Appendix I: Information from NICE clinical guideline 17 [2004]

I.1 Overview

This national guideline provides evidence-based recommendations for the primary care management of dyspepsia symptoms and underlying causes in adults. It was developed for use by the National Health Service in England and Wales. NHS healthcare professionals, patient representatives and researchers developed this guideline, incorporating comments received from referees and from an extensive national stakeholder consultation.

The guideline defines dyspepsia broadly and inclusively, reflecting its presentation and management in the primary care setting. Thus, dyspepsia refers to a spectrum of usually intermittent upper gastrointestinal symptoms, including epigastric pain and heartburn. Annually, 40% of the adult population may suffer from dyspepsia, although only about 2% consult their GP. Currently, prescribed drugs and endoscopies alone annually cost the NHS about £600 million; over-the-counter medication cost patients a further £100 million. The evidence review differentiates between uninvestigated dyspepsia and three main categories arising from investigation: gastro-oesophageal reflux disease, peptic ulcer disease and non-ulcer dyspepsia. Further sub-categories are discussed as the evidence allows.

For the majority of patients the consequence of dyspepsia is symptoms affecting their quality of life. The impact of dyspepsia upon quality of life is a personal experience; a recurring problem or a chronic complaint for which available treatments may be wholly effective or only partially relieve symptoms. Although lifestyle changes can help to avoid triggering dyspepsia, evidence for the long-term impact of lifestyle upon the disease is lacking and it is inappropriate to withhold treatment on lifestyle grounds.

In most patients without alarm signs it is appropriate to manage symptoms without a formal diagnosis. Endoscopy is used to investigate alarm signs and to identify gastric and duodenal ulcers as well as rare cases of oesophageal and gastric cancer. The important identification of the bacterium Helicobacter pylori in 1983, with development of effective antibiotic treatment, has revolutionised treatment for peptic ulcer disease.

After initial symptoms or acute pathologies have been managed, patients needing ongoing treatment should be offered a trial of low dose proton pump inhibitors (PPIs) using treatment as they feel they need it to control symptoms. Subsequent treatment can be tailored to the consequence of this trial but periodic review should empower patients to continue, reduce or cease therapy.

I.2 Contributors

I.2.1 The guideline development group

The guideline development group was composed of four types of members [iii]: relevant healthcare professionals, a patient representative, technical staff and a specialist small-group leader.

Healthcare professions approached included general practice, gastroenterology, nursing and pharmacy. The composition of the group was selected to ensure adequate relevant discussion of the evidence, of areas where there was no evidence, and of the subsequent

recommendations in the guideline. The group leader had the role of ensuring that the group process worked effectively. A methodologist ensured that guideline tasks were addressed and completed.

1.2.2 Authorship and citation

Authorship of this full guideline document is attributed to members of the guideline development group and support staff under group authorship. Professor James Mason led the guideline development process, and can be contacted by email: jmason123@orange.net. Please cite this document as:

North of England Dyspepsia Guideline Development Group. Dyspepsia: managing dyspepsia in adults in primary care. Centre for Health Services Research, report no. 112. Newcastle: University of Newcastle, 2004.

1.2.3 Involvement of stakeholders and referees

A substantial process of stakeholder involvement surrounds the development of national guidelines developed for the Institute. Generic details of this process are found on the Institute web site (http://www.nice.org.uk/) in the document: The Guideline Development Process – An overview for stakeholders, the public and the NHS. In brief the process involves identifying and registering relevant patient and professional organizations as stakeholders; obtaining their comments on the scope of the work; providing an opportunity for the submission of relevant evidence and commenting on two draft versions of the final document. Comments are collated by the Institute and a response is provided by the guideline developers and fed back to stakeholders. A panel is convened by the Institute to assess the draft versions and comments and has responsibility for reviewing the completed guideline.

Some stakeholder organizations are invited by the Institute to nominate individuals who because of their knowledge or experience may contribute as guideline development group members. Forty-seven stakeholders registered with the Institute to contribute to the process of developing this guideline. These are, in alphabetical order:

Table 1: Stakeholders registered for the guideline development process

Abbott Laboratories Limited (BASF/Knoll)	Joint Specialty Committee in Gastroenterology and Hepatology
Acute Care Collaborating Centre	National Assembly for Wales
AstraZeneca UK Ltd	NCC for Mental Health (British Psychological Society)+
British Dietetic Association	NCC for Mental Health (Royal College of Psychiatrists)+
British Geriatrics Society	NCC for Primary Care+
British In Vitro Diagnostics Association	NHS Information Authority (PHSMI Programme)
British Medical Association	Novartis Pharmaceuticals UK Ltd
British Psychological Society	Nursing & Supportive Care Collaborating Centre
British Society of Gastroenterology*	Oesophageal Patients Association*
Association of the British Pharmaceuticals Industry (ABPI)	Patient Involvement Unit for NICE
BUPA	Pharmacia Limited
Chester City Primary Care Group	Prodigy
Chronic Conditions Collaborating Centre	Proprietary Association of Great Britain (PAGB)

Contact a Family*	Reckitt Benckiser Healthcare (UK) Ltd
Department of Health	Royal College of General Practitioners*
Digestive Disorders Foundation*	Royal College of Nursing*
Eisai Limited	Royal College of Pathologists
Eli Lilly and Company Ltd	Royal College of Physicians
Faculty of Dental Surgery	Royal College of Psychiatrists
Gastroenterology Research Group	Royal College of Radiologists
General Medical Council	Royal College of Surgeons of England
GlaxoSmithKline UK	Royal Pharmaceutical Society of Great Britain
Health Technology Board of Scotland	Women's & Children's Collaborating Centre
Janssen-Cilag Ltd	Wyeth Laboratories
*Organisations asked to offer nominations for guideline group membership +National Collaborating Centre	

1.2.4 Additionally the guideline was reviewed by the following subject area experts:

John Atherton	Consultant Physician
Anthony Axon	Consultant Physician
Mike Bramble	Consultant Physician
Janet Grime	Researcher
Cliodna McNulty	Primary Care Co-ordinator & Consultant Medical Microbiologist
Kristian Pollock	Researcher
Greg Rubin	General Practitioner
Nicholas Talley	Consultant Physician

1.2.5 Acknowledgements

We are grateful to:

Victoria Thomas (of the Patient Involvement Unit for NICE), who drafted a summary of patient and GP views based on research from Keele University; and,

Julia Cook (GP Registrar in the National Guideline Research and Development Unit), who developed this writing reflecting discussions and experience in the guideline development group.

Janet Grime and Kristian Pollock (of the Department of Medicines Management, University of Keele), who provided helpful comments on our summary of their work on patient and GP perspectives of dyspepsia.

Cliodna McNulty (of the Gloucester and Primary Care Liaison for the Health Protection Agency), who provided a cost comparison of serology, stool antigen and breath testing for *H. pylori*.

Andrew Briggs (of the Institute of Health Sciences, University of Oxford), who allowed us to explore a model of the cost-effectiveness of GORD which he had developed with others.

David Simpson (of Primary Care Informatics), for helpful discussions about audit and for identifying codes for use in primary care.

The Upper Gastrointestinal and Pancreatic Diseases Cochrane Group for their support in systematic reviews on peptic ulcer disease, non-ulcer dyspepsia, gastro-oesophageal reflux disease and management of uninvestigated dyspepsia.

Shelly Soo (Consultant Gastroenterologist, South Teeside), who conducted the systematic review of non-ulcer dyspepsia.

Alex Ford (Lecturer in Gastroenterology, University of Leeds), who conducted the systematic review of *H. pylori* eradication in peptic ulcer disease

Clare Donnellan (Research Registrar, Leeds), who conducted the systematic review of maintenance therapy in gastro-oesophageal reflux disease.

Stakeholders, referees, and colleagues who have provided the guideline development group with comments and suggestions as the work progressed.

1.2.6 Funding

The National Guideline Research and Development Unit was commissioned by the National Institute for Clinical Excellence to develop this guideline.

1.3 Development Methods

1.3.1 Costs and consequences

Approaches to cost-effectiveness have assisted in reaching recommendations in a series of primary care evidence-based guidelines [xv,xvi]. This guideline involves a systematic appraisal of effectiveness, compliance, quality-of-life, safety and health service resource use and costs of a medical intervention provided in the British healthcare setting. Using the most current, pertinent and complete data available, the economic analysis attempts a robust presentation showing the possible bounds of cost-effectiveness that may result.

The guiding principle behind economic analysis is that it is desirable to use limited healthcare resources to maximise health improvements in the population. Well defined but narrow notions of health improvement may not reflect all aspects of value to patients, carers, clinicians or society. For example, evidence may lead the guideline group to recommend targeting additional resources to certain patient groups when unequal access to care is apparent. The group process allows discussion of what should be included in the definition of ‘improved health’ and, more broadly, of other concepts of value to society such as fairness, justice, dignity or minimum standards of care.

The range of values used to generate cost-effectiveness estimates reflects the available evidence and the concerns of the guideline development group. Recommendations are graded reflecting the certainty with which the costs and consequences of a medical intervention can be assessed. This practice reflects the desire of group members to have simple, understandable and robust information based on good data.

It is not generally helpful to present an additional systematic review of previous economic analyses that have adopted a variety of differing perspectives, analytic techniques and baseline data. However, the economic literature is reviewed to compare guideline findings with representative published economic analyses and to interpret any differences in findings when these occurred. A commentary is included when the group feel this aided understanding.

I.4 Evidence

I.4.1 Introduction

This guideline addresses the care of patients presenting in primary care with dyspepsia. Full details of the method of production of this guideline are found in the methods section (page 28).

The management of dyspepsia in primary care contains a number of interlocking issues. How should dyspepsia be defined and diagnosed? What is the relationship between dyspepsia and Helicobacter pylori, peptic ulcer and more serious pathologies? What are the potential benefits and harms of lifestyle and pharmacological interventions? How should the management of dyspepsia be organised and discussed by clinicians and patients? Should limited healthcare resources be targeted at certain patients or certain treatments, and if so, who or which? Recommendations for healthcare professionals, patients and carers are derived at relevant points in the evidence narrative, together with supporting statements of evidence. These summary findings form the basis of shortened clinical and patient versions of the guideline.

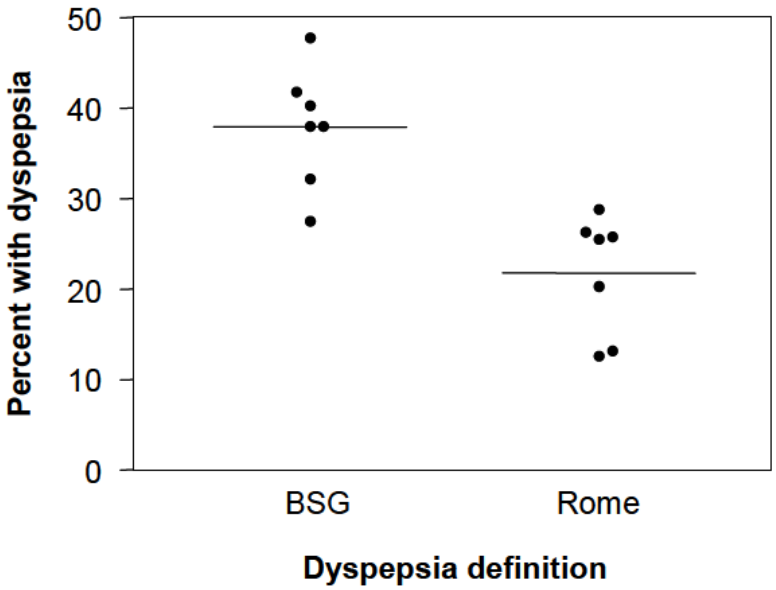
Users of this document will vary in their understanding of medicine, clinical studies and statistics. Discussion of the clinical evidence found in published studies is sometimes very technical. We have endeavoured to minimise jargon throughout this guideline, adding background reading at points in the text and explanations of analytic techniques in appendices. These sections can be omitted by more knowledgeable readers. Recommendations and supporting evidence statements are intended to be read and used by clinicians and patients to help inform healthcare decisions.

I.4.2 Dyspepsia: prevalence and definitions & information

I.4.2.1 Prevalence

Fourteen surveys evaluating community prevalence of dyspepsia in the last 12 years show that the prevalence of dyspepsia depends upon the definition taken (Figure 1).

Figure 1: Prevalence of adult dyspepsia according to dyspepsia definition



The pooled prevalence estimate was 34% although individual studies varied from 13% to 48% of adults (Table 11). The variation appears predominantly determined by the inclusion of dominant reflux symptoms: when included the average prevalence was 39% and 23% when excluded. The pooled results additionally found that dyspepsia may be slightly more common in women.

Table 2: Population surveys reporting the prevalence of adult dyspepsia 1988 - 2000

Authors	Year	Country	Definition*	Sample size	% Dyspepsia
Jones et al.	1989	England	BSG	2066	38.0%
Jones et al.	1990	England/Scotland	BSG	7428	41.8%
Bemersen et al.	1990	Norway	BSG	1802	27.5%
Agreus et al.	1995	Sweden	BSG	1156	32.2%
Penston et al.	1996	Great Britain	BSG	2112	40.3%
Rosenstock et al.	1997	Denmark	BSG	3589	47.8%
Moayyedi et al	2000	England	BSG	8350	38.0%
Talley et al.	1992	USA	Rome	835	25.5%
Drossman et al.	1993	USA	Rome	5430	25.8%
Holtmann et al.	1994	Germany	Rome	431	28.8%
Talley et al.	1994	Australia	Rome	1528	20.3%
Kennedy et al.	1998	England	Rome	3169	26.3%
Nandurkar et al.	1998	Australia	Rome	592	13/2%
Talley et al.	1998	Australia	Rome	730	12/6%
* Definition: see text					

Published surveys typically assessed patient recall of symptoms over a 3-12 month period, and did not differentiate between new or long term dyspepsia. Typically, dyspepsia is a chronic relapsing and remitting disorder. This complicates any definition of prevalence (the proportion of the population with dyspepsia at a given time), since there are individuals who have had dyspepsia symptoms, are now asymptomatic, but are at high risk of symptoms recurring. Thus surveys may underestimate dyspepsia by missing patients whose symptoms are ‘silent’.

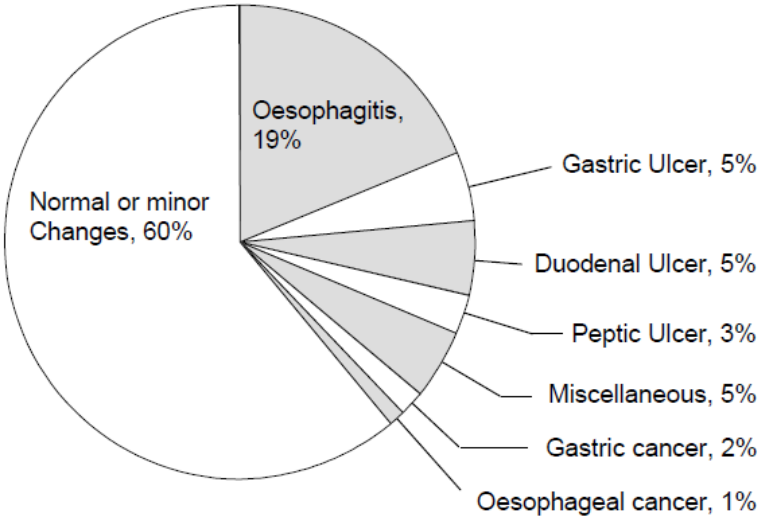
International Classification of Diseases 9th and 10th revisions reflect the disagreements about the way that dyspepsia should be defined and sub-divided. Using ICD 9, non-ulcer dyspepsia is classed together with habitual vomiting, whereas ICD 10 provides a new term of functional dyspepsia but excludes heartburn symptoms. Using ICD 9, diseases of the oesophagus do not include symptomatic reflux disease without oesophagitis. Using ICD-10, gastro-oesophageal reflux disease may be with or without oesophagitis.

Population surveys suggest approximately 25% of patients with dyspepsia will present with their symptoms to their general practitioner. National data show a steady rise in consultation rate for dyspepsia from 355 per 10,000 patient years at age 25-44 to 789 per 10,000 at age 75-84 [9]. Based on this data a GP with a list of 2,000 patients can expect 60 to consult with dyspepsia related illness (or 3%). This is somewhat lower than the 10% implied by population surveys. The discrepancy may be due to a combination of factors including patient recall and clinical coding of reasons for consultation.

The most common causes of dyspepsia are gastro-oesophageal reflux disease (GORD), peptic ulcer disease and non-ulcer dyspepsia (Figure 2). The true prevalence of these diseases is hard to establish since endoscopy is needed to make a formal diagnosis, but is

not performed in all patients. Most surveys describe findings only in those presenting for endoscopy, limiting their interpretation in primary care.

Figure 2: Findings at endoscopy: England 1994 Source: Hospital Episode Statistics [10]



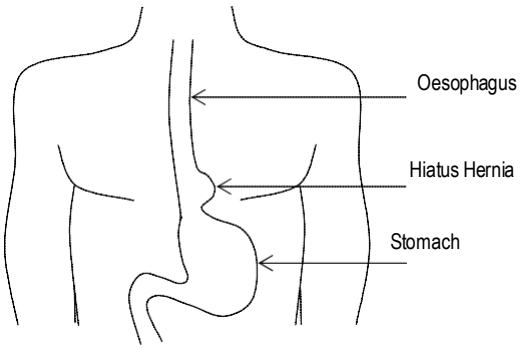
4.2.2 Univestigated dyspepsia

Uninvestigated dyspepsia describes the condition of any patient consulting for persistent symptoms of upper abdominal pain or discomfort, heartburn, acid reflux, nausea or vomiting, and not formally investigated by endoscopy.

4.2.3 Hiatus hernia

A hiatus hernia is occurs when part of the stomach moves up in the chest through a defect in the diaphragm (see Figure 3). It is a common problem occurring in about 10% of people and the hernia rarely causes symptoms on its own. The presence of a hiatus hernia can cause weakness of the lower oesophageal sphincter (valve between the stomach and the oesophagus (gullet)) and this in turn can cause reflux of the acidic stomach contents into the oesophagus. This causes the sensation of heartburn and patients with a hiatus hernia are more prone to heartburn than those without this defect. Nevertheless it is important to emphasise that not all patients with hiatus hernia have heartburn and some patients with heartburn do not have a hiatus hernia.

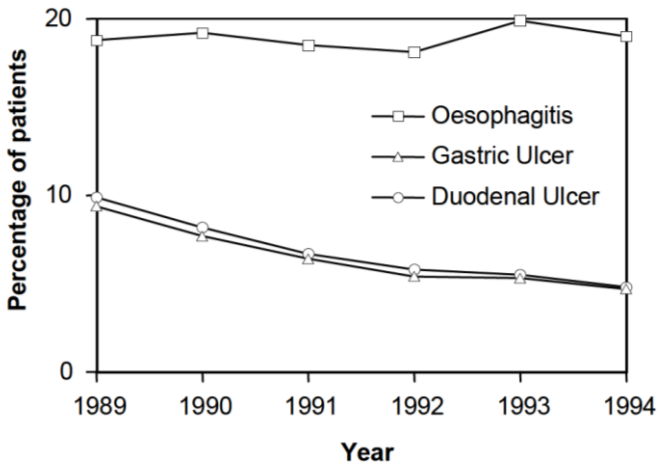
Figure 3: Illustration of hiatus hernia



4.2.4 Gastro-oesophageal reflux disease

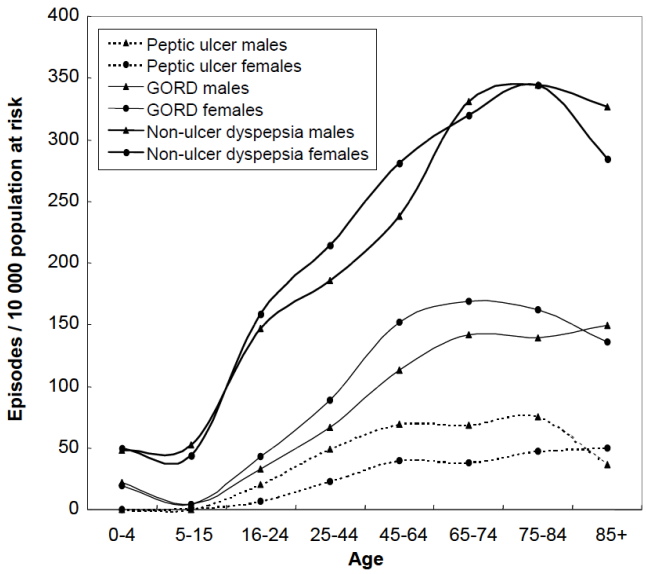
Gastro-oesophageal reflux disease (GORD) describes the sensation of stomach contents returning past the oesophageal sphincter, prolonging acid and pepsin exposure in the lower oesophagus and affecting patient well being [11,12,13]. Although some reflux is normal, it provokes symptoms in some people due to increased oesophageal sensitivity [14,15]. Endoscopy may reveal oesophageal mucosal breaks (termed oesophagitis) but findings are normal in over 50% of cases (termed endoscopy negative reflux disease or ENRD) [16]. Between 1989 and 1994 the prevalence of oesophagitis remained constant at about 20% (Figure 4).

Figure 4: Diagnosis of oesophagitis, duodenal ulcer and gastric ulcer at endoscopy: England, 1989-1994, Source: Hospital Episode Statistics [10]



However, case series from endoscopy units contradict this pattern, suggesting that oesophagitis has quadrupled over the last 10-20 years [17,18]. It is possible that an underlying increase is only found by the longer period of observation offered by these studies, although oesophagitis has been more readily diagnosed with the introduction and widespread uptake of PPIs as effective treatment. GORD increases in prevalence with age and is slightly more common in women (Figure 5).

Figure 5: First and new episodes of dyspepsia: England 1991-2 Source Morbidity Statistics in General Practice: Fourth National Study [9]

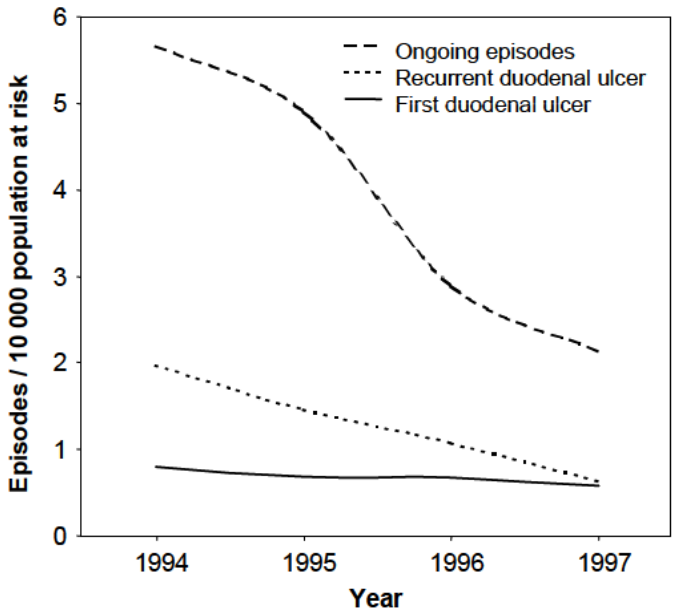


14.2.5 Peptic ulcer disease

A peptic ulcer is a break in the lining of the stomach or small intestine (formally a perforation in the gastrointestinal mucosa extending through the muscularis mucosae) due to the acid-peptic activity of the digestion. Gastric and duodenal ulcers refer respectively to ulcers sited in the stomach and small intestine. Gastric and duodenal ulcers may not have distinct symptoms and symptoms alone are inadequate to identify patients with ulcers [19]. *H. pylori* infection (see page 50) appears to be the main cause of duodenal ulcers, with 95% of cases being associated with this bacterium. Similarly, 80% of gastric ulcers are associated with *H. pylori* infection and the use of non-steroidal anti-inflammatory drugs is implicated in most other cases.

National hospital data show 10% of patients undergoing endoscopy had a peptic ulcer in 1994 (Figure 4), although numbers have fallen dramatically, decreasing by half since 1989. Duodenal ulcers previously treated with acid suppression may now be permanently cured with a course of *H. pylori* eradication therapy, providing an explanation for the striking fall in prevalence. This seen in the constant rate of newly diagnosed duodenal ulcer disease but a dramatic decline in recurrent episodes (Figure 6).

