Current and emerging therapies for the management of functional gastrointestinal disorders

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***Abstract*:** The functional gastrointestinal disorders are common disorders that are associated with significant quality-of-life impairment and considerable economic burden on the health-care system. They are frequently associated with a comorbid psychiatric condition; this, together with a striking lack of effective pharmacological therapies, means they represent a considerable therapeutic challenge to the treating physician. In this overview, we examine the evidence to support the use of agents currently used in the management of the more common functional gastrointestinal disorders and review emerging therapies.

***Keywords*:** antibiotics, antidepressants, cognitive behavioural therapy, functional dyspepsia, functional gastrointestinal disorders, functional heartburn, irritable bowel syndrome, probiotics, serotonin

Introduction and background

The functional gastrointestinal disorders (FGIDs) are symptom-based disorders that cannot be currently explained by definable structural or biochemical causes [Drossman, 2006]. These disorders are common: the presence of at least one FGID was identified in 70% of participants in a large US householder survey [Drossman *et al.* 1993]. An associated comorbid psychiatric condition such as anxiety, mood or panic disorder is seen in up to 60% of those attending gastroenterology outpatient clinics with a functional compliant [Drossman *et al.* 1999]. FGIDs are associated with significant impairment of quality of life and considerable economic burden on the healthcare system [Maxion-Bergemann *et al.* 2006; Akehurst *et al.* 2002; Koloski *et al.* 2000].

Although several classification systems exist for defining FGIDs, the Rome criteria are the most commonly used for research purposes. The most recent iteration, the Rome III diagnostic criteria was released in 2006 [Drossman, 2006]. It defines 28 distinct FGIDs in 6 major domains (Table 1). A Canadian householder survey using Rome II criteria found that functional bowel syndromes including irritable bowel syndrome (IBS) were the most prevalent, diagnosed in 41% of responders, followed by functional oesophageal syndromes, including functional heartburn, which were found in 28% [Thompson *et al.* 2002]. In addition, considerable overlap exists between the FGIDs, with 30% of those with IBS and 60% of those with functional heartburn also fulfilling criteria for the diagnosis of functional dyspepsia [Savarino *et al.* 2009; Wang *et al.* 2008].

The Rome III guidelines emphasize the importance of the therapeutic relationship in the management of FGIDs. A nonjudgmental interview, together with an explanation of why symptoms occur, reassurance that the condition is not life threatening and education regarding healthy lifestyle behaviours, may be important therapeutic tools. While invasive investigations to rule out organic pathology will be required in some, for many, a positive diagnosis based on symptom patterns can be made and the much more extensive and invasive 'diagnosis by exclusion' route avoided. Indeed, inappropriate or repeated tests suggest physician uncertainty to the patient and may lead to fear on the part of the patient and a cycle of ineffective management [Longstreth and Drossman, 2005]. In this overview, we focus on

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Table 1. Rome III Functional Gastrointestinal Disorders [Drossman, 2006].

A. Functional oesophageal disorders
- A1. Functional heartburn
- A2. Functional chest pain of presumed oesophageal origin
- A3. Functional dysphagia
- A4. Globus

B. Functional gastroduodenal disorders
- B1. Functional dyspepsia
  - B1a. Postprandial distress syndrome
  - B1b. Epigastric pain syndrome
- B2. Belching disorders
  - B2a. Aerophagia
  - B2b. Unspecified excessive belching
- B3. Nausea and vomiting disorders
  - B3a. Chronic idiopathic nausea
  - B3b. Functional vomiting
  - B3c. Cyclic vomiting syndrome
- B4. Rumination syndrome in adults

C. Functional bowel disorders
- C1. Irritable bowel syndrome
- C2. Functional bloating
- C3. Functional constipation
- C4. Functional diarrhoea
- C5. Unspecified functional bowel disorder

D. Functional abdominal pain syndrome

E. Functional gallbladder and Sphincter of Oddi (SO) disorders
- E1. Functional gallbladder disorder
- E2. Functional biliary SO disorder
- E3. Functional pancreatic SO disorder

F. Functional anorectal disorders
- F1. Functional faecal incontinence
- F2. Functional anorectal pain
  - F2a. Chronic proctalgia
    - F2a1. Levator ani syndrome
    - F2a2. Unspecified functional anorectal pain
  - F2b. Proctalgia fugax
- F3. Functional defecation disorders
  - F3a. Dyssynergic defecation
  - F3b. Inadequate defecatory propulsion

the management of the more common FGIDs: IBS, functional dyspepsia and functional heartburn.

