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Title: Functional Dyspepsia.

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Abbreviations:

5-HT	5-hydroxytryptamine
CI	confidence interval
CRH	corticotrophin-releasing hormone
EPS	epigastric pain syndrome

FD	functional dyspepsia
FODMAPs	fermentable oligo-, di-, and mono-saccharides and polyols
GORD	gastro-oesophageal reflux disease
H_2-RAs	histamine-$_2$-receptor antagonists
HPAA	hypothalamic-pituitary-adrenal axis
H. pylori	*Helicobacter pylori*
IBS	irritable bowel syndrome
IELs	intraepithelial lymphocytes
PDS	postprandial distress syndrome
PPI	proton pump inhibitor
RR	relative risk
RCT	randomised controlled trial
SSRIs	selective serotonin reuptake inhibitors
TCA	tricyclic antidepressant
TRPV1	transient receptor potential vanilloid type-1

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ABSTRACT

Dyspepsia is a complex of symptoms referable to the gastroduodenal region of the gastrointestinal tract, and includes epigastric pain or burning, postprandial fullness, or early satiety. Approximately 80% of individuals with dyspepsia will have no structural explanation for their symptoms, and are labelled as having functional dyspepsia (FD). FD affects up to 16% of otherwise healthy individuals in the community. Risk factors include psychological co-morbidity, acute gastroenteritis, female gender, smoking, use of non-steroidal anti-inflammatory drugs, and *Helicobacter pylori* (*H. pylori*) infection. The pathophysiology remains incompletely understood, but is probably related to disordered communication between the gut and the brain, leading to motility disturbances, visceral hypersensitivity, and alterations in gastrointestinal microbiota, mucosal and immune function, and central nervous system processing. Although technically a normal endoscopy is required to diagnose FD, the utility of endoscopy in all patients with typical symptoms is limited; its use should be restricted to those aged ≥55 years or those with concerning features, such as weight loss or vomiting. As a result of our limited knowledge of pathophysiology, FD is difficult to treat and, in most patients, the condition is chronic, and the natural history is one of fluctuating symptoms. Eradication therapy should be offered to *H. pylori*-positive patients with FD. Other therapies for which evidence of efficacy exists include proton pump inhibitors, histamine-$_2$-receptor antagonists, prokinetics, and central neuromodulators. The role of psychological therapies is uncertain. As our understanding of the pathophysiology of FD continues to increase, it is likely that the next decade will see the emergence of truly disease-modifying therapies for the first time.

INTRODUCTION

The prevalence of dyspepsia in the community is approximately 20%; [1] 80% of these individuals will have no explanation for their symptoms at endoscopy, [2] and have functional dyspepsia (FD). Overall, prevalence of FD is therefore approximately 16%, but may vary according to country and criteria used to define its presence. Characteristic symptoms include epigastric pain, epigastric burning, postprandial fullness, or early satiety, present for at least 6 months. [3] FD is a chronic functional gastrointestinal disorder with no cure; the condition therefore affects quality of life and social functioning. [4,5] Treatment approaches include eradication of *Helicobacter pylori* (*H. pylori*), if present, acid-suppression therapy, prokinetic drugs, and central neuromodulators. The economic impact is huge, estimated at over $18 billion per year in the USA. [6]

SEARCH STRATEGY AND SELECTION CRITERIA

We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials during the last 10 years using the terms “functional dyspepsia”, “non-ulcer dyspepsia”, “epidemiology”, “prevalence”, “incidence”, “aetiology”, “pathophysiology”, “diagnosis”, “investigation”, “management”, “therapy”, and “treatment”in order to identify relevant publications. In addition, we searched national guidelines for the management of dyspepsia, as well as clinicaltrials.gov for unpublished trials. We included only publications in English, and selected those whose findings were, in our view, of the greatest importance, favouring randomised controlled trials and meta-analyses.

EPIDEMIOLOGY

The current symptom-based criteria for FD are the Rome criteria, developed by a group of experts in functional gastrointestinal disorders, and currently in their fourth iteration. [3] The Rome IV criteria divide FD into two subgroups: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) (Table 1). These subgroups were established due to the predominance of meal-related symptoms observed in some patients, [7] and clustering of certain symptoms in factor analysis studies. [8] As the diagnosis of FD requires exclusion of an organic explanation for the symptoms, population-based studies that perform endoscopy prior to diagnosis provide best estimates of prevalence in the community. To date, only three such studies have been conducted, two from Scandinavia, [9,10] and one from Italy; [11] prevalence in these studies was between 10% and 16%. However, as 80% of adults with uninvestigated dyspepsia in the community have no organic pathology at endoscopy, [2] population-based cross-sectional surveys applying symptom-based criteria for FD without performing endoscopy also provide a close approximation of prevalence.

