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Functional Dyspepsia:
A Review of Scientific and Policy Issues

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ABSTRACT

Functional dyspepsia can be defined as chronic or recurrent upper abdominal pain or discomfort, for which no focal lesion or systemic disease can be found. It is a common complaint seen by physicians and, although it does not cause death or severe disability in the majority of cases, represents an important and costly health problem. It is estimated that each year the total pharmaceutical cost for functional dyspepsia ranges from £4.88 million to £41.84 million in England and Wales. The effect of treatment with various agents for functional dyspepsia has not been convincingly evaluated mainly because of lack of validated outcome measures and heterogeneity in patients. However evidence from clinical trials suggest that prokinetic agents may help to improve symptoms in the short-term among patients with dysmotility-like dyspepsia. The role of anti-secretory agents and treatment of Helicobacter pylori is less clear. Antacids do not relieve symptoms of functional dyspepsia more effectively than placebo. Due to great heterogeneity in patients with functional dyspepsia and the uncertainty of treatment effects, a variation in clinical management of dyspepsia is to be expected. Because there is a large pool of patients with dyspepsia, the potential growth of demand for investigation and treatment services for dyspepsia is great.

1. INTRODUCTION

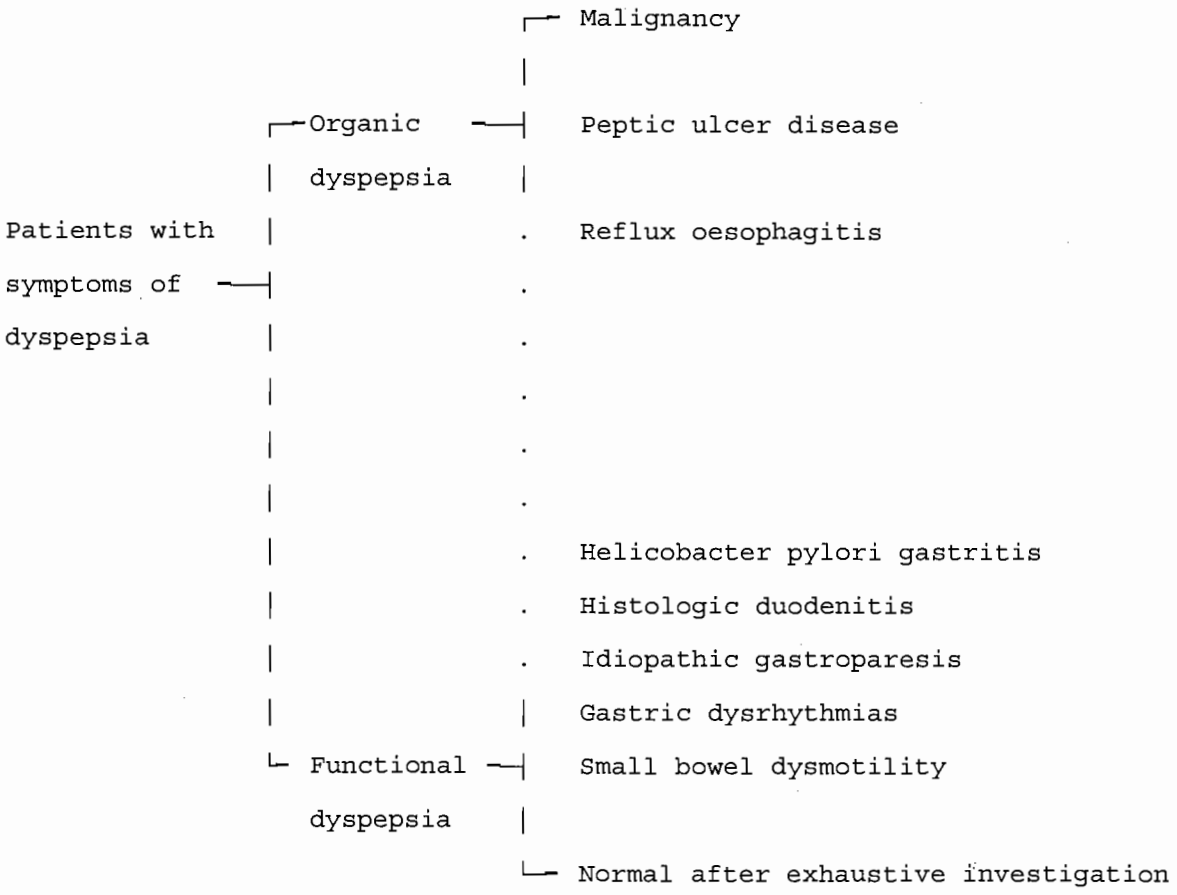
1.1 Definition

Dyspepsia can be defined as chronic or recurrent upper abdominal pain or discomfort. The symptoms of dyspepsia include postprandial fullness, abdominal bloating, belching, early satiety, anorexia, nausea, vomiting, heartburn, regurgitation, or other symptoms considered to be referable to the proximal alimentary tract.

Following investigation, patients with dyspeptic symptoms may be subdivided into three main categories (Nyren et al 1992): 1) those with a well established cause for the symptoms (e.g. chronic peptic ulcer disease, reflux oesophagitis and malignancy); 2) those with an identifiable morphological, physiological or microbiological abnormality of uncertain relevance (e.g. Helicobacter pylori gastritis, histologic duodenitis, idiopathic gastroparesis, gastric dysrhythmias, small bowel dysmotility); and 3) those without current identifiable explanation for their symptoms (Figure 1).

The findings of abnormality may or may not associated with dyspeptic symptoms. While it is common that abnormality cannot be found in a considerable number of patients with dyspepsia, many peptic ulcers do not cause dyspepsia (Akdamar et al 1986). In Norway 30% to 50% of the diagnoses of mucosal inflammation and peptic ulcer disease were made among subjects without dyspepsia (Johnsen et al 1991).

Figure 1. Classification of patients with dyspepsia



An international working party defined non-ulcer (functional) dyspepsia as "upper abdominal or epigastric pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the upper gastrointestinal tract, and lasting for more than four weeks, unrelated to exercise and for which no focal lesion or systemic disease can be found responsible (Colin-Jones et al 1988). Although the aetiology of functional (non-ulcer) dyspepsia remains unknown or inconclusive, several factors may be associated with dyspeptic symptoms. They include abnormal gastroduodenal motility, duodenogastric reflux, Helicobacter pylori infection, gastrointestinal peptide hormones, personality traits and stress.