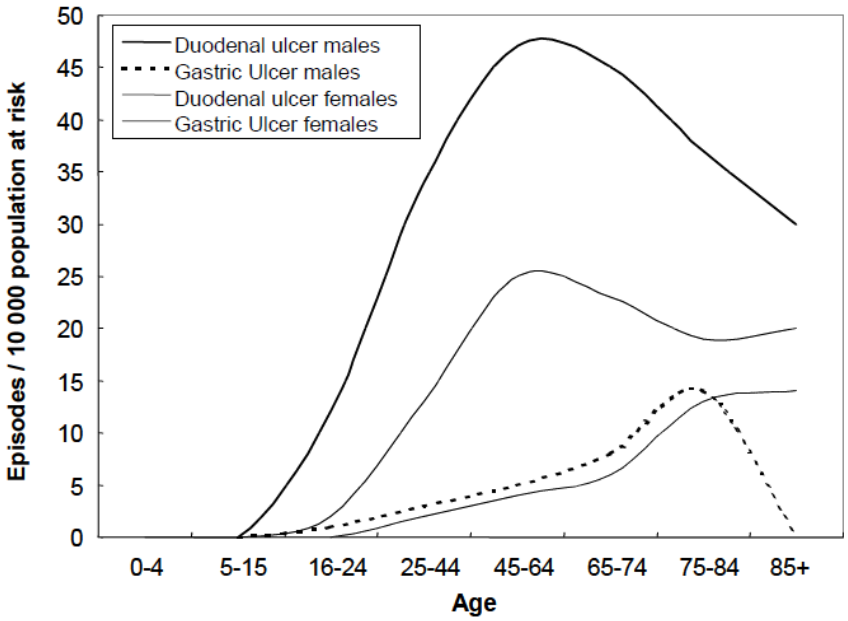
Figure 6: Ongoing, new and first episode rates for duodenal ulcer in England:1994-1997. Source: RCGP Birmingham Research Unit



Although 5% of patients endoscoped in 1994 were diagnosed as having a gastric ulcer (Figure 4), this may overestimate prevalence as patients are recommended to undergo repeat endoscopy to assess healing. Similarly to duodenal ulcer, the prevalence of gastric ulcer appears to have fallen dramatically between 1989 and 1994.

Duodenal and gastric ulcer differ in their incidence by age and sex. Duodenal ulcer peaks at age 45-64 and is twice as common in males as in females, whereas gastric ulcer is increasingly common with age and equally as common in females as in males (Figure 7).

Figure 7: New episodes of duodenal and gastric ulcer: England 1991-2 Source Morbidity Statistics in General Practice: Fourth National Study [9]



8.4.2.6 Functional dyspepsia

Patients with dyspepsia symptoms and a normal endoscopy are commonly classified as having functional dyspepsia. However, a proportion of these patients will have endoscopy negative reflux disease. Consequently, the Rome II definition excludes patients with predominant heartburn and acid reflux and the remaining patients are separated into ulcer-like and dysmotility-like subgroups. This subclassification of non-ulcer dyspepsia is problematic for primary care, since it is only useful after endoscopy, which as an invasive procedure may be inappropriate in many patients. Population surveys show there is substantial overlap between dyspepsia subgroups [20] and subjects that can be classified often change categories over time [21]. Instead this guideline addresses broadly defined dyspepsia and interprets available evidence in terms of patients with predominant symptoms, e.g. mainly reflux-like or dysmotility-like.

Functional dyspepsia is the most common diagnosis arising from endoscopy for dyspepsia (Figure 2). Primary care consultations for non-ulcer dyspepsia increase with age and the prevalence is similar in both genders (Figure 5). The change in prevalence of non-ulcer dyspepsia over time is uncertain given contemporaneous changes in definition.

8.4.2.7 Barrett's oesophagus

Although rare, long-segment Barrett's oesophagus is becoming more common in the UK and is currently diagnosed in 1.4% of endoscopies [22]. It is more common in patients with long-standing reflux symptoms [23], and becomes prevalent in adults over 40 [24]. The main concern with Barrett's oesophagus is the risk of developing adenocarcinoma: surveys have suggested the risk to be 1% per year although this may be an over-estimate due to publication bias [25]

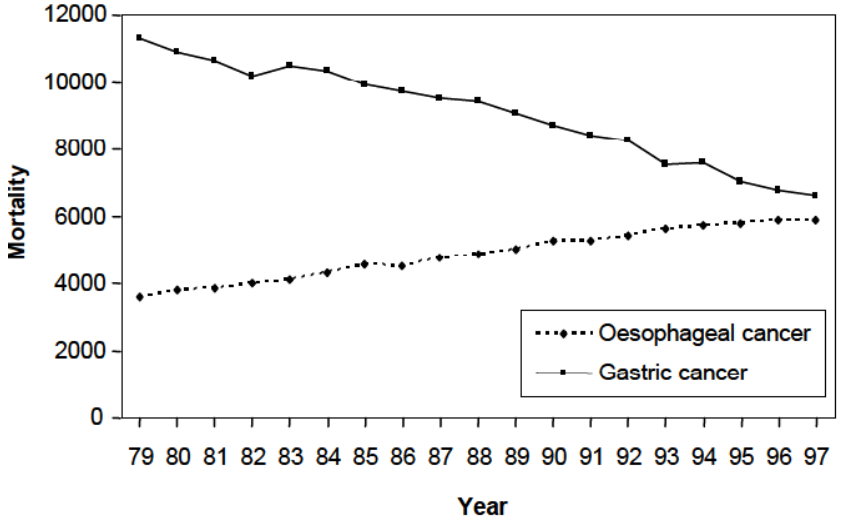
Barrett's oesophagus is defined as columnar lined oesophageal mucosa and should be diagnosed jointly by an endoscopist and pathologist [26]. It has been argued that intestinal metaplasia within the columnar mucosa is required to diagnose Barrett's oesophagus. However since metaplasia is patchy, this may be too stringent. Long segment Barrett's

oesophagus, diagnosed when at least 3 cm of the distal oesophagus is lined by columnar epithelium, has the greatest malignant potential and surveillance is recommended for this disorder. Short segment Barrett's oesophagus, for less than 3 cm of columnar lined oesophageal mucosa, is thought to have a lower malignant potential and the role of surveillance is uncertain [27]. Although no columnar lining may be visible, intestinal metaplasia may be found in biopsies taken at the gastro-oesophageal junction. While 20% of the population have evidence of intestinal metaplasia at the gastro-oesophageal junction, again the malignant potential of this lesion is uncertain and surveillance is not recommended [28].

1.4.2.8 Oesophageal and gastric cancer

Gastric and oesophageal cancers are rare, accounting annually for 1% of deaths from all causes. Gastric cancer is on the decline, while oesophageal cancer is on the increase (Figure 8). Gastric cancer may be declining because of the decreasing prevalence of *H. pylori* in the UK. It is unclear why oesophageal adenocarcinoma should be increasing although it has been suggested there may be a link with increasing prevalence of GORD [29].

Figure 8: Incidence of gastric and oesophageal cancer in England and Wales 1979 to1997
Source: Office of National Statistics



Squamous cell carcinoma and adenocarcinoma account for 95% of all oesophageal tumours. Traditionally squamous carcinoma was the most frequent lesion but in recent years adenocarcinoma has become the predominant disease in Europe and Northern America [30]. Adenocarcinoma of the oesophagus is believed to originate from columnar metaplasia of the oesophagus (Barrett's oesophagus), providing a rationale for endoscopic screening of patients with Barrett's oesophagus.

Adenocarcinoma is responsible for over 95% of all gastric malignancies. Half of patients are inoperable at the time of diagnosis and few of these survive five years, while of those undergoing operative treatment 20% are alive after 5 years. Overall 5 year mortality for this disease in the UK is therefore approximately 90%. Gastric neoplasia is strongly associated with *H. pylori* infection [31] but as the vast majority of *H. pylori* infected individuals do not develop gastric carcinoma other environmental and genetic factors must be important.

4.2.9 *Helicobacter pylori*

The gastric bacterium *H. pylori*, although strongly associated with peptic ulcer disease and distal gastric cancer, is widely present in the population but causes no harm in the majority of patients. It was first identified by Warren and Marshall in 1983 [32] *H. pylori* may be identified by a range of non- invasive tests or during upper gastrointestinal endoscopy (see page 61). There is now substantial evidence that peptic ulcer disease may be cured by eradicating *H. pylori*. The potential to reduce gastric cancer and ameliorate functional dyspepsia is more contentious as is the role of competing management strategies for *H. pylori*: initial endoscopy or initial *H. pylori* eradication.

H. pylori varies in prevalence widely with over 80% of Japanese and South American adults infected compared with approximately 40% in the UK and 20% in Scandinavia. Local differences in prevalence occur where there has been substantial immigration from countries with a higher prevalence. Transmission of *H. pylori* infection is uncertain. Person-to-person and faeco-oral or oro-oral route seem likely although *H. pylori* is rarely cultured from faeces or saliva [33]. Acute *H. pylori* infection causes a vomiting illness and recent evidence suggests *H. pylori* may be transmitted through vomit [34]. Epidemiological evidence suggests that many individuals acquire the infection in childhood: social deprivation, household crowding and number of siblings appear important risk factors [35,36].

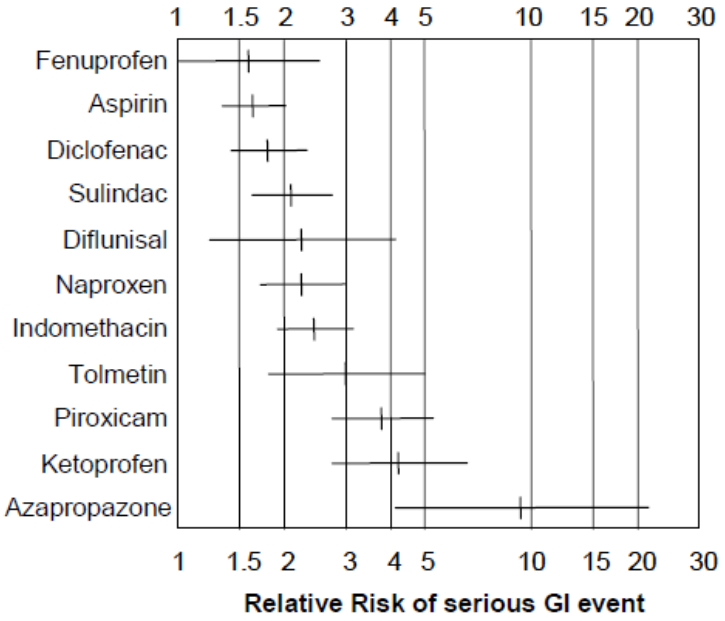
The prevalence of infection increases with age, although this may be largely a cohort effect. Poorer socio-economic conditions 70 years ago meant most children were infected with *H. pylori*. While the majority of 70 year olds are *H. pylori* positive only 10-20% of children are infected today [35]. This is consistent with the reduction over time of *H. pylori* related diseases such as peptic ulcer and distal gastric cancer. *H. pylori* infection is slightly more common in men [37] although the difference is small and this is unlikely to explain the gender differences in gastric cancer and peptic ulcer disease.

4.2.10 NSAID use and dyspepsia

- *The risk of serious ulcer disease leading to hospitalisation associated with NSAID use is of the order of one hospitalisation per 100 patient years of use in unselected patients. However, patients with previous ulceration are at higher risk.*
- *NSAID use is associated with increased risks of gastrointestinal bleeding in unselected patients, approximately fivefold for musculoskeletal pain and twofold for secondary prevention of cardiovascular disease with low dose aspirin.*

The extent of dyspepsia caused by long term NSAID use is not fully known. At the severe end of dyspeptic disease, ulceration has been used to explore the potential harm of NSAIDs using both bleeding ulcers (symptomatic disease) and endoscopically detected lesions (sub-clinical disease). The relative risk of hospitalisation due to serious gastrointestinal complications with older (COX unselective) NSAIDs has been studied [38]. Twelve epidemiological controlled studies were identified which examined the performance of 14 NSAIDs relative to ibuprofen (Figure 9).

Figure 9: Relative risk of serious gastrointestinal complication (named NSAID compared relative to Ibuprofen).



While epidemiological studies are less conclusive than randomised controlled trials, these findings suggest that NSAIDs vary significantly in their gastrointestinal toxicity. The review also found that the risk of gastrointestinal injury increases for higher doses of the same NSAID. High dose ibuprofen (2.4g daily) may be no safer than intermediate risk NSAIDs such as diclofenac and naproxen.

A case-control study (1,457 cases, 10,000 controls), based on the General Practice Research Database estimated an overall 4.7 (95%CI: 3.8 to 5.7) fold increase in risk of bleeding or perforated peptic ulcer associated with taking NSAIDs, but found higher risks with piroxicam (Odds Ratio (OR): 18.0) and azapropazone OR 23.4) [39].

A systematic review of case-control and cohort studies [40] (16 studies, 1625 people) found the risk finding peptic ulceration at endoscopy in NSAID users was significantly higher than for non-NSAID users (OR: 19.4; 95%CI 3.14 to 120), and that *H. pylori* infection increased the risk even further (OR: 3.5; 95%CI 2.16 to 5.75). The same systematic review (9 studies, 1895 people) found that *H. pylori* infection also increased the risk of finding a bleeding peptic ulcer (657/893 [73.6%] cases with bleeding peptic ulcer were infected v. 674/1002 [67.3%] matched controls without bleeding peptic ulcers, OR 1.67, 95%CI 1.02-2.72). Hence *H. pylori* eradication, on its own, might only partially reduce the risk of peptic ulceration in NSAID users.

A case control study of 1121 patients admitted with a upper gastrointestinal bleeding, and matched community and hospital controls, found increased risks of bleeding with both Aspirin and NSAID use, although the risk was lower in established users of Aspirin 75mg. OR 75mg 2.3 (95%CI: 1.2 to 4.4), OR 300mg 3.9 (95%CI: 2.5 to 6.3), first month (any dose) 9.2 (95%CI: 2.3 to 160.1), NSAID alone 4.9 (95%CI: 3.9 to 6.1).

In a large US trial, the control group of patients took a variety of different NSAIDs for rheumatoid arthritis [41]. In this cohort, the number needed to treat for a 6 month period to expect one serious gastrointestinal event was 105 (95%CI: 81 to 151), though it is unclear how many events were caused by the NSAID. Comparing the use of ibuprofen to no NSAID use, various case-control studies have estimated the rate of serious gastrointestinal damage to vary from no risk to a relative risk of 2 [42]. A meta-analysis of prevention trials found that

the absolute risk of an endoscopic ulcer in regular NSAID users was 20-30% [43] (11 trials), but in these studies all patients had gastroscopy and only a small proportion of these ulcers would ever have become symptomatic. Symptomatic ulcer disease is an uncommon side-effect of NSAID use when its occurrence is set against the huge volume of tablets taken (17.3 million prescriptions for cardiovascular dose aspirin, 19.4 million prescriptions for NSAIDs for musculoskeletal pain and considerable further over-the-counter sales in 2001) [44]. In 1995, there were 60,000 hospitalisations for gastrointestinal injury [45], of which a proportion will have been associated with NSAID use. The risk of hospitalisation for bleeding peptic ulcer associated with NSAID use is of the order of one for every hundred patient years of treatment.

Many patients with musculoskeletal pain require the symptomatic relief delivered NSAIDs to which must be added many patients using Aspirin in to prevent cardiovascular disease. Given the low absolute levels of harm only certain patients groups are considered at high risk: those with previous ulceration; those on other medication harmful to the gastric and duodenal lining; the elderly; and those on long term high dose NSAID use.

4.2.11 Recurrence of dyspepsia

- *Dyspepsia is a remitting and relapsing disease, with symptoms recurring annually in about half of patients. (II)*

Almost all causes of dyspepsia are recurrent and intermittent in nature. The only definitive treatments for dyspepsia are *H. pylori* eradication therapy, and surgery. Other treatments do not address underlying reasons for dyspepsia; once treatment stops symptoms may return. Table 12 shows the risks of untreated dyspepsia recurring, by cause, both within patients' lifetimes and in the year following first diagnosis.

Table 3: Annual and lifetime risks of recurrence for dyspepsia categories

Description	Risk, %	Source
Annual risk of recurrence		
Duodenal Ulcer (*H. pylori* positive)	15%	46, 47, 48
Gastric Ulcer (*H. pylori* positive)	5%	47, 48
Functional dyspepsia (overall)*	50%	49
Duodenal Ulcer (*H. pylori* negative)	1%	47
Gastric Ulcer (*H. pylori* negative)	1%	47
Reflux (overall)	50%	49
Lifetime risk of recurrence		
Duodenal Ulcer (*H. pylori* positive)	80%	50, 51
Gastric Ulcer (*H. pylori* positive)	60%	51, 52
Duodenal Ulcer (*H. pylori* negative)	5%	51, 52
Gastric Ulcer (*H. pylori* negative)	5%	51, 52
Functional dyspepsia (*H. pylori* positive)	50%	vii
Functional dyspepsia (*H. pylori* negative)	48%	vii
Reflux (overall)	80%	53

4.2.12 The role of symptom patterns in diagnosis

- *Dyspeptic symptoms are a poor predictor of significant disease. Between one quarter and one half of patients with symptoms meriting referral have significant*

disease confirmed by endoscopy. In primary care, described symptoms are a poor predictor of underlying pathology. (II)

A systematic review examined the extent to which symptom patterns could be used to predict final endoscopic diagnosis. The review identified four studies of unselected referred patients with dyspepsia where endoscopy was carried out on all patients by an investigator unaware of the symptom evaluation [54,55,56,57]

The overall performance of both individual symptoms and symptom clusters in predicting endoscopic diagnosis was poor (Table 13). The prevalence of significant disease was quite low in the studies with the effect that individual patients with 'classic' symptoms tended to have no better than a 50-50 chance of having a specific lesion. None of the studies recruited unselected patients from primary care, where performance on the basis of symptoms is likely to be poorer still.

None of these studies have examined unselected consecutive patients presenting in primary care. The CADET-PE study (presented at Digestive Disease Week 2003) reported 1,040 patients presenting with uninvestigated dyspepsia at one of 49 Canadian family physician centres, aged 18 years or older and undergoing endoscopy within 10 days of presentation. The findings were stratified according to whether the patients fitted the Rome II criteria (predominant heartburn is classed as GORD), or the Canadian guideline definition which only defines patients as having GORD where the sole symptom is of heartburn (Table 14). Even in patients without dominant heartburn 37% had oesophagitis and duodenal ulcer was as common in patients with dominant heartburn as epigastric pain [58].

Table 4: Performance of symptom evaluation as a predictive method for detecting endoscopically significant disease

	Edenholm, 1985	Talley, 1993	Adang, 1996	Muller-Hansen, 1998
Symptom predicting 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%, PPV 39 %, 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.
Symptom predicting oesophagitis				
Heartburn			Sensitivity 71%, Specificity 59%, Prevalence 27%, PPV 38%, NPV 85%,	

	Edenholm, 1985	Talley, 1993	Adang, 1996	Muller-Hansen, 1998
			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.
Symptom predicting 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.
Screening performance terms are explained in Appendix x on page 187				

Table 5: Relationship between dyspepsia symptoms presenting in primary care and endoscopic findings.

	Oesophagitis	Gastric Ulcer	Gastritis	Duodenal ulcer	Duodenitis
Canadian Dyspepsia definition	451 (43%)	31 (3.0%)	102 (10%)	29 (2.8%)	54 (5.2%)
Rome II Dyspepsia	236 (36%)	24 (3.7%)	62 (10%)	19 (2.9%)	29 (4.5%)
Rome II GORD	215 (54%)	7 (1.8%)	40 (10%)	10 (2.5%)	25 (6.4%)

1.4.3 Patients perspectives of dyspepsia

1.4.3.1 Experience of disease and treatment

A qualitative study of 82 patients and 26 GPs explored patients and doctors views of dyspepsia [59,60,61,62]. Many patients interviewed had long-standing experience of severe and unpleasant symptoms before seeking medical help, taking over-the-counter medication before consulting their doctor. The research uncovered stereotypes of doctors (anxious to ration prescribing), patients (demanding drugs to support an unhealthy lifestyle) and of PPIs themselves (a 'lifestyle' drug, used profligately). However, patients felt they were simply looking to live as normally as possible. While drugs such as PPIs might substantially improve patients' quality of life, they did not eradicate the need for caution and restraint in the way they lived their lives.

Some patients were perplexed by the lack of a 'cure' for their symptoms and worried that the availability of drug therapies such as PPIs to treat symptoms might inhibit further research

into the cause and cure of gastric disorders. Most patients wanted to dispense with their long-term need for PPIs.

There are frequent discrepancies between the individual accounts of illness given by doctors and their patients. Doctors seemed to vary considerably in their explanations of illness, value of treatment, and influence of lifestyle factors. Hence it appears particularly valuable to provide access to evidence- based patient information on the management of dyspepsia. Examples of texts for *H. pylori*, GORD, non-ulcer dyspepsia and peptic ulcer can be found on line at http://www.patient.co.uk/.

Patients wanted their need for appropriate treatment for (often severe) discomfort to be seen as urgent and real. More than half of the GPs in the studies displayed 'stereotypical' attitudes towards patients and drugs, with the concern that the legitimacy of patients' needs may be reduced. The study investigators comment that stereotyping may have reduced the perceived legitimacy of patients' need for treatment and helped justify cost reduction measures as a response to patient irresponsibility..

4.3.2 Doctor-patient interaction and patient expectations

There is a broader literature on why patients consult a general practitioner, much of it relevant to the treatment of dyspepsia. Zola identified five influences affecting patients' decisions to consult a doctor: the availability of medical care, whether the patient can afford it, the availability of non-medical therapies, how the patient perceives the problem, and how the patients' peers perceive the problem. Other triggering factors are required to 'medicalise' symptoms before they are perceived as illness and consultation considered. These triggers are, according to Zola: an interpersonal crisis; perceived interference with personal relationships; sanctioning by another individual (e.g. a relative); interference with work or physical functioning; and setting of external time criteria [63].

According to the health belief model, the decision to consult the general practitioner is determined by the presence of cues and the balance of costs and benefits modified by specific belief of the threat from, or vulnerability to, a condition [64,65]. A study in the Netherlands examined why patients consult their general practitioner, using two questionnaires completed in the waiting rooms of practices by 1,000 patients [66]. The health belief model showed a 98.9% predictive value for consultation, using multiple logistic regression to determine the principal predictors of consultation. Perceived efficacy of self care and perceived need for information also influenced the model but the frequency and duration of the complaint did not.

4.3.3 Interpreting symptoms

Although symptoms poorly predict upper gastrointestinal pathology, patients may contextualise them into their personal circumstances and outlook. A qualitative study of 46 working class women showed that although complex concepts of multi-factorial causation existed, women were most concerned with finding causal life events with which to invest their symptoms with individual relevance. 'Stomach disease' was most commonly linked to stress and worry [67]. A further study compared a random sample of 69 patients who had consulted their GP in the past six months with dyspepsia and 66 who had not [68]. The patients were interviewed, according to a standard schedule to explore psychological traits, life events and beliefs about dyspeptic symptoms. There was no difference in the frequency, or subjective severity of symptoms between the two groups. There were significantly more life events in the consulting group. Consulters were significantly more likely to believe that their symptoms were due to serious illness (74% v 17%) and cancer in particular (29% v 13%).

3.4.3.4 Fear of serious illness

A qualitative study of reasons for consultation with dyspepsia was conducted in Birmingham [69]. Randomly selected consulters and non-consulters with dyspepsia were interviewed in depth and transcribed tapes were subjected to a thematic analysis. Many of the subjects were fatalistic with respect to medical interventions and their ability to significantly alter the prognosis of illness. Beliefs about dietary or mechanistic causes may reflect patients' expectations of increasing age. The principal explanations for symptoms lay in the areas of degeneration (age), imbalance (e.g. of foods) and mechanical interpretations of bodily function.

The availability of medical care, the cost to the patient of over-the-counter medication, and the patients' belief in the ability of medical intervention to alter the course of serious illness, such as gastric cancer, were all important in this process. The principal predictors of consultation in this analysis were a family or close friend having being diagnosed with a serious condition, and the potential explanation of the patients' own symptoms being due to something similar. The paradoxical feature of some patients expecting the worse but not consulting can be explained within the model by reference to costs and benefits. The medical interventions, for cancer in particular, were perceived as costs, patients either not wishing to be told or not wanting 'to be messed around with'. As in a study of delay in seeking medical advice at the Massachusetts General Hospital [70], patients who worried more about cancer tended to delay seeking help more than non-worriers. An element of denial was also evident in the explanation of symptoms as being due to diet or increasing age.