A systematic review and meta-analysis of such studies demonstrated a pooled prevalence of dyspepsia worldwide of 21.8%. [1] This varied substantially between countries. Whether this relates to differences in methodology and diagnostic criteria used between individual studies, or ethic, genetic, and cultural differences between populations is unclear. There are few studies using the Rome IV criteria, but even when using only the previous iteration, the Rome III criteria, to define FD prevalence is highly variable (Figure 1). A three-nation study conducted in the general populations of Canada, the USA, and the UK reported a prevalence of 10%, based on the Rome IV criteria, but this varied from 8% in the UK and Canada to 12% in the USA. [12] In this survey, 61% of respondents had PDS, 18% EPS, and 21% overlap between the two. Studies using the Rome III criteria in referral populations demonstrate overlap in up to one-third of patients, [13] but the change in nomenclature in

moving from Rome III to Rome IV, with classification of those with any postprandial symptoms as PDS, reduced this to <20%, suggesting these subgroups could potentially be useful to direct therapy. [14] However, there is little evidence that the evolving definitions of FD have improved clinical care or defined a particular group of patients with a different prognosis or different response to treatment. [15]

FD often co-exists with other functional gastrointestinal disorders. [16] There is overlap with gastro-oesophageal reflux symptoms in as many as 40% to 50% of patients in both Asian and Western studies. [17,18] EPS appears to be associated with non-erosive reflux disease, [19] whereas PDS overlaps more frequently with functional heartburn. [20] Irritable bowel syndrome (IBS) also co-exists frequently; a previous meta-analysis reported an eight-fold higher odds of IBS in people with FD. [21] Overlap between PDS and IBS appeared more common in one study, and was associated with greater psychological co-morbidity. [22] Other medically unexplained conditions, such as chronic fatigue syndrome, fibromyalgia, and overactive bladder are also more common in patients with FD. [23-25]

RISK FACTORS

Numerous epidemiological studies demonstrate that female gender, smoking, use of non-steroidal anti-inflammatory drugs, and *H. pylori* infection are associated with dyspepsia in the community, but the magnitude of these associations is modest. [1] However, the Kyoto consensus suggests that infection with the bacterium is an organic cause of dyspepsia, termed *H. pylori*-associated dyspepsia; although this is contentious as the consensus also states that if symptoms persist or recur after successful eradication the patient should then be diagnosed with FD. [26] Higher body mass index was an independent predictor of development of FD in one longitudinal study. [27] The relationship between ethnicity and FD has not been explored extensively, due to the relatively uniform ethnic composition of most population-based

surveys. One multi-ethnic study in Malaysia reported a significantly higher prevalence of FD in Indian and Malay participants, compared with Chinese. [28]

Psychological co-morbidity plays a major role in the development of FD, particularly as the gut and brain communicate through the enteric nervous system and the hypothalamic-pituitary-adrenal axis (HPAA). In a Swedish population-based survey, anxiety led to an almost eight-fold increased odds of developing FD over a 10-year period. [29] Two Australian longitudinal studies demonstrated bi-directional effects between gut and brain; individuals with FD at baseline were more likely to develop anxiety or depression during follow-up, and individuals with anxiety and depression at baseline were more likely to develop FD. [30,31]

Acute gastroenteritis is also associated with new onset of FD, termed post-infection FD. A meta-analysis of 19 studies reported an almost three-fold increased odds of developing FD in exposed individuals >6 months post-infection. [32] Although post-infection FD has been reported predominantly in developed countries, a Bangladeshi study confirmed its occurrence in tropical countries. [33]

Up to 80% of patients with FD report meal-induced symptoms, [7] but the role of food in the development of FD is unclear. High fat foods may produce more symptoms, such as early satiety and bloating, compared with a high carbohydrate diet. [34] In Asia, a heavy chilli intake predicted FD. [28] Although Western studies have reported an association between lower socioeconomic status and FD, [11,35] a study conducted in both rural and urban South-east Asia reported a lower prevalence among rural adults of lower socioeconomic status. [28,36]

PATHOPHYSIOLOGY

Despite extensive research, and due to both its multifactorial nature and the heterogeneity of symptoms, the underlying pathophysiology of FD remains unclear. Symptom generation is part of a complex relationship between the gastroduodenal region of

the gut and the brain, triggered by factors including food, stress, and psychosocial co-morbidities (Figure 2). There are published disease models proposing that all of these factors could fit with a single pathogenesis. [37]

Gastrointestinal Sensory and Motor Dysfunction

Initially, altered gastrointestinal motility and sensitivity were proposed as the main underlying mechanisms in FD. PDS-type symptoms were thought to originate from gastric motor dysfunction, including impaired gastric accommodation [38,39] leading to distal redistribution of a meal and, consequently, antral overload. [40,41] Partial inhibition or enhancement of gastric accommodation can worsen or improve symptoms. [39,42] Delayed gastric emptying was also felt to be implicated, mostly in association with nausea, vomiting, and postprandial fullness. [43] However, the association between gastric emptying rate and symptoms is inconsistent. [44] Correlation between symptom improvement and acceleration in gastric emptying is also variable. [45,46] One systematic review found an acceleration of gastric emptying by 20 minutes resulted in a meaningful improvement in symptoms, [46] but only when restricting the analysis to low risk of bias studies using optimal methods to assess gastric emptying (scintigraphy or breath testing for at least 3 hours following a solid meal).

