Alimentary Pharmacology & Therapeutics

Review article: current and emerging therapies for functional dyspepsia

R. J. SAAD & W. D. CHEY

University of Michigan Medical Center, Ann Arbor, MI, USA

Correspondence to:
Dr W. D. Chey, GI Physiology Laboratory, University of Michigan Medical Center, 3912 Taubman Center, Box 0362, Ann Arbor, MI 48109, USA.
E-mail: wchey@umich.edu

Publication data
Submitted 13 February 2006
First decision 26 February 2006
Resubmitted 15 May 2006
Accepted 15 May 2006

SUMMARY

Functional dyspepsia represents a heterogeneous group of gastrointestinal disorders marked by the presence of upper abdominal pain or discomfort. Although its precise definition has evolved over the last several decades, this disorder remains shrouded in controversy. The symptoms of functional dyspepsia may overlap with those of other functional bowel disorders including irritable bowel syndrome and non-erosive reflux disease.

There may be coexistent psychological distress or disease complicating its presentation and response to therapy. Given the prevalence and chronicity of functional dyspepsia, it remains a great burden to society. Suspected physiological mechanisms underlying functional dyspepsia include altered motility, altered visceral sensation, inflammation, nervous system dysregulation and psychological distress. Yet the exact pathophysiological mechanisms that cause symptoms in an individual patient remain difficult to delineate. Numerous treatment modalities have been employed including dietary modifications, pharmacological agents directed at various targets within the gastrointestinal tract and central nervous system, psychological therapies and more recently, complementary and alternative treatments.

Unfortunately, to date, all of these therapies have yielded only marginal results. A variety of emerging therapies are being developed for functional dyspepsia. Most of these therapies are intended to normalize pain perception and gastrointestinal motor and reflex function in this group of patients.

Aliment Pharmacol Ther **24**, 475–492

doi:10.1111/j.1365-2036.2006.03005.x

INTRODUCTION

Although the precise definition of dyspepsia remains debatable, the most widely quoted definition is a chronic, recurrent pain or discomfort centred in the upper abdomen.[1] The word 'centred' is further defined as being mainly in or around the midline. Once an evaluation has been performed and organic aetiologies for the dyspeptic symptoms have been excluded, an affected patient is said to be suffering from functional dyspepsia (FD; previously termed non-ulcer dyspepsia).[2] FD has been defined by the Rome II international working group as 'at least 12 weeks, which need not be consecutive, within the preceding 12 months of: (i) persistent or recurrent dyspepsia (pain or discomfort centred in the upper abdomen), (ii) no evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms and (iii) no evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form' [i.e. not irritable bowel syndrome (IBS)].[3]

Epidemiological studies suggest that approximately 15% of the general population in western countries suffers with FD.[4, 5] The association between female gender and FD is not as clear-cut as in IBS.[6] FD is commonly diagnosed by gastroenterologists and increasingly, in the age of 'open-access' endoscopy, by primary care doctors.[7, 8] Nearly two-thirds of dyspeptic patients will eventually end up with a diagnosis of FD following an evaluation.[2] FD tends to be a chronic condition with long-term studies demonstrating persistent symptoms in >80% of affected patients after 6–7 years of follow-up.[9, 10]

Adding to the complexity of FD is the overlap in symptoms with other common gastrointestinal (GI) disorders, such as IBS and gastro-oesophageal reflux disease (GERD). Studies have found that up to half of patients with FD also suffer with IBS[11] and a number of epidemiological and pathophysiological similarities have been shown to exist between the two conditions.[12] There is also evidence to suggest significant overlap between GERD, particularly non-erosive reflux disease, and FD.[13] Further, psychological distress appears to coexist more commonly in those with FD compared with the general population.[14] Interestingly, a recent study found that psychological distress was no more likely in those with functional vs. organic causes of dyspepsia[15] and, perhaps more importantly, the severity of psychological distress correlated poorly with the severity of the dyspeptic symptoms in FD.[16]

Related to how commonly FD occurs, its tendency towards chronicity and frequent overlap with other common conditions, it should come as no surprise that the associated socioeconomic impact is profound. In the US, it has been estimated that FD accounts for billions of dollars in direct and indirect costs.[17] Other studies have consistently found that FD negatively affects quality of life.[18–20]

CLINICAL PRESENTATION

In addition to abdominal pain or discomfort, the FD symptom complex may include a variety of other symptoms including postprandial abdominal fullness, bloating, early satiety, nausea, retching, vomiting, or belching.[21] Any combination of these symptoms may intermittently occur over time.[5, 9] Subtyping dyspepsia has been suggested, initially for research purposes; however, over time, this practice has gained popularity in clinical practice.[22] The Rome II working group has suggested a subtyping scheme based on the predominant or most bothersome single symptom. Ulcer-like dyspepsia if the predominant symptom is that of pain centred in the upper abdomen. Dysmotility-like dyspepsia if the predominant symptom is a discomfort other than pain centred in the upper abdomen. This discomfort may be described as or associated with an upper abdominal fullness, early satiety, bloating, belching or nausea. Unspecified (non-specific) dyspepsia if the predominant symptom fails to meet one of two previous descriptions. Reflux-like dyspepsia is not included as this is believed to be a variant of GERD.[1] At present, it must be stated that there is little evidence to support the notion that such subtyping offers insight into the underlying pathophysiology or response to specific treatments in FD patients.[23–25] Time will tell to what extent such subtyping will be endorsed by the upcoming Rome III criteria for FD.

PATHOPHYSIOLOGICAL MECHANISMS

A wide variety of pathophysiological mechanisms have been postulated to contribute to the development of symptoms in patients with FD (Figure 1). Of the abnormalities proposed, alterations in gastroduodenal motor and reflex function have been most extensively studied. Delayed gastric emptying has been reported in 30–40% of FD patients.[26–31] More recently, a small study involving patients referred to the Mayo Clinic in

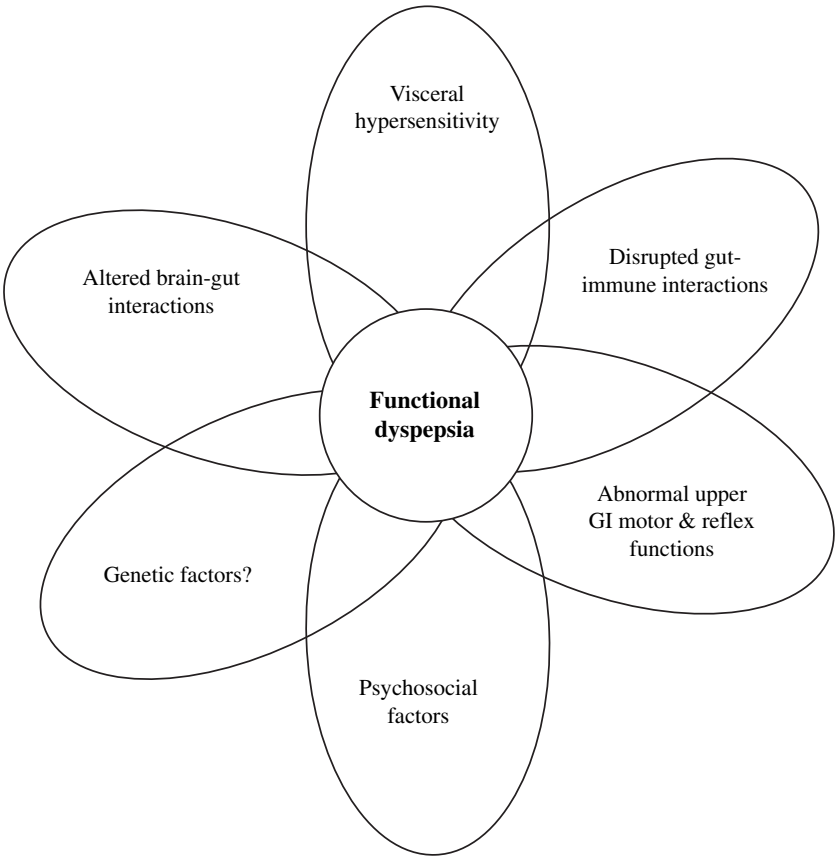

Figure 1. Proposed pathophysiological mechanism involved in functional dyspepsia.

Rochester, MN found that accelerated gastric emptying was identified as commonly as delayed gastric emptying in FD patients.[32] These provocative findings require validation at other centres. Further, as is the case with delayed emptying, whether accelerated gastric emptying is responsible for specific symptoms remains poorly validated. A number of small studies have demonstrated impaired accommodation of the proximal stomach to a meal in approximately 40% of FD patients.[24, 33–35] Although there is some evidence to suggest a correlation between abnormal accommodation and specific symptoms, this has not been confirmed by other studies.[36, 37] In addition to alterations in gastric emptying and accommodation, other abnormalities in gastroduodenal physiology have been reported including gastric antral hypomotility,[38] abnormal gastric myoelectrical activity,[39] small bowel hypermotility with increased duodenal retrograde contractions[40] and unsuppressed postprandial phasic contractility of the proximal small bowel.[41] At present, it remains unclear if any one or more likely, some combination of these abnormalities is responsible for symptoms in FD patients. For the field to move forward, investigators will need to carefully consider how these abnormalities interact with one another to affect the overall function of the upper GI tract and hopefully, symptoms.