The definition of functional dyspepsia may vary in different studies. Nyren et al argued that patients have 'functional' dyspepsia if investigations lead to findings with uncertain relevance or without identifiable abnormality (Nyren et al 1992). According to this definition, functional dyspepsia accounts for about 36% to 71% among dyspeptic patients (Warner et al 1993; Lindberg et al 1987; Gotthard et al 1987; Saunders et al 1986; Kagevi et al 1989; Johannessen et al 1990). If patients with Helicobacter pylori gastritis, histological duodenitis, and other findings of uncertain relevance are excluded, the proportion of patients with functional dyspepsia is considerably lower. The proportion of dyspeptic patients without abnormality after endoscopic evaluation is about 20% to 54% (Warner et al 1993; Hallissey et al 1990; Hungin 1987; Saunders et al 1986; Johnsen et al 1991). The proportion of patients with negative findings after endoscopic investigation is associated with many factors. For example, the proportion of patients with negative endoscopic findings is 33% in those aged less than 45, decreasing to 7% in those aged 75 and above (Warner et al 1993).

Because of multiple causes of dyspeptic symptoms and difficulties in excluding all possible

organic disease, diagnosis of functional dyspepsia is subject to considerable uncertainty. For example, Crean et al (1994) found that only 41% of 490 diagnoses of functional dyspepsia could be regarded as 'certain' (i.e. with a subjective probability equal to or greater than 0.9).

Patients with functional dyspepsia may be further classified into several subgroups according to particular symptom patterns (Heading 1991).

1. Ulcer-like dyspepsia: Dyspepsia with well-localized epigastric pain, relief of pain by food and antacids, and a pattern of remission and relapse.
2. Reflux-like dyspepsia: Dyspepsia with heartburn and regurgitation.
3. Dysmotility-like dyspepsia: Dyspepsia with bloating, early satiety, nausea, and poorly localized abdominal discomfort.
4. Nonspecific dyspepsia: Dyspepsia that does not fall into one of the above three categories.

The classification of functional dyspepsia may facilitate clinical practice and research. But these terms should not carry any implication that the symptom patterns can be attributed to particular pathogenetic processes. Furthermore, 43% of subjects with dyspepsia could be classified into more than one subgroup (Talley et al 1992).

1.2 Size of the problem

Dyspepsia represents an important and costly health problem, although not as a cause of death or severe disability in the majority of cases. The prevalence of dyspepsia varies in different

Table 1. Prevalence of Dyspepsia: recently published epidemiological studies

Study	Sample	Definition	Period Prevalence
Jones et al 1990	7428 patients registered with general practitioners in England and Scotland.	Indigestion for more than a few days (upper abdomen).	(Six-month Period) 41%
Kay & Jorgensen 1994	3606 Danes living in the western part of Copenhagen County.	Upper dyspeptic symptoms (epigastric pain, acid regurgitation, heartburn).	(One-year period) Women: 14.5% to 46.7% Men: 12.5% to 54.3%
Agreus et al 1994	1156 adult population of a Swedish municipality.	Upper abdominal pain or discomfort, heartburn, nausea, vomiting, or other symptoms referable to the upper gastrointestinal tract.	(Three-month period) 32.2%
Talley et al 1992	835 US white population.	Pain centred in the upper abdomen.	(One-year period) 25.8%

studies because of differences in definitions, period and populations (See Table 1). In a British study, it was found that approximately 41% of the sample had experienced either upper abdominal pain or discomfort or heartburn (lasting for a few days) in the last six months (Jones et al 1990).

Kay and Jorgensen (1994) evaluated the prevalence, incidence, natural history, and risk factors of upper dyspepsia in a random sample of Danes. One year period prevalence of upper dyspeptic symptoms is 54.3% among men and 46.7% among women. If only symptoms occurring frequently (pain stated as once a month or more often, heartburn and acid regurgitation as frequent or constant) were included, the one-year period prevalence of frequent symptoms is 12.5% among men and 14.5% among women. Five years later one-quarter of the subjects with upper dyspepsia were free of all symptoms, and two-thirds of the subjects reporting frequent upper dyspepsia were free of all symptoms, and two-thirds of the subjects reporting frequent upper dyspepsia were free of frequent symptoms. Psychic vulnerability was strongly related to upper dyspepsia incidence (Kay and Jorgensen 1994).

About one quarter of the dyspeptic patients had consulted a general practitioner about their symptoms (Jones et al 1990). Lydeard and Jones (1989) compared 69 dyspeptic patients who had consulted their general practitioners and 66 dyspeptic patients who had not. They found that consulters were more likely to be worried about the possible seriousness of symptoms (e.g. cancer and heart disease) and to have experienced more disruptive and or life threatening events than the non-consulters. It was also found that reading books and magazines about health and medicine was a predictor for non-consultation (P=0.039).

Jones et al (1990) found that the six month period prevalence of dyspepsia was unrelated to social class but this factor was associated with consultation for dyspepsia; the consultation rate was 17% in social class one rising to 29% in social class four among those with dyspeptic symptoms. The use of investigations was also strongly related to social class, independent of age. Almost twice as many patients in social class five had barium meals as those in social class one and almost three times as many endoscopies had been performed on patients in social class five as in social class one (Jones et al 1990).

It is estimated that between 1.6 and 5% of all general practice consultations are for dyspepsia (Nyren et al 1992). The annual consultation rate for a new episode of dyspeptic symptoms was 2.03% (cases lacking a firm pathological basis) or 2.70% (including all cases) in people registered in general practice in a Dutch study (Warndorff et al 1989).

According to data from the third national study of morbidity statistics from general practice (RCGP 1986), the consultation rate for conditions with dyspepsia symptoms is 114.2 per thousand (Table 2). Abdominal pain may include upper, central and lower abdominal pain and many other causes. If consultations for diseases are excluded and assuming that one-fourth of abdominal pain is upper abdominal pain, the consultation rate for dyspepsia is 47.5 per thousand. Therefore consultations for functional dyspepsia in 1981-82 may be estimated to range from 19.7/1000 (disorders of function of stomach) to 47.5/1000. This range of estimates includes 20.3 per thousand reported by Warndorff et al(1989).