EPS-type symptoms were thought to be due to mechanical hypersensitivity of the stomach. [47,48] However, hypersensitivity to gastric distention is also associated with non-painful sensations, such as postprandial fullness, bloating, and belching. [47,49] The role of chemical hypersensitivity has also been studied; increased sensitivity to exogenous and endogenous acid in the duodenum, and decreased clearance of acid, have been associated with nausea. [50,51] Exogenous acid in the duodenum, although at higher levels than those produced physiologically, decreases the threshold for discomfort to gastric balloon distention, and inhibits gastric accommodation in response to a meal. [52] Additionally, the transient

receptor potential vanilloid type-1 (TRPV1), selectively activated by capsaicin, induces release of neuropeptides, such as calcitonin gene-related peptide and substance-P, which may enhance visceral sensitivity and trigger symptoms including abdominal pain and nausea. [53] TRPV1 receptors were upregulated in FD in one study, [54] and are activated by mechanical stimulation, inflammatory mediators, acid, nerve growth factor, prostaglandins, and even microbes. [55] Paradoxically, prolonged exposure to capsaicin has analgesic effects, [56] and in some patients with FD leads to improvement in early satiety and bloating. [57] This may be via desensitisation of TRPV1 by depletion of neuropeptides, such as substance-P, or by inhibition of Piezo proteins, which are ion channels involved in the reduction of pain during mechanical stretching. [55,58]

Immune Dysfunction

Low-grade mucosal inflammation and increased levels of inflammatory cells, including intraepithelial lymphocytes (IELs) and mast cells, have been demonstrated in some other functional gastrointestinal disorders. [59] However, in FD the number of IELs is not increased, [60,61] but quantification of cell surface markers required for further proliferation and/or differentiation into specialised cells provides an indication of their activation state. In FD, decreased expression of two markers, CD95/Fas (involved in cell apoptosis and lymphocyte homeostasis) and HLA-DR (involved in B-cell proliferation), has been reported, reflecting alterations in duodenal lymphocyte populations. [61] Furthermore, duodenal eosinophilia, rather than increased mast cells, has been implicated, and is associated with PDS-type symptoms. [62,63]

Innate immune activation in the gut is complex. During type-2 immune responses, after antigen presentation, type-2 helper cells recruit eosinophils and mast cells to sites of inflammation. [64] Their activation and degranulation leads to release of pro-inflammatory

mediators, which induce tissue damage, and could potentially cause epithelial barrier dysfunction, as well as interfering with enteric nerve function. [64] The resulting increase in epithelial permeability may allow infiltration of secondary luminal antigens, further propagating the immune response, and contributing to symptom generation. This hypothesised association between impaired epithelial integrity, and the secretion of pro-inflammatory mediators by eosinophils and mast cells, is supported by studies demonstrating that patients with FD display impaired duodenal epithelial barrier function, both in vitro, with reduced expression of cell-to-cell adhesion proteins, [60] and in vivo, with decreased baseline impedance values. [65] Expression of zonulin occludens-1, a tight junction protein, was significantly lower in patients with FD in one study, [66] and the degree of impaired epithelial integrity correlated with mast cell and eosinophil counts. [60] Degranulation of eosinophils, with a resultant release of cytokines and chemokines, may also be increased, [62,67] although mast cells did not differ in their degranulation profiles, compared with those from healthy controls, but rather in their granular content. [67] Further evidence for the role of gastrointestinal inflammation includes the finding of enhanced small bowel-homing α4-, β7-integrin, chemokine receptor 9-positive T-lymphocytes and higher levels of cytokine production; both correlated with severity of symptoms. [68]

This increased immune cell activation, as well as increased duodenal permeability, may be associated with delayed gastric emptying. [68] Low-grade inflammation could also lead to disturbed gastrointestinal motility and visceral sensitivity via dysregulation of the neuro-immune system. There is evidence that immune cells interact with enteric nerves in order to influence gastrointestinal function. [69] Patients with FD demonstrate increased numbers of eosinophils and mast cells in close proximity to submucosal plexus neurones, with decreased neuronal responsiveness. [70] Fine nerve fibres are detected more frequently in the duodenum of patients with FD than healthy controls, and both degree of eosinophil activation and

presence of low-grade inflammation were associated with the grade of fine nerve fibre sprouting. [71]

Alterations in Gastrointestinal Microbiota

The small intestinal microbiome has been identified as another potential contributing factor. Although relative bacterial abundance in the small intestine is difficult to interpret, an increased duodenal mucosal bacterial load correlated with meal-related symptoms during a nutrient challenge test, and inversely correlated with quality of life, in one study. [71] It could be that small intestinal inflammation leads to alterations in the microbiome that, in turn, induce changes in the bile acid pool. [72] Alternatively, a reduction in primary bile acid levels may influence small intestinal microbial diversity, leading to overgrowth of pro-inflammatory bacteria and inducing low-grade inflammation, which could lead to epithelial barrier dysfunction. [72,73] Some patients with FD demonstrate reduced total bile acid concentrations during fasting, with a shift in the ratio of primary to secondary bile acids; [74] again implicating gastrointestinal microbial involvement.

Gut-brain Axis Dysfunction

The gut-brain axis is involved in a subset of patients. Alterations in epithelial barrier function, occurring due to disturbances of the immune system and the gastrointestinal microbiome, can regulate gut-brain communications, via the HPAA. Stress and corticotrophin-releasing hormone (CRH) pathways play an important role in gastrointestinal permeability. [75] This has been demonstrated in both animal models of FD and healthy volunteers undergoing a stressful experience, [76,77] and duodenal eosinophilia was associated with anxiety in one study. [63] Moreover, in response to stress, eosinophils release substance-P and CRH, [78] which may lead to mast cell activation and, ultimately, duodenal epithelial

barrier dysfunction. Magnetic resonance imaging in patients with FD reveals abnormalities of structural and functional connectivity in areas of the brain responsible for processing of visceral afferent information, [79,80] which appeared more marked in EPS. [80] Microbial alterations can modify the function of neurotransmitters, including serotonin, dopamine, acetylcholine, and gamma aminobutyric acid, either by synthesis or consumption of these substances, leading to alterations in emotional state and behaviour. [81,82] Finally, bile acids and their receptors have been detected in the brain, suggesting a potential role in gut-brain signalling. [83]

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Diagnosing FD confidently can be difficult for physicians due to unfamiliarity with its epidemiology, cardinal symptoms, co-morbid conditions, and current diagnostic criteria. Just as importantly, it is unlikely that a patient will arrive at a consultation announcing that they have FD. In addition, the symptoms of FD are indistinguishable from those of potential organic causes of dyspepsia (Table 2). A series of steps to overcome these impediments to an accurate diagnosis is outlined below.