Numerous studies have demonstrated the presence of altered visceral perception in FD. Between 34% and 66% of FD patients have evidence of heightened sensitivity to gastric balloon distention. Unfortunately, the significance of this physiological finding remains unclear as the presence of heightened perception of gastric balloon distention has not been consistently found to correlate with dyspeptic symptoms.[34, 42–44] There is evidence to suggests that duodenal hypersensitivity to lipids[45, 46] and gastric acid[47] also occur more commonly in FD. Such findings likely have relevance to a patient's frequent association of dyspeptic symptoms to eating a meal. The recent application of sophisticated brain imaging techniques is improving our understanding of the cortical sites responsible for the processing of painful and non-painful sensations arising from the stomach.[48, 49] Going forward, such information should prove useful both to better understand the pain pathways responsible for symptom development and ultimately, for the development of novel pharmacotherapeutic agents.

Table 1. Traditional pharmacological treatment strategies for functional dyspepsia

Therapeutic intervention	Efficacy	Evidence
Helicobacter pylori eradication	36% responding with treatment vs. 30% with placebo. NNT of 18	Meta-analysis of 13 RCTs totalling 3186 patients Previous meta-analyses and individual RCTs with discordant results
Proton pump inhibitors	33% responding with treatment vs. 23% with placebo. NNT of 9	Meta-analysis of 8 RCTs totalling 3293 patients
Prokinetics Erythromycin Metoclopramide Domperidone	Twice as likely as placebo to improve symptoms. NNT of 4 (assuming placebo response of 41%)	Meta-analysis of 14 RCTs totalling 1053 patients Efficacy may be overestimated due to publication bias and removal of cisapride from the market
Histamine-receptor antagonists	Benefit over placebo only in the treatment of epigastric pain and postprandial fullness	Meta-analysis of 11 RCTs totalling 2164 patients Similar findings in previous meta-analysis of 22 RCTs
Antidepressants TCAs Antianxiety agents	73% responding with TCA, desipramine, vs. 49% with placebo by PP analysis. NNT of 4. Relative risk of remaining symptomatic of 0.55 with use of either agent vs. placebo in meta-analysis	Single RCT only demonstrating efficacy by PP analysis and not ITT analysis Meta-analysis of 4 RCTs totalling 153 patients
Antacids	No better than placebo	Only 1 RCT meeting criteria totalling 109 patients
Bismuth salts	No better than placebo	Meta-analysis of 5 RCTs totalling 311 patients
Sucralfate	No better than placebo	Meta-analysis of 2 RCTs totalling 246 patients

NNT, number needed to treat; RCT, randomized-controlled trials; PP, per-protocol; ITT, intention-to-treat; TCA, tricyclic antidepressant.

A role for inflammation in the pathogenesis of FD has been postulated. So-called 'post-infectious' FD has been documented after acute enteric infection[50] and may occur by several mechanisms including defective resolution of inflammation, alterations in mucosal function, changes in the enteric nervous system and altered visceral sensation.[51] It has been estimated that previous enteric infection may play a role in the development of as many as a one-fifth of FD cases.[52] Similar reasoning has been postulated for *Helicobacter pylori*'s role in FD, although such an association remains somewhat controversial.[53] Further, a study by Hall *et al.* found increased gastric mucosal mast cells in patients with and without *H. pylori*-associated FD. They went on to suggest that these findings might contribute to FD by altering signalling in the brain-gut axis.[54]

Altered vagal activity has been observed in FD suggesting an aetiological role for autonomic dysfunction.[55, 56] In addition, psychological factors, such as stress and neuroticism, and their effects on central nervous function has been postulated as an underlying mechanism for the symptoms in FD.[57] A recent study found that experimentally induced anxiety (visual and auditory cues) can alter gastric sensorimotor function in healthy subjects.[58] This suggests that psychological factors can alter physiological function which may underlie some of the symptoms of FD.

DIAGNOSTIC TESTING

By definition, patients with FD should have no organic explanation for their symptoms. From a practical

Table 2. Non-pharmacological treatment strategies for functional dyspepsia

Therapeutic intervention	Efficacy	Evidence
Dietary modification Smaller, more frequent meals Low fat Avoidance of late evening meals Avoidance of food triggers	Unknown	Anecdotal only No RCTs
Psychological therapy Insight-oriented psychotherapy Relaxation and stress management training Cognitive behavioural therapy Biofeedback Hypnotherapy	Improvement in some symptoms, such as bloating, epigastric pain and nausea as well quality of life measures Reductions in need for antidepressant medications and consultative services	Individual trials suggest clinical benefit Systematic review unable to draw definitive conclusions
Complementary and alternative medicine STW 5 (Iberogast) Capsaicin Artichoke leaf extract	Reported improvement in 60–95% with treatment vs. 30–55% with placebo	Meta-analysis of 17 RCTs. However, results difficult to interpret due to significant methodological flaws. Agent purity and long-term safety unproven

RCT, randomized-controlled trial.

Table 3. Prokinetic agents[122]

Agent	Primary mode(s) of action	Proposed physiological effects (foregut)
Dopaminergic		
Metoclopramide	Dopamine-2-receptor antagonist Serotonin type 4 (5-HT_4)-receptor agonist	Antiemetic effect Accelerates gastric emptying Decreases visceral sensitivity Increases gastric antral motility
Domperidone	Dopamine-2-receptor antagonist	Antiemetic effect Accelerates gastric emptying Decreases visceral sensitivity
Itopride	Dopamine-2-receptor antagonist Cholinesterase inhibitor	Antiemetic effect Accelerates gastric emptying
Levosulpiride	Dopamine-2-receptor antagonist Serotonin type 4 (5-HT_4)-receptor agonist	Antiemetic effects Accelerated gastric emptying Decreases visceral sensitivity Increases gastric antral motility
Motilin		
Erythromycin ABT229	Motilin receptor agonist	Accelerates gastric emptying Reduces gastric fundic accommodation
Serotonergic		
Mosapride	Serotonin type 4 (5-HT_4)-receptor agonist Serotonin type 3 (5-HT_3)-receptor antagonist	Antiemetic effect Accelerated gastric emptying Increases gastric antral motility
Tegaserod	Partial serotonin type 4 (5-HT_4) -receptor agonist	Accelerates gastric emptying Increases gastric antral motility Increases gastric fundic accommodation

Table 4. Investigative pharmacological treatment strategies for functional dyspepsia

Therapeutic agent	Evidence
Prokinetics	
Mosapride	Three trials (1) Placebo-controlled trial in which mosapride no better than placebo (2) Trial in which mosapride demonstrated benefit but less than that of famotidine (3) Trial in which mosapride equivalent to famotidine
Tegaserod	Phase II trial demonstrating superiority to placebo in normalization of gastric emptying in FD Phase III trials underway
Itopride	Phase II trial demonstrating superiority to placebo in the treatment of global symptoms in FD Failed to show efficacy in European phase III trial
Levosulpiride	Single trial demonstrating efficacy equal to cisapride in relieving symptoms of dysmotility-like FD
κ-Opioid receptor	
Fedotozine	More effective than placebo in relieving dyspeptic symptoms in a preliminary multicentre trial Preliminary results not reproduced in a follow-up (unpublished) trial and drug development halted
Asimadoline	Decreased postprandial fullness and satiation in a randomized, double-blind, placebo-controlled trial involving 39 healthy adults
Serotonergic	
Sumatriptan	Induced fundic relaxation and increased perception threshold in healthy volunteers Failed to relieve postprandial symptoms in FD patients with impaired gastric accommodation
Alosetron	Superiority to that of placebo (54% vs. 43%) in relieving dyspeptic symptoms in women with FD in a dose ranging study
Afferent nervous system receptor	
Purinoceptor antagonists	Receptor antagonism reduced visceral pain in a mouse model
NMDA receptor antagonists Dextromethorphan Ketamine Memantine	Receptor antagonism reduced visceral pain response to distention in mouse model; however, increased sensation to gastric distention with dextromethorphan in a trial involving health adults
Protease-activator receptor agents	Receptors known to modulate gastrointestinal mucosal and smooth muscle function in an animal model
Vanilloid receptor agents	Receptors found in the gastric mucosa and muscle of animal models
Capsaicin (potent agonist)	Conflicting results with capsaicin compared to placebo in two trials
Sodium-channel receptor agents	Postulated to have a role FD through afferent pathways. No preclinical or clinical trials yet
Somatostatin receptors agents	Several small studies demonstrating the ability of octreotide to reduce the sensation of gastric fullness in healthy adults
Others	
CCK receptor antagonists Loxiglumide Dexloxiglumide	Loxiglumide shown in an open trial to control the dyspeptic symptoms produced by a CCK analogue Dexloxiglumide shown in double-blinded, placebo-controlled trial to prevent dyspeptic symptoms caused by lipid infusion in 12 patients with FD
Tachykinin receptor antagonists	Multicentre, placebo-controlled trial in which aprepitant demonstrated efficacy in treatment of chemotherapy-induced vomiting
Aprepitant (NK_1 antagonist) NK_3 antagonists	Preclinical animal trials demonstrated antinociceptive properties not reproducible in human studies
Corticotrophin-releasing factor antagonists	Preclinical animal studies suggesting a role of CRF antagonists in preventing stress-induced gastric dysmotility

FD, functional dyspepsia; NMDA, *N*-methyl-D-aspartate; CCK, cholecystokinin.