Irritable bowel syndrome

IBS is the most common and best described of the functional bowel disorders. It is characterized by abdominal pain or discomfort that is associated with changes in the frequency or consistency of stools and often accompanied by bloating and/or distension. Approximately 10–20% of adults in the West have symptoms consistent with IBS [Quigley *et al.* 2006; Saito *et al.* 2002]. A combination of visceral hypersensitivity, smooth muscle spasm and impairment of central pain processing [Aziz *et al.* 2000; Trimble *et al.* 1995] likely contribute to the pain associated with IBS, while altered intestinal motility underlies the disordered defecation experienced by some patients with IBS [McKee and Quigley, 1993].

Fibre, antispasmodics and peppermint

Traditionally, those with IBS were advised to increase their intake of dietary fibre to improve stool consistency and were prescribed one of a variety of antispasmodic agents to ameliorate the associated pain and bloating. A recent meta-analysis and systematic review looked at the efficacy of fibre, antispasmodics and peppermint oil in the treatment of IBS [Ford *et al.* 2008]. It found that fibre in the form of psyllium (ipsaghula husk) is moderately effective in the treatment of global symptoms of IBS; however, wheat bran was no more effective than placebo. Antispasmodics were also shown to be of benefit. Hyoscine was the individual compound with the best evidence to support its use and is a reasonable first-line treatment option for practitioners who wish to begin a trial of an antispasmodic agent. Data were limited however for many of the antispasmodics commonly used in the UK such as mebeverine, dicloverine and alverine. Peppermint oil, which is known to have antispasmodic properties [Hills and Aaronson, 1991], was superior to placebo in the treatment of IBS. It is worthwhile taking into account that bulking agents such as ipsaghula may cause bloating, abdominal pain and flatulence [Snook and Shepherd, 1994; Arffmann *et al.* 1985]. A gradual titration of the dose is, therefore, recommended particularly in those with predominant bloating or relatively little fibre in their diet. In addition, as antispasmodics are useful in relieving postprandial pain they are best used proactively approximately 30 minutes before meals. It must also be remembered that peppermint preparations can precipitate or aggravate heartburn, an issue that may be relevant to a number of patients, given the frequency of overlap between functional heartburn and IBS[Grigoleit and Grigoleit, 2005].

Laxatives

The disordered defecation of IBS is often treated with either laxatives or antidiarrhoeal agents, as required. The American College of Gastroenterology (ACG) IBS task force recently looked at the role of both of these agents in a systematic review on the management of IBS [Brandt *et al.* 2009]. Laxatives have mostly been studied in patients with chronic

constipation but not in randomized control trials in adults with IBS. Polyethylene glycol improved stool consistency, but not abdominal pain, in one small study in adolescents with IBS with constipation (IBS-C) [Khoshoo *et al.* 2006]. Polyethylene glycol is generally well tolerated and safe. It can easily be titrated by the patient under physician supervision. The antidiarrhoeal agent, loperamide, is an effective agent for the treatment of diarrhoea, improving both stool frequency and consistency. However, it is no more effective than placebo at reducing pain or global symptoms of IBS. Antidiarrhoeals may be used prophylactically as needed, such as before leaving the house or before a meal or stressful event. Treatment should begin with a low dose to avoid constipation; however, up to two tablets four times daily may be used to treat those with more severe diarrhoea.

Antidepressant medications

The severity of IBS-associated pain is highly predictive of related medical costs and quality-of-life impairment [Longstreth *et al.* 2003]. Antidepressants have been used in the treatment of IBS-associated abdominal pain both for their potential modulation of pain perception [McQuay *et al.* 1996] and for the treatment of coexistent psychiatric illness. A recent meta-analysis examining the role of antidepressants in the management of IBS [Ford *et al.* 2009c] demonstrated a benefit for both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) over placebo in the treatment of IBS. Both agents appeared to be equally effective. Data on the safety and tolerability of these agents in IBS is limited.