The first step is to take a careful history, which incorporates symptoms, in order to categorise patients into the appropriate subtype, [3] and a review of alarm symptoms or signs (Figure 3), termed “red flags”, which suggest an alternative diagnosis. Bloating often co-exists; [84] patients may refer to this as a sense of “gassiness” or “tightness”. Postprandial nausea is common, [85] although recurrent, persistent vomiting is not typical, and is a potential alarm symptom. If present, an alternative diagnosis should be considered, such as gastric outlet obstruction, gastroparesis, cyclic vomiting syndrome, or cannabis hyperemesis syndrome. Pictograms may assist patients in describing their symptoms. [86] As mentioned, a number of conditions co-exist with FD including gastro-oesophageal reflux, IBS, chronic

fatigue syndrome, migraine, overactive bladder, and fibromyalgia; [21,25,87] their co-occurrence should reassure the clinician that this is likely to represent FD.

The next step, a careful physical examination, is important for several reasons. Firstly, this reassures the patient that symptoms are being taken seriously. Secondly, although expected to be normal, the examination may reveal findings that point towards another diagnosis, even in a "typical" patient. Thirdly, identification of Carnett's sign during the examination distinguishes chronic abdominal wall pain from deeper, visceral pain. [88] This is elicited by asking the patient to raise their head from the bed, without using the arms, to contract the abdominal wall muscles. If the area of pain, which is usually quite small (≤2 cm), worsens with abdominal muscle contraction it is musculoskeletal in nature (positive Carnett's test). However, if the pain improves then it is likely visceral. The test has a diagnostic accuracy of ≥90% for chronic abdominal wall pain. [89] The patient should be observed during palpation; patients with an organic process often keep their eyes open and are attentive to this part of the examination, whereas patients with chronic functional pain are more likely to have closed eyes, as they know a significant new painful experience is unlikely. [90]

The last step is to consider the diagnosis. Although FD is common, [9,11] doctors often make an erroneous diagnosis of gastro-oesophageal reflux disease (GORD) when patients describe meal-related symptoms of epigastric pain, epigastric burning, and bloating. These symptoms are more likely to represent FD than GORD. [18] This diagnostic confusion is compounded by the fact that some patients with FD respond to empiric proton pump inhibitor (PPI) therapy, [91] similar to GORD.

INVESTIGATIONS

Unfortunately, a physician's history and examination cannot accurately distinguish FD from organic causes of dyspepsia, [92] and there is no accurate biomarker available to

facilitate the diagnosis. A validated diagnostic algorithm does not exist, and neither the Rome committee nor current guidelines support routine laboratory testing in all patients. [3,93] A full blood count should be requested, if not recently performed; the presence of anaemia may change the diagnosis. Concern over a possible hepatobiliary cause, if there is severe episodic epigastric pain, warrants checking of liver function tests. Routine screening for pancreatitis, via serum amylase or lipase, is not recommended, nor is routinely checking thyroid tests or coeliac serology. [94] Although technically a negative endoscopy is required to confirm a diagnosis of FD, [3] the majority of patients with dyspepsia will have no organic findings at endoscopy; <10% will have a peptic ulcer and <0.5% gastro-oesophageal malignancy. [2] With such a low yield, the most current guidelines for dyspepsia management discourage use of endoscopy in patients <60 years of age, even if alarm symptoms are present. [93] Non-invasive testing for *H. pylori*, with stool antigen or urea breath testing, should be performed, with endoscopy reserved for those with persistent symptoms and, if performed, gastric biopsies should be obtained; if *H. pylori* is detected it should be treated. [95,96] Requesting abdominal ultrasound or computed tomography routinely, in the absence of alarm symptoms or signs, is not recommended; the yield is low. [97] Despite considerable overlap of symptoms and diagnostic confusion between FD and gastroparesis, [43,98] gastric emptying studies are of limited value; up to 25% of patients with FD exhibit delayed gastric emptying. [99] In summary, yield of investigations in a patient with typical symptoms is low, and a positive approach to diagnosis is reasonable in the majority of patients.

