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British Society of Gastroenterology guidelines on the management of functional dyspepsia

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ABSTRACT

Functional dyspepsia (FD) is a common disorder of gut–brain interaction, affecting approximately 7% of individuals in the community, with most patients managed in primary care. The last British Society of Gastroenterology (BSG) guideline for the management of dyspepsia was published in 1996. In the interim, substantial advances have been made in understanding the complex pathophysiology of FD, and there has been a considerable amount of new evidence published concerning its diagnosis and classification, with the advent of the Rome IV criteria, and management. The primary aim of this guideline, commissioned by the BSG, is to review and summarise the current evidence to inform and guide clinical practice, by providing a practical framework for evidence-based diagnosis and treatment of patients. The approach to investigating the patient presenting with dyspepsia is discussed, and efficacy of drugs in FD summarised based on evidence derived from a comprehensive search of the medical literature, which was used to inform an update of a series of pairwise and network meta-analyses. Specific recommendations have been made according to the Grading of Recommendations Assessment, Development and Evaluation system. These provide both the strength of the recommendations and the overall quality of evidence. Finally, in this guideline, we consider novel treatments that are in development, as well as highlighting areas of unmet need and priorities for future research.

EXECUTIVE SUMMARY OF RECOMMENDATIONS

Doctor–patient communication, diagnosis and investigation of functional dyspepsia

- Clinicians should be aware that most patients with dyspepsia will have functional dyspepsia (FD) as the underlying cause of their symptoms after investigation (recommendation: strong, quality of evidence: low).
- We recommend that, in the absence of upper gastrointestinal alarm symptoms or signs, clinicians should diagnose FD in the presence of bothersome epigastric pain or burning, early satiation and/or postprandial fullness of greater than 8 weeks duration (recommendation: strong, quality of evidence: very low).
- Establishing an effective and empathic doctor–patient relationship and a shared understanding is key to the management of FD. This may reduce healthcare utilisation and improve quality of life (recommendation: strong, quality of evidence: very low).
- We recommend that the diagnosis of FD, its underlying pathophysiology and the natural history of the condition, including common symptom triggers, should be explained to the patient. FD should be introduced as a disorder of gut–brain interaction (DGBI), together with a simple account of the gut–brain axis and how this is impacted by diet, stress, cognitive, behavioural and emotional responses to symptoms and postinfective changes (recommendation: strong, quality of evidence: very low).
- We recommend that a full blood count is performed in patients aged ≥55 years with dyspepsia and coeliac serology in all patients with FD and overlapping irritable bowel syndrome (IBS)-type symptoms (recommendation: strong, quality of evidence: low).
- We recommend that if no other upper gastrointestinal alarm symptoms or signs are reported, urgent endoscopy is only warranted in patients aged ≥55 years with dyspepsia with weight loss, or those aged >40 years from an area at an increased risk of gastric cancer or with a family history of gastro-oesophageal cancer (recommendation: strong; quality of evidence: very low).
- We recommend that non-urgent endoscopy is considered in patients aged ≥55 years with treatment-resistant dyspepsia or dyspepsia with either a raised platelet count or nausea or vomiting (recommendation: strong, quality of evidence: very low).
- We recommend that urgent abdominal CT scanning is considered in patients aged ≥60 years with abdominal pain and weight loss to exclude pancreatic cancer (recommendation: strong; quality of evidence: very low).
- We recommend that all other patients with dyspepsia are offered non-invasive testing for *Helicobacter pylori* ('test and treat') and, if infected, given eradication therapy (recommendation: strong; quality of evidence: high).
- We recommend that successful eradication of *H. pylori* after 'test and treat' is only confirmed in patients with an increased risk of gastric cancer (recommendation: strong; quality of evidence: low).

- We recommend that patients without *H. pylori* infection are offered empirical acid suppression therapy (recommendation: strong; quality of evidence: high).
- Referral of patients with FD to gastroenterology in secondary care is appropriate where there is diagnostic doubt, where symptoms are severe, or refractory to first-line treatments, or where the individual patient requests a specialist opinion (recommendation: weak, quality of evidence: low).
- We recommend that gastric emptying testing or 24-hour pH monitoring should not be undertaken routinely in patients with typical symptoms of FD (recommendation: strong, quality of evidence: very low).
- We recommend that, ideally, patients with FD referred to secondary care are managed in a specialist clinic, with access to an interested clinician, dietetic and lifestyle support, with access to efficacious drugs and gut–brain behavioural therapies. Rates of *H. pylori* 'test and treat' prior to endoscopy, prevalence of *H. pylori* infection and use of endoscopy should be audited (recommendation: strong, quality of evidence: very low).

First-line treatment of FD

1. We recommend that all patients with FD are advised to take regular aerobic exercise (recommendation: strong, quality of evidence: very low).
2. There is insufficient evidence to recommend dietary therapies, including a diet low in fermentable oligosaccharides, disaccharides and monosaccharides, and polyols in FD (recommendation: weak; quality of evidence: very low).
3. Eradication therapy is an efficacious treatment for *H. pylori*-positive patients with FD. Adverse events are more common than with a control therapy (recommendation: strong; quality of evidence: high).
4. Histamine-$_2$-receptor antagonists may be an efficacious treatment for FD. These drugs are well tolerated (recommendation: weak, quality of evidence: low).
5. Proton pump inhibitors (PPIs) are an efficacious treatment for FD. There does not appear to be a dose response, so the lowest dose that controls symptoms should be used. These drugs are well tolerated (recommendation: strong, quality of evidence: high).
6. Some prokinetics may be an efficacious treatment for FD. However, efficacy varies according to drug class, and many of these drugs are unavailable outside of Asia and the USA. Most of these drugs are well tolerated (recommendation: weak, quality of evidence: low for acotiamide, itopride, and mosapride, recommendation: strong, quality of evidence: moderate for tegaserod).

Second-line treatment of FD

- Tricyclic antidepressants (TCAs) used as gut–brain neuromodulators are an efficacious second-line treatment for FD. They can be initiated in primary or secondary care, but careful explanation as to the rationale for their use is required, and patients should be counselled about their side effect profile. They should be commenced at a low dose (eg, 10 mg amitriptyline once daily) and titrated slowly to a maximum of 30–50 mg once daily (recommendation: strong, quality of evidence: moderate).
- Antipsychotics, such as sulpiride 100 mg four times a day or levosulpiride 25 mg three times a day, may be efficacious as a second-line treatment for FD. There should be careful explanation as to the rationale for their use and patients should be counselled on their side effect profile (recommendation: weak, quality of evidence: low).
- There is no evidence that selective serotonin reuptake inhibitors (SSRIs) used as gut–brain neuromodulators are an efficacious second-line drug for global symptoms in FD (recommendation: weak, quality of evidence: moderate).
- There is no evidence that serotonin norepinephrine reuptake inhibitors (SNRIs) used as gut–brain neuromodulators are an efficacious second-line drug for global symptoms in FD. However, as they are efficacious in other chronic painful conditions, more trials of these drugs are warranted (recommendation: weak, quality of evidence: low).
- Tandospirone 10 mg three times a day may be an efficacious second-line treatment for FD, but there is no evidence that other 5-hydroxytryptamine-$_{1A}$ agonists, including buspirone 10 mg three times a day, are efficacious. However, more trials of these drugs are warranted (recommendation: weak, quality of evidence: low).
- Pregabalin 75 mg once daily may be an efficacious second-line treatment for FD but further randomised controlled trials (RCTs) are needed and given its controlled drug status we advise this drug is only used in specialist settings (recommendation: weak, quality of evidence: low).
- Mirtazapine 15 mg once daily may be an efficacious second-line treatment for patients with FD with early satiation and weight loss, but further RCTs are needed (recommendation: weak, quality of evidence: very low).

Gut–brain behavioural therapies in FD

- Interpersonal psychodynamic informed psychotherapy may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).
- Cognitive–behavioural therapy (CBT) and metacognitive therapy may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).
- Stress management approaches may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).
- Hypnotherapy may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).

Management of severe or refractory FD

- We recommend a multidisciplinary support team should be involved for patients with severe or refractory FD (recommendation: strong, quality of evidence: low).
- We recommend opioids and surgery should be avoided in patients with severe or refractory FD to minimise iatrogenic harm (recommendation: strong, quality of evidence: very low).
- We recommend patients with severe or refractory FD presenting with weight loss and food restriction are assessed for eating disorders and disordered eating, including avoidant restrictive food intake disorder (ARFID) (recommendation: strong, quality of evidence: very low).
- We recommend early dietitian involvement in patients with severe or refractory FD to avoid an overly restrictive diet (recommendation: strong, quality of evidence: very low).

Research

1. Successful completion of large clinical trials requires pragmatic inclusion criteria, minimisation of the participant trial

burden, and virtual (remote access) trial approaches to reduce geographical, socioeconomic and minority ethnic exclusion.
2. Large-scale RCTs with cross-over phases or periods of open-label treatment so active therapy may be delivered to all participants should be considered.
3. A priority-setting partnership with patients would best discern valuable research questions.
4. Some future research themes include, but are not limited to:
   a. Characterisation of the illness to understand predictors (clinical, dietary, genetic, psychological and biological) of outcome and treatment response, determinants of refractory illness and burden of illness (particularly with respect to workplace productivity) by conducting large-scale epidemiological studies with extended observation.
   b. Consideration should be given to stratifying RCTs by FD severity and subtype, burden of extraintestinal symptoms, and psychological comorbidity.
   c. A better understanding of treatment combinations to uncover augmentation effects between therapies, such as dual therapy with histamine-$_1$ and histamine-$_2$-receptor antagonists or a TCA in combination with a SSRI.
   d. Modulation of pain and psychological responses using drugs (eg, SNRIs, mirtazapine, or 5-hydroxytryptamine-$_{1A}$ agonists) or behavioural approaches (eg, CBT) used earlier in the disease course.
   e. Trials of dietary approaches to managing symptoms in FD, including a diet low in fermentable oligosaccharides, disaccharides and monosaccharides, and polyols.
   f. Trials of drugs that have shown efficacy in gastroparesis, including ghrelin agonists, such as relamorelin, 5-hydroxytryptamine-$_4$ agonists, including prucalopride and velusetrag, and the neurokinin-$_1$-receptor antagonists aprepitant and tradipitant should be considered.
   g. Head-to-head trials of TCAs vs acid suppressant drugs, such as PPIs or histamine-$_2$-receptor antagonists, as first-line drug therapy for FD in primary care.

PATIENT SUMMARY

This guideline has been produced on behalf of the British Society of Gastroenterology (BSG) to update the previous one published in 1996. The guideline has been written by a team of specialists including gastroenterologists, psychiatrists, general practitioners (GPs) and physiologists. Patients have reviewed the guideline and added their perspective. The guideline is intended for healthcare professionals who look after patients with FD.

Dyspepsia, often referred to as indigestion, is very common. It consists of symptoms such as pain or burning in the upper part of the abdomen (tummy), feeling abnormally full-up early on in a meal, or experiencing a heaviness in the abdomen that may be worse after eating. These symptoms arise from problems with the stomach or the first part of the small intestine, called the duodenum. Together these are referred to as the upper gut. Sometimes these symptoms can be due to an underlying cause, such as an ulcer. However, in most cases, tests find no abnormality and this condition is referred to as FD.

Importantly, normal test results do not mean that there is no cause for FD. It is caused by issues with the two-way communication between the upper gut and the brain. Problems with the nerves supplying the stomach and duodenum may make them more sensitive to normal function. Sometimes the stomach may be slower to empty, contributing to feelings of early fullness. Psychological factors, such as stress, certain foods or changes in the micro-organisms (bugs) living in the upper gut may also play a role in triggering symptoms.

Some patients with FD learn to manage their symptoms themselves, by changing their lifestyle or diet or managing stress differently. Other patients will consult with their GP who can normally make a diagnosis of FD based on typical symptoms. However, if patients are older when their symptoms start, or if they have a family history of cancer of the oesophagus (gullet) or stomach, referral to a specialist for further tests is required. This may include a camera test (endoscopy) to look inside the oesophagus, stomach and duodenum, or a scan of the abdomen to exclude any serious cause for symptoms. Even among patients who undergo further investigation, the likelihood of finding serious problems, like cancer, remains low.

Regular exercise and lifestyle changes, like avoiding certain foods that may trigger symptoms, will be helpful for some patients. However, these is no evidence for any specialised diets for treating FD and restricting diet too much could lead to malnutrition or abnormal eating habits.

All patients with FD should be offered a stool test or breath test to look for a stomach infection called *H. pylori*. If the test is positive, they should receive a short course of antibiotic treatment for the infection to see if their symptoms improve. Patients who test negative, or patients who test positive, but whose symptoms continue after antibiotics, should be offered other medications to treat their symptoms.

This guideline has reviewed the evidence for which medications work, and the possible harms they may cause. We have only recommended medications with good evidence that they are more efficacious than a placebo. We have not recommended tests or treatments where the evidence is that they do not help, are harmful, or where there is not enough evidence. Some medications have most of their effect in the gut, often working to reduce stomach acid or helping the stomach to empty more quickly. Other drugs work at the level of the brain and the nervous system also present in the upper gut. These are so-called 'neuromodulators', and they help reduce the abnormal sensitivity of these nerves. Unfortunately, not all drugs that may be efficacious in FD are available in all countries.

There is some evidence to suggest that psychological or behavioural therapies may be beneficial for treating symptoms in FD. These therapies use the fact our brain and upper gut nerves are connected and can influence each other. With appropriate training our brain can help control the sensations from our upper gut. Work is needed to improve the availability of these treatments for patients.

Very severe symptoms that do not respond to any of the treatments discussed above are rare. In this situation, it is recommended that patients are managed by a multidisciplinary team of specialists, including GPs, dietitians, gastroenterologists and psychologists. This should help to ensure that patients have access to high-quality, expert, advice based on up-to-date research, while reducing harm from unnecessary investigations and procedures, or harmful drugs.

Our knowledge of the causes and treatment of FD has improved over the past 20 years. However, there are still things that we do not fully understand about the condition. This means that there are many active areas for future research and new treatments to be explored. We hope that this guideline will also help to highlight and prioritise these issues.

INTRODUCTION

Aims

The previous BSG dyspepsia management guidelines were published in 1996.[1] In the intervening years, an extensive amount of new evidence has emerged, improving understanding of the pathophysiology, diagnosis, investigation, and management of the condition. Importantly, it has been recognised that FD accounts for the majority of cases of dyspepsia seen in clinical practice,[2] and that FD is a DGBI. In addition, the Rome criteria, the gold-standard symptom-based diagnostic criteria for FD, are now in their fourth iteration.[3] Consequently, the primary aim of this guideline, commissioned by the BSG, was to consider all of these developments and create a new clinical guideline for the management of FD, including the initial diagnostic approach to the patient presenting with dyspepsia. The guideline is intended to be practical to use and to provide an authoritative framework for current, state-of-the-art, evidence-based clinical practice. It has been reviewed by the BSG Clinical Services and Standards Committee and selected reviewers from the BSG Council.

Methodology

A guideline working group was convened. In keeping with the recommendations of the Appraisal of Guidelines for Research and Evaluation guideline development protocol,[4] this comprised a diverse multidisciplinary team of clinicians and academics encompassing expertise from primary, secondary and tertiary care, together with liaison psychiatry. The working group also included representation from two patients who reviewed both the initial proposal and the final guideline to ensure implementation of a patient-centred approach.

Each section of the guideline was allocated a lead author responsible for performing a comprehensive literature search. Additionally, the section covering treatment was informed by a systematic review of the literature, the methodology for which is reported within that section. Eligible studies were graded according to the Oxford Centre for Evidence Based Medicine.[5] The Grading Recommendations Assessment, Development and Evaluation system was used to evaluate the strength of the recommendations and the overall quality of evidence.[6] Recommendations for each section were made based on the relevant evidence, informed by the literature searches, and were approved by all members of the working group, who met regularly. No formal Delphi voting process was used, but all recommendations achieved complete consensus following extensive review and discussion among the entire working group.

Conflicts of interest

All members of the guideline working group were asked to complete conflicts of interest declarations. These are available as online supplemental table.

Scheduled review

We would suggest these guidelines are reviewed and updated every 5 years.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Over the last 35 years, definitions of dyspepsia have evolved from a broad one, which included any symptom felt to be attributable to the stomach and duodenum, including heartburn, nausea or vomiting,[7] to one that includes only the cardinal symptoms of epigastric pain or burning, postprandial fullness, or early satiation (the feeling of fullness during ingestion of a meal, which acts as a terminating factor). Recent definitions recognise that belching, nausea, or upper abdominal bloating can also be present, but heartburn alone is not a symptom of dyspepsia, although it can coexist.[3] Vomiting is atypical and, if present, should prompt consideration of another disorder. FD is diagnosed in the absence of a structural abnormality to explain the symptoms. Therefore, to make a diagnosis, by definition, patients need to have been investigated to exclude evidence of organic, systemic or metabolic disease.

Symptoms alone are not reliable in distinguishing functional from organic causes of dyspepsia.[8] Nevertheless, 80% of people with dyspepsia will be diagnosed with FD following endoscopy.[2] FD is defined according to symptom-based diagnostic criteria developed by the Rome Foundation, and is classified into two distinct subtypes: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) (table 1).[3] Clinically, the EPS subtype separates those with epigastric pain or burning that is often present regardless of meals, from those with PDS who report early satiation and postprandial fullness, mainly triggered by meals. It is, however, recognised that patients with FD can have overlapping features of EPS and PDS, particularly in secondary and tertiary care.[9–11]

It is important to note how diagnostic criteria for FD have evolved over time. The Rome Foundation has attempted to define the minimum thresholds for frequency and severity of each individual symptom more precisely. For example, in the latest iteration, Rome IV, the term 'bothersome' is used to describe symptoms severe enough to interfere with daily activities. Moreover, the Rome IV criteria for FD require PDS symptoms to occur three times per week, and for EPS symptoms to occur at least once per week.[3] However, one of the more contentious issues when using the Rome IV criteria for FD in routine clinical practice is the requirement to have experienced symptoms for the last 3 months, with symptom onset at least 6 months before diagnosis.[3]

Although from a scientific and research perspective the Rome IV process may have improved the specificity of diagnostic criteria for FD,[9 12] the Rome Foundation has recently acknowledged that the restrictive symptom duration required limits the applicability of the Rome IV criteria for FD in routine clinical practice and could, potentially, delay its diagnosis and subsequent treatment.[13] This issue has also been highlighted by global epidemiological studies that have demonstrated a much lower prevalence of FD using the Rome IV criteria, compared with previous iterations.[14] In this context, the Rome Foundation has, therefore, developed less restrictive 'clinical criteria' for use in routine clinical practice.[13] These clinical criteria for FD only require the cardinal symptoms to have been present for 8 weeks, but are otherwise unchanged.[13] There is emerging evidence that the future classification of FD may benefit from incorporating clinical features beyond upper gastrointestinal symptoms. Recent data using latent class analysis have identified discrete patient phenotypes based on the relative extent of coexisting extraintestinal and psychological symptoms.[15] However, the clinical utility of this novel approach requires further validation.