TCAs are usually used at low doses in the treatment of IBS as the symptom improvement seen may be more related to their pain modulation and motility effects rather than treatment of psychological symptoms. The administration of the TCA, imipramine, prolonged both orocaecal and whole gut transit in a cohort of patients with IBS with diarrhoea (IBS-D) and healthy controls [Gorard *et al.* 1994]. This makes them an attractive option for the treatment of those with IBS-D, particularly in those where pain is a predominant feature. In contrast, the SSRI paroxetine has been shown to accelerate gut transit time [Chial *et al.* 2003]. SSRIs generally have a lower side-effect profile than TCAs [Cipriani *et al.* 2005] and should be considered in the treatment of IBS when psychological symptoms or coexistent somatic pain syndromes are present, or in those patients who have not responded to laxatives or antispasmodics. The same dose as that used for mood disorders is recommended [Pae *et al.* 2007]. While citalopram and escitalopram generally have less side effects and drug interactions than the other SSRIs [Cipriani *et al.* 2009a, 2009b], paroxetine can be considered in the treatment of IBS-C due to effects on gut transit. Data on the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) in the treatment of IBS is not currently available.

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) has been suggested to play a role in the pathogenesis of the IBS [Pimentel *et al.* 2003]. While more recent studies have, for the most part, failed to confirm a major role for SIBO in IBS [Ford *et al.* 2009b], in general, a number of studies have demonstrated some efficacy for antibiotic therapy in IBS. It has been suggested that these effects are mediated through a modulation of the colonic flora; a hypothesis supported by evidence of quantitative and qualitative changes in the colonic microbiota in IBS [Codling *et al.* 2010; Malinen *et al.* 2005]. Thus, studies have shown an improvement in patients with IBS treated with neomycin, metronidazole, doxycycline and ciprofloxacin [Yang *et al.* 2008; Pimentel *et al.* 2006a; Nayak *et al.* 1997]. However, routine use of these drugs is limited by concerns about potentially serious adverse effects and the development of microbial resistance.

Rifaximin is an oral nonabsorbable antibiotic that is approved in the US for the treatment of travellers' diarrhoea and hepatic encephalopathy. Its localized action in the gastrointestinal tract results in a low risk of adverse effects whilst providing targeted therapy against Gram-positive and Gram-negative aerobic and anaerobic enteric pathogens. It is not associated with clinically relevant antimicrobial resistance [Pimentel, 2009]. Three large randomized control trials have demonstrated the efficacy of rifaximin in relieving global symptoms of IBS, bloating and diarrhoea [Pimentel *et al.* 2006b; Sharara *et al.* 2006]. Rifaximin is therefore most likely to be of benefit to those with IBS-D or in IBS patients with a predominance of bloating. The appropriate dosage is 1100–1200 mg/day in divided doses for 10–14 days. Long-term safety data on rifaximin are not yet available [Brandt *et al.* 2009]; pending their arrival one must remain cautious

regarding the long-term or intermittent use of any antibiotic in such a chronic or remitting disorder.

Probiotics and prebiotics

Probiotics are defined as live organisms that may exert a health benefit on the host when ingested in adequate amounts [Quigley, 2007]. Their relative safety makes them an appealing option in a chronic condition such as IBS. Probiotics in clinical trials have varied widely in terms of species, strain and dose. This makes evaluation of the data in relation to IBS difficult. Like in other areas effects of probiotics in IBS are highly strain specific; some species and strains can improve individual IBS symptoms [Dolin, 2009; Nobaek *et al.* 2000], such as bloating or flatulence, while few provide overall benefit. Thus, while one recent meta-analysis [Moayyedi *et al.* 2010] concluded that probiotics as a whole appear to be efficacious in IBS, in another, only *Bifidobacterium infantis* improved global symptom relief in IBS [Brenner *et al.* 2009]. Further studies are needed to establish which species, strain and dose of probiotic will be of greatest benefit in the long term.

Given the encouraging results with probiotics, some attention is now being focused on the use of prebiotics in the treatment of IBS. Prebiotics are nondigestable but fermentable foods that selectively stimulate the growth of one or more species of bacteria in the gut and in doing so confer a health benefit to the host [Quigley, 2009]. A recent randomized controlled trial examined the effect of a prebiotic (galactooligosaccharide) in a small cohort of patients with IBS [Silk *et al.* 2009]. It demonstrated that the prebiotic in question specifically stimulated gut bifidobacteria in IBS patients and was effective in relieving symptoms. Although larger studies are warranted, this points towards a possible future role for prebiotics in the management of IBS.