NATURAL HISTORY AND IMPACT

The incidence of FD is 3% to 5% per year. [27,100] Population-based longitudinal studies demonstrate that prevalence remains relatively stable over time, between 13% and 16% in two 10-year follow-up studies from Scandinavia. [29,100] The long-term natural history is that of

a chronic, fluctuating disorder; approximately 50% of individuals have persistent symptoms, 10% to 20% experience symptom resolution, and 30% to 40% have a change of symptoms to either IBS, gastro-oesophageal reflux, or a combination of both. [29,100] In one study, anxiety influenced natural history; lower anxiety scores at baseline were associated with symptom resolution, but higher scores were associated with both new-onset FD and a change from FD to either gastro-oesophageal reflux or IBS. [29] Despite its chronic nature, longitudinal studies demonstrate no associated increase in mortality. [101]

As FD does not affect survival, its consequences are measured by its impact on patients and from a socioeconomic perspective. Health-related quality of life is consistently lower amongst people with FD compared with healthy controls. [5,12,28,36] Due to chronicity of symptoms, between 40% and 70% of patients consult a medical practitioner, [102-104] and in one study work absenteeism and presenteeism was reported by 32% and 78% of patients, respectively. [4] The economic impact of FD due to direct and indirect costs has been shown to be higher in the West, estimated at $80,000 per 1000 population, [6] compared with Asia, estimated at $35,000 per 1000 population. [105] Patients with FD appear willing to take substantial risks in return for symptom resolution; almost 50% would accept a >12% risk of sudden death in return for a 99% chance of cure. [106]

MANAGEMENT

Management of FD includes reassurance that there is no structural cause for the symptoms, explanation of the pathophysiology and natural history of the disorder, and treatment directed towards the predominant symptom, or symptoms, with realistic discussion of limitations of available therapies, in order to manage expectations. There is little evidence that lifestyle changes or exercise lead to symptom improvement and, although some foods are implicated in the generation of symptoms, [107] randomised controlled trials (RCTs) of dietary

manipulation are lacking. Medical therapy is therefore the mainstay of treatment, although most treatments have modest efficacy, and none are proven to alter the long-term natural history of FD. A management algorithm is provided in Figure 3, with evidence for efficacy of various treatments summarised in Table 3.

Eradication of *H. pylori*

Although it is estimated that 5% of dyspepsia in the community is attributable to *H. pylori*, [108] impact of eradication therapy in infected patients with FD is modest. The relative risk (RR) of symptoms persisting in a Cochrane meta-analysis of 17 RCTs was 0.90 (95% confidence interval (CI) 0.86 to 0.94). [109] Nevertheless, this is likely to be cost-effective. [96] 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 satiety or postprandial fullness, [110] suggesting benefit may be more pronounced in EPS.

Acid-suppression Therapy

Given evidence of impaired duodenal clearance of gastric acid and duodenal hypersensitivity to infused gastric acid in individuals with FD, [51] acid-suppression therapy is a logical treatment. There is no evidence to support use of antacids, sucralfate, or bismuth to improve symptoms. Efficacy of PPIs and histamine-$_2$-receptor antagonists (H_2-RAs) has been studied. A Cochrane meta-analysis reported a RR of remaining symptomatic of 0.88 (95% CI 0.82 to 0.94) with PPIs versus placebo in 18 RCTs; [91] 12 of these trials used omeprazole or lansoprazole. There was no difference in efficacy between H_2-RAs and PPIs in two RCTs making head-to-head comparisons. A prior version of this meta-analysis reported that H_2-RAs were more efficacious than placebo in 12 RCTs (RR 0.77; 95% CI 0.65 to 0.92), but trial quality was lower than for PPIs. [111] In two RCTs there was a trend towards a benefit of PPIs

in PDS, but no benefit in EPS. [91] In healthy volunteers, acid suppression with PPIs reduced postprandial fullness, which might explain potential benefit in PDS. However, the frequent overlap of PDS and EPS means PPI use is justifiable in many FD patients. [15,99]

Prokinetics

Some FD patients demonstrate abnormalities in gastric motility and fundal accommodation, [38,43] therefore drugs that enhance motility and accommodation may be of benefit. Prokinetic agents were more effective than placebo in a Cochrane meta-analysis of 29 RCTs (RR = 0.81; 95% CI 0.74 to 0.89). [112] However, quality of evidence was very low. Cisapride was the most used drug, but was withdrawn due to an increased risk of adverse cardiac events, including sudden death due to QT interval prolongation. Acotiamide is a novel acetylcholinesterase inhibitor that relaxes the gastric fundus, and is licensed for use in FD in Japan and India. [113] Drugs acting on 5-hydroxytryptamine (5-HT) receptors have also been tested. Buspirone and tandospirone, which are 5-HT_{1A} agonists, lead to fundal relaxation. In a cross-over trial in 17 patients, buspirone reduced bloating and postprandial fullness. [42] In a RCT in 144 Japanese patients, response rates after 4 weeks of treatment with tandospirone were superior to placebo. [114] Novel prokinetics that may be of benefit, and that are being assessed in FD, are discussed later.

Central Neuromodulators

Involvement of the brain-gut axis and abnormal central pain processing in functional gastrointestinal disorders is now established, although central neuromodulators, including low-dose antidepressants, have been suggested as a therapy for many years, due to their peripheral pain-modifying effects. A meta-analysis of 13 trials demonstrated no benefit of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake

inhibitors. [115] Tricyclic antidepressants (TCAs), including imipramine and amitriptyline, were more effective than placebo in three RCTs (RR = 0.74; 0.61 to 0.89), but adverse events were more common. [115] Secondary analyses from one of these trials demonstrated that amitriptyline appeared to be of greater benefit in EPS, [116] although the drug enhanced gastric accommodation, [117] suggesting it should actually benefit those with PDS. In an RCT of imipramine, epigastric pain, bloating, postprandial fullness, early satiety, and vomiting scores all improved significantly, versus placebo, compared with baseline. [118] However, in a subsequent placebo-controlled trial, nortriptyline was of no benefit in 61 Thai patients with FD. [119] Mirtazapine has been assessed in 34 patients with FD and weight loss; [120] compared with placebo the drug led to significant improvements in early satiety and quality of life.