Table 2. General Practitioner Consultations for Conditions with Dyspepsia Symptoms

	Consultants per 1,000	Patients per 1,000
GI symptoms		
Nausea and vomiting(787)	12.9	9.6
Heartburn(787.1)	3.5	2.1
Gas and wind(787.3)	3.8	2.4
Abdominal pain(789)	45.7	28.2
GI disease		
Oesophageal disease(530)	3.9	2.4
Hiatus hernia(551.3, 552.3, 553.3)	7.2	3.4
Gastric ulcer(531)	2.3	1.0
Duodenal ulcer(532)	9.6	3.6
Other peptic ulcers(533-4)	2.0	1.1
Other disease of stomach and duodenum(535-7)	3.6	2.7
Disorders of function of stomach(536)	19.7	12.7
Total	114.2	69.2

Royal College of General Practitioners. Office of Population Censuses and Surveys. Department of Health and Social Security. Morbidity statistics from general practice 1981-82. Third national study. HMSO. London, 1986.

Work loss is substantial among dyspeptic patients who are in employment. Disability from work was found to be equally frequent among those with organic and those with non-organic (functional) dyspepsia in Norway (Johannessen et al 1990). According to a database on dyspepsia in Southern General Hospital in Glasgow, each patient with functional dyspepsia in employment loses on average 18.3 weeks per year (Crean et al 1994). In a Swedish study it was found that patients with functional dyspepsia were on average responsible for 26 more days of lost production than the average employee and the production loss due to short-term sick-leave was the most dominant item among all social costs of dyspepsia (Nyren et al 1985).

2. TREATMENT OF FUNCTIONAL DYSPEPSIA

Patients with functional dyspepsia have been treated with prokinetic drugs, anticholinergics, antacids, H_2-receptor antagonists, selective muscarinic M1-receptor blockers, sucralfate, bismuth, antibiotics, and even surgery (Talley 1991). The large range of therapies prescribed reflects the uncertainty about pathogenesis and the lack of a satisfactory treatment. It is difficult to evaluate the efficacy of the treatment of functional dyspepsia because of the following problems:

1. There is a lack of consensus on definition about functional dyspepsia. Patients with functional dyspepsia are quite heterogeneous in terms of possible aetiology, symptom pattern, course, and demographic characteristics. Patients selection criteria are often different in various studies.
2. Most trials of functional dyspepsia have not used validated methods to measure changes in symptoms. Measurements of intensity of symptoms may be more reliable than poorly defined therapeutic success or numbers of patients with good results after treatment (Van Zanten et al 1989, 1993).
3. Between 30-60% of patients with functional dyspepsia will respond to placebo treatment (Talley and Phillips 1988). Spontaneous improvement may partially explain placebo response. As the causes of functional dyspepsia are unknown, it is not known why symptoms of dyspepsia improve without any active treatment in many patients.
4. Longer follow up is needed in order to evaluate better the efficacy of a treatment. The improvement in symptoms or the side-effects of a treatment may become more or less manifest as the period of follow-up becomes longer.

2.1 Controversial conclusions by reviewers

A meta-analysis was performed to produce a pooled estimate of a series of short term RCTs on the pharmacological treatment of functional dyspepsia with antisecretory and gastrokinetic drugs (Dobrilla et al 1989). The results were expressed in terms of 'therapeutic success' (TS), which includes symptom-free patients, patients with significant improvement in symptoms, excellent results, and so on. The authors concluded that the pooled estimate provides evidence of the short-term efficacy of both the antisecretory and gastrokinetic agents. The importance of the placebo effect in functional dyspepsia is also confirmed in this meta-analysis. There are some methodological problems in this study. The most important problem is that the measurement of outcome may not be valid. Measurements of intensity (eg mean scores) are more reliable than poorly defined "therapeutic success". However, trials using measurements of intensity were excluded.

Van Zanten et al (1989) carried out a review of the literature on Helicobacter pylori associated gastritis and functional dyspepsia to determine whether or not symptoms related to these conditions can be measured reliably and whether or not any study to date has shown that treatment alters symptoms. Of the 14 studies analyzed, only two were considered to measure symptoms reliably (Talley et al 1986; Nyren et al 1986). Neither showed a therapeutic benefit in symptoms. (It is interesting to note that these two studies were excluded from Dobrilla's meta-analysis.) van Zanten et al concluded that to date, no treatment is of proven benefit in the relief of symptoms associated with Helicobacter pylori and functional dyspepsia.

Talley (1991) reviewed drug treatment of functional dyspepsia and concluded that patients

with dyspepsia should not be lumped into one broad category; treatment needs to be individualized. If abnormalities of motility or related disorders are found to characterize certain dyspepsia subgroups, then the use of prokinetic agents is a logical choice. The role of H_2-receptor blockers is less clear but may be useful in patients with reflux-like and perhaps ulcer-like dyspepsia. It remains to be established whether treatment of Helicobacter pylori in functional dyspepsia is of value (Talley 1991).

2.2 Prokinetic agents

Prokinetic agents may be a choice of treatment in both dysmotility-like and reflux-like dyspepsia (Table 3). However, clinical trials that evaluated the efficacy of prokinetic agents often suffer from methodological defects. Some did not separate patients with organic from those with functional dyspepsia. Others give no information on how the diagnosis was obtained. In addition, the type of symptom improvement reported has been variable and has not correlated with accelerated gastric emptying in the studies in which these have both been measured.

Metoclopromide was reported to be superior to placebo in relief of some symptoms. In a randomized trial the proportion of patients with good/excellent global result was reported to be 74% in patients treated with metoclopramide and 31% in those treated with placebo ($P<0.05$) (De Loose 1979). Similar results were reported by other trials in which functional and organic dyspeptic patients were mixed (Johnson 1971; Perkel et al 1979). The problem with metoclopromide is its side effects, such as drowsiness, restlessness, and anxiety, and even rarely tardive dyskinesia in old patients.

