dosages of omeprazole + amoxycillin in treatment periods vs. omeprazole alone	Omeprazole-enhanced amoxycillin therapy is a simple and effective approach to the eradication of *H. pylori* colonisation
Marshall, 1993 USA	RCT, double-blind, placebo-controlled 2-week placebo run-in period. 50 patients with severe dyspepsia and *H. pylori* gastritis	3 weeks Bismuth subsalicylate, 512 mg q.d.s., vs. placebo	No significant change in level of dyspeptic symptoms. Bismuth subsalicylate suppresses but does not eradicate *H. pylori*. Results reported as number of days with symptoms in a week
Veldhuyzen van Zanten, 1995 [abstract] Canada	RCT 53 *H. pylori*-positive NUD patients	Bismuth subsalicylate, 302 mg q.d.s., + amoxycillin, 500 mg t.d.s., + metronidazole, 500 mg t.d.s., vs. placebo	No statistically significant difference between mean dyspepsia symptom score in eradication and control groups
David, 1996 [abstract] USA	RCT 41 patients with NUD and *H. pylori* infection confirmed by rapid urease test	2 weeks Ranitidine, 300 mg b.d., + amoxycillin, 500 mg t.d.s., + metronidazole, 250 mg t.d.s., vs. ranitidine, 300 mg b.d., + placebo antibiotics	Trend for *H. pylori* eradication to resolution symptoms at 6 weeks compared with placebo (82% vs. 62%) but no statistically significant difference
Kumar, 1996 India	RCT, double-blind, placebo-controlled trial 81 patients, colloidal bismuth subcitrate 18, placebo I 15, sucralfate 15, placebo II 15. NUD and *H. pylori* infection	Colloidal bismuth subcitrate, 240 mg b.d., vs. placebo I to sucralfate, and sucralfate, 2 g b.d., vs. placebo II to sucralfate	Colloidal bismuth subcitrate is more effective than sucralfate in inducing endoscopic and histology healing of *H. pylori*-related gastritis in NUD patients
Tham, 1996 Republic of Ireland	RCT 80 patients with dyspepsia of various aetiology including PUD, oesophagitis and those with normal endoscopy and *H. pylori* infection. Subgroup analysis not possible	2 weeks Omeprazole, 20 mg daily, + amoxycillin, 500 mg t.d.s., + metronidazole, 400 mg t.d.s., vs. ranitidine, 600 mg b.d., + amoxycillin, 500 mg t.d.s., + metronidazole, 400 mg t.d.s., vs. omeprazole, 20 mg daily, + placebo vs. omeprazole, 20 mg daily, + clarithromycin, 500 mg t.d.s.	*H. pylori* eradication rate with high dose ranitidine + amoxycillin + metronidazole may be similar to that of low dose omeprazole + same antibiotics or omeprazole + clarithromycin. Overall eradication rates low due to high incidence of metronidazole resistance
Hazell, 1997 Australia	RCT, double-blind, double-dummy 101 patients with PUD and NUD and H. pylori infection	4 weeks Lansoprazole, 30 mg daily, + placebo t.d.s. vs. lansoprazole, 30 mg daily, + amoxycillin, 500 mg t.d.s.	Inflammation improved in patients treated with lansoprazole + amoxycillin. Both duodenal ulcer and NUD patients showed improvement in symptoms irrespective of treatment arm. (Data not shown in article). Author contacted but no reply

continued

H. pylori eradication in NUD *contd*

Study/country	Participants	Intervention	Outcomes and results
Mitty, 1997 [abstract] USA	RCT 15 *H. pylori*-positive patients with dyspepsia and normal endoscopy	2 weeks Omeprazole, 40 mg o.d., clarithromycin, 500 mg t.d.s., vs. placebo	Statistically significant reduction in mean abdominal pain score in eradication group compared with placebo group at 6 months
Parente, 1998 Italy	RCT 38 patients with functional dyspepsia and *H. pylori* gastritis	Omeprazole, 40 mg daily, + clarithromycin, 250 mg b.d., + tinidazole, 500 mg b.d., for 1 week vs. ranitidine, 300 mg daily, for 3 weeks	Eradication of *H. pylori* in long run significantly reduces gastrin and pepsinogen I release as result of improvement in underlying antral gastritis, but this is not accompanied by modifications of gastric emptying of solids or acid secretion
Passos, 1998 [abstract] Brazil	RCT 81 *H. pylori*-positive patients with functional dyspepsia	5 days Amoxycillin, 500 mg t.d.s., + metronidazole, 250 mg t.d.s., + furazolidone, 200 mg t.d.s., vs. placebo	Mean dyspepsia symptom score at 36 months similar between two groups with no statistically significant differences
Catalano, 1999 Italy	RCT 126 elderly NUD patients with *H. pylori* infection	2 weeks Bismuth + amoxycillin + metronidazole vs. omeprazole + amoxycillin	Both regimens eradicated *H. pylori* in over 60% of patients with no significant difference between treatments in reducing dyspepsia symptoms
Hsu, 1999 [abstract] Taiwan	RCT 71 patients with NUD and *H. pylori* infection	Lansoprazole 'quadruple therapy' vs. placebo	Patients with successful eradication had significant improvement in symptoms at end of 12 months compared with control group
Florent, 2000 [abstract] France	RCT 121 patients with epigastric pain and *H. pylori* gastritis but no ulcer disease	10 days Lansoprazole, 30 mg o.d., + amoxycillin, 1000 mg b.d., + clarithromycin, 500 mg b.d., vs. placebo	31% of eradication group asymptomatic at 12 months compared with 22% of placebo group. Difference not statistically significant