Of particular importance, FD and gastroparesis are symptom-based constructs with significant overlapping features, which cannot be fully distinguished on the basis of either symptoms or gastric emptying studies.[16 17] The gastroparesis construct may over-emphasise motor deficits to the detriment of a more holistic approach,[18] and so the terms FD with or without delayed gastric emptying may be preferable.[19]

Table 1 The Rome IV criteria for functional dyspepsia[3]

Diagnostic criteria for functional dyspepsia	
One or more of the following: ► Bothersome epigastric pain. ► Bothersome epigastric burning. ► Bothersome postprandial fullness. ► Bothersome early satiation. ► Symptom onset at least 6 months prior to diagnosis. ► Symptoms should be active within the past 3 months. ► And, no evidence of structural disease (including at upper endoscopy) likely to explain the symptoms.	
Diagnostic criteria for epigastric pain syndrome (EPS)	**Diagnostic criteria for postprandial distress syndrome (PDS)**
Must include *one* or *both* of the following symptoms at least 1 day a week. 1. Bothersome epigastric pain (ie, severe enough to impact on usual activities). 2. Bothersome epigastric burning (ie, severe enough to impact on usual activities). Supportive criteria: 1. Pain may be induced by ingestion of a meal, relieved by ingestion of meal or may occur while fasting. 2. Postprandial epigastric bloating, belching and nausea can also be present. 3. Persistent vomiting likely suggests another disorder;. 4. Heartburn is not a dyspeptic symptom, but may often coexist. 5. The pain does not fulfil biliary pain criteria. 6. Symptoms that are relieved by evacuation of faeces or gas generally should not be considered as part of dyspepsia. 7. Other digestive symptoms (such as gastro-oesophageal reflux disease and irritable bowel syndrome) may coexist with the EPS.	Must include one or both of the following symptoms at least 3 days a week: 1. Bothersome postprandial fullness (ie, severe enough to impact on usual activities). 2. Bothersome early satiation (ie, severe enough to prevent finishing a regular sized meal). Supportive criteria: 1. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present. 2. Vomiting warrants consideration of another disorder. 3. Heartburn is not a dyspeptic symptom, but may often coexist. 4. Symptoms that are relieved by evacuation of faeces or gas should generally not be considered as part of dyspepsia. 5. Other individual digestive symptoms or groups of symptoms (such as gastro-oesophageal reflux disease and irritable bowel syndrome) may coexist with PDS.

EPIDEMIOLOGY

There have been numerous population-based studies reporting the prevalence of dyspepsia, summarised in previous systematic reviews and meta-analyses.[14 20] Prevalence using a broad definition of dyspepsia is estimated to be almost 30% at any one point in time.[20] However, this falls with each successive iteration of the Rome criteria.[14] Using the Rome IV criteria, prevalence was estimated at 7% in the recent Rome Foundation global survey, although this varied between individual countries with the lowest reported prevalence 2.4% in Japan, and the highest 12.3% in Egypt.[21] Risk factors for dyspepsia in the community include female sex, smoking, use of non-steroidal anti-inflammatory drugs (NSAIDs) and *H. pylori* infection,[20 22] although these associations are modest.

It is important to understand that most individuals with dyspepsia in the community will have FD as the underlying cause. A previous systematic review and meta-analysis of population-based studies performing endoscopy in individuals with dyspepsia, published in 2010,[2] reported that 13% had erosive oesophagitis, 8% peptic ulcer and less than 0.5% gastro-oesophageal cancer. The remainder would, therefore, be labelled as having FD. Although few of the included studies used the Rome criteria, this estimate is borne out by a more recent study from Bangladesh,[23] reporting that among healthy individuals with Rome III-defined dyspepsia in the community subjected to endoscopy, 20% had either peptic ulcer or erosive oesophagitis, with the remainder having no organic cause for their dyspepsia. Therefore, consistently, around 80% of people with dyspepsia in community surveys are likely to have FD and, as a result, population-based cross-sectional surveys provide a close approximation of the true prevalence of FD.

The division of FD into the subtypes of EPS and PDS dates from the development of the Rome III criteria.[24] These subgroups were established due to the observation that meal-related symptoms were predominant in a subgroup of patients,[25] and certain symptoms clustered together in factor analysis studies.[26] Although the aim of these subgroups is to identify groups of patients who respond better to a particular drug, there is little evidence to support this,[27] and overlap of EPS and PDS occurs in up to one-third of patients with Rome III-defined dyspepsia seen in referral populations.[10 11] However, preliminary evidence suggests that if the Rome IV criteria are adapted to classify those with any form of postprandial symptoms as having PDS, overlap is reduced to less than 20%.[28]

In terms of risk factors for FD, these include younger age, female sex, higher levels of somatoform-type symptom reporting, and other DGBI, including IBS.[29 30] Evidence for any association between socioeconomic status and FD is conflicting.[31 32] Impact of ethnicity has not been explored extensively, although a Malaysian multiethnic study reported that FD was less prevalent in Chinese participants.[33] The Rome Foundation global survey will likely study many of these potential risk factors in more detail in the future.[21] Psychological comorbidity is well known to play a role in the development of FD, with new onset of symptoms more likely in those with a history of anxiety or depression.[34 35] Some investigators have reported that a history of abuse is more common in FD.[36] Finally, similar to IBS, acute enteric infection is associated with the new onset of symptoms,[37] termed postinfection FD. A meta-analysis reported an almost threefold odds of developing FD 6 months or more after acute gastroenteritis.[38]

Symptoms of FD fluctuate, but are chronic in around two-thirds of patients,[39] and even among those who no longer meet criteria for FD, often their gastrointestinal symptoms have fluctuated to those of another DGBI.[40–42] The incidence of FD is less well-studied, but is estimated at between 3% and 5% per year.[39 43] There is no effect of FD on mortality.[44 45] However, it has a substantial impact on quality of life,[29] consultation rates with a physician are around 40%,[46 47] and presenteeism and absenteeism common.[48] The economic consequences of FD are, therefore, considerable, estimated at US$18.4 billion in the USA in 2009.[49]

PATHOPHYSIOLOGY

FD is a DGBI associated with abnormalities in motility, including delayed gastric emptying and impaired fundic accommodation,

visceral sensitivity to both physical and chemical stimuli, central nervous system processing, psychopathology, immune function, changes in the gastric and small bowel microbiome, epithelial permeability, and genetics.[50 51] Not all of these abnormalities are present in all patients, and if and how they associate with each other, and with dyspeptic symptoms themselves, requires clarification.

Altered motor function

Delayed gastric emptying and impaired fundic accommodation are well-recognised motor abnormalities affecting a subset of patients,[52 53] but they do not appear to be specific to either PDS or EPS.[53] Delayed gastric emptying is more frequent in some patients with early satiation, bloating, postprandial fullness, nausea and vomiting,[54 55] but this association is weak.[56] In fact, a recent multicentre study of tertiary care patients with chronic upper gastrointestinal symptoms reported that FD is indistinguishable from gastroparesis based on symptoms, gastric emptying testing and pathological features, such as loss of interstitial cells of Cajal and $CD206^{+}$ macrophages.[16] The authors concluded that both FD and gastroparesis may be part of the same spectrum of pathological gastric neuromuscular dysfunction, but this requires further study. Accelerating gastric emptying can associate with symptom improvement, but this appears to be influenced by whether optimal methods are employed to measure gastric emptying, including either scintigraphy or breath testing for at least 3 hours following a solid meal.[57] Impaired fundic accommodation associates with reduced drinking capacity, early satiation, postprandial fullness and weight loss.[52 58] Restoring fundic accommodation can improve symptoms.[52 58] Rapid gastric emptying has also been found in a subset of patients with FD and may represent another less considered therapeutic target.[59 60] Antral hypomotility and abnormal duodenal motility have also been reported.[61 62]

Altered visceral sensitivity

Both mechanical and chemical hypersensitivity have been demonstrated in subgroups of fasted patients with FD.[63–65] Mechanical sensitivity to balloon distension of the stomach is further increased following meal ingestion,[66] and associates with postprandial pain, and non-painful sensations, such as fullness, bloating and belching.[63 66 67] It is, therefore, not surprising that mechanical hypersensitivity is not specific to either EPS or PDS.[53] Increasing symptom severity, however, does associate with increasing mechanical sensitivity.[68]

Chemical sensitivity to exogenous and endogenous acid has been reported in a subset of patients.[69–71] Both acid infusion and excessive endogenous duodenal acid exposure worsen dyspeptic symptoms, particularly nausea, and are associated with decreased duodenal motility and clearance of acid from the duodenum.[69 70] Duodenal dysmotility may explain, in part, why some patients experience dyspeptic symptoms, despite secreting normal amounts of gastric acid.[72 73] Duodenal acid infusion has also been shown to increase visceral sensitivity to gastric distension and inhibit gastric accommodation following a meal in healthy volunteers,[74] both of which are pathophysiological features found in some patients with FD. Likewise, there is good evidence that lipid,[75] but not carbohydrate or protein,[76 77] infusion into the duodenum increases visceral sensitivity to gastric distension, an effect that is reduced by cholecystokinin-A receptor antagonism.[75] Lastly, capsaicin, which is the spicy component of red peppers, can induce nausea, warmth and pain, the severity of which is worse in patients with FD, compared with healthy volunteers.[78] This is mediated via activation of the transient receptor potential cation channel subfamily V member 1 (TRPV1), which leads to release of neurotransmitters, such as substance P and calcitonin gene-related peptide, and increased visceral sensitivity.[79] Recent studies suggest that TRPV1 receptors may be upregulated in FD,[80] and these can be activated by noxious temperatures, acid, mechanical stimulation, inflammatory mediators, nerve growth factors and prostaglandins.[81]

Central nervous system

Dyspeptic symptoms are often triggered or exacerbated by experimental mechanical (eg, balloon distension) and chemical (eg, food, fat) stimulation of the stomach and small intestine, or by stress and psychosocial comorbidities. Vagal and spinal pathways convey mechanical and chemical signals, along with signals from the microbiota, the immune system, and the endocrine systems of the gastrointestinal tract to the brain, including the nucleus of the solitary tract in the medulla for vagal pathways, and lamina I of the dorsal horn for spinal pathways. Subsequent brain processing appears to be disordered in patients with FD.[82 83] Studies using positron emission tomography or functional MRI, usually involving mechanical gastric distension, have reported structural and/or functional abnormalities in regions of the brain concerned with sensory and pain modulation, emotion, saliency, homoeostatic processing and descending pain modulation.[82 83]

Psychology

Anxiety and depression often associate with FD, although a causal relationship has not been confirmed.[50] Stress, in the form of pain or psychological comorbidities, can upregulate the hypothalamic–pituitary–adrenal axis and increase levels of corticotrophin-releasing hormone,[83] which activates local inflammatory processes, potentially affecting gut function, including epithelial permeability, immune function and the microbiome.[84] Indeed, anxiety has been shown to associate with duodenal eosinophilia in FD.[85] In response to stress, eosinophils release substance-P and corticotrophin-releasing hormone,[86] leading to mast cell activation and increased epithelial permeability. These peripheral changes may, in turn, alter afferent signalling to the brain, increasing bi-directional crosstalk between the gut and brain and, perhaps, the brain's neuroplasticity.

Stress and psychological comorbidities can also associate with autonomic nervous system dysfunction.[83] There is evidence from various small studies using the insulin hypoglycaemia test, sham feeding and spectral analysis of cardiac R-R interval that vagal tone may be reduced in patients with FD.[51] Moreover, reduced vagal tone has been shown to associate with delayed gastric emptying,[87] and slow deep breathing, which activates the vagus, improves nutrient volume tolerance and quality of life.[88]

Immune function, inflammation and epithelial permeability

Low-grade mucosal inflammation, especially in the duodenum has been observed and proposed as an important pathophysiological mechanism in patients with FD.[89] A recent meta-analysis reported increases in both eosinophils and mast cells in the stomach and duodenum of patients, compared with healthy controls.[89] In addition, elevated duodenal eosinophil levels were observed in both EPS and PDS. Observations regarding other inflammatory cells, such as enterochromaffin cells, neutrophils and intraepithelial lymphocytes are inconsistent,[89 90] although increased duodenal intraepithelial lymphocytes were observed in *H. pylori*-positive patients.[91] However, decreased expression of two lymphocyte activation markers, CD95/Fas (involved in

cell apoptosis) and HLA-DR (involved in B-cell proliferation), could reflect an altered population of duodenal lymphocytes in patients with FD.[91 92]

Notably, increased numbers of activated eosinophils and mast cells in the duodenal mucosa of patients correlate with both impaired duodenal mucosal integrity and reduced expression of cell-to-cell adhesion proteins,[93] as well as functional and structural submucosal neuronal changes.[94] Furthermore, studies have shown increased CD4+α4β7+CCR9+small bowel-homing T lymphocytes and cytokine levels correlate with delayed gastric emptying and the intensity of dyspeptic symptoms, including epigastric pain, nausea and vomiting.[95] It remains unclear to what extent impaired barrier function arises from an aberrant immune and stress response, or dysbiosis, or whether low-grade inflammation arises from a compromised epithelial barrier, dysbiosis or altered stress levels.

The microbiome

There is growing evidence that oesophageal,[96] gastric[96–98] and duodenal dysbiosis associate with FD,[96 99–101] and that such alterations in the microbiome may lead to disturbed motility and visceral sensitivity, via alterations in mucosal integrity, neuronal activity and immunity.[102] However, observations vary across studies,[96–98 101 103 104] likely in part because of other influencing factors, such as the fact that transfer of intestinal contents into the stomach, such as bacteria and bile acids, modify the microbiome[97 98] or the use of PPI therapy.[103 104] Lastly, small intestinal microbial dysbiosis does not correlate with small intestinal bacterial overgrowth, which usually reflects an overgrowth of anaerobes and does not associate with gastrointestinal symptoms.[100] However, small intestinal microbial diversity correlates inversely with small intestinal permeability and the appearance or worsening of gastrointestinal symptoms.[100] *H. pylori* infection is associated with dyspepsia in the community, but the magnitude of this association is modest.[22]

Genetics

Early studies support a familial genetic predisposition to FD,[105] but studies examining specific gene candidates have been conducted in small numbers of patients with FD and controls and their findings are, therefore, equivocal.[51 106] A more recent large-scale survey of comorbidity and genetic predisposition in FD confirmed a weak heritability of only 5%, but also suggested considerable clinical and genetic overlap with other conditions, including other gastrointestinal disorders, such as IBS and gastro-oesophageal reflux disease (GORD), personality traits, mood disorders and, interestingly, non-gastrointestinal diseases, such as rheumatological disorders and, to a lesser extent, cardiovascular disease.[106] This study also suggested genes likely to play a role in FD, namely those involved in synaptic transmission and neuroplasticity, and gastrointestinal development and integrity. However, additional large-scale studies are required to confirm these findings and identify other potential gene candidates.

PRESENTATION OF FD, DIAGNOSIS AND MANAGEMENT IN PRIMARY CARE

Overview

As previously stated, most patients with dyspepsia will have FD as the underlying cause and, therefore the term 'dyspepsia' in both primary and secondary care is likely to be synonymous with FD. Primary care remains the first point of contact for patients with dyspepsia in most of Europe, and many will be managed only in that setting. Gastrointestinal symptoms account for up to 10% of consultations in primary care, 50% of which are for upper gastrointestinal symptoms, such as dyspepsia.[107] In the UK, there are one million consultations per day in primary care and, therefore, 50 000 of these are likely to be for dyspepsia or other upper gastrointestinal symptoms.[108] Patients in primary care often present with undifferentiated symptoms, involving different body systems,[109 110] and the role of the GP is to formulate a working diagnosis to guide management.

Evolving definitions of dyspepsia over the last 30 years have left both GPs and gastroenterologists confused and, in reality, a specific working diagnosis as to the exact cause of dyspepsia is rarely made. Moreover, FD is still considered a diagnosis of exclusion, via endoscopy,[3] even though 80% of people with dyspepsia will be diagnosed with FD after this investigation.[2] In addition, endoscopy is not always readily available in primary care, and GPs may be discouraged from requesting endoscopy because of long-waiting lists and financial implications.

Recommendations

- Clinicians should be aware that most patients with dyspepsia will have FD as the underlying cause of their symptoms after investigation (recommendation: strong, quality of evidence: low).

Clinical history taking in dyspepsia

Clinical history taking in a patient with dyspepsia should commence with the collection of information concerning the duration and nature of the symptoms. The clinician should elucidate the actual commencement of symptoms, as the patient tends to remember only when symptoms got worse. This is particularly important because a longer symptom duration favours FD over organic disease. The patient should be asked about all possible upper gastrointestinal symptoms, including 'red flags', or alarm symptoms and signs. The clinician should enquire about epigastric pain or burning, early satiation, postprandial fullness, heartburn, nausea, vomiting, haematemesis, belching, regurgitation, dysphagia, including the level at which food sticks, and rumination, ensuring the patient understands what he/she means. There is some evidence that using pictograms can facilitate understanding of these terms by patients.[111] Weight loss is reported frequently by patients with FD.[52 63] Depending on the patient's age, this may be considered an alarm symptom, so attention should be paid to obtaining objective evidence of this. In the context of dyspepsia, guidelines for the assessment of patients with suspected gastro-oesophageal cancer from the National Institute for Health and Care Excellence (NICE) recommend that an urgent 2-week wait endoscopy should be offered in patients aged ≥55 years old with dyspepsia and weight loss, and non-urgent endoscopy considered in patients aged ≥55 years old with treatment-resistant dyspepsia, or aged ≥55 years old with dyspepsia with either nausea or vomiting or a raised platelet count.[112] The latter recommendation stems from a significant association between thrombocytosis and gastro-oesophageal cancer in a case–control study of almost 40 000 patients aged over 40 years in UK primary care.[113] All upper gastrointestinal alarm symptoms and signs relevant to suspected gastro-oesophageal cancer, as per NICE, are detailed in box 1. However, it is important to point out that these criteria were selected using a threshold of a positive predictive value for gastro-oesophageal cancer of only ≥3%.

In the absence of alarm symptoms or signs, FD is highly probable when epigastric pain or burning, early satiation, and/or postprandial fullness are reported, in line with the Rome IV

Box 1 Upper gastrointestinal alarm symptoms or signs* that are referral criteria for suspected gastro-oesophageal cancer according to NICE.[112]

Definite referral criteria for urgent endoscopy to assess for gastro-oesophageal cancer

1. People of any age with dysphagia
2. People aged ≥55 years with weight loss and any of the following:
   i. Dyspepsia.
   ii. Upper abdominal pain.
   iii. Reflux.

Probable referral criteria for non-urgent endoscopy to assess for gastro-oesophageal cancer

1. People with haematemesis.
2. People aged ≥55 years with:
   i. Treatment-resistant dyspepsia.
   ii. Dyspepsia with raised platelet count or nausea or vomiting.
   iii. Upper abdominal pain with low haemoglobin, raised platelet count or nausea or vomiting.
   iv. Reflux with raised platelet count, or nausea or vomiting.
   v. Nausea or vomiting with any of the following: weight loss, reflux, dyspepsia, or upper abdominal pain.

*An upper abdominal mass felt to be consistent with stomach cancer is a probable referral criterion for an outpatient clinic appointment within 2 weeks.
NICE, National Institute for Health and Care Excellence.

criteria, and endoscopy is unlikely to change the diagnosis, even though a normal endoscopy is required as part of these diagnostic criteria. In routine clinical practice, therefore, clinicians can use the recently proposed Rome IV clinical criteria,[13] which require the presence of one of more of these four cardinal symptoms, if reported as bothersome, for more than 8 weeks. Other symptoms can coexist but should not be predominant. Information about the characteristics of pain should be recorded. Usually, in FD, pain is in the upper abdomen or epigastrium, and may be present in fasting conditions, and/or precipitated or exacerbated by meal ingestion. Unlike in IBS, abdominal pain in FD is unrelated to the need to defaecate. All of this may help to differentiate patients with FD from those with IBS or to identify patients with FD with overlapping IBS, which can be of any subtype, and is reported to occur in up to 50% of patients.[114] In this situation, the patient will report the presence of two different types of abdominal pain, one related and one unrelated, to defaecation. Other functional bowel disorders, including functional diarrhoea, functional constipation, or functional abdominal bloating and distension can also overlap with FD.[21 115] Gastro-oesophageal reflux symptoms also coexist in approximately one-third of patients with FD and, in this situation, evidence suggests that clinicians tend to favour a diagnosis of GORD over that of FD.[116 117] The presence of a burning sensation that starts in the epigastrium but radiates to the chest may help to differentiate the heartburn of GORD from the epigastric pain of dyspepsia. The presence of eating disorders, or of disordered eating behaviour, is recognised increasingly in patients with FD, as discussed later.

Potential aetiological triggers should be screened for, including previous acute enteric infection, present in about 10% of patients.[118] Reported associated pathogens include Norovirus, Giardia lamblia, Salmonella spp, *Escherichia coli* O157 and Campylobacter spp.[51] The Kyoto consensus statement considers that dyspepsia associated with *H. pylori* infection should be considered a separate entity, referred to as *H. pylori*-associated dyspepsia,[119] and that only if symptoms persist after successful eradication of the infection should the patient be diagnosed with FD. However, there is little evidence to support this stance. Data are emerging about a possible role of COVID-19 infection in triggering some DGBI,[120] but more evidence is necessary to confirm this as a risk factor for FD. Psychological factors, in particular anxiety, have been reported to be associated with future development of FD in several longitudinal follow-up studies.[34 35 121] A pooled analysis of three population-based studies also identified smoking as a risk factor for PDS,[122] but not EPS. Evidence for any contribution of other lifestyle factors is conflicting.

