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REVIEW

Therapeutic strategies for functional dyspepsia and irritable bowel syndrome based on pathophysiology

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Abstract Functional gastrointestinal disorders (FGIDs) are common and distressing. They are so named because a defined pathophysiology in terms of structural or biochemical pathways is lacking. Traditionally FGIDs have been conceptualized as brain–gut disorders, with subgroups of patients demonstrating visceral hypersensitivity and motility abnormalities as well as psychological distress. However, it is becoming apparent that there are certain structural or biochemical gut alterations among subsets with the common FGIDs, most notably functional dyspepsia (FD) and irritable bowel syndrome (IBS). For example, a sodium channel mutation has been identified in IBS that may account for 2 % of cases, and subtle intestinal inflammation has been observed in both IBS and FD. Other research has implicated early life events and stress, autoimmune disorders and atopy and infections, the gut microbiome and disordered mucosal immune activation in patients with IBS or FD. Understanding the origin of symptoms in FGIDs will allow therapy to be targeted at the pathophysiological changes, not at merely alleviating symptoms, and holds hope for eventual cure in some cases. For example, there are promising developments in manipulating the microbiome through diet, prebiotics and antibiotics in IBS, and testing and treating patients for *Helicobacter pylori* infection remains a mainstay of therapy in patients with dyspepsia and this infection. Locally acting drugs such as linaclotide have been an advance in treating the symptoms of constipation-predominant IBS, but do not alter the natural history of the disease. A role for a holistic approach to patients with FGIDs is warranted, as brain-to-gut and gut-to-brain pathways appear to be activated.

Keywords Functional dyspepsia · Irritable bowel syndrome · Therapeutics

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Background

Functional gastrointestinal disorders (FGIDs) are so named because they appear to defy an understanding within the traditional pathology-based paradigm, as in the routine clinical setting structural or biochemical abnormalities that can explain symptoms are not evident [1]. The Rome III classification of FGIDs provides a convenient framework for symptom-based diagnosis of these conditions, grouping the symptom clusters into readily recognizable syndromes by site. Among the most recognized FGIDs are functional dyspepsia (FD) [2] and irritable bowel syndrome (IBS) [3] because of frequent presentations in primary care and gastroenterology clinics.

The Rome III classification defines FD by symptom onset at least 6 months prior to diagnosis, with current symptoms present for a minimum of 3 months, and including one or more of bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning, with no evidence of structural disease (including by endoscopy)

that likely explains the symptoms. The distinction is made between meal-induced symptoms of postprandial fullness and early satiation (diagnostic category postprandial distress syndrome, PDS), and symptoms characterized by epigastric pain or burning which may or may not be meal related (diagnostic category epigastric pain syndrome, EPS) [2]. FD was recognized when it became clear patients with ulcer-like symptoms did not always have a peptic ulcer [4]; this was originally termed 'non-ulcer dyspepsia' and is closest to the current EPS category of FD. It is now recognized PDS is commoner than EPS [5].

On the other hand, IBS is defined by recurrent abdominal pain or discomfort for at least 3 days per month, associated with two or more of the following: improvement with defecation, or onset associated with a change in stool form or stool frequency. The symptoms must be chronic; symptom onset should be at least 6 months prior to diagnosis, and current symptoms should have been present for at least 3 months. Subtypes of IBS are defined by stool form: namely, IBS with constipation, with hard or lumpy stools for 25 % or more of bowel movements and loose, watery or mushy stools for less than 25 % of bowel movements; IBS with diarrhoea (IBS-D), with loose, watery or mushy stools for 25 % or more of bowel movements and hard or lumpy stools for less than 25 % of bowel movements; mixed IBS, with hard or lumpy stools for 25 % or more of bowel movements and loose, watery or mushy stools for 25 % or more of bowel movements; and unsubtyped IBS, defined by insufficient abnormality of stool consistency to meet the criteria for IBS-D, IBS with constipation, or mixed IBS [3].

These conditions are remarkably commonplace in the population, as on average one in five individuals report episodes of uninvestigated dyspepsia [6]. In an assessment of more than 23,000 population-based subjects, the prevalence of any uninvestigated dyspepsia was highly variable across various geographic regions, ranging from 24 to 45 % [7]. IBS affects 7–21 % of various populations [8], or around 11 % globally [9]. Approximately 30 % of those with symptoms of IBS will consult a physician [9], and in a study of individuals followed for 10 years in the community, 42 % of those with symptoms of dyspepsia had consulted a physician in that time [10]. These disorders are also very costly in terms of health economics. In the USA, employees with FD had significantly increased yearly medical costs ($8544 compared with $3039 for those without FD) and increased work absences [11]. Similar data exist for IBS: in the USA, the indirect costs of IBS alone are $20.2 billion [12]. These data most likely underestimate the true burden since significant numbers of patients may never receive a diagnosis and their symptoms may be attributed to incidental comorbidities (e.g. diverticular disease).