Other Therapies

Despite burgeoning interest in the small intestinal microbiome, and in contrast to IBS, 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. [121] More RCTs are needed before any definitive conclusions can be drawn. Similarly, unlike in IBS, [122] there is little evidence for any role of psychological therapies in FD. A meta-analysis identified only four trials, two of which used cognitive behavioural therapy, although there was a benefit in reducing persistent symptoms (RR 0.53; 95% CI 0.44 to 0.65). [93]

The nine-herb combination product iberogast, or STW5, appears beneficial; [123] it enhances antral motility and gastric relaxation. [124] A duodenal-release formulation of caraway oil and L-menthol in combination improved symptoms in those with EPS in one 4-week RCT. [125] The herbal remedy Rikkunshito also appeared beneficial, with significant improvements in epigastric pain, and higher rates of improvement of postprandial fullness, in

a Japanese RCT, [126] but this was not replicated in a subsequent Belgian trial. [127] Finally, electro-acupuncture, consisting of intermittent electric stimulation of acupuncture needles to maximum pain tolerance during 20 sessions over 4 weeks, demonstrated a benefit over a sham procedure in one Chinese trial conducted in 200 patients with refractory PDS. [128]

FUTURE DIRECTIONS AND CONTROVERSIES

Despite the Rome IV criteria being widely accepted, FD continues to be underdiagnosed and confused with gastroparesis, even by experts. [84,129] Biomarkers to discriminate FD from other disorders with similar or overlapping symptoms are needed, rather than relying only on symptom-based criteria and a "negative" endoscopy. Duodenal eosinophilia is now an established biomarker linked to symptoms of PDS, particularly early satiety, [62,63] but this requires counting eosinophils in five higher power fields, adding time and cost to patient evaluation. Although epithelial barrier disruption has been observed, [65] serum zonulin levels have not been of diagnostic value, [130] but this may reflect technical issues with measurement. FD can arise after acute gastroenteritis, [32] and antibodies to a common bacterial antigen, cytolethal distending toxin, may be increased, but these do not appear to be a useful diagnostic approach. [131] Although FD is associated with an increased risk of autoimmune diseases, [132] measurement of vinculin in blood, a proposed autoimmune biomarker of post-infection IBS, also appears unhelpful. [131] A more promising approach may be to identify immune activation, such as an increase in small bowel-homing T-cells, which is now established to be present in FD, [68] or specific alterations in the upper gastrointestinal microbiome. [71] However, easy and rapid tests are currently unavailable.

A better understanding of disease mechanisms should lead to improved diagnostic tests and, potentially, new therapeutic targets. Animal models representative of human

disease are key and, although gastric models once dominated, [133] the breakthrough findings demonstrating subtle duodenal pathology in some patients suggest that small intestinal models of disease are needed. [76] As FD overlaps with gastro-oesophageal reflux, IBS, gastroparesis, and psychological distress, [21,31,84,87] such disease models may also provide important new insights into these disorders.

Surprisingly, dietary interventions have been little studied despite the fact that FD symptoms often occur postprandially, [7] and can be induced reproducibly by test meals. [107] FD overlaps with non-coeliac wheat sensitivity; [134] both disorders may have duodenal eosinophilia, and wheat proteins could conceivably induce both pathology and symptoms, suggesting RCTs of wheat-free diets in FD are timely. Fermentable carbohydrates have also been associated with symptoms, [107] and a diet low in fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) diet may be helpful, but a gluten-free diet is also low in FODMAPs; again adequately powered RCTs are needed before recommendations to change practice can be advocated.

Novel drug targets have been identified. Histamine is released by mast cells and by the microbiome. Blockade of H_1- and H_2-receptors using available, inexpensive, over-the-counter drugs is a promising treatment approach, [135] representing a target for future RCTs. PPIs may reduce eosinophilia and normalise duodenal permeability in FD, [136] but placebo-controlled trials are needed to confirm that eosinophilic suppression by PPIs leads to symptom reduction. [137] A new class of acid-suppression drugs, known as potassium-competitive acid blockers, have already been tested in patients with GORD, and it is expected that there will be future trials in FD, although whether these drugs reduce gastrointestinal eosinophilia is unknown, and any benefit in FD may be modest. [138]

The role of locally delivered budesonide, targeting increased eosinophils, is under investigation but, as yet, the results of this approach are unavailable. Novel drugs that

suppress gastrointestinal eosinophils are also undergoing testing, and may have applications in FD. For example, a monoclonal antibody directed against an inhibitory receptor selectively expressed on both eosinophils and mast cells, Siglec-8, appears promising in animal models, [139] and is undergoing assessment in clinical trials in eosinophilic gastrointestinal diseases.

