3 Dyspepsia

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1 Summary

Statement of the problem

The term 'dyspepsia' describes a clinical problem referring to a cluster of upper gastrointestinal symptoms that has been defined in many ways. As this chapter is concerned with broad population needs, we have used the 1988 Working Party definition, which includes patients with heartburn. As dyspepsia is a common condition, with costly investigations and treatment, the cost to the NHS has been estimated at £1.1 billion per year (in 1998). Particular concerns in managing dyspepsia are therefore the cost-effective use of resources, the appropriate choice of potentially curative treatments (*Helicobacter pylori* eradication) rather than symptomatic therapies (acid suppression), and the need for prompt diagnosis of upper gastrointestinal malignancy.

Sub-categories

Dyspepsia is a symptom, not a diagnosis. Patients with dyspepsia can be divided into subgroups on the basis of final endoscopic diagnosis, but if we are to accept that endoscopic diagnosis is not cost-effective in all patients, a sub-category 'uninvestigated dyspepsia' is necessary to consider what management is appropriate for patients presenting with a new episode.

- Uninvestigated dyspepsia: patients presenting with a new episode who have not had endoscopic investigation.
- Gastro-oesophageal reflux disease (GORD) refers to patients with symptomatic heartburn and acid regurgitation. Approximately 50% of these patients will also have oesophagitis.
- Peptic ulcer disease can be subdivided into gastric and duodenal ulcers. *Helicobacter pylori* and non-steroidal anti-inflammatory drugs are the predominant causes.
- Oesophageal and gastric cancer.
- Non-ulcer dyspepsia: patients without peptic ulcer, malignancy or oesophagitis on endoscopic investigation.

Prevalence and incidence

Dyspepsia is a chronic, relapsing and remitting symptom. The terms incidence and prevalence are difficult to apply in this context, because of the problem of classifying patients with a history of symptoms, who are currently asymptomatic, but are at high risk of further episodes. In addition, the definition and classification of dyspepsia has changed between ICD-9 and ICD-10. Community surveys vary in their findings according to the definition used. It is estimated that 40% of the population suffer from dyspepsia

if reflux symptoms are included, 23% if not. However, the range of the 14 surveys found was wide at 14–48%.

The proportion of patients undergoing endoscopy where a peptic ulcer is detected has fallen dramatically in the past 12 years from 20% in 1989 to 10%. The prevalence of *H. pylori* infection is related to social deprivation in childhood. *H. pylori* infection is declining in the population as successive birth cohorts have a lower risk of childhood acquisition. At present the prevalence of *H. pylori* in 20–30 year olds is 10–20%, rising as a percentage with age to 50–60% in 70 year olds. First generation immigrants from developing countries are very likely to have *H. pylori* infection, as the infection is endemic in these conditions. The fall in peptic ulcer disease may be due to a reduction in recurrent ulcer disease as *H. pylori* is eradicated in patients presenting with peptic ulcer.

Oesophagitis is present in 20% of patients at endoscopy, and may be rising with time, although the condition may be more frequently diagnosed with the availability of effective treatment in the form of proton pump inhibitors.

Gastric cancer is the fifth commonest cancer in the UK. The incidence has been declining steadily, with a concomitant rise in adenocarcinoma of the oesophagus. This may reflect an increasing prevalence of GORD.

Non-ulcer dyspepsia accounts for 60% of cases at endoscopy, and is the commonest sub-category.

Services available and their costs

Consultations for dyspepsia account for between 1.2 and 2.7% of all consultations with general practitioners, rising with age from 355 per 10 000 patient years at age 25–44 to 789 per 10 000 at age 75–84. There is a suggestion from comparisons between the 1990 fourth morbidity survey in general practice and RCGP weekly returns data for 1997 that the consultation rate may have fallen by as much 75%, but comparisons between the two datasets are difficult on account of changing definitions and different population bases.

Qualitative research has shown that between 25 and 50% of patients with dyspepsia will consult their GP. Factors predicting consultation are worry about serious disease, such as cancer or heart disease, and the availability of effective medical therapy.

Prescription Pricing Authority data show a steady rise in the cost of prescribing for dyspepsia since the introduction of proton pump inhibitors (PPIs). In 1999, £471 million was spent, £323 million on PPIs, £124 million on H_2RAs and £24 million on antacids. The costs and numbers of prescriptions for dyspepsia have risen steadily over the past eight years. PPI prescribing has increased steadily, with little substitution of either antacids or H_2 receptor antagonists.

In 2000 there were 539 gastroenterologists working in England and Wales, and it has been estimated that 50% of their workload is accounted for by dyspepsia. Although demand for upper GI endoscopy rose sharply with the availability of 'open access' services to GPs, the rate has stabilised at 1% of the population undergoing the procedure each year. In 2000, £130 million was spent on 451 000 endoscopies. The 2000 NHS reference cost for diagnostic upper GI endoscopy as a day case was £250, but with a very wide range (£52–£1333).

Non-invasive tests for *H. pylori* are also available. Serology is available in most areas, but has poor predictive value where the prevalence of *H. pylori* is low. Near patient tests are also available, but perform less well than serology. Both urea breath tests and stool antigen tests are much more accurate, but either involve the ingestion of a test dose of (non-radioactive) labelled urea and the collection of breath samples for analysis in a mass spectrometer, or collection of stool samples. Both these tests are also more expensive

than serology. Several breath test 'kits' are available on NHS prescription, but stool antigen testing is not yet widely available.

The effectiveness of *H. pylori* eradication therapy for peptic ulcer disease and acid-suppression therapy has greatly reduced the role of surgical procedures in dyspepsia. Most gastric surgery is now performed for malignant disease. Most patients are unsuitable for surgery, as the disease is too far advanced at detection, and long-term survival even after surgery is poor at less than 20%.

Effectiveness of services and interventions

Uninvestigated dyspepsia: Symptom patterns are not sufficiently predictive or specific to be of value in managing patients with dyspepsia. Trials comparing acid suppression therapies in uninvestigated patients are either lacking or for short-term outcomes only. PPIs have been the most studied, and have been shown to reduce the proportion of symptomatic patients by 29% compared with antacids and 37% compared with H_2 receptor antagonists. Heartburn responds more than epigastric pain. Management based on an initial endoscopy may be associated with a small reduction in symptoms (12%) compared with empirical acid suppression. Two recent RCTs have shown that *H. pylori* 'test and treat' is as effective as endoscopy, but reduces costs, as only 1/3 of the endoscopies are needed. There is no evidence as to whether 'test and treat' is cost-effective compared to empirical acid suppression as an initial strategy.

Peptic ulcer disease: *H. pylori* eradication is highly effective in both healing and reducing the recurrence rates of both duodenal and gastric ulcers. Ninety-six percent of duodenal ulcers will heal after *H. pylori* eradication, and recurrence rates at one year are reduced to 8%, compared with 83% with 4 weeks of acid-suppression alone (NNT = 1.3).

Oesophagitis: Both H2 receptor antagonists and PPIs are effective in healing oesophagitis (NNTs: H_2 receptor antagonists 6; PPI 2). PPIs are more effective than H2 receptor antagonists (NNT = 3). Both PPIs and H_2 receptor antagonists are also more effective than placebo at reducing heartburn symptoms in patients without oespohagitis (NNTs: H_2 receptor antagonists 8; PPI 5). Eighty percent of patients with successfully treated GORD will suffer relapse within one year without maintenance. Evidence for long-term therapy is less strong, but three RCTs have found a significant reduction in relapse with PPI compared to H2 receptor antagonists.

Non-ulcer dyspepsia: One trial found that antacids were no more effective than placebo, a meta-analysis of trials found no significant reduction in symptoms with H_2 receptor antagonists, although the trials were small and of poor quality. A meta-analysis of trials of PPI against placebo found a significant reduction in symptoms (NNT = 7). *H. pylori* eradication was also associated with a significant reduction in dyspeptic symptoms at one year in a meta-analysis (NNT = 15). Given the uncertainty in trial data, and the potentially important clinical differences between patients, it is important that the response to treatment of all non-ulcer dyspepsia patients is carefully monitored.

Quantified models of care

When the risk of malignancy is low: A discrete event simulation model indicates that endoscopy is not cost-effective in these patients. The choice of strategies should be between empirical acid suppression and *H. pylori* 'test and treat'. The point at which to test for *H. pylori* is sensitive to the underlying likelihood of *H. pylori* infection and the cost of recurrent acid-suppression therapy that could be avoided by successful treatment. However, the additional cost for a month's less symptoms was quite high on switching from

empirical acid suppression to 'test and treat', of the order of £50–60 per month. Data from a RCT is awaited to confirm these model findings.

When the risk of malignancy is high: Patients in whom malignancy is suspected should all receive prompt endoscopic investigation. However, patients with overt symptoms such as weight loss or dysphagia are likely to have inoperable cancer. If malignancy is to be detected early, endoscopy needs to be performed in patients without overt symptoms, but at high risk. Previously, an age above 45–55 was used as a crude indicator of risk. Recent data, combined with an economic model, suggests that restricting endoscopy to patients with continuous epigastric pain and/or symptoms of less than one year's duration (in addition to those with alarm symptoms) would improve the cost/life year gained from £50 000/life year to £8400/life year in men. Gastric cancer is less common in women and investigation cannot be justified on economic grounds until age 65.

2 Introduction and statement of the problem

Definitions of dyspepsia

Dyspepsia is derived from the Greek, meaning 'bad digestion'. This vague description is fitting for a constellation of symptoms that has no universally agreed definition. A review of the literature identified 23 different descriptions of dyspepsia[1] and since this review there has been a further international expert meeting to try and reach a consensus.[2] All agree that dyspepsia is a group of symptoms that is thought to arise from the upper gastrointestinal tract and most imply that the term represents a symptom complex and not a diagnosis.

The first influential definition was the 1988 Working Party classification[3] that stated dyspepsia was any symptom considered to be referable to the upper gastrointestinal tract. Symptoms needed to be present for 4 weeks and included upper abdominal pain or discomfort, heartburn, acid reflux, nausea and vomiting. This classification further subdivided patients on the basis of symptom patterns into 'ulcer-like' (epigastric pain), 'reflux-like' (heartburn and acid regurgitation), 'dysmotility-like' (bloating and nausea) and 'unclassifiable'. The Rome I working group[5] suggested that the key symptom needed to define dyspepsia was pain or discomfort centered in the upper abdomen and excluded patients with heartburn or acid reflux as their only symptom.[4] The upper abdominal symptoms needed to be present for more than one month and occur greater than 25% of the time to fulfil the criteria for dyspepsia.

A multinational consensus panel further developed these Rome I criteria.[5] The 'Rome II' criteria state that patients need to have predominant pain or discomfort centred in the upper abdomen for at least 12 weeks in the last 12 months to be classified as having dyspepsia. The British Society of Gastroenterology (BSG), however, took a broader view, stating that dyspepsia was any group of symptoms that alerts doctors to consider disease of the upper gastrointestinal tract.[161] The BSG definition is therefore closer to the 1988 Working Party definition of dyspepsia.

The Rome II criteria were developed to standardise the type of patient enrolled into functional (non-ulcer) dyspepsia trials where organic pathology has been excluded by normal investigations. This important advance will make future non-ulcer dyspepsia trials more comparable but this definition is less relevant for uninvestigated patients. This chapter is concerned with population needs, where the diagnosis is often not established. A broader definition is more appropriate for this purpose and this chapter therefore used the 1988 Working Party and BSG guidelines definition of dyspepsia.[6]

Problems in the management of dyspepsia

Dyspepsia is common, with a primary care consultation rate of 2 per 1000 population per year, and, for many patients, is a lifelong intermittent and relapsing disorder. Dyspepsia drugs have been the single highest cost prescription item in the past two years and 3% of the population may be taking long-term therapy.[7] In any six month period 40% of the population will suffer an episode of dyspepsia, and half of those will consult their general practitioner.[8] The costs of managing dyspepsia outstrip all other conditions in the NHS, £1.1 billion in 1998.[9]

The frequent occurrence of dyspeptic symptoms, the widespread availability of empirical treatments and the high cost of definitive investigation mean that the guiding principle of managing dyspepsia lies in the cost-effective use of both treatments and investigations appropriate to an individual patient. This is in preference to first defining the cause of the symptoms by definitive investigation of all patients. Any assessment of health need relating to dyspepsia must consider both the management of previously uninvestigated cases, and cases where a cause has been established by gastroscopy. This paper attempts to categorise patients according to the potential risk of treatable disease and considers both the treatment of established causes of upper gastrointestinal disease and the evidence relating to the choice of management for uninvestigated cases. In the latter, both direct comparative research evidence and modelling based on case mix and the likely effects of treatments on underlying causes will be used. The two most important factors to consider are the role of testing and eradication of *H. pylori* and the role of endoscopy for the early diagnosis of malignancy.

H. pylori

The gastric pathogen *Helicobacter pylori* is aetiologically implicated in peptic ulcer disease and distal gastric cancer, but is widely present in the population and causes no harm in the majority of patients. A range of invasive and non-invasive tests for *H. pylori* are available. The majority of those investigated by endoscopy do not have significant pathology. Of the conditions that may be detected, most interest has centered on peptic ulcer disease, as this condition may now be cured by the eradication of *H. pylori*. There is also the potential to decrease the incidence of gastric cancer by *H. pylori* eradication. *H. pylori* may also play a role in eradication in functional dyspepsia. A number of strategies for managing dyspeptic patients incorporating non-invasive tests for *H. pylori* followed by either endoscopy or *H. pylori* eradication therapy restricted to those testing positive have been suggested.

The role of endoscopy in detecting early upper gastrointestinal cancer

Some patients with dyspeptic symptoms will prove to have malignancy, principally adenocarcinoma of the stomach or oesophagus. Although most patients with dyspeptic symptoms present at an inoperable stage, some patients may benefit from surgery if investigated promptly by endoscopy.[10] This chapter considers in detail the evidence and potential for early diagnosis of curable malignancy by selective prompt endoscopy in specific subgroups of high risk patients.

3 Sub-categories

Uninvestigated dyspepsia

Uninvestigated dyspepsia describes patients fitting the 1988 Working Party definition of dyspepsia who have not undergone endoscopic investigation. The focus of this chapter is on the cost-effectiveness of initial management strategies for dyspeptic patients in primary care.