Table 5. Rome III diagnostic criteria: functional dyspepsia.[150]

(i)	One or more of the following symptoms: a. Postprandial fullness b. Early satiety c. Epigastric pain d. Epigastric burning
(ii)	No evidence of structural disease that is likely to explain symptoms (including upper endoscopy)
(iii)	Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

standpoint, this means that a symptomatic patient should have no evidence of structural disease by upper endoscopy or barium radiography to qualify for the diagnosis of FD. The separation of patients with dyspepsia by the presence or the absence of visible structural disease is reasonably reliable. However, it is important to remember that there is evidence to suggests that a subgroup of those initially diagnosed with FD are at-risk for the subsequent development of peptic ulcer disease.[59] Most agree that patients with symptom onset over the age of 50–55 years or the presence of 'alarm features', such as dysphagia, vomiting, weight loss, anaemia or GI bleeding, should undergo structural evaluation with endoscopy. A recent evaluation from the CORI database found that dyspepsia served as the indication for 43% of over 117 000 upper endoscopic procedures.[60] Thirty-six percentage of dyspeptic patients were under the age of 50 years and had no alarm features. Gastric malignancy was found in 0.3% and was associated with increasing age, male sex, Asian or Native American race, and alarm features including weight loss and vomiting. Peptic ulcer disease and oesophageal inflammation were identified in 5% and 16% respectively. A recent meta-analysis found that the negative predictive value of having any alarm feature was excellent (99%), but the positive predictive value of alarm features was poor (6%).[61] These findings confirm what most clinicians already know: the absence of alarm symptoms makes the likelihood of finding important structural causes for dyspepsia very unlikely, but the vast majority of patients with alarm symptoms will have no significant structural explanation for their symptoms on upper endoscopy.

The Rome II definition for FD has been criticized for being vague and of limited utility in clinical practice. As has already been discussed, attempts to use symptom clusters to identify subgroups of patients with specific physiological abnormalities, such as abnormal gastric emptying and/or accommodation have met with limited success. For the most part, symptoms and physiological abnormalities correlate poorly in patients with FD. There is some evidence to suggest that postprandial fullness, nausea and vomiting are reported more commonly in patients with abnormal gastric emptying of solids, whereas early satiety and weight loss are more commonly reported by patients with impaired gastric accommodation.[36] Unfortunately though, these symptoms occurred more commonly in patients with delayed gastric emptying and/or abnormal accommodation but there was considerable overlap in symptoms between those with and without these abnormalities. Perhaps most importantly, to date, the identification of functional abnormalities has not clearly translated to improved outcomes in response to specific therapies. Related to these points, the clinical utility of detailed testing to identify physiological abnormalities in gastric emptying (scintigraphy, octanoate breath testing), accommodation (barostat, Single photon emission computed tomography, Ultrasound, nutrient drink test) and gastric electrical rhythmicity (electrogastrography) remains to be determined.

CURRENT TREATMENT OPTIONS

A wide variety of treatments have been used to manage FD including dietary and lifestyle modifications, *H. pylori* eradication, antacids, mucosal protectants, antisecretory agents, prokinetics, antidepressants, behavioural therapies as well as complementary and alternative medical (CAM) therapies (Tables 1 and 2). The fact that no single available therapy consistently provides relief to the majority of FD patients validates the heterogeneity of this disorder. Given this heterogeneity, it is difficult to generalize about the characteristics, which predict a greater or lesser response to therapy for this condition. Acknowledging this point, several authors have tried to identify predictors of response to therapy. A recent systematic review reported several characteristics of FD patients that negatively affect symptom remission including symptom duration exceeding 2 years, lower educational level, greater psychological vulnerability, coexistent *H. pylori* infection, use of aspirin, history of peptic ulcer disease and treatment for GERD.[5] An earlier review of the literature reported limited evidence to suggest that older age, male sex, single marital status and more frequent occurrence of abdominal pain had a negative

impact on the prognosis of FD, although these findings are more controversial.[62] Recent evidence suggests that patients with overlapping FD and IBS report more severe symptoms and are more likely to exhibit visceral hypersensitivity in response to gastric distention.[11] Another recent study found that patients with overlapping GERD symptoms and IBS reported more severe heartburn than those with GERD symptoms alone.[63] These finding suggest that patients with multiple GI symptoms may represent a distinct subgroup with more severe symptoms, perhaps related to a more generalized disorder of altered visceral pain sensation. It is attractive to hypothesize that such patients may be more likely to respond to centrally acting therapies and less likely to respond to peripherally acting agents though this remains to be proven in clinical trials.

Dietary modifications

There are no trials which have formally evaluated the efficacy of various dietary or lifestyle modifications in patients with FD. Such treatment approaches have evolved from the observation that the symptoms of FD are frequently temporally related to the ingestion of food. A recent systematic review on this topic concluded that although a relationship between the ingestion of food and dyspeptic symptoms is frequently reported by FD patients, this relationship has not been formally assessed in careful clinical trials.[64] This review reported that factors, such as food intolerances and eating patterns have only been anecdotally reported to play a role in the symptoms of FD. However, there is some, albeit limited, evidence that dietary fat ingestion is associated with dyspeptic symptoms.[45, 65] Despite the lack of evidence, modifications similar to those recommended for GERD can be considered including smaller, more frequent meals; a low fat diet and avoidance of late evening meals. A food diary may be used to facilitate the identification of specific foods that trigger symptoms. Foods frequently reported to worsen dyspeptic symptoms include onions, peppers, citrus fruit, coffee, carbonated beverages and spices. Though not evidence-based, these recommendations are not associated with significant costs and unlikely to be associated with adverse outcomes.

H. pylori eradication

The role of *H. pylori* eradication in the treatment of FD remains controversial. Two recent trials concluded that *H. pylori* eradication improved quality of life[66] and provided symptomatic benefit in FD.[67] This is in contrast to other contemporary studies demonstrating no clear benefit compared with placebo or antisecretory agents.[68–71] A recent analysis of two multicentre, multinational randomized-controlled trials (RCT) revealed no benefit to *H. pylori* eradication over placebo although a subgroup analysis revealed a significant benefit in reflux-like and ulcer-like dyspepsia as well as a benefit in those with healing of gastritis.[72] In an effort to clarify the ambiguity that exists amongst clinical trials, several meta-analyses have been published also revealing discordant results.[73–77] Three analyses concluded that a small yet statistically significant benefit existed with *H. pylori* eradication over placebo.[73, 76, 77] One analysis revealed that no benefit existed[74] and one revealed that insufficient evidence existed to make a determination.[75] Further evaluation of these meta-analyses determined that only 11–38% of dyspeptics were symptom-free as a result of *H. pylori* eradication.[78] The most recent update of the Cochrane database reported a small but statistically significant symptomatic benefit to curing *H. pylori* in patients with FD [*H. pylori* cure = 36% vs. placebo = 30%, relative risk reduction: 8%; 95% CI: 3–12%, number needed to treat (NNT) = 18].[79] At present, it is reasonable to conclude that on a population basis, there appears to be a small but statistically significant benefit to *H. pylori* eradication in FD although the factors predicting a treatment response remain largely unknown.[80] On a practical level, the clinician should understand that the prevalence of *H. pylori* is dropping or already low in many parts of the world and even when the organism is identified, the likelihood of achieving symptom improvement in FD patients following eradication therapy is likely to be <50%.

Antacids

Antacids have been evaluated in a small number of trials and consistently found to be no better than placebo in the treatment of FD.[81–83] The Cochrane Collaboration reported that only the trial by Gotthard *et al.*[81] met methodological criteria for inclusion in their review on the pharmacological interventions for FD.[84] This trial assessed the effects of antacids on epigastric pain, bloating and nausea, only demonstrating marginal improvement in the symptom of bloating with antacids over that of placebo. A systematic

review by Moayyedi *et al.* also concluded that antacids were not significantly superior to placebo.[85]

Bismuth

The Cochrane review identified a total of nine RCTs comparing the efficacy of bismuth to placebo.[84] From these studies, five trials were included in a meta-analysis totalling 311 patients.[85] Significant heterogeneity was noted and these trials tended to include patients with *H. pylori* infection. This analysis revealed that bismuth was no more effective than placebo though there was a trend towards improvement that favoured bismuth. Given concerns regarding accumulation and associated toxicity, bismuth should be reserved for the treatment of infrequent dyspeptic symptoms.

Sucralfate

Sucralfate has been studied in a limited number of clinical trials and found to be no more effective than placebo in the treatment of FD. A Cochrane review identified three RCTs in which sucralfate was compared with placebo in FD.[84] Two of these trials were included in a meta-analysis (246 patients) which demonstrated no benefit of sucralfate over placebo for FD.