Other prokinetics are undergoing testing in FD. Ghrelin agonists, like relamorelin, [140] and 5-HT_4 agonists, such as prucalopride and velusetrag, [141,142] alter gastric physiology in patients with gastroparesis, but efficacy in FD is unclear. Ghrelin agonists worsen gastric fundal relaxation postprandially, [140] suggesting a benefit in FD would be unlikely. Neuromodulators that reduce upper gastrointestinal visceral sensation may have a role in future therapy, but convincing RCTs are lacking. Gabapentin appeared to improve symptoms in one retrospective case series. [143]

A future strategy will be the development of novel drugs and the repurposing of existing therapies to target promising new mucosal disease targets, as animal and human model work progresses Alternatively, modulation of relevant gastric or small intestinal microbiome alterations may transform management in a subset. Our increased understanding of the pathophysiology of FD is exciting, and will likely see the emergence of truly disease-modifying therapies for the first time.

Contributors

ACF, SM, MFC, BEL, and NJT did the literature search, wrote the manuscript, and drafted the figures. ACF and NJT revised the initial manuscript. All authors critically revised subsequent versions of the manuscript and approved the final version of the manuscript.

Declaration of Interests

ACF has no conflicts of interest. SM reports grants from Otsuka Pharmaceuticals, outside the submitted work. BEL reports personal fees from Ironwood, personal fees from Salix, personal fees from Takeda, grants from Bausch, personal fees from Viver, all outside the submitted work. MFC has no conflicts of interest. NJT reports personal fees from Allergan PLC (GI Development Programs), personal fees from Viscera Labs (IBS), personal fees from IM Health Sciences (FD), personal fees from Napo Pharmaceutical (IBS), personal fees from Outpost Medicine (IBS), from Progenity Inc San Diego (capsule SIBO), from Allakos (gastric eosinophilic disease), personal fees from Samsung Bioepis (IBD), personal fees from Synergy (IBS), personal fees from Takeda (gastroparesis), personal fees from Theravance (gastroparesis), grants and personal fees from Viscera USA (IBS), grants from Commonwealth Diagnostics (International) Inc (IBS), non-financial support from HVN National Science Challenge NZ (IBS), grants and personal fees from GI therapies (constipation), personal fees from Cadila Pharmaceuticals (CME), personal fees from Planet Innovation (Gas capsule), personal fees from Danone (Probiotic), personal fees from Pfizer (IBS), from Dr. Reddy's Laboratories (Webinar), personal fees from Arlyx (IBS), personal fees from Sanofi (Probiotic), all outside the submitted work; in addition, Dr. Talley has a patent Biomarkers of IBS licensed, a patent Licensing Questionnaires Talley Bowel Disease Questionnaires licensed to Mayo/Talley, a patent Nestec European Patent licensed, a patent Singapore Provisional Patent “Microbiota Modulation Of BDNF Tissue Repair Pathway” issued, and a patent Nepean Dyspepsia Index licensed to Talley copyright and Committees: Australian Medical Council (AMC) [Council Member]; Australian Telehealth Integration Programme; MBS Review Taskforce; NHMRC Principal Committee (Research Committee) Asia Pacific Association of Medical Journal Editors. Boards: GESA Board Member, Sax Institute, Committees of the Presidents of Medical Colleges. Community group: Advisory

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TABLES.

Table 1. The Rome IV Criteria for Functional Dyspepsia*.

<table>
<tr><th colspan="2">Diagnostic Criteria for Functional Dyspepsia</th></tr>
<tr><td colspan="2">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</td></tr>
<tr><th>Diagnostic Criteria† for Epigastric Pain Syndrome (EPS)</th><th>Diagnostic Criteria§ for Postprandial Distress Syndrome (PDS)</th></tr>
<tr><td>Must include one or both of the following symptoms at least 1 day a week:
1. Bothersome epigastric pain (i.e., severe enough to impact on usual activities);
2. Bothersome epigastric burning (i.e., severe enough to impact on usual activities)

And no evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at endoscopy).

†Criteria fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis.

Supportive criteria:</td><td>Must include one or both of the following symptoms at least 3 days a week:
1. Bothersome postprandial fullness (i.e., severe enough to impact on usual activities);
2. Bothersome early satiation (i.e., severe enough to prevent finishing a regular sized meal)

And no evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at endoscopy).

§Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Supportive criteria:
1. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present;</td></tr>
</table>

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.	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 open with (e.g. from gastro-oesophageal reflux disease and irritable bowel syndrome) may coexist with PDS.

***Modified from reference 3.**

Table 2. Differential Diagnoses for Symptoms of Dyspepsia*.

Functional dyspepsia
Gastro-oesophageal reflux disease
Drugs e.g. non-steroidal anti-inflammatory drugs, iron, calcium antagonists, angiotensin-converting enzyme inhibitors, methylxanthines, glucocorticoids, antibiotics (e.g. tetracyclines or erythromycin)
Symptomatic gallstone disease, sphincter of Oddi dysfunction, biliary dyskinesia, or gallbladder cancer
Peptic ulcer disease (and infection with *H. pylori)*
Crohn's disease
Gastro-oesophageal malignancy
Gastroparesis
Hepatocellular carcinoma
Chronic pancreatitis or pancreatic cancer
Gastrointestinal complications of parasites e.g. giardia lamblia, strongyloides, anisakiasis
Infiltrative diseases e.g. eosinophilic gastroenteritis, sarcoid, amyloid
Chronic mesenteric ischaemia

***In order of frequency, based on incidence estimates in Europe and North America.**

Table 3. Summary of Evidence for Efficacy of Treatment Approaches for Functional Dyspepsia*.