Summary of reasons for trials being excluded from the *H. pylori* eradication review

Study	Inclusion criteria				
	Prior endoscopy excluding PUD and oesophagitis	Predefined *H. pylori* eradication regimen	Comparative intervention	Dyspeptic or quality-of-life scores	RCT
Antacids/pirenzepine vs. placebo					
Berstad, 1988		No		No	
Antacids vs. bismuth + amoxycillin					
Holcome, 1992		No			
Bismuth vs. placebo					
Goh, 1991		No			
Kang, 1990		No			
Kazi, 1990		No			
Kumar, 1996		No			
Lambert, 1989		No			
Lanza, 1989		No		No	
Loffeld, 1989		No			
Marshall, 1993		No			
Rokkas, 1988		No			
Vaira, 1992		No			
Bismuth and metronidazole vs. placebo					
Frazzoni, 1993		No			
Bismuth vs. erythromycin vs. placebo					
McNulty, 1986	No	No			
McNulty, 1990	No	No			
Bismuth vs. cimetidine					
Humphreys, 1988	No	No		No	
Bismuth vs. ampicillin vs. bismuth + ampicillin					
Nafeeza, 1992		No			
Bismuth vs. metronidazole + ampicillin vs. bismuth + metronidazole					
Patchett, 1991		No			No
Omeprazole vs. omeprazole + amoxycillin					
Labenz, 1993				No	No
Unge, 1989	No			No	No
Omeprazole + amoxycillin + clarithromycin vs. ranitidine					
Parente, 1998				No	
Omeprazole + amoxycillin + metronidazole vs. ranitidine + amoxycillin + metronidazole vs. omeprazole + clarithromycin vs. omeprazole + placebo					
Tham, 1996	No			No	
Lansoprazole + amoxycillin vs. lansoprazole					
Hazell, 1997				No	
Amoxycillin vs. placebo					
Glupczynski, 1988		No			
Pirenzepine vs. placebo					
Gad, 1989		No			
Gad, 1989		No			No
Furazolidone vs. metronidazole vs. placebo					
Xiao, 1990		No			
Furazolidone vs. nitrofurantoin vs. placebo					
Morgan, 1988		No			
Bismuth + amoxycillin + metronidazole vs. omeprazole + amoxycillin					
Catalano, 1999		No			

Appendix 4

Other summary tables

Characteristics of patients recruited into NUD trials

Study	Dyspepsia			Source	Recruitment	Seen by specialists
	Definition	Duration	Subgroups			
Antacids						
Gotthard, *et al.*, 1988[179]	Yes	3 months	No	2	Outpatients	Yes
H_2-receptor antagonists vs. placebo						
Delattre, *et al.*, 1985[181]	Yes	3 months	No	Unclear	Unclear	Unclear
Gotthard, *et al.*, 1988[179]	Yes	3 months	No	2	Outpatients	Yes
Hadi, 1989[180]	Yes	No	No	2	Outpatients	Unclear
Hansen, *et al.*, 1998[164]	Yes	88 months (mean)	4	1	Outpatients	Unclear
Kelbaek, *et al.*, 1985[183]	Yes	1 month	Ulcer-like pain	1	Outpatients	Yes
Nesland & Berstad, 1985[182]	Yes	6 months	Epigastric pain	2	Outpatients	Unclear
Saunders, *et al.*, 1986[184]	Yes	2 weeks	Epigastric pain	1	Outpatients	Unclear
Singal, *et al.*, 1989[73]	Yes	1 month	Epigastric pain	Unclear	Unclear	Unclear
H_2-receptor antagonists vs. antacids						
Casiraghi, *et al.*, 1986[199]	Yes	1 month	No	Unclear	Unclear	Unclear
Gotthard, *et al.*, 1988[179]	Yes	3 month	No	2	Outpatients	Yes
H_2-receptor antagonists vs cisapride						
Carvalhinhos, *et al.*, 1995[198]	Yes	1 month	4	2	Outpatients	Unclear
Hansen, *et al.*, 1998[164]	Yes	88 months (mean)	4	1	Outpatients	Unclear
H_2-receptor antagonists vs. sulcrafate						
Misra, *et al.*, 1992[201]	Yes	1 month	No	Unclear	Unclear	Unclear
H_2-receptor antagonists vs. pirenzipine						
Dal Monte, *et al.*, 1989[200]	No	No	No	2	Outpatients	Unclear
Fedeli, *et al.*, 1982[285]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Prokinetics vs. placebo/others						
Cisapride vs. placebo						
Agorastos, *et al.*, 1991[174]	Yes	1 month	No	Unclear	Unclear	Unclear
Al-Quorain, *et al.*, 1995[165]	Yes	No	3	2	Outpatients	Unclear
Champion, *et al.*, 1997[167]	Yes	1 month	No	2	Outpatients	Unclear
Chung, 1993[168]	Yes	3 months	No	Unclear	Outpatients	Unclear
Creytens, *et al.*, 1984[176]	Yes	No	No	Unclear	Unclear	Unclear
De Nutte, *et al.*, 1989[169]	Yes	2 months	No	Unclear	Unclear	Unclear
Deruyttere, *et al.*, 1987[178]	Yes	1 month	No	Unclear	Outpatients	Unclear
Francois & DeNutte, 1987[170]	Yes	3 months	No	2	Outpatients	Unclear
Hannon, 1987[171]	Unclear	No	2	Unclear	Unclear	Unclear
Hansen, *et al.*, 1998[164]	Yes	88 months (mean)	4	1	Outpatients	Unclear
Jian, *et al.*, 1989[283]	Yes	3 months	No	Unclear	Unclear	Unclear