Although some patients with FGIDs may simply be 'concerned' that their symptoms are due to a life-threatening disorder, in those with severe symptoms quality of life is substantially impaired [13]. A considerable proportion of patients have psychiatric comorbidities [14], and in the general population psychological distress with IBS is the rule [15]. In addition, patients with FGIDs often present with a broad spectrum of extraintestinal symptoms and comorbidities (including chronic headache, back pain, fatigue, joint pain, fibromyalgia, interstitial cystitis or chronic pelvic pain) that should be considered when treating patients with FGIDs [16].

Until a cure for FGIDs is available, treatment has in the main been aimed at alleviating symptoms rather than tackling the root cause. However, some patients with mild symptoms may not require specific treatments that target symptoms. Reassurance that the symptoms are not caused by a life-threatening underlying disease and thoughtful lifestyle advice are often sufficient to manage these patients' conditions in primary care. Although randomized controlled trials are lacking, it has been shown that a positive interaction between the physician and the patient reduces the need for follow-up visits for IBS-related symptoms [17]. However, if the quality of life is substantially impaired, even the exclusion of structural causes and lifestyle advice cannot be considered sufficient to manage these patients' conditions, and further treatment may be necessary.

Although structural disease is an exclusion criterion for these conditions, recent advances in research show that in a proportion of cases of FD and IBS there are tangible but subtle disorders of gut function, immunological disorders, and dysbiosis which may be amenable to therapies aimed at the disease rather than at symptom relief. This review aims to unravel current thinking in gut pathophysiology and demonstrate treating the cause of disease and not the symptoms in "functional" gastrointestinal disorders may have greater success.

Organic disease and FGID symptoms

Symptoms of organic disease may overlap those of FGIDs, and in clinical studies exclusion of organic disease is central to the diagnosis of FGIDs. However, excluding organic diseases to make a diagnosis is a simplistic concept and a moving target; it may be preferable to consider FGID symptoms as arising from a number of different processes, although a large idiopathic group remains (albeit shrinking in size). For example, inflammatory bowel disease (IBD), microscopic colitis and coeliac disease may all present with the classic symptoms of IBS [18]. In a meta-analysis, the pooled prevalence of IBS-type symptoms in all patients with IBD was 39 % [95 % confidence interval (CI),

30–48 %], and this was significantly higher in Crohn's disease than in ulcerative colitis [46 % vs 36 %, odds ratio (OR), 1.62; 95 % CI 1.21–2.18] [19]. It may be that IBS symptoms are more likely to manifest themselves if the small intestine is or has also been inflamed. In coeliac disease, 38.0 % of patients (95 % CI, 27.0–50.0 %) had IBS symptoms, which were worse in those patients non-adherent to a gluten-free diet [20]. Recent studies on the prevalence of bile acid malabsorption suggest this may be a common cause of IBS-D symptoms (up to one in four cases), and targeted therapeutic intervention with a bile acid binder (e.g. cholestyramine) may be warranted [21, 22].

Improved methods to diagnose bile acid malabsorption are needed, and the fibroblast growth factor 19 assay based on a simple, inexpensive commercial ELISA holds promise as a serological test compared with exposure to radiation scanning with selenium homocholic acid taurine [23, 24].

Peptic ulcer disease (PUD) by definition excludes the diagnosis of FD. However, it is remarkable that a considerable proportion of patients with PUD remain asymptomatic until complications such as bleeding occur [25]. Notably, PUD patients with symptoms had significantly higher cumulative symptom responses to a nutrient challenge test compared with healthy controls and patients with PUD who presented with a complication such as bleeding [25]. Augmented symptom responses to a nutrient challenge are also a characteristic of at least a subgroup of patients with FD [26]. Other data support the concept that symptoms may not manifest themselves in the presence of an organic lesion unless visceral sensory function is altered. In a prospective trial, gastric mucosal lesions were induced in healthy subjects and in subjects with a history of FD who were asymptomatic on entry to the study. After 5 days of aspirin treatment, significantly more patients with FD reported dyspeptic symptoms, and importantly the manifestation of symptoms was associated with visceral sensory dysfunction but not the severity of the mucosal lesions [27].