Other relevant items in the clinical history include previous surgical interventions, due to misattribution of the symptoms of FD to other causes, such as gallstones,[123] and the presence of other non-gastrointestinal chronic painful or 'functional' disorders,[124 125] which support a diagnosis of FD. It is also important to ensure there is no family history of gastro-oesophageal cancer, inflammatory bowel disease, or coeliac disease. Recent changes in diet, alcohol excess or drugs that can alter gut motility, such as opioids or NSAIDs, are also relevant. In addition to their well-known role in inducing gastrointestinal damage, the latter have been found to be associated with dyspepsia in multiple population-based studies.[20] As some might consider collecting all the above information to be difficult in a busy clinical practice, an aide memoire is provided in figure 1.

Recommendations

- We recommend that, in the absence of upper gastrointestinal alarm symptoms or signs, clinicians should diagnose FD in the presence of bothersome epigastric pain or burning, early satiation, and/or postprandial fullness of greater than 8 weeks duration (recommendation: strong, quality of evidence: very low).

Communicating a diagnosis and management plan

It is important to build rapport and trust in the doctor–patient relationship by adopting the principles of empathic listening to optimise the consultation.[126] The clinician should appear confident and, after the clinical assessment is complete, communicate a positive diagnosis of FD based on presence of typical symptoms. This needs to be done using simple words and explanations. It should be explained that FD is a chronic disorder,[39–41] with recurrent fluctuating symptoms triggered by some of the factors mentioned above, but is not associated with an increased risk of cancer or mortality.[44 45] FD should be explained as a DGBI that can be impacted by diet, stress, cognitive, behavioural, or emotional responses to symptoms, and postinfection changes. This aims to assist the patient in understanding and accepting the diagnosis and engaging with a shared management plan. It is particularly important to explain the mechanisms of action, potential side effects and rationale for the use of dietary modifications, drugs, or behavioural treatments within the context of the gut–brain axis. This approach is supported by a recent RCT conducted in patients with dyspepsia without alarm symptoms comparing a self-managed web-based educational intervention vs prompt endoscopy. This demonstrated that the web-based educational intervention, which explained normal gastric function, the natural history of dyspepsia, and the role and limited added value of endoscopy in its management, significantly decreased the number of endoscopies required to manage the condition

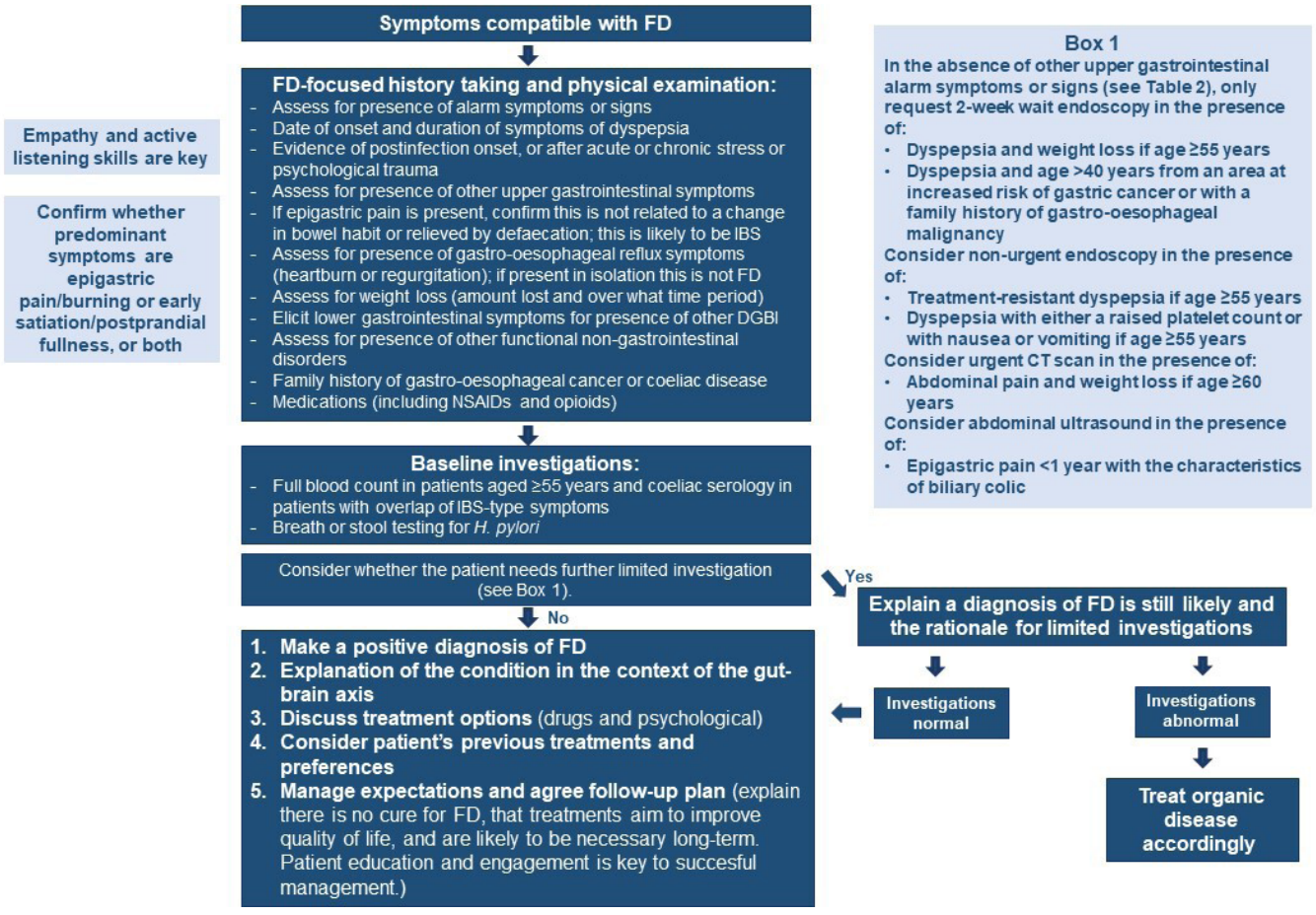

Figure 1 Diagnostic algorithm for functional dyspepsia. DGBI, disorder of gut–brain interaction; FD, functional dyspepsia.

and was associated with similar improvements in symptoms and quality of life, compared with prompt endoscopy.[127]

Recommendations

- Establishing an effective and empathic doctor–patient relationship and a shared understanding is key to the management of FD. This may reduce healthcare utilisation and improve quality of life (recommendation: strong, quality of evidence: very low).
- We recommend that the diagnosis of FD, its underlying pathophysiology, and the natural history of the condition, including common symptom triggers, should be explained to the patient. FD should be introduced as a DGBI, together with a simple account of the gut–brain axis and how this is impacted by diet, stress, cognitive, behavioural, and emotional responses to symptoms, and postinfective changes (recommendation: strong, quality of evidence: very low).

Management of dyspepsia in primary care

The initial approach to the diagnosis and management of dyspepsia in primary care is empirical, based on the knowledge of the patient, their circumstances and the requirement to manage the symptoms. GPs are also aware of the need to avoid overwhelming secondary care services and must balance any requirement for referral with other patient-related factors. The key first step in the initial management is the exclusion of the possibility of upper gastrointestinal cancer, via judicious application of alarm symptoms and signs. However, as mentioned earlier, the performance of these in predicting malignancy as a cause of dyspepsia is modest,[128] perhaps due to the absence of a clear definition of each (eg, the amount of weight that needs to be lost to qualify as an alarm symptom). In addition, as symptoms alone do not discriminate FD from organic conditions,[8] historically, prompt endoscopy was considered mandatory to exclude gastro-oesophageal malignancy in all patients with dyspepsia. However, the yield of this approach to detect cancer is low.[129 130] A previous systematic review and meta-analysis of studies performing endoscopy in individuals with dyspepsia in the community demonstrated that 13% had erosive oesophagitis, 8% peptic ulcer and less than 0.5% gastro-oesophageal malignancy, with the remaining 80% of individuals having a normal endoscopy and, therefore, likely having FD.[2] Given this meta-analysis included several studies conducted over 20 years ago, before the widespread use of *H. pylori* eradication therapy and PPIs, this suggests that the prevalence of organic pathology at endoscopy is likely to be even lower in the current era. In one study, the cost of diagnosing each case of malignancy in primary care detected via endoscopy was estimated at over US$80 000.[131] For a health service with a finite budget, this is probably prohibitive. Prompt endoscopy might be justified on the basis of providing reassurance to the individual patient that there is no sinister underlying cause for their symptoms, but this effect appears to be relatively short-lived.[132]

In terms of other investigations, there is a lack of evidence to support the role of routine laboratory testing to exclude other organic diseases in all patients with dyspepsia. However, a full blood count should be performed in patients aged ≥55 years, in line with NICE recommendations concerning possible

non-urgent endoscopy in patients with dyspepsia in the presence of a raised platelet count. Screening for coeliac disease is not recommended, as the prevalence is not increased compared with the healthy population.[133] However, this should be performed in patients with overlapping dyspepsia and IBS-type symptoms, as the latter do have an increased risk of coeliac disease.[134] Beyond this, several management strategies for dyspepsia exist, detailed below.

It is estimated that 5% of dyspepsia in the community is attributable to *H. pylori*.[22] In addition, a positive test for *H. pylori* will identify most cases of peptic ulcer disease as an underlying cause of dyspepsia,[135] for which eradication therapy is extremely efficacious.[136] Therefore, testing for *H. pylori* and eradicating the bacterium in patients with dyspepsia in primary care who are found to be infected is logical. This is termed a 'test and treat' strategy and can be done via faecal antigen or carbon-urea breath testing, where available, which have a similar accuracy to rapid urease testing of biopsies obtained at endoscopy.[137 138] *H. pylori* serology is not recommended as an alternative, as the specificity is lower than other non-invasive tests.[139–141] Given that most patients with dyspepsia in primary care will have FD as the cause,[2] repeat testing to confirm successful treatment after an initial course of eradication therapy is not recommended,[142] although a meta-analysis suggested the magnitude of the effect of eradication therapy in FD was larger if *H. pylori* had been successfully treated.[143]

Given that approximately 20% of patients with dyspepsia will have either peptic ulcer or erosive oesophagitis as the underlying cause,[2] the use of empirical acid suppression therapy as a potential management strategy is a reasonable one, as this is an efficacious treatment for both.[144 145] There is also evidence to suggest that PPI therapy is an efficacious treatment for FD.[146] Other empirical approaches studied include a symptom-based strategy, based on historical subgrouping of patients with dyspepsia,[147] with those with 'reflux-like' or 'ulcer-like' dyspepsia, who probably had EPS, treated with acid suppression and those with 'dysmotility-like' dyspepsia, now termed PDS, a prokinetic drug.

In an attempt to ration use of endoscopy, another approach that has been examined has been to test for *H. pylori* and only perform endoscopy in those who test positive, based on the theory that these individuals are more likely to have an organic explanation for their symptoms, a so-called 'test and scope' approach. However, this has not been shown to be any more effective than other management strategies,[148 149] and has never been adopted formally.

There have been multiple RCTs comparing these various management strategies, including prompt endoscopy, for dyspepsia head-to-head. However, until recently, there was equipoise between some of them, and uncertainty as to which was the optimal first-line approach. Pairwise meta-analyses, and even individual patient data meta-analyses, were unable to resolve this uncertainty completely. Although prompt endoscopy is expensive, it was superior to empirical acid suppression or symptom-based management in terms of effect on symptoms in some RCTs,[148 150] and was superior to 'test and treat' in an individual patient data meta-analysis, but it was not cost-effective.[129] Another individual patient data meta-analysis of 'test and treat' versus empirical acid suppression demonstrated no difference in either costs or effects between the two strategies.[130] Guidelines to date have, therefore, recommended the use of either first-line,[142 151] depending on local prevalence of *H. pylori* infection, because a modelling study suggested that 'test and treat' was unlikely to remain cost-effective below a prevalence of infection of 20%.[152]

A recent network meta-analysis identified 15 eligible RCTs comparing prompt endoscopy, 'test and treat', 'test and scope', empirical acid suppression, and symptom-based management, recruiting 6162 patients.[153] This demonstrated that, although no strategy was superior to another, 'test and treat' ranked first in terms of reducing the relative risk (RR) of remaining symptomatic at 12 months (RR of remaining symptomatic=0.89; 95% CI 0.78 to 1.02), with prompt endoscopy ranked second (RR of remaining symptomatic=0.90; 95% CI 0.80 to 1.02). In addition, patients allocated to 'test and treat' were significantly less likely to require endoscopy (RR vs prompt endoscopy 0.23; 95% CI 0.17 to 0.31) than with all other management strategies, except symptom-based management. Patients receiving prompt endoscopy were, however, significantly less likely to be dissatisfied with management, compared with those randomised to 'test and treat' or empirical acid suppression. Nevertheless, this suggests that 'test and treat' should be the preferred first-line management strategy for dyspepsia in primary care, although it is important to point out that many of the included trials were published over 15 years ago and, therefore, prevalence of *H. pylori* infection may have declined in Western populations during this time.

Prompt endoscopy is, therefore, not required for most patients with dyspepsia and should be reserved for those with other risk factors, defined above. However, there is variation in age-based gastric cancer risks, which are lower in the majority of Western populations, excluding African-Americans and Latin-Americans,[154] and higher in South-east Asian countries, such as China, Japan and Korea. A reduction in the age threshold is also required in patients with a family history of gastro-oesophageal cancer.

As pancreaticobiliary disease can present with upper gastrointestinal symptoms, this may need to be considered in the differential diagnosis of dyspepsia. However, a previous systematic review demonstrated that gallstones are only associated with abdominal pain with the characteristics of biliary colic, not with symptoms suggestive of dyspepsia.[155] Moreover, response following cholecystectomy for uncomplicated gallstones, in terms of the resolution of abdominal pain, appears to be associated with the presence of episodic pain with a duration of less than 1 year prior to surgery.[123] This suggests that indiscriminate use of abdominal ultrasound in patients with symptoms suggestive of dyspepsia should be avoided, unless the upper abdominal pain has the characteristics of biliary colic, and has been present for less than 1 year. NICE states that imaging should be considered in patients≥60 years old with new onset abdominal pain and weight loss to exclude the possibility of pancreatic cancer.[112]

Based on all the above, we recommend urgent endoscopy only in patients aged ≥55 years with dyspepsia with evidence of weight loss. Non-urgent endoscopy can be considered in patients aged ≥55 years with treatment-resistant dyspepsia or dyspepsia with either a raised platelet count or nausea or vomiting. In those with aged ≥60 years with abdominal pain and weight loss urgent CT scanning should be considered. In patients from areas at high risk of gastric cancer, or those with a family history of gastro-oesophageal malignancy, the age limit for endoscopy should be reduced to >40 years. Recommendations as to when to consider endoscopy in patients with dyspepsia and overlapping gastro-oesophageal reflux symptoms are as for patients with dyspepsia alone.

In all other patients with dyspepsia a 'test and treat' strategy should be preferred, with those testing negative receiving a course of empirical acid suppression, using the lowest dose that improves their symptoms. Successful eradication of *H. pylori*

after 'test and treat' should only be confirmed in those with an increased risk of gastric cancer, as recommended elsewhere in other guidance.[140] As in any other condition, clinical judgement may still suggest the need for endoscopy in individual cases. Similarly, the patient may insist an endoscopy is performed. In the latter instance, it should be reiterated that the yield is likely to be low and the expected diagnosis is FD, with the patient counselled about the risks and benefits of a potentially unnecessary invasive investigation.

Recommendations

- We recommend that a full blood count is performed in patients aged ≥55 years with dyspepsia and coeliac serology in all patients with FD and overlapping IBS-type symptoms (recommendation: strong, quality of evidence: low).
- We recommend that if no other upper gastrointestinal alarm symptoms or signs are reported, urgent endoscopy is only warranted in patients aged ≥55 years with dyspepsia with weight loss, or those aged >40 years from an area at an increased risk of gastric cancer or with a family history of gastro-oesophageal cancer (recommendation: strong; quality of evidence: very low).
- We recommend that non-urgent endoscopy is considered in patients aged ≥55 years with treatment-resistant dyspepsia or dyspepsia with either a raised platelet count or nausea or vomiting (recommendation: strong, quality of evidence: very low).
- We recommend that urgent abdominal CT scanning is considered in patients aged ≥60 years with abdominal pain and weight loss to exclude pancreatic cancer (recommendation: strong; quality of evidence: very low).
- We recommend that all other patients with dyspepsia are offered non-invasive testing for *H. pylori* ('test and treat') and, if infected, given eradication therapy (recommendation: strong; quality of evidence: high).
- We recommend that successful eradication of *H. pylori* after 'test and treat' is only confirmed in patients with an increased risk of gastric cancer (recommendation: strong; quality of evidence: low).
- We recommend that patients without *H. pylori* infection are offered empirical acid suppression therapy (recommendation: strong; quality of evidence: high).

PRESENTATION AND INVESTIGATION IN SECONDARY CARE

Presentation of dyspepsia to secondary care

Symptoms of dyspepsia are one of the most common reasons for referral to secondary care, with approximately 10% of all patients in a gastroenterology clinic ultimately being diagnosed with FD.[156] Due to unfamiliarity with current diagnostic criteria, the majority of patients are referred without a specific working diagnosis of FD, even though most of the investigations necessary to reach such a diagnosis have often been performed in primary care. Patients are referred to secondary care for consideration of endoscopy, when the GP cannot access this investigation directly, with a request for further investigations where there is diagnostic doubt, or in the case of non-response to treatment. If the necessary investigations have been already performed, a careful clinical history is usually enough to confirm the diagnosis, reassure the patient, demonstrate the commitment of the clinician to help, and offer appropriate treatment.

Investigations in secondary care

Regarding possible additional investigations to be considered in secondary care, there are few other conditions to consider in the differential diagnosis in a patient with typical symptoms and a negative endoscopy. One area of controversy is the potential overlap of symptoms of FD with those of gastroparesis.[18] Both delayed and accelerated gastric emptying have been reported in patients with FD. However, gastric emptying test results have not been demonstrated to predict treatment response consistently.[51] Scintigraphy, which is considered the gold standard to assess gastric emptying, but also other tests, such as the breath test or the smart pill, are not widely available, nor are their methods or interpretation standardised across different centres.[157] Most other guidelines, therefore, do not recommend gastric emptying tests as part of the diagnostic work-up for patients with typical symptoms of FD.[51 151 158] A recent study has demonstrated that patients with upper gastrointestinal symptoms, which could be indicative of either FD or gastroparesis, and delayed gastric emptying are no different from such patients with normal gastric emptying, in terms of symptom severity, age, gender, race, healthcare utilisation, health-related quality of life or depression and anxiety scores.[16] In addition, the two groups of patients were not stable; during 1 year of follow-up 40% in each group moved to the other group, based on repeat gastric emptying testing. This questions the distinction between FD and gastroparesis based on gastric emptying rates alone,[18] although it is possible that patients presenting with severe nausea, which is not a cardinal symptom of FD, and those with coexistent chronic constipation may represent a subgroup of patients in whom symptoms do correlate with delayed gastric emptying and/or whole gut transit.[17] However, this remains a subject for future research. There is the potential for iatrogenic harm, due to invasive interventions, from attaching a label of gastroparesis, based on the results of gastric emptying studies, to a patient who otherwise meets criteria for FD and has no risk factors for gastroparesis.