continued

Characteristics of patients recruited into NUD trials *contd*

Study	Dyspepsia			Source	Recruitment	Seen by specialists
	Definition	Duration	Subgroups			
Cisapride vs. placebo contd						
Kellow, *et al.*, 1994[172]	Yes	3 months	2	Unclear	Unclear	Unclear
Rosch, 1987[82]	Yes	No	2	2	Outpatients	No
Testoni, *et al.*, 1990[177]	Yes	6 months	No	Unclear	Unclear	Unclear
Yeoh, *et al.*, 1997[284]	Yes	4 months	No	Unclear	Unclear	Unclear
Domperidone vs. placebo						
Bekhti & Rutgeerts, 1979[166]	Unclear	No	No	Unclear	Unclear	Unclear
Cisapride vs. metoclopramide						
Fumagali & Hammell, 1994[84]	Yes	1 month	2	2	Outpatients	Yes
Cisapride vs. domperidone						
Halter, *et al.*, 1997[202]	Yes	1 month	2	2	Unclear	Unclear
Metoclopramide vs. domperidone						
van Outryve, *et al.*, 199385	Yes	2.8 months (mean)	No	Unclear	Outpatients	Unclear
PPI						
Talley, *et al.*, 1998[185]	Yes	1 month	4	1 and 2	Outpatients	Yes
Mucosal protecting agents						
Bismuth vs. placebo						
Goh, *et al.*, 1991[191]	Yes	1 month	No	Unclear	Unclear	Unclear
Kang, *et al.*, 1990[187]	Yes	1 month	No	Unclear	Unclear	Unclear
Kazi, *et al.*, 1990[188]	Yes	No	No	Unclear	Unclear	Unclear
Kumar, *et al.*, 1996[186]	Yes	1 month	No	2	Outpatients	Unclear
Lambert, *et al.*, 1989[192]	Yes	3 months	No	2	Outpatients	Unclear
Loffeld, *et al.*, 1978[189]	Yes	No	No	Unclear	Unclear	Unclear
Vaira, *et al.*, 1992[190]	No	No	No	2	Unclear	Unclear
Sucralfate vs. placebo						
Gudjonsson, *et al.*, 1993[197]	Yes	1 month	No	Private	Outpatients	Yes
Kairaluoma, *et al.*, 1987[76]	Yes	3 months	No	2	Outpatients	No
Kumar, *et al.*, 1996[186]	Yes	1 month	No	2	Outpatients	Unclear
Sucralfate vs. bismuth						
Kumar, *et al.*, 1996[186]	Yes	1 month	No	2	Outpatients	Unclear
Misoprostol vs. placebo						
Hausken, *et al.*, 1990[195]	Yes	3 months	No	2	Outpatients	Unclear
Pazzi, *et al.*, 1994[196]	Yes	Unclear	No	2	Outpatients	Unclear
Antimuscarinics vs. placebo						
Gad & Dobrillon, 1989[193]	Yes	3 months	Ulcer-like pain	Unclear	Outpatients	Unclear
Hradsky & Wikander, 1982[194]	No	No	No	Unclear	Outpatients	Unclear

Quality of trials included in the pharmacological interventions for NUD

Study	Randomisation	Concealment	Masking	Drop-out	ITT	Completion (%)
Antacids						
Gotthard, *et al.*, 1988[179]	Unclear	Unclear	Double-blind	Yes	No	77
H_2-receptor antagonists vs. placebo						
Delattre, *et al.*, 1985[181]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	Yes	94
Gotthard, *et al.*, 1988[179]	Unclear	Unclear	Double-blind	Yes	No	77
Hadi, 1989[180]	Unclear	Unclear	Double-blind	Yes	No	86
Hansen, *et al.*, 1998[164]	Truly random	Adequate	Double-blind, patients masked (identical placebo)	No	No	85
Kelbaek, *et al.,* 1985[183]	Unclear	Unclear	Double-blind, patients, clinicians masked (identical placebo)	Yes	No	96
Nesland & Berstad, 1985[182]	Unclear	Unclear	Double-blind	Yes	No	90
Saunders, *et al.*, 1986[184]	Truly random	Adequate	Double-blind, patients, clinicians masked (identical placebo)	Yes	No	88%
Singal, *et al.*, 1989[73]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	84%
H_2-receptor antagonists vs. antacids						
Casiraghi, *et al.*, 1986[199]	Truly random	Unclear	Double-blind, patients, clinicians masked (identical placebo)	No	No	83
Gotthard, *et al.*, 1988[179]	Unclear	Unclear	Double-blind	Yes	No	77
H_2-receptor antagonists vs. cisapride						
Carvalhinhos, *et al.*, 1995[198]	Truly random	Adequate	Double-blind, patients, clinicians masked (identical placebo)	Yes	Yes	93
Hansen, *et al.*, 1998[164]	Truly random	Adequate	Double-blind, patients masked (identical placebo)	No	No	85
H_2-receptor antagonists vs. sucralfate						
Misra, *et al.*, 1992[201]	Unclear	Unclear	Open trial	Yes	Yes	87
H_2-receptor antagonists vs. pirenzepine						
Dal Monte, *et al.*, 1989[200]	Unclear	Unclear	Double-blind, patients, clinicians, outcome assessor masked (identical placebo)	Yes	No	95
Fedeli, *et al.*, 1982[285]	Unclear	Unclear	Unclear	None	100%	100
Prokinetics vs. placebo						
Cisapride vs. placebo						
Agorastos, *et al.*, 1991[174]	Truly random	Adequate	Double-blind, patients, clinicians, outcome assessor masked (identical placebo)	Yes	100%	100