Eight RCTs evaluated the efficacy of domperidone on functional dyspepsia and all reported

Table 3. Randomized double-blind placebo controlled trials of gastrokinetic drugs in functional dyspepsia

Study	Drug	Patients (N)	Weeks	Outcome measures	Treated	Placebo	
De Loose 1979	Metaclopramide	Dysmotility/reflux-like(139)	2	% Good/excellent results	73.5%	31.0%	(P<0.05)
	Domperidone		2	% Good/excellent results	91.1%	31.0%	(P<0.05)
Bekhti & Rutgeerts 1979	Domperidone	Dysmotility-like(40)	4	% Good/excellent results	65.0%	20.0%	(P<0.01)
Van de Mierop et al 1979	Domperidone	Dysmotility/reflux-like(32)	4	% Good/excellent results	70.6%	13.3%	(P<0.01)
Van Ganse et al 1978	Domperidone	Dysmotility/reflux-like(44)	2	% Good/excellent results	82.0%	24.0%	(P<0.05)
Arts et al 1979	Domperidone	Dysmotility/reflux-like(14)	2	Reduction(%) in symptom score	76%	16%	(P<0.01)
Agorastos et al 1981	Domperidone	Dysmotility/reflux-like(18)	3	Reduction in symptom score	46.1%	41.7%	(P>0.05)
Sarin et al 1986	Domperidone	Dysmotility/relux-like(44)	2	% symptomatic improvement	84%	?	(P<0.05)
Davis et al 1988	Domperidone	Dysmotility-like(16)	6	Reduction(%) in symptom score	78%	42%	(P<0.05)
Hui et al 1986	Sulpiride	Dysmotility-like (98)	4	% Symptom-free or improved	75%	37%	(P<0.01)
Rosch 1987	Cisapride	Dysmotility-like(118)	4	% Good/excellent results	81%	31%	(P<0.01)
Van Ganse & Reyntjens 1987	Cisapride	Dysmotility/reflux-like(8)	1	% Good/excellent results	88%	13%	(P<0.05)
Corinaldesi et al 1987	Cisapride	Dysmotility/reflux-like(12)	2	Score of nine symptoms	9.0	9.2	(P=0.09)
Goethal & Van DeMierop 1987	Cisapride	Dysmotility/reflux-like(24)	4	% Good/excellent results	63%	29%	(P<0.05)
Francois & DeNutte 1987	Cisapride	Dysmotility/reflux-like(34)	3	% Good/excellent results	82%	41%	(P<0.05)
Hannon 1987	Cisapride	Dysmotility-like(22)	3	% Good/excellent results	64%	27%	(P<0.05)
Deruyttere et al 1987	Cisapride	Dysmotility-like(56)	3	% Good/excellent results	75%	55%	(P<0.05)
Jian et al 1989	Cisapride	Dysmotility-like(28)	6	Changes in global score	-18	-10	(P>0.05)
DeNutte et al 1989	Cisapride	Dysmotility-like (32)	4	% Good/excellent results	83%	47%	(P<0.05)
Wood et al 1993	Cisapride	Functional dyspepsia (11)	4	Score for epigastric pain/discomfort	26.3	23.2	(P=0.95)
Van Outryve et al 1993	Cisapride	Resistant to domperidone or metoclopramide (53)	2	% Good/excellent results	65%	22%	(P=0.02)
Chung 1993	Cisapride	Dysmotility-like(29)	4	% Good/excellent results	71.4%	20.0%	(P<0.01)

symptomatic improvement over placebo (Table 3). On average the proportion of patients with good/excellent global result was about 80% in the domperidone group and 28% in the placebo group.

Cisapride is a new prokinetic agent, licensed for the treatment of symptoms and mucosal lesions associated with reflux-oesophagitis. A double-blind fluoroscopic study demonstrated that cisapride significantly improved antral contractility and enhanced gastric emptying compared with placebo (Degryse et al 1993). Clinical trials in patients with functional dyspepsia showed that 60% to 90% of patients treated with cisapride for 2-4 weeks had good to excellent responses, which were greater than the responses observed with placebo (5% to 60%) (Table 3). The most common side effect of cisapride was reported to be diarrhoea (Sabbatini et al 1991).

It has been suggested that cisapride should be the first choice of medication for the treatment of motility-like dyspepsia (Kellow 1992), although limited data are available to compare cisapride with other prokinetic agents. In a well designed randomized double-blind trial, cisapride was found to be as effective as metoclopromide and ranitidine (an H_2-receptor inhibitor) in 60 patients with functional dyspepsia (Archimandritis et al 1992). Patients with oesophagitis and active gastric or duodenal ulcer were identified by endoscopy and excluded from the study. The score of dyspeptic symptoms was reduced by 75% with cisapride, by 85% with metoclopromide, and by 65% with ranitidine four weeks after the end of therapy (the duration of therapy was 8 weeks). The number of patients reporting adverse effects was 4 in the cisapride group, 7 in the metoclopramide group, and 7 in the ranitidine group. Because of small sample size, the conclusion that cisapride was associated with fewer adverse effects may not be appropriate. (in fact, 2 patients in the cisapride group dropped out due to adverse experiences compared with 1 in the metoclopramide group and 2 in the ranitidine group).

The efficacy and tolerability of cisapride and metoclopramide were compared in a RCT in 60 patients with functional dyspepsia (Fumagalli & Hammer 1994). After 4 weeks treatment the symptom severity was improved significantly in both groups. The percentage of responders (with no or only mild symptoms) was 87% in the cisapride group and 77% in the metoclopramide group (difference between groups not statistically significant). Two weeks after completion of the trial it was found that there were significantly more patients in the cisapride group with no or mild symptoms (73%) than that in the metoclopramide group (47%). Four patients in the cisapride group reported adverse effects (abdominal cramps, loose stools, fatigue, and essential tremor) and two in the metoclopramide group (essential tremor and somnolence). Three patients in the cisapride group dropped out due to adverse effects. Authors concluded that cisapride may result in a better, more sustained overall response when compared with metoclopramide (Fumagalli & Hammer 1994).