3.4.4 Resource implications of managing dyspepsia

- *Dyspepsia is expensive, costing the NHS £463 million in drugs in 2001 and £130 million on endoscopies in 2000.*
- *Over-the-counter and pharmacy-only medication is estimated to have cost about £100 million in 2002.*

Services for managing dyspepsia are provided in both primary and secondary care. Patients with dyspepsia present at the pharmacy, general practice or the accident and emergency department with dyspeptic symptoms or upper gastrointestinal bleeding. Upper GI endoscopy is normally provided in secondary care, although some primary care centres and GP-run community hospitals also offer facilities. Most GPs have open access to endoscopy, although waiting times vary widely. Non-invasive tests for *H. pylori* are also available in primary and secondary care.

In 2001, £463 million was spent on drugs for dyspepsia: £364 million on PPIs; £54 million on H_2 receptor antagonists (H_2RAs); and £24 million on antacids, alginates and proprietary indigestion remedies, see Table 15 [71]. There is considerable variation within classes of drug, notably between maintenance and healing dose prescription of PPIs. Reflecting the current use of these drugs within class, maintenance doses cost on average £15.40 per month while healing doses cost £28.50 per month. Omeprazole is due to come off patent at the time of writing and this may result in a fall in PPI costs.

Table 6: Prescription cost analysis for dyspepsia-related drugs: England 2001: totals by BNF sub-paragraphs [71]

BNF chemical name	BNF no.	PXS[1] (1,000s)	OWC2[2] (1,000s)	NIC[3] (£ 1,000s)	NIC/PXS (£)
Antacids and Dimethicone	1.1.1.0	942.5	105.7	2,283.6	2.42

BNF chemical name	BNF no.	PXS[1] (1,000s)	OWC2[2] (1,000s)	NIC[3] (£ 1,000s)	NIC/PXS (£)
Sodium Bicarbonate	1.1.1.2	5.6	0.0	90.6	16.32
Other Drugs for Dyspepsia and GORD[4]	1.1.2.1	5,724.4	34.7	21,465.8	3.75
Antispasmodic & Other Drugs Altered Gut Motility	1.2.0.0	2,736.1	793.8	20,175.2	7.37
Test for *Helicobacter pylori*	1.3.0.0	2.1	0.3	45.1	21.12
H_2-Receptor Antagonists	1.3.1.0	5,657.7	661.8	53,500.7	9.46
Selective Antimuscarinics	1.3.2.0	0.1	0.1	3.0	25.79
Chelates And Complexes	1.3.3.0	30.7	6.7	273.3	8.90
Prostaglandin Analogues	1.3.4.0	43.2	36.7	623.1	14.41
Proton Pump Inhibitors	1.3.5.0	13,211.1	12,396.8	364,351.5	27.58
Other Ulcer-Healing Drugs	1.3.6.0	6.3	0.1	150.4	23.77

1 PXS: Prescription items dispensed
2 OWC2: class 2 drugs reimbursed at the proprietary price when generic unavailable
3 NIC: Net Ingredient Cost: cost of the drug before discounts and excluding dispensing costs
4 Primarily alginates.

The cost of endoscopy varies according to whether it is performed as a day case or inpatient procedure, and whether any therapeutic intervention is performed. The cost of day case diagnostic endoscopy was on average £250 in 2000, ranging from £52 to £1,333 with an interquartile range of £203-£380. In 2001, £132.2 million was spent on 424,600 upper GI endoscopies, principally for investigative upper gastrointestinal endoscopy.

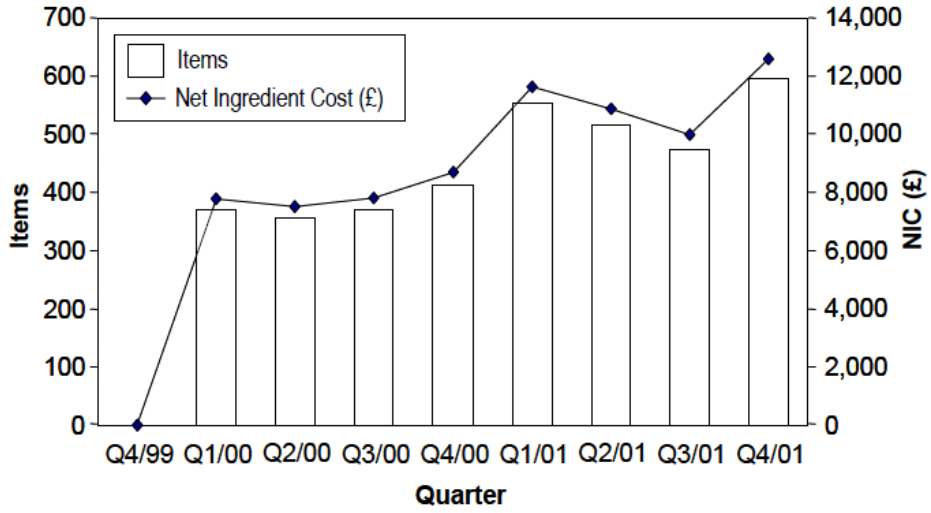
Table 7: Cost of Upper Gastrointestinal Endoscopy in England [72]

	Mean cost of diagnostic endoscopy	Mean cost of therapeutic endoscopy	Total NHS expenditure 2000 £ million
HRG code	F06 & F16	F05 & F15	
Day case	£287, £274	£368, £321	105.1
Elective inpatient	£562, £490	£732, £526	8.6
Non-elective inpatient	£450, £431	£782, £502	18.5

National data are not available on the volume of use of serology tests, and local data show that their use by GPs is variable [73]. Carbon-13 (^{13}C) Urea breath tests are available on prescription, but are not widely used in primary care. Figure 10 shows the number of ^{13}C urea

breath tests prescribed in England 1999-2001. Estimated costs of detecting *H. pylori* using serology, stool antigen and breath testing are found on page 191

Figure 10: Trends in prescribing of Urea Breath Tests, Source: Prescription Pricing Authority



4.4.1 Consultation in secondary care

There are an estimated 539 gastroenterologists working in England and Wales, currently increasing at a rate of approximately 7% per year [74]. There is a wide variation in the number of gastroenterologists working per head of population with 8-fold differences seen when comparing English regions. This may impact upon the capacity of local secondary care services to support primary care. Although national data are unavailable, dyspepsia is estimated to account for 50% of a gastroenterologist's workload [75]. General physicians, nurse specialists or practitioners, medical microbiologists, clinical scientists, laboratory staff and surgeons all contribute to the secondary care management of dyspepsia although their level of resource is unknown.

4.4.2 Self-medication

The market for over-the-counter (OTC) and pharmacy only (P) indigestion remedies is dominated currently by three pharmaceutical companies Reckitt Benckiser, Roche and GlaxoSmithKline, with most commonly used products being Gaviscon, Rennie and Zantac 75 (Table 17). The market for indigestion and heartburn remedies is estimated to be worth about £100 million in 2002, having grown 9% since 1997. Unlike prescription only medicines (POMs), direct marketing of these products is allowed and several market leaders are associated periodically with multi-million pound advertising campaigns [76]. Advertising, some targeted at younger people, and new product developments featuring chewable formats and claims of multiple action, immediate action and longer lasting effect are likely to have driven growth.

Table 8: Manufacturer and brand shares in indigestion remedies, 2000 and 2002 [76]

Manufacturer/brand	£m, 2000	%	£m, 2002*	%	% change ('02-'00)
Reckitt Benckiser	**25.7**	**27.0**	**31.7**	**32.0**	**+23.3**
Gaviscon Liquid	2.4	2.5	3.0	3.0	+25.0
Gaviscon Tablets	16.6	17.5	18.8	19.0	+13.3
Gaviscon Advance	6.7	7.1	9.9	10.0	+47.8

Manufacturer/brand	£m, 2000	%	£m, 2002*	%	% change ('02-'00)
Roche	**27.6**	**29.0**	**26.7**	**27.0**	**-3.3**
Rennie Original	19.0	20.0	19.1	19.3	+0.5
Rennie Rapeze	3.5	3.7	3.7	3.7	+5.7
Rennie Deflatine	3.8	4.0	3.4	3.4	-10.5
Rennie Duo	1.2	1.3	0.5	0.5	-58.3
GlaxoSmithKline	**20.9**	**22.0**	**19.8**	**20.0**	**-5.3**
Tums	3.5	3.7	2.7	2.7	-22.9
Milk of Magnesia	3.8	4.0	3.5	3.5	-7.9
Andrews Antacid	1.2	1.3	0.7	0.7	-41.7
Setlers	2.9	3.1	1.6	1.6	-44.8
Setlers Wind-eze	3.2	3.4	2.9	2.9	-9.4
Zantac 75	6.3	6.6	8.4	8.5	+33.3
SSL (Remegel)	4.5	4.7	4.7	4.7	+4.4
Wyeth (Bisodol)	4.7	4.9	4.0	4.0	-14.9
J&J (Pepcid)	0.6	0.6	2.5	2.5	+316.7
Thornton & Ross (Asilone)	1.4	1.5	0.7	0.7	-50.0
Others, incl own-label	9.6	10.1	8.8	8.9	-8.3
Total	***95.0***	***100.0***	***99.0***	***100.0***	***+4.2***

* Estimated
Data may not equal totals due to rounding
Source: Mintel

1.4.5 Relevant existing national guidance

The National Institute for Clinical Excellence issued guidance on the use of the use of Proton Pump Inhibitors for Dyspepsia in July 2000 (NICE Technology Appraisal No. 7). The summary guidance is reproduced for reference (Box 1). Additionally the Institute produced guidance on the use of selective COX-II inhibitors in July 2001 (NICE Technology Appraisal No. 27), some of which relates to the management of gastrointestinal side-effects in patients treated for arthritis. Relevant parts of the summary guidance are reproduced below (Box 2). There are no major inconsistencies between this previously issued guidance and the recommendations of this guideline. Differences in methodology, definitions and scope when developing guidance using appraisals and guidelines make it unhelpful to compare recommendations from the two processes directly. Given its broader scope, direct input from relevant healthcare professionals and rigorous evidence review, this guideline should be considered to update previous guidance on the management of dyspepsia.

Box 1: NICE guidance on the use of the use of PPIs in Dyspepsia [77]

1.1	In patients with documented duodenal or gastric ulcers, a treatment strategy of testing for *Helicobacter pylori* and, where positive, eradicating the infection is recommended. Long-term acid-suppressing therapy should not be used. Those patients who are *H. pylori* negative or remain symptomatic after eradication therapy should be treated as described in 1.6.
1.2	For patients with a documented non-steroidal anti-inflammatory drug (NSAID)-induced ulcer, who must unavoidably continue with NSAID therapy (e.g. those with severe rheumatoid arthritis), an acid suppressor, usually a proton pump inhibitor (PPI), should be prescribed. After the ulcer has healed, the patient, where possible, should be stepped

	down to a maintenance dose of the acid suppressor.
1.3	Patients who have severe gastro-oesophageal reflux disorder (GORD) symptoms or who have a proven pathology (e.g. oesophageal ulceration, Barrett's oesophagus) should be treated with a healing dose of a PPI until symptoms have been controlled. After that has been achieved, the dose should be stepped down to the lowest dose that maintains control of symptoms. A regular maintenance low dose of most PPIs will prevent recurrent GORD symptoms in 70-80% of patients and should be used in preference to the higher healing dose. Where necessary, should symptoms re-appear, the higher dose should be recommenced. In complicated oesophagitis (stricture, ulcer, haemorrhage), the full dose should be maintained. Patients with mild GORD symptoms and/or those who do not have a proven pathology can frequently be managed by alternative therapies (at least in the first instance) including antacids, alginates, or H_2RAs (H_2 receptor antagonists).
1.4	Patients diagnosed with non-ulcer dyspepsia (NUD) may have symptoms caused by different aetiologies and should not be routinely treated with PPIs. Should the symptoms appear to be acid-related, an antacid or the lowest dose of an acid suppressor to control symptoms should be prescribed. If they do not appear to be acid-related, an alternative therapeutic strategy should be employed.
1.5	Patients presenting in general practice with mild symptoms of dyspepsia may be treated on either a "step-up" or a "step-down" basis. Neither group should normally be treated with PPIs on a long-term basis without a confirmed clinical diagnosis being made.
1.6	In circumstances where it is appropriate to use a PPI and where healing is required, the optimal dose to achieve this should be prescribed initially. Once healing has been achieved, or for conditions where it is not required, the lowest dose of the PPI that provides effective symptom relief should be used.
1.7	The least expensive appropriate PPI should be used.
1.8	The use of PPIs in paragraphs 1.1 to 1.7 refers for each indication only to those PPIs which have been licensed for that use.
1.9	On present evidence, PPIs do not have any serious contraindications for the vast majority of users, and have been in common use for some eight or nine years. While their use in sufficient dosage to cure, or to control symptoms, is well warranted in terms of their clear benefits, any additional use cannot be recommended.

Box 2: Selected NICE guidance on the use of selective COX-II inhibitors for osteoarthritis and rheumatoid arthritis [78]

1.2	Of particular concern is the propensity of NSAIDs, including the Cox II selective agents, to cause gastro-intestinal adverse events, which can include life threatening gastro-intestinal perforations, ulcers or bleeds. These agents should therefore only be prescribed after careful consideration of their risks and benefits, especially in patients who may be at increased risk of such adverse events.
1.3	Cox II selective inhibitors are not recommended for routine use in patients with rheumatoid arthritis (RA) or osteoarthritis (OA). They should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of RA or OA only in patients who may be at 'high risk' of developing serious gastrointestinal adverse effects.
1.4	Patients at 'high risk' of developing serious gastrointestinal adverse events include those of 65 years of age and over, those using concomitant medications known to increase the likelihood of upper gastrointestinal adverse events, those with serious co- morbidity or those requiring the prolonged use of maximum recommended doses of standard NSAIDs (See Section 2.10). The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation.
1.6	There is no evidence to justify the simultaneous prescription of gastroprotective agents with Cox II selective inhibitors as a means of further reducing potential gastrointestinal

adverse events.

1.5 Treatments and procedures for dyspepsia

1.5.1 Pharmacological interventions

Details of the uses, cautions and contraindications of pharmacological treatments for dyspepsia can be found in the British National Formulary [79]. A brief summary of common therapeutics is provided here. Recommendations for the use of these therapeutics are made in the evidence section.

1.5.1.1 Antacids and alginates

Antacids come in liquid or solid form and commonly contain aluminium or magnesium compounds, and are used to relieve or prevent symptoms of dyspepsia. They effectively reduce acid but evidence of a healing effect has not been demonstrated. Antacids with magnesium may be laxative in some patients while those with aluminium may cause constipation. Although a range of simple and more complex preparations are available, none have a clear advantage in symptom relief. Dimethicone is an antifoaming agent added to some antacids to reduce flatulence. Antacids combined with alginates are understood to form a ‘raft’ floating on top of the stomach contents thus reducing reflux and protecting the oesophageal lining. Thus these preparations may have advantages over simple antacids for reflux- like symptoms.

Indigestion preparations on sale to the public include antacids with other ingredients such as alginates, dimeticone, and peppermint oil. Sodium bicarbonate has largely fallen from use for the treatment of dyspepsia.

1.5.1.2 *Helicobacter pylori* infection

One-week triple-therapy regimens including a PPI, amoxicillin, and either clarithromycin or metronidazole is shown in this guideline to eradicate *H. pylori* in about 90% of cases. Selection of clarithromycin or metronidazole may depend upon rates of local *H. pylori* resistance to these agents, if known. Other combinations of antibiotics or two week regimens are occasionally used, notably in treatment resistant patients, and ranitidine bismuth citrate (a H_2 receptor antagonist) is sometimes used instead of a PPI.

1.5.1.3 H_2 receptor antagonists

H_2 receptor antagonists block histamine H_2 receptor sites in the gastric mucosa. Blockade reduces gastric acid output thus promoting ulcer healing and relieving gastro-oesophageal reflux symptoms. They are sometimes used as maintenance treatment in patients with severe recurring symptoms, and to treat NSAID-associated ulcers.

1.5.1.4 Prostaglandin analogues

Misoprostol is a synthetic prostaglandin analogue. It reduces acid secretion and protects the gastric and duodenal linings, promoting ulcer healing. It can reduce ulceration in patients in whom NSAID therapy cannot be withdrawn.

1.5.1.5 Proton pump inhibitors

Proton pump inhibitors (or PPIs) reduce gastric acid by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the ‘proton pump’) in the gastric lining. PPIs are

used to treat gastric and duodenal ulcers, gastro-oesophageal reflux disease, and oesophagitis; to prevent and treat NSAID-associated ulcers; and are used together with antibacterials to eradicate *H. pylori*. Currently available PPIs are omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

1.5.2 Investigations

Since dyspepsia is common, decisions about investigations and their sequencing will impact upon the care of substantial numbers of patients.

1.5.2.1 Endoscopy

Endoscopy allows a clinician to view the gastrointestinal tract and, if necessary, perform therapeutic procedures. An endoscope is used to view the oesophagus, stomach and proximal duodenum. The development of fibre optic technology first allowed direct imaging in the 1960s. Endoscopy has now become the ‘gold standard’ test for detecting oesophageal, gastric and duodenal lesions. Demand for endoscopy has increased during the 1990s to stabilise at about 1% of the population of England having an endoscopy each year [10]. Studies suggest the patient acceptability of upper gastrointestinal endoscopy is similar [80] or greater than double contrast barium meal (DCBM) [81]. Unlike DCBM it is possible to biopsy suspicious lesions and biopsies for *H. pylori* can also be obtained. Endoscopy may be performed with local anaesthetic throat spray or light intravenous benzodiazepine sedation may be given. Patients are recommended not to drink alcohol, drive a car, use machinery and sign binding documents for 24 hours after receiving intravenous sedation. The morbidity and mortality rates of upper gastrointestinal endoscopy are low (1 in 200 and 1 in 2000 respectively in the UK [82]). These are possibly overestimates, based on a more secondary-care higher-risk patient population than those referred for dyspepsia from primary care. Nonetheless these risks need to inform patient decision making.

Typical findings from endoscopy are shown in Figure 2 on page 45.

1.5.2.2 Investigations for *Helicobacter pylori*

H. pylori causes most peptic ulcer disease. Non-invasive testing for this organism is achieved by serology, faecal antigen tests or the labelled C-urea breath tests. Additionally the presence of *H. pylori* can be determined by biopsy during endoscopy.

Serology

Serology involves measuring the antibody response to the organism in the patients’ serum. This is the cheapest test but also the least accurate with 80-90% sensitivity and specificity [83]. This technique can be adapted to provide a near patient test giving a diagnosis within 5 minutes. This is convenient in the primary care setting [84] and some studies have shown sensitivities and specificities approaching 90% [85]. The specificity of near patient *H. pylori* tests have been disappointing in other centres [86] and local validation is important before using these kits in primary care.

Faecal antigen testing

The stool antigen test detects *H. pylori* antigens in a provided stool sample and is more accurate than serology with a 90-100% sensitivity and specificity [87,88,89,90,91,92].

Labelled C-urea breath tests

Urea breath tests use the powerful urease enzyme possessed by *H. pylori* to diagnose infection [93]. Urea labelled with either ^{13}C or ^{14}C is given orally to the patient and if *H. pylori* infection is present this will be hydrolysed to isotopically labelled CO_2. This is absorbed from the stomach into the blood and excreted by the lungs. Urea breath tests have a sensitivity and specificity >95% [94] and are more accurate than serology [95]. The ^{14}C-urea breath test is simple and cheap [96], but ^{14}C is radioactive and needs to be administered in a medical physics department, which is not ideal for primary care [93]. ^{13}C is not radioactive so it avoids these problems but it is difficult to detect, requiring expensive mass spectrometry equipment. There have been a number of technological advances in ^{13}C-urea breath tests making analysis cheaper [97,98] but the test is still expensive compared with other non-invasive alternatives.

15.2.3 Surgical procedures

The discovery of *H. pylori* and the development of powerful acid suppressive therapy have revolutionised the medical therapy of peptic ulcer and gastro-oesophageal reflux disease. This has made peptic ulcer surgery almost obsolete. Anti-reflux surgery is reserved for selected patients with documented acid reflux whose symptoms are unresponsive to medical therapy or who do not wish to take long term PPI treatment.

Anti-reflux surgery

The Nissen fundoplication and the Hill posterior gastropexy are the two commonest anti-reflux procedures. The Nissen fundoplication involves mobilisation of the fundus of the stomach that is then wrapped around the lower oesophagus. The gastro-oesophageal junction is sutured to the median arcuate ligament in a Hill posterior gastropexy and the stomach is also held in position by a partial anterior fundic wrap. Surgery is associated with a 1% mortality and a 2-8% morbidity consisting mainly of gas-bloat syndrome and dysphagia. The short-term success rate of surgery in carefully selected cases is 85% but 10% of patients have a recurrence of symptoms during follow up [99]. Laparoscopic Nissen fundoplication may make surgery more attractive although one randomised-controlled trial suggested it was associated with more morbidity than the open procedure [100].

Peptic ulcer surgery

Now rarely performed, operations include an antrectomy with a gastro-duodenal anastomosis (Billroth I), an antrectomy with gastro-jejunal anastomosis (Billroth II), a vagotomy and pyloroplasty or a highly selective vagotomy.

Surgery for gastric cancer

Although the prognosis is poor, surgical resection is the only procedure that provides a potential cure for advanced gastric malignancy. The extent of surgery however remains controversial. A total or subtotal gastrectomy with removal of lymph nodes within 3 cm of the stomach (a D1 resection) has been the traditional approach in Europe. This has been shown to have a significantly lower post- operative mortality than more radical surgery removing more distant lymph nodes and performing a splenectomy (a D2 resection) with similar three year survival [101]. The long-term survival from surgery in the UK, however, is disappointing with only 20% surviving more than five years [102]. The Japanese report less post-operative mortality and better survival with D2 resections [103]. This may be due to the Japanese presenting with gastric cancer at a younger age or more technical expertise at performing radical resections. One report from a UK unit with a high volume of D2 resections reported a

70% five year survival rate [104] and a low post-operative mortality attributed to preservation of the spleen [105].

Oesophageal cancer surgery

Historically oesophageal resection has been associated with one of the highest post-operative mortality of any of the routine surgical procedures [106]. The operation now has a < 10% post-operative mortality in specialised centres although five year survival from potentially curative resections is still less than 30%. The best treatment modality remains controversial: randomised controlled trials are currently being conducted to assess whether chemotherapy, radiotherapy or combined adjuvant therapy can improve survival.

Double contrast barium meal

Radiological investigation was the hospital-based procedure of choice until the 1980s but this was superseded by endoscopy because of its perceived greater accuracy and ability to take biopsies [107]. Double contrast barium meals (DCBM) provide better gastric mucosal coating and superior images to single contrast methods. DCBM are almost as sensitive as upper gastrointestinal endoscopy in detecting oesophageal cancer, advanced gastric cancer, duodenal and gastric ulceration [108,109,110] but are less sensitive at identifying early gastric cancer [111], oesophagitis and more subtle duodenal inflammation [112]. The other disadvantage of radiology is that biopsies of suspicious lesions cannot be obtained.

I.6 Auditing care

At the time of writing, the guideline developers are unable to identify any evidence of workable strategies to audit the care of patients with dyspepsia. MIQUEST is funded by the NHS Information Authority and is the recommended method of expressing queries and extracting data from different types of practice systems. Primary Care Informatics who implement MIQUEST have identified READ codes that may be helpful in investigating the care of patients with dyspepsia (Table 18), although the guideline development group express the reservation that coding of patient consultations in primary care may be inconsistent limiting the current value of this form of audit.

A more basic approach is to audit levels and proportions of drugs prescribed for dyspepsia. This data is available to practices through PACT (Prescribing Analysis Costs and Trends). Levels of use of drugs can be usefully compared when general practice populations are similar. However, they are not directly linked to the reason for prescription; clinical need and appropriateness cannot be assessed.

Information about MIQUEST and the Primary Care Information Services (PRIMIS) that helps Primary Care trusts using systems like MIQUEST and other initiatives of the NHS Information Authority can be found on the following websites: http://www.miquest.co.uk/, http://www.primis.nhs.uk/, and http://www.nhsia.nhs.uk/.