Histamine-receptor antagonists

Though the histamine-receptor antagonists (H_2RAs) are commonly used to treat FD, the evidence supporting their efficacy is modest at best. Available studies suggest that their benefits may be limited to the symptom of epigastric pain. A meta-analysis performed by Redstone *et al.* which included 22 RCTs reported superiority of the H_2RAs over placebo for improvement and complete resolution of epigastric pain but not global symptoms in FD patients.[86] More recently, an analysis of 11 RCTs performed by Moayyedi *et al.* involving 2164 patients concluded that overall improvement in dyspepsia was significantly greater with H_2RAs compared to placebo.[85] The investigators noted that significant heterogeneity existed amongst the studies. They also pointed out that the benefit of the H_2RAs over placebo may have been inflated by the poor methodological quality of the studies included. This possibility was reiterated by another recent publication addressing the methodological quality of treatment trials for FD.[87]

Proton pump inhibitors

Proton pump inhibitors (PPIs) have been evaluated in a number of large, well-designed RCTs. Based on the results of a meta-analysis, including eight studies and 3293 treated patients, PPI therapy given for 2–8 weeks was more effective in relieving or eliminating symptoms than placebo in patients with FD (33% and 23% response rates with PPI and placebo, respectively; relative risk of remaining symptomatic = 0.86, 95% CI: 0.78–0.95; NNT = 9).[88] Though there was significant heterogeneity amongst the included trials, no asymmetry was found on a funnel plot decreasing concerns about publication bias. The risk ratio for remaining dyspeptic was similar between standard- and low-dose PPI regimens. Furthermore, patients with reflux-like symptoms and symptoms described with the words 'burning' or 'sour' are more likely to improve with PPI therapy. On the other hand, patients with symptoms suggestive of dysmotility, such as nausea and bloating are less likely to respond to PPIs.[89] Additionally, the cost-effectiveness of PPI therapy for FD varies widely among different countries and is highly dependent upon the local cost of PPI therapy and whether therapy needs to be given continuously or only intermittently to control symptoms.[80]

Prokinetics

The term prokinetic refers to a diverse group of medications that share the common characteristic of accelerating GI motility. Broadly speaking, these drugs exert their physiological actions through effects on a variety of neurotransmitter receptors including acetylcholine, dopamine, motilin and serotonin. Some examples of prokinetic drugs and their proposed mechanism of actions can be found in Table 3.

A fundamental question regarding the prokinetics is the mechanism/s by which they benefit symptoms. As has been mentioned, the relationship between accelerating gastric emptying and symptom improvement is tenuous. This point is perhaps best illustrated by the motilin receptor agonists, erythromycin and ABT-229. While these agents clearly accelerate gastric emptying, they often have little effect on and sometimes can actually worsen symptoms, particularly at higher doses.[90, 91] It has been proposed that this disconnect may in part be related to the deleterious effects of these drugs on accommodation.[90, 91] At present, it is safe to conclude that different classes of prokinetic

agents benefit symptoms by mechanisms which may include but clearly extend beyond their effects on gastric emptying.

A recent systematic review reported that as a class, prokinetics appear to be more effective than placebo in the treatment of FD.[84] Fourteen RCTs totalling 1053 patients were pooled demonstrating that prokinetics were twice as likely as placebo to improve dyspeptic symptoms. However, caution should be exercised in the interpretation of these results as the majority of the RCTs evaluated cisapride (a mixed 5-HT_4 agonist and 5-HT_3 antagonist that is no longer commercially available), the quality of many of these studies was marginal, heterogeneity existed amongst the included studies and a funnel plot suggested that publication bias may have influenced the results. Another meta-analysis pooling the results of 17 studies evaluating cisapride and four studies evaluating the dopaminergic antagonist, domperidone (not licensed in the US) revealed a marginal benefit compared with placebo based on the investigator's or patient's assessment of global symptoms.[92] A more recent meta-analysis demonstrated that the observed benefit of prokinetics over placebo was lost when an the analysis was restricted to high quality studies.[87]

At present, the greatest activity appears to be focused on the development of serotonergic and dopaminergic drugs. Conflicting data currently exists on the efficacy of the mixed 5-HT_4 agonist and 5-HT_3 antagonist, mosapride.[93–95] Tegaserod is a 5-HT_4-receptor agonist that is currently approved for the treatment of women with the IBS and constipation and men and woman under the age of 65 years with chronic constipation. Tegaserod has been preliminarily shown to accelerate gastric emptying of solids in patients with FD and delayed gastric emptying.[96–98] In a phase II RCT evaluating patients with FD, a dose of 6 mg t.d.s. normalized gastric emptying in 80% vs. 50% for placebo ($P < 0.058$).[98] In a recent small trial, tegaserod 6 mg b.d. improved gastric accommodation after eating a meal in functional dyspeptics with normal gastric emptying.[96] Phase III trials evaluating tegaserod in patients with FD are currently nearing completion in North America.

In a randomized trial, the dopaminergic antagonist, levosulpiride was as effective as cisapride in relieving symptoms in patients with dysmotility-like FD.[99] Like another dopaminergic antagonist, domperidone, levosulpiride can be associated with breast tenderness and galactorrhea. This drug is available in some parts of the world but is currently not available in the US. A recent high quality phase II trial randomized 554 patients with FD to placebo or one of three doses of itopride, a dopaminergic antagonist with weak muscarinic agonist activity. Itopride significantly improved global dyspeptic symptoms and composite symptom score using the Leeds Dyspepsia Questionnaire. Overall, this drug was safe and well tolerated.[100] However, a recent European phase III trial with itopride failed to meet its primary end point in confirming efficacy in the treatment of FD. A phase III trial in North America is currently ongoing with results pending. Further data analysis and the results of this ongoing trial should clarify what role itopride may play in patients with FD.

Antidepressants and antianxiety agents

Antidepressant and anxiolytic use in FD remains largely based on anecdotal data. A recent systematic review addressed antidepressant and antianxiety use in FD.[101] Thirteen studies met the researcher's inclusion criteria with 11 demonstrating improvement in dyspeptic symptoms following treatment. Unfortunately, significant variability amongst the studies existed regarding the definition of FD, the measured outcomes, and the agent evaluated. Meta-analysis could only be performed on four of the trials (153 total subjects) demonstrating significant benefit of treatment with antianxiety drugs or antidepressants over placebo (relative risk: 0.55, 95% CI: 0.36–0.85).

The first high quality randomized trial comparing the efficacy of a tricyclic antidepressant or TCA (desipramine) to placebo in patients with functional gastrointestinal disorders (FGID) was recently published by Drossman *et al.*[102] Most of the patients had IBS though some patients with other functional symptoms were also included. The intention-to-treat (ITT) analysis did not show a statistically significant improvement in a composite symptom scale between the desipramine and placebo groups (60% vs. 47%, $P = 0.13$). This was largely due to the 28% of patients who did not complete the trial related to adverse drug effects or non-compliance. When these patients were excluded from the analysis (per-protocol analysis), desipramine resulted in a statistically significant benefit compared with placebo (73% vs. 49%, $P = 0.006$, NNT = 4). From this data, we can conclude that many patients will not tolerate TCAs but those who can tolerate these medications are likely to experience symptomatic

benefit. A *post hoc* analysis from this study suggested that many of the 'adverse effects' attributed to TCA therapy were present before the initiation of therapy and thus, may not actually have been caused by the TCA.[103]

In a small randomized trial of seven patients with FD, amitriptyline (50 mg qHS) was found to be more effective than placebo in improving symptoms.[104] Most recently, Otaka *et al.* demonstrated the efficacy of amitriptyline in 14 FD patients who initially failed treatment with famotidine or mosapride reporting a response rate of 71%.[95] Clinical benefit has not been found to correlate with changes in perception of gastric balloon distention, suggesting that the analgesic effects of TCAs are likely to be mediated centrally, perhaps through effects on the cortical processing of painful visceral sensations.[105, 106]

When the TCAs are used for FD patients, lower doses are typically necessary than when treating depression. For FGID, target doses for the TCAs range from 10 to 100 mg/day. Higher doses are necessary in the presence of comorbid psychological conditions like depression. These drugs are usually dosed in the evening to minimize problems related to their sedative effects. Patients should also be warned about the possibility of dry mouth and eyes as well as weight gain and constipation. Secondary amines, such as nortriptyline and desipramine may be better tolerated than the older tertiary amines (amitriptyline, imipramine). Unlike when used for depression, the clinical benefits of TCAs for functional disorders are often seen within 2 weeks of initiating therapy.

To date, there have been no randomized, placebo-controlled trials published in manuscript form which have evaluated selective serotonin reuptake inhibitors (SSRIs) for FD. Recent studies suggest that the SSRIs, paroxetine and sertraline, do not alter the sensation of gastric balloon distention[107, 108] but may alter accommodation[107] in healthy volunteers. Similarly, there is no data addressing the physiological or clinical effects of newer antidepressants, such as venlafaxine or mitazapine in patients with FD. Though it is clear that these agents are of benefit to comorbid depression and/or anxiety, it remains unclear whether they offer any benefit to GI symptoms associated with FD in the absence of concomitant psychiatric conditions. Because of the social stigma attached to their use and their narrow therapeutic window, it seems fair to suggest that antidepressants should be reserved for patients with persistent, moderate to severe symptoms who have failed to improve with the more conventional forms of medical therapy.