Traditionally, malignancy as a cause of chronic gut symptoms concerns clinicians. In a systematic review of prompt investigation as an initial management strategy for uninvestigated dyspepsia in Asia, a malignancy detection rate of 1.3 % among dyspepsia patients was noted [28]. Importantly, alarm features were found to be of limited value for predicting underlying malignancy. The incidences of organic lesions, including PUD and oesophageal disease, among dyspepsia patients were as high as 26.4, 11.9 and 5.5 %, respectively [28]. This may reflect a higher prevalence of *Helicobacter pylori* in this region. In IBS, colonoscopy is recommended in patients with alarm features and those over 50 years of age (to exclude malignancy), and additionally random colonic biopsies in IBS-D to exclude microscopic colitis can be performed, although the cost-effectiveness has been debated [29]. Similarly to FD, alarm features in IBS are a disappointing indicator of malignancy in patients [29]. Guidelines support investigation if patients with typical FGID symptoms are older (45 years has been commonly applied) or have alarm features or in whom first-line empiric therapy fails, although in most cases no serious disease is uncovered [30–32].

Appropriate and prompt therapy can then be instituted in the minority of cases with an established organic basis for what otherwise would be assumed to be FD and IBS symptoms.

Overlap of FGIDs

Although FGID symptoms can be conveniently grouped into separate categories using the Rome classification, it is notable that overlap is common. In a Danish population, the prevalence of gastro–oesophageal reflux disease, FD and IBS was 11.2, 7.7 and 10.5 %, respectively; 30.7 % of individuals had overlap between two or all three conditions [33]. In a study from Japan, similar rates of overlap were found, with overlaps being found in 46.9 % of patients with gastro–oesophageal reflux disease, 47.6 % of patients with FD, and 34.4 % of patients with IBS, and there was a worse health-related quality-of-life score in the overlap groupings [34].

FGIDS—a holistic approach

Although specific pathophysiological alterations localized to the stomach, duodenum and colon are now emerging as possible generators of symptoms in FD and IBS, it is increasingly apparent that a holistic approach to tackling these disorders is also needed. The cause of symptoms in FGIDs may be embedded in genetic predisposition, early life events, stress, allergy and atopy disposition, dysbiosis (including current and previous infection) and brain–gut (and gut–brain) axis dysfunction.

Genetics

Is there an all-encompassing genetic background that predisposes to FGIDs? Homozygous *GNB3* 825C carrier status is associated with unexplained upper abdominal symptoms in FD [35] and is linked to predominant EPS-type FD in a Japanese population [36]. In IBS, a mutation identified in the $Na_v1.5$ sodium channel gene (*SCN5A*) has been identified in IBS [37], and may explain up to 2 % of IBS cases. Importantly, the sodium channel changes may be amenable to pharmacological intervention as suggested by a proof-of-principle study in one patient.

In a large-scale genome-wide association study of 11,326 Swedish twins looking for genetic associations with IBS, a suggestive locus at 7p22.1 was identified, and these genetic risk effects were replicated in other case–control cohorts. The genes *KDLER2* and *GRID2IP* map to the associated locus, and genetic variation in this region modulates *KDLER2* messenger RNA expression [38]. The biological processes of this gene are establishment of protein localization and protein transport. In another genome-wide association study, peak association was observed for a cluster of 21 perfectly correlated SNPs on chromosome 10, each of which showed genome-wide significant association with IBS ($P \sim 9 \times 10^{-9}$) [39]. These SNPs spanned a 9-kb region centred on exon 11 of the protocadherin 15 gene (*PCDH15*). In humans, *PCDH15* mutations are involved in Mendelian syndromes of cochlear and retinal defects. A group of correlated SNPs spanning a 500-kb region on chromosome 4 showed genome-wide significant association with IBS-D (peak $P = 2.5 \times 10^{-8}$ at rs9999118). This chromosome 4 region contains several genes, including fibroblast growth factor 2 (*FGF2*), the overlapping *NUDT6* gene, thought to regulate *FGF2* expression, and *SPRY1*, encoding a negative regulator of fibroblast growth factor signalling [39].

In a search for the mechanistic patterns of disease, the prevalence of lactase non-persistence was not different between IBS patients and controls (15 % vs 14 %), suggesting that this autosomal recessive trait is unlikely to explain IBS, let alone explain the familial aggregation of IBS [40]. The search for a sound genetic inheritance pattern is likely hampered by the heterogeneity of these disorders.