Table 9: Read codes to audit care of patients with dyspepsia in primary care

Read Codes for PPI Associated Morbidities				
Condition	**Information**	**Prompt**	**Read v1 (4 byte)**	**Read v2 (5 byte)**
Dyspepsia, indigestion NOS	Dyspepsia	Date	I264	JI6y4
Duodenal ulcer	DU	Choices*& Date	I23.	J12.
Gastric ulcer	GU	Choices*& Date	I22.	J11.

Oesophagitis	GORD+	Date	I212	J101.
Oesophageal reflux without oesophagitis	GORD without oesophagitis	Date		J10y4
Barrett's oesophagus		Date	I218	J1016
Oesophageal strictures and stenosis		Date	I214	J103.
Oesophageal ulcers		Date	I213	J102.
Gastritis and duodenitis		Choices* & Date	I25.	J15.

Codes useful for monitoring patients on PPIs – Read v2

Condition/Procedure	Information	Prompt	Code
Prophylactic drug therapy	Use free text to include "NSAID (gastro protection)"	Date	8B6.
Gastroscopy normal	Gastroscopy result normal	Date	36140*
Gastroscopy abnormal	Gastroscopy result abnormal	Date	36150*
Barium meal normal	Barium meal result normal	Date	5482
Barium meal abnormal	Barium meal result abnormal	Date	5483

Read Codes for *Helicobacter pylori* Associated Morbidities

Condition/Procedure	Information	Prompt	Read v1 (4 byte)	Read v2 (5 byte)
Helicobact eradication therapy	Eradication therapy for *Helicobacter pylori*	Date	8BAA	8BAC.
Dual therapy helicobacter	Dual therapy regime used	Date	8BAC	8BAE.
Triple therapy helicobacter	Triple therapy regime used	Date	8BAD	8BAF
Helicobacter serology positive	Positive serology test result for *H. pylori*	Date	4JD6	4JD6.
Helicobacter serology negative	Negative serology test result for *H. pylori*	Date	4JD7	4JD7.
Helicobacter serology equivocal	Equivocal serology test result for *H. pylori*	Date	4JDB	4JDB.
Helicobacter breath test	Breath test performed	Date	4JM.	4JM.
Helicobacter breath test pos	Positive breath test result for *H. pylori*	Date	4JM0	4JM0.
Helicobacter breath test neg	Negative breath test result for *H. pylori*	Date	4JM1	4JM1.
Helicobacter not tested	Breath test not performed	Date	4JM2	4JM2.
CLO test for *Helicobacter pylori*	CLO test performed	Date	4JO.	4JO.
CLO test positive	Positive CLO test result for *H. pylori*	Date	4JO0	4JO0.
CLO test negative	Negative CLO test result for *H. pylori*	Date	4JO1	4JO1.

+Use free text to indicate whether with 'mild oesophagitis', 'severe oesophagitis' or with 'oesophageal haemorrhage'

* Unavailable in Read code version 1 (4 byte)

I.7 Appendix

I.7.1 Appendix 1: describing the results of trials

I.7.1.1 Binary outcomes

A binary outcome provides two possibilities, for example: alive or dead; still on treatment or withdrawn from treatment. Binary data may be expressed in several ways in clinical studies. These are primarily odds ratios, risk ratios (also known as relative risks) and risk differences. Binary data from a comparative trial can be shown in a two by two table:

	Dead	Alive
Intervention Group	A	B
Control	C	D

Odds ratios are defined as: $\frac{A}{B} \Big/ \frac{C}{D}$

In other words, the odds ratio is the odds of death in the intervention group (number of deaths divided by the number of survivors) divided by the odds of death in the control group.

Risk Ratios are defined as: $\frac{A}{A+B} \Big/ \frac{C}{C+D}$

The risk ratio is the proportion of deaths in the intervention group (number of deaths in the intervention group divided by the total number allocated to the intervention) divided by the proportion of deaths in the control group. Trials sometimes refer to relative risk reductions (RRRs) which are calculated as one minus the risk ratio

Risk Differences are defined as: $\frac{A}{A+B} - \frac{C}{C+D}$

The risk difference is the proportion of deaths in the intervention group (number of deaths in the intervention group divided by the total number allocated to the intervention) minus the proportion of deaths in the control group.

Worked example:

In a trial of an ACE inhibitor in patients with heart failure there were 452 deaths among 1,285 patients randomised to receive enalapril, and 510 deaths among 1,284 allocated to control after an average follow-up of 4.5 years [a]. Shown in a two by two table this is:

SOLVD trial	Dead	Alive
Intervention Group	452	833
Control	510	774

Using the formulae provides an odds ratio of 0.82, a risk ratio of 0.89, and a risk difference of -0.045 (or a 4.5% reduction in the risk of death).

Each measure has advantages and disadvantages. The Odds Ratio is a statistically robust measure, but is hard to interpret clinically. The Risk Ratio is superficially easier to interpret, and both odds ratios and risk ratios may be particularly useful when attempting to combine studies which are estimating the same common underlying effect, but in which both severity of condition and length of follow up may vary. Neither measure is sufficient for clinical decision making alone: an odds ratio or risk ratio apparently showing a large effect from an intervention will not lead to large benefits in practice where the events are rare, and an apparently small relative effect may have a substantial impact where events are very common.

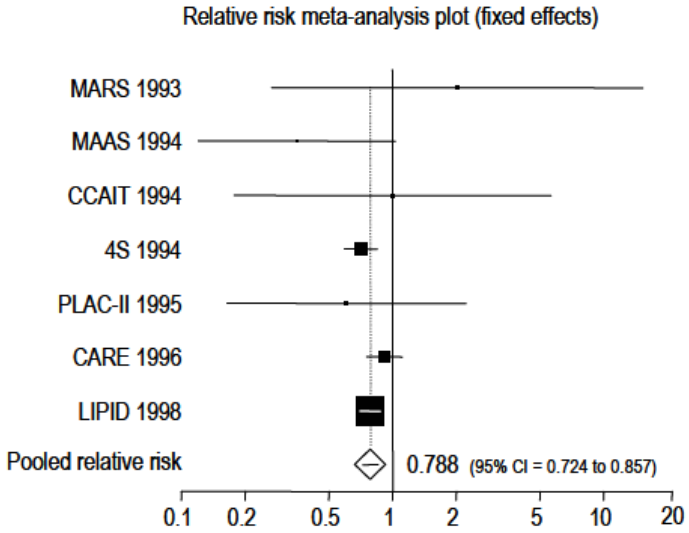
Risk Differences are not very helpful for exploring common underlying effects, but are very useful for describing the practical importance of the effects of treatment. Similarly, Number Needed to Treat is used to describe absolute benefits (NNT is the inverse of the risk difference: 1/0.045 or 22 in our example). It expresses the number of patients that would have to receive the intervention for one patient to receive (or avoid) the outcome described in a trial. A main advantage of the risk difference is that it expresses the practical value of interventions and allows comparisons between alternative treatments. However, a standard problem for risk differences and numbers needed to treat is that they are often derived from trials that have different lengths of follow up. The risk difference tends to become bigger as follow-up increases. Thus the incidence risk difference is used to estimate treatment effects using a common time frame, for example the number of deaths avoided as a result of treating 1,000 patients for a year [b].

Trials enrol a sample from the population of all patients and estimate the effect of treatments. These estimates have a degree of uncertainty which becomes less the bigger the sample size. A Confidence Interval (CI) for a treatment effect estimated in a trial is the range in which the actual population treatment effect is assumed to lie, with a specified probability. The specified probability is arbitrary: 95% is the most commonly chosen value, meaning that the true underlying treatment effect is assumed to lie within the range 19 times out of 20. The smaller the confidence interval, the greater the precision of measurement in the study. More precise confidence intervals are achieved, all things being equal, by studies which enrol more patients. The best and most likely estimate of effect is the point estimate at the centre of the confidence interval range. For our example the best estimate was that after nearly 5 years of treatment, an ACE inhibitor achieves a 4.5% reduction in the risk of death with a 95% confidence interval of 0.8% to 8.3%.

17.1.2 Meta-analysis of binary data

Commonly more than one trial exists to inform the value of a particular treatment. Where studies feature similar designs and use adequately similar outcomes it is possible to combine these to obtain an overall estimate of effect. This statistical process, called meta-analysis, involves taking a weighted average of the results of trials, where the most informative trials (biggest and with most events) contribute most to the overall result. Figures called forest plots are often used to display the findings of meta analyses. The example below shows a meta-analysis of the results of trials of statin therapy following a myocardial infarction to reduce the risk of subsequent mortality. The finding from each trial is shown as a mark on a graph with a line showing its confidence interval. In this instance, the mark used is a box, the size of which indicates how important the trial is to the combined, or pooled, result. The pooled finding is shown after the individuals studies (in the example as a lozenge) and indicates a risk ratio for death of 0.79 or 79% for patients receiving a statin when compared to those receiving placebo. Alternatively this may be expressed as a 21% relative reduction in the risk of death. The 95% confidence indicates, 19 times out of 20, that the true effect of

the drug will lie between a relative reduction of 72% and 86%: the range excludes the line of no effect or no change (one). The advantage of meta analysis is it provides the most precise guess at the effect of treatment reflecting all available studies. However, if the studies themselves have limitations or differ in important ways, then meta analysis can be misleading.



7.1.3 Meta-analysis of continuous data

Many outcomes are not binary but continuous (or nearly so), such as blood pressure readings and pain or symptom scores. With continuous data, the mean score for treatment and control groups in each trial are subtracted to calculate a mean difference (for example a reduction in blood pressure) and confidence intervals for this change are calculated using standard formulae that reflect the spread of the data (referred to as the standard deviation). Where studies use a common continuous outcome measure, meta-analysis can combine these to calculate a summary weighted mean difference comparing treatment and control groups.

Dichotomising data that are naturally continuous (for example into treatment failures and successes) is not generally advisable. It is often arbitrary, may result in pooling scores based on different cut-offs in different studies or cut-offs that have been identified with knowledge of the data and thus show the data in a favourable light. Dichotomisation may exaggerate small differences in effect, and more fundamentally the approach removes much information from the original data.

Standardisation

When there are concerns that measurement between studies is not undertaken using a common metric, standardised mean differences can be calculated for each trial. Examples might be where different but related measures are used to estimate the same outcome in patients, or where it is likely that measures are used inconsistently by different investigators. Standardisation is achieved by dividing mean differences from studies by their standard deviation [c,d]. Standardised weighted mean differences lack physical interpretation but can be worked back to a value on an original physical scale.

6.7.1.4 Studies examining different doses

Sometimes trials examine multiple dose regimens compared with a single control group. These trials are often conducted early during product development, are designed to examine the most appropriate dosage of a drug and may include groups receiving doses both within and outside the range ultimately licensed. It is important that such comparisons are not considered separately in the analyses, since they share a single control group and the resulting confidence intervals will be inappropriately narrow. In order to include all relevant information without undue statistical precision, an average effect is estimated for the range of therapeutic doses available.

6.7.1.5 Naturalistic studies

Double-blind randomised trials are occasionally criticised for inadequately representing treatment in the real world. In other words, trials that use a well defined population without co-morbidity, limit treatment options and make both the doctor and patient blind to the treatment received may provide different results from those realised in practice. The evaluation of pharmaceuticals is best undertaken using a series of experimental studies. This is reflected in phase II and III studies (small-scale dose ranging through to larger trials, often for licensing). Studies in phase IV may relax some of the requirements of the earlier trials in order to better reflect the real world: these may include relaxation of blinding, limiting clinical strategies such as choice of drug after initial randomisation and co-morbidity. Such studies have been described as ‘contaminated with the real world’ [e] and it may be difficult to work out what is being estimated (particularly with, say, strong patient or doctor preferences for one treatment). However, when examined with the earlier phase III trials, they may add useful information.

6.7.1.6 Meta-regression analysis

Where a number of trials examine the same underlying question, more complex techniques may be used to understand trial evidence. Regression models can explore whether the size of benefit from treatments varies with certain factors such as age or the presence of other diseases [f].

6.7.2 Describing the results of diagnostic tests

Before any tests are conducted, patients have a certain likelihood of disease. This may be determined as the population average or arise from a clinical assessment. Diagnostic tests try to improve the likelihood that individuals do or do not have disease, but do not usually provide certainty. A test may draw on a variety of data to understand or predict health status: these include psychological or physical characteristics, patient history, symptoms or signs, and findings from tests or equipment.

In diagnostic studies conducted to understand whether a test will be helpful, the test is compared with a reference standard (a proxy for true disease status). Reference standards are not always very good and their closeness to the gold standard (the test that would give absolute certainty about disease status) has to be assessed. Populations studied may vary in their relevance when addressing a clinical question within a guideline group [I,II].

	True +	True -	All
Screen +	79	950	1,029
Screen -	21	8,950	8,971
All	100	9,900	10,000

How tests are evaluated can be illustrated by examining mammographic screening for breast cancer [III]. The results are based on a cohort of ten thousand patients and the test performance found in published studies. The prevalence of breast cancer in this example is 1% or 100 in 10,000. Findings can be characterised by whether a positive test suggesting cancer (screen positive) is confirmed by the reference standard as a true positive case. Studies have found that 79 out of 100 cases of suspected breast cancer arising from mammographic screening are subsequently confirmed by biopsy, a sensitivity of 79%. Similarly 8,950 out of 9,900 patients without breast cancer are correctly excluded by screening, a specificity of 90%. On receipt of a positive screening result, the probability of biopsy confirming breast cancer is 79 out of 1,029 patients or 8%, the positive predictive value. A positive test increases a women's likelihood of having cancer from 1% to 8%. Similarly, a negative result decreases her likelihood from 1% to 0.2% (or from 1 in 100 to about 1 in 500).

As a rule of thumb, tests with sensitivities and specificities of 80% or more are considered useful. Whether this is the case depends upon the seriousness of missed disease or likelihood and consequence of unnecessary treatment for a false positive diagnosis.

	True +	True -	All
Screen +	a	b	a+b
Screen -	c	d	c+d
All	a+c	b+d	a+b+c+d

Formally, the following quantities are usually provided to describe the performance of diagnostic tests.

- Prevalence = (a+c)/(a+b+c+d)
- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- Positive Predictive Value PPV = a/(a+b)
- Negative Predictive Value NPV = d/(c+d)
- Likelihood ratio (positive), LR+ = sensitivity/(1-specificity)
- Likelihood ratio (negative), LR- = (1-sensitivity)/specificity)

17.3 Appendix 3: Prescription cost analysis for dyspepsia-related drugs. England 2001: totals by chemical entities [71]

BNF Chemical name	BNF no.	PXS[2] (1,000s)	OWC2[3] (1,000s)	NIC[4] (£ 1,000s)	NIC/PXS (£)
Antacids and Dimethicone	1.1.1.0	942.5	105.7	2,283.6	2.42
○ Aluminium & Magnesium & Act Dimethicone		161.3	1.3	364.4	2.26
○ Aluminium & Magnesium & Oxethazaine		91.5	2.6	157.2	1.72
○ Aluminium Hydroxide		32.2	5.6	119.5	3.71
○ Co-Magaldrox(Magnesi		283.9	62.8	704.1	2.48

BNF Chemical name	BNF no.	PXS[2] (1,000s)	OWC2[3] (1,000s)	NIC[4] (£ 1,000s)	NIC/PXS (£)
um/Aluminium Hydrox)					
○ Co-Simalcite (Act Dimethic/Hydrotalcite)		55.1	12.9	148.0	2.69
○ Dimethicone		136.0	20.2	297.9	2.19
○ Gripe Mixtures		0.1	0.0	0.2	2.14
○ Hydrotalcite		5.3	0.0	12.0	2.27
○ Magnesium Carbonate		5.3	0.0	112.6	21.28
○ Magnesium Hydroxide		1.4	0.2	7.3	5.15
○ Magnesium Oxide		0.9	0.0	74.0	82.50
○ Magnesium Trisilicate		169.7	0.0	286.5	1.69
Sodium Bicarbonate	1.1.1.2	5.6	0.0	90.6	16.32
○ Sodium Bicarbonate		5.5	0.0	90.4	16.52
Other Drugs for Dyspepsia and GORD	1.1.2.1	5,724.4	34.7	21,465.8	3.75
○ Alginic Acid Compound Preparations		5,722.0	34.5	21,413.6	3.74
○ Calcium Carbonate		1.1	0.0	46.6	42.43
○ Other Preparations		1.3	0.1	5.5	4.31
Antispasmodic & Other Drugs Altered Gut Motility	1.2.0.0	2,736.1	793.8	20,175.2	7.37
○ Alverine Citrate		289.4	209.6	3,171.1	10.96
○ Alverine Citrate Compound Preparations		4.2	0.9	55.4	13.06
○ Atropine Sulphate		3.7	0.0	77.4	20.70
○ Belladonna Alkaloids		1.8	0.0	2.2	1.24
○ Cisapride		1.1	0.9	27.7	24.99
○ Compound Antispasmodic Preparations		0.1	0.0	1.0	8.59
○ Dicyclomine HCl Compound Preparations		87.5	0.8	180.8	2.07
○ Dicyclomine Hydrochloride		261.8	156.6	1,170.1	4.47
○ Glycopyrronium Bromide		0.9	0.5	84.2	92.84

BNF Chemical name	BNF no.	PXS[2] (1,000s)	OWC2[3] (1,000s)	NIC[4] (£ 1,000s)	NIC/PXS (£)
○ Hyoscine Butylbromide		268.0	129.1	903.2	3.37
○ Mebeverine HCl Compound Preparations		97.1	17.1	1,450.3	14.94
○ Mebeverine Hydrochloride		1,362.2	81.0	9,397.2	6.90
○ Peppermint Oil		322.1	175.1	3,176.0	9.86
○ Propantheline Bromide		36.2	22.3	475.9	13.16
Test for *Helicobacter pylori*	1.3.0.0	2.1	0.3	45.1	21.12
○ Other Preparations		2.1	0.3	45.1	21.12
H2-Receptor Antagonists	1.3.1.0	5,657.7	661.8	53,500.7	9.46
○ Cimetidine		1,248.7	16.8	7,759.2	6.21
○ Famotidine		46.2	0.5	1,271.9	27.51
○ Nizatidine		573.4	539.0	9,281.0	16.18
○ Ranitidine Bismuth Citrate		1.3	1.0	36.3	27.98
○ Ranitidine Hydrochloride		3,788.0	104.4	35,151.6	9.28
Selective Antimuscarinics	1.3.2.0	0.1	0.1	3.0	25.79
○ Pirenzepine		0.1	0.1	3.0	25.79
Chelates And Complexes	1.3.3.0	30.7	6.7	273.3	8.90
○ Sucralfate		26.7	5.6	253.7	9.50
○ Tripotassium Dicitratobismuthate		4.0	1.1	19.6	4.90
Prostaglandin Analogues	1.3.4.0	43.2	36.7	623.1	14.41
○ Misoprostol		43.2	36.7	623.1	14.41
Proton Pump Inhibitors	1.3.5.0	13,211.1	12,396.8	364,351.5	27.58
○ Esomeprazole		357.5	266.3	8,647.6	24.19
○ *Helicobacter pylori* Eradication Therapy		60.8	5.1	2,157.4	35.46
○ Lansoprazole		6,249.4	6,066.8	140,338.8	22.46
○ Omeprazole		4,813.0	4,544.6	174,664.4	36.29
○ Rabeprazole Sodium		571.9	530.5	12,734.2	22.27
Other Ulcer-Healing Drugs		1,158.5	983.5	25,809.0	22.28
○ Carbenoxolone Sodium Compound Prep's	1.3.6.0	6.3	0.1	150.4	23.77

2 PXS: prescriptions

3 OWC2: class 2 drugs reimbursed at the proprietary price when generic unavailable

BNF Chemical name	BNF no.	PXS[2] (1,000s)	OWC2[3] (1,000s)	NIC[4] (£ 1,000s)	NIC/PXS (£)
4 NIC: Net Ingredient Cost: cost of the drug before discounts and excluding dispensing costs					

1.7.4 Appendix 4: A cost comparison of serology, stool antigen and breath testing for *H. pylori*

(The following is an edited version of an analysis received from Dr Cliodna McNulty, Consultant Microbiologist, Gloucester and Primary Care Liaison for the Health Protection Agency Helicobacter Pylori Working Group).

The purchase cost and performance of tests using serology, the stool antigen testing and the urea breath testing are estimated in Table 19and Table 20.

Table 10: Unit cost of non-invasive tests for *H. pylori*

	Serology	Dako Stool Antigen	Meridian Stool Antigen	Urea Breath Test
Kit cost (£/no. of tests)	£138.06/96	£460/96	£225/48	£14.55*/single
Cost per test+	£1.53	£5.11	£5.11	N/A
Technician time @ £15/hour	£2.25	£3.00	£3.00	N/A
Needle/vacutainer or stool collection vial	£0.07	£0.12	£0.12	N/A
Syringe	£0.06	N/A	N/A	N/A
Practice Nurse @ £15/hour	£2.50	N/A	N/A	£4.25
Transport and handling	£3.20	£3.20	£3.20	N/A
Total#	**£9.61**	**£11.43**	**£11.43**	**£18.80**

Assumptions
+ Assuming testing in batches of 30 some tests are unused.
* Pylobactell prescription test cost/test to pharmacist is £20.75. £6.20 paid by patient as prescription charge and £14.55 as an NHS cost.
# Costs include VAT and are agreed by the manufacturers.

Table 11: Performance of non-invasive tests for *H. pylori*

	Sensitivity	Specificity	
Serology	**92%**	**83%**	Leheij RJF, Straatman H, Jansen JBMJ, Verbeek ALM *J Clin Microbiol* Oct 1998: 2803-09
Dako Stool Antigen	**95.9%**	**97.6%**	
	95.5%	97.8%	Malfertheiner *et al Gut* Sept 2001; 49 (Supplement u):A97
	88.0%	97.6%	Andrews J *et al. J Clin Pathol* 2003;56:769-71.
	94.3%	93.8%	Leodolter A *et al. Am J Gastroenterol* 2002;97:1682-86

	Sensitivity	Specificity		
	98.2%	98.1%	Makristathis A *et al. J Clin Microbiol* Oct 2000;38:3710-14	
	98%	99%	Koletzko S *et al. Gut* 2003;52:804-6	
Meridian Stool Antigen	**92.4%**	**91.9%**	Gisbert *et al. Am J Gastroenterol* 2001;96:2829-38	
Urea Breath Test	**94.7%**	**95.7%**	Vaira D. *Gut* 2001;48:287-89	
* Weighted mean values are shown for reviews and imputed for the Dako Stool Antigen Test				
	True +ve	**False +ve**	**True -ve**	**False -ve**
Serology	460	255	1245	40
Dako Stool Antigen	488	62	1462	17
Meridian Stool Antigen	462	122	1378	38
Urea Breath Test	473	65	1435	27
* Sensitivity = true positives/(true positives+false negatives), Specificity = true negatives/(true negatives+false positives) 2000 tests with 25% prevalence gives 500 postives and 1500 negatives				

980

These data are used in an analysis comparing the cost and performance of serology, the stool antigen kit and the urea breath test. The analysis assumes a population of 400,000, with 4% of general practice consultations for dyspepsia (16,000), and 10% of these being referred for further investigation. Current GP serology testing rate in microbiology laboratories varies from 0 to 56 patients per 1,000 GP practice population, with a mean of 5 per 1,000 GP practice population. The analysis assumes 2,000 patients will be tested per annum and that the prevalence of *H. pylori* is 25% (Table 21).