Psychological therapies

A variety of different psychotherapeutic modalities have been used to treat FGID including insight-oriented psychotherapy, relaxation and stress management training, cognitive-based behavioural therapy, biofeedback and hypnotherapy.[109, 110] The best studied of these techniques is cognitive-behavioural therapy. This form of psychotherapy is designed to teach patients how to identify maladaptive behaviours and manage their responses to emotional and life stresses. Haug *et al.* randomized 100 patients with FD to cognitive psychotherapy or no therapy and found that the psychotherapy patients experienced significant improvement in symptoms, such as bloating, epigastric pain and nausea.[111] Mine *et al.* randomized 198 FD patients to a combination of medical, psychiatric and psychotherapeutic treatments vs. medical therapy alone and found that multimodality therapy afforded significantly improved outcomes compared with medical therapy alone.[112] Hamilton *et al.* sought to determine if brief psychodynamic-interpersonal psychotherapy was superior to reassurance alone. At the end of the therapy period, FD patients in the psychotherapy group had significant symptom reduction compared to the group treated with reassurance alone. A *post hoc* analysis at 1 year, removing patients with severe heartburn symptoms, indicated a potential benefit for the psychotherapy group.[113] Another recent study in FD patients found that hypnotherapy yielded a greater improvement in symptoms as well as quality of life measures, reduced antidepressant medication and reduced consultation rates compared with supportive therapy or medical therapy.[110]

Though individual trials suggest clinical benefits, a recent systematic review concluded that there was insufficient evidence to support the efficacy of psychological therapies for FD.[114] Despite this evidence-based conclusion, it does appear that addressing life stresses and improving coping mechanisms can be a useful adjunct to traditional therapies once organic GI disease has been excluded. Unfortunately, several factors make the implementation of psychological therapy challenging in clinical practice. In addition to overcoming the stigma of referring patients for psychological therapy and the failure of many insurance plans to cover this form of out-patient treatment, it

can be difficult to find a mental health professional with the training and/or willingness to take on patients with a FGID.

Complementary and alternative medicine

A number of alternative treatment strategies to that of pharmaceuticals or psychological therapy have been employed in FD. A recent systematic review reported that at least 44 different herbal products have been recommended alone or in combination for the treatment of dyspeptic symptoms.[115] This review included 17 RCTs, the largest number of studies having assessed peppermint and caraway in the treatment of FD. This analysis revealed symptom improvement in 60–95% of patients receiving herbal therapy vs. 30–55% in patients receiving placebo. Unfortunately, the baseline patient profiles in these trials were not always well defined and methods of symptom assessment were variable often relying on scoring systems lacking validation.

A more recent meta-analysis of the combination herbal remedy, STW 5 (Iberogast), pooled the data of three RCTs which included 273 FD patients. This meta-analysis found that STW 5 was superior to placebo at improving the most bothersome FD symptom reported by study participants ($P = 0.001$, odds ratio: 0.22, 95% CI: 0.11–0.41).[116]

Capsaicin, the active ingredient of red chilli pepper, has been evaluated in small clinical trials, which have yielded conflicting results. A RCT assessing capsaicin in 30 patients with FD demonstrated significant improvement in overall symptoms, epigastric pain, fullness and nausea compared with placebo.[117] On the other hand, an earlier placebo-controlled crossover trial evaluating 11 patients with a primary complaint of heartburn and associated dyspepsia was unable to show significant improvements in postprandial dyspepsia scores with capsaicin.[118] Interestingly, this study demonstrated worsening in immediate postprandial heartburn when capsaicin was ingested with a meal.

A RCT assessing artichoke leaf extract in 247 patients with FD demonstrated a significant improvement in both overall symptoms and disease-specific quality of life compared with placebo.[119]

Several issues regarding CAM therapies deserve mention. Available trials almost all suffer from significant methodological flaws making the results difficult to interpret. Further, because these agents are not regulated as pharmaceuticals, questions regarding agent purity and potency have been raised. Finally, though the short-term use appears relatively safe, the long-term safety of these agents has not been established.

Future therapies

A number of agents with antinociceptive properties are under investigation for the treatment of FD. κ-Opioid receptor agonists that may inhibit somatic and visceral pain pathways through their effects on peripheral opioid receptors, are being developed as a possible treatment for FD. One such agent, fedotozine, yielded promising preliminary results in the treatment of FD.[120] Unfortunately, data from North America proved disappointing (unpublished data) and the development of this drug was halted. Another opioid agonist, asimadoline, has also shown some possible application for the treatment of dyspeptic symptoms.[121]

Other potential targets for emerging agents with possible effects on visceral sensation include purinoceptors, *N*-methyl-D-aspartate (NMDA) receptors, protease-activator receptors (PAR)-2, the vanilloid receptors, sodium-channel receptors and somatostatin receptors.[122] The P2X purinoceptors are ligand-gated cation-channels located along pH-sensitive vagal and spinal afferent pathways.[123] Although the role of these receptors in the generation of GI pain remains uncertain, antagonism of the P2X receptor suppressed inflammation-induced visceral pain in a mouse model.[124]

N-Methyl-D-aspartate receptors represent another class of ligand-mediated ion-channels expressed by afferent neurones in the enteric nervous system. NMDA receptors may play a role in visceral hypersensitivity, although the limited available evidence remains inconclusive. NMDA antagonism was initially shown to reduce the nociceptive response to colonic distention in a rat model.[125] Paradoxically, the NMDA antagonist, dextromethorphan, increased the nociceptive response to gastric distention in small study involving nine healthy adults.[126] This response has been ascribed to dextromethorphan's low affinity for the NMDA receptor. Future studies utilizing more selective NMDA receptor antagonists are eagerly awaited.

Protease-activator receptors consist of a family of four large G-protein-coupled receptors. Two of the receptor types, PAR-1 and PAR-2, have been found

throughout the GI tract with a number of modulatory effects on mucosal and smooth muscle function.[127] PAR-2 receptors have been identified on gastric mucosal sensory neurones in a rat model.[128] Given their possible roles in the modulation of gastric motor and sensory function, PAR-2 agonists and antagonists may be potential candidates for the treatment of FD.

Vanilloid receptors are non-selective cation-channels located on afferent nerve endings that are activated by capsaicin, acid and temperature changes. Nerve fibres containing these vanilloid receptors have been identified in the mucosal and muscular layers of the gastric fundus and antrum in several animal models.[129] Such receptors have therefore been postulated to play a role in gastric nociception.

Proton-gated sodium-channels also known as acid-sensing ion-channels have been found on primary afferent neurones. These channels have been suggested to play a role in the sensory responses of the gastroduodenal mucosa to acid exposure.[130] Such a hypothesis remains to be tested in asymptomatic volunteers and dyspeptic patients.

Somatostatin is a neurotransmitter affecting GI motility, sensation and visceral sensation through six different G-protein-coupled receptors. The somatostatin analogue, octreotide, has been shown in several small studies to reduce the sensation of gastric fullness in healthy patients.[131–133] The exact role of somatostatin receptors in FD requires further study.

Acting through alternative pathways, several additional agents including cholecystokinin (CCK) receptor antagonists,[134] tachykinin receptor antagonists[135] and corticotrophin-releasing factor (CRF) antagonists[136] have been postulated to be potentially beneficial for FD. CCK is a neuropeptide released into the gut in response to the presence of intraluminal lipids. It is believed to mediate pain in the gut and known to inhibit gastric emptying through vagal afferent pathways.[137, 138] CCK hyperresponsiveness or the interaction of CCK pathways with those of serotonergic pathways has been postulated to play a role in FD.[139] Administration of the synthetic CCK analogue, CCK-8, has been shown to reproduce dyspeptic symptoms in 90% of a cohort of FD patients and the administration of a CCK antagonist, loxiglumide, was effective in controlling dyspeptic symptoms.[139] A double-blind, placebo-controlled trial involving 12 FD patients demonstrated the ability of the CCK antagonist, dexloxiglumide, to prevent the dyspeptic symptoms produced by duodenal lipid infusion, reduce dyspeptic symptoms experienced by lipid infusion combined with gastric distention, and reduce sensitivity to distention.[46]

The tachykinins, substance P, neurokinin A and neurokinin B, exert their effects through their interaction with tachykinin receptors NK_1, NK_2 and NK_3. The NK_1 antagonist, aprepitant, has demonstrated antiemetic properties and is currently approved for the treatment of chemotherapy-induced nausea and vomiting.[140, 141] NK_1 antagonism has demonstrated antinociceptive effects in preclinical animal studies, although such findings have not been reproduced in humans.[142] The precise role of NK_3-receptor antagonism in gastrovagal functions, gastric motility and nociception remain largely unknown.[143]

The hypothalamic-pituitary-adrenal (HPA) axis serves as the primary endocrine stress system in humans and provides an important interface between the brain and the gut-immune system. Activators of the HPA axis including physical and psychological stress have been suggested to play a role in FD. A recent study involving IBS patients found overactivation of the HPA axis with associated increases in proinflammatory cytokines.[144] There is evolving evidence that CRF receptor antagonists may reduce stress-related alterations in upper gut function.[145] CRF_2-receptor antagonism has been shown to prevent CRF-induced alternations in gastric motility in a rat model.[146] Further, animal studies have found that CRF_1-receptor antagonism abolishes the gastric ileus that occurs immediately following celiotomy and caecal palpation.[147] It is hoped that such preliminary findings may predict clinical applications for CRF antagonists in the treatment of FD.