continued

Quality of trials included in the pharmacological interventions for NUD *contd*

Study	Randomisation	Concealment	Masking	Drop-out	ITT	Completion (%)
***Prokinetics vs. placebo* contd**						
Cisapride vs. placebo *contd*						
Al-Quorain, *et al.*, 1995[165]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	91
Champion, *et al.*, 1997[167]	Unclear	Unclear	Double-blind	Yes	Yes	78
Chung, 1993[168]	Unclear	Unclear	Double-blind	No	No	97
Creytens, 1984[176]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	None	100%	100
De Nutte, *et al.*, 1989[169]	Unclear	Unclear	Double-blind	None	100%	100
Deruyttere, *et al.*, 1987[178]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	93
Francois & DeNutte, 1987[170]	Unclear	Unclear	Double-blind	Yes	No	94
Hannon, 1987[171]	Truly random	Adequate	Double-blind, patients, clinicians, outcome assessor masked (identical placebo)	None	100%	100
Hansen, *et al.*, 1998[164]	Truly random	Adequate	Double-blind, patients masked (identical placebo)	No	No	85
Jian, *et al.*, 1989[183]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	Yes	82
Kellow, *et al.*, 1994[172]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	92
Rosch, 1987[82]	Unclear	Unclear	Double-blind	Unclear	No	84
Testoni, *et al.*, 1990[177]	Unclear	Unclear	Single-blind	None	100%	100
Yeoh, *et al.*, 1997[284]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	73
Domperidone vs. placebo						
Bekhti & Rutgeerts, 1979[166]	Unclear	Unclear	Double-blind, patients, clinicians, outcome assessor masked (identical placebo)	None	100%	100
Cisapride vs. metoclopramide						
Fumagali & Hammell, 1994[84]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	Yes	95
Cisapride vs. domperidone						
Halter, *et al.*, 1997[202]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	Yes	89

continued

Quality of trials included in the pharmacological interventions for NUD *contd*

Study	Randomisation	Concealment	Masking	Drop-out	ITT	Completion (%)
***Prokinetics vs. placebo* contd**						
Metoclopramide vs. domperidone						
van Outryve, *et al.*, 1993[85]	Unclear	Unclear	Double-blind	Yes	No	86
PPI						
Talley, *et al.*, 1998[185]	Truly random	Adequate	Double-blind, patients, clinicians, outcome assessor masked (identical placebo)	Yes	Yes	97
Mucosal protecting agents						
Bismuth vs. placebo						
Goh, *et al.*, 1991[191]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	85
Kang, *et al.*, 1990[187]	Truly random	Adequate	Double-blind, patients, clinicians masked (identical placebo)	Yes	No	70
Kazi, *et al.*, 1990[188]	Unclear	Unclear	Patients masked (identical placebo)	None	100%	100
Kumar, *et al.*, 1996[186]	Truly random	Adequate	Double-blind, patients, clinicians masked (identical placebo)	Yes	No	78
Lambert, *et al.*, 1989[192]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	95
Loffeld, *et al.*, 1978[189]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	No	No	88
Vaira, *et al.*, 1992[190]	Truly random	Adequate	Double-blind, patients, clinicians, outcome assessor masked (identical placebo)	Yes	No	98
Sucralfate vs. placebo						
Gudjonsson, *et al.*, 1993[197]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	Yes	91
Kairaluoma, *et al.*, 1987[76]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	86
Kumar, *et al.*, 1996[186]	Truly random	Adequate	Double-blind, patients, clinicians masked (identical placebo)	Yes	No	78
Sucralfate vs. bismuth						
Kumar, *et al.*, 1996[186]	Truly random	Adequate	Double-blind, patients, clinicians masked (identical placebo)	Yes	No	78
Misoprostol vs. placebo						
Hausken, *et al.*, 1990[195]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	Yes	84

continued

Quality of trials included in the pharmacological interventions for NUD *contd*

Study	Randomisation	Concealment	Masking	Drop-out	ITT	Completion (%)
***Mucosal protecting agents* contd**						
Misoprostol vs. placebo *contd*						
Pazzi, *et al*., 1994[196]	Unclear	Unclear	Double-blind	Yes	No	83
Antimuscarinics vs. placebo						
Gad & Dobrillon, 1989[193]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	84
Hradsky & Wikander, 1982[194]	Unclear	Unclear	Double-blind, patients masked (identical placebo)	Yes	No	81