Lubiprostone

Lubiprostone is a highly selective activator of type 2 chloride channels in the GI tract. It increases secretion of chloride-rich enteric fluid without affecting serum chloride, sodium and potassium levels. The increase in intestinal fluid eases stool passage and, thereby, improves stool frequency and form [Ambizas and Ginzburg, 2007]. Lubiprostone was initially used in the treatment of chronic constipation. A dose of 24 μg twice daily was found to be efficacious in improving stool frequency, stool form and straining in both men and women with chronic constipation [Johanson *et al.* 2008b]. An improvement in abdominal pain was seen in a subset of the patients in these trials and this led to the evaluation of lubiprostone in subjects with IBS-C. Three large randomized controlled trials [Drossman *et al.* 2009; Johanson *et al.* 2008a] have recently demonstrated that patients with IBS-C receiving lubiprostone at a dose of 8 μg twice daily were almost twice as likely to report an improvement in the global symptoms of IBS as those receiving placebo. Lubiprostone was generally well tolerated with nausea, vomiting and abdominal cramping being the most common side effects. As most of the subjects in clinical trials of lubiprostone were female, lubiprostone is approved by the FDA for the treatment of IBS-C in women at a dose of 8 μg twice daily. It should be taken with meals to reduce nausea.

Guanylate cyclase C

Guanylate cyclase C (GC-C) is a transmembrane protein located in intestinal epithelial cells. Activation of intestinal GC-C induces secretion of fluid, sodium and bicarbonate in the intestinal lumen [Andresen *et al.* 2007]. Linaclotide is a synthetic GC-C agonist. Initial studies in subjects with chronic constipation and IBS-C have shown it to be an effective agent in terms of its effect on stool consistency and frequency and abdominal discomfort. In addition, it appeared to be safe and well tolerated suggesting it may be a promising new agent in the treatment of IBS-C and chronic constipation [Camilleri, 2010].

Serotonin

Serotonin (5-HT) is an important neurotransmitter in both the brain and gastrointestinal tract. It plays a key role in gut motility, secretion and sensitivity [Kim and Camilleri, 2000]. Postprandial plasma serotonin levels have been found to be decreased in IBS-C and increased in IBS-D [Gershon and Tack, 2007]. Several drugs acting on the 5-HT receptor system have shown significant therapeutic benefit in the treatment of IBS. Tegaserod, a 5-HT4 receptor partial agonist has shown significant benefit in improving abdominal discomfort, bowel habits and bloating in subjects with IBS-C [Ford *et al.* 2009a]. In contrast, alosetron, a 5-HT3 receptor antagonist, demonstrated sustained relief of abdominal pain and urgency in subjects with

IBS-D [Ford *et al.* 2009a]. However, despite their therapeutic benefit, tegaserod was withdrawn from the US market in 2007 because of its association with cardiac side effects. Alosetron had been withdrawn in 2000 due to its association with severe constipation and ischaemic colitis but was reintroduced under a risk management plan for women with severe IBS-D under 55 years of age. Similarly, cisapride, a 5-HT4 agonist, was withdrawn from the market in 2000 due to its association with cardiovascular side effects and deaths due to arrhythmias [Shekhar and Whorwell, 2009].

Despite these difficulties much of the focus of new drug development for IBS remains centred on the serotonergic receptors in the gut. Three new 5-HT4 receptor agonists, prucalopride, AT-7505 and velusetrag (TD-5108) are currently been evaluated in clinical trials involving subjects with chronic constipation. Indeed, prucalopride has recently been approved by the European Medicines Agency for the treatment of chronic constipation in women at a dose of 2 mg daily.

As a result of the potential association of tegaserod and cisapride with cardiac and vascular adverse events, new drugs in this class must prove selectivity for the 5-HT4 receptor over other receptors and must demonstrate safety through studies of arrhythmogenic potential [Camilleri, 2010]. Early results are promising [Shekhar and Whorwell, 2009]. Ramosetron is a novel 5-HT3 receptor antagonist. A global improvement in symptoms was seen in both men and women with IBS treated with ramosetron in two randomized control trials without serious adverse events [Matsueda *et al.* 2008a, 2008b].