The term 'dyspepsia' describes a group of symptoms and is not a diagnosis. However, many patients consulting with dyspepsia are referred for investigation to determine the cause of their symptoms. A diagnosis can then be reached and patients will have one or more of the following diseases.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) refers to subjects experiencing reflux of gastric contents into the oesophagus causing symptoms that impair health-related well-being.[11] The distal oesophagus has abnormally prolonged acid and pepsin exposure in the majority of patients with GORD.[12,13] Normal levels of reflux provoke symptoms in a minority of cases, possibly due to increased oesophageal sensitivity.[14,15] Endoscopy may reveal oesophageal mucosal breaks (oesophagitis) in some patients with GORD, but endoscopy results are normal in over 50% of cases.[16]

Peptic ulcer disease

A peptic ulcer is defined as a defect in the gastrointestinal mucosa extending through the muscularis mucosae due to the acid-peptic action of gastric juice. These can be subdivided into gastric and duodenal ulcers, depending on the site of the defect. The traditional view that gastric and duodenal ulcers have distinct symptoms has been shown to be incorrect; indeed, symptoms are inadequate to identify patients with ulcers.[17] *H. pylori* infection is the main cause of duodenal ulcers, with 95% of cases being associated with this organism. Eighty percent of gastric ulcers are also associated with *H. pylori* infection, and non-steroidal anti-inflammatory drugs are implicated in most of the remainder.

Non-ulcer dyspepsia

Patients with dyspepsia symptoms with a normal endoscopy are often classified as having non-ulcer dyspepsia. The problem with this definition is that a proportion of these patients will have endoscopy negative reflux disease. It is because of this concern that the Rome II definition excludes patients with predominant heartburn and acid reflux. Patients are then subdivided into 'ulcer-like' and 'dysmotility-like' subgroups. There are several problems with this subclassification of non-ulcer dyspepsia. They all require the patient to have normal investigations whereas the main focus of this chapter will be uninvestigated dyspepsia. Population surveys have shown there is substantial overlap between dyspepsia subgroups[18] and subjects that can be classified often change categories over time.[19] The incomplete separation of the different subgroups and their lack of consistency makes them difficult to apply to populations. The Rome II subgroups have not been prospectively validated and remain speculative. Subgroups do not adequately identify the needs of the population and this paper, therefore, avoids the use of these terms. We use instead a broad definition of dyspepsia, including patients with heartburn and acid regurgitation, and subdivide on the basis of whether the patient has undergone definitive investigation or not.

Barrett's oesophagus

Barrett's oesophagus is a diagnosis made on the basis of both endoscopic and pathologist findings and is defined as columnar-lined oesophageal mucosa.[21] Some suggest that intestinal metaplasia should be seen within the columnar mucosa before a diagnosis of Barrett's oesophagus is made, but as metaplasia is patchy, this requirement is usually thought to be too stringent. Long-segment Barrett's oesophagus is diagnosed when at least 3 cm of the distal oesophagus is lined by columnar epithelium. This has the greatest malignant potential, and surveillance programmes have been recommended for this disorder. Short-segment Barrett's oesophagus is defined as less than 3 cm of columnar-lined oesophageal mucosa and this also has malignant potential.[21] The risk may be less than for long-segment Barrett's oesophagus and the role of surveillance in this disorder is uncertain. There may be no visible columnar-lined oesophagus but intestinal metaplasia may be present in biopsies taken at the gastro-oesophageal junction. The malignant potential of this lesion is uncertain and as 20% of the population have evidence of intestinal metaplasia at the gastro-oesophageal junction,[22] surveillance is not recommended.

Oesophageal neoplasia

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.[23] Adenocarcinoma of the oesophagus is believed to originate from columnar metaplasia of the oesophagus (Barrett's oesophagus) and endoscopic screening of patients with Barrett's oesophagus has been advocated.

Gastric neoplasia

Adenocarcinoma is responsible for over 95% of all gastric malignancies. Half the patients are inoperable at the time of diagnosis and virtually all of these are dead within five years. The 50% undergoing operative treatment have a 20% five year survival. The overall mortality for this disease in the UK is therefore approximately 90%. Gastric neoplasia is strongly associated with *H. pylori* infection,[24] but as the vast majority of infected individuals do not develop gastric carcinoma, other environmental and genetic factors must be important.

4 Prevalence and incidence

Prevalence and incidence are the two most commonly used measures of disease frequency in epidemiology. Incidence refers to the number of **new cases** of disease per population at risk over a specified time period. Prevalence is the proportion of the population with the disease at a given point in time. Prevalence is concerned with the total number of cases rather than new events and is therefore a function of the incidence and chronicity of the disease. Incidence is the most useful measure for studies evaluating factors associated with disease, whereas prevalence provides information that is useful for health service planning for chronic disorders. Prevalence is relatively simple to calculate for diseases that remain stable until cure or death.

Dyspepsia is a chronic relapsing and remitting disorder, often with an insidious onset, and measuring prevalence in this situation is more problematic. There is no controversy about classifying those subjects

with symptoms (either new or ongoing) as having dyspepsia and those that have never had symptoms as not having dyspepsia. The difficult group are those that have had dyspepsia symptoms but are now asymptomatic. These individuals are at high risk of developing recurrent symptoms in the future and therefore may not be 'cured' of their condition. Classifying them as having dyspepsia, however, ignores the fact that a substantial minority will have no further symptoms and could indeed be considered as 'cured'. Including asymptomatic subjects with previous dyspepsia symptoms will therefore overestimate the true prevalence of the disorder whilst excluding them will underestimate the prevalence. This paper will assume asymptomatic subjects with previous symptoms are cured and therefore may be underestimating the true prevalence in the population.

Cross-sectional surveys assessing population dyspepsia rates typically assess the number of subjects with characteristic symptoms over a 3–12 month period. These surveys usually do not usually ascertain whether symptoms are new and are therefore assessing the prevalence of dyspepsia. The commonest causes of dyspepsia are GORD, peptic ulcer disease and non-ulcer dyspepsia. These are all chronic relapsing and remitting disorders and again it is usually the prevalence of the disorder that is measured. The true prevalence of these diseases is hard to establish, however, as endoscopy is needed to obtain the diagnosis. The population at risk is the total adult population and it would be difficult to persuade the general population to undergo endoscopy. Most surveys describe the proportion of patients with upper gastrointestinal disease in those presenting for endoscopy. This type of study is easier to conduct but the 'population at risk' is those referred for endoscopy and this selected group is not particularly meaningful in public health terms.

A further problem is that there are fundamental differences between the International Classification of Diseases' 9th and 10th revisions in the way that dyspepsia is defined and sub-divided. Under ICD-9 non-ulcer dyspepsia was classed with habitual vomiting and achlorhydria as 'disorders of stomach function' (536). In ICD-10, the term 'functional dyspepsia' is provided (K30), but, following the Rome definition, excludes heartburn symptoms. Similarly, in ICD-9, diseases of the oesophagus (530) do not include symptomatic reflux disease without oesophagitis. ICD-10 uses gastro-oesophageal reflux disease, either with oesophagitis (K21.0) or without (K21.9). Similar problems arise when trying to collect data from primary care. The NHS now stipulates that practice computer systems record data using the Read coding system (currently a 5 digit system). **Table 1** shows the mapping adopted to transfer Read codes, ICD-9 and ICD-10 diagnoses.

Table 1: Read codes and International Classification of Disease codes 9 and 10 used in this chapter.

Main condition	Subgroup	Read (5) Code	ICD-9	ICD-10
GORD		J10..	530	K21.9
	Oesophagitis	J101.	530.1	K21.0
Gastric ulcer		J11..	531	K25
	Perforated gastric ulcer	J1102, J1112, J11y2	531.1, 531.5	K25.1/2/5/6
	Bleeding GU	J1101, J1111, J11y1	531.0, 531.4	K25.0/2/4/6
Duodenal ulcer		J12..	532	K26
	Duodenal scar	J1733, J17y7	537.3, 537.8	–
	Perforated duodenal ulcer	J1202, J1212, J12y2	532.1, 532.5	K26.1/2/5/6
	Bleeding duodenal ulcer	J1201, J1211, J12y1	532.0, 532.4	K26.0/2/4/6
	Peptic ulcer (unspec.)	J13..	533	K27
	Perforated peptic ulcer	J1302, J1312, J13y2	533.1, 533.5	K27.1/2/5/6
	Bleeding peptic ulcer	J1301, J1311, J13y1	533.0, 533.4	K27.0/2/4/6
Functional dyspepsia		J16y.	536.8	K30 (excludes heartburn alone)
	Gastritis and duodenitis	J15..	535	K29

Even if differences in diagnostic criteria, classification and period of data collection are allowed for, there will still be differences between populations and data recorded from community surveys, primary care and secondary care. The data sources available for this chapter are shown in **Figure 1**. Two important sources of data from primary care are the decennial 'Morbidity survey in general practice' conducted by the OPCS (the fourth survey was conducted in 1990–91), and the RCGP 'weekly returns' service. Both these surveys involve general practitioners recording every contact and every diagnosis in their daily work. The RCGP data in particular are valuable for comparing trends, as the same practices collect the data and great effort is put into data monitoring and consistent mapping. Hospital Episode Statistics provide useful information on pathology seen at endoscopy from a secondary care perspective and the Office of National Statistics provides information on upper gastrointestinal malignancy.

Surveys of the proportion of *H. pylori* positive adults are measuring prevalence, as once the organism is acquired it usually becomes a chronic life-long infection. Gastric and oesophageal carcinomas are usually fatal and therefore incidence is the appropriate measure to describe the frequency in the population.

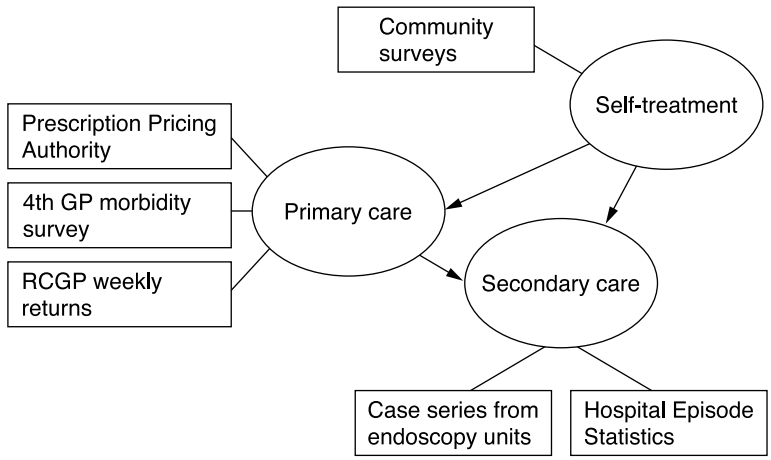

Figure 1: Data sources used in this chapter.

Prevalence of dyspepsia

A review of the literature identified 14 surveys that evaluated the prevalence of dyspepsia in the community in the last 12 years. The pooled estimate of the prevalence of dyspepsia was 34.4% (95% confidence intervals [CI]: 33.9–34.9%) but there was a wide range in the proportion of subjects with dyspepsia ranging from 13% to 48% (*see* **Table 2**). The majority of this variation was due to differences in the definition of dyspepsia. Surveys that included dominant reflux symptoms in the definition gave a prevalence of 39.4% whereas studies that excluded subjects with predominant heartburn and acid regurgitation reported a prevalence of 23.2% (mean difference = 16.2%; 95% CI: 15.3–17.0%; *see* **Figure 2**). A meta-analysis of these trials suggests that dyspepsia is slightly more common in women.

Recent UK trials have tended to use broad definitions of dyspepsia and report a prevalence of 40%.[8,25] The earliest UK study reported a 30% prevalence of dyspepsia in 354 workers in coke oven plants in the 1940s and a 30% prevalence was reported 10 years later in a sample of 5951 English males.[26] A study of Scottish men in 1968 reported a 29% prevalence in 1487 Scottish men.[27] The prevalence of dyspepsia therefore appears to have increased slightly from 30% to 40% in recent years, although the definitions used in the earlier reports may not be comparable to later studies.

Table 2: Population surveys reporting the prevalence of dyspepsia 1988–2000.

Authors	Year of report	Country	Dyspepsia definition	Number studied	% dyspepsia
Jones *et al.*	1989	England	BSG	2,066	38.0
Jones *et al.*	1990	England/Scotland	BSG	7,428	41.8
Bernersen *et al.*	1990	Norway	BSG	1,802	27.5
Talley *et al.*	1992	USA	Rome	835	25.5
Drossman *et al.*	1993	USA	Rome	5,430	25.8
Holtmann *et al.*	1994	Germany	Rome	431	28.8
Talley *et al.*	1994	Australia	Rome	1,528	20.3
Agreus *et al.*	1995	Sweden	BSG	1,156	32.2
Penston *et al.*	1996	Great Britain	BSG	2,112	40.3
Rosenstock *et al.*	1997	Denmark	BSG	3,589	47.8
Kennedy *et al.*	1998	England	Rome	3,169	26.3
Nandurkar *et al.*	1998	Australia	Rome	592	13.2
Talley *et al.*	1998	Australia	Rome	730	12.6
Moayyedi *et al.*	2000	England	BSG	8,350	38.0

BSG: dyspepsia definitions that include epigastric pain and heartburn.
Rome: dyspepsia definitions that only include pain or discomfort centred in the upper abdomen as the predominant symptom.

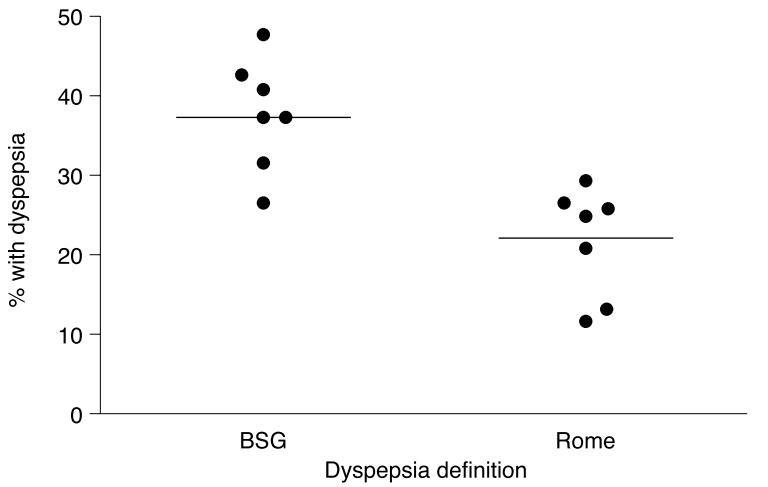

Figure 2: Prevalence of dyspepsia according to dyspepsia definition.

Prevalence of *Helicobacter pylori* infection

The prevalence of *H. pylori* varies widely between countries, 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 will exist where there has been substantial immigration from countries with a higher prevalence of infection. The mode of acquisition of *H. pylori* infection is uncertain, although person to person transmission seems likely. The organism could be transmitted by the faeco-oral or oro-oral route, although *H. pylori* has only rarely been cultured from faeces and saliva.[28] Acute *H. pylori* infection causes a vomiting illness and recent evidence suggests *H. pylori* may be transmitted through vomitus.[29] Whatever the method of transmission, epidemiological data suggests that most individuals acquire the infection in childhood with social deprivation, household crowding[27,30] and number of siblings[31] being important risk factors.