Impaired accommodation of the gastric fundus has been also reported in patients with FD, but none of the techniques used to detect this, to date, are widely available in clinical practice.[159] Interestingly, several studies have reported the presence of decreased volume tolerance to both liquid nutrients and water drinking test in FD,[58] but this has not been adopted as part of the diagnostic work-up. GORD and FD overlap more than expected by chance, and symptoms such as epigastric burning may be similar in patients with gastro-oesophageal reflux and EPS. Abnormal oesophageal acid exposure, measured by pH monitoring, is found in up to 30% of patients presenting with FD symptoms and in up to 50% of patients with EPS.[72 160] However, there is no evidence that pH monitoring is able to predict patients who will respond to acid suppression. Routine pH monitoring to assess for evidence of pathological acid reflux is, therefore, not recommended in patients with FD.

Management of dyspepsia as a partnership between primary and secondary care

Currently, primary and secondary care work as separate entities, often referring patients with dyspepsia back and forth multiple times. However, a crucial factor in the effective diagnosis and management of patients with FD at local level is likely to be good collaboration between GPs and gastroenterologists, and, increasingly, the involvement of patients in the design of services. As discussed, at present there are no specific additional tests that secondary care clinicians can or should offer patients with FD. However, discharge from secondary care clinics to primary care

with 'reassurance' that there is 'no cause' for the symptoms, or a reluctance to receive referrals with dyspepsia from primary care to secondary care does not reassure the patient at all. A clear diagnosis of FD should be given to the patient and this diagnosis should be recognised formally by the healthcare system, with a specific diagnostic code. The management of dyspepsia has blurred primary and secondary care boundaries and needs to become patient-centred, rather than primary or secondary care-centred. In some specialities, such as in mental health, problems are normally managed across health boundaries and with the help of different health professionals. Pathways for FD may benefit from a similar paradigm with the inclusion of experts in gastroenterology, psychology, diet, lifestyle and symptom management in a specialist clinic, with auditing of rates of testing for, and treating, *H. pylori* pre-endoscopy, rates of *H. pylori* infection and rates of endoscopy.

Recommendations

- Referral of patients with FD to gastroenterology in secondary care is appropriate where there is diagnostic doubt, where symptoms are severe, or refractory to first-line treatments, or where the individual patient requests a specialist opinion (recommendation: weak, quality of evidence: low).
- We recommend that gastric emptying testing or 24-hour pH monitoring should not be undertaken routinely in patients with typical symptoms of FD (recommendation: strong, quality of evidence: very low).
- We recommend that, ideally, patients with FD referred to secondary care are managed in a specialist clinic, with access to an interested clinician, dietetic and lifestyle support, with access to efficacious drugs and gut–brain behavioural therapies. Rates of *H. pylori* 'test and treat' prior to endoscopy, prevalence of *H. pylori* infection, and use of endoscopy should be audited (recommendation: strong, quality of evidence: very low).

TREATMENT OF FD

General overview

It is important to stress that, as with other DGBI, cure of FD is unlikely, and most treatments are of modest efficacy. An explanation of the relapsing and remitting natural history of FD, as well as the fact that treatment is offered with the aim of improving symptoms, social functioning, and quality of life is vital. Although there is little evidence that lifestyle changes lead to symptom improvement, a recent small RCT of aerobic exercise, in addition to conventional management, demonstrated a significant benefit on dyspepsia symptoms, compared with conventional management alone.[161] As recommended above, the first step should be to test the patient for *H. pylori* infection, because presence of the infection will dictate initial management. If testing has been done previously, and infection was either not present, or was present but FD symptoms have not responded to eradication therapy, treatment should commence with first-line drugs,

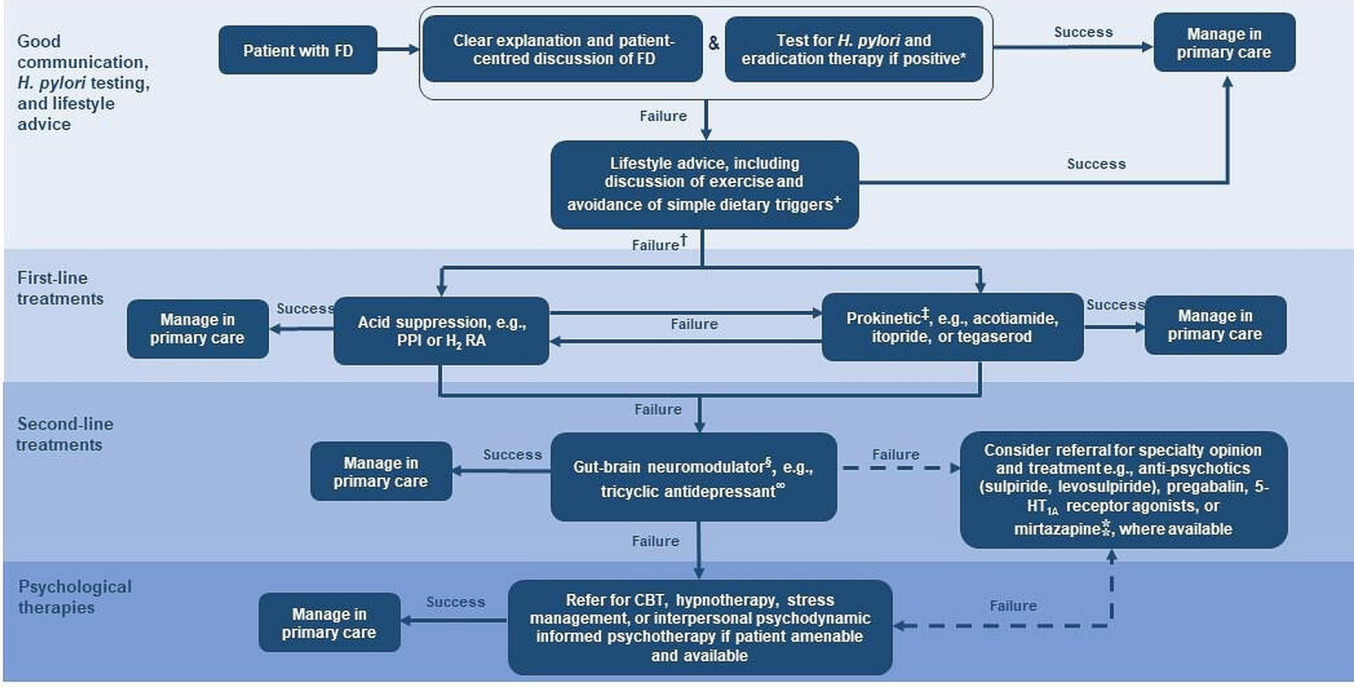

Figure 2 Treatment algorithm for functional dyspepsia. *Successful eradication of *H. pylori* should only be confirmed in those with an increased risk of gastric cancer. +Triggers may include spicy food or alcohol, for example, but there is insufficient evidence to recommend specific dietary therapies, including a diet low in fermentable oligosaccharides, di- and monosaccharides, and polyols in FD. †Overall, there is insufficient evidence to make recommendations regarding whether any treatment should be preferred in patients with EPS or PDS. ‡Efficacy of prokinetics varies according to drug class, and many of these drugs are unavailable outside of Asia and the USA. Most trials of acotiamide have been conducted in patients with PDS. §There is no evidence that selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors, used as gut–brain neuromodulators, are an efficacious treatment for FD. ∞Tricyclic antidepressants should be used as a first-choice gut–brain neuromodulator. They can be initiated in primary or secondary care, starting at a dose of 10 mg at night, and titrating slowly (eg, by 10 mg per week) according to response and tolerability. Continue for at least 6–12 months if the patient reports a symptomatic benefit. ⁂Mirtazapine may be useful in patients with FD and early satiation and weight loss. EPS, epigastric pain syndrome; FD, functional dyspepsia; PDS, postprandial distress syndrome.

according to patient choice (figure 2). Second-line drugs are reserved for those whose symptoms do not improve with these measures. All decisions regarding treatment choices should be made by the patient, with advice and support from the clinician.

Recommendations

- We recommend that all patients with FD are advised to take regular aerobic exercise (recommendation: strong, quality of evidence: very low).

Diet

The intake of food frequently triggers symptoms in people with FD, with over 80% of patients fulfilling Rome IV criteria for PDS.[29] However, evidence to support the use of dietary interventions in FD is limited, with data mainly derived from observational studies, not RCTs. The mechanism by which food items evoke symptoms in FD is heterogeneous and incompletely understood, but is thought to relate to alterations in gastroduodenal motility, gastric accommodation, immune activation, visceral hypersensitivity, microbial composition and central perception.[162–164] Following meal ingestion, symptoms manifest quickly and reach a peak within 15–30 min of eating, often lasting beyond 4 hours.[25] The time-course of individual symptoms varies, with early peaks for postprandial fullness and bloating, intermediate peaks for nausea and belching, and late peaks for epigastric pain and burning.[25] The most commonly reported food triggers are fatty foods, dairy products, alcohol, coffee, red meat, carbonated drinks, vegetables, spicy food, carbohydrates, wheat and citrus.[165]

Not surprisingly, individuals with FD adjust their dietary patterns, with food diary studies providing evidence that patients eat smaller, more frequent, meals with reduced fat content, compared with healthy controls.[166] Analysis of dietary data collected from more than 30 000 French adults found the consumption of ultraprocessed foods, which are high in saturated fat and additives, to be associated with FD, although this was only apparent when FD coexisted with IBS, rather than in those with FD alone.[167] In addition, intraduodenal lipid infusion stimulates cholecystokinin release and increases visceral hypersensitivity, while reducing gastric motility.[168] However, the role of a diet low in fat or ultraprocessed food in patients with FD is unclear. With regard to beverages, observational studies evaluating alcohol consumption in FD are conflicting. Although some studies report no association,[32 169] others have found beer and wine to be particularly problematic,[170] and increasing alcohol consumption to be associated with worsening of dyspeptic symptoms,[171] suggesting that avoidance or reduction of alcohol is advisable.[163] Similarly, caffeine has been associated with symptom induction in 50% of patients.[163] One-in-two people with FD demonstrate chemical hypersensitivity to capsaicin, a component of spicy foods, with desensitisation following chronic ingestion.[172 173]

Individuals with FD may also report sensitivity to wheat-based products,[174] although the prevalence of coeliac disease in FD is not significantly different than among healthy controls.[133] A small open-label study comprising 22 patients with FD reported that a gluten-free diet improved symptoms in over 80% of cases, although only one-quarter reacted to gluten-containing capsules following a subsequent double-blind placebo-controlled rechallenge.[175] A double-blind placebo-controlled crossover trial was unsuccessful in its attempt to identify which component of wheat may trigger symptoms in FD, as it recruited only 11 of the 60 participants needed.[176]

The efficacy of a diet low in fermentable oligosaccharides, disaccharides, and monosaccharides, and polyols (FODMAPs) has been explored in FD. One study suggested it was more effective than standard or traditional dietetic advice, which included reducing intake of caffeine, alcohol, fat, fibre, and food additives, with a response rate of 50% vs 16%, respectively.[177] However, this was small and non-randomised, and most individuals had overlapping IBS. Moreover, the low FODMAP diet was only followed for 4 weeks, incorporating only the strict elimination phase where all FODMAPs are excluded; long-term outcomes following re-introduction of FODMAPs, and personalisation of the diet were not explored. An RCT from India has since addressed some of these issues, reporting no significant difference in response rates between a low FODMAP diet and traditional dietary advice in FD, both in the short-term at 4 weeks (67% vs 57%) and at 12-week follow-up (46% vs 41%).[178] On subgroup analysis, patients with PDS appeared to respond better to a low FODMAP diet, whereas no difference was seen in EPS. However, these findings should be viewed with caution as the study was not powered to examine response rates according to individual FD subtype.

Further large RCTs of dietary therapies in FD are, therefore, needed. However, it is important to emphasise that up to 50% of people with FD may have ARFID,[179] and care should be taken before recommending complex dietary interventions such as the low FODMAP diet. Patients with, or at high risk of developing, eating disorders can be screened for using simple eating disorder questionnaires (eg, SCOFF) and identifying those with psychological distress.[180]

Recommendations

- There is insufficient evidence to recommend dietary therapies, including a diet low in fermentable oligosaccharides, disaccharides, and monosaccharides, and polyols in FD (recommendation: weak; quality of evidence: very low).

Methodology for systematic reviews of drug therapy for FD

To inform this guideline, we updated a series of systematic reviews and pairwise or network meta-analyses, some of which were conducted by the authors.[27 146 181–185] The aim was to assess the efficacy of *H. pylori* eradication therapy and licensed or unlicensed drugs in FD. We considered RCTs comparing drugs with placebo or each other, with cross-over trials eligible for inclusion, provided extractable data were available at the end of the first treatment period, prior to cross-over. Studies recruited adults from primary, secondary, or tertiary care with FD diagnosed by any criteria (including clinical impression). It is important to point out that, unlike in IBS, there is no accepted or approved endpoint to judge symptom response in FD, and therefore, most RCTs use measures such as improvement in, satisfactory relief of, or cure of, global FD symptoms or epigastric pain. Eligible trials had to report efficacy of treatment in terms of any of these endpoints as a dichotomous assessment.

We considered the following treatments: eradication therapy for patients with FD who were *H. pylori*-positive, histamine-$_2$-receptor antagonists (H_2RAs), PPIs, prokinetics (including drugs acting on dopamine receptors, such as domperidone, itopride or metoclopramide, 5-hydroxytryptamine (5-HT) receptor agonists, such as mosapride or tegaserod, or the acetylcholinesterase inhibitor acotiamide) or gut–brain neuromodulators (including TCAs, SSRIs, SNRIs, antipsychotics, such as sulpiride or levosulpiride, drugs acting on 5-HT_{1A} receptors, such as buspirone or tandospirone, or gabapentinoids) (online supplemental table 1).

As this was an update of prior meta-analyses,[27 146 181–185] we searched MEDLINE, EMBASE, EMBASE Classic and the Cochrane central register of controlled trials between January 2006 and October 2021 for RCTs of eradication therapy in *H. pylori*-positive FD, and between January 2019 and October 2021 for RCTs comparing these different drugs with each other or placebo in *H. pylori*-negative FD. We provide the search strategies used in online supplemental materials. We did not apply restrictions regarding language of publication. We conducted a recursive search of the bibliography of eligible articles. The lead reviewer (ACF) screened titles and trial abstracts that had been identified by the search strategy for articles that could possibly be eligible for the review, and then screened the selected trials to confirm eligibility, using predesigned eligibility forms. A second reviewer, masked to the initial assessment, also evaluated all identified trials for eligibility. We resolved discrepancies by discussion and used the kappa statistic to measure the degree of agreement for judging study eligibility.

Our literature search identified 1381 citations, of which 11 were incorporated into this guideline,[186–196] and used to update meta-analyses. Agreement between reviewers for study eligibility was excellent (kappa statistic=0.90). Of these 11 studies, 10 compared *H. pylori* eradication therapy with a control or placebo,[186–195] and were used to update a previous pairwise meta-analysis,[182 185] and one compared pregabalin with placebo,[196] and was used to update both a previous pairwise meta-analysis and a network meta-analysis.[27 181] Recommendations for all other treatments are, therefore, made based on the results of existing pairwise and network meta-analyses.

All data for newly identified RCTs were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA). Again, we resolved disagreements between investigators by discussion. We extracted data as intention-to-treat analyses, with all drop-outs assumed to be treatment failures, wherever trial reporting allowed this. We incorporated data from newly identified trials into existing pairwise and network meta-analyses. As we examined binary outcomes, (global FD symptoms or epigastric pain cured or not cured, or global FD symptoms or epigastric pain improved or not improved), we expressed the impact of each intervention as an RR of global FD symptoms or epigastric pain not being cured or not improving, together with 95% CIs, where if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of the intervention over the control. This approach is the most stable, compared with RR of improvement, or using the OR, for some meta-analyses.[197]

We used Review Manager V.5.4.1 (RevMan for Windows 2020, the Nordic Cochrane Centre, Copenhagen, Denmark) for updates to pairwise meta-analyses. We conducted an updated network meta-analysis using the frequentist model, with the statistical package 'netmeta' (V.0.9–0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (V.4.0.2). Network meta-analysis usually gives a more precise estimate, compared with results from standard, pairwise meta-analysis.[198 199] It allows ranking of treatments to inform clinical decisions,[200] according to a P-score, which is a value between 0 and 1, with higher scores indicating a greater probability of a treatment being ranked as best.[201] For both pairwise and network meta-analyses, we pooled data using a random effects model, to give a more conservative estimate of efficacy of individual therapies,[202] and we assessed heterogeneity using the I^2 statistic, which ranges from 0% to 100%, with 0% representing no observed heterogeneity, and larger values indicating increasing heterogeneity. We chose a value ≤50% to represent low levels of heterogeneity.[203]

H. pylori eradication therapy

Given that 5% of dyspepsia in the community is attributable to *H. pylori*,[22] and up to 80% of individuals with dyspepsia have FD,[2] eradicating the bacterium in patients diagnosed with FD who are found to be *H. pylori*-positive is logical. Updating the prior meta-analysis of *H. pylori* eradication therapy for infected patients with FD,[182 185] with 10 new trials recruiting 2896 patients,[186–195] demonstrated a significant benefit over a control of antisecretory therapy or prokinetics, with or without placebo antibiotics, or a placebo alone in terms of symptom cure or improvement.[143] The RR of symptoms not being cured or improving in 29 trials, containing 6781 patients, was 0.87 (95% CI 0.83 to 0.92) (online supplemental figure 1), with significant heterogeneity between studies (I^2=64%). The effect was even larger in individuals whose infection was eradicated successfully, compared with those receiving control therapy, in 16 trials containing 2809 patients (0.74; 95% CI 0.64 to 0.85) (online supplemental figure 2). When only those trials that reported symptom cure were included in the analysis, most of which assessed this at 12 months, there was still a significant benefit of *H. pylori* eradication therapy (RR of symptoms not being cured=0.91; 95% CI 0.88 to 0.94) (online supplemental figure 3), with low heterogeneity between studies (I^2=7%). Total numbers of adverse events were only reported by eight RCTs, containing 1937 patients, but were significantly more common with eradication therapy. Individual adverse events were not reported in sufficient detail by the trials to allow further assessment. Withdrawals due to adverse events were reported by 18 trials and were again significantly more likely than with control therapy.

Although the treatment effect is modest, cure of symptoms at 12 months is a stringent endpoint, and it is likely that eradication therapy for *H. pylori*-positive patients with FD is cost-effective, as it only needs to be taken for 1–2 weeks.[185] In terms of which patients are more likely to respond, one trial demonstrated a significant effect of eradication therapy on epigastric pain and burning, but not early satiation or postprandial fullness,[190] suggesting the benefit may be more pronounced in EPS.

Recommendations

- Eradication therapy is an efficacious treatment for *H. pylori*-positive patients with FD. Adverse events are more common than with a control therapy (recommendation: strong; quality of evidence: high).