FGIDs, autoimmune diseases and atopy

In two large studies of UK primary care patients, an association with autoimmune diseases and atopy was examined. A significantly higher prevalence of autoimmune disorders, particularly rheumatological autoimmune disorders, was more frequent in those with FD, constipation and multiple FGIDs [41]. This association was not explained by differences in age or gender. In this same group, atopic conditions were also found in excess among all FGID groups considered when compared with controls [42]. This association may be explained by a shared genetic susceptibility, or common disruption of the microbiome and similar immunological disorders in these conditions [43]. A study from the USA showed similar findings, in that adults with atopic symptoms report a high prevalence of IBS, suggesting a link between atopy and IBS [44]. In a study of endoscopy all-comers in London, UK, duodenal eosinophilia was significantly commoner in patients with a history of allergy (OR 5.04, 95 % CI 2.12–11.95), and patients with PDS were significantly more likely to report a history of allergy than those without upper gastrointestinal tract symptoms (OR 4.82, CI 1.6–14), also supporting an important link between allergy and FGIDs [45]. Whether symptoms of FGIDs wax and wane with the severity of these associated conditions is yet to be determined.

Early life

Population-based data support a possible birth cohort phenomenon in IBS, and early-life risk factors likely play a key role in the development of IBS [46]. These risk factors have been defined as affluent socioeconomic status, trauma and social learning of illness behaviour. Whether early symptom management may be of benefit alongside cognitive therapy in these patients and in children needs testing in terms of modulating early learned illness behaviour [47]. For example, in a study of Norwegian twins, a low birth weight below 1500 g (OR 2.4, 95 % CI 1.1–5.3) contributed to development of IBS, which appeared 7.7 years earlier than in higher-weight groups [48]. In this context, environmental factors such as specific diets, lifestyle, or hygiene factors at key stages of life may contribute to the manifestation of FGIDs. Indeed, in contrast to IBS, a recent study demonstrated that the prevalence of dyspeptic symptoms was inversely associated with the GDP per capita [7].

Stress and the brain–gut axis

Stress is defined as an acute physical or psychological threat to the homeostasis of an organism which provokes an adaptive response [49]. In subjects with gastrointestinal symptoms, health care consultations are significantly increased in those with psychological distress, anxiety and depression [50]. Chronic stress is a major risk factor for FGIDs, likely through dysregulation of the brain–gut axis via the hypothalamic–pituitary axis [51]. This in turn may lead to increased intestinal permeability, resulting in enhanced uptake of potentially noxious agents [52], disordered motility [53] and visceral hypersensitivity [54] with mast cell degranulation and activation of an inflammatory state [55].

Psychological and behavioural therapies which reduce the stress trigger in tandem with empirical symptom management can alleviate symptoms [49]. Specifically in IBS, there is a significant effect in favour of psychological therapies. With a number needed to treat (NNT) of 4 (95 % CI 3–5), the greatest benefit has been shown with cognitive behavioural therapy (CBT) [56]. The use of

pharmacological antidepressants [both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)] is recommended by the American College of Gastroenterology guidelines [56] for management of IBS. On the other hand, the American Gastroenterological Association guidelines [57] suggest using TCAs (over no drug treatment) in patients with IBS, but do not recommend using SSRIs in patients with IBS. Both guidelines are conditional recommendations with at best moderate-quality evidence, and side effects are common, which may limit tolerance of these drugs [56, 57].

Relatively few controlled trials have evaluated the efficacy of psychological therapies in FD. In small trials there is a greater improvement of symptoms in patients treated with cognitive psychotherapy than in a control group that received no specific treatment, and in FD patients with refractory symptoms, CBT was effective for the control of concomitant anxiety and depression, but more studies are needed in this area [14]. For the management of FD, there is now reasonably convincing evidence that SSRIs and selective serotonin norepinephrine reuptake inhibitors are not efficacious [58, 59]. In addition, SSRIs can cause dyspepsia, and are associated with an increased risk of upper gastrointestinal tract bleeding [60].

The efficacy of TCAs is less clear, but a recent North American FD treatment trial concluded that low-dose TCA therapy (amitriptyline, 50 mg for 3 months) has a borderline modest benefit over placebo in FD, particularly in EPS, but when therapy was stopped, relapse was not prevented [61]. Further, gastric physiology (e.g. slow gastric emptying) failed to predict the outcome of antidepressant therapy [62]. On the other hand, data from a randomized trial in refractory patients with dyspepsia suggest that the effect of intensified medical therapy including a low dose of a TCA (doxepine) was superior to that of standard therapy and not different from that of CBT [14].

Mirtazepine therapy in a small randomized trial appeared to be superior to placebo in FD, but more data are needed [63]. Importantly, negative results in limited trials do not exclude a positive result with other antidepressants, and further studies are awaited [58].