Table 12: A cost comparison of serology, stool antigen and breath testing for *H. pylori*

	Serology	Dako Stool Antigen	Meridian Stool Antigen	Urea Breath test
Sensitivity	92.0%	97.6%	92.4%	94.7%
Specificity	83.0%	95.9%	91.9%	95.7%
Total no. of positives	715	550	584	538
No. of false positives detected	255	62	122	65
No. of true positives detected	460	488	462	473
Cost of test	£9.61	£11.43	£11.43	£18.80
Total cost of 2000 tests	£19,220	£22,860	£21,860	£37,600
Cost of treating all positives	£11,747	£9,036	£9,595	£8,839
Total cost of test and treat	**£30.967**	**£31,896**	**£32,455**	**£46,439**
If 50% of those symptomatic at follow-up are retested				
Cost of eradication test in 36% of false positives	*£1,730*	*£156*	*£474*	*£440*
Cost of eradication test in 32% of true positives	*£2,767*	*£1,748*	*£1,597*	*£2,845*
Total cost of testing post treatment	*£4,497*	*£1,904*	*£2,071*	*£3,285*
Total cost of test & treat and follow-up testing	***£35,464***	***£33,800***	***£33,526***	***£49,724***

Assumptions:

1. All positive patients are assumed treated, at a cost of £18/patient (BNF: *lansoprazole 30mg bd, amoxycillin 1g bd and metronidazole 400mg bd)*
2. All patients who respond symptomatically to treatment do not need post treatment tests.
3. At one year, the *H. pylori* eradication treatment response rate is estimated as 36% (range 21-58%) and the mean placebo response rate as 28% (range 7-51%) [395]. Thus 64% and 72% of patients with true and false positive tests will be symptomatic. The analysis assumes half of these reconsult and are retested (32% and 36%).
4. Serology positive patients are tested by urea breath test if symptomatic post treatment
5. Breath test positive patients will be tested by urea breath test if symptomatic post treatment
6. Stool antigen positive patients will be tested by stool antigen if symptomatic post treatment

The findings indicate that laboratory based serology, the most commonly used non-invasive test in the UK for *H. pylori*, may perform less well than alternative breath testing or stool antigen testing. At a prevalence of 25%, 40% of patients positive by serology will be incorrectly diagnosed with helicobacter and receive inappropriate treatment. With the stool antigen test (Dako) or urea breath test, only 10% of positive patients will be incorrectly treated. The stool antigen or breath tests lead to less inappropriate antibiotic treatment and

less confusion in post treatment follow-up. Although initial test costs of the stool antigen tests are slightly higher than serology these are offset by reduced follow-up costs.

17.5 Appendix 5: Patients' and GPs' views of dyspepsia

This section draws upon research undertaken by the Department of Medicines Management at Keele University and is augmented with the comments and experience of the guideline development group [59,60,61,62]. The investigators conducted in-depth interviews with 26 general practitioners from 7 practices and 82 patients with chronic dyspepsia. GPs were invited to take part in the study and 4-5 patients per GP were randomly selected from those requiring repeat scripts for PPIs. Out of the 156 patients selected, 83 were interviewed, 8 were deemed inappropriate by GP vetting, 38 refused, 23 proved unobtainable and 4 were no longer taking PPIs. The role of PPIs in the treatment of dyspepsia was explored alongside generic healthcare issues relevant to patients.

17.5.1 Experience of dyspepsia

Dyspepsia is a common condition which most people experience at some time. Dyspeptic symptoms may be very uncomfortable and painful, and can impose severe restrictions on patients' activities and quality-of-life. Patients reported a range of symptom severity with appropriately a quarter expressing these as mild-moderate; however, the majority interviewed felt their symptoms were severe and incapacitating. In addition, GPs viewed symptoms as variable but nearly a half of those interviewed agreed with patients that symptoms were usually severe at the point when PPIs were prescribed.

"It wasn't a pain. It was an uncomfortable feeling. It wasn't intense or anything, but it was just very uncomfortable and I was burping a lot."

"I started to get horrendous chest pains, shortness of breath, pains down my arm, waking up in the night, and if I had to go anywhere on my own and I hadn't got any transport, the pain was just so bad."

17.5.2 Understanding and coping with dyspepsia

In twenty-five percent of cases, there were significant differences in diagnostic terms used by patients and doctors. Patients most frequently used the term hiatus hernia while GPs referred to oesophagitis. Moreover, patients studied often felt poorly informed about their condition; lacking a clear explanation made it harder to cope with their condition. Younger patients who received a firm diagnosis felt they had a frame of reference within which to manage their dyspepsia and expressed the importance of diagnostic tests to enable them to make the connection between symptoms and disease. However, some patients found it difficult to equate the severity of their symptoms with what they perceived to be a diagnosis of a relatively minor condition.

"If you're in pain 24 hours a day, you are saying to yourself, 'well this (bacteria on the stomach lining) isn't causing this pain.'"

17.5.3 Modifying lifestyle

Nearly sixty percent of doctors expressed the view that patients used PPIs to support unhealthy lifestyles including poor diet, excessive alcohol consumption and smoking. This ran counter to the experience of patients who felt they were simply aspiring to live normally. Patients reported having made changes to improve their health and were following moderate or even abstemious ways of living and did not regard their behaviour as contributing

substantially to their stomach problems. This dichotomy of opinion has implications for effective doctor-patient relationships.

"Well I suppose a sensible diet would help. But I've cut out cheese; well I've almost cut out cheese and cheese dishes, animal fats and fatty meats. I've cut down on coffee but I haven't cut it out".

From a GP's perspective, there was lack of agreement about the influence that lifestyle has on the disease process and the effectiveness of lifestyle measures. Most gave lifestyle advice as they felt that there was scope for symptom reduction but a few questioned the evidence base for this rationale. Most GPs recognised that changing behaviour was difficult.

Two-thirds of patients remember receiving lifestyle advice and of those who followed recommendations, 50% found it to be beneficial. However, lifestyle advice received by patients was often felt to be superfluous or impractical. Some patients found the link between smoking and gastric disorders hard to understand or accept and some GPs were unable to offer a clear explanation. Many people in the studies found that their age and/or infirmity resulting from additional health problems constrained their ability to adopt healthy behaviours and limited their choices relating to lifestyle. Patients found advice unhelpful where it was inappropriate to their particular circumstances.

17.5.4 Views about receiving treatment

Treatment with a PPI was often second or third line therapy with the majority of patients having tried 'over-the-counter' medicines before seeking help from the GP. Both patients and doctors reported PPIs as the best treatment drugs, although patients did not rate their effectiveness as highly. Patients described occasional symptoms despite the use of PPIs but in general, it was felt PPIs restored a degree of predictability and normality to everyday living with long-term symptom management a key factor in improving quality of life. Some patients expressed the concern that PPIs, whilst providing much needed symptomatic relief, were not a cure and were anxious about the prospect of taking medicine for the rest of their lives. Furthermore, patients were worried that reliance on drug therapies such as PPIs might inhibit further research into the cause and cure of gastric disease. Most patients offered their support to any initiative that would dispense with their long-term need for PPIs.

"The only thing that does bother me, like I say, is this going to be it? Is all you have got to look forward to, taking drugs? There just seems to be no ending to it."

The investigators suggest that greater awareness of the patient perspective might enable doctors to help patients control their symptoms more effectively and explore alternative ways of treating and managing their disorder. In particular greater understanding of prolonged PPI use would enable patients to make better informed decisions about treatment.

17.5.5 Safety and costs of PPIs

Most GPs thought that they were using available guidelines to prescribe PPIs appropriately. They described a demanding patient stereotype but in reality few patients asked for PPIs directly and often GPs felt if patients had tried over-the-counter antacids and H2RAs, they were left with few prescribing options except PPIs. The overall pressure on prescribing was economic not clinical, and thus conflict arose between clinical need and cost. Doctors felt that discontinuation, or reduction from treatment to maintenance therapy was more problematic as patients were naturally concerned that symptoms would return.

"I'm so much better with the Losec I didn't feel that I wanted to change".

Side effects of PPIs were underestimated by doctors and were generally not discussed within the consultation. Doctors in the study were unaware of the concern felt by some patients about prolonged use of PPIs and possible harmful effects. Likewise, over half the doctors expressed concern regarding the theoretical risk of gastric cancer with prolonged PPI use and the difficulty of explaining this to patients.

Most patients were aware that PPIs were expensive drugs but felt that the severity of their symptoms justified the cost. Patients accepted the need to reduce costs otherwise drugs might not be available in the future but wanted reassurance that if changes to their medication proved ineffective they could revert to the more effective and costly regime. GPs underestimated patients' willingness to change to minimum treatment with communication highlighted as an essential component of a favourable response to alterations in medication. Some practices had implemented a policy of 'double switching'- changing brand and lowering dose at the same time, with the dose reduction producing most of the cost saving. When this happened, patients were often unaware of the dose reduction, only the brand change. If symptoms returned they believed the brand was ineffective rather than dose. Double switching often failed, with patients reverting back to the full dose of PPI.

GPs reported making considerable efforts to change their prescribing habits to reduce prescribing costs of PPIs but their overriding concerns were that of patient need and clinical effectiveness. Overall, PPIs were considered as cost effective drugs.

17.5.6 Treatment adherence

Of 82 patients, nearly two thirds reported not deviating from the prescribed dose. Of the remainder most experimented with self regulation reducing the dose of PPI taken. Six reported taking more than the prescribed dose in response to inadequate symptom relief, although dose reduction by the GP may have contributed in some of these patients.

"…my doctor told me I need to take one tablet but sometimes I take two. I know I shouldn't have done that. But the pain, if it was terrible, I thought well, I'll take two, perhaps I'll double the amount of substance in the tablet that might help. And I did find taking two at a time was helpful, but not all the time."

Patient self-regulation of medication was highlighted as a possible strategy for reducing PPIs. Eleven doctors encouraged their patients to self regulate. In general, patients who experimented with PPI doses felt more comfortable asking questions within the consultation.

17.5.7 Study conclusions

The study investigators recognised the complexity of factors surrounding the prescribing of PPIs and the need to look beyond stereotypes of 'profligate prescribers', 'demanding patients' or 'adverse lifestyles'. There was no evidence to support the perceived practice of trivial prescribing of PPIs for minor complaints and it was felt that long term prescribing was based on clinical need. Both patients and GPs were aware of the economic implications of prescribing expensive drugs and highlighted that patient self regulation was a possible rationing strategy that could be further explored. Moreover, patients did not seem well informed about their gastrointestinal complaints and there was a need for evidence based guidelines for GPs to aid appropriate prescribing and patient information packs on the management of dyspepsia to help educate and empower patients to make decisions in relationship to their healthcare needs.

I.7.6 Appendix 6: Randomised controlled trials of therapies for undiagnosed dyspepsia

Study	Location Design Interventions	Participants	Methods	Treatment n/N, Control n/N†	Outcomes, Notes
Asante 1998	UK. RCT Main: Endoscopy Control: No endoscopy, returned to GP with advice that OGD unlikely to be helpful.	417 Consecutive *H. pylori* positive patients age 18 - 43 years, referred by their GP for investigation. Exclusions: *H. pylori* positive by serology (Helico G) , symptoms suggestive of malignancy, pregnancy, using NSAIDs.	Randomisation: simple Concealment of allocation: sealed numbered envelopes Blinding: none Site of recruitment: Secondary care Site of Randomisation: secondary care. Site of intervention: Secondary care Analysis reported: ITT. Economic analysis: comparison of total costs and resources only.	Global status: 27/61,26/59	Symptoms: Patient self report of improvement on a 3 point scale (same, better, worse). Quality of life: None. Satisfaction: one question on a 4 point scale. Resource use: GP visits, endoscopies, prescribing, sick days,. Costs: from local unit costs with sensitivity analysis. Only randomised *H. pylori* negative patients who had already been referred. See Delaney 1999b for a similar primary care-based trial.
Bytzer 1994	Denmark. RCT Main: Early endoscopy: endoscopy without prior treatment. Comparison: Emirical treatment with 4 weeks of Ranitidine 150 mg bd. Endoscopy co-interventions: duodenal ulcer Ranitidine, 2 courses then maintenance at 150 mg daily. Oesophagitis, Ranitidine then Omeprazole 20-40mg daily according to response. Gastric ulcer, Ranitidine then endoscopy at 6 weeks. Control patients were endoscoped if symptoms persisted after 8 weeks.	414 Patients age 18 and over, with symptoms of upper GI disease, without a previous history of PUD or oesophagitis, of sufficient severity for GP prescribe acid suppression. Exclusions: H_2RA or PPI in past 2 months, symptoms suggestive of malignancy, pregnancy, serious intercurrent illness, lack of co-operation.	Randomisation: Blocked 25 Concealment of allocation: Unknown Blinding: none Site of recruitment: Primary care Site of Randomisation: secondary care. Site of intervention: Secondary care Analysis reported: ITT. Economic analysis: comparison of total costs and resources (cost minimisation).	Global assessment: 27/187,27/186	Symptoms: Individual symptom scores for epigastric pain, vomiting, day time heartburn and night time heartburn at 1 year. Patient self report of improvement on a 4 point scale. Quality of life: None. Satisfaction: one question on a 4 point scale. Resource use: GP visits, endoscopies, prescribing, sick days. Costs: not clear. No *Helicobacter pylori* eradication for PUD, likely to mimimise effect of intervention as no definitive treatment given.

Study	Location Design Interventions	Participants	Methods	Treatment n/N, Control n/N†	Outcomes, Notes
Chiba 2002	Canada RCT Main: omeprazole 20mg, metronidazole 500mg and clarithromycin 250 mg twice daily for seven days Comparison: omeprazole 20mg, placebo metronidazole and placebo clarithromycin twice daily for seven days	294 patients with at least moderate severity dyspepsia in the preceding month Exclusions: GORD, investigated by upper GI endoscopy, barium study or both less than 6 months before randomisation or on more than two separate occasions within preceding 10 years; *H. pylori* eradication therapy less than 6 months before randomisation, previous gastric surgery, previous ulcer disease or endoscopic oesophagitis, irritable bowel syndrome or clinically significant laboratory	Randomisation: computer in blocks of 4 Concealment of allocation: sealed, sequentially numbered envelopes Blinding: patients and investigators Site of recruitment: primary care Site of randomisation: primary care Site of intervention: primary care Analysis reported: ITT Economic analysis: mean costs per patient over year of studyabnormalities.	Global assessment: 61/145,80/149 Endoscopies: 11/145,16/149	Syptoms: 7 point Likert-type scale (GOS scale) Quality of life: quality of life in reflux and dyspepsia (QOLRAD) Costs: compared the mean annual cost of *H. pylori* eradication treatment with that of placebo. Use of resources measured prospectively at monthly intervals by telephone and clinic interviews with a questionnaire. Direct costs included visits to the physician (specialist, family physician) and other healthcare professionals, drugs (prescription, over the counter), and investigations (for example, laboratory tests, radiography, endoscopy). Indirect costs of days lost through dyspepsia took into consideration whether the patient was employed, unemployed, or a senior citizen (aged over 65) and were calculated from Canadian labour force and unpaid work estimates.
Delaney 1999	UK RCT Main: Early open access endoscopy. Comparison: v. Empirical acid suppression with selective endoscopy at GPs discretion. Co-interventions: *H. pylori* eradication and prescribing at discretion of participating physicians.	442 patients with dyspepsia aged 50 years and over. Dyspepsia defined according to 1988 working party. Exclusions: Endoscopy in past 3 years.	Randomisation: computer Concealment of allocation: sealed envelopes. Blinding: none Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: cost-effectiveness-cost per case symptom free at study end point	Global assessment: 113/188,86/133	Symptoms: Birmingham Dyspepsia symptom score. Quality of Life: Korman. Satisfaction: Questionnaire. Resource use: GP consultations, prescribing, investigations, outpatient and inpatient episodes.

Study	Location Design Interventions	Participants	Methods	Treatment n/N, Control n/N†	Outcomes, Notes
Delaney 1999b	England RCT Main: Test and endoscopy Comparison: v usual practice by GP Co-interventions: Those in the test and scope group testing negative were treated with acid suppresson treatment according to GPs choice.	478 participants less than 50 years old consulting with dyspepsia Exclusions: previous endoscopy, barium meal within last 3 years, not consulted previously and symptomatic for less than 4 weeks, pregnancy, unfit for endoscopy, unable to give informed consent.	Randomisation: computer generated simple random number sequence Concealment of allocation: Sealed envelopes Blinding: None Site of recruitment: Primary care Site of randomisation: Primary care Site of intervention: Usual care - primary care; HP test- primary care; endoscopy-secondary care Analysis reported: ITT Economic analysis: cost-effectiveness-cost per case symptom free at study end point	Global status: 116/183,74/106	Symptoms:Birmingham Dyspepsia Symptom Score Quality of Life: Questionnaire Satisfaction: Validated questionnaire Resource use and costs: Costs for all medication, all procedures and hospital appointments, GP visits/consultations, number of GI or surgical OPD appointments for dyspepsia.
Duggan 1999	RCT England 1. Prompt endoscopy 2. *H. pylori* test and endoscope if positive. 3. *H. pylori* test and treat if positive 4. PPI four weeks.	762 participants age over 18 years consulting with dyspepsia Exclusions: previous endoscopy, barium meal within last 3 years, not consulted previously with dyspepsia and symptomatic for less than 4 weeks, symptoms suggestive of malignancy, pregnancy, unfit for endoscopy, unable to give informed consent.	Randomisation: computer generated simple random number sequence Concealment of allocation: Sealed envelopes Blinding: None Site of recruitment: Primary care Site of randomisation: Primary care Site of intervention: Usual care - primary care; HP test- primary care; endoscopy-secondary care; HP eradication-Primary care. Analysis reported: ITT Economic analysis: cost-effectiveness-cost per case symptom free at study end point (results not yet available)	1. vs 4. Global assessment: 48/140,54/136 2. vs 4. Global status: 86/141,86/136 3 vs. 1. Global assessment: 67/142,48/140 3 vs. 4. Global assessment: 67/142,54/136	Symptoms:Nottingham Dyspepsia Symptom Score Quality of Life: Questionnaire Satisfaction: Validated questionnaire Resource use and costs: Costs for all medication, all procedures and hospital appointments, GP visits/consultations, number of GI or surgical OPD appointments for dyspepsia. A number of possible comparisons, only some data currently available in abstract. Initial OGD v. PPI, Hpylori test and treat v. OGD included in current review
Goodson 1989	USA RCT Main: Early Barium Meal Comparison: Maalox 15-30 ml 7 times a day. Co-interventions: Treatment of breakthrough dyspepsia with H_2RA.	101 patients, age 18 and over, presenting in primary care clinics and emergency rooms with 4 days of symptoms fitting 1998 Working party criteria. Exclusions: Using H_2RA, ulcer in past 2 years, tetracycline therapy, drug or alcohol abuse, symptoms suggestive of malignancy, GI bleeding, lack of coopoeration or fluent English.	Randomisation: unclear Concealment of allocation: unclear Blinding: none. Site of recruitment: Primary care (Emergency rooms) Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT Economic analysis. Comparison of total costs alone.		Symptoms: Dyspepsia score (unvalidated). Quality of Life: Sickness Impact Profile. Satisfaction: none. Resource use: use of H_2RA at 26 week endpoint only. Only 101 recruited of 405 eligible (mainly refusals), only 78 completed trial.

Study	Location Design Interventions	Participants	Methods	Treatment n/N, Control n/N†	Outcomes, Notes
Goves 1998	UK. Multicentre RCT Main: Omeprazole 10-20 mg for 4 weeks. Comparison: Open label Gaviscon 10ml qds for 4 weeks. Co-interventions: none.	670 primary care patients, age 18+, from 100 practices. Symptoms fitting 1988 Working Party of at least 1 month and in at least 2 days of the week prior to starting the 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.	Randomisation: random number. Concealment of allocation: sealed pack. Blinding: patients and investigators. Sie of recruitment: primary care. Site of randomisation: primary care: Site of intervention: primary care. Analysis reported: ITT	Global assessment: 117/322,228/325 Heartburn: 117/322,228/325 Epigastric pain: 105/332,142/324 Patient satisfaction: 85/331,277/327	Assessments at 2 weeks and 4 weeks. Symptoms: Epigastric pain, heartburn, belching. Dyspepsia symptom score (unvalidated), Gastrointestinal Symptom Rating Scale (GSRS), Side effects, Global assessment of 'complete and sufficient' relief of symptoms. Quality of life: Psychological well being (PGWB). Satisfaction: none. Resource use: Antacid consumption only. Costs: none.
Heaney 1999	Ireland RCT Main: Endoscopy without further investigation Comparison: v empirical eradication therapy without further investigation Co-interventions: Patients endoscoped were given treatment according to findings. PUD: 1 week *H. pylori* eradication, PUD and oesophagitis: eradication and omeprazole 20mg bd for further 3 weeks; oesophagitis; omeprazole 20mg bd for 4 weeks, *H. pylori* -ve NUD; symptomatic treatment (antacids/ gaviscon/ ranitidine /omeprazole). All patients were given lifestyle advice.	104 patients aged less than 45 years old who were *H. pylori* positive and presented with an ulcer-like dyspepsia Exclusions: Alarm symptoms e.g weight loss or dysphagia, symptoms of GORD, history of GI bleeding, regular use of NSAIDs, symptoms suggestive of gallstones, pregnancy, traetment with HP eradiaction therapy in previous 2 weeks.	Randomisation: Stratified to take in to account sex, tobacco use and alcohol use. Concealment of allocation: Unknown Blinding: None Site of recruitment: Secondary care Site of intervention Secondary care Analysis reported: ITT Economic analysis: None	Global assessment: 28/49,35/50	Symptoms: Comparison of dyspepsia score and personality traits in both groups. Quality of Life: Comparison of baseline and 12 month quality of life scores Satisfaction: None Resource use: None Costs: None No controls were used (previously excluded)
Jones 1997	UK Multicentre RCT. Main: Lansoprazole 30 mg 1 od + placebo 1 od for 4 weeks. Comparison: Ranitidine 150 mg bd for 4 weeks. Identical formulation. Co-interventions: none.	450 patients, age 18-80, from 32 general practices, fitting 1988 Working Party criteria Exclusions: nonspecific or dysmotility-type symptoms. Symptoms of less than 2 weeks or 4 out of 7 days in the week preceding study entry.	Randomisation: computer. Concealment of allocation: sealed pack. Blinding: patients and investigators. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT Economic analysis: none.	Global assessment: 42/137,81/145 Heartburn: 23/137,53/146 Epigastric pain: 38/137,58/146	Symptoms: day and night epigastric pain and heartburn, global improvement, mean use of antacid top-up at 2 and 4 weeks. Quality of life: none. Satisfaction: none. Resource use: none. Costs: none.
Jones 1999a	UK Multi-centre RCT Main: Lansoprazole 15 mg 1 od. Comparison: Omeprazole 10mg 1 od for 4 weeks. Co-interventions: none.	562 patients, age 18-80, recruited from 52 practices, with dyspepsia meeting 1988 Working Party criteria, but excluding confirmed oesophagitis, peptic ulcer disease and non acid-related dyspepsia in diagnostic criteria. Symptoms 'persistent' and of more than 4 days duration in week preceding entry.	Randomisation: computer. Concealment of allocation: sealed packs. Blinding: patients and investigators. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none.	Global assessment: 116/283,137/279	Symptoms: Daytime and nocturnal epigastric pain and heartburn at 4 weeks. Global dyspepsia score (not validated), global assessment of symptoms. Quality of life: none. Satisfaction: none. Resource use: Consumption of open-label antacids. Costs: none.