Appendix 5

Detailed results of DES model for the management of dyspepsia in primary care

Models of the management of dyspepsia in primary care

Study/country	Interventions modelled	Type of model	Costs included	Benefits measured	Principal findings	Comments
Read, *et al.*, 1982[359] USA	Antacids alone H_2-receptor antagonists alone Barium meal and H_2-receptor antagonists for gastric ulcer Barium meal and endoscopy for gastric ulcer	Expected utility-based cost-effectiveness	Direct costs: medication; tests; office visits; surgery	Mortality Pain-free days Pain-free patients	Antacids alone cheapest H_2-receptor antagonists alone best symptom relief Barium meal then endoscopy lowest mortality	No PPIs Used barium meal rather than endoscopy Out-of-date No sensitivity analysis
Sonnenberg, 1996[129] USA	Test-and-treat	Simple cost–benefit model	Direct costs: medication; tests; endoscopy; office visits	Costs of prevented: peptic ulcer; gastric cancer	Test-and-treat likely to be cost-saving Sensitive to cost of PUD, prevalence of *H. pylori*, effect of eradication in NUD	No direct comparisons Considered PUD and NUD only. US costs very high, e.g. ulcer disease $4000
Silverstein, *et al.*, 1996[127] USA	Early endoscopy H_2-receptor antagonists and endoscopy for failure	Expected utility-based cost–benefit	Direct costs: medication; tests; endoscopy; office visits	Differences in life expectancy Costs of prevented: peptic ulcer; gastric cancer	7–10% less cost over 1 year with initial H_2-receptor antagonist Average loss in life expectancy of 0.82 years for a 55-year-old man with gastric cancer not initially endoscoped	No PPI No *H. pylori* eradication Life-years lost apply only to older patients
Phillips & Moore, 1996[230] UK	Test-and-treat	Simple cost–benefit	Direct costs: medication; tests; endoscopy	Costs of prescribing avoided	Over 5 years, test-and-treat might save £225–475 per newly presenting patient with dyspepsia	Limited analysis of costs. Many direct costs missing
Briggs, *et al.*, 1996[20] UK	Cimetidine alone Test-and-endoscope	Markov	Direct costs: medication; tests; endoscopy; consultations	Cumulative costs over 10 years Proportion of time spent without a recurrent ulcer	Costs of test-and-endoscope may take up to 7 years to recoup in prescribing savings. Varied from 5 to 18 years on sensitivity analysis	PPIs not included *H. pylori* test-and-treat strategy not included
Ebell, *et al.*, 1997[231] USA	*H. pylori* eradication PPI Early endoscopy (*H. pylori* eradication for peptic ulcer) Barium meal Test-and-treat Early endoscopy (with test to confirm *H. pylori* if peptic ulcer) Barium meal (with test to confirm *H. pylori* if peptic ulcer).	Cost–utility analysis	Payer perspective: charges used as proxies for costs; medication; tests; office visits; X-rays; endoscopies	QALYs applied from routine data	Cost-effective strategies were PPI only test-and-treat and empirical *H. pylori* eradication Benefits were very similar: main differences were in costs with empirical eradication being cheapest	Prescribing strategy limited to PPI alone, neglecting cheaper alternatives US costs for health resource utilisation and prescribing higher than in UK

continued

Models of the management of dyspepsia in primary care *contd*

Study/country	Interventions modelled	Type of model	Costs included	Benefits measured	Principal findings	Comments
Laheij, *et al.*, 1997[228] The Netherlands	Initial PPI for 2 weeks, then modelled treatment failures to: endoscopy; further 10 weeks PPI then *H. pylori* test-and-treat for failures, then endoscopy if relapse	Cost minimisation	Payer perspective: medication; tests; consultations; X-rays; endoscopies	N/A	PPI followed by test-and-treat for failures was cheaper ($517 vs. $590 over 1 year) Predicted 26% decrease in endoscopy use	Analysis limited to costs and use of endoscopy. No analysis of effectiveness in terms of symptom relief
Ofman, *et al.*, 1997[232] USA	Test-and-endoscopy Test-and-treat	Cost minimisation	Medicare costs for diagnostic and therapeutic procedures Medication costs	Assumed to be equal	Test-and-treat on average $465 cheaper per patient at 1 year. Robust to sensitivity analyses	No differences in effectiveness modelled No prescribing strategies explored
Sonnenberg, *et al.*, 1997[233] USA	Test-and-treat Empirical *H. pylori* eradication	Simple cost–benefit	Direct costs: medication; tests; endoscopy; office visits	Costs of prevented: peptic ulcer; gastric cancer	Test-and-treat likely to be more cost-saving than empirical *H. pylori* eradication Sensitive to effect of eradication in NUD	US costs very high, e.g. ulcer disease $4000
McIntyre, *et al.*, 1997[234] UK	Test-and-treat H_2-receptor antagonists at under 45 years of age, with early endoscopy at over 45 years	Cost minimisation	Direct costs: medication; tests; endoscopy; consultations	N/A	Test-and-treat cheaper over 5 years (average £113.89 vs. £155.64)	No differences in effectiveness explored
Delaney & Hobbs, 1998[360] UK	H_2-receptor antagonists alone Early endoscopy Test-and-endoscope	Markov	Direct costs: medication; tests; endoscopy; consultations	Measured in terms of recurrent ulcers	Test-and-endoscope more cost-effective than early endoscopy to all limits of sensitivity analysis. Payback for endoscopy varied from 1.5 to 15 years, depending on prescribing costs	Effectiveness limited to recurrence of peptic ulcers. NUD and reflux not considered

Summary tables of sensitivity analyses undertaken (pages 171–174)

These tables summarise the various experiments listed in the sensitivity analysis. In each row, the non-dominated strategies are numbered in order from cheapest and least effective to most expensive and most effective. Unnumbered strategies are dominated under the assumptions used for that row.