The prevalence of infection is strongly correlated with age. Older individuals are more likely to be infected with *H. pylori* and studies suggest this is an age cohort effect. Socio-economic conditions were poor 70 years ago and so most children were infected with *H. pylori*. The majority of 70-year-olds are therefore *H. pylori* positive, but as childhood socio-economic conditions improved the prevalence fell so that today 10–20% of children are infected.[30] This is consistent with the observation that the incidence of peptic ulcer and distal gastric cancer are falling with time, as these are *H. pylori* related diseases.

H. pylori infection is slightly more common in men,[32] although the difference is small and this is unlikely to explain the gender differences in gastric cancer and peptic ulcer disease.

Prevalence of peptic ulcer disease

Ten percent of patients undergoing endoscopy have a diagnosis of duodenal ulcer (*see* **Figure 3**). This proportion has been falling dramatically over recent years, with 20% of patients having duodenal ulcer in 1989 (*see* **Figure 4**). This observation is confirmed by primary care data. The RCGP figures for the last four years available show a striking 60% decline in the episode rate for duodenal ulcer, from 8.43 to 3.34 consultations per 10 000 patient years (*see* **Figure 5**). Previously, duodenal ulcers were treated with acid suppression, whereas now they are usually permanently cured with a course of *H. pylori* eradication therapy. This striking fall in the prevalence of duodenal ulcer over a short period of time is therefore predictable. There should also be a reduction in the incidence of duodenal ulcer as the prevalence of *H. pylori* falls, but this is unlikely to be as pronounced over short time frames. This is confirmed by the RCGP data that show little change in the rate of newly diagnosed duodenal ulcer disease but a dramatic decline in recurrent episodes (*see* **Figure 5**).

Ten percent of patients endoscoped were diagnosed as having a gastric ulcer (*see* **Figure 3**). This will be an overestimate of the true prevalence as it is recommended that patients with a diagnosis of gastric ulcer have a repeat endoscopy to ensure healing. RCGP data show that the prevalence of gastric ulcer is half to a quarter of duodenal ulcer disease (*see* **Figure 6**). The prevalence of gastric ulcer is also falling dramatically (*see* **Figure 4**).

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. Gastric ulcer is increasingly common with age and equally as common in females as in males (*see* **Figure 6**). Peptic ulcer disease is more common in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) and bleeding is a particular complication associated with this therapy. Overall there is a 4.7-fold increase in risk of bleeding peptic ulcer in patients taking NSAIDs. This risk increases with age and patients over 60 years of age are 13.2 times as likely to develop bleeding peptic ulcer disease with NSAIDs compared with younger age groups.[33]

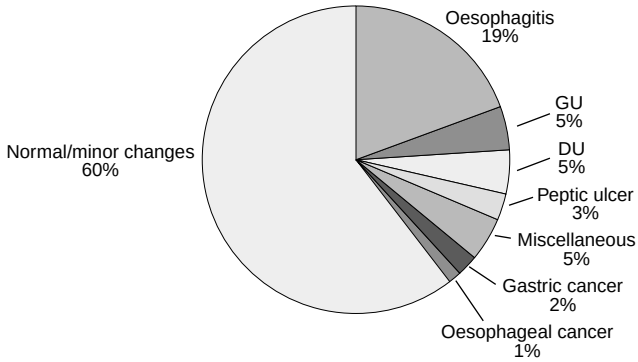

Figure 3: Findings at endoscopy – *Hospital Episode Statistics* 1994.

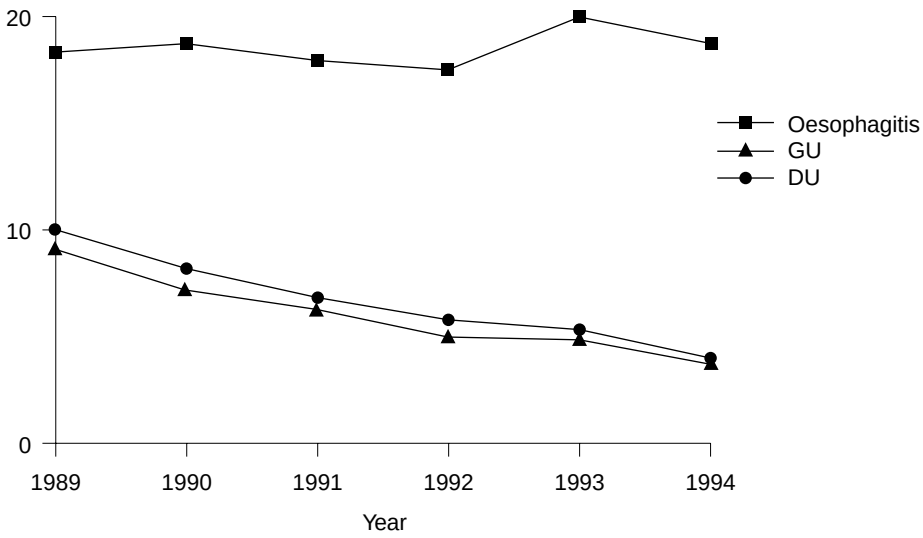

Figure 4: Diagnosis of oesophagitis, duodenal ulcer and gastric ulcer at endoscopy 1989–94 – *Hospital Episode Statistics.*

Prevalence of gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease is more common than peptic ulcer disease, with oesophagitis present in 20% of endoscopy patients (*see* **Figure 3**). This is an underestimate of the prevalence of GORD, as only 25–50% of patients with this disorder have oesophagitis. Hospital Episode Statistics suggest the prevalence of oesophagitis is remaining stable, although this is based on only eight years of follow-up (*see* **Figure 4**). Case series from endoscopy units suggest that the diagnosis of oesophagitis is increasing with time.[30,31,34,35] These studies suggest the prevalence has quadrupled over a 10–20 year period. It is likely

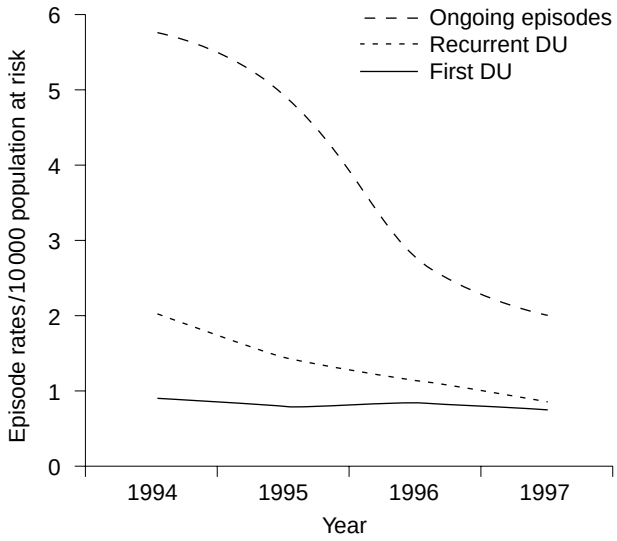

Figure 5: Ongoing, new and first episode rates for duodenal ulcer 1994–97, RCGP.

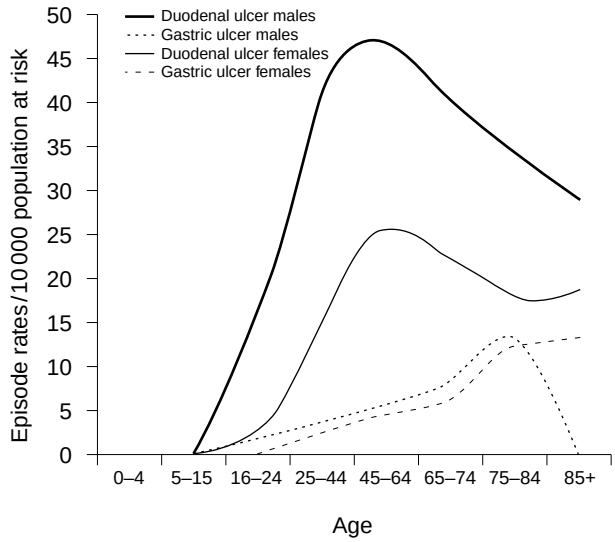

Figure 6: Incidence of duodenal and gastric ulcer by age and gender from fourth GP morbidity survey.

that this reflects a true increase in the prevalence of GORD, but the magnitude of the increase may be overestimated, as the condition is more readily diagnosed with the advent of proton pump inhibitors as effective therapy for the condition. The prevalence of GORD increases with age and is slightly more prevalent in women (*see* **Figure 7**).

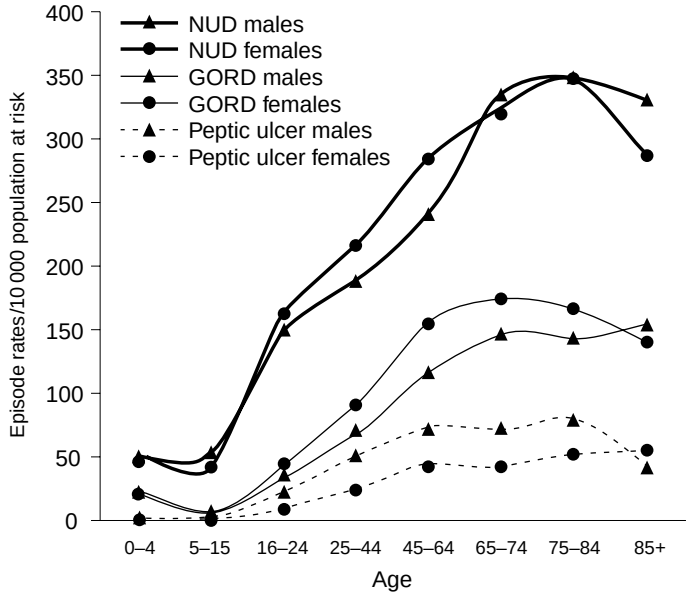

Figure 7: First and new episodes from fourth GP morbidity survey by age, sex and diagnosis.

Prevalence of non-ulcer dyspepsia

This is the most common diagnosis in dyspepsia patients referred for endoscopy (*see* **Figure 3**). Primary care consultations with non-ulcer dyspepsia increase with age and the prevalence is similar in both genders (*see* **Figure 4**). The change in prevalence of non-ulcer dyspepsia with time is difficult to establish as the definition of this condition is continually changing.

Prevalence of Barrett's oesophagus

The prevalence of long-segment Barrett's oesophagus is increasing in the UK and at present the diagnosis is made in 1.4% of all endoscopies.[35] It is more common in patients with long-standing reflux symptoms.[37] The prevalence of Barrett's also increases dramatically over the fifth decade and is a rare diagnosis uncer the age of 40 years.[38] The main concern with Barrett's oesophagus is the risk of developing adenocarcinoma. Surveys have suggested that the risk of developing oesophageal adenocarcinoma is 1% per year although this may be an overestimate due to publication bias.[39]

Prevalence of gastric and oesophageal cancer

Gastric cancer is the fifth commonest cause of cancer death in the UK. The incidence has declined dramatically in recent years with a concomitant rise in incidence of adenocarcinoma of the oesophagus (*see* **Figure 8**). The overall incidence of upper gastrointestinal malignancy has fallen slightly over recent years. Gastric neoplasia incidence is probably falling because of the decreasing prevalence of *H. pylori* in the UK.

The reasons for the increasing incidence of oesophageal adenocarcinoma are not clear but may relate to the increasing prevalence of GORD in the developed world.[36]

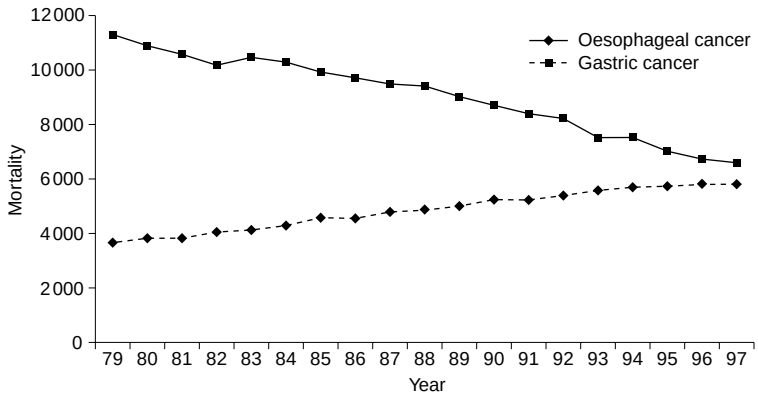

Figure 8: Incidence of gastric and oesophageal cancer in England and Wales 1979 to 1997 from the Office of National Statistics.

5 Services available and their costs

Services for managing dyspepsia are provided in both primary and secondary care. Patients with dyspepsia will consult their general practitioner or present in A&E with dyspeptic symptoms or upper gastrointestinal bleeding. Upper GI endoscopy is primarily provided in secondary care, although some primary care centres and GP-run community hospitals also offer facilities. Most GPs are now able to obtain open access to endoscopy, although waiting times vary widely. Non-invasive tests for *H. pylori* are also available in primary and secondary care.

Primary care services

There are 32 000 general practitioners in England and Wales. Population surveys suggest approximately 25% of subjects with dyspepsia will present with their symptoms to their general practitioner. Data from the fourth GP morbidity survey shows 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. As age increases, an increasing number of ongoing (chronic) cases add to the burden of disease (*see* **Figure 9**). Total consultations for all conditions were 29 000 per 10 000 person years at risk. Consultations for dyspepsia were thus between 1.2 and 2.7% of total consultations.

Data from the RCGP from 1997 shows a similar pattern, with a rising episode rate with age, but the overall consultation rates are lower, 76 per 10 000 patient years at age 15–44 and 220 at age 65. At age 65, 54% of consultations are for ongoing disease.

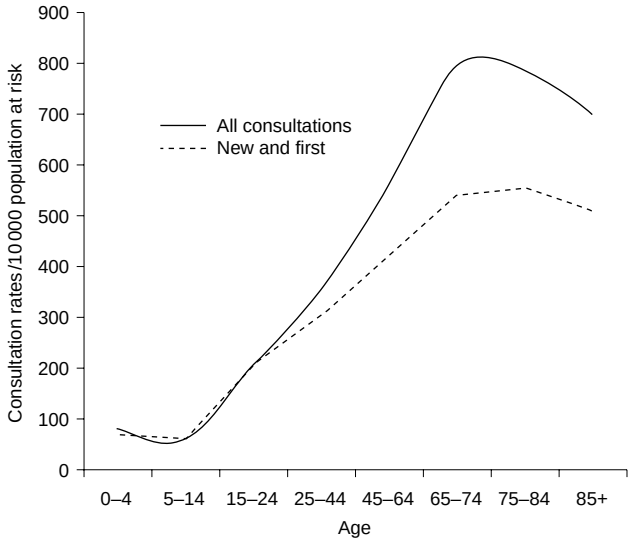

Figure 9: Consultation rates for dyspepsia by age: fourth GP morbidity survey 1991.