Other serotonergic agents are also being investigated for their possible role in the treatment of FD. Preliminary work with the 5-HT_1 agonist, sumatriptan, has stimulated interest in the development and evaluation of other 5-HT_1 agonists for the treatment of FD.[24, 34] In a dose ranging study involving women and men with FD who received placebo or three different doses of the 5-HT_3-receptor antagonist alosetron, only women who received a dose of 1 mg b.d. achieved statistically significant improvements in adequate relief of their dyspeptic symptoms (54% vs. 43%, $P < 0.05$).[148] In the US, this use of alosetron is restricted to women with severe IBS that has proven refractory to traditional treatments because of its association with occasional severe constipation and rare cases of ischaemic colitis. Other serotonergic agents which may offer benefit to FD include the 5-HT_4 antagonists and 5-HT_7 agonists.[149]

CONCLUSION

The symptoms of FD arise from a heterogeneous group of pathophysiological abnormalities. The varied symptoms that can constitute FD have been acknowledged in the recently published Rome III criteria.[150] The Rome III criteria for FD offer a general definition meant more for clinical practice and definitions for two subgroups, postprandial distress syndrome or epigastric pain syndrome, which are intended for clinical research. It is important to understand that this newly proposed classification system has not been formally validated in clinical trials and as such, has no bearing on the current management strategies for FD patients. At present, it is fair to conclude that available therapies are effective only in subgroups of FD patients. There is evidence to suggest that eradication of *H. pylori* infection and potent antisecretory therapy benefit some patients with this disorder. Though gastrokinetic drugs have long been of interest for the treatment of FD, it is becoming increasingly apparent that the benefits of these drugs are not solely the consequences of their effects on gastric emptying. Normalization of accommodation and perhaps most importantly, the co-ordination of functions between the proximal and distal stomach are likely to be more important than a specific drug's effect on gastric emptying. Antidepressants and psychological therapies appear to offer benefit to appropriately selected patients. Results from preliminary studies of alternative therapies for FD appear promising but should be considered hypothesis generating rather than definitive evidence of therapeutic benefit. Numerous agents with effects on upper GI motor and sensory function are currently in development and hopefully will expand the therapeutic toolbox available for this sometimes challenging group of patients.

ACKNOWLEDGEMENT

Dr Chey is on the speaker's bureau for Novartis, Santarus, and TAP and is a consultant for Santarus, TAP and Axcan.

REFERENCES

1 Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. In: Drossman DA, ed. *Rome II: the Functional Gastrointestinal Disorders*. McLean, VA, USA: Degnon, 2000: 299–350.
2 Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology* 2005; **129**: 1756–80.
3 Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; **45** (Suppl. 2): II37–42.
4 Shaib Y, El-Serag HB. The prevalence and risk factors of functional dyspepsia in a multiethnic population in the United States. *Am J Gastroenterol* 2004; **99**: 2210–6.
5 El-Serag HB, Talley NJ. Systemic review: The prevalence and clinical course of functional dyspepsia. *Aliment Pharmacol Ther* 2004; **19**: 643–54.
6 Chang L. Review article: Epidemiology and quality of life in functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2004; **20** (Suppl. 7): 31–9.
7 Heikkinen M, Pikkarainen P, Takala J, Rasanen H, Julkunen R. Etiology of dyspepsia: four hundred unselected consecutive patients in general practice. *Scand J Gastroenterol* 1995; **30**: 519–23.
8 Mitchell CM, Drossman DA. Survey of the AGA membership relating to patients with functional gastrointestinal disorders. *Gastroenterology* 1987; **92** (5 Pt 1): 1282–4.
9 Heikkinen M, Farkkila M. What is the long-term outcome of the different subgroups of functional dyspepsia? *Aliment Pharmacol Ther* 2003; **18**: 223–9.
10 Agreus L, Svardsudd K, Talley NJ, Jones MP, Tibblin G. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population-based study. *Am J Gastroenterol* 2001; **96**: 2905–14.
11 Corsetti M, Caenepeel P, Fischler B, Janssens J, Tack J. Impact of coexisting irritable bowel syndrome on symptoms and pathophysiological mechanisms in functional dyspepsia. *Am J Gastroenterol* 2004; **99**: 1152–9.
12 Cremonini F, Talley NJ. Review article: The overlap between functional dyspepsia and irritable bowel syndrome – a tale of one or two disorders? *Aliment Pharmacol Ther* 2004; **20** (Suppl. 7): 40–9.
13 Quigley EM. Functional dyspepsia (FD) and non-erosive reflux disease (NERD): overlapping or discrete entities? *Best Pract Res Clin Gastroenterol* 2004; **18**: 695–706.
14 Locke GR III, Weaver AL, Melton LJ III, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004; **99**: 350–7.
15 Pajala M, Heikkinen M, Hintikka J. Mental distress in patients with functional or organic dyspepsia: a comparative study with a sample of the general population. *Aliment Pharmacol Ther* 2005; **21**: 277–81.
16 Jones MP, Sharp LK, Crowell MD. Psychosocial correlates of symptoms in functional dyspepsia. *Clin Gastroenterol Hepatol* 2005; **3**: 521–8.
17 Nyren O, Lindberg G, Lindstrom E, Marke LA, Seensalu R. Economic costs of functional dyspepsia [see comments]. *Pharmacoeconomics* 1992; **1**: 312–24.
18 Halder SL, Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III.