Drugs used first line for *H. pylori*-negative FD or after a lack of response to eradication therapy in *H. pylori*-positive FD

Acid suppression therapy

In patients with FD who test negative for *H. pylori*, or who are positive but in whom eradication therapy does not lead to an improvement in symptoms, there are several drug classes that are proposed to be of benefit. Although there is no evidence to suggest that the pathophysiology of FD is related to an overproduction of gastric acid, some individuals with FD demonstrate impaired duodenal clearance of acid and duodenal hypersensitivity to infused gastric acid.[69] There is little data to support use of antacids, alginates, sucralfate or bismuth to improve FD symptoms,[184] although given antacids and alginates are available over the counter they are likely to be used by people with FD. However, there is evidence that acid suppression therapy with H_2RAs or PPIs is beneficial. Although these drugs reduced acid secretion, some studies have shown that there is increased duodenal permeability and duodenal inflammation in

FD, with infiltration of eosinophils and mast cells seen,[93 204–206] and in close proximity to submucosal plexus neurones.[94] This phenomenon seems to be associated more strongly with PDS type symptoms, rather than EPS.[206] Interestingly, in one study, pantoprazole led not only to symptom improvement in patients with FD, but also a reduction in duodenal eosinophilia and mast cell counts and reduced duodenal permeability.[207]

We identified no new trials of either H_2RAs or PPIs since a network meta-analysis published in 2019,[27] so used the pairwise data from that meta-analysis to inform this guideline. Overall, there was a benefit of H_2RAs over placebo. The RR of symptoms not improving in 12 trials, containing 2268 patients, was reduced with H_2RAs versus placebo (0.79; 95% CI 0.68 to 0.92) (online supplemental figure 4). Similarly, the RR of symptoms not being cured in eight RCTs, randomising 1668 patients, was reduced with H_2RAs vs placebo (0.83; 95% CI 0.71 to 0.98) (online supplemental figure 5). Total adverse events and treatment withdrawals were no more likely with H_2RAs than with placebo in seven trials. However, trial quality was low, there was significant heterogeneity between studies (I^2=77% for symptom improvement and I^2=87% for symptom cure), and many of these RCTs were older and recruited patients whose symptom profiles would no longer be considered compatible with FD, including those with reflux-predominant dyspepsia. In the network meta-analysis, doses of PPIs<20 mg were classed as low dose,≥20 mg to ≤30 mg standard dose, and >30 mg high dose. There were 16 RCTs of PPIs, using low, standard or high doses of these drugs in FD, containing 6017 patients, which reported on improvement in symptoms. Overall, standard dose PPIs (RR=0.86; 95% CI 0.78 to 0.95) and low dose PPIs (RR=0.89; 95% CI 0.81 to 0.97) were more efficacious than placebo, but there was no benefit of high dose PPIs (RR=0.86; 95% CI 0.74 to 1.01) (online supplemental figure 6), with significant heterogeneity between studies in all these analyses. However, there was no difference in efficacy between the different doses on subgroup analysis (p value for χ^2=0.90). In terms of symptom cure, there were 10 RCTs, containing 4667 patients. In this analysis there was a benefit of all doses of PPIs, with no heterogeneity for high dose PPIs but significant heterogeneity for standard and low dose PPIs, suggesting there may be lower confidence in the effect estimate for standard or low dose PPIs. There were no significant differences between these subgroup analyses by dose according to the χ^2 test (p value for χ^2=0.92) (online supplemental figure 7). Adverse events were no more likely than with placebo in five trials, and dropouts due to adverse events were not significantly higher in seven RCTs.

Trials of H_2RAs predated the Rome IV subgrouping of FD, and too few RCTs of PPIs reported symptom data according to whether patients had EPS or PDS to allow any meaningful analysis. The fact that duodenal eosinophilia is more strongly associated with PDS may favour PPI use in this group but, given there is frequent overlap of PDS and EPS in clinical practice,[9–11] H_2RA or PPI use is reasonable in most patients with FD.

Prokinetics

A subset of patients with FD demonstrates abnormal gastric motility, hypersensitivity to gastric distension and impaired fundal accommodation.[52 54 58 63 208] Drugs that enhance gastroduodenal motility and accommodation of the gastric fundus to a meal may, therefore, be a potentially effective treatment. However, there is a lack of placebo-controlled trials of the more readily available prokinetics, such as domperidone or metoclopramide, so whether they are efficacious in FD is unclear. In addition, there are safety concerns with these drugs, due to the risk of cardiac arrhythmias or extrapyramidal side effects, respectively. In terms of other prokinetics, acotiamide, which is an acetylcholinesterase inhibitor, itopride, which is a dopamine antagonist, and mosapride and tegaserod, which are 5-HT_4 receptor agonists, have all been evaluated in FD. However, none are available in the UK. Again, we identified no new trials of prokinetics since a network meta-analysis of drugs for FD,[27] so used pairwise data from that meta-analysis, including 7539 patients, to inform this guideline. Overall, this class of drugs appeared efficacious for FD, in terms of improvement of symptoms (RR of symptoms not improving=0.89; 95% CI 0.84 to 0.95) (online supplemental figure 8). However, there was significant heterogeneity between studies, suggesting pooling these different drugs with varying mechanisms of action may not be appropriate. In addition, among individual drugs only tegaserod, which is not widely available outside of the USA, and is unlicensed for FD, was more efficacious than placebo, although these two trials were rigorously conducted.[209] Only three RCTs of prokinetics reported effect on cure of symptoms, meaning that firm conclusions cannot be drawn. Adverse event rates were no higher than with placebo in five trials. Treatment discontinuation due to adverse events was significantly more likely with tegaserod in two RCTs, but comparable with placebo for trials of acotiamide, itopride, and mosapride.

As with RCTs of H_2RAs and PPIs, there were insufficient studies reporting on efficacy of prokinetics in patients with EPS or PDS to make recommendations as to whether their use should be preferred in a subset of patients. Most RCTs of acotiamide have been conducted in PDS, and one placebo-controlled trial of itopride assessed the impact on individual FD symptoms and demonstrated a significant reduction in PDS symptoms such as postprandial fullness, early satiation and upper abdominal bloating.[210] In addition, many of these drugs have limited availability outside of the USA and Asia.

Recommendations

- Histamine-$_2$-receptor antagonists may be an efficacious treatment for FD. These drugs are well tolerated (recommendation: weak, quality of evidence: low).
- PPIs are an efficacious treatment for FD. There does not appear to be a dose response, so the lowest dose that controls symptoms should be used. These drugs are well-tolerated (recommendation: strong, quality of evidence: high).
- Some prokinetics may be an efficacious treatment for FD. However, efficacy varies according to drug class, and many of these drugs are unavailable outside of Asia and the USA. Most of these drugs are well-tolerated (recommendation: weak, quality of evidence: low for acotiamide, itopride, and mosapride, recommendation: strong, quality of evidence: moderate for tegaserod).

Drugs used second line for FD: gut–brain neuromodulators

Involvement of the brain–gut axis and abnormal central pain processing in functional gastrointestinal disorders is now established, and FD has been retermed a DGBI.[211] In fact, gut–brain neuromodulators, including low-dose antidepressants, have been suggested as a therapy for many years, due to their peripheral pain-modifying properties,[212] as well as their effects on gastrointestinal motility.[213] The intestinal enterochromaffin cells contain 90% of the body's total stores of 5-HT,[214] which is integral to gut motility. Since most trials of these drugs have been conducted in referral populations, it would seem reasonable to

consider their use in patients with FD who are *H. pylori*-negative who derive no benefit from either acid suppression therapy and/or prokinetics, or in *H. pylori*-positive patients after a lack of symptomatic response to eradication therapy, acid suppression therapy, and/or prokinetics.

We incorporated the results of the trial of pregabalin in FD into a previous meta-analysis,[27 196] including 1302 patients.[181] Overall, there was a benefit of gut–brain neuromodulators in FD, with an RR of symptoms not improving of 0.77 (95% CI 0.67 to 0.89) (Supplementary Figure 9). However, there was significant heterogeneity between studies (I^2=64%), and the effect was limited to TCAs at a dose of 10–50 mg once daily in four RCTs (0.75; 95% CI 0.62 to 0.90, I^2=4%), the antipsychotic drugs sulpiride 100 mg four times a day or levosulpiride 25 mg three times a day in three trials (RR=0.50; 95% CI 0.37 to 0.67, I^2=0%), and pregabalin 75 mg once daily in one trial (RR=0.53; 95% CI 0.29 to 0.96). Trials of sulpiride and levosulpiride were at unclear risk of bias, and the number of included patients was small, meaning that firm conclusions cannot be drawn from these data, whereas RCTs of TCAs were more rigorous. Moreover, levosulpiride is unavailable in some countries, including the UK. There was no evidence of a benefit of SSRIs in two RCTs (sertraline 50 mg once daily or escitalopram 10 mg once daily), or the SNRI venlafaxine 150 mg once daily in one trial. Although the trial of venlafaxine was negative,[215] the dose was down-titrated to 75 mg once daily during the final 2 weeks of the study and SNRIs are efficacious in other chronic painful disorders,[216 217] suggesting more RCTs in FD are required. 5-HT_{1A} agonists, as a group, were no more efficacious than placebo, but a Japanese trial demonstrated a benefit of tandospirone 10 mg three times a day in 150 patients with FD.[218] Rates of adverse events, such as dizziness and drowsiness, were significantly higher among those taking gut–brain neuromodulators, although when individual drug classes were studied this was only the case for TCAs in two RCTs. However, adverse events leading to treatment discontinuation were no more likely with TCAs. Dizziness was particularly an issue with pregabalin, reported by over 50% of patients assigned to the drug.[196]

Primary care physicians are increasingly aware of the concept of low dose antidepressants as gut–brain neuromodulators in DGBI. As with their use in IBS,[219] the rationale for the benefits of these drugs, in the context of DGBI, as well as their side effect profile, needs to be explained carefully.[212] This may require an open and thoughtful negotiation with some patients who might interpret this approach as implying that they have a mental health problem. There needs to be clarification that these drugs are being used at low doses for their pain modulatory properties and peripheral effects on gastrointestinal motor and sensory function, rather than at a dose that is used to treat common mental disorders. In this regard, clinicians should be aware of their unconscious bias toward these medications and should help patients to overcome the stigma around their traditional use as antidepressants.[220] Due to their sedating effects, they should be taken in the evening before bedtime. It should be made clear that these drugs take time to have a benefit and that side effects, such as drowsiness, tend to ameliorate after the first 1 or 2 weeks of treatment. To minimise side effects and maximise tolerability, they should be commenced at a low dose (eg, 10 mg of amitriptyline once daily) and titrated slowly in 10 mg increments, to a maximum of 30–50 mg once daily, with follow-up to assess efficacy and tolerability. Patients often ask how long they will need to take these drugs for. If beneficial, the drugs are likely to be continued for a minimum of 6–12 months and, in some cases, this may be even longer term. In an RCT of 478 patients with depression who were taking antidepressants for 2 years or longer, relapse rates of depression were two-fold higher among those randomised to discontinue their drug.[221] However, whether this can be extrapolated to patients with DGBI, such as FD, is unclear.

Information from individual trials may better elucidate which subgroups of patients to consider use of these drugs in. An RCT of amitriptyline 50 mg once daily or escitalopram 10 mg once daily versus placebo demonstrated that amitriptyline appeared to be of greater benefit in EPS,[222] although the drug enhanced gastric accommodation,[223] suggesting it may also benefit those with PDS. In an RCT of imipramine 25–50 mg once daily epigastric pain, bloating, postprandial fullness, early satiation, and vomiting scores all improved significantly, versus placebo, compared with baseline.[224] In a placebo-controlled trial of mirtazapine 15 mg once daily,[225] recruiting 34 patients with FD and weight loss, without anxiety or depression and not taking any other neuromodulators, there was no benefit on global symptoms but the drug led to significant improvements in early satiation and quality of life. Finally, in a small Belgian crossover RCT, buspirone 10 mg three times a day had significant effects on postprandial fullness, early satiation, and upper abdominal bloating, and increased gastric accommodation.[226] Further, larger, trials of mirtazapine and 5-HT_{1A} agonists in FD are warranted.

Recommendations

- TCAs used as gut–brain neuromodulators are an efficacious second-line treatment for FD. They can be initiated in primary or secondary care, but careful explanation as to the rationale for their use is required, and patients should be counselled about their side effect profile. They should be commenced at a low dose (eg, 10 mg amitriptyline once daily) and titrated slowly to a maximum of 30–50 mg once daily (recommendation: strong, quality of evidence: moderate).
- Antipsychotics, such as sulpiride 100 mg four times a day or levosulpiride 25 mg three times a day, may be efficacious as a second-line treatment for FD. There should be careful explanation as to the rationale for their use and patients should be counselled on their side effect profile (recommendation: weak, quality of evidence: low).
- There is no evidence that SSRIs used as gut–brain neuromodulators are an efficacious second-line drug for global symptoms in FD (recommendation: weak, quality of evidence: moderate).
- There is no evidence that SNRIs used as gut–brain neuromodulators are an efficacious second-line drug for global symptoms in FD. However, as they are efficacious in other chronic painful conditions, more trials of these drugs are warranted (recommendation: weak, quality of evidence: low).
- Tandospirone 10 mg three times a day may be an efficacious second-line treatment for FD, but there is no evidence that other 5-hydroxytryptamine-$_{1A}$ agonists, including buspirone 10 mg three times a day, are efficacious. However, more trials of these drugs are warranted (recommendation: weak, quality of evidence: low).
- Pregabalin 75 mg once daily may be an efficacious second-line treatment for FD but further RCTs are needed and given its controlled drug status we advise this drug is only used in specialist settings (recommendation: weak, quality of evidence: low).

- Mirtazapine 15 mg once daily may be an efficacious second-line treatment for patients with FD with early satiation and weight loss, but further RCTs are needed (recommendation: weak, quality of evidence: very low).

Comparative efficacy of drugs for FD

We updated the prior network meta-analysis of RCTs of all the above drugs for FD,[27] compared with placebo or each other, incorporating the trial of pregabalin.[196] Overall, there were 72 trials, containing 19 315 patients. Of these, 12 573 received a drug for FD and 6742 a placebo, allocated as described in online supplemental table 2. There were more trials, and more drugs studied, than in the pairwise meta-analyses of placebo-controlled trials reported above, due to the incorporation of head-to-head RCTs comparing one drug directly with another.

Network meta-analysis suggested that, compared with placebo, antipsychotics (sulpiride or levosulpiride) were ranked first (RR of symptoms not improving=0.49; 95% CI 0.36 to 0.69, p=0.97) (online supplemental figure 10), followed by pregabalin (RR=0.53; 95% CI 0.28 to 1.01, p=0.89), with TCAs ranked third (RR=0.71; 95% CI 0.58 to 0.87, p=0.83), and with significant heterogeneity between studies (I^2=59%). However, although TCAs were ranked third in in our primary analysis, there was moderate confidence in estimates of their efficacy, and they were ranked second when only low risk of bias trials were included. It is also important to point out that four of the five trials of TCAs recruited patients whose symptoms were refractory to acid suppression therapy, prokinetics, or both. In contrast, the three trials of sulpiride and levosulpiride were all at unclear risk of bias, and contained only 86 patients, and the trial of pregabalin was small, and the overall result not statistically significant in this analysis. Of the top three ranked drugs, the results for TCAs are, therefore, likely to be the most robust. All this suggests that earlier use of TCAs in FD may be beneficial, and that large head-to-head studies of TCAs versus conventional therapies, such as PPIs, are required in primary care. Other drugs with a benefit, compared with placebo, included H_2RAs (RR 0.81; 95% CI 0.74 to 0.90, p=0.68), standard dose PPIs (RR=0.84; 95% CI 0.77 to 0.91, p=0.61), low dose PPIs (RR=0.86; 95% CI 0.79 to 0.94, p=0.51), itopride (RR=0.87; 95% CI 0.77 to 0.99, p=0.49), and acotiamide (RR=0.89; 95% CI 0.79 to 0.99, p=0.44). There was no benefit of domperidone, tegaserod, high dose PPIs, mosapride, SNRIs, SSRIs, or 5-HT_{1A} agonists. When we assessed comparative efficacy, antipsychotics were superior to all other agents, except pregabalin, TCAs, and mirtazapine. TCAs were superior to SSRIs, mosapride, and 5-HT_{1A} agonists. H_2RAs and both low and standard dose PPIs were comparable with each other.

Gut–brain behavioural therapies

For many years, it has been suggested that DGBI are influenced by the biopsychosocial model of gastrointestinal illness.[227] The symptoms of FD have a significant impact on quality of life.[228] With this impact in mind, it is worth considering the role of psychological and social factors that may accompany the gastrointestinal symptoms, as well as comorbid psychological or psychiatric disorders. Gastric sensitivity in patients with FD has been shown to be influenced by psychosocial factors, with significant associations with a history of sexual abuse, physical abuse, and somatisation.[229] Between 15% and 70% of people with FD exhibit psychological comorbidity, significantly higher than controls.[230 231] It has also been shown that individuals with FD are more likely to have moderate to severe anxiety or depression when compared with those with organic dyspepsia.[232]

A broad range of treatment modalities have been studied, but the four main gut–brain behavioural interventions that have received focus in FD are psychodynamic therapy, CBT, stress management and mindfulness, and hypnotherapy. Overall, the evidence base for these approaches in FD remains limited, although other DGBI, such as IBS, have received more research attention.[233] Moreover, the lack of data needs to be considered in the context of the difficulties that psychological therapy research faces generally. With respect to RCTs, these difficulties include small sample sizes, difficulties in establishing control groups, heterogeneity of patients and establishing long-term benefits. In turn, meta-analysis of gut–brain behavioural therapies in FD has proven difficult due to the underlying heterogeneity of individual RCTs.[234]

Psychodynamic interpersonal therapy is a form of therapy, delivered in set sessions via a manual (manualised), that focuses on the patient's interpersonal difficulties, which are then explored, revealed, and modified. It has been shown to be useful in depression, but also as a treatment in IBS.[235] The single RCT conducted in patients with FD, to date, included 95 patients who had failed to respond to conventional pharmacological approaches.[236] The intervention arm received seven sessions of psychodynamic interpersonal psychotherapy, with the control arm randomised to receive supportive therapy and attention that was equivalent, in both time and frequency, to the intervention. By the end of treatment, patients who had undergone psychodynamic interpersonal therapy reported a significantly greater improvement in symptoms at 12 weeks, compared with control. However, 1 year later, a benefit was only seen when patients with severe heartburn were excluded, although assessing efficacy at this point was hampered by the dropout rate.

Core conflictual relationship therapy, which is another psychodynamic-informed modality of psychotherapy that focuses on interpersonal conflicts and emotion changes, led to a significant improvement in all symptoms of FD, compared with standard management, at the end of treatment, and 1 month and 12 months later.[237] Patients included had experienced persistent dyspepsia for at least 3 months and had been treated for *H. pylori* infection, if appropriate, and received either an H_2RA or a PPI. The active treatment arm also demonstrated reduced symptoms of depression, anxiety and interpersonal sensitivity. However, this was an intensive intervention, consisting of 16 sessions over a 4-month period, with two preliminary sessions before therapy started.

The largest study of a gut–brain behavioural therapy in FD included 158 patients meeting Rome III criteria randomised to either medical treatment plus psychotherapy or medical therapy alone.[238] The psychotherapy was delivered as eight group therapy sessions and two individual sessions. The psychotherapy focused on teaching coping strategies for FD and included adapted cognitive behavioural principles. Compared with other studies of gut–brain behavioural therapy, there was a higher non-completion rate for the intervention group, with only 55% completing the full course of treatment. Both treatment arms showed an improvement in symptoms at 6-month follow-up, but with a statistically significant difference in FD symptoms, pain intensity, general health, and psychological status favouring the active intervention. Patients in the psychotherapy group also had higher levels of satisfaction with dyspepsia-related health and felt the benefits were more meaningful and worthwhile compared with the control arm. However, as the study did not include a supportive therapy arm, it could be argued that it is

not clear what aspect of the therapy was beneficial to the patient and whether improvements were because the intervention arm received more time and attention compared with control.

The potential benefits of CBT and stress management are that they allow patients to increase their coping skills and improve social support. They have been shown to be effective in other DGBI, such as IBS.[233] For patients with FD, flexible coping psychotherapy appeared beneficial in one RCT.[239] Seventy-five participants were randomised to receive a manualised psychotherapy, which included psychoeducation, exploring sources of stress, and how this influenced gastric symptoms, with the aim of developing focused coping strategies. The control group received supportive therapy sessions, where they were asked to express their feelings and distress related to FD symptoms, also receiving a degree of psychoeducation. Both groups had a reduction in FD symptoms and anxiety, but only the intervention group reported symptoms at a comparable level with a healthy community sample at follow-up.

Another RCT compared long-term outcomes with standardised symptom-oriented 4-month therapy, intensive medical therapy with testing for and targeting of abnormalities of motor and sensory function, or intensive medical therapy plus either progressive muscle relaxation or CBT in patients whose symptoms did not improve with conventional therapies.[240] In the 12 months following treatment, symptom intensity and health-related quality of life improved in patients in the intensive medical therapy, intensive medical therapy plus progressive muscle relaxation, and intensive medical therapy plus CBT groups, compared with standard therapy. However, there was inequity in delivery of the interventions, with those randomised to CBT receiving 20 sessions, compared with only five in the progressive muscle relaxation arm. This difference, or the therapeutic nature of the modalities, may explain the fact that although improvements in anxiety and depression were seen in all groups, other than the standard therapy group, the most significant reductions were seen in the intensive medical therapy plus CBT arm.