Reasons for consultation with dyspepsia

According to the health belief model, the decision to consult the general practitioner is determined by the presence of cues, and the balance between costs and benefits is modified by specific belief in threat from, or vulnerability to, specific conditions.[40,41] A study in the Netherlands examined why patients consult their general practitioner, by means of two questionnaires completed in the waiting rooms of practices by 1000 patients.[42] Multiple logistic regression was used to determine the principal predictors of consultation, and the health belief model showed a 98.9% predictive value for consultation. Perceived efficacy of self-care and perceived need for information also influenced the model, but frequency and duration of complaint did not.

Zola has identified five influences as to whether patients 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 triggers are required to force a medicalisation of the 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.[43]

Severity of symptoms

As far as dyspepsia is concerned, several groups have emphasised the poor predictive value of symptoms for upper GI pathology.[44,45] 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.[46] Jones and Lydeard studied a random sample of 69 patients who had consulted their GP in the past six months with dyspepsia and 66 who had not.[47] 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%).

Fear of serious illness

Jones and Lydeard's study was essentially positivist in nature, concentrating on facts (in this case the reasons for consulting with dyspepsia), and analysed in a quantitative manner. A qualitative approach to the subject may provide more information about feelings and motives that would be of value in meeting the needs of patients in the consultation. An alternative, interactionist approach to the subject would aim to obtain authentic insight into patients' experiences.[48] In addition, although exploring the issue of vulnerability, Jones and Lydeard's study did not examine the threat component of the health belief model in terms of utility.

A qualitative study of reasons for consultation with dyspepsia was conducted in Birmingham.[49] Consulters and non-consulters with dyspepsia were identified similarly to Jones and Lydeard, but 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, and the belief in dietary or mechanistic aetiology may reflect patients' expectations of increasing age. Viewed in terms of theories of illness causation, the patients interviewed displayed a predominantly 'personalistic' view. The principal explanations for symptoms lay in the areas of degeneration (age), imbalance (of foods, etc.) and mechanical interpretations of bodily function.

The availability of medical care, the cost to the patient of OTC medication, and the patients' belief in the opportunity for 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 patient's 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 Hackett's study of delay in seeking medical advice at the Massachusetts General Hospital, patients who worried more about cancer tended to delay seeking help more than non-worriers.[50] An element of denial was also evident in the explanation of symptoms as being due to diet or increasing age.

Secondary care services

There are an estimated 539 gastroenterologists working in England and Wales and this figure increases at a rate of approximately 7% per year.[51] There is a wide variation in the number of gastroenterologists working per head of population between Health Authorities (*see* **Figure 10**). Some of this variation may be explained by differences in gastrointestinal disease rates, but this is unlikely to account for the eight-fold differences seen in some regions (*see* **Figure 10**). The number of sessions that each of these gastroenterology consultants undertakes for the NHS each week is uncertain. Cross-sectional studies estimate that dyspepsia accounts for 50% of a gastroenterologist's workload.[52] although national databases do not record this information. General physicians and surgeons are also involved with the secondary care management of dyspepsia, but the proportion of time devoted to this is difficult to quantify.

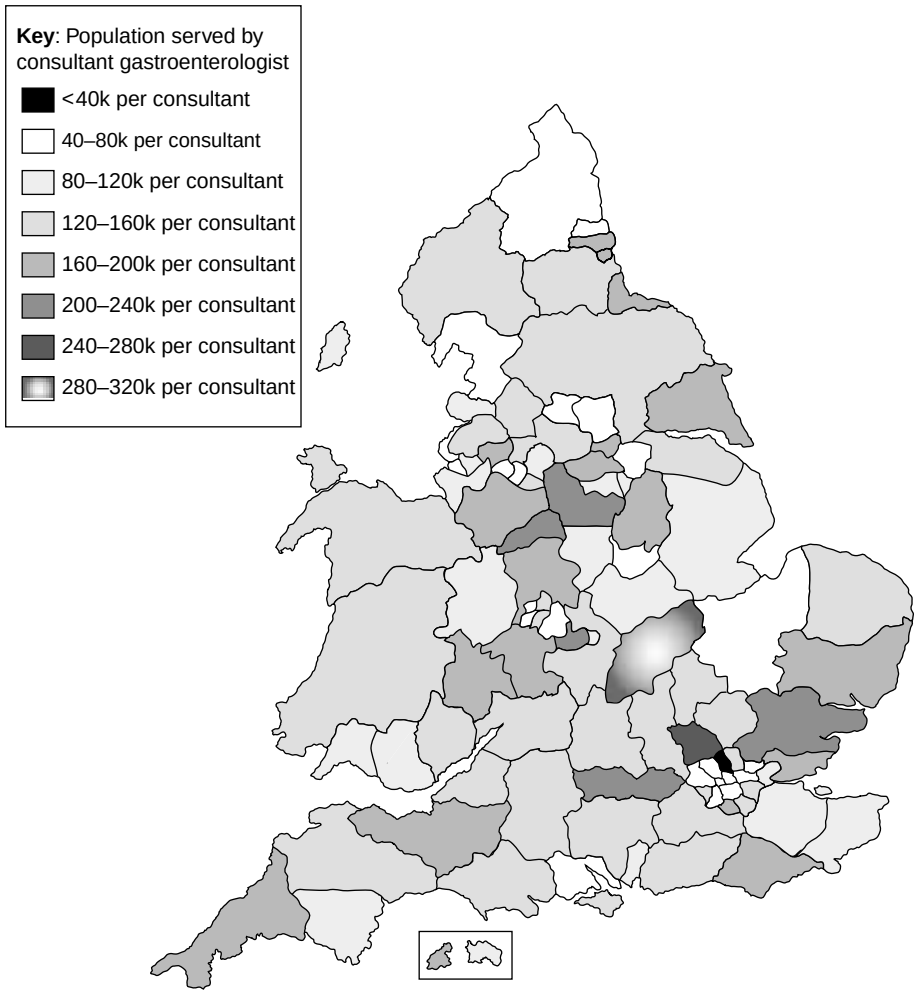

Figure 10: Number of gastroenterologists per head of population in England and Wales by Health Authority.

Investigations available

Dyspepsia is common, and investigation of this symptom complex is therefore likely to be in demand. The investigation of choice until the 1980s was a barium meal but now this has been superseded by endoscopy. This is because upper gastrointestinal endoscopy is perceived to be more accurate, biopsies can be taken of suspicious lesions, and access has improved with development of open access services.[53] The demand for endoscopy doubled in the first five years of the last decade (*see* **Figure 11**). The number of patients having this procedure is now stabilising, with 1% of the population of England having an endoscopy each year (*see* **Figure 11**). There is some variation in endoscopy rates between English regions but it remains a popular procedure throughout the UK (*see* **Table 3**).

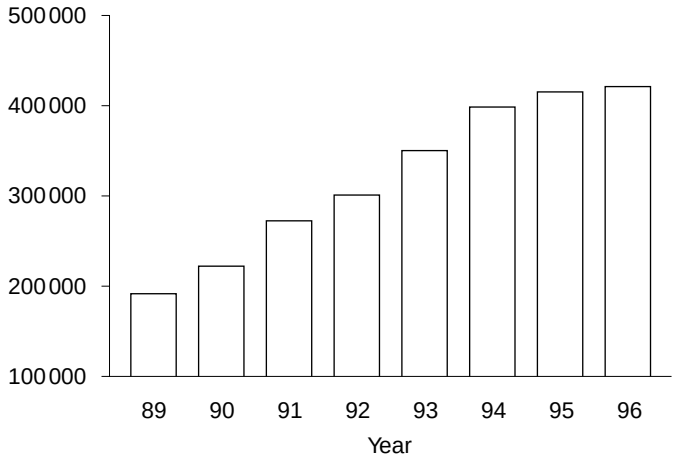

Figure 11: Number of endoscopies performed in England from *Hospital Episode Statistics* 1989–94.

Table 3: Proportion of the population endoscoped by English Health Authority – *Hospital Episode Statistics* 1993

Region	Total population (thousands)	Number of endoscopies	Endoscopy per 1,000 of population
Northern	3,102	28,563	9.21
Yorkshire	3,708	28,490	7.68
Trent	4,766	35,901	7.53
East Anglia	2,095	13,062	6.24
North West Thames	3,521	23,475	6.67
North East Thames	3,812	23,430	6.15
South East Thames	3,718	22,871	6.15
South West Thames	2,999	20,869	6.96
Wessex	3,154	22,552	7.15
Oxford	2,593	16,863	6.50
South Western	3,331	23,213	6.97
West Midlands	5,290	37,350	7.06
Mersey	2,413	25,383	10.52
Total	48,533	359,243	7.40

Double contrast barium meals

Radiology has been the traditional investigation for upper gastrointestinal disease. 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,[54,56] but are less sensitive at identifying early gastric cancer,[57] oesophagitis and more subtle duodenal inflammation.[58] The other disadvantage of radiology is that biopsies of suspicious lesions cannot be obtained.

Upper gastrointestinal endoscopy

Fibreoptic technology allowed the development of direct imaging of the upper gastrointestinal tract using endoscopy in the 1960s. This has now become the 'gold standard' test for detecting oesophageal, gastric and duodenal lesions. Studies suggest the patient acceptability of upper gastrointestinal endoscopy is similar[59] or greater than DCBM.[60] It is possible to biopsy suspicious lesions and biopsies for *H. pylori* can also be obtained at endoscopy and this is an advantage over DCBM. Endoscopy can be performed with local anaesthetic throat spray, although light intravenous benzodiazepine sedation is often given. The patient is unable to work or drive for 24 hours if sedation is given. The morbidity and mortality rates of upper gastrointestinal endoscopy are low (1 in 200 and 1 in 2000 respectively in the UK),[61] but they still need to be considered when referring a patient for this procedure. This figure is based on secondary-care data and therefore includes high risk patients. It is likely that the risks of endoscopy in healthy patients will be lower. Complications can be minimised by obtaining intravenous access before the procedure, careful monitoring of the patient and giving oxygen via nasal cannulae whilst performing the endoscopy.

Non-invasive tests for Helicobacter pylori

H. pylori causes most peptic ulcer disease, and non-invasive testing for this organism has emerged as an important alternative to imaging the upper gastrointestinal tract in the management of dyspepsia. The three main non-invasive tests for *H. pylori* are serology, faecal antigen tests and the labelled C-urea breath tests.

Serology involves measuring the antibody response to the organism in the patients' serum. This is the cheapest test but also the least accurate, with a 80–90% sensitivity and specificity.[62] 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[63] and some studies have shown sensitivities and specificities approaching 90%.[64] The specificity of near patient *H. pylori* tests have been disappointing in other centres[65] and local validation is important before using these kits in primary care.

- The stool antigen test detects *H. pylori* antigens in the stool and is more accurate with a 92–100% sensitivity and 93–95% specificity.[66,67] The test is more expensive than serology and involves giving a stool sample, which is not acceptable to all patients.
- Urea breath tests use the powerful urease enzyme possessed by *H. pylori* to diagnose the infection.[68] 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. The urea breath tests have a sensitivity and specificity >95%[69] and are more accurate than serology.[70] The ^{14}C-urea breath test is simple and cheap[71] but ^{14}C is radioactive and needs to be administered in a medical physics department, which is not ideal for primary care.[68] ^{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[72,73] but the test is still expensive compared with other non-invasive alternatives.

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 and anti-reflux surgery is reserved for a selected group of patients with symptoms responsive to medical therapy and documented acid reflux, but who do not wish 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% have a recurrence of symptoms during follow-up.[74] Laparoscopic Nissen fundoplication may make surgery more attractive although one randomised controlled trial suggested it was associated with more morbidity than the open procedure.[75]

Peptic ulcer surgery

The success of *H. pylori* eradication therapy in preventing long-term recurrence of peptic ulcer disease means that ulcer surgery is now rarely performed. Operations that have been recommended 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

Surgical resection is the only procedure that provides a potential cure for 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.[76] The long-term survival from surgery in the UK, however, is disappointing, with only 20% surviving more than five years.[77] The Japanese report less post-operative mortality and better survival with D2 resections.[78] 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[79] and a low post-operative mortality, attributed to preservation of the spleen.[80]

Oesophageal cancer surgery

Oesophageal resection was associated with one of the highest post-operative mortality of any of the routine surgical procedures.[81] 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%. Randomised controlled trials are currently being conducted to assess whether chemotherapy, radiotherapy or combined adjuvant therapy can improve survival.

Costs of investigations and interventions

The principal costs of investigation are those relating to upper GI endoscopy. 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. However, as with all reference costs, there is a considerable range. The mean cost of day case diagnostic gastroscopy was £250 in 2000, the range £52–£1333, and the interquartile range £203–£380. The mean costs of gastroscopy, with and without intervention, for day case, inpatient and non-elective inpatient are shown in **Table 4**. In 2000, £129.9 million was spent on 451 000 upper GI endoscopies.

Table 4: Cost of upper gastrointestinal endoscopy in England.

	Mean cost diagnostic endoscopy	**Mean cost therapeutic endoscopy**	**Total NHS expenditure 2000 (£ million)**
HRG code	F06 & F16	F05 & F15	
Day case	£249, £250	£314, £266	96.8
Elective inpatient	£562, £490	£732, £526	9.8
Non-elective inpatient	£450, £431	£782, £502	23.3

Prescription Pricing Authority data show a steady rise in the cost of prescribing for dyspepsia since the introduction of proton pump inhibitors (PPIs). In 1999, £471 million was spent; £323 million on PPIs, £124 million on H_2RAs and £24 million on antacids. The costs and numbers of prescriptions for dyspepsia have risen steadily over the past eight years (*see* **Figure 12**). Examination of the figures below indicate that PPI prescribing has increased steadily, with little substitution of either antacids or H_2 receptor antagonists (H_2RAs). Costs of H_2RAs have fallen and there was a small levelling off for PPI costs in 1998, presumably as a result of price competition. Omeprazole is due to come off patent in 2002 and this may result in a fall in PPI costs.

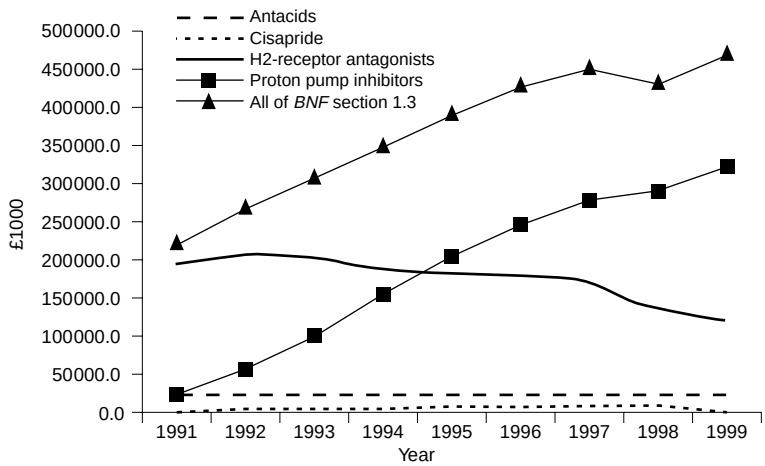

Figure 12: Cost of dyspepsia medication 1991–99.