Study	Location Design Interventions	Participants	Methods	Treatment n/N, Control n/N†	Outcomes, Notes
Laheij 1998	Holland RCT Main: Endoscopy Comparison: Empirical treatment with omeprazole or if *H. pylori* positive to give eradication therapy. Co-interventions: Those in empirical treatment group if not improved had endoscopy. If symptoms improved they had a further 2 weeks of omeprazole, if relapsed were given omeprazole 20mg od for 8 weeks. Patients who presented with a second relapse within the study period of 1 year had a *H. pylori* serological test. If positive were given eradiaction with quadruple therapy.	84 patients aged over 18 years with persistent dyspeptic symptoms sufficient to justify referring for OGD. Exclusions: Use of PPIs, signs or suspicions of malignancy (food transit complaints, weight loss, anaemia, vomiting of blood), treatment with NSAIDs, previous GI surgery, pregnancy or lactation, chronic alcoholism or drug abuse or lack of motivation.	Randomisation: Computer generated patient numbers Concealment of allocation: Unknown Blinding: None Site of recruitment: Primary care Site of randomisation: not stated (presumed primary care) Site of intervention; not stated (assumed primary care) Analysis reported: ITT not stated, 4 protocol violaters were excluded from analysis in OGD group. Economic analysis: Cost per patient: mediacl and non-medical costs.	Symptom-free days: 31/74,45/81	Symptoms: Daily diary over 1 year study period Quality of Life: Dartmouth COOP functional health assessment charts/ WONCA. Resource use: days off work, out-of-pocket costs, GP visits. Costs: Societal perspective; include endoscopy, personnel, administrative staff, maintenance, hospital overhead costs, laboratory costs and OPD appointments. Costs based on 1995 prices. Main effect measure symptom-free days.
Lassen 1998	Denmark RCT Main: Endoscopy Comparison: v *H. pylori* test and treat Co-interventions: *H. pylori* +ve: lansoprazole 30mg od, metronidazole 500mg tds and amoxycillin 1g bd for 2 weeks. Endoscopy if no improvement or relapse. Endoscopy if *H. pylori* -ve + NSAIDs or aspirin in last 1 month. *H. pylori* –ve, no NSAIDs: PPIs (lansoprazole 30 mg od for 1 month) continued as necessary, and endoscopy if no improvement. Patients endoscoped were treated according to the findings. DU had eradiacton therapy and 2 weeks of PPI. GU had treatment according to H.P. status with either eradication therapy followed by 4 weeks of PPI or 6 weeks of PPI.Reflux oesophagitis were given PPI for 8 weeks and then this was continued on a when needed basis.	500 patients over 18 years old with greater than 2 weeks symptoms of dyspepsia sufficient for GP to warrant acid suppression treatment. Exclusions: less than 18 years old, treatment with ulcer healing drugs within the preceding 1 month, sign or suspicion of upper GI bleeding or anaemia or jaundice, unintended weight loss of more than 3 kg, any contraindication to endoscopy, previous GI surgery to upper GI tract, pregnancy, serious or fatal conditions or suspected lack of cooperation.	Randomisation: Tables with random numbers Concelament of allocation: Sealed , numbered envelopes Blinding: Yes, as above Site of recruiment: Primary care Site of randomisation: Primary care Site of intervention: *H. pylori* testing; primary care and endoscopy secondary care. Analysis reported: ITT Economic analysis: Resource use was compared but no unit costs were applied to compare total costs	Global assessment: 45/223,54/224	Symptoms: Daily diary to record symptoms and grade them. Symptoms measured on a visual analogue scale. Quality of Life: used self administered, validated questionnaire, Psychological well being index. Satisfaction: Graded on 4 point scale Resource use: Numbers of endsocopies, *H. pylori* tests, eradication treatments and PPI consumption. Sick leave days and GP visits, hospital OPD clinics and admissions Costs: None

Study	Location Design Interventions	Participants	Methods	Treatment n/N, Control n/N†	Outcomes, Notes
Lewin 1999a	Netherlands. RCT 1. Treatment based on symptom pattern (ulcer-like and reflux-like given Ranitidine of Cimetidine, non-specific given Cisapride or Domperidone) 2. Omeprazole 20 mg od 3. Cisapride 10mg tds	263 patients age 18-80. Recruited by 95 general practitioners	Randomisation: computer generated. Concealment of allocation: centralised telephone service. Blinding: open trial. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none yet available.	Global assessment: 62/84,62/80	Only 130/263 patients available for symptom score at 14 weeks. 247/263 available for re-attendance.
Lewin 1999b	Netherlands. RCT Main: Early endoscopy. Comparison: Empirical treatment (70% had H_2RA, 25% Prokinetic and 5% PPI) Co-interventions: endoscopy if treatment unsuccessful in empirical group.	176 patients age 18-80 Recruited by 95 general practitioners.	Randomisation: computer generated. Concealment of allocation: centralised telephone service. Blinding: open trial. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none yet available.	Global assessment: 31/74,45/81	Symptoms: Symptom score (Utrecht score) at 8 and 14 weeks. Quality of life: none. Satisfaction: none: Resource use: Re-attendance after 8 weeks up to 1 year. 43% of empirical treatment group went on to endoscopy. 162/176 available for analysis
Mason 1997	UK. Multicentre RCT Main: Omeprazole 10-40mg Comparison: Gaviscon (Reckitt and Colman) 10 ml qds and Ranitidine 150 mg as required. Treatment for 16 weeks.	703 patients, age 18-80, with dyspepsia from 131 practices. Exclusions: Patients with definite previous diagnosis of peptic ulcer disease or oesophagitis.	Randomisation: random number. Concealment of allocation: unclear. Blinding: none. Sie of recruitment: primary care. Site of randomisation: primary care: Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none	Global assessment: 107/289,176/269 Epigastric pain: 40/291,66/269 Heartburn: 54/291,107/269 Patient satisfaction: 46/289,152/269	Symptoms: Epigastric pain and heartburn at 4 and 16 weeks. Global assessment of improvement. Quality of life: none. Satisfaction: none: Resource use: none.
McColl 2002	UK RCT Main: endoscopy plus breath test for *H. pylori* Comparison: breath test alone	586 patients referred by their general practitioners to the hospital for endoscopic investigation of upper gastrointestinal symptoms Exclusions: age over 55, the use of non-steroidal anti-inflammatory drugs (excluding low dose aspirin), and the presence of sinister symptoms	Randomisation: tables of random numbers Concealment of allocation: sealed envelope Blinding: Site of recruitment: primary care Site of randomisation: secondary care site of intervention: secondary care analysis reported: Economic analysis: none	Global assessment: 33/293,42/291	Symptoms: 0-6 integer scale; interview by non-medical, non-nursing staff; Glasgow dyspepsia severity score Quality of life: SF-36 Costs: none

Study	Location Design Interventions	Participants	Methods	Treatment n/N, Control n/N†	Outcomes, Notes
Meiniche-Schmidt 97	Denmark. RCT A - Main: Omeprazole 20mg od. Comparison: Cimetidine 400 mg bd for 2 weeks. B - Main: Omeprazole 20mg od. Comparison: Placebo 1 od for 2 weeks.	1017 patients, age 18-75, with 1988 Working Party dyspepsia excluding categories III and IV, from 63 practices. Divided into A- patients with proven peptic ulcer disease or oesophagitis (469), B- uninvestigated dyspepsia (548).	Randomisation: computer generated. Concealment of allocation: double dummy packs. Blinding: blind to patients and investigators. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none.	A Global assessment: 110/207,147/220 Heartburn: 25/180,62/200 Epigastric pain: 74/179,108/200 B Global assessment: 136/273,173/266 Heartburn: 44/243,79/228 Epigastric pain: 114/243,110/228	Symptoms: Epigastric pain at 15 days. Dyspepsia symptom score, total symptom relief at 15 days Quality of life: none. Satisfaction: none: Resource use: none.
Paton 1995	UK. Multicentre RCT Main: Gaviscon (Reckitt and Colman) 10-20 ml qds Comparison: Ranitidine 300mg od. Treatment for 24 weeks.	255 patients, age range not reported, with heartburn only recruited from 42 general practices.	Randomisation: unclear Concealment of allocation: unclear. Blinding: none. Site of recruitment: primary care. Site of randomisation: primary care: Site of intervention: primary care. Analysis reported: ITT. Economic analysis: total costs.	Global assessment: 62/119,72/136 Heartburn: 8/83,9/80	Symptoms: Heartburn, Symptom scores and Global assessment. Quality of life: Nottingham Health Profile. Satisfaction: none Resource use: none. Costs: prescribing. Quality of life data not reported.
Stevens 2001	UK and Norway RCT Only *H. pylori* positive patients randomised: Main: eradication therapy (lansoprazole 30mg, clarithromycin 250mg and amoxycillin 1g bd) for 1 week followed by lansoprazole 30mg od for 3 or 7 weeks. Comparison: placebo antibiotics and lansoprazole 30mg od for 4 or 8 weeks NB: All *H. pylori* negative patients were given Lansoprazole 30mg daily for 4-8 weeks without randomisation.	Country: Subjects: 543 patients from 64 primary care centres. Age 18 and over, with predominant epigastric pain of at least one month duration, and testing *H. pylori* positive. Exclusions: patients with alarm symptoms, now onset dyspepsia if over 45 years of age, history of confirmed duodenal or gastric ulcer, oesophagitis, requiring NSAIDS.	Randomisation: random number table Concealment of allocation: sealed envelope Blinding: patients and investigators Site of recruitment: primary care Site of randomisation: primary care site of intervention: primary care analysis reported: ITT Economic analysis: Not yet available	Global assessment: 47/127,73/142	Symptoms: Epigastric pain and other gastro-intestinal (GI) symptoms, GI consultations, GI prescriptions and GI investigations

I.7.7 Appendix 7: Randomised controlled trials of therapies for gastro-oesophageal reflux disease

Study	Location Design	Participants	Concealment of allocation Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Angelini 1993	Italy RCT Multi-centre ? Double blind	102 patients with healed oeosphagitis	Inadequate Omeprazole 20mg OD vs ranitidine 300mg OD		Oesophagitis (at least gII)
Baldi 2002	Italy RCT Multi-centre Double blind	137 patients with healed oeosphagitis	Adequate Lansoprazole 15mg OD vs 30mg alt days (subdivided into morning or evening for both)		Oesophagitis and symptoms
Baldi ?	RCT Multi centre Double blind	906 patients with healed oesophagitis	Inadequate lansoprazole 15mg OD vs 30mg OD vs omeprazole 20mg OD		Primary: endoscopic remission rates at 52/52
Bardhan 1998	UK RCT Single centre Double blind	263 patients with healed grade II oesophagitis or greater	Adequate omeprazole 10mg OD vs placebo		Oesophagitis healing, symptom relief
Bate 1995	W Europe RCT Multi centre Double blind	193 patients with healed oesophagitis	Inadequate omeprazole 20mg vs 10mg OD vs placebo		Oesophagitis and symptom relief
Bate 1998	UK RCT Multi centre Double blind	156 patients with treated oesophagitis or ENRD	Inadequate omeprazole 10mg OM vs cimetidine 800mg nocte		Time to symptomatic relapse, individual symptoms and patient/Dr satisfaction
Birbara 2000	Europe RCT Multi-centre Double-blind	288 patients with healed oeosphagitis	Inadequate rabeprazole 10mg, 20mg or placebo		Primary: grade 2 or greater oeosphagitis at 4,13,26,39, 52/52. Secondary: severity & freq of heartburn, amount of antacid taken, overall physical well-being.
Blum 1993	W Europe RCT Multi-centre Double-blind	443 patients with healed oesophagitis	Inadequate Cisapride 20mg nocte vs 10mg BD vs placebo		Oesophagitis and GRSS

† Symptom Scores: n/N - number of patients not improved/total number of patients.

Study	Location Design	Participants	Concealment of allocation Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Caos 2000	USA RCT Multi-centre Double-blind	209 patients with healed oesophagitis	Inadequate Rabeprazole 10mg, 20mg or placebo		Primary: no oesophagitis at 13,26,39, 52/52. Secondary: Heartburn freq and severity, amount of antacid used
Carling 1998	W Europe RCT Multi-centre Double-blind	248 patients with healed g II/III/IV oeosphagitis	Inadequate lansoprazole 30mg OD vs omeprazole 20mg OD		Oesophagitis and symptom relief
Dent 1994	Australia RCT Multi-centre Double blind	159 patients with healed (min g II) oesophagitis	Inadequate omeprazole 20mg daily vs Fri/Sat/Sun vs ranitidine 150mg BD		Oesophagitis, symptomatic relapse (reflux, heartburn)
Escourrou 1999	W Europe RCT Multicentre Double blind	396 patients with healed gII/III oesophagitis	Inadequate pantoprazole 20mg vs 40mg		Primary: time to oesophagitis relapse. Secondary: safety, tolerability, time to symptomatic relapse.
Gough 1996	UK RCT Multi-centre Double blind	266 with healed oesophagitis	Inadequate lans 30mg OD vs 15mg OD vs ranitidine 300mg BD		Oesophagitis and symptom relief (heartburn)
Hallerback 1994	W Europe RCT Multi-centre Double blind	392 patients with healed gII/III/IV oesophagitis	Inadequate omep 20mg OD vs 10mg OD vs ranitidine 150mg BD		Oesophagitis and symptom relief
Hatlebakk 1997 cis	Scandanavia RCT Multi-centre Double blind	535 patients with symptomatic relief from oesophagitis or proven GORD	Inadequate Cisapride 20mg OD vs 20mg BD vs placebo		Time to relapse, measured by increased symptoms or greater than 2 antacids/day
Hatlebakk 1997 Lan	Norway RCT Single centre Double blind	103 patients with healed oesophagitis	Inadequate lansoprazole 15mg OD vs 30mg OD		Oesophagitis and symptom relief (heartburn, regurgitation, dysphagia)
Hegarty 1997	W Europe RCT Multi-centre Double blind	279 patients with healed oeosphagitis	Inadequate Ranitidine 150mg BD vs 300mg BD vs placebo BD		Oesophagitis and symptom relief

National Institute for Health and Care Excellence 2014.

Study	Location Design	Participants	Concealment of allocation Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Henk 1999	W Europe RCT Multi-centre Double blind	263 patients with g I/II oesophagitis given 4 or 8/52 of omeprazole or ranitidine	Inadequate omeprazole 10mg OD vs ranitidine 150mg BD		Global reflux symptom scores
Houcke 2000	France RCT Multi-centre Double blind	52 patients with healed gII/III/IV oesophagitis	Inadequate lansoprazole 15mg OD vs 30mg alt days		Oesophagitis and symptom relief
Johnson 2001	USA RCT Multi-centre Double blind	318 patients with healed oesophagitis	Adequate Esomeprazole 10mg vs 20mg vs 40mg OD vs placebo		Oesophagitis healing, Symptom relief
Kaul 1986	Norway RCT Single centre Double blind	24 patients with symptomatic relief from oesophagitis	Inadequate Cimetidine 400mg OD vs placebo		Symptom relief
Kimmig 1995	Germany RCT Single centre Open randomisation	194 patients with healed oesophagitis	Inadequate Cisapride 5mg TDS vs nothing		Relapse rate of oesophagitis
Kimmig 1997	Germany RCT Single centre Blinding not stated	153 patients with healed gI/II oesophagitis	Inadequate Omeprazole 20mg OD vs cisapride 10mg BD vs nothing		Relapse rate of oesophagitis and mean time to recurrence of symptoms
Lauritsen 2003	Europe S Africa RCT Multi-centre Double-blind	1224 patients with healed oeosphagitis	Adequate Esomeprazole 20mg vs lansoprazole 15mg		Oesophagitis and symptom relief
Lundell 1991	RCT Multi-centre Double-blind	63 patients with healed gII/III/IV oesophagitis	Unknown Omeprazole 20mg OD vs ranitidine 150mg BD		Relapse of oeosphagitis
McDougall 1997	UK RCT Two centres Double-blind	42 patients with healed oesophagitis	Inadequate Cisapride 20mg nocte vs placebo		GRSS and SF-36

National Institute for Health and Care Excellence 2014.

Study	Location Design	Participants	Concealment of allocation Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Metz 2003	USA RCT Multi-centre Double-blind	371 patients with healed oesophagitis	Inadequate Pantoprazole 10mg OD, vs 20mg OD vs 40 mg OD vs Ranitidine 150mg BD		Relapse of oesphagitis
Pace 1990	Italy RCT Single centre Double-blind	36 patients with healed oesophagitis	Inadequate Ranitidine 150mg vs 300mg nocte		Oesophagitis, symptom relief
Plein 2000	W Europe RCT Multi-centre Double-blind	433 patients with healed gII/III oeosphagitis	Inadequate Pantoprazole 20mg vs 40mg		Primary: time to g I+ oesophagitis. Secondary: tolerability, safety, time to symptomatic relapse
Robinson 1996	USA RCT Multi-centre Double-blind	170 patients with healed gII/III/IV oeosphagitis	Adequate Lansoprazole 15mg OD vs 30mg OD vs placebo		Primary: time to 1st recurrence of oesophagitis gII+. Secondary: symptom relief, severity of heartburn, frequency of antacid use
Schotborgh 1989	Holland RCT Single centre Double-blind	26 patients with healed oesophagitis	Inadequate Sucralfate 1g QDS vs sucralfate + cimetidine 400mg nocte		Oesophagitis and symptom relapse at 6 months
Sherbaniuk 1984	Canada RCT Multi-centre Double-blind	73 patients with improved (by 1 grade) oesophagitis	Inadequate Ranitidine 150mg BD vs placebo 26/52, then 150mg OD for 26/52		Oesophagitis and symptom relief (retrosternal pain, dysphagia, epigastric pain, regurgitation)
Simon 1995	USA RCT Multi-centre Double-blind	172 patients with healed oesophagitis	Inadequate Famotidine 20mg BD vs 40mg BD vs placebo		Oesophagitis relapse and global assessment responses
Sontag 1996	USA RCT Multi-centre Double-blind	163 patients with healed oesophagitis	Inadequate Lansoprazole 30mg OD vs 15mg OD vs placebo		Oesophagitis and symptom relief
Sontag 1997	USA RCT Multi-centre Double-blind	406 patients with healed gII/III/IV oesophagitis	Inadequate omeprazole 20mg OD, vs 20mg for 3/7 consecutively each week vs placebo		Oeosphagitis and symptom relief,

Study	Location Design	Participants	Concealment of allocation Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Staerk 1995	Denmark RCT Single centre Double-blind	168 patients with healed oesophagitis	Inadequate omeprazole 10mg OD vs 20mg OD vs placebo		Oesophagitis and symptom relief
Thjodleifsson 2000	W Europe RCT Multi-centre Double-blind	243 patients with healed oesophagitis	Inadequate rabeprazole 10mg OD vs 20mg OD vs omep 20mg OD		Primary: relapse of oeosphagitis. Secondary: time to relapse, daytime/nighttime heartburn, overall physical well-being, antacid use, impact on daily living at 1 year 1st year report of Thjod 2003
Thjodleifsson 2003	W Europe RCT Multi-centre Double-blind	243 patients with healed oesophagitis	Unknown rabeprazole 10mg OD vs 20mg OD vs omep 20mg OD		Primary: relapse of oeosphagitis. Secondary: time to relapse, daytime/nighttime heartburn, overall physical well-being, antacid use, impact on daily living at 5 years Final (5 year) report of Thjod 2000
Toussaint 1991	W Europe RCT Multi-centre Double-blind	81 patients with treated oeosphagitis	Inadequate cisapride 10mg BD vs placebo		Oesophagitis and symptom relief
Tytgat 1992	W Europe RCT Multi-centre Double-blind	298 patients with healed gI/II/III oesophagitis	Inadequate Cisapride 20mg BD vs placebo		Oesophagitis and symptom relief
Tytgat 1995 AJG	W Europe RCT Multi-centre Double-blind	144 patients with healed gI/II oesophagitis	Inadequate sucralfate 2gm BD vs placebo		Oesophagitis and symptom relief
Vakil 2001	USA RCT Multi-centre Double-blind	375 patients with treated oesophagitis	Adequate esomeprazole 40mg vs 20mg vs 10mg OD vs placebo		Primary: endoscopic remission rates. Secondary: symptoms, relationship to patient demographics
Venables 1997	UK RCT Multi-centre Double-blind	495 patients with healed oesophagitis	Inadequate Omeprazole 10mg OD vs placebo		Time to treatment discontinuation due to symptoms/adverse events, GSRS, PGWB scores

Study	Location Design	Participants	Concealment of allocation Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Vigneri 1995	Italy RCT Multi-centre Endoscopists blinded. Unclear if patients also blinded.	175 patients with healed gI/II/III oeosphagitis	Inadequate Cisapride 10mg TDS vs Ranitidine 150mg TDS vs Omeprazole 20mg OD vs Ranitidine 150mg TDS + Cisapride 10mg TDS vs Omeprazole 20mg OD + Cisapride 10mg TDS		Oesophagitis and symptom relief

I.7.8 Appendix 8: Economic analyses addressing management of gastro-oesophageal reflux disease (GORD)

Study	Methods	Outcomes	Comparisons	Results							
Stalhammar, 1993 Sweden	Markov Deterministic 1 year Discount NA	Societal costs (SEK 1991) Healthy days	Erosive oesophagitis I1: Intermittent: Omeprazole 20mg on relapse I2: Maintenance: Omeprazole 20mg from start Both groups could step up to 40mg		I1:	I2:					
				Cost	8468	8925					
				Effect	290	353	ICER: SEK16/health day				
Harris et al, 1997 USA	Markov Deterministic 1 year Discount NA	Direct costs (US$ 1995) Recurrence	Erosive oesophagitis I1: Maintenance dose PPI I2: Maintenance 2X dose H_2RA I3: Maintenance with healing dose PPI		I1:	I2:					
				Cost	1290	1157					
				Effect	0.151	0.549	ICER: $335/recurrence High dose H_2RA dominated.				
Gerson et al, 2000 USA	Expected utility Deterministic 1 year, but model extrapolates to lifetime costs and QALYs assuming steady state reached. Discount: Not clear	Direct costs (US$) QALYs	I1: antacids I2: Maintenance H_2RA I3: Step up H_2RA – PPI I4: Step down PPI –H_2RA I5: PPI on demand I6: Maintenance PPI		I1:	I2:	I3:	I4:	I5:	I6:	
				Cost ($)	0	4329965	27846	9137641	26167	41112	
				Effect (QALYs)		23.66	24.42	24.37	24	24	24.65
				ICER: $20934/QALY							
				PPI on demand over antacids. All other comparisons dominated.							
Ofman et al, 2002 USA	Expected utility Deterministic 1 year. Discount: NA	Direct costs (1997 US$) % symptom free	I1: Step up [antacids, H_2RA, PPI, investigate] I2: Step down [PPI trial, H_2RA, antacids]		I1:	I2:					
				Cost	$1045	$1172					
				Effect	50%	75%	ICER $510 in favour of step down				
Briggs et al, 2002 Canadian	Expected Utility with Monte Carlo Simulation Stochastic 1 year	Costs (2000 CAN$)	I1: Intermittent Healing dose PPI I2: Continouous healing PPI I3: Maintenance H_2RA I4: Prokinetic I5: Step down PPI- H_2RA I6: Step down PPI- Maintenance PPI	See charts							

I.7.9 Appendix 9: Randomised controlled trials of therapies for peptic ulcer

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Asaka 2001	Japan Multi-centre RCT, Double-blinded	536 patients with gastric or duodenal ulcer	Inadequate 7 weeks PPI triple therapy {5 weeks (DU)/7 weeks (GU) lansoprazole 30mg bd, 1 week amoxicillin 750mg bd and clarithromycin 200 mg/400mg bd} versus PPI {5 weeks (DU)/7 weeks (GU) lansoprazole 30mg bd}	DU2: 34/ 205, 10/ 51 GU1: 65/ 225, 11/ 55 AE: 217/ 430, 42/ 106	Ulcer healing, *H. pylori* eradication rates Eradication rates:, PPI triple therapy group 76.9%, PPI group 1.89%
Avsar 1996	Turkey Single centre RCT, Single-blinded	45 patients with duodenal ulcer	Inadequate 1 year Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds, 2 weeks tetracycline 250mg qds and metronidazole 250mg tds) versus PPI (8 weeks omeprazole 40mg od)	DU2: 2/ 23, 10/ 22 DU3: 3, 17, 6/ 10 AE: 0/ 23, 0/ 22	Ulcer healing, Ulcer recurrence at 1 year , *H. pylori* eradication rates Eradication rates: , Bi triple therapy group 78.3%, PPI group 36.4%
Axon 1997	UK and Eire Multi-centre RCT, Double-blinded	129 patients with gastric ulcer	Inadequate 8 weeks /1 year PPI dual therapy (8 weeks omeprazole 40mg od and 2 weeks amoxycillin 750mg bd) versus PPI (8 weeks omeprazole 40mg od)	GU1: 20/ 87, 13/ 42 GU2: 16/ 72, 17/ 35 AE: 0/ 87, 1/ 42	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, PPI dual therapy group 48.3%, PPI group 4.8%
Bardhan 1997	Multi-national Multi-centre RCT, Double-blinded	232 patients with duodenal ulcer	Inadequate 4 weeks/28 weeks RBC dual therapy (2 weeks RBC 400mg/800mg bd and clarithromycin 250mg qds, then 2 weeks RBC 400mg bd) versus RBC (4 weeks RBC 400mg bd)	DU2: 4/ 141, 6/ 74 DU3: 10, 133, 25/ 63 AE: 25/ 141, 15/ 74	Ulcer healing, Ulcer recurrence at 28 weeks, *H. pylori* eradication rates Eradication rates:, RBC dual therapy 76.6%, RBC 1.4%
Bayerdorffer 1992	Germany Multi-centre RCT, Single-blinded	58 patients with duodenal ulcer	Inadequate 6 weeks PPI dual therapy (10 days omeprazole 40mg bd and amoxycillin 1g bd, then 4 1/2 weeks omeprazole 20mg od) versus PPI (10 days omeprazole 40mg bd then 4 1/2 weeks omeprazole 20mg od)	DU2: 2/ 29, 4/ 29 AE: 0/ 29, 1/ 29	Ulcer healing, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 75.9%, PPI 0%, Linked to Miehlke