Impact of functional gastrointestinal disorders on health-related quality of life: a population-based case-control study. *Aliment Pharmacol Ther* 2004; **19**: 233–42.
19 Koloski NA, Talley NJ, Boyce PM. The impact of functional gastrointestinal disorders on quality of life. *Am J Gastroenterol* 2000; **95**: 67–71.
20 Talley NJ, Weaver AL, Zinsmeister AR. Impact of functional dyspepsia on quality of life. *Dig Dis Sci* 1995; **40**: 584–9.
21 Fischler B, Tack J, De Gucht V, *et al*. Heterogeneity of symptom pattern, psychosocial factors, and pathophysiological mechanisms in severe functional dyspepsia. *Gastroenterology* 2003; **124**: 903–10.
22 Chiba N, Bernard L, O'Brien BJ, Goeree R, Hunt RH. A Canadian physician survey of dyspepsia management. *Can J Gastroenterol* 1998; **12**: 83–90.
23 Stanghellini V, Tosetti C, Paternic A, *et al*. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996; **110**: 1036–42.
24 Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998; **115**: 1346–52.
25 Talley NJ, Meineche-Schmidt V, Pare P, *et al*. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998; **12**: 1055–65.
26 Quartero AO, de Wit NJ, Lodder AC, Numans ME, Smout AJ, Hoes AW. Disturbed solid-phase gastric emptying in functional dyspepsia: a meta-analysis. *Dig Dis Sci* 1998; **43**: 2028–33.
27 Perri F, Clemente R, Festa V, *et al*. Patterns of symptoms in functional dyspepsia: role of *Helicobacter pylori* infection and delayed gastric emptying. *Am J Gastroenterol* 1998; **93**: 2082–8.
28 Talley NJ, Verlinden M, Jones M. Can symptoms discriminate among those with delayed or normal gastric emptying in dysmotility-like dyspepsia? *Am J Gastroenterol* 2001; **96**: 1422–8.
29 Sarnelli G, Caenepeel P, Geypens B, Janssens J, Tack J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003; **98**: 783–8.
30 Pallotta N, Pezzotti P, Calabrese E, Baccini F, Corazziari E. Relationship between gastrointestinal and extra-gastrointestinal symptoms and delayed gastric emptying in functional dyspeptic patients. *World J Gastroenterol* 2005; **11**: 4375–81.
31 Talley NJ, Locke GR III, Lahr B, *et al*. Functional dyspepsia, delayed gastric emptying and impaired quality of life. *Gut* 2005; **55**: 933–939.
32 Delgado-Aros S, Camilleri M, Cremonini F, Ferber I, Stephens D, Burton DD. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. *Gastroenterology* 2004; **127**: 1685–94.
33 Kim DY, Delgado-Aros S, Camilleri M, *et al*. Noninvasive measurement of gastric accommodation in patients with idiopathic nonulcer dyspepsia. *Am J Gastroenterol* 2001; **96**: 3099–105.
34 Boeckxstaens GE, Hirsch DP, Kuiken SD, Heisterkamp SH, Tytgat GN. The proximal stomach and postprandial symptoms in functional dyspeptics. *Am J Gastroenterol* 2002; **97**: 40–8.
35 Piessevaux H, Tack J, Walrand S, Pauwels S, Geubel A. Intragastric distribution of a standardized meal in health and functional dyspepsia: correlation with specific symptoms. *Neurogastroenterol Motil* 2003; **15**: 447–55.
36 Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; **127**: 1239–55.
37 Savoye G, Bouin M, Denis P, Ducrotte P. Delayed postprandial fundic relaxation: a new abnormal finding in functional dyspepsia. *Scand J Gastroenterol* 2005; **40**: 354–5.
38 Camilleri M, Brown ML, Malagelada JR. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. *Gastroenterology* 1986; **91**: 94–9.
39 Lin Z, Eaker EY, Sarosiek I, McCallum RW. Gastric myoelectrical activity and gastric emptying in patients with functional dyspepsia. *Am J Gastroenterol* 1999; **94**: 2384–9.
40 Jebbink HJ, van Berge-Henegouwen GP, Akkermans LM, Smout AJ. Small intestinal motor abnormalities in patients with functional dyspepsia demonstrated by ambulatory manometry. *Gut* 1996; **38**: 694–700.
41 Simren M, Vos R, Janssens J, Tack J. Unsuppressed postprandial phasic contractility in the proximal stomach in functional dyspepsia: relevance to symptoms. *Am J Gastroenterol* 2003; **98**: 2169–75.
42 Mertz H, Fullerton S, Naliboff B, Mayer EA. Symptoms and visceral perception in severe functional and organic dyspepsia. *Gut* 1998; **42**: 814–22.
43 Rhee PL, Kim YH, Son HJ, *et al*. Evaluation of individual symptoms cannot predict presence of gastric hypersensitivity in functional dyspepsia. *Dig Dis Sci* 2000; **45**: 1680–4.
44 Tack J, Caenepeel P, Fischler B, Piessevaux H, Janssens J. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. *Gastroenterology* 2001; **121**: 526–35.
45 Barbera R, Feinle C, Read NW. Abnormal sensitivity to duodenal lipid infusion in patients with functional dyspepsia. *Eur J Gastroenterol Hepatol* 1995; **7**: 1051–7.
46 Feinle C, Meier O, Otto B, D'Amato M, Fried M. Role of duodenal lipid and cholecystokinin A receptors in the pathophysiology of functional dyspepsia. *Gut* 2001; **48**: 347–55.
47 Samsom M, Verhagen MA, van Berge Henegouwen GP, Smout AJ. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. *Gastroenterology* 1999; **116**: 515–20.
48 Ladabaum U, Minoshima S, Hasler WL, Cross D, Chey WD, Owyang C. Gastric distention correlates with activation of multiple cortical and subcortical regions. *Gastroenterology* 2001; **120**: 369–76.
49 Vandenbergh J, Dupont P, Fischler B, *et al*. Regional brain activation during proximal stomach distention in humans: a positron emission tomography study. *Gastroenterology* 2005; **128**: 564–73.
50 Mearin F, Perez-Oliveras M, Perello A, *et al*. Dyspepsia and irritable bowel syndrome after a *Salmonella* gastroenteritis outbreak: one-year follow-up cohort study. *Gastroenterology* 2005; **129**: 98–104.
51 Spiller RC. Inflammation as a basis for functional GI disorders. *Best Pract Res Clin Gastroenterol* 2004; **18**: 641–61.
52 Tack J, Demedts I, Dehondt G, *et al*. Clinical and pathophysiological characteristics of acute-onset functional dyspepsia. *Gastroenterology* 2002; **122**: 1738–47.

53 Danesh J, Lawrence M, Murphy M, Roberts S, Collins R. Systematic review of the epidemiological evidence on *Helicobacter pylori* infection and non-ulcer or uninvestigated dyspepsia. *Arch Intern Med* 2000; **160**: 1192–8.

54 Hall W, Buckley M, Crotty P, O'Morain CA. Gastric mucosal mast cells are increased in *Helicobacter pylori*-negative functional dyspepsia. *Clin Gastroenterol Hepatol* 2003; **1**: 363–9.

55 Hausken T, Svebak S, Wilhelmsen I, *et al*. Low vagal tone and antral dysmotility in patients with functional dyspepsia. *Psychosom Med* 1993; **55**: 12–22.

56 Holtmann G, Goebell H, Jockenhoevel F, Talley NJ. Altered vagal and intestinal mechanosensory function in chronic unexplained dyspepsia. *Gut* 1998; **42**: 501–6.

57 Berstad A. Functional dyspepsia – a conceptual framework. *Gut* 2000; **47** (Suppl. 4): iv3–4; discussion iv10.

58 Geeraerts B, Vandenberghe J, Van Oudenhove L, *et al*. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. *Gastroenterology* 2005; **129**: 1437–44.

59 Hsu PI, Lai KH, Lo GH, *et al*. Risk factors for ulcer development in patients with non-ulcer dyspepsia: a prospective two year follow up study of 209 patients. *Gut* 2002; **51**: 15–20.

60 Lieberman D, Fennerty MB, Morris CD, Holub J, Eisen G, Sonnenberg A. Endoscopic evaluation of patients with dyspepsia: results from the national endoscopic data repository. *Gastroenterology* 2004; **127**: 1067–75.

61 Fransen GA, Janssen MJ, Muris JW, Laheij RJ, Jansen JB. Meta-analysis: The diagnostic value of alarm symptoms for upper gastrointestinal malignancy. *Aliment Pharmacol Ther* 2004; **20**: 1045–52.

62 Janssen HA, Muris JW, Knottnerus JA. The clinical course and prognostic determinants of non-ulcer dyspepsia: a literature review. *Scand J Gastroenterol* 1999; **34**: 546–50.

63 Nojkov B, Chey WD, Adlis S, Shaw M. Predictors of response to PPI therapy in patients with GERD: the influence of co-morbid IBS and psychological disease. *Gastroenterology* 2005; **128** (Suppl. 2): A-61 (abstract).

64 Feinle-Bisset C, Vozzo R, Horowitz M, Talley NJ. Diet, food intake, and disturbed physiology in the pathogenesis of symptoms in functional dyspepsia. *Am J Gastroenterol* 2004; **99**: 170–81.

65 Barbera R, Feinle C, Read NW. Nutrient-specific modulation of gastric mechanosensitivity in patients with functional dyspepsia. *Dig Dis Sci* 1995; **40**: 1636–41.

66 Suzuki H, Masaoka T, Sakai G, Ishii H, Hibi T. Improvement of gastrointestinal quality of life scores in cases of *Helicobacter pylori*-positive functional dyspepsia after successful eradication therapy. *J Gastroenterol Hepatol* 2005; **20**: 1652–60.

67 Malfertheiner P, Fischbach W, Layer P, *et al*. *Helicobacter pylori* eradication is beneficial in the treatment of functional dyspepsia. *Aliment Pharmacol Ther* 2003; **18**: 615–25.

68 Gisbert JP, Cruzado AI, Garcia-Gravalos R, Pajares JM. Lack of benefit of treating *Helicobacter pylori* infection in patients with functional dyspepsia. Randomized one-year follow-up study. *Hepatogastroenterology* 2004; **51**: 303–8.

69 Veldhuyzen van Zanten SJ, Fedorak RN, Lambert J, Cohen L, Vanjaka A. Absence of symptomatic benefit of lansoprazole, clarithromycin, and amoxicillin triple therapy in eradication of *Helicobacter pylori* positive, functional (nonulcer) dyspepsia. *Am J Gastroenterol* 2003; **98**: 1963–9.

70 Koelz HR, Arnold R, Stolte M, Fischer M, Blum AL. Treatment of *Helicobacter pylori* in functional dyspepsia resistant to conventional management: a double blind randomised trial with a six month follow up. *Gut* 2003; **52**: 40–6.

71 Koskenpato J, Farkkila M, Sipponen P. *Helicobacter pylori* eradication and standardized 3-month omeprazole therapy in functional dyspepsia. *Am J Gastroenterol* 2001; **96**: 2866–72.

72 Veldhuyzen van Zanten SJ, Talley NJ, Blum AL, Bolling-Sternevald E, Sundin M, Junghard O. Combined analysis of the ORCHID and OCAY studies: does eradication of *Helicobacter pylori* lead to sustained improvement in functional dyspepsia symptoms? *Gut* 2002; **50** (Suppl. 4): iv26–30; discussion iv31–2.

73 Moayyedi P, Soo S, Deeks J, *et al*. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2003; **1**: CD002096.

74 Laine L, Schoenfeld P, Fennerty MB. Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; **134**: 361–9.

75 Danesh J, Pounder RE. Eradication of *Helicobacter pylori* and non-ulcer dyspepsia. *Lancet* 2000; **355**: 766–7.

76 Jaakkimainen RL, Boyle E, Tudiver F. Is *Helicobacter pylori* associated with non-ulcer dyspepsia and will eradication improve symptoms? A meta-analysis. *BMJ* 1999; **319**: 1040–4.

77 Laheij RJ, Jansen JB, van de Lisdonk EH, Severens JL, Verbeek AL. Review article: Symptom improvement through eradication of *Helicobacter pylori* in patients with non-ulcer dyspepsia. *Aliment Pharmacol Ther* 1996; **10**: 843–50.