In a Dutch general practice open study, 599 patients with symptoms of dyspepsia were treated with cisapride. The response to 5 mg three times daily was rated excellent or good in 61% of patients at week 2. On increasing the dose to 10 mg three times daily in 132 patients with poor to moderate response, the result at the end of treatment was rated as good or excellent in 45% of these patients. Cisapride also proved effective in patients previously treated with prokinetic agents (72% response rate), antacids (66%) and H_2-receptor antagonists (48%). On long-term follow-up, dyspepsia relapse among the total patient population and the patients fully 'cured' after 4 weeks of cisapride were respectively 30% and 27% after 6 months. The majority of relapsing patients (88%) responded well to repeated treatment with cisapride. In conclusion, most patients responded well to a short therapeutic trial with cisapride and remained free from relapse in the subsequent 6 months. Repeated treatment in patients with recurrent symptoms appeared to be successful (Heyse et al 1993).

2.3 Anti-ulcer drugs

Antacids

During 1978-1983 in Sweden, a survey found that the most frequently used drug type to treat dyspepsia was antacids (77% of the prescriptions) (Loof et al 1985). However, data from three controlled studies suggest that antacids, although widely used by patients with upper abdominal pain, do not relieve symptoms more effectively than placebo in patients with function dyspepsia (Table 4).

Anti-secretory agents

H_2-receptor antagonists (cimetidine, ranitidine) reduce gastric acid outputs as a result of H_2-receptor blockade. A well designed RCT showed that neither antacid nor cimetidine treatment resulted in significant better effect than placebo in patients with dyspepsia (Nyren et al 1986). The results of clinical trials listed in Table 4 suggest that the number of patients with symptoms improvement was greater in treated groups (34% to 80%) than in the placebo group (31% to 62%). A small subgroup of functional dyspepsia patients (reflux/ulcer-like) may benefit from antisecretory treatment. But further studies are needed to identify patients who are likely to respond.

Pirenzepine is a selective antimuscarinic drug which inhibits gastric acid and pepsin secretion. Results from clinical trials on pirenzepine and functional dyspepsia are conflicting (Table 4). Two early trials show that significantly more patients are symptom-free in the treated group than in the placebo group after 4 weeks of treatment. However, a well designed trial using a more valid method of outcome measurement found that symptoms of patients are worse in

Table 4. Randomized double-blind placebo controlled trials of antacids and antisecretory drugs in functional dyspepsia

Study	Treatment	Patients (N)	Weeks	Outcome-measures	Results Treated	Placebo	
Nyren et al 1986	Antacids	Mixed (159)	3	Reduction(%) in the Pain Index	36%	31%	(NS)
	Cimetidine				34%	31%	(NS)
Gotthard et al 1988	Antacids	Mixed (222)	6	% improved or symptom-free	37%	38%	(NS)
	Cimetidine				54%	38%	(NS)
Weberg & Berstad 1988	Antacids	NUD+EPC (90)	4	% improvement in pain	84%	80%	(NS)
	Pirenzepine				85%	79%	(NS)
Kelbaek et al 1985	Cimetidine	Mixed (50)	3	% improvement of symptoms	54%	62%	(NS)
Lance et al 1986	Cimetidine	Ulcer/dysmotility-like (60)	4	% improved	62%	54%	(P=0.5)
Nesland & Berstad 1985	Cimetidine	NUD+EPC(100)	4	% good/very good (global assessment)	48%	30%	(NS)
				% Improvement in epigastric pain	75%	65%	(P<0.05)
Delattre et al 1985	Cimetidine	Dysmotility/reflux-like (414)	4	Patients global evaluation	77%	57%	(P<0.05)
Singal et al 1989	Cimetidine	Mixed (56)	4	% Symptom-free or improved	69%	38%	(P<0.05)
Talley et al 1986	Cimetidine	Mixed (62)	4	Pain severity index	6.63	7.03	(P<0.01)
	Pirenzepine				6.81	6.24	(P=0.09)
Saunders et al 1986	Ranitidine	NUD(251)	6	% free from pain/discomfort	80%	59%	(P<0.01)
Olubuyide et al 1986	Ranitidine	NUD(45)	4	Days & nights per week with pain	6.6	8.6	(NS)
Dal Monte et al 1983	Pirenzepine	Ulcer-like (40)	4	% symptom-free	58%	19%	(P<0.05)
Hradsky & Wikander 1983	Pirenzepine	NUD (48)	4	% Symptom-free or clinical improvement	84%	56%	(P<0.05)

Note: NUD: nun-ulcer dyspepsia; EPC: erosive prepyloric changes; NS: Statistically nonsignificant.

the pirenzepine treated group (Talley et al 1986).

Sucralfate

Sucralfate is a mucosal cytoprotective drug that acts as a protective barrier against the deleterious effects of acid, pepsin, and bile acids by forming adherent complexes with ulcers and inflamed and normal mucosa. The results from three trials conflict however. Symptoms were significantly improved after treatment of sucralfate in one study (Kairaluoma et al 1987). However, two other studies did not confirm this finding (Skoubo-Kristensen et al 1989; Gudjonsson et al 1993).

2.4 Treatment of Helicobacter Pylori (H.pylori)

The relation between Helicobacter pylori, a gram-negative spiral bacterium found in the human stomach, and functional dyspepsia is controversial, although a strong association between Helicobacter pylori and gastritis and peptic ulcer disease has been shown (Berstad et al 1993). The prevalence of positive culture for Helicobacter pylori was 48% in dyspeptic subjects and 36% in non-dyspeptic subjects (Bernersen et al 1992).

Several controlled trials using bismuth or antibiotics have been performed but the results have been variable (Table 5). The antibiotics used to supress or eradicate Helicobacter pylori include colloidal bismuth subcitrate (CBS), bismuth salicylate (BSS), erythromycin, amoxycillin, diosmectite. Helicobacter pylori was eradicated (or suppressed) in 7% to 90% in the treated group compared with 0% to 17% in the placebo group. However, convincing symptom improvement after clearance of Helicobacter pylori from the stomach has not been demonstrated. In an observational study it was found that the mean symptom score in those

Table 5. Randomized trials of anti-Helicobacter pylori therapy for functional dyspepsia.