† DU1: Acute duodenal ulcer healing, hp eradication + ulcer healing drug vs. no treatment, healed/not healed
DU2: Acute duodenal ulcer healing hp eradication + ulcer healing drug vs. ulcer healing drug alone, healed/not healed
DU3: Recurring duodenal ulcer, hp eradication + ulcer healing drug vs. no treatment, recurred/not recurred
DU4: Recurring duodenal ulcer, hp eradication + ulcer healing drug vs. ulcer healing drug, recurred/not recurred
GU1: Acute gastric ulcer healing, hp eradication + ulcer healing drug vs. ulcer healing drug alone, healed/not healed
GU2: Recurring gastric ulcer , hp eradication + ulcer healing drug vs. no treatment, recurred/not recurred
AE: Overall adverse events, ocurred/not occurred

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Bayerdorffer 1995	Germany Multi-centre RCT, Double-blinded	264 patients with duodenal ulcer	Inadequate 6 weeks/1 year PPI dual therapy (2 weeks omeprazole 40mg tds and amoxycillin 750mg tds, then 4 weeks omeprazole 20mg od) versus PPI (2 weeks omeprazole 40mg tds then 4 weeks omeprazole 20mg od)	DU2: 4/ 136, 12/ 128 DU3: 15, 132, 51/ 116 AE: 11/ 136, 3/ 128	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 88.9%, PPI 0%
Bayerdorffer 1996	Germany Multi-centre RCT, Single-blinded	130 patients with gastric ulcer	Adequate 8 weeks/18 months Bi triple therapy (8 weeks bismuth subsalicylate 600mg tds, 10 days amoxicillin 500mg bd and tinidazole 1g bd) versus PPI (8 weeks omeprazole 20mg od)	GU1: 13/ 65, 3/ 65 GU2: 4/ 52, 34/ 62 AE: 16/ 65, 0/ 65	Ulcer healing, Ulcer recurrence at 18 months, *H. pylori* eradication rates Eradication rates: , Bi triple therapy 66.1%, PPI 7.7%, If ulcer not healed at 8 weeks Bi/PPI continued for a further 4 weeks
Carpintero 1997	Spain Single centre RCT, Unblinded	122 patients with duodenal ulcer	Inadequate 6 weeks/18 months Bi triple therapy (6 weeks colloidal bismuth subcitrate 120mg qds, 12 days amoxicillin 500mg tds and metronidazole 500mg bd) or H_2RA triple therapy (6 weeks ranitidine 300mg qds, 12 days amoxicillin 500mg tds and metronidazole 500mg bd) versus H_2RA (6 weeks ranitidine 300mg qds)	DU2: 3/ 78, 3/ 44 DU3: 31, 72, 34/ 39 AE: 13/ 78, 1/ 44	Ulcer healing, Ulcer recurrence at 18 months, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 86.8%, H_2RA triple therapy 25%, H_2RA 0%
Chen 1995	Taiwan Single centre RCT, Single-blinded	62 patients with duodenal ulcer	Inadequate 1 year Bi triple therapy (1 or 2 weeks colloidal bismuth subcitrate 120mg qds, amoxycillin 500mg tds and metronidazole 500mg tds) versus no treatment	DU3: 10, 31, 27/ 29 AE: 24/ 49, 0/ 29	Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 93.9%, No treatment 0%
Figueroa 1996	Chile Single centre RCT, Unblinded	113 patients with duodenal ulcer	Inadequate 4 weeks/1 year Bi quadruple therapy (4 weeks omeprazole 20mg qds, bismuth subsalicylate 524mg qds, amoxicillin 500mg tds and metronidazole 250mg tds) versus PPI (4 weeks omeprazole 20mg od)	DU2: 4/ 57, 4/ 43 DU3: 3, 53, 34/ 39	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, Bi quadruple therapy 82.5%, PPI 0%
Fukuda 1995a	Japan Single centre RCT, Unblinded	65 patients with gastric ulcer	Inadequate 8 weeks PPI dual therapy (8 weeks lansoprazole 30mg od and 2 weeks clarithromycin 200mg tds) versus PPI (8 weeks omeprazole 20mg od or lansoprazole 30mg od)	GU1: 0/ 32, 1/ 33 AE: 0/ 32, 0/ 33	Ulcer healing, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 62.5%, PPI 24.2%, All patients received 4 weeks ranitidine 150mg od after initial therapy
Fukuda 1995b	Japan Single centre RCT, Single-blinded	86 patients with gastric ulcer	Inadequate 8 weeks/40 weeks PPI dual therapy (8 weeks lansoprazole 30mg qds and 2 weeks clarithromycin 200mg tds/amoxicillin 500mg tds) versus PPI (8 weeks omeprazole 20mg qds or lansoprazole 30mg qds)	GU1: 0/ 37, 1/ 49 GU2: 3/ 36, 19/ 48 AE: 1/ 37, 0/ 49	Ulcer healing, Ulcer recurrence at 40 weeks, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 48.6%, PPI 12.2%, All patients received 4 weeks ranitidine 150mg od after initial therapy

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Furuta 1995	Japan Single centre RCT, Unblinded	67 patients with gastric or duodenal ulcer	Inadequate 6 weeks PPI dual therapy (6 weeks lansoprazole 30mg qds and 2 weeks amoxicillin 1-2g qds) versus PPI (6 weeks lansoprazole 30mg qds)	DU2: 0/ 20, 0/ 20 GU1: 0/ 12, 2/ 15	Ulcer healing, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 62.5%, PPI 0%
Graham 1991	USA Single centre RCT, Single-blinded	105 patients with duodenal ulcer	Inadequate 16 weeks Bi triple therapy (2 weeks bismuth subsalicylate 300mg qds/150mg tds + 300mg nocte, tetracycline 500mg qds and metronidazole 250mg tds) versus H_2RA (16 weeks ranitidine 300mg od)	DU2: 4/ 53, 10/ 52 AE: 6/ 53, 0/ 52	Ulcer healing, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 82.7%, H_2RA 0%, All patients received 16 weeks H_2RA
Graham 1992	USA Single centre RCT, Single-blinded	109 patients with gastric or duodenal ulcer	Inadequate 1 year Bi triple therapy (2 weeks bismuth subsalicylate 300mg qds/150mg tds + 300mg nocte, tetracycline 500mg qds and metronidazole 250mg tds) versus H_2RA (16 weeks ranitidine 300mg od)	DU3: 6, 47, 34/ 36 GU2: 2/ 15, 8/ 11 AE: 7/ 77, 7/ 109	Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 88.7%, H_2RA 0%, All patients received 16 weeks H_2RA
Graham 1998	USA and Puerto Rico Multi-centre RCT, Double-blinded	153 patients with duodenal ulcer	Inadequate 4 weeks/6 months RBC dual therapy (4 weeks RBC 400mg bd, 2 weeks amoxicillin 500mg qds) versus Bi (4 weeks RBC 400mg bd) and placebo	DU1: 22/ 77, 25/33 DU2: 22/ 77, 27/ 76	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, RBC dual therapy 40%, RBC 0%, Placebo 0%H_2RA
Harford 1996	USA Multi-centre RCT, Double-blinded	196 patients with duodenal ulcer	Inadequate 2 weeks PPI dual therapy (2 weeks lansoprazole 30mg bd/tds and amoxicillin 1g tds) versus PPI (2 weeks lansoprazole 30mg tds)	DU2: 36/ 127, 25/ 69 AE: 24/ 127, 5/ 69	Ulcer healing, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 55.1%, PPI 0%
Hentschel 1993	Austria Two centre RCT, Double-blinded	104 patients with duodenal ulcer	Inadequate 6 weeks/1 year H_2RA triple therapy (6 weeks ranitidine 300mg od, 12 days amoxicillin 750mg tds and metronidazole 500mg tds) versus H_2RA (6 weeks ranitidine 300mg od)	DU2: 1/ 52, 3/ 52 DU3: 4, 50, 42/ 49 AE: 8/ 52, 1/ 52	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, H_2RA triple therapy 88.5%, H_2RA 1.9%, If ulcer not healed at 6 weeks ranitidine continued for a further 4 weeks
Hosking 1992	Hong Kong Single centre RCT, Single-blinded	155 patients with duodenal ulcer	Adequate 4 weeks Bi quadruple therapy (4 weeks omeprazole 40mg qds, 1 week colloidal bismuth subcitrate 120mg qds, tetracycline 500mg qds and metronidazole 400mg qds) versus PPI (4 weeks omeprazole 40mg qds)	DU2: 8/ 78, 21/ 77 AE: 6/ 78, 6/ 77	Ulcer healing, *H. pylori* eradication rates Eradication rates:, Bi quadruple therapy 89.7%, PPI 3.9%, Linked to Sung 1994
Kato 1996	Japan Single centre RCT, Unblinded	119 patients with gastric or duodenal ulcer	Inadequate 8 weeks/1 year PPI dual therapy {6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od and 2 weeks amoxycillin 500mg qds} versus PPI {6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od}	DU2: 0/ 28, 1/ 23 DU3: 3, 27, 12/ 18 GU1: 5/ 35, 3/ 33 GU2: 8/ 28, 11/ 26 AE: 4/ 63, 0/ 56	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 36.5%, PPI 1.8%

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Katoh 1995	Japan Single centre RCT, Unblinded	133 patients with gastric or duodenal ulcer	Inadequate 8 weeks PPI dual therapy {6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od and 2 weeks amoxycillin 500mg qds} versus PPI {6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od}	DU2: 0/ 27, 1/ 25 GU1: 7/ 40, 3/ 39	Ulcer healing, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 38.8%, PPI 9.4%
Kepecki 1999	Turkey Single centre RCT, Unblinded	73 patients with duodenal ulcer	Inadequate 4 weeks/2 years PPI triple therapy (1 week omeprazole 20mg bd, amoxycillin 1g bd and metronidazole 500mg tds, then 3 weeks omeprazole 20mg od) versus PPI (1 week omeprazole 20mg bd then 3 weeks 20mg od)	DU2: 7/ 39, 4/ 34 DU4: 7/ 29, 5/ 30	Ulcer healing, Ulcer recurrence at 2 years, *H. pylori* eradication rates Eradication rates:, PPI triple therapy 82%, PPI 0%, PPI group received long-term famotidine 20mg od
Kim 2002	South Korea Single centre RCT, Single-blinded	53 patients with duodenal ulcer	Inadequate 30 months PPI triple therapy (1 week omeprazole 20mg bd, amoxicillin 1g bd and clarithromycin 500mg bd) versus no treatment	DU3: 2, 36, 5/ 17	Ulcer recurrence at 30 months, *H. pylori* eradication rates Eradication rates:, PPI triple therapy 83.3% , No treatment 0%, Patients not eradicated with triple therapy received Bi quadruple therapy
Lam 1997	Hong Kong Single centre RCT, Double-blinded	97 patients with duodenal ulcer	Adequate 2 weeks Clarithromycin monotherapy (2 weeks clarithromycin 250mg qds) versus placebo	DU1: 8/ 48, 23/49 AE: 2/ 48, 0/ 49	Ulcer healing, Global symptoms cured, *H. pylori* eradication rates Eradication rates:, Clarithromycin monotherapy 70.8%, Placebo 10.2%, Clarithromycin patients also received amoxicillin and metronidazole
Lazzaroni 1997	Italy Single centre RCT, Double-blinded	59 patients with gastric ulcer	Inadequate 4 weeks/1 year PPI dual therapy (4 weeks omeprazole 20mg bd and 2 weeks amoxicillin 1g tds) versus PPI (4 weeks omeprazole 20mg bd)	GU1: 0/ 29, 2/ 30 GU2: 6/ 28, 16/ 24 AE: 4/ 29, 2/ 30	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 62.1%, PPI 6.7%
Lin 1994	Taiwan Single centre RCT, Unblinded	42 patients with duodenal ulcer	Inadequate 4 weeks/1 year Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds, 1 week metronidazole 250mg qds and amoxicillin 500mg qds) versus H_2RA (4 weeks famotidine 20mg bd)	DU2: 0/ 21, 2/ 21 DU3: 1, 18, 11/ 18 AE: 5/ 21, 0/ 21	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 100%, H_2RA 4.8%
Logan 1995	UK Multi-centre RCT, Double-blinded	148 patients with duodenal ulcer	Inadequate 4 weeks/1 year PPI dual therapy (4 weeks omeprazole 40mg od and 2 weeks clarithromycin 500mg tds) versus PPI (4 weeks omeprazole 40mg od)	DU2: 2/ 70, 6/ 78 DU3: 3, 51, 47/ 62 AE: 28/ 70, 23/ 78	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 81.4%, PPI 1.3%
Malfertheiner 1999	Germany, Hungary and Poland Multi-centre RCT, Double-blinded	145 patients with gastric ulcer	Inadequate 1 week/6 months PPI triple therapy (1 week omeprazole 20mg bd, amoxycillin 1g bd and clarithromycin 500mg bd or 1 week omeprazole 20mg bd, metronidazole 400mg bd and clarithromycin 250mg bd) versus PPI (omeprazole 20mg bd)	GU1: 20/ 97, 10/ 48 GU2: 12/ 97, 13/ 48 AE: 12/ 97, 6/ 48	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, PPI triple therapy 82.4%, PPI 4.2%, PPI given until ulcer healing in control arm

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Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Mantzaris 1993	Greece Single centre RCT, Single-blinded	33 patients with duodenal ulcer	Inadequate 8 weeks/18 months Bi triple therapy (8 weeks colloidal bismuth subcitrate 120mg qds, 2 weeks tetracycline 500mg qds and metronidazole 500mg tds) versus Bi (8 weeks colloidal bismuth subcitrate 120mg qds)	DU2: 5/ 17, 8/ 16 DU3: 2, 12, 6/ 8 AE: 3/ 17, 0/ 16	Ulcer healing, Ulcer recurrence at 18 months, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 58.8%, Bi 6.3%
Meining 1998	Germany Multi-centre RCT, Double-blinded	185 patients with gastric ulcer	Adequate 4 weeks/3 months PPI dual therapy (2 weeks omeprazole 40mg bd and amoxicillin 750mg tds then 2 weeks omeprazole 20mg od) versus PPI (2 weeks omeprazole 40mg bd then 2 weeks omeprazole 20mg od)	GU1: 23/ 100, 15/ 85 GU2: 0/ 77, 10/ 70 AE: 23/ 100, 5/ 85	Ulcer healing, Ulcer recurrence at 3 months, *H. pylori* eradication ratres Eradication rates:, PPI dual therapy 61%, PPI 5.9%
Miehlke 1995	Germany Multi-centre RCT, Single-blinded	As Bayerdorffer	Inadequate 2 years As Bayerdorffer 1	DU3: 6, 26, 19/ 25	Ulcer recurrence at 2 years, Linked to Bayerdorffer 1992
Mones 2001	Spain Multi-centre RCT, Double-blinded	85 patients with duodenal ulcer	Inadequate 4 weeks/1 year PPI triple therapy (1 week omeprazole 20mg bd, amoxicillin 1g bd and clarithromycin 500mg bd then 3 weeks omeprazole 20mg od) versus PPI (1 week omeprazole 20mg bd then 3 weeks omeprazole 20mg od)	DU2: 5/ 42, 7/ 43 DU4: 4/ 37, 4/ 36	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, PPI triple therapy 76.2%, PPI 0%, PPI patients given 1 year of ranitidine 150mg od
O'Morain 1996	Eire, Germany and New Zealand Multi-centre RCT, Double-blinded	208 patients with duodenal ulcer	Inadequate 4 weeks/6 months PPI dual therapy (2 weeks omeprazole 40mg od and clarithromycin 500mg tds, then 2 weeks omeprazole 20mg od) versus PPI (2 weeks omeprazole 40mg od then 2 weeks 20mg od)	DU2: 9/ 102, 15/ 106 DU3: 8, 78, 41/ 82 AE: 38/ 102, 13/ 106	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 62.7%, PPI 0.9%
Parente 1996	Italy Single centre RCT, Unblinded	96 patients with duodenal ulcer	Inadequate 4 weeks PPI dual therapy (4 weeks lansoprazole 30mg bd and 2 weeks amoxicillin 1g tds) and Bi quadruple therapy (4 weeks lansoprazole 30mg od, 2 weeks bismuth 240mg bd, amoxicillin 1g tds and tinidazole 500mg bd) versus PPI (4 weeks lansoprazole 30mg od)	DU2: 7/ 63, 1/ 33 AE: 6/ 63, 0/ 33	Ulcer healing, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 51.6%, Bi quadruple therapy 81.3%, PPI 3%
Pinero 1995	Venezuela Single centre RCT, Unblinded	60 patients with duodenal ulcer	Adequate 4 weeks/3 months Bi triple therapy (2 weeks colloidal bismuth subcitrate 120mg qds, amoxicillin 500mg tds and metronidazole 500mg tds) versus PPI (4 weeks omeprazole 20mg od)	DU2: 8/ 30, 7/ 30 DU3: 3, 19, 13/ 20 AE: 2/ 30, 0/ 30	Ulcer healing, Ulcer recurrence at 3 months, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 63.3%, PPI 10%
Porro 1993	Italy Single centre RCT, Unblinded	32 patients with duodenal ulcer	Inadequate 4 weeks Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds, 1 week amoxicillin 1g tds and tinidazole 500mg bd) versus sucralfate (4 weeks 1g qds)	DU2: 2/ 17, 9/ 15	Ulcer healing, *H. pylori* eradication rates, If no ulcer healing patients crossed over to other therapy, therefore unable to extract eradication rates

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Porro 1996	Italy Single centre RCT, Double-blinded	183 patients with duodenal ulcer	Inadequate 4 weeks/1 year PPI triple therapy (4 weeks omeprazole 20mg od, 2 weeks metronidazole 250mg qds and amoxycillin 1g tds) versus PPI (4 weeks omeprazole 20mg od)	DU2: 7/ 91, 12/ 92 DU3: 8, 71, 52/ 66 AE: 11/ 91, 7/ 92	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, PPI triple therapy 78%, PPI 1.1%
Pounder 1997	Multi-national Multi-centre RCT, Double-blinded	91 patients with duodenal ulcer	Inadequate 4 weeks/2 months RBC dual therapy (2 weeks RBC 400mg/800mg bd and clarithromycin 250mg qds, then 2 weeks RBC 400mg bd) versus RBC (4 weeks 400mg bd)	DU2: 5/ 61, 8/ 30 DU3: 0, 56, 4/ 22 AE: 21/ 61, 7/ 30	Ulcer healing, Ulcer recurrence at 2 months, Global symptoms cured, *H. pylori* eradication rates Eradication rates:, RBC dual therapy 57.4%, RBC 0%
Rauws 1990	Netherlands Single centre RCT, Single-blinded	66 patients with duodenal ulcer	Inadequate 4 weeks/1 year Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds and amoxicillin 375mg tds, 10 days metronidazole 500mg tds) versus Bi (4 weeks colloidal bismuth subcitrate 120mg qds)	DU2: 7/ 24, 5/ 26 DU3: 1, 17, 16/ 21 AE: 5/ 24, 0/ 26	Ulcer healing, Ulcer recurrence at 1year, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 62.5%, Bi 7.7%, All patients received a further 4 weeks ranitidine 150mg od
Schwartz 1998	USA Multi-centre RCT, Double-blinded	352 patients with duodenal ulcer	Inadequate 2 weeks/6 months PPI dual (2 weeks lansoprazole 30mg bd and clarithromycin 500mg bd/tds or 2 weeks lansoprazole 30mg bd/tds and amoxicillin 1g tds) and triple therapy (2 weeks lansoprazole 30mg bd, amoxicillin 1g bd and clarithromycin 500mg bd) versus PPI (2 weeks lansoprazole 30mg tds)	DU2: 168/ 292, 44/ 60 DU3: 19, 124, 11/ 16 AE: 80/ 292, 9/ 60	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 65.5%, PPI triple therapy 93.6%, PPI 1.9%
Shirotani 1996	Japan Single centre RCT, Single-blinded	50 patients with duodenal ulcer	Inadequate 6 weeks/6 months H_2RA triple therapy (6 weeks cimetidine 400mg bd, 2 weeks amoxicillin 300mg tds and metronidazole 250mg tds) versus H_2RA (6 weeks cimetidine 400mg bd)	DU2: 4/ 25, 6/ 25 DU3: 2, 18, 9/ 14 AE: 4/ 25, 0/ 25	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, H_2RA triple therapy 56%, H_2RA 0%
Sobhani 1995	France Multi-centre RCT, Double-blinded	119 patients with duodenal ulcer	Inadequate 6 weeks/6 months H_2RA triple therapy (6 weeks famotidine 40mg od, 1 week amoxicillin 500mg qds and tinidazole 500mg tds) versus H_2RA (6 weeks famotidine 40mg od then 20 weeks 20mg od)	DU2: 7/ 59, 15/ 60 DU4: 6/ 45, 12/ 43 AE: 10/ 59, 3/ 60	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, H_2RA triple therapy 42.4%, H_2RA 1.7%
Spinzi 1994	Italy Multi-centre RCT, Unblinded	53 patients with duodenal ulcer	Inadequate 4 weeks/6 months PPI dual therapy (4 weeks omeprazole 20mg od, 2 weeks amoxicillin 1g bd) versus PPI (4 weeks omeprazole 20mg od)	DU2: 2/ 24, 3/ 29 DU3: 3, 22, 15/ 26 AE: 1/ 24, 0/ 29	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 41.7%, PPI 6.9%

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Suarez 1999	Cuba Single centre RCT, Unblinded	60 patients with gastric and duodenal ulcer	Inadequate 6 weeks Bi triple therapy (6 weeks colloidal bismuth subcitrate 240mg bd, 10 days metronidazole 500mg tds and tetracycline 500mg tds/amoxicillin 750mg bd) versus Bi (6 weeks colloidal bismuth subcitrate 240mg bd)	AE: 11/ 40, 3/ 20	Ulcer healing, Global symptoms cured, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 22.5%, Bi 0%
Sung 1994	Single centre RCT, Single-blinded	As Hosking	Adequate 1 year As Hosking	DU3: 2, 61, 22/ 45	Ulcer recurrence at 1 year, Linked to Hosking 1992
Sung 1995	Hong Kong Single centre RCT, Unblinded	96 patients with gastric ulcer	Adequate 4 weeks/1 year Bi triple therapy (1 week colloidal bismuth subcitrate 120mg qds, tetracycline 500mg qds and metronidazole 400mg qds) versus PPI (4 weeks omeprazole 20mg od)	GU1: 6/ 51, 7/ 45 GU2: 1/ 22, 12/ 23 AE: 5/ 51, 0/ 45	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 80.4%, PPI 11.1%, If no healing at 4 weeks triple therapy patients received antacids and PPI patients received further PPI
Unge 1993a	Sweden Multi-centre RCT, Double-blinded	233 patients with duodenal ulcer	Inadequate 6 months PPI dual therapy (4 weeks omeprazole 40mg od and 2 weeks amoxicillin 750mg bd) versus PPI (4 weeks omeprazole 40mg od)	DU3: 48, 157, 50/ 76	Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, PPI dual therapy 53.5%, PPI 3.9%
van Zanten 1999	Canada Multi-centre RCT, Double-blinded	146 patients with duodenal ulcer	Inadequate 4 weeks/6 months PPI triple therapy (1 week omeprazole 20mg bd, amoxycillin 1g bd and clarithromycin 500mg bd or 1 week omeprazole 20mg bd, metronidazole 400mg bd and clarithromycin 250mg bd then 3 weeks omeprazole 20mg od) versus PPI (4 weeks omeprazole 20mg od)	DU2: 0/ 98, 3/ 48 DU3: 10, 98, 25/ 45	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication Eradication rates:, PPI triple therapy 81.6%, PPI 0%
Wang 1993	Taiwan Single centre RCT, Unblinded	59 patients with duodenal ulcer	Inadequate 4 weeks/6 months Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds, 2 weeks tetracycline 500mg qds and metronidazole 250mg qds) versus H_2RA (4 weeks ranitidine 150mg bd) and Bi (4 weeks colloidal bismuth subcitrate 120mg qds)	DU2: 3/ 23, 6/ 36 DU3: 1, 20, 18/ 26	Ulcer healing, Ulcer recurrence at 6 months, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 82.6%, H_2RA 0%, Bi 0%
Wang 1996	Taiwan Single centre RCT, Unblinded	112 patients with gastric and duodenal ulcer	Inadequate 4 weeks Bi triple (4 weeks colloidal bismuth subcitrate 300mg qds, 1 week amoxiciliin 750mg bd and metronidazole 500mg tds) and PPI dual therapy (4 weeks omeprazole 20mg bd/qds and 10 days amoxicillin 750mg bd) versus PPI (4 weeks omeprazole 20mg qds) and H_2RA (4 weeks nizatidine/ranitidine 150mg bd)	AE: 13/ 69, 0/ 43	Ulcer healing, *H. pylori* eradication rates Eradication rates:, Bi triple therapy 68%, PPI dual therapy 50%, PPI 4.5%, H_2RA 0%, All patients received 4 weeks H_2RA after initial therapy