6 Effectiveness of services and interventions

This evidence-based summary for dyspepsia was largely developed using a recent systematic review funded by the NHS R&D HTA programme,[82] three recently published Cochrane reviews[83–85] and abstracts of recently completed trials.

Management of uninvestigated dyspepsia

Patients presenting with uninvestigated dyspepsia are a common problem in primary care and the appropriate management strategy is uncertain. Symptoms alone are not sensitive and specific enough to make the diagnosis in most cases. One study suggested that 30% of patients with a major pathological lesion would be misclassified, including 50% of ulcer patients.[45] The positive predictive value of 'typical' symptoms for non-ulcer dyspepsia was only slightly better than chance alone.[86] Patients with predominant reflux symptoms (heartburn, acid regurgitation) may have GORD. Although symptoms are not specific for **oesophagitis**, reflux symptoms respond well to acid suppression, particularly with a proton pump inhibitor (PPI), and a 4-week therapeutic trial of PPI may be used to pragmatically define GORD. Epigastric pain in uninvestigated patients and patients with non-ulcer dyspepsia may respond less well.[87]

The choices available to general practitioners are: empirical acid-suppression therapy; early endoscopy (with or without a screening questionnaire); *H. pylori* screening followed by endoscopy of patients who have positive results; and *H. pylori* screening followed by eradication therapy for patients who have positive results.

Empirical anti-secretory therapy/Treat and endoscope

This involves treating dyspeptic patients with antacids, H_2 receptor antagonists or proton pump inhibitors and only investigating those that fail to respond. This strategy reserves costly investigation to those patients who are consuming more medication and hence might recover the cost of investigation in decreased prescribing. However, patients with peptic ulcer disease may receive intermittent anti-secretory drugs, responding promptly at each recurrence, whereas *H. pylori* eradication is now the treatment of choice for this group.[88] Nevertheless, empirical anti-secretory therapy or early endoscopy is the usual approach general practitioners take when initially investigating younger patients with dyspepsia.

Antacids

Antacids have been used for centuries to treat dyspepsia and are still the most popular over the counter medication for upper gastrointestinal symptoms. The popularity of antacids in clinical practice has waned since the introduction of H_2 receptor antagonists and it is easy to overlook the fact that antacids are safe, cheap and effective drugs. The main disadvantage of antacids is the frequency with which they need to be taken, up to seven times a day. Open use of antacid for symptom relief is common in dyspepsia trials, and no trial has examined antacid v. no treatment.

H_2 receptor antagonists

Cimetidine was the first H_2 receptor antagonist to be developed and is the cheapest drug in this class. H_2 receptor antagonists are also now available over the counter. The main disadvantage with cimetidine is that it competitively displaces dihydrotestosterone from androgen binding sites and gynaecomastia can

occasionally occur in men. The newer H_2 receptor antagonists, ranitidine, nizatidine and famotidine, are more potent inhibitors of acid secretion on a weight basis and do not have anti-androgenic side effects. An inconclusive single RCT has compared H_2RA with antacids in primary care. Evidence is lacking as to their relative cost-effectiveness.[89]

Proton pump inhibitors

These drugs irreversibly inhibit the gastric H^+, K^+ ATPase pump and reduce both basal and stimulated gastric acid output more effectively than H_2 receptor antagonists. A systematic review has found that, in the short term, PPIs were more effective at controlling dyspeptic symptoms in unselected patients in primary care than both antacids and H_2RA. Pooled relative risk reductions were –29% (95% CI: –21% to –36%) for PPI:antacids and –37% (95% CI: –15% to –53%) for PPI:H_2RA. The effect on heartburn was highly significant (RRR = 48%; 95% CI: 55% to –40%), but epigastric pain did not respond as well; in fact, for this there was no significant difference between PPI and antacids.[83] Long-term PPI might usefully be limited to patients with either proven oesophagitis[90] or symptoms shown to be responsive to PPIs on careful review.

The National Institute for Clinical Excellence issued guidance on the use of PPIs in July 2000 (NICE Technology Appraisal No. 7). The guidance states that patients with mild symptoms of dyspepsia without a confirmed diagnosis of GORD should not be treated on a long-term basis with PPIs without further investigation. Patients with peptic ulcer should receive testing and treatment of *H. pylori* infection, and patients with non-ulcer dyspepsia should be carefully reviewed for therapeutic response.

Prokinetics

Metoclopramide reduces nausea and vomiting and is more effective than placebo in healing oesophagitis. The drug is cheap and is generally well tolerated but it does cross the blood-brain barrier and occasionally extrapyramidal side effects occur, particularly when large doses are given to elderly subjects. Domperidone has a similar efficacy to metoclopramide, but does not cross the blood-brain barrier and therefore has a much lower propensity to cause extrapyramidal side effects. Cisapride is chemically related to metoclopramide but does not have any anti-dopaminergic activity.[91] The drug has now been withdrawn from the UK as it can prolong the QT interval and could be associated with serious cardiac arrhythmias. There is insufficient evidence to determine the effectiveness of prokinetic agents in unselected dyspeptic patients in primary care.

Combination strategies

In order to limit the prescribing of more expensive and more powerful acid-suppression therapy to patients who seem to need them most to control their symptoms, a number of possible strategies have been proposed. These fall into 'step up' regimens from antacids via H_2RA to PPI, with only patients remaining symptomatic receiving more powerful therapy, or 'step down' from PPI to antacid via H_2RA, aiming to obtain good symptom control at the outset. The role of prokinetics is less clear, being much less commonly used in the UK than in other European countries. Possible strategies include using them first-line in patients with 'dysmotility-like' dyspepsia (predominant nausea, bloating and belching), or trying them after acid suppression had failed.

Initial endoscopy

An alternative strategy is to investigate all dyspeptic patients before initiating a prescription. This strategy takes into account the potential for patients over the age of 50 to have underlying upper gastrointestinal cancer. Approximately one in 300 patients had a potentially curable gastric cancer in a large cohort study of unrestricted early endoscopy in Birmingham.[92] Sufficiently large RCTs are unlikely to be carried out, and cost-effectiveness is likely to be low. At present, patients over the age of 55 with recent onset of symptoms or constant pain and all those patients with symptoms suggestive of malignancy (weight loss, dysphagia, early satiety, jaundice or anaemia) should be investigated by prompt endoscopy under the '2 week rule'.[93]

A meta-analysis of three prospective randomised studies[86,94,95] has indicated that early endoscopy as a strategy may be more effective in terms of cure of dyspeptic symptoms than empirical antacid therapy, particularly in the older age group. Incorporation of a further large trial gives a relative risk of 0.88 (95% CI: 0.77–1.00) for dyspepsia in initial endoscopy compared with usual management.[83]

Initial endoscopy is associated with additional costs. The economic analysis from one of these studies indicates that the incremental cost-effectiveness ratio of initial endoscopy compared with usual management is £1728 per patient additionally free of symptoms at a baseline cost of endoscopy of £246. A sensitivity analysis showed that if the cost of endoscopy could fall to £100 the ICER would fall to only £165.[96]

Non-invasive H. pylori *testing and endoscopy*

H. pylori may be identified by urea breath testing (UBT), serology, stool antigen tests or near patient tests (NPT). UBT and stool antigens are more accurate, but more costly than serology or NPTs. At present there is insufficient evidence as to which test is most cost-effective for initial diagnosis in primary care, but serology or NPT cannot be used as a predictor of cure.

Strategies based on testing for *H. pylori* have been proposed. These include selective endoscopy only in those patients testing positive (test and scope)[97] and *H. pylori* eradication.[98] *H. pylori* is associated with nearly all peptic ulcers in patients not taking non-steroidal anti-inflammatory drugs (NSAIDs). A strategy of screening patients for *H. pylori* with serology or urea breath test and only investigating those infected has been suggested by several groups. This could reduce endoscopies in young dyspeptics by 23–66% whilst detecting almost 100% of peptic ulcers in those not taking NSAIDs.[99] However, a recent primary care-based RCT has shown that test and scope is more costly than usual management in primary care, and does not lead to any difference in dyspeptic symptoms.[100]

Non-invasive H. pylori *testing and eradication*

Two RCTs have found that *H. pylori* eradication therapy is at least as effective in relieving dyspeptic symptoms as endoscopy-guided management. One trial randomised 500 subjects referred by the primary care physician having presented with more than 2 weeks of epigastric pain either to ^{13}C-urea breath test and *H. pylori* eradication if positive or to prompt endoscopy.[101] No difference in symptom-free days was found between the two groups, but the endoscopy rate in the *H. pylori* eradication group was 40% that of the prompt endoscopy group. The other trial randomised 104 *H. pylori* positive subjects under age 45 years to either *H. pylori* eradication or endoscopy.[102] The endoscopy subjects received targeted treatment of *H. pylori* eradication for peptic ulcer alone, PPI for oesophagitis and step-up acid-suppression therapy for non-ulcer dyspepsia. At 12 months follow-up 57% of the 'test and treat' group were symptomatic compared with 70% of the endoscopy group (RR = 0.82; 95% CI: 0.59–1.1).

Both the Lassen and Heaney trials randomised subjects in the secondary care setting. The Lassen trial stipulated that GPs should refer all eligible dyspeptic patients, whereas the Heaney trial entered routine

referrals only. It is possible that similar results might not be obtained in primary care, where less severe cases might be treated, eradication rates might be lower, and the potentially reassuring effect of a specialist consultation might not be obtained. Three primary care-based trials are due to report shortly. It is unknown whether *H. pylori* eradication is as effective as empirical acid-suppression therapy as no comparisons have yet been published.

Empirical H. pylori *eradication*

The simplest *H. pylori* management strategy of all would be to prescribe empirical *H. pylori* eradication therapy to all young dyspeptic patients. This avoids the inconvenience and cost of testing for *H. pylori* and a published model[103] has suggested this may be the most cost-effective strategy for managing dyspepsia. Empirical treatment was only slightly cheaper than the screening and treatment strategy and resulted in 50–70% of young dyspeptics who are *H. pylori* negative receiving antibiotics unnecessarily. Whether the increase in antibiotic exposure is worth this small cost saving is debatable, and given current concerns over antibiotic resistance, empirical eradication is not recommended. In addition, 30–40% of patients taking *H. pylori* eradication therapy will suffer temporary side effects (nausea, diarrhoea), although only 1% may need to discontinue treatment.

Management of dyspepsia subgroups after endoscopic investigation

Early endoscopy may not be the appropriate management strategy for young patients presenting with dyspepsia. Nevertheless, in older patients, imaging the upper gastrointestinal tract may be appropriate and endoscopy will be performed in a few young patients with persistent symptoms. These patients will be diagnosed as either having peptic ulcer disease, gastro-oesophageal reflux disease or non-ulcer dyspepsia. We have identified systematic reviews that evaluate pharmacological therapies for these diseases.

Peptic ulcer disease

Peptic ulcer disease is found in less than 10% of patients undergoing endoscopy for dyspepsia. The fourth GP morbidity survey found consultation rates of 0.5% per year and new episode rates of 0.4% per year for peptic ulcer disease. Hospitalisation and surgery rates for uncomplicated ulcers have declined in the US and Europe over the past 30 years; however, the number of admissions for bleeding ulcers is relatively unchanged.[104] Despite advances in treatment, overall mortality has remained at approximately 6–8% for the past 30 years, due in part to increasing patient age and prevalence of concurrent illness.[97]

A systematic review of *H. pylori* eradication therapy for healing duodenal ulcer found seven trials of *H. pylori* triple therapy v. placebo in which *H. pylori* was eradicated in 93% (95% CI: 91–95%) and 96% (95% CI: 94–98%) of duodenal ulcers were healed at 6 weeks.[105] A further systematic review found healing rates in the range 91–97% for *H. pylori* eradication and 20–90% for anti-secretory drugs in 15 RCTs with direct comparison of eradication therapy and 4 weeks of anti-secretory therapy.[106] The same review found that *H. pylori* eradication heals 83% (95% CI: 78–88%) of gastric ulcers and reduces recurrence rates at one year from 49% to 9%. Recurrence of duodenal ulcer was also examined by the systematic reviews. In indirect comparison, both systematic reviews found a highly significant reduction in ulcer recurrence rates. In one, the risk of ulcer recurrence at one year *H. pylori* eradication was 8.8% and 83% with 4–6 weeks histamine H_2 receptor antagonist alone;[105] in the other, duodenal ulcer recurred in 12% of *H. pylori* eradication subjects and 58% anti-secretory subjects.[106]

An RCT of *H. pylori* eradication v. bismuth alone and two small RCTs of *H. pylori* eradication v. PPI in subjects with a bleeding duodenal ulcer have been published. Re-bleeding was reduced from 20% with bismuth alone to 10% with *H. pylori* eradication (RR = 0.5; 95% CI: 0.2–1.2).[107] Pooling the data from the two PPI trials in a meta-analysis gave a RR of 0.07 (95% CI: 0.01–0.52) for recurrent bleeding at 12 months.[108,109]

NSAIDs and NUD are associated with most peptic ulcers not caused by *H. pylori*. Patients with peptic ulcer disease that are taking NSAIDs should discontinue the drug. If this is not possible, proton pump inhibitors have been shown to be more effective than H_2RAs at healing the ulcer and preventing recurrence.[110] Misoprostil also heals NSAID ulcers and prevents relapse, but randomised controlled trials suggest proton pump inhibitors are more effective at preventing relapse and are better tolerated.[111]

The anti-inflammatory properties of NSAIDs are due to the inhibition of cyclooxygenase-2 (COX-2), whereas the protection of the gastro-duodenal mucosa is through COX-1. Highly selective cyclooxygenase-2 (COX-2) inhibitors should therefore have analgesic properties similar to other NSAIDs but with few gastrointestinal adverse events. Two COX-2 selective inhibitors are available, celecoxib and refocoxib, and both are associated with a rate of peptic ulcers similar to placebo and much lower than traditional NSAIDs.[112,113] COX-2 selective inhibitors are worth considering in high risk elderly patients that need to take NSAIDs. These drugs are more expensive than traditional NSAIDs and they are therefore not cost-effective for patients at low risk of bleeding peptic ulcer disease.

Gastro-oesophageal reflux disease

Acute healing of oesophagitis

One systematic review indirectly compared proton pump inhibitors, H2 antagonists and prokinetics in healing oesophagitis.[90] This meta-analysis pooled results across treatment arms to give an overall healing rate for each of the three drugs. This is an inaccurate method of determining the relative effectiveness of therapies. A more appropriate analysis is to compare the relative effects of therapies in each randomised trial and then to pool the data to determine an overall relative effect. We have re-analysed the trial identified in the systematic review by Chiba *et al.* and also updated the articles included using a Medline search.