Dysbiosis, diet and the gut–brain (and brain–gut) axis

Although dysregulation of the brain–gut axis can be driven by stress, it is also apparent that central nervous system dysfunction in FGIDs is bidirectional. An important study establishing interdependence of the brain and the gut showed that symptoms of FGID at entry to a study in those free of anxiety or depression were significantly associated with higher levels of anxiety and depression at follow-up (over a 12-year period), and similarly those with anxiety or depression at the baseline who were free of FGID symptoms were at a significantly increased risk of developing FGID symptoms over time [64]. Similarly, in a large IBS and control cohort from Taiwan with more than 30,000 patients in each group, the incidence of new-onset major depression was significantly increased 2.6-fold in those with IBS over 10 years, with those also having autoimmune disease or asthma being at higher risk [65].

It is a logical hypothesis that the gut–brain axis is driven by dysbiosis of the microbiome and ingested constituents interacting with the microbiome and the mucosa [66]. To support this concept, in an elegant functional magnetic resonance imaging study it was been shown that in healthy females, administration of a fermented milk probiotic product containing *Bifidobacterium animalis* subsp. *lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus* and *Lactococcus lactis* subsp. *lactis* altered the brain response to an emotional faces attention task [67].

Postinfectious FGIDs

Following the Walkerton outbreak of bacterial dysentery caused by microbial contamination of the municipal water supply in 2002, follow-up of affected individuals found that a significant proportion (32 %) developed new-onset IBS [68], and notably this was related to key genetic susceptibilities in the regulation of mucosal immune response [69]. Symptoms of dyspepsia at an 8-year follow-up were also significantly more prevalent in those exposed to gastroenteritis than in those who were unaffected [70]. A similar study from Europe identified that 10 % of patients with an intestinal bacterial infection report postinfectious symptoms up to 10 years after the infectious event, and revealed four significant factors affecting the occurrence of postinfectious IBS symptoms: namely, gender (female), severe symptoms during the infection, infected by *Salmonella* as opposed to *Escherichia coli*, and higher anxiety, depression and somatization baseline scores [71]. Although infection is now an established cause of FGIDs, and may account for some cases with both IBS and FD, Koch's postulates have not been completely fulfilled, and there is no work on modification of this risk in preventing a later FGID.

The gut microbiome—stomach, duodenum and colon

Although originally the acid environment of the stomach was considered a hostile environment for bacteria, except for acid-adapted *Helicobacter* species, recent studies

categorizing resident microbiota have shown surprising results, with a plethora of other bacteria at this site [72]. The role of the gastric microbiome is influenced by atrophy, and loss of acid can also influence colonic microbiota, with colonization of the colon by significantly higher levels of members of two oropharyngeal genera, *Veillonella* and *Lactobacillus* [73]. The study of the influence of gastric microbiota in FGIDs is nascent, apart from the role of *H. pylori* in FD [74], which is discussed in the next section.

Studies of the duodenal microbiome are also largely lacking, but PCR investigations of duodenal brush samples in patients with all types of IBS have shown that there is a reduction of the numbers of *Bifidobacterium catenulatum* in both duodenal mucosa and faecal microbiota [75]. It was also shown that *Pseudomonas aeruginosa* was predominant in numbers and frequency in IBS [76]. It is unknown whether or not these microbial differences contribute to the pathophysiological changes or are an epiphenomenon in these patients. Larger studies on well-characterized patients with FD and IBS may provide answers as to the role of duodenal microbiota.

The small intestine is also a challenging environment for bacteria, as there is a short transit time (3–5 h), and bile acids inhibit growth [77]. Jejunal and ileal microbiota consist mainly of facultative anaerobes, including streptococci, lactobacilli, the genus *Veillonella*, *Proteobacteria* and *Bacteroides* [78]. Archaea are not well represented, and fall below the detection limit of quantitative PCR [78]. These studies were performed on healthy subjects by sampling ileostomy outputs, and as with the upper gastrointestinal tract studies, are scant and lacking clinical correlation to any disease states.

In IBS research, the microbiota of the colon is a prominent target for investigation of the generation of symptoms and possible manipulation. There is a blossoming literature on this topic, and excellent reviews conclude that it is clear that the colonic microbiome may play a major role in IBS [79–82]. A summary of current thinking is presented below [79–82]:

1. In animal studies it has been shown that the colonic microbiome alters visceral pain responses, intestinal permeability and brain function and behaviour.
2. There is interaction with bacteria, with both gut and brain alterations linked to bacterial function.
3. Inflammation, stress, diet, exercise and the environment influence the microbiome, and thus may be linked to IBS and possibly FD symptoms.
4. Although IBS patients have a microbiome different from that of healthy counterparts in several but not all studies, as yet there is no distinct pattern to act as a biomarker, and it may be that phenotypically identical but microbially distinct subsets exist.
5. There are small but reasonably convincing studies on the influence of diet, prebiotics, probiotics and antibiotics on symptom relief in IBS.