Study	Treatment	N	Weeks	Suppression of H. pylori (%)	Symptoms Improvement	Symptom measures
McNulty et al 1986	Bismuth salicylate	18	3	78%	87% (NS)	The symptom scores of nausea/vomiting, heartburn
	Erythromycin	15		7%	64%	indigestion, and belching were added for each patient
	Placebo	17		0%	67%	giving a possible score ranging from -4 to +4.
Borody et al1987	CBS	22	4	NA	NA	Significant improvement in treated group in pain/burning,
	Placebo	21		NA	NA	abdominal distension and nausea but not in food intolerance.
Lambert et al 1987	CBS	15	4	73%	NA	CBS resulted in significant relief of pain during the day
	Placebo	18		6%	NA	and night, with no significant changes in severity of heartburn, feeling of fullness, flatulence or nausea/vomiting.
Rokkas et al 1988	CBS	25	8	83%	32.7 (P<0.05)	Symptom score.
	Placebo	27		0%	53.9	
Loffeld et al 1989	CBS	26	4	30%	50% (NS)	
	Placebo	24		0%	71%	
Kang et al 1990	CBS	28	8	89%	46% (P<0.05)	Number of patients without symptoms.
	Placebo	23		0%	35%	
Goh et al 1991	CBS	38	4	81%	19.5 (NS)	Symptom score.
	Placebo	33		0%	42.1	
Vaira et al 1992	CBS	40	4	54%	82% (P<0.01)	Number of patients absent or improved symptoms.
	Placebo	40		0%	5%	
deKorwin et al 1993	Diosmectite	61	4	35%	48% (P<0.05)	Number of patients without pain.
	Placebo	64		14%	27%	
Marshall et al 1993	BSS	23	3	65%	3.1 (NS)	Number of severe symptom days per week.
	Placebo	27		0%	3.5	
Glupczynski et al1988	Amoxycillin	22	8 days	91%	NA	No significant improvement.
	Placebo	23		17%	NA	
Morgan et al 1988	Furazolidone	14	2	54%	NA	No significant difference. Nitrofurantoin related
	Nitrofurantoin	24		58%	NA	with more nausea and furazolidone with more vomiting.
	Placebo	31		3%	NA	

Note: CBS, colloidal bismuth subcitrate. NA: not available. NS: no significant difference.

whom H.pylori had been eradicated was similar to that in patients in whom the organism had not been eradicated after one week of treatment. However, after 1 year follow-up, the mean symptom score in patients with persistent H.pylori infection was 5.24, compared with 1.62 ($P<0.01$) in patients who remained free of infection (O'Morain & Gilvarry 1993).

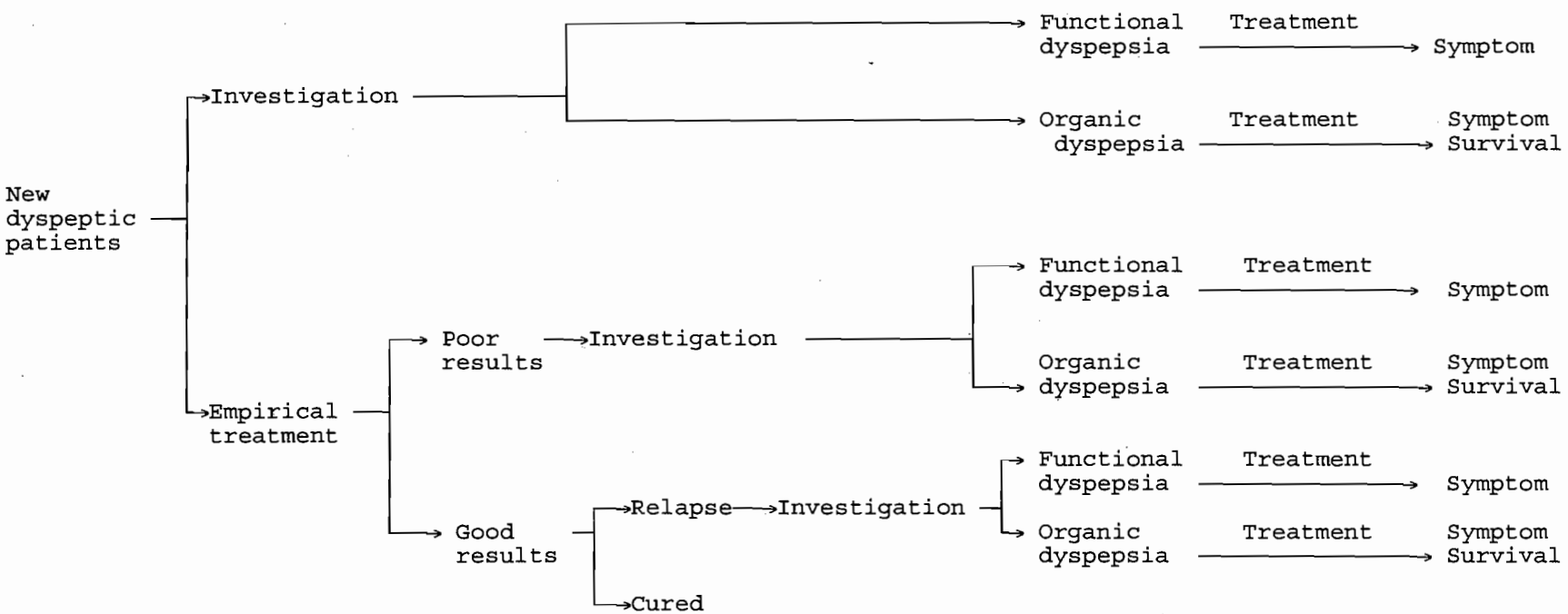
3. INVESTIGATION OR TREATMENT

Un-investigated dyspepsia is a mixture of various organic and functional conditions and should not be considered the same as functional dyspepsia. There are different views about whether dyspeptic patients should be treated empirically before investigation or whether initial investigation should be carried out to find out causes of dyspepsia (Jones 1985; Brown & Rees 1990; Kerrigan et al 1990; Heatley 1993).

Many questions need to be answered about this issue (Figure 2). Can patients with organic dyspepsia be identified without complex investigations? Can investigation correctly diagnose those with organic abnormality? What are the consequences of delaying investigation/treatment of patients with organic dyspepsia? What is the proportion of organic dyspepsia in total patients with dyspeptic symptoms? Are there great differences between the treatments of functional dyspepsia and organic dyspepsia? What are the results of treatment of functional and organic dyspepsia? How many patients with dyspepsia can be cured by empirical treatment without investigation? What is the cost of investigation of dyspepsia? What is the cost of treatment of functional and organic dyspepsia? Is there any risk and inconvenience associated with investigation?