H_2 receptor antagonists were effective in healing oesophagitis[114–122] (relative risk reduction [RRR] = 21%; 95% CI: 13–28%) (number needed to treat [NNT] = 6; 95% CI: 5–10) (*see* **Figure 13**).

PPIs were also effective[112,113] (RRR = 69%; 95% CI: 25–87%) (NNT = 2; 95% CI: 1–5) (*see* **Figure 14**). PPIs were more effective than H_2RAs in healing oesophagitis in RCTs that compared the two drugs[125–136] (RRR = 50%; 95% CI: 42%–57%) (NNT = 3.3; 95% CI: 2.9–3.9) (*see* **Figure 15**).

One RCT also reported that PPI was superior to a prokinetic in patients with oesophagitis.[137]

Acute healing of endoscopy negative reflux disease

A systematic review reported that proton pump inhibitors were significantly better than placebo, with 60% of the treatment group becoming symptom-free on treatment compared with 33% of the control group (RRR of heartburn on PPI compared with placebo = 32%; 95% CI: 12–47%) in endoscopy negative reflux disease (NNT = 5; 95% CI: 3–12).[138] A further RCT also supports the conclusion that PPI therapy is superior to placebo in endoscopy negative reflux disease.[139] The review also found that H_2 receptor antagonists were more effective than placebo at relieving heartburn (35% v. 22% symptom-free respectively) (RRR = 16%; 95% CI: 5–26%) (NNT = 8; 95% CI: 5–26).

Proton pump inhibitors were superior to H_2 receptor antagonists in two randomised trials that directly compared the two classes of drug, but this did not reach statistical significance (53% symptom free on PPI

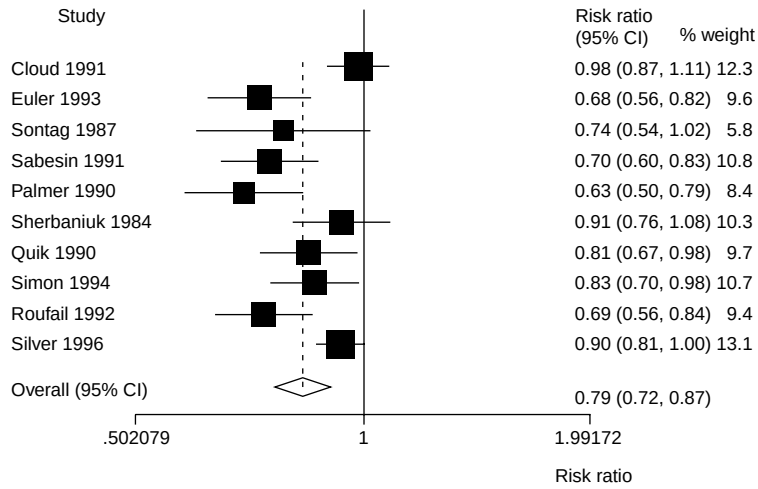

Figure 13: Efficacy of H_2 receptor antagonists compared with placebo in oesophagitis.

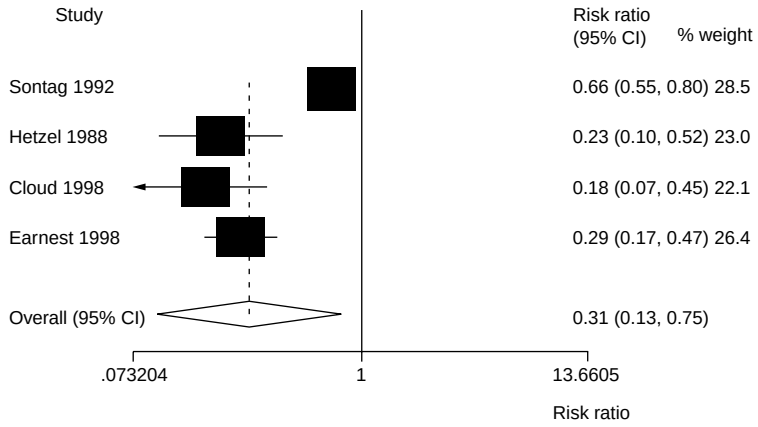

Figure 14: Efficacy of proton pump inhibitors compared with placebo in oesophagitis.

v. 42% on H_2 receptor antagonists) (RRR = 31%; 95% CI: 20–61%). We identified a further trial published since this systematic review that reported patients randomised to PPI therapy had significantly lower heartburn scores compared to those allocated to H_2 receptor antagonist therapy.[140] The review also found that PPI therapy was superior to prokinetic treatment although the evidence for this came from one trial (40% symptom-free on prokinetic v. 30% on placebo) (RRR = 28%; 95% CI: 8–44%).

Maintenance therapy of oesophagitis and endoscopy negative reflux disease

Eighty percent of patients with successfully treated GORD will have a symptomatic relapse within one year if not given any maintenance therapy. Whilst it is important to give a patient a trial without medication, many will require further courses of treatment. We found no systematic review evaluating the efficacy of medical therapy in preventing relapse in patients with oesophagitis or endoscopy negative reflux disease.

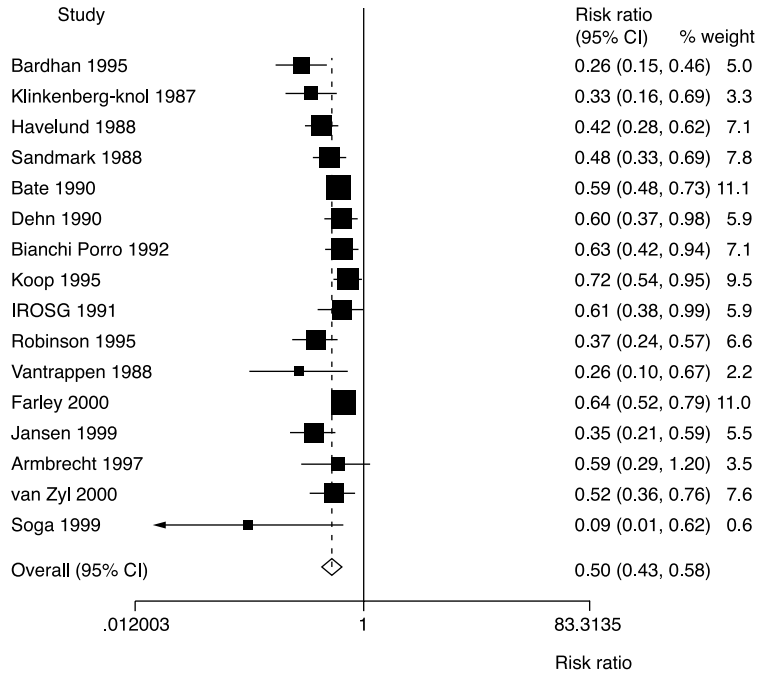

Figure 15: Efficacy of omeprazole compared with H_2 receptor antagonists in the treatment of oesophagitis.

Three RCTs compared PPI with an H_2RA (with or without a prokinetic) in people with endoscopically confirmed oesophagitis who had already received a PPI for 4 weeks.[141,142] At 1 year, people treated with daily PPI were significantly less likely to relapse than those on an H_2RA in all three trials. Recent data suggest intermittent PPI therapy may also be effective in controlling long-term GORD symptoms.[143]

An alternative approach to patients who require long-term medication is to offer anti-reflux surgery. Two RCTs have compared medical versus surgical treatment in GORD patients. One reported that surgery was better than maintenance medical therapy that did not include a PPI.[144] A further study has indicated that gastro-oesophageal reflux scores were significantly lower in the surgery arm compared to patients randomised to long-term PPI therapy.[145] There were, however, no statistically significant differences in relapse rates for treatment failures (as defined by the authors) between the two groups after three years.

The National Institute for Clinical Excellence issued guidance on the use of PPIs in July 2000 (NICE Technology Appraisal No. 7). The guidance states that patients with severe GORD symptoms or oesophagitis (or Barrett's) should be treated with a PPI to achieve healing and then stepped down to the lowest possible acid suppression for control of symptoms. Patients with complicated oesophagitis should receive maintenance treatment with a PPI.

Non-ulcer dyspepsia

There has been considerable controversy over the most effective treatments for non-ulcer dyspepsia. Treatments include antacids, H2 receptor antagonists, PPIs, prokinetic agents and *H. pylori* eradication. There have been three reviews of *H. pylori* eradication therapy in non-ulcer dyspepsia, but these have

not included recent trials. There have also been no recent systematic reviews of other pharmacological therapies in non-ulcer dyspepsia. We therefore conducted a systematic review with a similar protocol to the uninvestigated dyspepsia review.

Non-ulcer dyspepsia was defined as patients with dyspepsia and with insignificant findings at endoscopy or barium meal and who were not required to have had 24-hour oesophageal pH studies, upper abdominal ultrasounds or computerised tomography. Patients with hiatus hernia, less than five gastric erosions or mild duodenitis were included, as these lesions correlate poorly with dyspepsia symptoms. We included studies evaluating adult patients (age 16–80 years) presenting in secondary care with diagnosis of NUD. All patients must have had either an endoscopic or barium meal examination to exclude peptic ulcer disease. Interventions that were evaluated included antacids, prokinetics, proton pump inhibitors, mucosal protecting agents and *H. pylori* eradication therapy. Trials comparing these therapies with each other or with placebo were included. Global dyspepsia symptoms expressed as a dichotomous outcome (same/worse versus improved) was the principal outcome measure.

One trial has suggested antacids were no more effective than placebo in NUD.[146] A meta-analysis of trials comparing H_2RAs with placebo showed H_2RAs were more effective than placebo (RRR, prokinetics – H_2RA = 29%; 95% CI: 47–4%), but trials were often of poor quality and there was significant heterogeneity between studies.[84] Whilst awaiting further research, H_2RA seem a reasonable choice of treatment for NUD.

Proton pump inhibitors were more effective than placebo in an updated meta-analysis of non-ulcer dyspepsia trials. There was a RRR of 17% (95% CI: 12–21%) in the PPI group compared with placebo (NNT = 7; 95% CI: 6–11) (*see* **Figure 16**). PPI trials were better designed than other classes of drugs and the results are therefore more reliable. Nevertheless, a Markov model suggested that PPIs are unlikely to be a cost-effective treatment for NUD.[82]

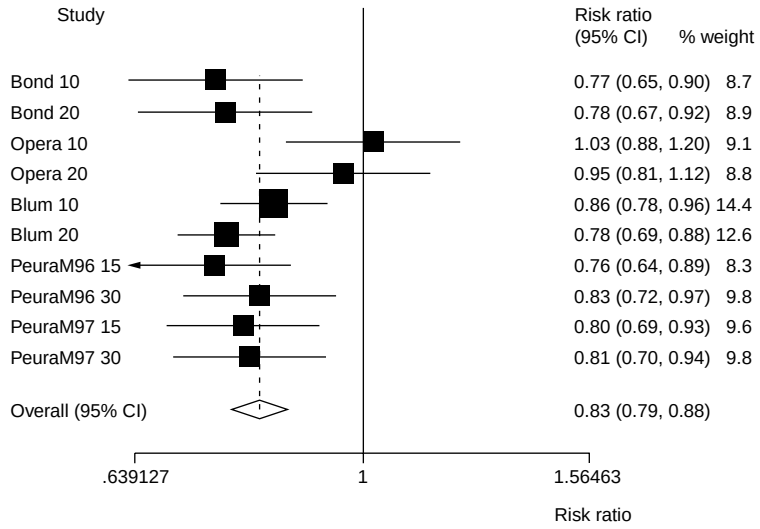

Figure 16: Meta-analysis of the efficacy of PPI therapy compared with placebo in non-ulcer dyspepsia.

Prokinetics were more effective than placebo in a meta-analysis (RRR = 50%; 95% CI: 30–70%), but there was significant heterogeneity between trials.[84] This heterogeneity could be partly explained by year of publication, larger more recent trials being less likely to show an effect. A funnel plot revealed that the results of the prokinetic meta-analysis could be due to publication bias or related quality issues. Most of

these trials evaluated cisapride, which has now been withdrawn from the UK market. The relative tolerability and cost-effectiveness of metoclopramide and domperidone in NUD remain to be established.

In a meta-analysis of nine high quality RCTs, *H. pylori* eradication was associated with a 9% (95% CI: 14–4%) relative risk reduction, and an NNT of 15 (95% CI: 10–31) was calculated based on a control event rate of 72% (*see* **Figure 17**).[147] Economic modelling, based on these data, suggests *H. pylori* eradication would be cost-effective with an incremental cost-effectiveness ratio against antacid alone of £56 per month. Sensitivity analysis indicated that *H. pylori* eradication therapy would be cost-effective provided the payer was willing to accept a 20% probability of the policy being incorrect and was willing to pay £75 for each month free of dyspepsia.[147] It is possible that the effect of *H. pylori* eradication in NUD is based on a subgroup of patients with an 'ulcer diathesis' where the treatment prevents the development of future peptic ulcers. This hypothesis is difficult to prove, but provides one explanation as to why an effect is seen, where no association has been observed between chronic *H. pylori* gastritis and dyspeptic symptoms.

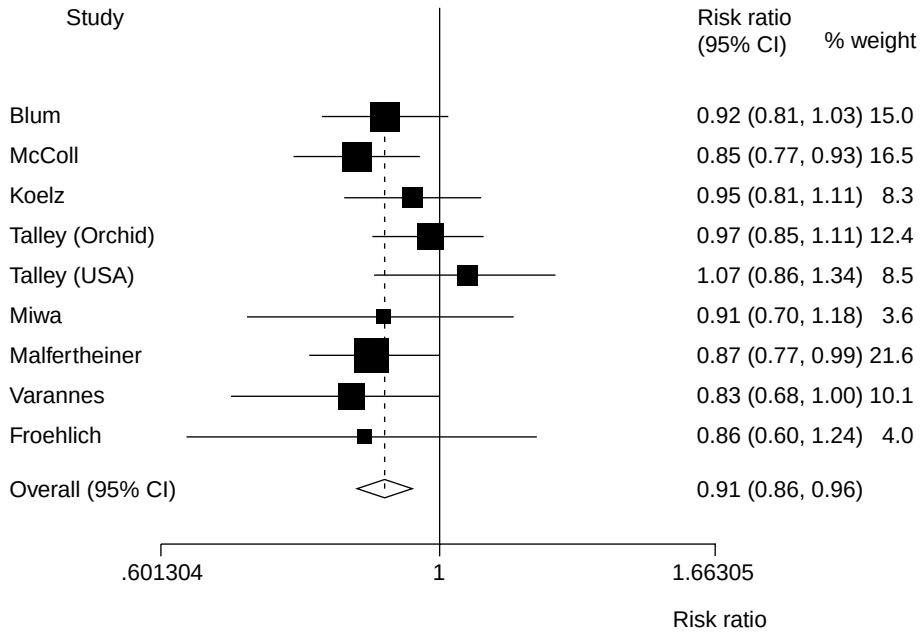

Figure 17: A meta-analysis of *H. pylori* eradication therapy versus placebo antibiotics in non-ulcer dyspepsia.