Immune activation

There is now good evidence for immune activation, detectable in the colonic mucosa [Ohman *et al.* 2009; Gwee *et al.* 2003] as well as in the systemic circulation [Dinan *et al.* 2008; Liebregts *et al.* 2007], in IBS. Whether this immune activation reflects interactions between the (altered) microbiota and the host remains to be defined. Initial studies with specific probiotic strains [O'Mahony *et al.* 2005] as well as the anti-inflammatory agent, mesalamine [Barbara *et al.* 2009], are encouraging and suggest that this may be a future therapeutic strategy in IBS.

Nonpharmacological therapies

Nonpharmacological therapies that have been used in the management of IBS include dietary manipulation and psychological therapies. Postprandial worsening of symptoms [Ragnarsson and Bodemar, 1998] and a perceived intolerance to one or more food types [Simren *et al.* 2001] is frequently reported by patients with IBS, but is there evidence to support dietary manipulation in its management? As already mentioned, the addition of soluble fibre in the form of psyllium (ipsaghula husk) has proven beneficial in some patients but insoluble fibre in the form of wheat or corn bran does not significantly improve symptoms [Ford *et al.* 2008]. Some patients find that fibre-containing foods actually worsen their symptoms. Foods rich in carbohydrates or containing starch, lactose, fructose or sorbitol as well as fatty foods and food agents such as coffee, alcohol and spices were all reported to exacerbate IBS symptoms in one study [Simren *et al.* 2001]. The precise contributions of specific food intolerances, the physiological response to food, the ability of food ingestion to potentiate pre-existing visceral hypersensitivity or dysmotility, interactions between the ingested food and the microbiota or psychological factors in the genesis of food-related symptoms remains to be fully elucidated.

What is clear is that there is little correlation between skin prick testing or serum immunoglobulin (Ig) E levels and reported food allergies in IBS patients [Dainese *et al.* 1999; Zwetchkenbaum and Burakoff, 1988]. In addition, evidence to support the benefit of lactose, fructose and sorbitol exclusion diets is inconclusive at best [Morcos *et al.* 2009]. Although some evidence does exist to support a role of food 'allergy' testing based on IgG antibodies and of some benefit for exclusion diets based on its results in IBS [Park and Camilleri, 2006; Atkinson *et al.* 2004], methodological shortcomings in existing studies examining the role of food allergy and elimination diets in IBS led the ACG IBS task force to conclude that, at present, there is insufficient evidence to support the routine use of elimination diets outside of clinical trials [Brandt *et al.* 2009].

Psychotherapeutic interventions

Psychotherapeutic interventions that have been used in the treatment of IBS include cognitive behavioural therapy (CBT), dynamic psychotherapy, hypnotherapy and relaxation therapy.

Although high-quality evidence evaluating the role of psychological intervention in IBS is somewhat lacking, available evidence suggests that CBT, dynamic psychotherapy and hypnotherapy are beneficial in the treatment of IBS and indeed may be as effective as antidepressants in this setting [Ford *et al.* 2009c]. One of the major obstacles to objective data in this field is the challenge of performing a double-blind placebo-controlled trial. The best evidence is for CBT [Brandt *et al.* 2009], which teaches patients to identify the relationship between thoughts and physical symptoms and to modify dysfunctional beliefs and sick role behaviour [Zijdenbos *et al.* 2009]. There is insufficient evidence to support the role of relaxation therapy in the treatment of IBS [Brandt *et al.* 2009].

Functional dyspepsia

Dyspepsia is defined as chronic or recurrent pain or discomfort centred in the upper abdomen. Discomfort may incorporate a variety of symptoms including epigastric burning, early satiety or upper abdominal fullness. According to the Rome criteria for functional dyspepsia, heartburn and acid regurgitation are, however, excluded from the definition and those who suffer predominantly from these symptoms should be considered to have gastroesophageal reflux disease (GORD) until proven otherwise [Talley and Vakil, 2005]. In clinical practice, this may be less easy than it sounds in theory. Dyspepsia is a common disorder and may affect up to 30% of the general population [Talley and Vakil, 2005; Knill-Jones, 1991]. Functional dyspepsia is diagnosed in the absence of an underlying pathological cause such as peptic ulcer disease, GORD, malignancy or pancreato-biliary disease. Therefore, unlike IBS where a positive diagnosis can be made based on symptoms, functional dyspepsia remains a diagnosis of exclusion. Indeed, given its clinical overlap with IBS and the commonality of proposed pathogenetic mechanisms between the two disorders, some would question whether, indeed, IBS and functional dyspepsia are simply really part of the spectrum of the same disorder. Approximately two thirds of those with dyspeptic symptoms have functional dyspepsia [Locke *et al.* 2005].