There is no convincing evidence to identify one strategy of management of dyspeptic patients as superior to another. In an Australian study, patients were randomized to either a 'British'

Figure 2. Investigation or Treatment: Management of Dyspeptic Patients



group treated freely at the discretion of their general practitioner without necessarily being investigated or an 'Australian' group where useof H_2-receptor antagonists (H_2-A) was allowed only after gastroscopy or a barium meal had demonstrated a peptic ulcer or ulcerative oesophagitis. It was found that over a six-month period the cost of early investigation of heartburn and dyspepsia was equivalent to the cost of a therapeutic trial of H_2-A (Goulston et al 1991).

Read and colleagues (1982) carried out a decision analysis to compare symptomatic therapy, ulcer therapy, or upper gastrointestinal x-ray investigation followed by further endoscopy tests or therapy. None of the three strategies was best on all of the evaluated outcomes (morbidity, mortality, and costs) and therefore no particular strategy can be preferred. It was found that mortality was minimized if investigation was performed prior to selection of therapy at a cost of $1.6-$2.3 million per life-year saved (compared with initial ulcer therapy).

In order to reduce the workload and potential risks from invasive procedures, it would be preferable to reach a diagnosis without using invasive investigations. Johannessen et al (1990) assessed the ability of the medical history to predict endoscopic findings. They found that organic dyspepsia can be predicted with a sensitivity and specificity of approximately 70% where pain is relieved by antacids, age is above 40, previous peptic ulcer disease, male, symptoms provoked by berries, and night pain relieved by antacids and food.

In a British study, endoscopy was performed to investigate 2659 patients aged 40 or over referred with dyspepsia (Hallissey et al 1990). Gastric cancer was identified in 57 patients, only one of whom was under 55 years-old.

It is inappropriate to treat dyspeptic patients with expensive drugs without a firm diagnosis,

and without knowing whether the same effect might have been achievable with placebo. On the other hand, it is not practicable to initiate diagnostic investigations immediately in every single patient who presents with dyspepsia. Because the extra risks associated with postponing definite diagnosis for 4-8 weeks in dyspeptic patients in younger age groups may be exceedingly small (Jessop 1986; Colin-Jones 1988; Nyren 1991), a therapeutic trial without a firm diagnosis may be an acceptable alternative in those aged less than 45 years.

The main object of a therapeutic trial without investigation is perhaps not to cure the patients with functional dyspepsia but to postpone diagnostic study for a while so that those with benign self-limiting dyspeptic symptoms are diverted away from unnecessary, expensive, and potentially hazardous investigations. Nyren (1991) recommended early investigation of dyspeptic patients in the following situations: 1) Newly developed dyspepsia in patients more than 45 years old; 2) In patients with 'alarm' symptoms such as unexplained weight loss, dyspepsia with gastrointestinal bleeding, clinical signs of anaemia jaundice, or a palpable mass; 3) when the main object of the consultation is to confirm or refute patients' suspicion of malignancy or 'serious disease'.

A Working Party of the British Society of Gastroenterology sets out suggested indications for upper gastrointestinal endoscopy (Lennard-Jones et al 1990). Early investigation is suggested when the following indications are met: patients aged over 45 with new dyspepsia; symptoms recur after adequate therapy; recurrent symptoms from a known gastric ulcer; presence of one or more warning features including dysphagia, vomiting, weight loss, bleeding, and anaemia. The Working Party also sets out situations in which the examination is unlikely to be helpful: age less than 45; known duodenal ulcer; no trial of antacids; no trial of H_2 blocker; typical reflux symptoms; symptoms suggest irritable bowel syndrome.

The upper gastrointestinal tract can be examined either by endoscopy or double contrast barium radiology. (An endoscope is an instrument for viewing the interior of the body. For example, the gastrointestinal tract can be visualised from the mouth downwards through the oesophagus and stomach to the duodenum.) The two techniques have different strengths and weaknesses. The double-contrast barium meal is safer, gives a permanent record, shows extrinsic lesions, and demonstrates motility and gastric emptying better. Endoscopy is more accurate to show mucosal lesions, can be used to take biopsy, but there is a slight risk of mortality. In Britain the cost of the two procedures is similar (Colin-Jones 1986). Endoscopy is increasingly used as the primary investigation of gastro-intestinal symptoms and there is a trend for endoscopy to replace barium meal. It has been suggested that the performance of both types of investigation for one patient should be limited (Lennard-Jones et al 1990).

The costs of dyspepsia-related physician visits, radiologic tests, and drugs during the 6 months following a gastroenterologist consultation with endoscopy were compared with the expenses after barium radiography in the United States (Longstreth 1992). If initial costs of investigation were not included, the costs were lower for the endoscopic approach ($134.0 vs. $435.3). However, the initial costs of endoscopic investigation are much greater than costs of radiological investigation. All costs together, the cost comparison favours the radiologic approach over endoscopy ($567.3 vs $1258.0). Considering the greater cost, the additional risk of the procedure, and the lack of detectable improvement in results, the use of endoscopy rather than barium radiography in these patients has been questioned (Gelfand and Maglinte 1992).

One of the great innovations of health care in the 20th century has been said to be minimally invasive technology (MIT, or called minimally invasive surgery, minimal access surgery), which includes diagnostic and therapeutic endoscopic activities. MIT has important

implications for changes in health services but because of the pressure from patients MIT has spread rapidly without adequately assessment (Banta 1993). According to the estimate from a working group, in 10 years time 70-80% of surgical operations may be done endoscopically (Choo 1994).

It was found that the current uptake of endoscopy for dyspepsia is high (about 3.3 per 1,000 population) and potential growth of endoscopy for dyspepsia is estimated to be very large because of a large pool of patients with dyspepsia, ulcer and non-ulcer related conditions (Warner et al 1993).