Given the uncertainty surrounding the definition, aetiology and cost-effectiveness of treatments for NUD, it is essential that patients should be reviewed after treatment changes to determine the most appropriate choice of treatment for each individual patient.

Barrett's oesophagus

Columnar metaplasia in the oesophagus is thought to develop in response to gastro-oesophageal reflux[148] and the management of Barrett's oesophagus aims to relieve reflux symptoms as well as reduce the risk of neoplasia. Reflux symptoms are best treated with proton pump inhibitor therapy. The impact acid suppression has on cancer risk is unclear and needs evaluating in randomised controlled trials. Endoscopic

surveillance every two years with quadrantic biopsies every 2 cm has been recommended for patients with no dysplasia that are fit for surgery by the International Society for Diseases of the Esophagus.[149] The consensus was that patients with low-grade dysplasia should have endoscopy annually. Patients with high-grade dysplasia should have a repeat endoscopy with multiple biopsies and a second pathologist should review the histology. If the diagnosis was confirmed, oesophageal resection should be considered.

The risk of oesophageal adenocarcinoma has concerned clinicians, and 70% of a randomly selected group of British Society of Gastroenterology members were offering surveillance[150] The evidence for the efficacy of surveillance has been challenged and economic models have suggested that the cost-effectiveness of this programme may be expensive by UK standards.[151] More evidence is therefore needed before recommendations can be made on the need for surveillance of Barrett's oesophagus.

Gastric and oesophageal cancer

These lesions are usually diagnosed at endoscopy or barium meal and are inoperable at the time of diagnosis in over 50% of cases. These patients can only be offered palliative care at the present time. Surgical resection (with or without adjuvant chemotherapy or radiotherapy in the case of oesophageal cancer) is the treatment of choice for operable lesions. The prognosis is still poor, even for an operable lesion, unless it is detected at an early stage before the tumour has invaded the submucosa.[152] Mortality from oesophagectomy has fallen over the last three decades from 30% to around 5%, with the lowest mortality seen in high volume centres (>50 resections per year).[153]

7 Models of care and recommendations

The appropriate strategy for managing dyspepsia when risk of malignancy is low

A recent report for the HTA programme has developed a model based on a form of discrete event simulation.[82] The principal benefit of using this approach is that individuals can be given attributes: these determine the distribution of time taken in any particular state and the probability of transition to other states. In the dyspepsia model, an individual at any time may or may not be infected with *H. pylori* and may or may not have any combination of duodenal ulcer, gastric ulcer, non-ulcer dyspepsia and reflux dyspepsia.

Five strategies were examined in the model:

1 *H. pylori* eradication for all patients
2 endoscopy for all patients
3 *H. pylori* test, followed by endoscopy if positive
4 *H. pylori* test, followed by eradication therapy if positive
5 initial empirical pharmacological therapy.

Fourteen follow-on prescribing strategies were also specified:

1 prescription antacid only
2 H_2RA only

3 prokinetics only
4 PPI only
5 antacid, H_2RA, PPI, prokinetics and stay
6 antacid, H_2RA/prokinetics, PPI and stay
7 antacid, H_2RA, PPI and stay
8 antacid, H_2RA, PPI, prokinetics and down
9 antacid, H_2RA/prokinetics, PPI and down
10 antacid, H_2RA, PPI and down
11 prokinetics, PPI, H_2RA, antacid and stay
12 PPI, H_2RA/prokinetics, antacid and stay
13 PPI, H_2RA, antacid and stay
14 try PPI or prokinetics until one of them works.

All combinations of strategies were compared. One strategy is said to be simply dominated by another if it is both more costly and less effective. Of the 70 possible combinations of investigation and prescribing strategies, all but nine were eliminated by simple dominance. **Table 5** shows the list of non-dominated options, also shown in **Figure 18**.

Table 5: Non-dominated strategies in the base case

Point	Investigation strategy	Prescription strategy	Cost over 5 yrs/£	Std. error	Dyspepsia-free months in 5 yrs	Std. error	Extra cost for one month's extra benefit compared to	
							previous	cheapest
A	Medication only	Antacid only	169.05	0.43	35.59	0.056		
B	Test and eradicate	Antacid only	221.60	0.55	36.42	0.058	62.77	62.77
C	Medication only	H_2RA	274.73	0.67	42.25	0.047	9.12	15.86
D	Medication only	Antacid, H_2RA, PPI and down	319.63	0.27	43.12	0.014	51.36	19.98
E	Medication only	PPI, H_2RA, antacid and stay	324.57	0.26	43.17	0.015	105.98	20.51
F	Medication only	Antacid, H_2RA, PPI and stay	328.56	0.88	43.49	0.046	12.57	20.19
G	Medication only	PPI only	357.17	0.89	44.23	0.046	38.41	21.76
H	Test and eradicate	PPI only	395.08	0.93	44.88	0.046	58.73	24.32
I	Test and eradicate	PPI or prokinetic if effective	479.37	1.16	45.13	0.047	329.04	32.50

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

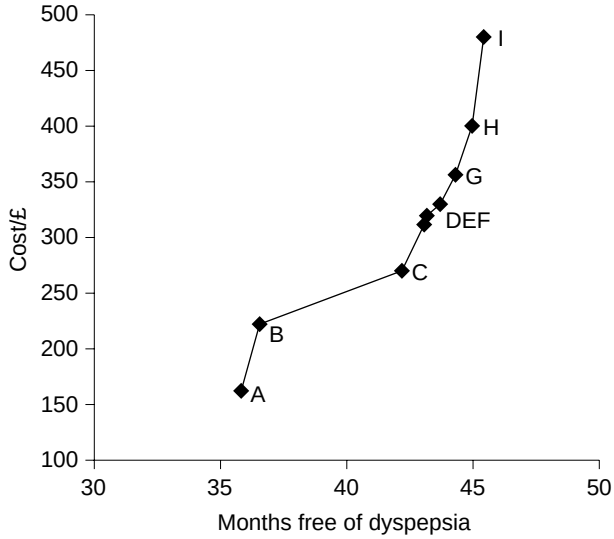

Figure 18: Cost-effectiveness of non-dominated strategies for managing dyspepsia.

All strategies involving endoscopy were dominated. Strategies involving medication only were invariably cheaper, but slightly less effective, than those strategies using an initial *H. pylori* test with the same prescribing strategy. The additional cost of the 'test and eradicate' strategies included the immediate cost of the *H. pylori* test and subsequent eradication therapy in those testing positive. This expense was offset against the cost saving in terms of recurrent ulcers prevented. The additional costs and benefits were both greater in the case where the prescribing strategy is to use antacids, but the ratio between them was lower.

The model was sensitive to the prevalence of *H. pylori*; allowing it to go up to 60% meant that more strategic combinations involving 'test and eradicate', and some involving 'eradicate all', became non-dominated. Varying the effectiveness of medication made more substantial changes to the choice of non-dominated prescribing strategies, as did varying the price. However, the choice of initial strategies remained unchanged.

The appropriate age to promote upper gastrointestinal endoscopy

Endoscopy is not the most cost-effective strategy for managing dyspeptic patients with a low risk of malignancy. The main drive to perform endoscopy is therefore to detect upper gastrointestinal malignancy in a higher risk population, as the prognosis for these cancers is poor unless diagnosed early. Endoscopy is expensive and resources are scarce so it is important to limit this investigation to those that are most likely to benefit.

The traditional method of assessing the cost-effectiveness of life-saving healthcare interventions is in terms of cost/life year saved. We explored the cost-effectiveness of endoscopy at detecting early upper gastrointestinal malignancy, in terms of cost/life year saved, according to age, gender and high risk symptom groups using a Markov model.

Data incorporated into the decision analysis model

The decision analysis model evaluates gastric cancer, as evidence that prompt endoscopy or increased volume of endoscopy increases the proportion of early oesophageal cancer is limited. There is no evidence that investigating patients early will detect a higher proportion of early gastric cancer. There is evidence, however, that more widespread use of endoscopy detects more early gastric cancer (EGC) and this model assumes that reducing waiting times will increase demand for endoscopy. One percent of the population has an endoscopy each year (Finished Consultant Episode data from the Department of Health) and data suggests that doubling the number of endoscopies performed increased the proportion of EGC by 3.75%. The model assumes that if the whole population were endoscoped each year 100% of gastric cancers would be EGC. At present 1% of the population is endoscoped and as demand for endoscopy increases the proportion of EGC detected is given by the following equation giving a heteroscedastic curve (*see* **Figure 19**):

$$EGC = p\_egc \times ied^{\ln(1/p\_egc)/\ln 100)}$$

Where:

EGC = Total proportion of EGC detected
p_egc = increase in proportion of EGC with each unit increase in endoscopy demand
ied = increase in endoscopy demand

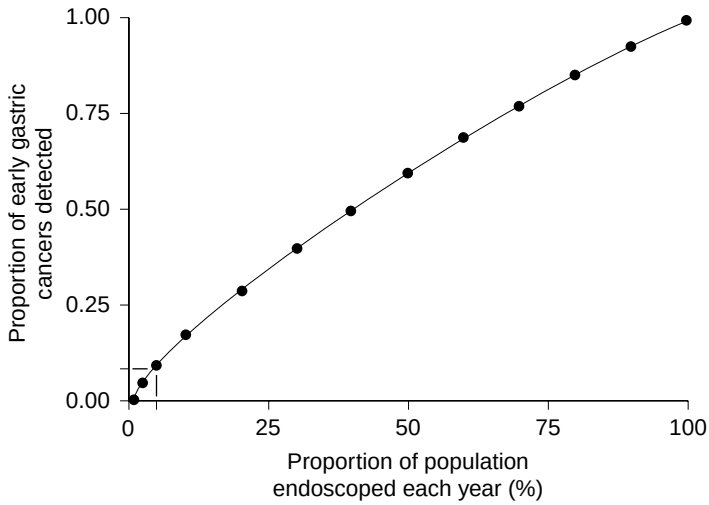

Figure 19: Probability of detecting early gastric cancer with increasing endoscopy demand.

Population surveys indicate only 20% of patients with dyspepsia are currently referred by their general practitioner for endoscopy.[8] There is therefore potential for a five-fold increase in workload assuming all patients would consent to endoscopy. Should this occur, the above equation indicates that there will be approximately a 10 percentage point increase in the proportion of EGCs detected.

The importance of detecting EGC is that 90% of patients survive five years compared with 5% of patients with advanced disease. These figures, together with the cost of endoscopy and gastric surgery, (*see* **Table 6**) were incorporated into a Markov model (*see* **Figure 20**). The model compared a hypothetical early endoscopy strategy allowing everyone with dyspepsia to be investigated with existing services (20% of

dyspepsia sufferers presenting to the general practitioner endoscoped, which is equivalent to 1% of the population per year).

Table 6: Data used in the Markov model

Variable	Baseline	Range for sensitivity analyses
Cost of endoscopy	£246	£186–299
Cost of gastric surgery	£2,405	£1,809–5,015
Survival from EGC	90%	80–99%
Proportion of EGC with each unit increase in endoscopy	3.75%	1%–7.5%

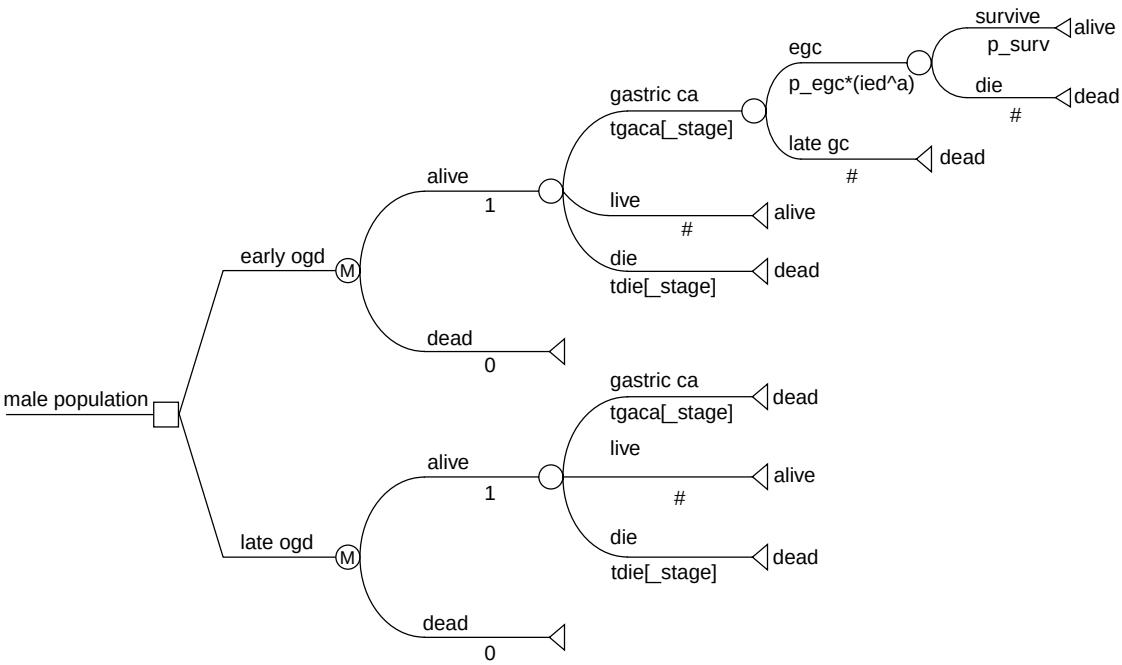

Figure 20: Markov model to evaluate the cost-effectiveness of early endoscopy.

Results

Five hundred and eighty-seven life saving interventions have been evaluated in the United States, and the median cost is approximately £26 000/life year saved.[154] This is expensive by UK standards but could be taken as the upper limit of what would be acceptable to the NHS. The cost-effectiveness analyses were performed with this upper limit in mind.

What is the lowest age limit we can afford to set for endoscoping all men with dyspepsia?

The base case scenario suggests the average cost-effectiveness for endoscoping all men presenting with dyspepsia is £25 241/life year saved. This is superficially attractive, but this figure hides the extra cost of offering endoscopy to younger men. Endoscoping all men over 70 with dyspepsia costs £12 563/life year saved (*see* **Table 7**). Reducing this age limit to 65 costs an extra £15 779/life year saved compared with just offering this service to those over 70. The incremental costs of lowering the age limit further dramatically increases the cost/effectiveness ratio so that endoscoping patients over 40 costs £454 000/life year saved compared with endoscoping patients over 45 (*see* **Table 7**). These data suggest early endoscopy should only be offered to men over 60. This age limit may be unacceptable to many general practitioners and identifying those at higher risk of malignancy may improve the cost-effectiveness ratio, allowing lower age groups to be investigated early.