Reflux more likely than NUD	Reflux more likely if *H. pylori* negative	*H. pylori* prevalence 60%	*H. pylori* prevalence 10%	Base	Case	Initial strategy	Prescribing strategy
1	1	1	1	1		Medication only	Antacid only
2	2	2	2	2		Test & eradicate	Antacid only
3	3	3	3	3		Medication only	H_2-receptor antagonist only
		7	4			Test & eradicate	H_2-receptor antagonist only
		8				Eradicate all	H_2-receptor amtagonist only
						Medication only	Prokinetics only
						Test & eradicate	Prokinetics only
						Medication only	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
						Test & eradicate	Prokinetics, PPI, H_2-receptor antagonist, antacid, stay
						Test & eradicate	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
						Medication only	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
4	4	4	5	4		Medication only	Antacid, H_2-receptor antagonist, PPI, down
5	5	5	6	5		Medication only	PPI, H_2-receptor antagonist, antacid, stay
6	6	6	7	6		Medication only	Antacid, H_2-receptor antagonist, PPI, stay
						Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, down
		10				Test & eradicate	Antacid, H_2-receptor antagonist, PPI, down
		11				Test & eradicate	PPI, H_2-receptor antagonist, antacid, stay
		12				Test & eradicate	Antacid, H_2-receptor antagonist, PPI, stay
						Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
						Test & eradicate	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
7	7	9	8	7		Medication only	PPI only
						Test & eradicate	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
		13				Eradicate all	Antacid, H_2-receptor antagonist, PPI, stay
8	8	14	9	8		Test & eradicate	PPI only
		15				Eradicate all	PPI only
			10			Medication only	PPI or prokinetics until one of them works
9	9	16	11	9		Test & eradicate	PPI or prokinetics until one of them works

Case	Base	Oesophagitis, 10% of reflux	Oesophagitis, 50% of reflux	Near patient test only for *H. pylori*	Urea breath test only for *H. pylori*	Lifetimes more widespread	Lifetimes less widespread	Lifetimes shorter	Lifetimes longer	Initial strategy	Prescribing strategy
										Initial strategy	**Prescribing strategy**
	1	1	1	1	1	1	1	1	1	Medication only	Antacid only
	2	2	2	2	2	2	2	2	2	Test & eradicate	Antacid only
	3	3	3	3	3	3	3	3	3	Medication only	H_2-receptor antagonist only
										Test & eradicate	H_2-receptor antagonist only
										Eradicate all	H_2-receptor antagonist only
										Medication only	Prokinetics only
										Test & eradicate	Prokinetics only
										Medication only	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
										Test & eradicate	Prokinetics, PPI, H_2-receptor antagonist, antacid, stay
										Test & eradicate	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
										Medication only	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
	4	4	4	4	4	4	4	4	4	Medication only	Antacid, H_2-receptor antagonist, PPI, down
	5	5	5	5	5	5	5	5	5	Medication only	PPI, H_2-receptor antagonist, antacid, stay
	6	6	6	6	6	6	6	6	6	Medication only	Antacid, H_2-receptor antagonist, PPI, stay
										Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, down
										Test & eradicate	Antacid, H_2-receptor antagonist, PPI, down
										Test & eradicate	PPI, H_2-receptor antagonist, antacid, stay
										Test & eradicate	Antacid, H_2-receptor antagonist, PPI, stay
										Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
										Test & eradicate	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
	7	7	7	7	7	7	7	7	7	Medication only	PPI only
										Test & eradicate	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
										Eradicate all	Antacid, H_2-receptor antagonist, PPI, stay
	8	8	8	8	8	8	8	8	8	Test & eradicate	PPI only
										Eradicate all	PPI only
										Medication only	PPI or prokinetics until one of them works
	9	9	9	9	9	9	9	9	9	Test & eradicate	PPI or prokinetics until one of them works

Case	Base	Antacid minimum effectiveness	Antacid maximum effectiveness	H_2-receptor antagonist minimum effectiveness	H_2-receptor antagonist maximum effectiveness	PPI minimum effectiveness	PPI maximum effectiveness	Prokinetic minimum effectiveness	Prokinetic maximum effectiveness	Initial strategy	Prescribing strategy
										Initial strategy	**Prescribing strategy**
	1	1	1	1	1	1	1	1	1	Medication only	Antacid only
	2	2	2	2		2	2	2	2	Test & eradicate	Antacid only
	3	3			2	3	3	3	3	Medication only	H_2-receptor antagonist only
					3	4				Test & eradicate	H_2-receptor antagonist only
										Eradicate all	H_2-receptor antagonist only
										Medication only	Prokinetics only
										Test & eradicate	Prokinetics only
										Medication only	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
										Test & eradicate	Prokinetics, PPI, H_2-receptor antagonist, antacid, stay
										Test & eradicate	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
										Medication only	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
	4	4	3				4	4	4	Medication only	Antacid, H_2-receptor antagonist, PPI, down
	5		4				5	5	5	Medication only	PPI, H_2-receptor antagonist, antacid, stay
	6	5					6	6	6	Medication only	Antacid, H_2-receptor antagonist, PPI, stay
									7	Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, down
			5							Test & eradicate	Antacid, H_2-receptor antagonist, PPI, down
										Test & eradicate	PPI, H_2-receptor antagonist, antacid, stay
										Test & eradicate	Antacid, H_2-receptor antagonist, PPI, stay
									8	Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
										Test & eradicate	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
	7	6	6	3				7	9	Medication only	PPI only
									10	Test & eradicate	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
										Eradicate all	Antacid, H_2-receptor antagonist, PPI, stay
	8	7	7	4			8	8	11	Test & eradicate	PPI only
										Eradicate all	PPI only
						5				Medication only	PPI or prokinetics until one of them works
	9	8	8	5		6		9	12	Test & eradicate	PPI or prokinetics until one of them works