However, not all of those with uninvestigated dyspeptic symptoms need undergo oesophagogastroduodenoscopy (OGD). A test-and-treat strategy involving testing for *Helicobacter pylori* using a noninvasive test or an empiric trial of acid suppression with a proton-pump inhibitor (PPI) may be adopted in those aged under 55 without alarm symptoms (bleeding, anaemia, early satiety, unexplained weight loss, dysphagia, odynophagia, family history of gastrointestinal cancer, oesophagogastric malignancy, previous peptic ulcer, lymphadenopathy or abdominal mass) [Talley and Vakil, 2005]. PPIs, however, have only a small benefit over placebo in the treatment of functional dyspepsia [Moayyedi *et al.* 2006]. *H. pylori* eradication cures most cases of peptic ulcer disease and improves symptoms in a minority of those with functional dyspepsia; as *H. pylori* is an important risk factor for the development of gastric adenocarcinoma, eradication is deemed worthwhile even in the absence of symptomatic improvement [Talley and Vakil, 2005]. An OGD is warranted in those whose symptoms persist after *H. pylori* eradication and empiric treatment with a PPI.

Prokinetic agents

Prokinetic agents do appear to be beneficial in the treatment of confirmed functional dyspepsia with the greatest benefit seen in those with symptoms of early satiety, postprandial discomfort and epigastric fullness [Moayyedi *et al.* 2006]. However, many of these trials involved the prokinetic cisapride, which has since been withdrawn from the market. Currently available prokinetics are domperidone and metoclopromide but the evidence supporting their efficacy is less robust. In addition, the long-term use of metoclopromide is limited by its central nervous system side effects, particularly tardive dyskinesia.

Antidepressant medications

Although further large-scale studies are warranted, available evidence suggests that antidepressive agents may be beneficial [Hojo *et al.* 2005]. A low dose of amitriptyline is generally used. A multicentre randomized controlled trial is currently underway in the US to determine the benefit of a TCA or SSRI over placebo in the treatment of functional dyspepsia.

Serotonin

Effective pharmacological therapies for the treatment of functional dyspepsia other than those described above are lacking. This is largely due to the heterogeneity of the disorder. It appears that several different pathophysiological disturbances are associated with specific symptom patterns. These mechanisms include delayed gastric

emptying, hypersensitivity to gastric distension, impaired gastric accommodation to ingestion of a meal, altered duodenal sensitivity to lipids and altered duodenojejenal motility [Tack *et al.* 2004].

In a similar fashion to IBS, some of the focus for new drug development in functional dyspepsia has centred on the serotonergic receptors in the gut. Sumatriptan is a 5-HT1D and 5-HT1B receptor agonist commonly used in the treatment of migraine. It induces relaxation of the gastric fundus and allows larger intragastric volumes before thresholds for discomfort or perception are reached in healthy individuals [Tack *et al.* 2000]. When administered subcutaneously, sumatriptan restored gastric accommodation and significantly improved meal-induced satiety in patients with functional dyspepsia [Tack *et al.* 1998]. However, intranasal administration failed to induce a significant relaxation in healthy volunteers, probably as a result of lower bioavailability [Sarnelli *et al.* 2001].

Recent studies with newer 5-HT1 receptor agonists have shown conflicting results. Tandospirone citrate is a partial agonist of the 5HT1A receptor that is used as an anxiolytic in Japan and China [Takahashi *et al.* 2010]. In a recent multicentre randomized control trial, it showed a significant benefit over placebo in improving abdominal pain in those with functional dyspepsia. However, R-137696, another 5-HT1A receptor agonist, had failed to demonstrate a benefit over placebo in patients with functional dyspepsia in a previous study [Tack *et al.* 2009]. Both cisapride and tegaserod are 5-HT4 receptor agonists, cisapride is also a 5-HT3 receptor antagonist. They increase gastric fundus compliance and gastric emptying in healthy individuals [Tonini and Pace, 2006]. Both were shown to provide symptomatic relief of functional dyspepsia before their withdrawal from the market due to concerns regarding cardiovascular adverse events [Vakil *et al.* 2008; Hiyama *et al.* 2007]. Whether the newer, more highly selective 5-HT4 receptor agonists will be of benefit in this patient group remains to be seen.