Metacognitive therapy shares many characteristics with CBT, but instead of challenging intrusive thoughts and dysfunctional beliefs it addresses approaches to dealing with these thoughts and preventing their persistence. Ten 45 min sessions of metacognitive therapy were effective in FD, reducing anxiety and depression significantly, compared with either nortriptyline or a control group receiving usual medical therapy.[241] The impact of metacognitive therapy was also shown 3 months after treatment. There was no significant difference in emotion regulation difficulties between the three treatment arms.

Stress management has also been shown to be effective in reducing anxiety and depression, as well as global symptoms in one small trial, recruiting 28 patients with FD.[242] This intervention was relatively easy to deliver and brief, consisting of seven sessions. However, follow-up was only 3 weeks duration, meaning the long-term effects are unknown.

For patients with IBS, hypnotherapy has one of the largest evidence bases for both short-term and long-term efficacy.[233] The treatment has been delivered using IBS-specific protocols and the content of the therapy can be tailored to the patient's symptoms.[243 244] Despite evidence of effectiveness in IBS, there has only been one RCT of hypnotherapy in FD,[245] comparing it with either supportive care or treatment with an H_2RA. The intervention group received 12 30 min sessions of hypnotherapy over a 4-month period, which was well tolerated with no withdrawals due to lack of efficacy. The supportive care group received 12 sessions of support, although one-third of patients withdrew due to lack of response. Hypnotherapy was shown to be effective in reducing symptoms of FD, anxiety and depression in both the short and long term, compared with the other two treatment arms. Hypnotherapy reduced healthcare utilisation, with 90% of the patients in the H_2RA group and 82% of patients in the supportive therapy group commencing another medication for FD during follow-up, compared with 0% in the hypnotherapy group. The hypnotherapy group visited their GP or gastroenterologist significantly less than those in the supportive group (median <1 visit vs 4 visits, respectively). Like many forms of gut–brain behavioural therapy, the evidence base for hypnotherapy in FD is positive, but limited, and there are concerns regarding availability, cost of delivery, time intensity and expertise to deliver it.

In summary, a wide range of different modalities of gut–brain behavioural interventions have shown potential benefits for patients with FD, not only in terms of psychological symptoms, but also gastrointestinal symptoms and quality of life. The offer of gut–brain behavioural intervention should, therefore, not be restricted to those with psychological symptoms or distress. However, to date, RCTs are heterogeneous, focusing on different forms of therapy, duration, symptoms and intensity of delivery. Although studies have invariably shown benefits to patients, the small samples, varying methodology and differences in the forms of gut–brain behavioural therapy used mean it is not possible to recommend one form over another. What is offered to patients is therefore likely to depend on local availability of the different modalities, patient preference for the nature of the therapy, duration and intensity. More RCTs of gut–brain behavioural therapies are needed to elucidate when to use these treatments, and in which patients.

Recommendations

- Interpersonal psychodynamic informed psychotherapy may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).
- CBT and metacognitive therapy may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).
- Stress management approaches may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).
- Hypnotherapy may be an efficacious treatment for global symptoms in FD (recommendation: weak, quality of evidence: very low).

Approach to the patient with severe or refractory symptoms

Severe FD lacks a precise consensus definition but a number of validated severity scores are available, including the Glasgow Dyspepsia Severity Score,[246] The Functional Dyspepsia Symptom Diary[247] and the Leuven Postprandial Distress Scale,[248] used primarily in research settings. Refractory FD is a related, but distinct, term again with no consensus definition. It is considered to encompass the 20%–40% of patients who do not respond to first-line measures,[249] and the 25% of patients who exhibit either more persistent or severe symptoms.[250]

Investigative findings associated with increasing FD severity in small studies include shorter time to satiety,[251] delayed gastric emptying and increased small bowel contractility on wireless motility capsule,[252] longer gastric half emptying time and lag phase on gastric emptying studies,[253 254] and altered high resolution electrogastrography spatial patterns.[255] Visceral hypersensitivity, adjusted for tendency to report symptoms, is also commoner in both severe EPS and PDS, especially after meals,[66]

as well as in those with coexistent anxiety and depression.[53 68] Although these studies highlight potential biomarkers associated with severe FD, their findings should be viewed as preliminary only, and need to be further validated by larger studies.

Overlap with IBS is common in severe or refractory FD,[256] with more primary and secondary care consultations, prescriptions, and more severe pain. Somatisation and female sex are also associated features.[257 258] The largest multicentre study of refractory FD, which was conducted in China, also reported associations with unhealthy eating behaviours, lack of physical activity, sleeping disorders, more medical consultations, increased drug costs and worse quality of life.[250] A highly diverse and large range of associations have been reported in patients with severe or refractory FD, including iatrogenic,[259] psychological,[260] physiological,[261 262] genetic,[263] comorbid,[264 265] socioeconomic[266] and dietary.[267] It is, therefore, clear that a multidisciplinary and multimodal management approach is needed. One RCT reported superior outcomes with an integrated approach involving gastroenterologists, dietitians and clinical psychologists, rather than a gastroenterologist alone, in a mixed population of patients with DGBI, almost one-third of whom had FD.[268]

Patients with FD are willing to accept considerable risk in return for symptom cure. In one study, when asked about a hypothetical medication that could cure their symptoms, 50% of respondents reported they would accept a mean 13% risk of sudden death for a 99% chance of cure.[269] This risk profile underscores that it is important to avoid iatrogenesis in those with severe or refractory FD. This includes avoiding opioids, which are associated with vomiting, constipation, more severe dyspeptic symptoms, higher rates of depression and worse quality of life in FD.[270] Unnecessary surgery may also be a danger for patients with severe FD, and more severe symptoms and opioid use were more likely after cholecystectomy.[259] Use of opioids should prompt consideration of the differential of the narcotic bowel syndrome, and chronic continuous abdominal pain with minimal association with physiological events raises the possibility of centrally-mediated abdominal pain syndrome.[271]

Unfortunately, most RCTs conducted in FD do not stratify patients by severity, so a specific evidence base for severe FD is lacking. Several approaches have, however, been documented in small RCTs for severe or refractory FD. The neuropathic analgesic gabapentin as an adjunct to PPI therapy helped abdominal pain and indigestion in one RCT, conducted in 126 'resistant' patients with FD.[272] In another RCT, recruiting 95 patients, a duodenal-release formulation of a spasmolytic combination of caraway oil and l-menthol improved epigastric pain and early satiation within 24 hours in 75% of patients with more severe symptoms, compared with usual treatment alone.[273] The anticholinergic clidinium, combined with the anxiolytic chlordiazepoxide, as add-on therapy improved dyspeptic symptoms and quality of life significantly in one trial conducted in 78 patients, but its availability is limited.[274] A combination preparation of the anxiolytic flupenthixol and the antidepressant melitracen showed potential efficacy in a crossover RCT of 25 patients with refractory FD.[275] As previously discussed, one trial used a multimodal approach in 100 patients with refractory FD, which involved intensified medical management testing for and targeting of abnormalities of sensory and motor function including gastric emptying, a standardised nutrient challenge and, if clinically indicated, 24-hour pH monitoring, manometry and breath tests. When this was combined with gut–brain behavioural intervention, it yielded superior long-term-outcomes, including improvements in concomitant anxiety and depression, compared with standard approaches.[240] Finally, in another RCT, recruiting 132 patients with refractory FD, electroacupuncture plus on-demand gastrocaine, which consists of a combination of the local anaesthetic oxethazaine with the antacids aluminium and magnesium hydroxide, provided significant symptom relief.[276]

In terms of uncontrolled studies, in an open-label study of 59 patients refractory to first-line treatment, early satiation and half gastric emptying time improved with the 5-HT_{1A} agonist buspirone, and postprandial fullness with amitriptyline.[254] Acotiamide in combination with a PPI improved otherwise refractory symptoms in an open-label study in 23 patients.[277] Hypnotherapy also appears promising in refractory FD.[278] A TCA in conjunction with a gut–brain behavioural therapy or psychiatric input may be considered in patients not responding to single modality treatment.[279 280] For refractory pain in severe EPS, a combination of gut–brain neuromodulators, termed augmentation, might be considered. However, clinicians should be aware of the risk of serotonin syndrome with combined use of an SSRI and an SNRI[212]; the risk of this is much lower with combinations involving a low dose TCA.

The most challenging presentation of severe or refractory FD is when accompanied by substantial dietary restriction, weight loss or malnutrition. In tertiary care, weight loss in FD is strongly associated with early satiation, and also nausea and vomiting, but its predictive value for underlying organic disease is limited.[281] Weight loss is more strongly associated with depression, a history of abuse, and somatisation than with gastric sensorimotor function, especially in viscerally hypersensitive patients,[282] with more frequent physician visits and reduced quality of life,[283] and is more frequent in female patients with overlap of FD and IBS.[114]

In patients with FD and restricted diet or weight loss it is vital to screen for ARFID, and other eating or feeding disorders, to assist with behavioural management.[179 252] ARFID is a feeding and eating disorder described recently in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders.[284] There is a substantial overlap with DGBI, especially those with dyspepsia, nausea, vomiting, or abdominal pain components.[285] Indeed, patients with FD frequently meet criteria for ARFID, irrespective of alterations in gastric emptying.[179] This suggests that the restricted eating patterns reported by patients with FD may actually be driven primarily by ARFID. Unlike anorexia nervosa and bulimia, ARFID is not driven primarily by concerns about body shape or weight, but rather by other core motivations, of which fear avoidance of gastrointestinal symptoms is the most prevalent in DGBI.[285] However, the precise relationship between DGBI and ARFID remains to be determined.[285] These may be different names for the same presentation, separate comorbidities that frequently coexist, or else ARFID may develop secondary to a DGBI in some individuals.[285] Caution has been advised regarding the risks of giving overly restrictive and avoidant dietary advice in DGBI,[286] because ARFID may often go unrecognised. Moreover, nasogastric tube feeding may impair both nutritional rehabilitation and psychological recovery in ARFID.[287] In contrast with some dietary approaches for FD, which avoid specific foods or reduce food volume, exposure-based CBT helps patients with ARFID re-build tolerance to specific foods and food volume systematically and gradually, decreasing fear and anxiety related to precipitating gastrointestinal sensations or symptoms, while regulating hunger satiety cues.[179]

Early dietitian involvement should, therefore, be considered to avoid over-restriction of diet in severe or refractory FD.[288] Optimised oral nutrition is the best management option for most patients. If, and when, to escalate to clinically assisted nutrition or hydration support is a finely balanced risk versus benefit

decision, which should be made in a multidisciplinary nutrition support team setting, and driven primarily by objective markers of malnutrition, rather than by severe symptoms alone.[289] In terms of optimising weight, in a small RCT recruiting 34 patients with FD, without anxiety and depression and not on antidepressants, mirtazapine improved early satiation, quality of life, gastrointestinal-specific anxiety, nutrient tolerance and weight loss significantly, compared with placebo,[225] but this requires confirmation in larger studies before widespread adoption in clinical practice.[290]

Recommendations

- We recommend a multidisciplinary support team should be involved for patients with severe or refractory FD (recommendation: strong, quality of evidence: low).
- We recommend opioids and surgery should be avoided in patients with severe or refractory FD to minimise iatrogenic harm (recommendation: strong, quality of evidence: very low).
- We recommend patients with severe or refractory FD presenting with weight loss and food restriction are assessed for eating disorders and disordered eating, including ARFID (recommendation: strong, quality of evidence: very low).
- We recommend early dietitian involvement in patients with severe or refractory FD to avoid an overly restrictive diet (recommendation: strong, quality of evidence: very low).

Drugs in development and other therapies

Alterations in the duodenal microbiota may also be implicated in the pathophysiology of FD.[99] Despite increasing interest in the small intestinal microbiome, and in contrast to IBS,[291] there has been only one RCT of antibiotics in FD. This trial of the minimally absorbed antibiotic rifaximin, conducted in Hong Kong, demonstrated significantly higher rates of adequate relief of global symptoms and postprandial fullness,[292] but more RCTs are needed before any definitive conclusions can be drawn. Any evidence for a benefit of probiotics in FD is even less clear than in IBS.[293] However, in an RCT, 8 weeks of *Bacillus coagulans* MY01 and *Bacillus subtilis* MY02 was more efficacious than placebo in terms of likelihood of symptom improvement in 68 patients.[294] Both a decrease in Th17 signalling and an increased relative abundance of *Faecalibacterium* were associated with efficacy. Rikkunshito, which is a traditional Japanese kampo medicine that appears to have effects on 5-HT, was beneficial in one trial,[295] with significant improvements in epigastric pain, and higher rates of improvement of postprandial fullness. However, a subsequent Belgian RCT did not demonstrate any benefit over placebo.[296] In patients with PDS, acupuncture was superior to a sham procedure in one Chinese trial recruiting over 200 patients, but this needs confirmation in other geographical regions.[297]

It is hoped that a better understanding of disease mechanisms in FD will lead to new therapeutic targets and, therefore, either development of novel drugs, or repurposing of existing ones. Histamine is released by mast cells and the intestinal microbiome. A small uncontrolled study suggested simultaneous use of H_1RAs and H_2RAs may be a promising approach.[298] In this study, 14 patients with refractory symptoms were prescribed loratadine and ranitidine, with 10 (71%) experiencing symptom improvement subsequently. Higher duodenal eosinophil counts predicted response. RCTs of this strategy should be considered.

Duodenal eosinophilia may also represent a target for future treatment. As discussed, PPIs appear to reduce eosinophilia and normalise duodenal permeability in FD.[207] However, there are novel drugs undergoing testing in eosinophilic gastrointestinal disorders that may have applications in FD. Lirentelimab is a monoclonal antibody that targets SIGLEC-8, which is expressed selectively on both eosinophils and mast cells. In an RCT, patients with gastrointestinal symptoms, including abdominal pain and nausea, underwent endoscopy to confirm gastric or duodenal eosinophil counts≥30 per high power field.[299] As well as reducing eosinophil counts in the stomach and duodenum, in a *post hoc* analysis 64% of patients randomised to lirentelimab had a 50% or more improvement in total symptom score, compared with 15% of placebo patients. Given that duodenal eosinophil counts in this study were well within the range seen in patients with FD,[93] and that some participants likely had symptoms compatible with FD, this suggests that trials of the drug for this indication may be warranted.

Potassium-competitive acid blockers, which are a relatively new class of acid suppression drugs, have already been tested in patients with GORD,[300] and it is hoped that there will be future trials in FD. However, given that excess acid production is not involved in FD pathophysiology, any benefit may be modest as with PPIs. In addition, the drugs are still unavailable outside of Asia. As FD and idiopathic gastroparesis are indistinguishable clinically,[18] and patients seem to move between these two diagnoses during extended follow-up,[16] drugs undergoing testing in gastroparesis may also have applications in patients with FD. Ghrelin agonists, like relamorelin,[301] 5-HT_4 agonists, such as prucalopride or velusetrag,[302 303] and aprepitant and tradipitant, which are neurokinin-$_1$-receptor antagonists,[304 305] alter gastric physiology and improve symptoms in patients with gastroparesis. RCTs of these drugs in patients with FD should, therefore, be considered.

RESEARCH: BARRIERS, PRIORITIES AND IMPLICATIONS FOR FUTURE STUDY DESIGN

A better understanding of the pathophysiology of FD and its disease mechanisms should lead to improved diagnostic tests to discriminate FD from other disorders with similar or overlapping symptoms for research purposes, rather than merely relying on symptom-based criteria and a negative endoscopy, improved subgrouping of patients and, potentially, identifying new therapeutic targets.[50] The resulting improvement in characterisation of patients may help reduce heterogeneity in both research and clinical practice. However, current biomarkers for FD, such as duodenal eosinophilia, require endoscopy and biopsy,[85 204] yet the utility of endoscopy in patients with typical symptoms of FD is minimal,[2] which may limit the suitability of this approach.

Current drug treatments for FD are modest in their efficacy,[27 146 181–185] and patients may be dissatisfied with current available medicines and seek out alternatives.[306] The lack of availability of, or safety concerns related to, some efficacious drugs, including most prokinetics in many geographical regions, exacerbates these problems. There are also logistical difficulties in organising large-scale RCTs to test new medicines for FD. Despite this being a highly prevalent condition, trials are not easy to run and patient recruitment may be slow or even inadequate. The latter probably relates to several factors. These include overly rigid eligibility criteria, the theoretical necessity to employ endoscopy to make a diagnosis of FD, and the false belief that gastric emptying studies are required to differentiate between FD and gastroparesis.[16] There may also be a lack of understanding among many GPs and gastroenterologists of the symptoms that constitute FD, as well as confusion with GORD.[117]

Moreover, recruitment to RCTs may depend on specialist clinics in secondary and tertiary care, whereas most patients with FD are seen and treated in primary care.[107] Patient-level factors are also important. There may be reluctance to participate in trials if this entails too many visits, invasive procedures, or a high burden of symptom data collection, such as daily diaries. In addition, despite FD being a chronic DGBI with fluctuating symptoms that can significantly impair quality of life,[29] and in contrast to IBS, the role of dietary therapies, some gut–brain neuromodulators, and most gut–brain behavioural therapies has not been explored adequately and remains uncertain.[234]

Thus, future trials may need to consider a more pragmatic approach, with patients recruited using a less rigid definition of FD, avoidance of the need for endoscopy to 'diagnose' the condition by excluding patients with alarm symptoms or signs, and only the minimum important data collected. More RCTs in primary care, where the bulk of patients with FD are seen and managed, are also required. Placebo-controlled treatment trials may also need to consider a cross-over to, or open-label treatment with, the active drug after follow-up for the primary endpoint has been reached, as has been done in other trials in DGBI,[307] to increase appeal to patients. More head-to-head studies of one drug versus another are also required, similar to the direct comparisons of management strategies for dyspepsia that have taken place in multiple RCTs.[153] A virtual approach to recruitment, already introduced in other DGBI,[308 309] with remote methodology and no geographical exclusions, may also lead to faster successful recruitment to large pragmatic trials.

Recommendations

1. Successful completion of large clinical trials requires pragmatic inclusion criteria, minimisation of the participant trial burden, and virtual (remote access) trial approaches to reduce geographical, socioeconomic, and minority ethnic exclusion.
2. Large-scale RCTs with cross-over phases or periods of open-label treatment so active therapy may be delivered to all participants should be considered.
3. A priority-setting partnership with patients would best discern valuable research questions.
4. Some future research themes include, but are not limited to:
   i. Characterisation of the illness to understand predictors (clinical, dietary, genetic, psychological and biological) of outcome and treatment response, determinants of refractory illness and burden of illness (particularly with respect to workplace productivity) by conducting large-scale epidemiological studies with extended observation.
   ii. Consideration should be given to stratifying RCTs by FD severity and subtype, burden of extraintestinal symptoms, and psychological comorbidity.
   iii. A better understanding of treatment combinations to uncover augmentation effects between therapies, such as dual therapy with histamine-$_1$ and histamine-$_2$-receptor antagonists or a TCA in combination with a SSRI.
   iv. Modulation of pain and psychological responses using drugs (eg, SNRIs, mirtazapine, or 5-hydroxytryptamine-$_{1A}$ agonists) or behavioural approaches (eg, CBT) used earlier in the disease course.
   v. Trials of dietary approaches to managing symptoms in FD, including a diet low in fermentable oligosaccharides, disaccharides, and monosaccharides, and polyols.
   vi. Trials of drugs that have shown efficacy in gastroparesis, including ghrelin agonists, such as relamorelin, 5-hydroxytryptamine-$_4$ agonists, including prucalopride and velusetrag, and the neurokinin-$_1$-receptor antagonists aprepitant and tradipitant should be considered.
   vii. Head-to-head trials of TCAs versus acid suppressant drugs, such as PPIs or histamine-$_2$-receptor antagonists, as first-line drug therapy for FD in primary care.

CONCLUSIONS

FD is a complex, multifactorial DGBI, which is highly prevalent in the community, and is one of the conditions most frequently encountered in the gastroenterology outpatient clinic, although the majority of patients are seen and managed in primary care. An effective approach to the diagnosis and management of FD is, therefore, important to healthcare systems, patients and society. This guideline summarises current evidence to provide a practical guide for clinicians seeing patients with the condition, underlining the importance of effective communication, making a positive diagnosis, and reducing unnecessary investigation. It recommends instituting appropriate, evidence-based treatments according to presence of *H. pylori*, global patient assessment, and patient choice, to address both symptoms and quality of life within a biopsychosocial framework. It has also highlighted emerging new therapeutic options for FD and priority areas for ongoing research.