However, the assessment of the mucosa-associated microbiome requires biopsies. With current techniques, cross-contamination of biopsy samples is likely to occur.

Targeting pathophysiological changes in FD

Patients with PDS and/or EPS are currently classified according to the Rome III criteria, which are based on subjective symptom descriptions, not on well-defined and objective evidence of disease [83]. The pathophysiology of FD is poorly understood and has been little studied, and current diagnostic methods are limited. In the stratification of patients with *H. pylori* infection, unmarried status, sleep disturbance, depression and coffee consumption have been associated with PDS, but not with EPS [84].

H. pylori

The link between *H. pylori* and FD has been addressed in systematic reviews [85]. The most recent of these compared *H. pylori* eradication therapy versus placebo in patients with FD, and showed a benefit, with a relative risk reduction of up to 10 %, the NNT being 14. There is evidence from this study that patients with EPS show a more significant benefit from eradication than patients with PDS, although the effect is relatively modest [86].

The response to *H. pylori* eradication in Asian countries suggests possibly a higher relative benefit in Asian patients with FD compared with patients with FD in the rest of the world [87]. *H. pylori* infection causes chronic active gastritis, and in early infection there is predominant antral gastritis, with loss of somatostatin secreting D cells and consequent high gastrin and acid secretion, with duodenal acid hypersensitivity and risk of duodenal ulcer [88, 89]. The active inflammation that accompanies infection may cause ischaemia–reperfusion injury, which induces delayed gastric emptying by inactivating interstitial cells of Cajal in the circular and longitudinal muscularis in the stomach and also neuronal nitric oxide synthase positive nerves, as demonstrated in a rat model of ischaemic mucosal injury [90]. It is now apparent from numerous studies that *H. pylori* can cause dyspeptic symptoms in a small proportion of those infected, and a test and treat policy is warranted and eradication therapy should be offered to those who test positive [91]. As the overall gain is limited, it is possible that the effect of *H. pylori* eradication is linked not only to the cure of *H. pylori* infection but also to other effects on the gastrointestinal microbiome.

FD and gastric dysfunction

Traditionally, gastric dysfunction (notably, slow gastric emptying) has been implicated in but does not reliably correlate with symptoms in FD, and is thought unlikely that there is a causal link [92]. Studies of gastric physiology of the separate subtypes of FD show mixed results. Although patients with FD and defined EPS and PDS had no difference in delayed gastric emptying and no differences in their symptom pattern induced by nutrient challenge [26], in another study, slower gastric emptying was observed in patients with PDS than in patients with EPS [93]. Prokinetic therapy is superior to placebo in FD, but the response is not predicted by accelerated gastric emptying [94]. Gastric dysaccommodation (failure of normal fundic relaxation) occurs in up to 40 % of patients with FD, and has been linked to early satiety in some but not all studies [95].

A newer therapy for FD, acotiamide, enhances the gastric accommodation reflex and gastric emptying rate in FD patients by antagonism of M1 and M2 muscarinic receptors and inhibition of acetycholinesterase [96]. In a well-conducted study from Japan, 52 % in the acotiamide group and 35 % in the placebo group had global improvement in FD symptoms ($P < 0.001$) [97]. A recent meta-analysis also concluded acotiamide had a significantly more beneficial effect on the reduction of PDS symptoms compared with EPS symptoms [98].

A carefully conducted study from Italy showed that there was a significantly higher prevalence of fasting hypersensitivity to gastric distension (measured by a barostat) in FD patients with PDS (37 % vs 9 % in patients with EPS), with no difference in gastric accommodation between FD subtypes and healthy volunteers, although EPS was characterized by an alteration of gastric compliance [99]. Sensitivity to acid in the stomach and in the duodenum in FD patients has been studied. In a study of acid infusion into the stomach of FD patients (Rome III classification but not divided into subgroups), both water and acid (to a greater degree) provoked FD symptoms, suggesting that upper intestinal visceral hypersensitivity plays a role in the generation of FD symptoms [100]. In the duodenum, duodenal hypersensitivity to acid was noted in FD patients, with no significant difference in scores between patients with PDS and patients with EPS [101]. Duodenal acidification regulates gastric emptying, and a high level of acid slows gastric emptying, which may induce postprandial distress [102].

Acid suppression with proton pump inhibitors (PPIs) is a standard therapy for FD, both in individuals without *H. pylori* infection and in individuals with persistent symptoms following *H. pylori* eradication. A systematic review of eight trials endorsed the use of PPIs as cost-effective, with the NNT being 9 [103]. In that study, it was shown that PPIs were more effective in individuals with EPS than in individuals with PDS.