4. CURRENT PRACTICE

In a Dutch study, the general practitioner prescribed medication in 70% of patients with dyspepsia; less commonly the patient was referred for X-ray (14%), endoscopy (13%) or to a specialist (11%). The drugs prescribed could be divided into seven groups: antacids/mucosal protective agents (36% of patients); H_2-receptor antagonists (23%); domperidone (19%); antispasmodics (10%); antiemetics (6%); anxiolytics (3%); miscellaneous (3%). The authors concluded that dyspepsia is managed well in general practice and is only rarely associated with major lesions (Warndorff et al 1989). However, less than 10% of patients in this study were suffering from peptic ulcer disease although at least 25% of patients were prescribed antacids/mucosal protective agents.

It was found that drug therapy was used in 92% of the patients with gastritis in a Swedish study (Loof et al 1985). Antacids were prescribed in 77%, anticholinergic/spasmolytic drugs in 36% and H_2-receptor antagonists in 4%. The extensive use of drugs was said to be the result of the lack of convincing data from clinical trials (Loof et al 1985).

Table 6. Pharmaceutical Costs of Functional Dyspepsia Treatment.

Population (England and Wales 1993, 15 year old and above):	41,251,900
Total no. of GP consultations for dyspepsia(1.97% to 4.75%):[a]	812,662 to 1,959,465
Total no. of prescriptions:[b]	601,370 to 1,450,004
Types of Drugs and cost for 4 weeks:[c]	
Antacids/mucosal protective agents (36%):	£3.12 to £13.36.
Antisecretory agents (29%):	£15.60 to £39.52.
Prokinatic agents(35%):	£7.04 to £36.00.
Costs of pharmaceuticals:	
Antacids/mucosal protective agents:	£675,459 to £6,973,939.
H_2-receptor antagonists (29%):	£2,720,598 to £16,618,206.
Prokinatic agents(35%):	£1,481,776 to £18,270,050.
Total:	£4,877,833 to £41,862,195.

a. See section 2.

b. Assuming 74% of consultants resulting use of medication (Warndorff et al 1992).

c. Proportion of drugs prescribed is estimated based on Warndorff et al 1989. Price of drugs is estimated from British National Formulary 1993 (see Table 7).

Table 7. Cost of drugs

Drugs	Dosage	Cost(£) for one week
Prokinetic agents		
Cisapride(Prepulsid)	10mg 3-4 times daily	6.75 to 9.0
Metoclopramide(Maxolon)	10mg 3 times daily	2.2
Domperidone(Motilium)	10-20mg every 4 to 8 hours	1.76 to 7.06
Anti-secretory agents for reflux oesophagitis		
Cimetidine(Dyspamet)	400mg twice daily	3.9
Ranitidine(Zantac)	150mg twice daily	6.9
Omeprazole(Losec)	20mg daily	9.09
Pirenzepine(Gastrozepin)	50mg 2-3 times daily	6.59 to 9.88
Antacids/mucosal protective agents		
Co-magaldrox(Maalox)	1-2 tablets 4 times daily	0.78
Topal(Innovex)	1-3 tablets 4 times daily	3.34

Estimated from British National Formulary No. 26, 1993

In an Irish study, a group of general practitioners were studied to examine their prescribing patterns in commonly occurring clinical situations (Holmes 1992). Prescribing for non-ulcer (functional) dyspepsia showed the greatest variation in drug choice and was also the most expensive area of the cases in the study. In this study twenty-two of thirty doctors (73%) use H_2-antagonist medication as their choice of treatment for non-ulcer dyspepsia (Holmes 1992).

In Britain there is no recently published study about the management of functional dyspepsia in general practice. The demand for GP consultations for functional dyspepsia is estimated by using data from the third national study of morbidity statistics from general practice (Table 6). Based on data from the British National Formulary 1993, each year the total pharmaceutical cost for functional dyspepsia is estimated from £4.88 million to £41.84 million in England and Wales. Since only one quarter of people with dyspeptic symptoms have consulted general practitioners for their symptoms (Jones et al 1990), the potential growth in

demand for treatment should be considerable.

Due to great heterogeneity in patients with dyspepsia and the uncertainty of treatment effects, the variation of clinical management of dyspepsia is to be expected. Rizzo (1993) argues that the cost of medical care has been substantially raised because physicians tend to make clinical decisions based on the "when in doubt, do it" approach whenever information about the effectiveness of treatment is poor.

5. CONCLUDING REMARKS

1. Further research is needed to understand the mechanisms of functional dyspepsia, so that therapy can be targeted more appropriately at correcting the actual pathophysiologic disturbance.

2. The treatment effect with various agents for functional dyspepsia has been evaluated by many randomized clinical trials. However the conclusion is not convincing because of many methodological problems. Perhaps the most important difficulty is lack of validated outcome measures. The research in this area should be strengthened.

3. Evidence from clinical trials suggests that prokinetic agents may help to improve symptoms in patients with dysmotility-like dyspepsia. The role of anti-secretory agents and treatment of Helicobacter pylori is less clear. Antacids do not relieve symptoms more effectively than placebo. Many patients with functional dyspepsia respond to treatment with placebo and therefore resources would be wasted if these patients were treated with expensive drugs whose benefit is unproven.

4. Further research is needed to examine how the patients with dyspepsia are managed in general practice. By evaluating treatments, setting practice guideline and comparing current clinical behaviour in relation to scientific evidence, the management of functional dyspepsia may become more cost-effective.

5. General practitioners are subject to continuous pressure to prescribe new drugs both from the pharmaceutical industry and "patient awareness" (MeReC 1992). Reliable data from clinical trials are needed to compare new drugs not only with placebo, but also with old drugs. Cisapride is more expensive than other prokinetic agents (metoclopramide and domperidone) without convincing better treatment-effect in patients with dyspepsia. The expensive drugs (eg. pirenzepine) should be compared with cheaper drugs (eg. cimetidine) in randomized clinical trials to examine relative effectiveness.

6. Expensive investigations (endoscopy) should be targeted on selected patients. Pressure arising from increased patients' awareness may affect general practitioners decisions and a considerable amount of expensive investigation in patients with dyspepsia is used only to confirm the absence of serious organic illnesses. Health education may help to relieve unnecessary anxiety in patients with dyspepsia and therefore possibly to reduce demand for investigation and treatment.

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