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SUPPLEMENT

Search Strategy

MEDLINE, EMBASE and EMBASE Classic, and the Cochrane central register of controlled trials were searched. The search was limited to humans. No restrictions were applied with regard to language of publication. A recursive search of the bibliography of relevant articles was also conducted. Conference proceedings from Digestive Diseases Week, Asia Pacific Digestive Week, and United European Gastroenterology Week were searched. The literature search used is given below.

For randomised controlled trials of eradication therapy for *H. pylori*-positive functional dyspepsia:

1 exp Dyspepsia/

2 dyspep* or "NUD" or "FD"

3 indigestion or indigestive

4 1 or 2 or 3

5 exp helicobacter

6 exp helicobacter infections

7 exp helicobacter pylori

8 helicobacter or pylori or pyloridis or "HP" or Campylobacter

9 5 or 6 or 7 or 8

10 4 and 9

11 randomized controlled trial

12 controlled clinical trial.pt

13 random*

14 placebo

15 drug therapy

16 trial

17 groups

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

19 exp animals/ not

20 18 not 19

21 10 and 20

For randomised controlled trials of drugs for functional dyspepsia:

1 dyspepsia.mp. or Dyspepsia/

2 dyspep$.mp.

3 1 or 2

4 Antidepressive Agents, Second-Generation/ or Antidepressive Agents/ or venlafaxine.mp. or Serotonin Uptake Inhibitors/

5 psychotropic drugs.mp. or Psychotropic Drugs/

6 antidepressive agents.mp. or Antidepressive Agents/

7 Antidepressive Agents, Tricyclic/ or Desipramine/ or tricyclic.mp. or Nortriptyline/ or Serotonin Uptake Inhibitors/ or Imipramine/

8 desimipramine.mp.

9 doxepin.mp. or Doxepin/

10 dothiepin.mp. or Dothiepin/

11 Amitriptyline/ or amitryptiline.mp.

12 paroxetine.mp. or Paroxetine/

13 sertraline.mp. or Sertraline/

14 fluoxetine.mp. or Fluoxetine/

15 citalopram.mp. or Citalopram/

16 trimipramine.mp. or Trimipramine/

17 desipramine.mp. or Desipramine/

18 imipramine.mp. or Imipramine/

19 nortiptyline.mp. or Nortriptyline/

20 venlafaxine.mp.

21 duloxetine.mp.

22 escitalopram.mp.

23 Sulpiride/ or levosulpiride.mp.

24 mirtazapine.mp.

25 pregabalin

26 gabapentin

27 Histamine 2 receptor antagonists.mp.

28 Histamine-2 receptor antagonists.mp.

29 H2 receptor antagonists.mp.

30 H-2 receptor antagonists.mp.

31 famotidine.mp.

32 nizatidine.mp.

33 ranitidine.mp.

34 cimetidine.mp.

35 proton pump inhibitors.mp.

36 PPIs.mp. 35 omeprazole.mp.

37 esomeprazole.mp.

38 lansoprazole.mp.

39 dexlansoprazole.mp.

40 rabeprazole.mp.

41 pantoprazole.mp.

42 zantac.mp.

43 tagamet.mp.

44 losec.mp.

45 prilosec.mp.

46 zoton.mp.

47 nexium.mp.

48 pariet.mp.

49 protium.mp.

50 mosapride.mp.

51 itopride.mp.

52 Ganaton.mp.

53 acotiamide.mp.

54 Acofide.mp.

55 tegaserod.mp.

56 zelnorm.mp.

57 serotonin norepinephrine reuptake inhibitors.mp or Serotonin and Noradrenaline Reuptake Inhibitors/

58 Serotonin 5-HT1 Receptor agonists/ or tandospirone.mp or Receptor, Serotonin, 5-HT1A/

59. buspirone.mp or Buspirone/

60 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59

61 3 and 60

Supplementary Table 1. Summary of Evidence from Randomised Controlled Trials of Drugs in Functional Dyspepsia.

Intervention	Number of RCTs	Number of Patients	FD Subtype	Relative Risk of Symptoms not Improving (95% CI)	Recommendation	Quality of Evidence
***H. pylori* eradication therapy is effective in FD**	29	6781	Not stated	0.87 (0.83 to 0.92)	Strong	High
Histamine-$_2$-receptor antagonists may be effective in FD	12	2268	Not stated	0.79 (0.68 to 0.92)	Weak	Low
Proton pump inhibitors are effective in FD						
Any dose	16	6017	Not stated	0.88 (0.83 to 0.93)	Strong	High
High dose	5	1627	Not stated	0.86 (0.74 to 1.01)	Strong	High
Standard dose	9	2890	Not stated	0.86 (0.78 to 0.95)	Strong	High
Low dose	9	2755	Not stated	0.89 (0.81 to 0.97)	Strong	High

Prokinetics may be effective in FD						
Acotiamide	6	2429	Mainly PDS	0.89 (0.78 to 1.00)	Weak	Low
Itopride	5	1854	Not stated	0.88 (0.77 to 1.01)	Weak	Low
Mosapride	1	589	Not stated	0.99 (0.80 to 1.23)	Weak	Low
Tegaserod	2	2667	Not stated	0.89 (0.82 to 0.96)	Strong	Moderate
Antipsychotic drugs (sulpiride and levosulpiride) may be effective in FD	3	172	Not stated	0.50 (0.37 to 0.67)	Weak	Low
Tricyclic antidepressants are effective in FD	4	400	Not stated	0.75 (0.62 to 0.90)	Strong	Moderate
Selective serotonin reuptake inhibitors are not effective in FD	2	388	Not stated	1.01 (0.89 to 1.15)	Weak	Moderate
Serotonin norepinephrine reuptake inhibitors are not effective in FD	1	160	Not stated	1.02 (0.80 to 1.30)	Weak	Low
Tandospirone may be effective in FD	1	150	Not stated	0.79 (0.66 to 0.94)	Weak	Low
Buspirone is not effective in FD	1	16	Not stated	0.48 (0.20 to 1.15)	Weak	Low

Pregabalin may be effective in FD	1	72	Not stated	0.53 (0.29 to 0.96)	Weak	Low

Supplementary Table 2. Total Number of Trials of Each Treatment, and Total Number of Included Patients Assigned to Each Drug and Placebo in the Network Meta-analysis of Drugs Used First or Second Line in FD.

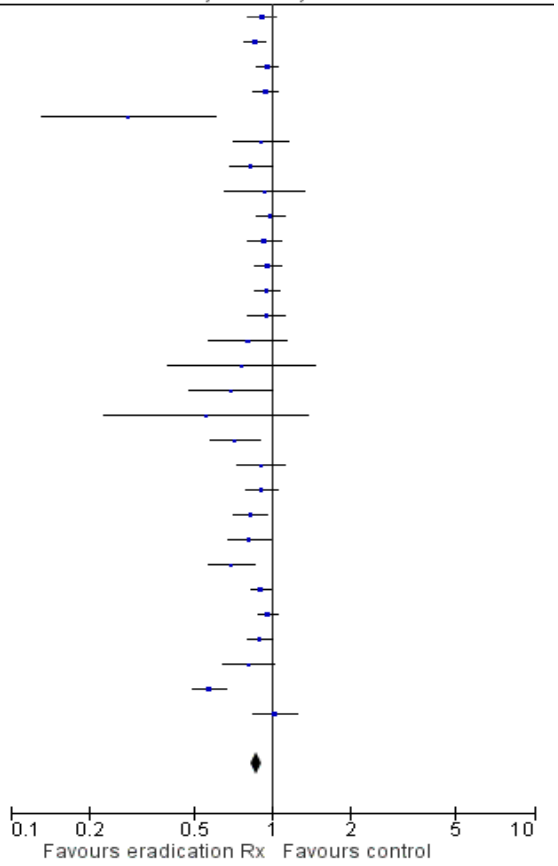
Treatment	Number of RCTs	Total Number of Patients
H_2-receptor antagonists	16	1293
Itopride	13	1653
Standard dose proton pump inhibitors	11	1693
Low dose proton pump inhibitors	10	1431
Mosapride	8	908
High dose proton pump inhibitors	7	1288
Domperidone	7	587
Acotiamide	6	1540
Tricyclic antidepressants	5	228
5-HT_{1A} agonists	5	158
Selective serotonin reuptake inhibitors	3	216
Antipsychotics	3	86
Tegaserod	2	1337
Mirtazapine	2	37
Serotonin norepinephrine reuptake inhibitors	1	80
Pregabalin	1	38

Placebo	55	6742

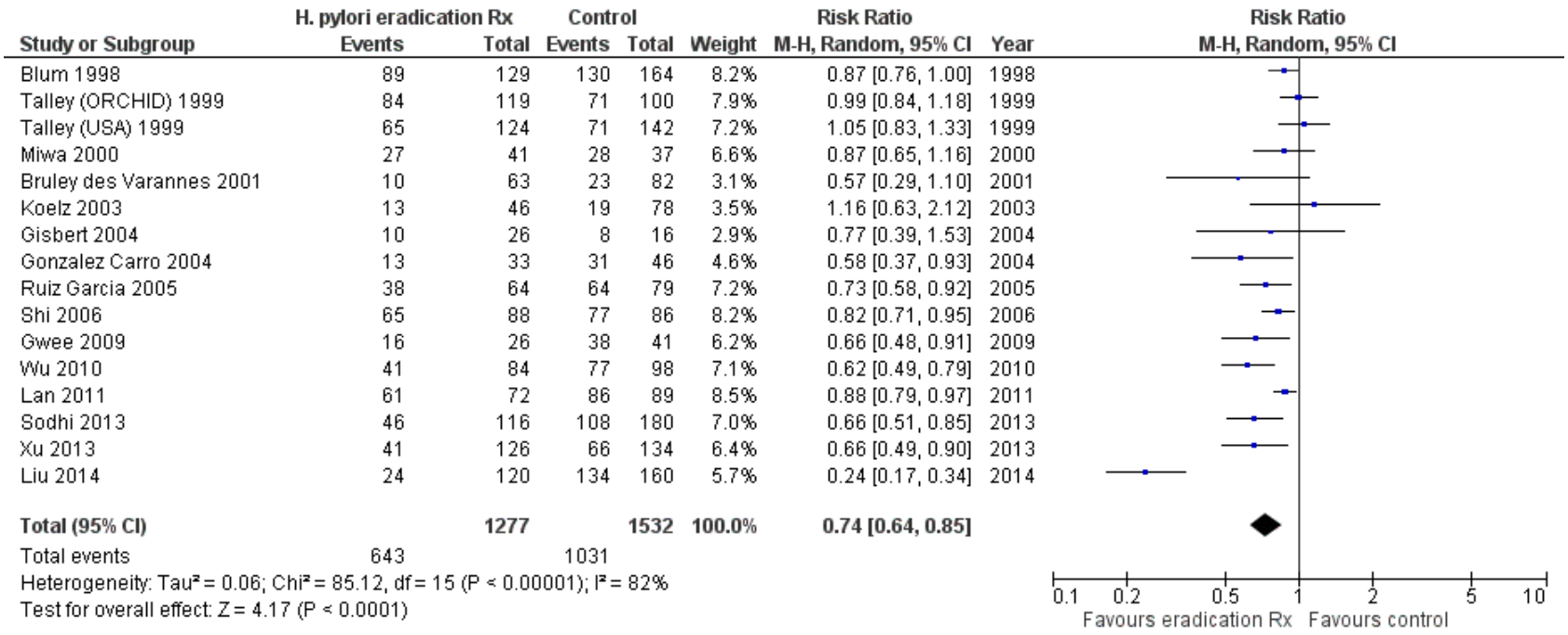
Supplementary Figure 1. Forest Plot of Randomised Controlled Trials of Eradication Therapy in *H. pylori*-positive FD in Terms of Effect on Cure or Improvement of Symptoms: Pairwise Meta-analysis.

	H. pylori eradication Rx		Control			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Blum 1998	119	164	130	164	4.6%	0.92 [0.81, 1.03]	1998
McColl 1998	127	160	147	158	5.3%	0.85 [0.78, 0.93]	1998
Talley (ORCHID) 1999	115	135	127	143	5.3%	0.96 [0.88, 1.05]	1999
Talley (USA) 1999	128	170	134	167	4.8%	0.94 [0.84, 1.05]	1999
Dhali 1999	6	32	20	30	0.4%	0.28 [0.13, 0.60]	1999
Miwa 2000	35	50	31	40	2.5%	0.90 [0.71, 1.16]	2000
Bruley des Varannes 2001	74	129	86	124	3.3%	0.83 [0.68, 1.00]	2001
Hsu 2001	34	81	36	80	1.5%	0.93 [0.66, 1.33]	2001
Froehlich 2001	77	92	75	88	4.6%	0.98 [0.87, 1.11]	2001
Koskenpato 2001	61	77	63	74	4.1%	0.93 [0.80, 1.08]	2001
Alizadeh-Naeeni 2002	72	84	65	73	4.7%	0.96 [0.85, 1.08]	2002
Malfertheiner 2003	338	534	177	266	5.0%	0.95 [0.85, 1.06]	2003
Koelz 2003	67	89	73	92	3.9%	0.95 [0.81, 1.11]	2003
Veldhuyzen van Zanten 2003	31	75	42	82	1.6%	0.81 [0.57, 1.14]	2003
Gisbert 2004	13	34	8	16	0.5%	0.76 [0.40, 1.46]	2004
Gonzalez Carro 2004	22	47	31	46	1.4%	0.69 [0.48, 1.00]	2004
Martinek 2005	5	20	9	20	0.3%	0.56 [0.23, 1.37]	2005
Ruiz Garcia 2005	46	79	64	79	2.9%	0.72 [0.58, 0.89]	2005
Ang 2006	49	71	45	59	3.0%	0.90 [0.73, 1.12]	2006
Mazzoleni 2006	39	46	42	45	4.1%	0.91 [0.79, 1.05]	2006
Shi 2006	65	88	77	86	4.2%	0.82 [0.71, 0.95]	2006
Gwee 2009	31	41	38	41	3.2%	0.82 [0.67, 0.99]	2009
Wu 2010	55	100	79	100	3.1%	0.70 [0.57, 0.85]	2010
Lan 2011	86	98	94	97	5.5%	0.91 [0.83, 0.98]	2011
Mazzoleni 2011	166	201	175	203	5.5%	0.96 [0.88, 1.04]	2011
Sodhi 2013	185	280	204	276	4.9%	0.89 [0.80, 1.00]	2013
Xu 2013	105	262	66	134	2.7%	0.81 [0.65, 1.02]	2013
Liu 2014	100	200	174	200	4.1%	0.57 [0.50, 0.67]	2014
Yazdanbod 2015	99	186	90	173	3.2%	1.02 [0.84, 1.25]	2015
Total (95% CI)		**3625**		**3156**	**100.0%**	**0.87 [0.83, 0.92]**	
Total events	2350		2402				

Heterogeneity: Tau² = 0.01; Chi² = 77.80, df = 28 (P < 0.00001); I² = 64%
Test for overall effect: Z = 5.47 (P < 0.00001)



Supplementary Figure 2. Forest Plot of Randomised Controlled Trials of Eradication Therapy in *H. pylori*-positive FD in Terms of Effect on Cure or Improvement of Symptoms in Patients with Successful Eradication of *H. pylori*: Pairwise Meta-analysis.

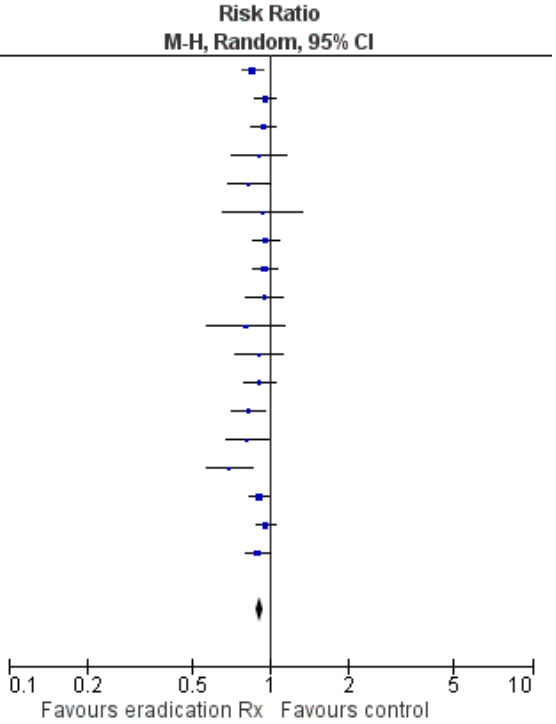


Supplementary Figure 3. Forest Plot of Randomised Controlled Trials of Eradication Therapy in *H. pylori*-positive FD in Terms of Effect on Cure of Symptoms: Pairwise Meta-analysis.

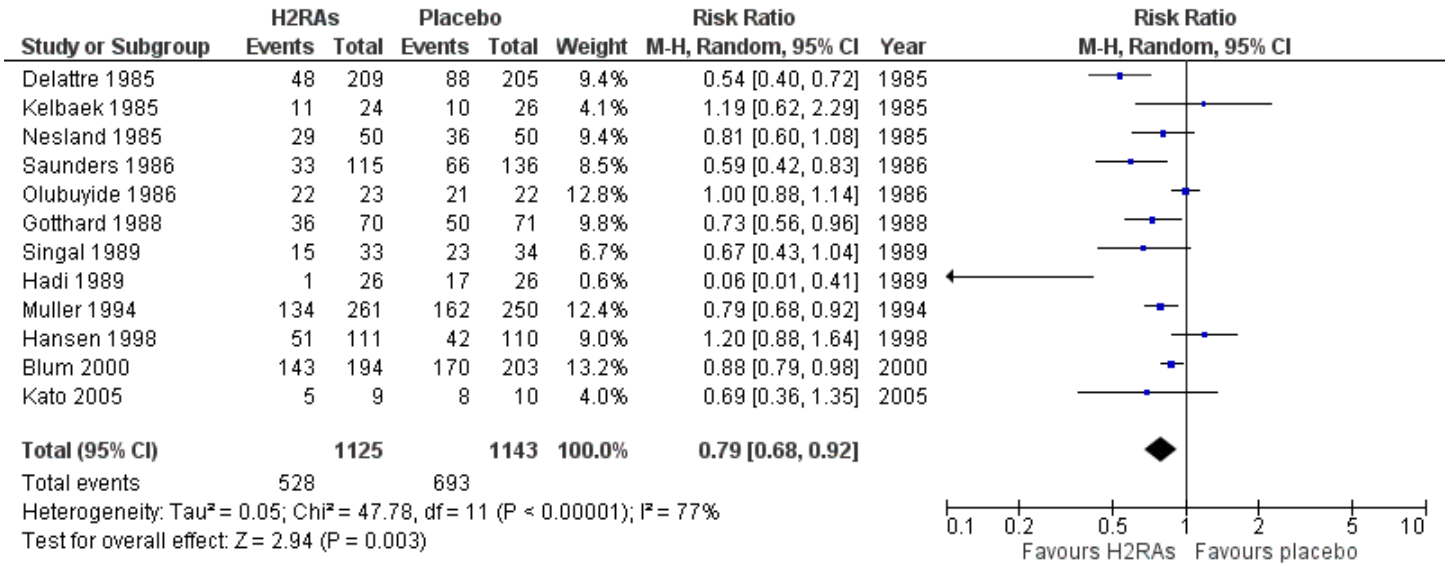
Study or Subgroup	H. pylori eradication Rx Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
McColl 1998	127	160	147	158	10.7%	0.85 [0.78, 0.93]	1998
Talley (ORCHID) 1999	115	135	127	143	10.4%	0.96 [0.88, 1.05]	1999
Talley (USA) 1999	128	170	134	167	6.9%	0.94 [0.84, 1.05]	1999
Miwa 2000	35	50	31	40	1.6%	0.90 [0.71, 1.16]	2000
Bruley des Varannes 2001	74	129	86	124	2.7%	0.83 [0.68, 1.00]	2001
Hsu 2001	34	81	36	80	0.8%	0.93 [0.66, 1.33]	2001
Alizadeh-Naeeni 2002	72	84	65	73	6.5%	0.96 [0.85, 1.08]	2002
Malfertheiner 2003	338	534	177	266	7.8%	0.95 [0.85, 1.06]	2003
Koelz 2003	67	89	73	92	3.8%	0.95 [0.81, 1.11]	2003
Veldhuyzen van Zanten 2003	31	75	42	82	0.8%	0.81 [0.57, 1.14]	2003
Ang 2006	49	71	45	59	2.2%	0.90 [0.73, 1.12]	2006
Mazzoleni 2006	39	46	42	45	4.4%	0.91 [0.79, 1.05]	2006
Shi 2006	65	88	77	86	4.5%	0.82 [0.71, 0.95]	2006
Gwee 2009	31	41	38	41	2.5%	0.82 [0.67, 0.99]	2009
Wu 2010	55	100	79	100	2.3%	0.70 [0.57, 0.85]	2010
Lan 2011	86	98	94	97	12.5%	0.91 [0.83, 0.98]	2011
Mazzoleni 2011	166	201	175	203	12.0%	0.96 [0.88, 1.04]	2011
Sodhi 2013	185	280	204	276	7.5%	0.89 [0.80, 1.00]	2013
Total (95% CI)		**2432**		**2132**	**100.0%**	**0.91 [0.88, 0.94]**	
Total events	1697		1672				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 18.21$, $df = 17$ ($P = 0.38$); $I^2 = 7\%$