The role of herbal therapy is unclear. STW 5 (iberogast) has been reported to be superior to placebo, but the quality of the initial trials is low [104]. A randomized trial of the Japanese herbal product rikkunshito showed overall it was not beneficial over placebo [105].

Taken together, these studies show that there are consistent patterns of disordered gastric physiology in FD, but a direct link to symptoms is less clear. However, careful classification of patients' symptoms to Rome III classification EPS and PDS probably helps tailor symptomatic therapy.

Immunological disorders in FD

Recent studies have demonstrated that FD is associated with duodenal disease, including the expansion of activated eosinophils in the duodenum in a substantial proportion of patients (47 % with early satiety) [45], and eosinophils and innate immunity in the duodenum are increasingly accepted as key players in the pathogenesis of dyspepsia [106, 107]. There is also evidence of aberrant immune activation in the peripheral blood of patients with FD. The levels of gut-homing T cells are increased, and cultured peripheral blood immune cells produce excess inflammatory cytokines that are linked to delayed gastric emptying [108]. This work suggests that a proportion of FD is an immune-mediated disease driven by allergic type T_h2 inflammation. In children with FD, a robust clinical response to montelukast, a competitive cysteinyl leucotriene 1 receptor antagonist, has been reported [109], but this has not been tested in adults. However, this work supports exploring therapies aimed at immune disturbance in FD.

It remains to be determined what the ideal treatment of FD is—a test and treat strategy for *H. pylori* is recommended, PPIs constitute a primary treatment especially in EPS, and prokinetics, including acotiamide, show promising results for PDS. These treatments are likely optimal in given types of FD; therefore, careful evaluation of symptoms should be undertaken before embarking on empiric therapy [58].

Targeting pathophysiological changes in IBS

Immunological disorders and IBS

Although the mainstay of treatment currently relies on relief of IBS symptoms, which are heterogeneous, evidence of specific pathophysiological changes to account for these symptoms is slowly emerging. Alterations in innate immunity are a fruitful avenue to explore, as subtle changes in

the immune milieu show a switch to a predominant T_h1-type response reported in postinfectious IBS [110, 111] and a T_h2-type response in other FGIDs [112]. Major cells of interest in T_h2 innate immune responses are mast cells and eosinophils. The levels of mast cells in IBS have been shown to be increased in the duodenum, and the small and large intestine, in proximity to nerves [113]. Colonic eosinophilia was reported in a recent study which also links current infection (spirochaetosis) to IBS. In a general population study from Sweden, there was a threefold increased incidence of colonic spirochaetosis, which was also heralded by specific disease, colonic eosinophilia and lymphoid aggregates [114]. There were similar histological findings in a study from South Korea, not apparently associated with colonic spirochaetosis, but a pointer to disturbance in the innate immune milieu causing IBS symptoms [115]. Specific treatments have targeted mast cells in IBS. In a study evaluating the effects of the mast cell stabilizer ketotifen, this drug reduced visceral hypersensitivity in IBS, and additionally downregulated symptoms, although the symptom response was not conclusive [116]. On the other hand, the anti-inflammatory 5-aminosalasylic acid drug mesalazine was not superior to placebo in IBS, although a small subgroup of patients may improve [117]. There have been no trials of targeted treatments for eosinophil downregulation in IBS.

Targeting the gut microbiome in IBS

Given evidence of a link to IBS with previous and current infection, and the link of the gut microbiome to the brain and to disruption of immune regulation, it is likely that prebiotics and synbiotics may be of benefit in this condition. However, a recent meta-analysis demonstrates relatively scant evidence for a positive effect for these; however, probiotics show value, with an NNT of 7 and improvement of specific symptom scores for abdominal pain, bloating and flatulence [118].

The very poorly absorbed antibiotic rifaxamin has been evaluated in well-designed randomized controlled trials [119], in which patients with non-constipating IBS showed a significant improvement in both global and bloating IBS symptoms, although this antibiotic is not yet approved for use in this condition by the FDA [56].

Patients with IBS have been shown to benefit from a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet [120, 121]; this fermentable carbohydrate restriction reduces symptoms, and also showed a reduction in the concentration and proportion of luminal bifidobacteria. FODMAP are fermented by bacteria in the large intestine, and excess gas production and water retention leads to distention and probable symptom generation. Restriction therefore reduces these symptoms [122]. Whether a FODMAP-depleted diet has an effect other than improving symptoms by reduced gastrointestinal gas production remains an open question.