Therapy and Drugs Tested	FD Subgroup Studied	Efficacy	Quality of Data	Adverse Events	Limitations of Data
H. pylori eradication therapy (e.g. 1-week course of PPI triple therapy)	Unselected patients, reasonable to use in EPS or PDS	Effective	High	Total adverse events only reported by two trials	None, other than limited reporting of adverse events
PPIs (e.g. omeprazole 20mg or lansoprazole 30mg once daily)	Unselected patients, reasonable to use in EPS or PDS	Effective	Moderate	Total adverse events no more common with PPIs in a meta-analysis of six trials	Heterogeneity between studies
H_2-RAs (e.g. ranitidine 150mg once daily)	Unselected patients, reasonable to use in EPS or PDS	May be effective	Low	Total adverse events poorly reported	Few trials at low risk of bias; heterogeneity between studies; possible publication bias; some trials included patients with gastro-oesophageal reflux symptoms
Prokinetics (e.g. acotiamide 100mg or itopride 50mg three times daily)	Most newer trials recruit patients with PDS	May be effective	Very low	Total adverse events poorly reported	Few trials at low risk of bias; heterogeneity between studies; possible publication bias; imprecision around the estimate of effect; many drugs not available due to safety concerns; acotiamide licensed in Japan and India, but few trials in Western patients with FD; itopride not available in the UK or USA
5-HT_{1A} agonists	Unselected patients, reasonable to use in EPS or PDS	May be effective	Low	Total adverse events no more common with 5-HT_{1A} agonists in a meta-analysis of three RCTs	Only three trials; heterogeneity between studies; effective in unselected patients in one study and significantly improved postprandial symptoms in a second study; imprecision around the estimate of effect
TCAs (e.g. amitriptyline or imipramine started at a dose of 10-25 mg once daily at night and titrated to 50mg once daily at night)	Unselected patients, although seemed to be more effect in EPS	Effective	Moderate	Total adverse events significantly more common with TCAs in a meta-analysis of two RCTs, particularly dry mouth and drowsiness	Only four trials; imprecision around the estimate of effect; tolerability may be an issue
SSRIs (e.g. fluoxetine or paroxetine 20mg once daily)	Unselected patients	Not effective	Moderate	Total adverse events no more common with SSRIs in a meta-analysis of two RCTs	Only two RCTs
Mirtazapine (usual dose is 15mg once daily, titrated to 30mg to 45mg once daily)	Unselected patients, although all had weight loss	May be effective	Moderate	Total adverse events no higher with mirtazapine	Only one small single-centre RCT although a trend towards improvement in global symptoms and early satiety also improved.

Psychological therapies (e.g. cognitive behavioural therapy)	Unselected patients	May be effective	Very low	Adverse events not reported in individual RCTs, precluding their assessment in a meta-analysis of four RCTs	All RCTs at high risk of bias due to the nature of the interventions studied; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each intervention; time consuming due to need for therapist contact; limited availability in some countries

***Data adapted from reference 93.**

FIGURE LEGENDS.

Figure 1. Prevalence of Functional Dyspepsia Worldwide Using the Rome III Criteria.

Figure 2. Pathophysiology of Functional Dyspepsia: A Proposed Disease Model.

The pathophysiology of functional dyspepsia is likely complex and heterogeneous. Multiple bidirectional pathways are proposed to contribute to dyspeptic symptoms. (1) Central signalling, including via corticotrophin-releasing hormone (CRH) and neurotransmitters, can alter peripheral gastrointestinal function, including the gastrointestinal immune system, the microbiome, and bile acid metabolism. (2) Intestinal immune dysfunction and the microbiome can modulate central nervous system function. There is a delicate balance between environmental factors (e.g. acute infections, food antigens, acid, capsaicin) and the gastrointestinal tract lumen and gut microbiome, and alterations in this steady state may lead to dysfunction of the intestinal epithelial barrier, increasing mucosal permeability. Antigens may then be recognised by immune cells, leading to a low-grade inflammatory response, with further immune activation. (3) Inflammatory mediators and cytokines released by activated intestinal eosinophils and mast cells may then sensitise enteric nerves, thereby causing visceral hypersensitivity and motor dysfunction.

Figure 3. Management Algorithm for Dyspepsia*.

***Adapted from reference 93. Note that this guideline increased the age threshold for endoscopy to ≥60 years, but that in Far Eastern countries where incidence of gastric cancer is higher, the recommended age threshold is 35-55 years.**

†Offer urgent endoscopy to patients with dysphagia or aged ≥55 years and weight loss with any of upper abdominal pain, reflux, or dyspepsia; consider non-urgent endoscopy in patients with haematemesis, treatment-resistant dyspepsia, upper abdominal pain with low haemoglobin, a raised platelet count in association with nausea, vomiting,

weight loss, reflux, dyspepsia, or upper abdominal pain, or nausea and vomiting in association with weight loss, reflux, dyspepsia, or upper abdominal pain (see https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer#upper-gastrointestinal-tract-cancers)

±Stool antigen or 13-carbon urea breath test.

§Oesophagitis, peptic ulcer, gastro-oesophageal cancer.

‡If symptoms persist, consider endoscopy, although yield is low.

⁑Prokinetics may be of greater benefit in PDS, and TCAs in EPS.

⁂Discharge is realistic if symptoms resolve with a prokinetic, but continued follow-up and monitoring is more appropriate if a TCA is still being used.

⁋Evidence for the role of pychological therapies in FD is limited; there have been two RCTs of cognitive behavioural therapy (see reference 93).