Case	Base	Prokinetic for NUD, PPI for reflux	Antacid cheapest	Antacid most expensive	H_2-receptor antagonist cheapest	H_2-receptor antagonist cheapest but weak for NUD	H_2-receptor antagonist most expensive	PPI cheapest	Prokinetic cheapest	Initial strategy	Prescribing strategy
										Initial strategy	**Prescribing strategy**
	1	1	1				1	1		Medication only	Antacid only
	2	2	2				2	2		Test & eradicate	Antacid only
	3	3	3	1	1	1		3		Medication only	H_2-receptor antagonist only
		4			2	2				Test & eradicate	H_2-receptor antagonist only
										Eradicate all	H_2-receptor antagonist only
									1	Medication only	Prokinetics only
									2	Test & eradicate	Prokinetics only
									3	Medication only	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
									4	Test & eradicate	Prokinetics, PPI, H_2-receptor antagonist, antacid, stay
									5	Test & eradicate	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay
									6	Medication only	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
	4		4	2	3	3		4		Medication only	Antacid, H_2-receptor antagonist, PPI, down
	5	5	5	3	4	4		5		Medication only	PPI, H_2-receptor antagonist, antacid, stay
	6		6	4	5	5		6		Medication only	Antacid, H_2-receptor antagonist, PPI, stay
										Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, down
					6	6				Test & eradicate	Antacid, H_2-receptor antagonist, PPI, down
						7				Test & eradicate	PPI, H_2-receptor antagonist, antacid, stay
					7	8				Test & eradicate	Antacid, H_2-receptor antagonist, PPI, stay
8		6								Medication only	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
9										Test & eradicate	PPI, H_2-receptor antagonist/prokinetics, antacid, stay
7	7	7	7	5	8	9	3	7		Medication only	PPI only
		8								Test & eradicate	Antacid, H_2-receptor antagonist/prokinetics, PPI, stay
10										Eradicate all	Antacid, H_2-receptor antagonist, PPI, stay
	8		8	6	9	10	4	8		Test & eradicate	PPI only
										Eradicate all	PPI only
11		9								Medication only	PPI or prokinetics until one of them works
	9	10	9	7	10	11	5	9		Test & eradicate	PPI or prokinetics until one of them works

Complete listing of all strategies in the base case

Investigation strategy	Prescription strategy	Costs (£ over 5 years)	Standard error	Benefits (dyspepsia-free months in 5 years	Standard error
Eradicate all	Antacid only	251.34	0.55	36.18	0.058
Eradicate all	H_2-receptor antagonists only	348.25	0.74	42.73	0.049
Eradicate all	Prokinetics only	568.28	1.27	42.12	0.049
Eradicate all	PPI only	420.08	0.93	44.80	0.047
Eradicate all	Antacid, H_2-receptor antagonists, PPI, prokinetics, stay	450.65	1.17	43.06	0.049
Eradicate all	Antacid, H_2-receptor antagonists/ prokinetics, PPI, stay	441.28	0.96	43.36	0.047
Eradicate all	Antacid, H_2-receptor antagonist, PPI, stay	396.09	0.92	44.01	0.047
Eradicate all	Antacid, H_2-receptor antagonists, PPI, prokinetics, down	434.34	1.13	42.99	0.048
Eradicate all	Antacid, H_2-receptor antagonists/ prokinetics, PPI, down	441.75	0.97	43.06	0.047
Eradicate all	Antacid, H_2-receptor antagonists, PPI, down	387.84	0.90	43.66	0.047
Eradicate all	Prokinetics, PPI, H_2-receptor antagonists, antacid, stay	510.79	1.18	42.92	0.049
Eradicate all	PPI, H_2-receptor antagonists/ prokinetics, antacid, stay	433.40	0.98	43.94	0.047
Eradicate all	PPI, H_2-receptor antagonists, antacid, stay	392.25	0.87	43.75	0.047
Eradicate all	PPI or prokinetics until one of them works	499.71	1.15	45.02	0.047
Endoscope all	Antacid only	412.98	0.93	35.97	0.056
Endoscope all	H_2-receptor antagonists only	511.17	1.05	41.95	0.047
Endoscope all	Prokinetics only	734.24	1.48	41.19	0.049
Endoscope all	PPI only	587.05	1.19	43.82	0.046
Endoscope all	Antacid, H_2-receptor antagonists, PPI, prokinetics, stay	623.17	1.41	42.20	0.048
Endoscope all	Antacid, H_2-receptor antagonists/ prokinetics, PPI, stay	597.36	1.21	42.81	0.046
Endoscope all	Antacid, H_2-receptor antagonists, PPI, stay	561.24	1.18	43.30	0.046
Endoscope all	Antacid, H_2-receptor antagonists, PPI, prokinetics, down	604.63	1.38	42.16	0.047
Endoscope all	Antacid, H_2-receptor antagonists/ prokinetics, PPI, down	598.77	1.21	42.48	0.046
Endoscope all	Antacid, H_2-receptor antagonists, PPI, down	551.88	1.17	42.95	0.046