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Treatment n/N, Control n/N†	Outcomes, Notes
Wong 1999	Hong Kong Single centre RCT, Single-blinded	114 patients with duodenal ulcer	Inadequate 2 weeks/1 year Clarithromycin monotherapy (2 weeks 250mg qds) versus PPI (1 year omeprazole 20mg od)	DU2: 9/ 57, 6/ 57 2/ 48, 5/ 51 AE: 6/ 57, 1/ 57	Ulcer healing, Ulcer recurrence at 1 year, *H. pylori* eradication rates Eradication rates:, Clarithromycin monotherapy 66.7%, PPI 7%, Clarithromycin patients also received 4 weeks sucralfate 1g qds and 2 weeks metronidazole 300mg qds

I.7.10 Appendix 10: Economic analyses addressing *H. pylori* eradication in peptic ulcer disease

Study	Methods	Outcomes	Comparisons	Results
Ikeda et al, 2001 Japan	Markov model 5 years Deterministic 3% discount p.a. to both costs and effects	Direct costs (1999 Yen) Disease free days over 5 years (DFD)	I1: *H. pylori* eradication confirmed by OGD. No maintenance, relapse treated with PPI I2: Maintenance dose H_2RA after ulcer healing, step up to PPI with relapses	Duodenal ulcer: DFDs I1: 1503 I2: 1387 Costs I1: 134786Y 324689Y Eradication dominates Gastric ulcer: DFDs I1: 1454 I2: 1313 Costs I1. 169719Y I2: 390921Y Eradication dominates
Habu et al, 1997 Japan	Markov model 5 years Deterministic 5% discount p.a. to costs.	Direct costs (1995 Yen) Days with ulcer symptom over 5 years and % patients relapsing.	I1: *H. pylori* eradication I2: Maintenance H_2RA and PPI for relapse on maintenance	Duodenal ulcer: % relapse I1: 25% I2: 35% Costs 200000Y 300000Y Eradication dominates
Fendrick et al, 1997 USA	Markov model 1 year Deterministic Discount N/A	Direct costs US$ Symptom months per 100 patient years	I1: *H. pylori* eradication I2: maintenance H_2RA with *H. pylori* eradication if recurrence on maintenance	Duodenal ulcer: Ulcer months /100 patient years I1: 28.7 I2: 36.8 Costs I1: $587 $767 Eradication dominates
Badia et al, 1997 Spain	Markov model 10 years Deterministic 5% discount p.a. to both costs and effects	Direct costs Pesetas 1995 Symptom free days	I1: Eradication therapy I2: Intermittent H_2RA	Duodenal ulcer: Symptom free days I1: 2876 I2: 2871 Cost I1: 64270 Pta I2: 111829 Pta Eradication dominates
Briggs et al, 1996 UK	Markov model 10 years Deterministic 6% discount on costs.	Direct costs UK£ 1995 % time symptom free	I1: Eradication therapy I2: Intermittent H_2RA	Duodenal ulcer: % time symptom free I1: 99 I2: 95 Costs I1: £209 I2: £812 Eradication dominates
Jonsson, 1996 Sweden	Markov model 5 years Deterministic 5% discount p.a. to both costs and effects	Direct costs of outpatient Rx only in 1995 Swedish Krona Symptom free days	I1: Eradication therapy I2: Episodic H_2RA I3: Maintenance H_2RA	Duodenal ulcer: Symptom free days I1: 1802 (99%) I2: 1755 (96%) I3: 1791 (98%) Cost I1: 6139 SEK I2: 8141 SEK I3: 18,420 SEK Eradication dominates
O'Brien, 1995 USA	Expected utility 1 year Deterministic Discount N/A	Direct costs 1995 CAN$ Ulcer recurrences per 100 patients.	I1: Eradication therapy I2: Episodic H_2RA I3: Maintenance H_2RA	Duodenal ulcer Symptomatic recurrent ulcer per 100 patients I1: 15 I2: 81 I3: 15 Cost I1: 253 CAN$ I2: 329 CAN$ I3: 386 CAN$ Eradication dominates
Imperiale et al, 1995	Expected utility	Direct costs 1995 US$	I1: Eradication therapy	Duodenal ulcer Cost per ulcer cure I1: 372 $/cure I2: 679 $/cure Eradication

USA	1 year Deterministic Discount N/A	Symptomatic ulcer recurrences	I2: Episodic H_2RA	dominates

I.7.11 Appendix 11: Randomised controlled trials of therapies for non-ulcer dyspepsia

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Global Symptom Score [treatment, control]	Notes
H_2RAs for NUD					
Blum	Germany Multicentre RCT. Double blind placebo controlled trial	792 patients with normal endoscopy, Rome criteria for dyspepsia. 203 on placebo, 194 on ranitidine, 202 on omeprazole 10 mg and 193 on omeprazole 20 mg	Unclear 2 weeks ranitidine 150 mg od in the evening or omeprazole 10 mg od or 20 mg od in the morning versus placebo	improved/total 49/193, 32/203	Two outcomes:. 1. lack of dyspeptic symptoms requiring further management.. 2. Absence of global dyspepsia symptoms
Delattre	USA. RCT, double-blind, placebo-controlled.	414 patients with NUD	Unclear 4 weeks Cimetidine 200mg qid. Placebo	improved/total 155/209, 107/209	Pain episodes. Individual and global symptom scores
Gotthard	Sweden. RCT. Double-blind placebo-controlled trial.	210 patients. 73 on cimetidine. 74 on antacid. 75 on placebo. 3/12 of dyspepsia of unknown origin. Acid output studies performed. 16% duodenitis.	Unclear 6 weeks Cimetidine 400mg bid vsPlacebo vs Antacid 10 ml qid	improved/total 34/63, 21/55	Cimetidine was superior to both placebo and antacid in relieving pain and nausea but not bloating.
Hadi	Indonesia. RCT. Double-blind placebo-controlled trial.	52 total. 26 on Ranitidine. 26 on placebo. Duration of dyspepsia unclear. Gastritis on all OGD.Drop out rate for placebo was 23% and Ranitidine was 4%	Unclear 4 weeks Ranitidine 300mg daily vs Placebo.	improved/total 26/26, 8/25	Ranitidine was effective as a short term treatment for patients with endoscopically proven gastritis.
Hansen	Denmark. Primary care recruitment. RCT. Double-blind placebo-controlled trial.	330 patients. 109 on cisapride. 111 on Ranitidine. 110 on placebo. Mean duration of dyspeptic symptom was 88 months. 4 subgroups: ulcer-like (13%), reflux-like (23%), dysmotility-like (46%) and unclassified (18%). Included superficial erosions on OGD. 85% completed trial.	Adequate 2 weeks Cisapride 10mg tid vsNizatidine 300mg nocte vs placebo.	improved/total pr60/111, 68/110	The effects of a 2-week course of Cisapride or Nizatidine recruited from primary care were not superior to those of placebo. Symptom subgrouping was not predictive of response to treatment.
Kelbaek	Denmark. Primary care recruitment. RCT. Double-blind placebo-controlled trial.	52 patients. 24 on cimetidine. 26 on placebo. One month of epigastric pain. Acid output studies performed. Had OGD. 14 patients who were symptom free at end of treatment had 3 months follow-up. 96% completed trial.	Unclear 3 weeks Cimetidine 200mg tid and 400mg nocte vsPlacebo.	improved/total 13/24, 16/26	Cimetidine does not seem to be superior to placebo in NUD.

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Global Symptom Score [treatment, control]	Notes
Muller	Germany RCT. Randomised double blind controlled trial	652 patients with normal endoscopy. All upper gastrointestinal symptoms included in defintion.	Not used 4 weeks of ranitidine 150 mg bd versus placebo	improved/total 127/254, 88/244	Complete relief of global symptoms
Nesland	Norway. RCT. Double-blind placebo-controlled trial.	100 patients. 44 on cimetidine. 6 months of predominantly ulcer-like pain and with erosive prepyloric changes. 46 on placebo. 90% completed trial.	Unclear 4 weeks Cimetidine 400mg bid vs Placebo.	improved/total 21/44, 14/46	Patients with NUD and erosive prepyloric changes who have epigastric pain/discomfort as a prominent symptom seem to profit from treatment with Cimetidine.
Olubuyide	Nigeria RCT. Double blind placebo controlled trial.	Recruited duodenal ulcer and NUD patients but the two groups were analysed seperately. 45 NUD patients - all upper gastrointestinal symptoms included	Not used 4 weeks ranitidine 300 mg od versus placebo	improved/total 1/23, 1/22	1. Acid output. 2. Absence of dyspepsia symptoms. 3. General Health Questionnaire (not reported).
Saunders	UK. RCT. Double-blind placebo-controlled multicentre trials. Primary care recruitment.	251 patients with NUD. 115 on Ranitidine. 136 on placebo. 88% completed trial. One-year follow-up, but the results included other peptic disease.	Adequate 6 weeks Ranitidine 150mg bid vs placebo.	improved/total 82/103, 70/118	There was a significantly more NUD patients became symptom free with taking Ranitidine compared with placebo.
Singal	India. RCT. Double-blind placebo-controlled trial.	67 patients. 33 on cimetidine. 34 on placebo. 1 month of primary symptom of upper abdominal discomfort. IBS excluded.	Unclear 4 weeks Cimetidine 400mg bid vsPlacebo.	improved/total 17/27, 10/29	Abdominal pain and other secondary dyspeptic symptoms were relieved in higher proportions in the Cimetidine-treated group, though the difference was not significant.
PPIs for NUD					
Blum	Germany Multicentre RCT. Double blind placebo controlled trial	792 patients with normal endoscopy, Rome criteria for dyspepsia. 203 on placebo, 194 on ranitidine, 202 on omeprazole 10 mg and 193 on omeprazole 20 mg	Unclear 2 weeks ranitidine 150 mg od in the evening or omeprazole 10 mg od or 20 mg od in the morning versus placebo	substantially improved/total 121/395, 32/203	Two outcomes:. 1. lack of dyspeptic symptoms requiring further management.. 2. Absence of global dyspepsia symptoms
Lauritsen	Denmark RCT. Double blind placebo controlled	197 patients with normal endoscopy. Predominant reflux or IBS symptoms excluded	Not used 2 weeks omeprazole 20 mg od versus placebo	substantially improved/total 29/84, 11/84	No dyspeptic symptoms on the last two days of assessment
Peura M96	USA RCT. Double blind randomised controlled trial.	393 evaluable patients with normal endoscopy and predominant upper abdominal pain.	Not used 8 weeks Lansoprazole 30 mg od versus lansoprazole 15 mg od versus placebo	substantially improved/total 96/261, 27/131	Complete relief of global dyspepsia symptoms
Peura M97	USA RCT Double blind randomised controlled trial.	382 evaluable patients with normal endoscopy and predominant upper abdominal pain.	Not used 8 weeks Lansoprazole 30 mg od versus lansoprazole 15 mg od versus placebo	substantially improved/total 85/249, 24/133	Complete relief of global dyspepsia symptoms

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Global Symptom Score [treatment, control]	Notes
Talley (BOND)	Australia RCT, double-blind placebo-controlled trial.	OperA+BOND: 1262 patients with functional dyspepsia. Some with Hp gastritis. 96.6% completed trial.	Adequate 4 weeks Omeprazole at 2 different doses: 204 patients on 10mg/day vs 219 patients on 20mg/day vs placebo	substantially improved/total 181/423, 29/110	Statistical improvement in GSRS between Omeprazole 20mg and placebo but not 10mg and placebo. PGWB improved in all groups, results not significant between the 3 treatment arms.
Talley (OPERA)	Australia RCT, double-blind placebo-controlled trial.	OperA+BOND: 1262 patients with functional dyspepsia. Some with Hp gastritis. 96.6% completed trial.	Adequate 4 weeks Omeprazole at 2 different doses: 201 on 10mg/day vs. 202 on 20mg/day vs placebo.	substantially improved/total 126/403, 31/102	Statistical improvement in GSRS between Omeprazole 20mg and placebo but not 10mg and placebo. PGWB improved in all groups, results not significant between the 3 treatment arms.
Wong	China RCT. Double blind placebo controlled trial	453 patients with normal endoscopy with pain or discomfort in the upper abdomen as the predominant complaint.	Not used 4 weeks lansoprazole 30 mg od. versus lansoprazole 15 mg od. versus placebo	substantially improved/total 70/301, 45/152	Validated dyspepsia questionnaire (Hong Kong Dyspepsia Index) assessed complete relief of symptoms. SF-36
Prokinetics for NUD					
Al-Quorain	Saudi Arabia. RCT. Double-blind placebo-controlled trial.	89 patients. 44 on cisapride. 45 on placebo. 3 subgroups: ulcer-like, reflux-like, dysmotility-like. 2-week placebo run-in period. 91% completed trial.	Unclear 4 weeks Cisapride 5mg tid vs placebo.	improved/total 38/44, 13/45	Cisapride was significantly superior to placebo in improving heartburn, postprandial bloating, epigastric pain, early satiety, epigastric burning and nausea.
Bekhti	Belgium. RCT. Double-blind placebo-controlled trial.	40 patients. 20 in each arm. Chronic dyspepsia and weak antral contractions and delayed gastric emptying tests. Radiological examination only. 15% radiological reflux. No dropouts.	Unclear 4 weeks Domperidone 10mg tid vs placebo.	improved/total 13/20, 4/20	Global evaluation was significantly in favour of Domperidone. Few side effects.
Champion	Canada. RCT. Double-blind placebo-controlled trial.	123 patients with NUD. 42 on cisapride 10mg, 41 on cisapride 20mg, 40 on placebo. 2-week placebo run-in period. Had OGD. 78% completed trial.	Unclear 6 weeks of 2 different doses of cisapride at 10mg tid vs 20mg tid vs placebo.	improved/total 40/83, 7/20	Cisapride at both doses were not effective compared with placebo in improving symptoms in NUD patients. Side effects profile comparable to that of placebo.
Chung	Korea. RCT. Double-blind placebo-controlled trial.	29 patients with chronic dyspepsia. 14 on cisapride, 15 on placebo. 97% completed trial.	Unclear 4 weeks Cisapride 10mg tid vs placebo	improved/total 10/14, 3/15	Bloating and epigastric discomfort were significantly reduced compared with placebo. Good or excellent global response in 71.4%. No significant side effects noted.
De Groot	Netherlands RCT. Double blind placebo controlled trial	121 patients, 61 took cisapride, 60 took placebo. Upper abdominal pain for at least 4 weeks. Normal endoscopy	Unclear 4 weeks cisapride 10 mg tds versus placebo	improved/total 35/56, 25/57	Success defined as patient rating treatment good or excellent on 4 point likert scale

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De Nutte	Italy. RCT. Double-blind placebo-controlled trial.	59 patients. 59 on Pirenzepine, 55 on cimetidine. Dyspepsia definition and duration not stated. All had chronic erosive gastritis on OGD. 95% completed trial.	Unclear 6 weeks Pirenzepine 50mg bid vsCimetidine 400mg bid.	improved/total 14/17, 7/15	At the end of treatment, 64% of the Pirenzepine group and 62% of the Cimetidine group were free of symptoms and endoscopy revealed healing of lesions in 78% and 80%, respectively. Differences between the groups were not significant.
Francois	Belgium. RCT. Double-blind placebo-controlled trial.	36 with dyspepsia (3/12). 18 in each arm. 64% had either gastritis and/or bulbitis. 2 weeks drug withdrawal. 94.4% completed trial.	Unclear 3 weeks Cisapride 5mg tid vs placebo.	improved/total 14/17, 7/17	Cisapride was significantly superior to placebo in relieving epigastric burning or pain, heartburn, regurgitation, and abdominal distension.
Hannon	Belgium. RCT. Double-blind placebo-controlled crossover trial.	22 patients with NUD. 11 patients in each arm. 2 weeks wash-out period. No dropouts.	Adequate 3 weeks Cisapride 5mg tid vsPlacebo.	improved/total 8/11, 2/11	Cisapride was superior to placebo in relieving a cluster of dyspeptic symptoms, in particular epigastric burning and early satiety. Global therapeutic effect was good or excellent in treatment group (64%) compared with the control group (27%).
Hansen	Denmark. Primary care recruitment. RCT. Double-blind placebo-controlled trial.	330 patients. 109 on cisapride. 111 on Ranitidine. 110 on placebo. Mean duration of dyspeptic symptom was 88 months. 4 subgroups: ulcer-like (13%), reflux-like (23%), dysmotility-like (46%) and unclassified (18%). Included superficial erosions on OGD. 85% completed trial.	Adequate 2 weeks Cisapride 10mg tid vsNizatidine 300mg nocte vs placebo.	improved/total 68/109, 68/110	The effects of a 2-week course of Cisapride or Nizatidine recruited from primary care were not superior to those of placebo. Symptom subgrouping was not predictive of response to treatment.
Holtmann	Germany RCT. Double blind placebo controlled trial	185 private patients with normal endoscopy. Rome definition of dyspepsia - predominant reflux symptoms excluded	Unclear 8 weeks therapy with cisapride 10 mg tds or simethicone 105 mg tds versus placebo	improved/total 8/59, 9/61	Proportion of patients judging treatment to be very good was used in the meta-analysis. No difference between cisapride and placebo for this measure although there was a difference in mean scores in favour of cisapride. Simethicone superior to placebo and cisapride but this was not reported in this study.
Kellow	Australia. RCT, double-blind placebo-controlled trial.	61 total. 30 on cisapride. 31 on placebo. 2 months of symptoms. Need total scores >5 after 2-week placebo run-in period. 2 subgroups: reflux-like and dysmotility. Randomised according to gastritis (HP checked). Gastric emptying test performed. 91.8% completed trial.	Not used 4 weeks Cisapride 10mg tid vsPlacebo	improved/total 23/28, 18/28	Major differences in the 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.

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Global Symptom Score [treatment, control]	Notes
Rosch	Germany. RCT, double-blind.	118 patients with NUD	Unclear 4 weeks Cisapride 10mg tid. Placebo	improved/total 44/54, 17/55	Individual and global symptom scores. Significant improvement with regard to frequency and severity of symptoms
Wood	UK RCT.. Double blind placebo controlled trial	11 patients with normal endoscopy. Predominant epigastric pain.	Not used 4 weeks cisapride 10 mg tds versus placebo	improved/total 5/6, 3/5	Absence of epigastric pain (day and night).
Yeoh	Singapore. RCT. Double-blind placebo-controlled trial.	104 patients with functional dyspepsia. 38 patients in each arm, consisting of one group with gastritis and one without. 2 weeks antacid run-in period. 73% completed trial.	Unclear 4 weeks Cisapride 10mg tid vs. placebo.	improved/total 21/38, 19/38	Cisapride produced a good or better global response in 58% with gastritis and 53% in those without gastritis compared with 47% and 52% respectively, of patients on placebo. There was no significant difference between the groups.
***Helicobacter pylori* Eradication for NUD**					
Blum (OCAY) 1998	Switzerland Multicentre (OCAY) RCT, double-blind	348 patients with Hp infection and dyspeptic symptoms. Reflux excluded.	Adequate 12 months 1 week Omeprazole 20mg bid, amoxycillin 1g bid and clarithromycin 500mg bid vs Omeprazole 20mg bid	improved/total 119/164, 130/164 hp erad. 79% (ITT) 87% (per-protocol)	Global symptom score GSRS(dyspepsia symptom score) QoL (PGWB)
Froehlich 2001	Switzerland RCT double blind multi-centre	158 patients with normal endoscopy and hp +ve. Dyspepsia > 3 months. Reflux excluded	Adequate 12 months One week of lansoprazole 30 mg bid, clarithromycin 500 mg bid, amoxycillin 1g bid or lansoprazole 30 mg bid plus matching placebos.	improved/total 31/74, 34/70 hp erad. 72%	Success defined as a dyspepsia score of less than 10 using a validated dyspepsia questionnaire (van Zanten et al.). Quality of life using SF-12
Gisbert 2002	Spain RCT No blinding Single centre	50 *H. pylori* infected patients Rome II criteria NUD	Unclear Ten days of omeprazole 20 mg bd, clarithromycin 500mg bd, amoxycillin 1g bd, versus ten days of ranitidine 150 mg bd.	improved/total 13/34, 8/16 hp erad. 76%	Overall treatment success defined as >three point improvement on global dyspepsia score (Likert scale)
Hsu 2001	China RCT double blind single centre	161 hp positive patients. Rome II criteria for NUD	Inadequate 12 months One week of lansoprazole 30mg bd, metronidazole 250mg qds, tetracycline 500 mg qds versus lansoprazole 30 mg bd and placebo antibiotics for one week	improved/total 34/81, 36/80 hp erad. 78%	Absence of dyspepsia symptoms
Koelz 1998	Germany RCT, double-blind, Multicentre trial	181 patients with chronic therapy resistant functional dyspepsia. Reflux excluded.	Adequate 6 months 2 weeks of Omeprazole 40mg bid plus amoxycillin or Omeprazole 20mg/day	improved/total 67/89, 73/92 hp erad. 52% (ITT)	Global symptom scores

Study	Location Design	Participants	Concealment of allocation Study duration Treatment regimens	Global Symptom Score [treatment, control]	Notes
Koskenpato 2001	Finland RCT double blind Single centre	151 hp postive patients with dyspepsia. Normal OGD, normal ultrasound, predominant reflux excluded	Unclear 12 months 2 weeks omeprazole 20 mg bd, amoxycillin 500mg qds, metronidazole 400 mg tds followed by omeprazole 20 mg od for 3 months, placebo for the next 9 months versus same regimen but placebo antibiotics over the first 2 weeks	improved/total 61/77, 63/74 hp erad. 81%	dyspepsia responders (at least 50% improvement in dyspepsia score)
Malfertheiner 2000	Germany RCT double blind multi-centre	860 patients. Normal endoscopy, hp +ve. Dyspepsia fo > 4 weeks. Unclear if reflux excluded	Adequate 12 months One week of Lansoprazole 30/15mg bid, clarithromycin 500 mg bid and amoxycillin 1g bid for 7 days or Lansoprazole 15 mg od and matching placebos	improved/total 269/460, 143/214 hp erad. 80%	Success: no or minimal symptoms in previous week using validated German dyspepsia questionnaire
McColl 1998	UK RCT, double-blind single centre	330 patients with Hp infection and dyspepsia. Reflux included	Adequate 12 months 2 weeks Omeprazole 20mg bid, amoxycillin 500mg tid (or tetracyline 500mg tid) and metronidazole 400mg tid or Omeprazole 20mg bid	improved/total 121/154, 143/154 Hp erad. 88% (ITT)	Global symptom score Glasgow Dyspepsia Severity Scores GDSS
Miwa 2000	Japan RCT double blind single centre	90 patients with NUD (normal endoscopy and Hp +ve) Reflux excluded	Adequate 3 months One week of omeprazole 20 mg bid, amoxycillin 500 mg tds, clarithromycin 200 mg bid or placebos	improved/total 33/48, 28/37 hp erad. 85%	No or minimal symptoms on GSRS
Talley (ORCHID) 1999	Australia multicentre RCT, double-blind	Primary and secondary care patients. Reflux excluded 287 patients with functional dyspepsia and Hp infection	Adequate 12 months 1 week Omeprazole 20mg bid, amoxycillin 1g bid and clarithromycin 500mg bid or placebo	improved/total 101/133, 111/142 hp erad. 85%. ITT	Global symptom scores GSRS(dyspepsia symptom score) QoL (PGWB).
Talley (USA) 1999	USA Multicentre, RCT, double blind	293 *H. pylori* positive patients with NUD. Reflux excluded.	Adequate 12 months 2 weeks omeprazole 20 mg bd, amoxycillin 1g bd and clarithromycin 500 mg bd	improved/total 81/150, 72/143 hp erad. 90%	Global symptom score GSRS QoL (SF-36)
Varannes 2001	France RCT, double blind, multi-centre	253 patients with normal endoscopy and hp +ve. Dyspepsia > 3 months. Reflux excluded	Adequate 12 months One week of ranitidine 300 mg bid, amoxycillin 1g bid, clarithromycin 500 mg bid or matching placebos.	improved/total 74/129, 86/124 hp erad. 70%	No epigastric pain on Likert scale in previous week