Ghrelin

Ghrelin is an orexigenic hormone that is produced by enteroendocrine cells in the stomach. It increases appetite, suppresses inflammation and modulates energy balance; it also enhances the secretion of growth hormone [Ueno *et al.* 2010]. Ghrelin accelerates gastric emptying and improves meal-related symptom scores in patients with gastroparesis [Murray *et al.* 2005; Tack *et al.* 2005]. Abnormally low preprandial ghrelin levels and absence of significant postprandial decrease of ghrelin levels has been demonstrated in a subset of patients with functional dyspepsia [Lee *et al.* 2009]. Furthermore, twice daily intravenous infusion of ghrelin for 2 weeks increased daily food intake in patients with dyspepsia-related anorexia [Akamizu *et al.* 2008]. The ability of ghrelin to stimulate hunger and increase food intake as well as its prokinetic effects suggests that ghrelin or ghrelin-receptor agonists may represent an attractive new therapeutic strategy in the treatment of motility disorders including functional dyspepsia.

Cholecystokinin

Cholecystokinin (CCK) is a gut peptide that is released from the upper intestine in response to the intraluminal presence of the digestive products of fats and proteins [Moran and Dailey, 2009]. CCK functions as a satiety signal and is involved in the control of food intake [Lieverse *et al.* 1993]. Fasting and postprandial CCK levels are higher in patients with functional dyspepsia than in healthy controls [Pilichiewicz *et al.* 2008]. The presence of fat in the upper small intestine can induce dyspeptic symptoms in patients with functional dyspepsia [Barbera *et al.* 1995]. CCK appears to be a mediator of this effect. Dexloxiglumide is a highly selective CCK type 1 (CCK1) receptor antagonist that abolishes fat-induced dyspeptic symptoms [Feinle *et al.* 2001]. The results of further studies with this medication are awaited but like ghrelin it may represent a potential new treatment strategy.

Psychotherapeutic interventions

Although several trials have shown some clinical benefit from psychological interventions such as CBT and hypnotherapy [Talley and Choung, 2009], a recent Cochrane review [Soo *et al.* 2005] concluded that there was insufficient evidence to support the efficacy of psychological therapy for functional dyspepsia. At present available therapies are effective only in subgroups of patients with functional dyspepsia. While several agents with effects on upper gastrointestinal sensory and motor function are currently undergoing evaluation in this patient group, a clearer understanding of the pathogenesis of functional dyspepsia will likely be required to aid new drug development.

Functional heartburn

Like functional dyspepsia, functional heartburn remains a diagnosis of exclusion. The Rome III criteria define it as burning retrosternal pain or discomfort at least 1 day/week for the past 3 months with symptom onset at least 6 months previously. The absence of gastroesophageal reflux as per ambulatory pH monitoring and the absence of a manometrically defined oesophageal motility disorders is also required [Drossman, 2006].

Symptoms of gastroesophageal reflux are present in up to 40% of the population. Approximately 25% of those with typical reflux symptoms will have evidence of erosive oesophagitis at upper GI endoscopy [Ronkainen *et al.* 2005]. This group of patients with erosive reflux disease (ERD) are generally very responsive to PPI therapy [Dean *et al.* 2004]. The remaining patients with nonerosive reflux disease (NERD) are a heterogeneous group with a poorer response to PPIs [Fass and Sifrim, 2009]. A proportion of those with NERD will have a positive correlation between symptoms and abnormal acid exposure on 24-hour ambulatory pH monitoring and are considered part of the spectrum of GERD and can be expected to respond to acid-suppressive therapy. Those with a normal oesophageal acid exposure and a negative symptom association can be classified as having functional heartburn once an oesophageal motility disorder has been ruled out. This group exhibits the lowest symptom response to PPIs [Fass and Sifrim, 2009]; many, characteristically, will have no response. The mechanisms underlying functional heartburn are poorly understood but putative causes include oesophageal hypersensitivity, subtle oesophageal motor abnormalities, duodenogastric or nonacid reflux, as well as psychological factors.