continued

Complete listing of all strategies in the base case *contd*

Investigation strategy	Prescription strategy	Costs (£ over 5 years)	Standard error	Benefits (dyspepsia-free months in 5 years	Standard error
Endoscope all	Prokinetics, PPI, H_2-receptor antagonists, antacid, stay	652.08	1.37	42.23	0.048
Endoscope all	PPI, H_2-receptor antagonists/prokinetics, antacid, stay	600.41	1.23	42.95	0.046
Endoscope all	PPI, H_2-receptor antagonists, antacid, stay	555.96	1.14	42.82	0.046
Endoscope all	PPI or prokinetics until one of them works	678.97	1.40	44.67	0.047
Test and endoscope	Antacid only	281.33	0.94	35.97	0.056
Test and endoscope	H_2-receptor antagonist only	382.88	1.06	42.29	0.047
Test and endoscope	Prokinetics only	616.33	1.50	41.45	0.049
Test and endoscope	PPI only	461.16	1.21	44.24	0.046
Test and endoscope	Antacid, H_2-receptor antagonist, PPI, prokinetics, stay	493.95	1.43	42.51	0.048
Test and endoscope	Antacid, H_2-receptor antagonists/ prokinetics, PPI, stay	477.36	1.21	42.96	0.046
Test and endoscope	Antacid, H_2-receptor antagonists, PPI, stay	433.86	1.20	43.57	0.046
Test and endoscope	Antacid, H_2-receptor antagonists, PPI, prokinetics, down	475.60	1.39	42.46	0.048
Test and endoscope	Antacid, H_2-receptor antagonists/ prokinetics, PPI, down	477.70	1.22	42.65	0.046
Test and endoscope	Antacid, H_2-receptor antagonists, PPI, down	424.29	1.18	43.22	0.046
Test and endoscope	Prokinetics, PPI, H_2-receptor antagonists, antacid, stay	546.57	1.39	42.39	0.048
Test and endoscope	PPI, H_2-receptor antagonists/prokinetics, antacid, stay	474.96	1.25	43.35	0.046
Test and endoscope	PPI, H_2-receptor antagonists, antacid, stay	429.39	1.15	43.20	0.046
Test and endoscope	PPI or prokinetics until one of them works	552.66	1.40	44.86	0.047
Test and eradicate	Antacid only	221.60	0.55	36.42	0.058
Test and eradicate	H_2-receptor antagonists only	320.64	0.74	42.87	0.048
Test and eradicate	Prokinetics only	544.29	1.26	42.20	0.049
Test and eradicate	PPI only	395.08	0.93	44.88	0.046
Test and eradicate	Antacid, H_2-receptor antagonists, PPI, prokinetics, stay	423.53	1.16	43.17	0.048
Test and eradicate	Antacid, H_2-receptor antagonists/ prokinetics, PPI, stay	414.93	0.95	43.47	0.047
Test and eradicate	Antacid, H_2-receptor antagonists, PPI, stay	369.15	0.91	44.12	0.046

continued

Complete listing of all strategies in the base case *contd*

Investigation strategy	Prescription strategy	Costs (£ over 5 years)	Standard error	Benefits (dyspepsia-free months in 5 years	Standard error
Test and eradicate	Antacid, H_2-receptor antagonists, PPI, prokinetics, down	406.68	1.13	43.10	0.048
Test and eradicate	Antacid, H_2-receptor antagonists/ prokinetics, PPI, down	414.86	0.96	43.18	0.047
Test and eradicate	Antacid, H_2-receptor antagonists, PPI, down	360.38	0.89	43.78	0.046
Test and eradicate	Prokinetics, PPI, H_2-receptor antagonists, antacid, stay	485.60	1.17	43.00	0.049
Test and eradicate	PPI, H_2-receptor antagonists/prokinetics, antacid, stay	408.00	0.97	44.02	0.047
Test and eradicate	PPI, H_2-receptor antagonists, antacid, stay	365.64	0.86	43.83	0.047
Test and eradicate	PPI or prokinetics until one of them works	479.37	1.16	45.13	0.047
Medication only	Antacid only	169.05	0.43	35.59	0.056
Medication only	H_2-receptor antagonists only	274.73	0.67	42.25	0.047
Medication only	Prokinetics only	531.32	1.32	41.04	0.049
Medication only	PPI only	357.17	0.89	44.23	0.046
Medication only	Antacid, H_2-receptor antagonists, PPI, prokinetics, stay	392.74	1.19	42.34	0.048
Medication only	Antacid, H_2-receptor antagonists/ prokinetics, PPI, stay	377.44	0.92	42.78	0.046
Medication only	Antacid, H_2-receptor antagonists, PPI, stay	328.56	0.88	43.49	0.046
Medication only	Antacid, H_2-receptor antagonists, PPI, prokinetics, down	373.90	1.15	42.29	0.048
Medication only	Antacid, H_2-receptor antagonists/ prokinetics, PPI, down	378.11	0.92	42.46	0.046
Medication only	Antacid, H_2-receptor antagonists, PPI, down	318.86	0.86	43.13	0.045
Medication only	Prokinetics, PPI, H_2-receptor antagonists, antacid, stay	464.19	1.22	42.00	0.048
Medication only	PPI, H_2-receptor antagonists/prokinetics, antacid, stay	373.52	0.96	43.27	0.046
Medication only	PPI, H_2-receptor antagonists, antacid, stay	324.14	0.82	43.17	0.046
Medication only	PPI or prokinetics until one of them works	448.85	1.15	44.56	0.046

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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ISSN 1366-5278