Table 7: Cost-effectiveness of early endoscopy for all men with dyspepsia.

Age	Cost (£)	Effectiveness (life years saved)	Average c/e*	Incremental cost (£)	Incremental effectiveness	Incremental c/e*
70	91.80	0.00731	12,563	/	/	/
65	123.20	0.00930	13,261	31.40	0.00199	15,779
60	159.80	0.01070	14,995	36.60	0.0014	26,142
55	199.10	0.01170	17,021	39.30	0.001	39,300
50	240.50	0.01250	19,303	41.40	0.0008	51,750
45	283.80	0.01290	21,998	43.30	0.0004	108,250
40	329.20	0.01300	25,242	45.40	0.0001	454,000

* c/e= cost-effectiveness £/life year saved.

Can identifying high risk groups lower the age limit at which early endoscopy is economically feasible?

Data from the group has shown that certain symptoms predict upper gastrointestinal neoplasia. The main concern is that cancer is not missed and therefore the symptom pattern with the lowest negative likelihood ratio should be the most appropriate group to analyse (*see* **Table 8**). Patients with continuous symptoms, anorexia, dysphagia and/or symptoms for less than one year meet this criteria (*see* **Table 8**).

Table 8: Identifying high-risk groups.

Risk group	Sensitivity	Specificity	+ve LR*	–ve LR*
Continuous symptoms and dysphagia	21%	99%	21	0.8
Continuous symptoms and anorexia	23%	98%	12.5	0.79
Continuous symptoms and both of the above	19%	99%	19	0.82
Any of: Continuous symptoms, anorexia, dysphagia, symptoms less than one year**	92%	68%	2.875	0.11
Continuous symptoms for less than one year	29%	98%	14.5	0.72
Continuous symptoms for less than one year including either anorexia or dysphagia	22%	99%	22	0.79

* LR=likelihood ratio (from data provided by Peter McCulloch).
** group most appropriate to analyse.

It was assumed that only offering early endoscopy to patients with these symptoms would reduce endoscopy workload by 33% (a range of 10–50% was used in the sensitivity analyses). The Markov model shows selecting this high-risk group is the most cost-effective. The average cost-effectiveness for endoscoping men over 70 with these high-risk symptoms is £8398/life year saved. Offering early endoscopy to all men over 70 costs an extra £45 925/life year saved.

Incremental cost-effectiveness ratios suggest that men over 55 with high-risk symptoms should be offered early endoscopy (*see* **Table 9**, **Figure 21**).

Table 9: Cost-effectiveness of early endoscopy for men with high risk symptoms.

Age	Cost (£)	Effectiveness (life years saved)	Average c/e*	Incremental cost (£)	Incremental effectiveness	Incremental c/e*
70	54.60	0.00650	8,398	/	/	/
65	73.00	0.0083	8,828	18.40	0.0018	10,222
60	94.30	0.0095	9,950	21.30	0.0012	17,750
55	117.30	0.0104	11,269	23.00	0.0009	25,556
50	141.50	0.0111	12,758	24.20	0.0007	34,571
45	166.70	0.0115	14,521	25.20	0.0004	63,000
40	193.20	0.0116	16,645	26.50	0.0001	265,000

* c/e = cost-effectiveness £/life year saved.

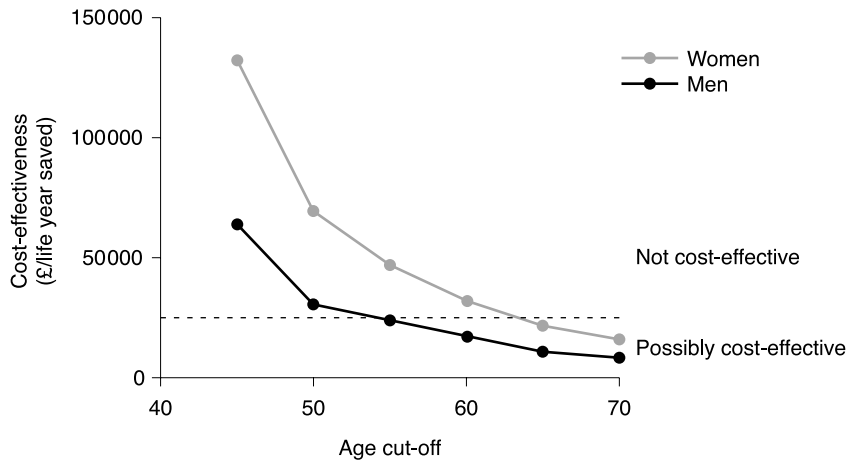

Figure 21: Incremental cost-effectiveness of early endoscopy with age at which endoscopy starts in high risk patients.

The cost-effectiveness of early endoscopy in women

Gastric cancer is less common in women and an early endoscopy strategy will therefore be less cost-effective in women. It is only cost-effective to endoscope women over 65 with the high risk symptoms described above (*see* **Table 10**, **Figure 21**). Differentiating the age cut-off at which early endoscopy is recommended according to gender may be ethically unacceptable to policy makers. Setting the age cut-off at 55 years for everyone would be more equitable although this is not justified on economic grounds.

Table 10: Cost-effectiveness of early endoscopy for women with high risk symptoms.

Age	Cost (£)	Effectiveness (life years saved)	Average c/e*	Incremental cost (£)	Incremental effectiveness	Incremental c/e*
70	67.80	0.00361	18,799	/	/	/
65	89.20	0.00458	19,460	21.40	0.00097	22,062
60	112.70	0.00529	21,298	23.50	0.00071	33,099
55	137.40	0.00585	23,477	24.70	0.00056	44,107
50	162.60	0.00621	26,174	25.20	0.00036	70,000
45	188.70	0.00641	29,430	26.10	0.00020	130,500
40	215.70	0.00658	32,760	27.00	0.00017	158,823

* c/e = cost-effectiveness £/life year saved.

Sensitivity analyses

The Markov model is based on several assumptions. To evaluate the robustness of the model a maximum and a minimum value was set for each variable (*see* **Table 6**). Worst and best case scenarios were therefore generated for each variable (*see* **Table 11**). The average cost-effectiveness ratios were not affected greatly, indicating that the model is robust (*see* **Table 11**). The model was most affected by the assumptions regarding the proportion of EGC detected for each unit increase in endoscopy.

Table 11: One-way sensitivity analyses for men over 55 with high risk symptoms.

Variable	Range for sensitivity analyses	Worst case (average £/life year saved)	Best case (average £/life year saved)
Cost of endoscopy	£186–299	13,627	8,560
Cost of surgery	£1,809–5,015	11,620	11,189
Survival from EGC	88–99%	12,677	11,331
Proportion of EGC detected with each increase in endoscopy	1–7.5%	27,893	7,067

Assumptions inherent in the model

The decision analysis model was constructed from a health service perspective. A societal perspective would have given higher cost estimates, as travel costs, loss of leisure time and time off work were not considered.

The model did not incorporate any extra medical costs in those surviving longer as a result of early endoscopy. This would make early endoscopy less cost-effective but inclusion of these costs is controversial.

Monetary costs and health benefits were not discounted in the model. Discounting is normal practice, as capital spent on health care now would have been invested and is not worth the same several years later. If a 6% discount rate is used for costs and benefits, the average cost-effectiveness ratio in men over 55 with high risk symptoms increases from £11 269 to £34 808.

The cost-effectiveness calculations were expressed in terms of years of life saved and therefore implicitly all years of life are valued equally. This is a common perspective to take, but it could be argued that many of

the life years saved would be in the elderly, some of whom would be frail. This problem could be overcome by incorporating health-related quality of life measures such as Quality Adjusted Life Years (QALYs). Data on QALYs in the normal elderly population is limited and this approach was not taken in this decision analysis model.

The Markov model assumes that gastric cancer cases have no extra comorbidity. Subjects that have early gastric cancers detected therefore have the same age-standardised life expectancy as the general population. If subjects developing gastric cancer are less healthy than the general population, then this model will overestimate the cost-effectiveness of early endoscopy.

The model assumes that all gastric cancers would be detected early if the entire population was endoscoped once a year. This would appear reasonable, as data suggests that time of progression from EGC to advanced cancer is 3 years.[152] The model assumed that all EGC would progress to advanced gastric cancer unless the patient has gastric surgery. Data suggest that some EGC do not progress[155] and this would make an early endoscopy strategy slightly more expensive.

Cost minimisation

Endoscopy is expensive, and although this could be justified in terms of early cancer detected, it would cost billions of pounds to deliver the ideal service. This is clearly not feasible and it is important to minimise costs by reducing the demand for endoscopy in younger age groups. A third of endoscopies are performed in patients under 45.[156] Four randomised controlled trials have shown that screening for *H. pylori* and treating those infected is as effective as endoscopy and less expensive.[102,157–159] A test and treat strategy has also been shown to reduce endoscopy workload in young patients with dyspepsia in clinical practice.[160] Symptomatic treatment or an *H. pylori* screen and treat policy should therefore be encouraged in younger age groups so that existing resources can be used to endoscope those that would most benefit.

Conclusion

Economic analysis suggests that early endoscopy could be advocated for patients over 55 with continuous symptoms, anorexia, dysphagia and/or symptoms less one year. Alternatives to endoscopy should be promoted in younger dyspeptic patients.

8 Outcome measures

Detecting upper gastrointestinal malignancy

Patients seeking health care for dyspepsia are often concerned about the possibility of their symptoms being due to cancer. One of the main aims of the health service should be to detect upper gastrointestinal neoplasia at a treatable stage. Management should focus on detailed investigation of patients at high risk of malignancy and the main determinant of this risk is age. Endoscopy should be encouraged in older age groups and alternative management strategies promoted in younger patients. Assessing whether this has occurred with present forms of data collection is difficult. Hospital Episode Statistics record the number of endoscopies conducted in the UK and the diagnosis. Recording the number of endoscopies in five- or ten-year age bands would make this routine form of data collection more informative.

Routine data collection should be able to evaluate whether a health care intervention is effective as well as whether it has been implemented. Survival from oesophageal and gastric cancer is collected by Cancer Registries and this could be correlated with the number of endoscopies performed within different regions over time. This type of ecological analysis can be difficult to interpret but would act as supportive evidence that increasing endoscopy in older age groups improved survival.

The most important outcome measures to evaluate the efficacy of early diagnostic strategies to detect early upper gastrointestinal malignancy are:

- number of endoscopies in the appropriate age band
- number of gastric and oesophageal cancers detected
- number of early gastric and oesophageal cancers detected
- overall survival from gastric and oesophageal cancer.

Treatment of dyspepsia

Patients also seek health care to relieve symptoms. The health service should therefore aim to improve or cure symptoms. There are a number of validated dyspepsia questionnaires to evaluate response to treatment. This can be measured as a change in dyspepsia score, but a more useful approach is to dichotomise patients into cured (no or minimal symptoms) versus not cured. Cure rates are more meaningful to patients and health care workers than mean change in dyspepsia score. Dyspepsia is a common condition and therefore the cost of the intervention as well as the effect is important.

Routine data collection should be able to assess whether appropriate drugs are prescribed. The most appropriate approach for undiagnosed dyspepsia is less certain. The most effective drugs for gastro-oesophageal reflux disease are PPIs. These drugs are also effective in NUD, as is *H. pylori* eradication therapy. The latter is probably the most cost-effective treatment for NUD and is the treatment of choice for peptic ulcer disease. The most cost-effective therapy to prescribe for undiagnosed dyspepsia on present evidence is PPIs. There is some evidence that reflux symptoms respond well to PPIs, but epigastric pain less well.

At this point, it might be useful to return to the Rome II criteria and label patients with reflux symptoms responding to PPIs as having either endoscopy negative reflux disease or oesophagitis. Some patients with epigastric pain (NUD) will also respond to PPIs. In all patients, a careful review of symptoms' response and either a step-down to H_2RA or intermittent PPI therapy should be undertaken. PCOs should be able to obtain audit data from practices as to whether regular reviews of treatment have been undertaken. NICE guidance on PPIs has recommended that PPIs should not be used for more than three months without investigation (either *H. pylori* test and treat or OGD). OGD in young patients without alarm symptoms is not cost-effective; whether *H. pylori* test and treat is more cost-effective than continuing PPI therapy is the subject of an ongoing MRC trial.

The most important outcome measures in evaluating the effects of intervention on dyspepsia symptoms are therefore:

- efficacy of intervention in terms of proportion of patients 'cured'
- cost-effectiveness of the intervention
- appropriateness of drug prescribing
- regular review of patients on long-term treatment.

9 Information and research requirements

Detecting upper gastrointestinal malignancy

Open access endoscopy services have flourished without careful evaluation of the efficacy of this strategy in terms of detection of upper gastrointestinal neoplasia or dyspepsia management. A randomised controlled trial of the efficacy of endoscopy in detecting early neoplastic lesions would be difficult as such, as the sample size needed would be prohibitively expensive. There would also be little equipoise amongst patients and clinicians with the present availability of open access services. Nevertheless, the appropriateness of future expansion of endoscopy services could be evaluated. A cluster randomised trial would be the most appropriate design for this, with certain centres allocated to 'usual care' and others to increased availability of endoscopy.

Treatment of dyspepsia

More information is needed on the appropriate management strategy for dyspepsia. Our model suggests that endoscopy is not a cost-effective option when dyspepsia is the outcome of interest. *H. pylori* test and treat or empirical drug therapy are the most cost-effective options and a randomised controlled trial is needed to evaluate these two options. Whatever the outcome of such a trial, pharmacological therapy will be needed to treat uninvestigated dyspepsia in some patients. Trials suggest PPIs are the most effective therapy but the most cost-effective drug to use is still uncertain.

Many patients will continue to undergo endoscopy where a specific diagnosis can be reached. The evidence that *H. pylori* eradication therapy is the most cost-effective treatment of peptic ulcer disease is conclusive. There is also firm evidence that PPIs are the most effective treatment of GORD. Systematic reviews suggest PPIs and *H. pylori* eradication therapy are also likely to be effective in NUD. Good evidence of cost trials are, however, needed to establish the following:

- the most cost-effective therapy for gastro-oesophageal reflux disease
- the efficacy of H_2RA and prokinetic therapy in NUD
- the most cost-effective therapy for NUD.

The main areas of uncertainty relate to cost-effectiveness data. Trials that evaluate this will need to be more pragmatic to reflect what actually occurs in clinical practice. These types of studies usually show that one form of therapy is more effective but also more expensive compared to the alternative. It is useful to know the value of treating dyspepsia in these circumstances, yet we are unaware of any studies that have evaluated this. The value of relief of symptoms either in terms of Quality Adjusted Life Years or in monetary terms would help inform decision makers on the most cost-effective approach to manage dyspepsia.

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