Proton-pump inhibitors

The majority of patients with symptomatic reflux are managed in the community by physicians without ready access to endoscopy or ambulatory pH monitoring. Therefore, empiric acid suppression is usually given without knowledge of whether symptoms relate to ERD, NERD or functional heartburn. Indeed, empiric therapy is successful in a substantial proportion of patients and they never warrant further investigation. The Vevey NERD consensus group recently issued guidelines for the management of patients presenting with symptoms of gastroesophageal reflux [Modlin *et al.* 2009]. They recommend that, in the absence of alarm symptoms such as progressive dysphagia or weight loss, those presenting with typical symptoms of GORD may be treated with a standard dose course of empiric PPI therapy and should be re-evaluated at 2–4 weeks, although symptom response may take up to 12 weeks. The persistence of reflux symptoms at 12 weeks despite adequate antisecretary therapy requires further investigation with upper gastrointestinal endoscopy. For those with a normal endoscopy and ongoing symptoms, twice daily dosage with a PPI is often considered; however, it has not been definitively established that doubling the dose of a PPI will provide incremental benefit. Compliance with medication and appropriate timing of PPI administration (which should, ideally, be taken 30 minutes before breakfast) should be assessed. Therapy may be augmented with alginates or antacids but the addition of a histamine H2-receptor antagonist is unlikely to be of benefit. For those with NERD who are fully compliant with medication and continue to have symptoms after 12 weeks of twice daily PPI therapy, their symptoms are unlikely to be related to acid reflux and the need for continued PPI therapy should be re-evaluated. Twenty-four hour pH monitoring may be useful. Oesophageal motility disorders such as achalasia or systemic sclerosis should be ruled out.

Failed PPI therapy

So what are the treatment options for those with functional heartburn who have failed PPI therapy? Unfortunately, helpful data on therapies demonstrating a therapeutic benefit for this challenging patient group is limited, if not nonexistent. A promotility agent could be considered, particularly if there is a suggestion of delayed gastric emptying; however; there is no available evidence to support its therapeutic benefit. Low-dose tricyclics, standard-dose SSRIs and trazadone have all been shown to improve oesophageal pain in noncardiac chest pain [Fass and Sifrim, 2009] and may, therefore, have a theoretical benefit in functional heartburn. Psychological distress is greater in patients who have failed PPI therapy [Nojkov *et al.* 2008] which suggests that psychological therapies may be of benefit but, again, the data to support this is lacking.

The development of new therapeutic strategies will likely require further delineation of this heterogeneous patient group. The advent of oesophageal intraluminal impedance monitoring

allows the detection of all types of acid reflux (acidic, weakly acidic and weakly alkaline). Studies using this technique suggest that symptoms of GORD in some of those classified as having functional heartburn may be related to less acidic or gas reflux that is not detected by pH-metry [Sifrim, 2004]. Bilitic monitoring quantifies duodenogastroesophageal reflux (DGOR) which has been implicated in those who have persisting symptoms on PPI therapy [Karamanolis *et al.* 2008]. It is important to emphasize that weakly acidic or nonacidic reflux is not synonymous with DGOR. Most reflux events including acid and nonacid reflux as well as DGOR occur during transient relaxations of the lower oesophageal sphincter (TLOSRs). Therefore, if the use of bilitic and impedance monitoring can convincingly demonstrate that nonacid reflux and DGOR are a cause of symptoms in functional heartburn patients, then therapy aimed at reducing the number of reflux episodes would be more appropriate than current antireflux drugs that alter the pH of the refluxate.

Baclofen is a GABA agonist which reduces the TLOSR rate and the number of reflux episodes [Tsoukali and Sifrim, 2010]. Baclofen at a dose of 20 mg three times daily significantly reduced the DGOR exposure and associated reflux symptoms in those with PPI-refractory GORD [Koek *et al.* 2003]. However, use of baclofen is limited by its CNS side effects including somnolence, dizziness and confusion. Lesogaberan is a peripherally restricted GABA receptor agonist that is devoid of the CNS side effects observed with baclofen [Lehmann *et al.* 2010]. It is currently undergoing preclinical trials but may be a promising new agent in the treatment of functional heartburn.

Conclusion

The FGIDs are chronic, often disabling conditions that affect a substantial proportion of the population. There is a striking lack of effective therapeutic options. While there is reason for optimism in the management of IBS with several promising new agents currently undergoing clinical trials, this is not the case for many of the other FGIDs, including functional dyspepsia and functional heartburn. A clearer understanding of the physiopathologic mechanisms underlying these complex conditions, as well as a clearer understanding of interrelationships between these disorders, will likely be required before effective drug therapies can be found.

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Conflict of interest statement

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