Targeting symptoms in IBS

We are slowly defining the pathophysiological changes underlying IBS; however, the mainstay of treatment is in alleviating symptoms by applying gut-direct therapies. The recent American College of Gastroenterology [56] and American Gastroenterological Association [57] guidelines provide an evidence-based summary of the therapeutic options based on available randomized controlled trials.

The results are summarized below and in Tables 1 and 2.

The best evidence of efficacy is with drugs that target constipation in IBS through increased intestinal secretion. Linaclotide is a 14 amino acid peptide drug that activates guanylate cyclase on the luminal intestinal surface, leading to the cystic fibrosis transmembrane conductance regulator being activated [123]. Because the drug acts locally in the intestine to increase fluid secretion, it is well tolerated, but may cause diarrhoea (number needed to harm of 6). In randomized controlled trials, linaclotide was superior to placebo, with an NNT of 6 overall (and an NNT of 8 for pain) [56]. Lubiprostone is a chloride channel 2 activator, also acting locally in the intestine. It is also efficacious in IBS (NNT of 12.5) [56]. Diarrhoea is a side effect, and in practice nausea can be an issue in up to one in five patients, although the mechanism of nausea is unknown [124]. Normally one of these options may be considered if first-line dietary and laxative therapy has failed in patients with IBS and constipation. There is lack of evidence the laxative poly(ethylene glycol) helps relieve overall IBS symptoms or pain [56].

In diarrhoea-predominant IBS, loperamide may help diarrhoea but not other symptoms of IBS. 5-HT_3 antagonists slow intestinal transit and improve diarrhoea and urgency in IBS. Ondansetron failed to improve abdominal pain [125] but alosetron, available in the USA, improves IBS symptoms, including pain, with an NNT of 8 [56]. Alosetron can cause ischaemic colitis, and although there are positive trial data in males, alosetron is only approved by the FDA for women with severe diarrhoea-predominant IBS [56].

Intestinal spasm has been documented in IBS by applying sophisticated imaging [126]. Certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverium and dicyclomine) provide symptomatic short-term relief in IBS. Adverse events are commoner with antispasmodics than with placebo, but the quality of the evidence is low [56]. There is better evidence that peppermint oil is superior to placebo in IBS (with an NNT of 3) [56].

Table 1 Evidence-based gut-directed therapies for irritable bowel syndrome (*IBS*) with constipation [56, 57]

Drug class	Efficacy	Comment
Linaclotide (guanylate cyclase activator)	NNT 6	Useful 2nd-line therapy
Lubiprostone (chloride channel activator)	NNT 12.5	Useful 2nd-line therapy
Poly(ethylene glycol) (osmotic laxative)	Not established	Worth a trial for constipation but not pain
Psyllium (bulking agent)	NNT 7	Overall relief of IBS

NNT number needed to treat

Table 2 Evidence-based gut-directed therapies for irritable bowel syndrome with diarrhoea [56, 57]

Drug class	Efficacy	Comment
Loperamide (μ-opioid receptor agonist)	Not established	Improves diarrhoea, not pain
Bile salt binder	Not established	Limited evidence, worth a trial
Alosetron (5-HT_3 antagonist)	NNT 8	Approved in females
Ondansetron (5-HT_3 antagonist)	Not established	Improves diarrhoea, not pain

NNT number needed to treat

Notably there are almost no trials testing combination therapies. In a proof-of-concept randomized controlled trial comparing standard therapy with intensive medical therapy based on identified motor and sensory abnormalities versus combining intensive medical therapy with psychological therapy (CBT), amongst 100 patients with FD, intensive medical therapy was superior in reducing symptoms, lowering anxiety and depression, and improving quality of life [14]. Adding psychotherapy to standard medical care in FD in another trial produced benefits out to 6 months after treatment [127].

These trials needs to be replicated in FD and tested in IBS with sufficient power to tease out subgroups.

Summary

Recent decades have seen major advances in our understanding with the identification of subsets of FGIDs that have tangible pathophysiological changes affecting the gut–brain axis and brain-gut axis. A genetic predisposition is important in at least some cases. Atopic and autoimmune diseases, early life events and stress, and dysbiosis and diet likely play a role. An emerging area is the change in the gut microbiome and specific infections that likely alter innate immune disturbances, providing a plausible explanation for some but not all FGIDs and new treatment targets. Successful therapy for patients with FD and IBS currently relies on careful exclusion of organic disease, with treatment of this if required. All patients require advice on simple measures (reassurance and change in diet and lifestyle), and then targeting symptoms with evidence-based drugs as needed. Eventually research should reveal further pathological conditions which can be targeted in FGIDs, and for some patients maybe a cure is even in sight.

Conflict of interest The authors declare that they have no conflict of interest.

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