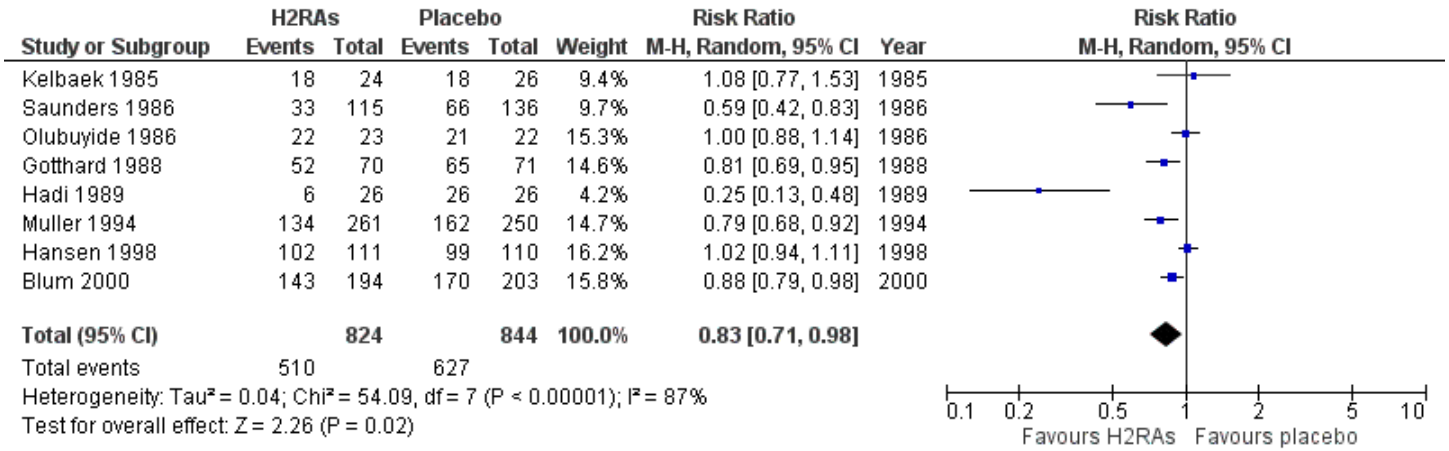
Test for overall effect: $Z = 6.10$ ($P < 0.00001$)



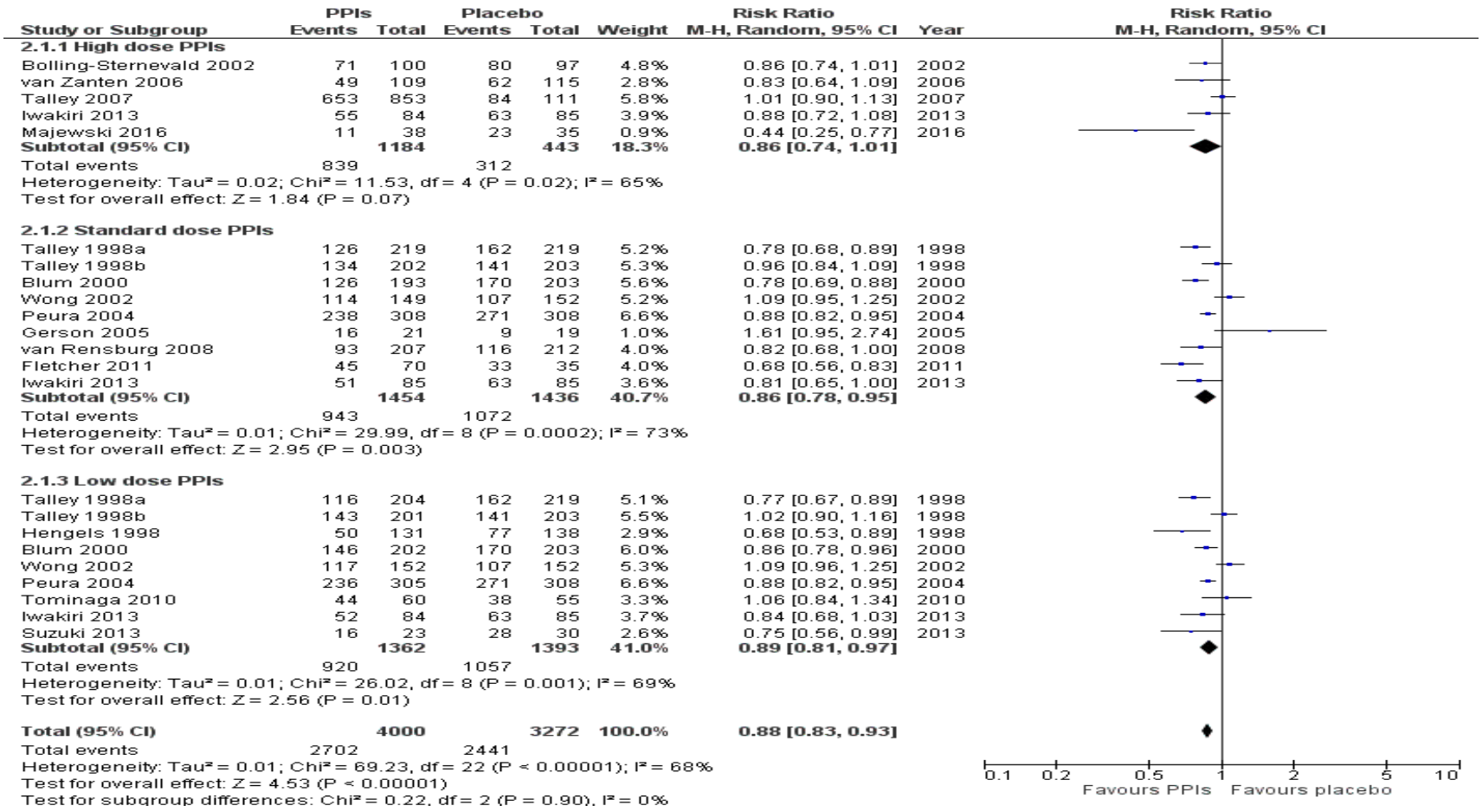
Supplementary Figure 4. Forest Plot of Randomised Controlled Trials of Histamine-$_2$-Receptor Antagonists in FD in Terms of Effect on Improvement of Symptoms: Pairwise Meta-analysis.



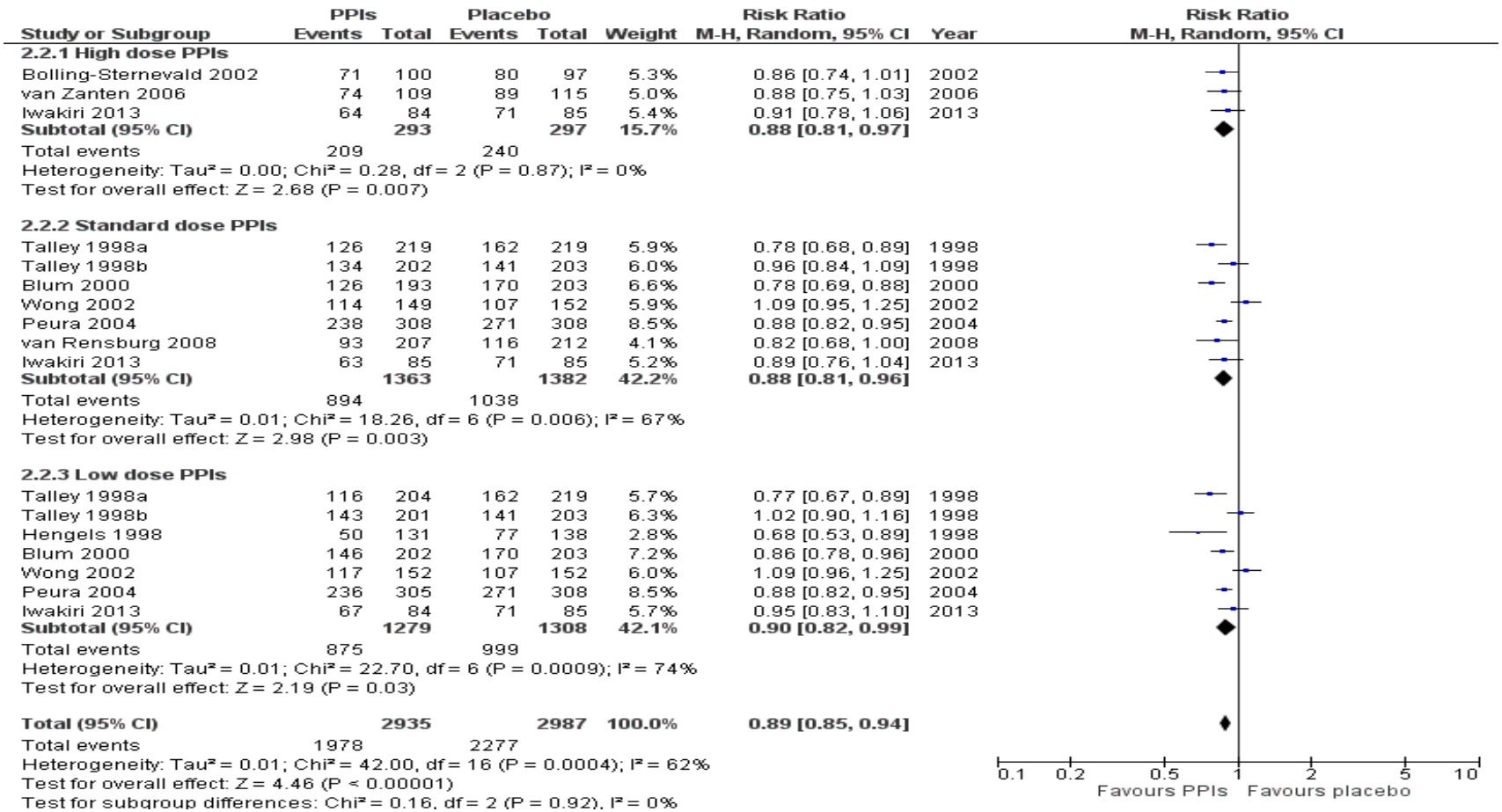
Supplementary Figure 5. Forest Plot of Randomised Controlled Trials of Histamine-$_2$-Receptor Antagonists in FD in Terms of Effect on Cure of Symptoms: Pairwise Meta-analysis.



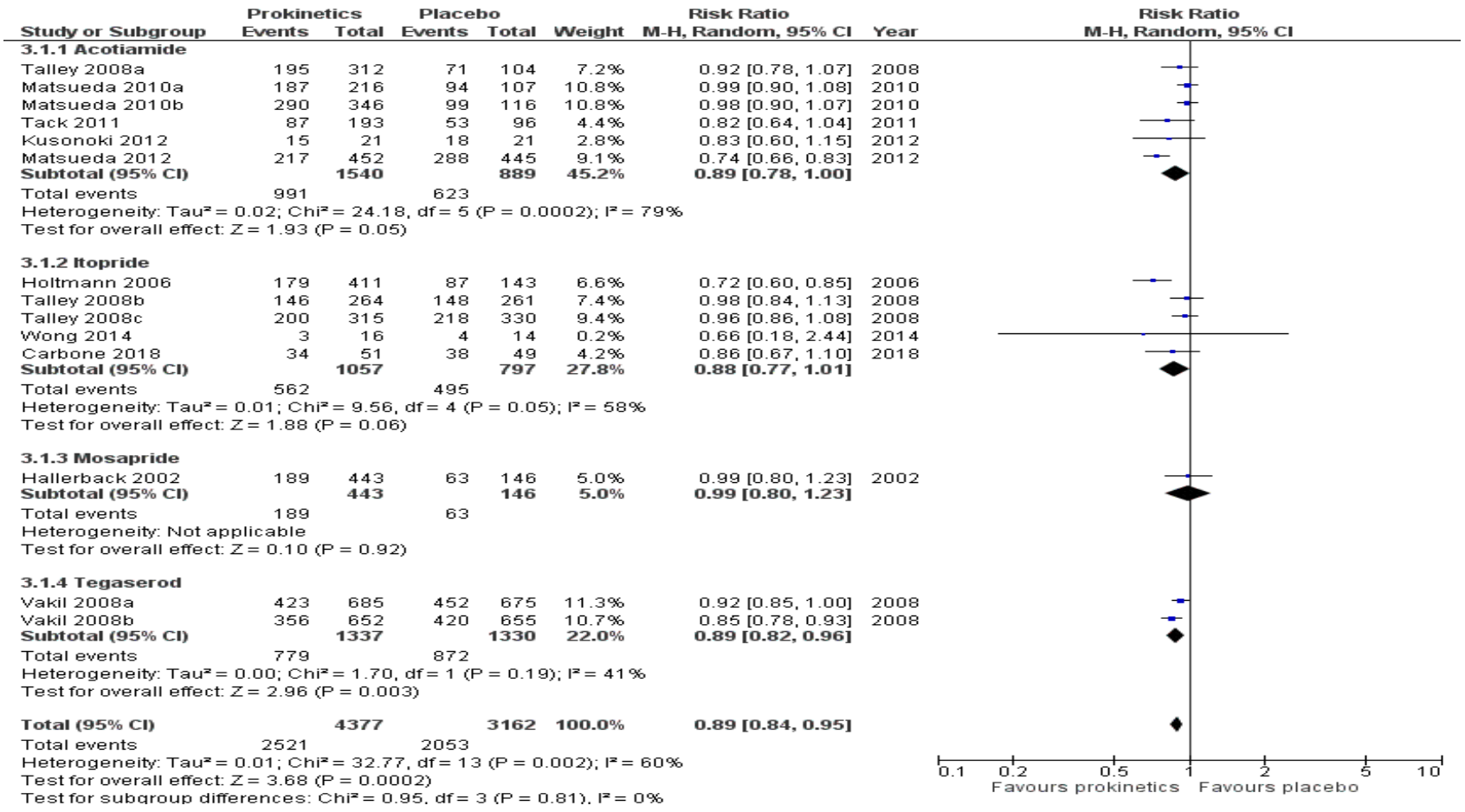
Supplementary Figure 6. Forest Plot of Randomised Controlled Trials of Proton Pump Inhibitors in FD in Terms of Effect on Improvement of Symptoms: Pairwise Meta-analysis.



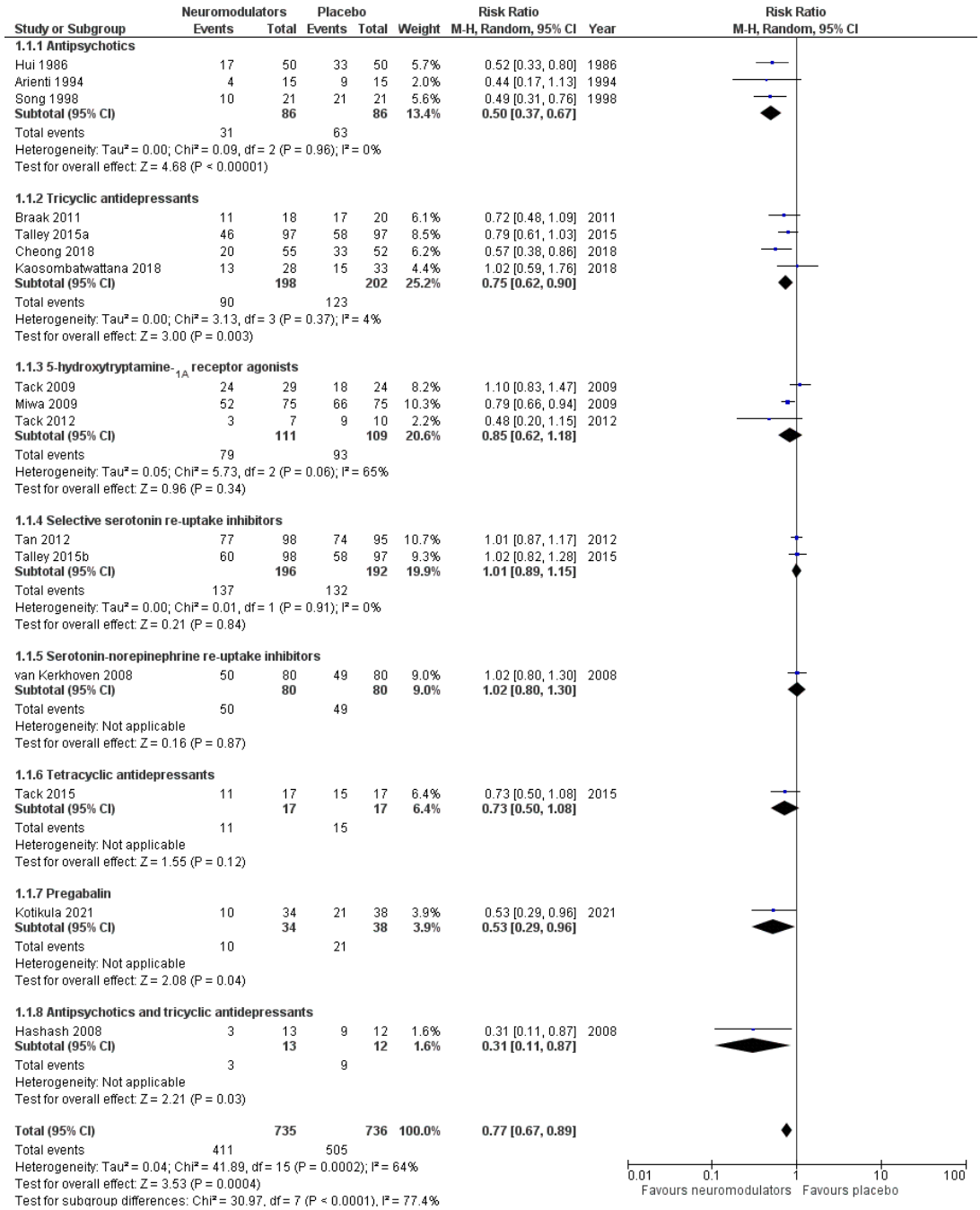
Supplementary Figure 7. Forest Plot of Randomised Controlled Trials of Proton Pump Inhibitors in FD in Terms of Effect on Cure of Symptoms: Pairwise Meta-analysis.



Supplementary Figure 8. Forest Plot of Randomised Controlled Trials of Prokinetics in FD in Terms of Effect on Improvement of Symptoms: Pairwise Meta-analysis.



Supplementary Figure 9. Forest Plot of Randomised Controlled Trials of Gut-brain Neuromodulators in FD in Terms of Effect on Improvement of Symptoms: Pairwise Meta-analysis.



Supplementary Figure 10. Forest Plot of Randomised Controlled Trials of Drugs Used First or Second Line in Terms of Effect on Improvement of Symptoms: Network Meta-analysis.