78 Laheij RJ, van Rossum LG, Verbeek AL, Jansen JB. *Helicobacter pylori* infection treatment of nonulcer dyspepsia: an analysis of meta-analyses. *J Clin Gastroenterol* 2003; **36**: 315–20.

79 Moayyedi P, Soo S, Deeks J, *et al*. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2005; **1**: CD002096.

80 Chey WD, Moayyedi P. Review article: Uninvestigated dyspepsia and non-ulcer dyspepsia-the use of endoscopy and the roles of *Helicobacter pylori* eradication and antisecretory therapy. *Aliment Pharmacol Ther* 2004; **19** (Suppl. 1): 1–8.

81 Gotthard R, Bodemar G, Brodin U, Jonsson KA. Treatment with cimetidine, antacid, or placebo in patients with dyspepsia of unknown origin. *Scand J Gastroenterol* 1988; **23**: 7–18.

82 Nyren O, Adami HO, Bates S, *et al*. Absence of therapeutic benefit from antacids or cimetidine in non-ulcer dyspepsia. *N Engl J Med* 1986; **314**: 339–43.

83 Weberg R, Aubert E, Dahlberg O, *et al*. Low-dose antacids or cimetidine for duodenal ulcer? *Gastroenterology* 1988; **95**: 1465–9.

84 Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2004; **4**: CD001960.

85 Moayyedi P, Soo S, Deeks J, *et al*. Systematic review: Antacids, H2-receptor antagonists, prokinetics, bismuth and sucralfate therapy for non-ulcer dyspepsia. *Aliment Pharmacol Ther* 2003; **17**: 1215–27.

86 Redstone HA, Barrowman N, Veldhuyzen van Zanten SJ. H2-receptor antagonists in the treatment of functional

(nonulcer) dyspepsia: a meta-analysis of randomized controlled clinical trials. *Aliment Pharmacol Ther* 2001; **15**: 1291–9.
87 Abraham NS, Moayyedi P, Daniels B, Veldhuyzen van Zanten SJ. Systematic review: the methodological quality of trials affects estimates of treatment efficacy in functional (non-ulcer) dyspepsia. *Aliment Pharmacol Ther* 2004; **19**: 631–41.
88 Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. *Gastroenterology* 2004; **127**: 1329–37.
89 Meineche-Schmidt V. Classification of dyspepsia and response to treatment with proton-pump inhibitors. *Aliment Pharmacol Ther* 2004; **20**: 1171–9.
90 Arts J, Caenepeel P, Verbeke K, Tack J. Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005; **54**: 455–60.
91 Talley NJ, Verlinden M, Snape W, *et al*. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2000; **14**: 1653–61.
92 Veldhuyzen van Zanten SJ, Jones MJ, Verlinden M, Talley NJ. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. *Am J Gastroenterol* 2001; **96**: 689–96.
93 Hallerback BI, Bommelaer G, Bredberg E, *et al*. Dose finding study of mosapride in functional dyspepsia: a placebo-controlled, randomized study. *Aliment Pharmacol Ther* 2002; **16**: 959–67.
94 Kinoshita Y, Hashimoto T, Kawamura A, *et al*. Effects of famotidine, mosapride and tandospirone for treatment of functional dyspepsia. *Aliment Pharmacol Ther* 2005; **21** (Suppl. 2): 37–41.
95 Otaka M, Jin M, Odashima M, *et al*. New strategy of therapy for functional dyspepsia using famotidine, mosapride and amitriptyline. *Aliment Pharmacol Ther* 2005; **21** (Suppl. 2): 42–6.
96 van der Voort I, Schmidtmann M, Fach K, *et al*. Tegaserod improves gastric emptying and alters myoelectric activity in dyspeptic patients. *Gastroenterology* 2004; **126** (Suppl. 2): A-643.
97 Tack J, Vos R, Bisschops G, Tougas G, Janssens J, Phillipps T. Effect of tegaserod, a 5-HT_4 receptor agonist, on sensory and motor function of the proximal stomach in functional dyspepsia. *Gastroenterology* 2005; **128** (Suppl. 2): A-94 (abstract).
98 Tougas G, Chen Y, Luo D, Salter J, D'Elia T, Earnest D. Tegaserod improves gastric emptying in patients with gastroeparesis and dyspeptic symptoms. *Gastroenterology* 2003; **124** (Suppl. 1): A-54 (abstract).
99 Mearin F, Rodrigo L, Perez-Mota A, *et al*. Levosulpiride and cisapride in the treatment of dysmotility-like functional dyspepsia: a randomized, double-masked trial. *Clin Gastroenterol Hepatol* 2004; **2**: 301–8.
100 Holtmann G, Talley NJ, Liebregts T, Adam B, Parow C. A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006; **354**: 832–40.
101 Hojo M, Miwa H, Yokoyama T, *et al*. Treatment of functional dyspepsia with antianxiety or antidepressive agents: systematic review. *J Gastroenterol* 2005; **40**: 1036–42.
102 Drossman DA, Toner BB, Whitehead WE, *et al*. Cognitive-behavioral therapy vs. education and desipramine vs. placebo for moderate to severe functional bowel disorders. *Gastroenterology* 2003; **125**: 19–31.
103 Dalton C, Diamant NE, Morris CB, *et al*. Are side effects of tricyclic antidepressants (TCAs) really side effects? *Gastroenterology* 2004; **126** (Suppl. 2): A-250.
104 Mertz H, Fass R, Kodner A, Yan-Go F, Fullerton S, Mayer EA. Effect of amitriptyline on symptoms, sleep, and visceral perception in patients with functional dyspepsia. *Am J Gastroenterol* 1998; **93**: 160–5.
105 Fioramonti J, Bueno L. Centrally acting agents and visceral sensitivity. *Gut* 2002; **51** (Suppl. 1): i91–5.
106 Gorelick AB, Koshy SS, Hooper FG, Bennett TC, Chey WD, Hasler WL. Differential effects of amitriptyline on perception of somatic and visceral stimulation in healthy humans. *Am J Physiol* 1998; **275** (3 Pt 1): G460–6.
107 Tack J, Broekaert D, Coulie B, Fischler B, Janssens J. Influence of the selective serotonin re-uptake inhibitor, paroxetine, on gastric sensorimotor function in humans. *Aliment Pharmacol Ther* 2003; **17**: 603–8.
108 Ladabaum U, Glidden D. Effect of the selective serotonin reuptake inhibitor sertraline on gastric sensitivity and compliance in healthy humans. *Neurogastroenterol Motil* 2002; **14**: 395–402.
109 Talley NJ, Owen BK, Boyce P, Paterson K. Psychological treatments for irritable bowel syndrome: a critique of controlled treatment trials. *Am J Gastroenterol* 1996; **91**: 277–83.
110 Calvert EL, Houghton LA, Cooper P, Morris J, Whorwell PJ. Long-term improvement in functional dyspepsia using hypnotherapy. *Gastroenterology* 2002; **123**: 1778–85.
111 Haug TT, Wilhelmsen I, Svebak S, Berstad A, Ursin H. Psychotherapy in functional dyspepsia. *J Psychosom Res* 1994; **38**: 735–44.
112 Mine K, Kanazawa F, Hosoi M, Kinukawa N, Kubo C. Treating nonulcer dyspepsia considering both functional disorders of the digestive system and psychiatric conditions. *Dig Dis Sci* 1998; **43**: 1241–7.
113 Hamilton J, Guthrie E, Creed F, *et al*. A randomized controlled trial of psychotherapy in patients with chronic functional dyspepsia. *Gastroenterology* 2000; **119**: 661–9.
114 Soo S, Forman D, Delaney BC, Moayyedi P. A systematic review of psychological therapies for nonulcer dyspepsia. *Am J Gastroenterol* 2004; **99**: 1817–22.
115 Thompson Coon J, Ernst E. Systematic review: Herbal medicinal products for non-ulcer dyspepsia. *Aliment Pharmacol Ther* 2002; **16**: 1689–99.
116 Melzer J, Rosch W, Reichling J, Brignoli R, Saller R. Meta-analysis: Phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast). *Aliment Pharmacol Ther* 2004; **20**: 1279–87.
117 Bortolotti M, Coccia G, Grossi G, Miglioli M. The treatment of functional dyspepsia with red pepper. *Aliment Pharmacol Ther* 2002; **16**: 1075–82.
118 Rodriguez-Stanley S, Collings KL, Robinson M, Owen W, Miner PB Jr. The effects of capsaicin on reflux, gastric emptying and dyspepsia. *Aliment Pharmacol Ther* 2000; **14**: 129–34.
119 Holtmann G, Adam B, Haag S, Collet W, Grunewald E, Windeck T. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. *Aliment Pharmacol Ther* 2003; **18**: 1099–105.

120 Read NW, Abitbol JL, Bardhan KD, Whorwell PJ, Fraitag B. Efficacy and safety of the peripheral kappa agonist fedotozine vs. placebo in the treatment of functional dyspepsia. *Gut* 1997; **41**: 664–8.

121 Delgado-Aros S, Chial HJ, Cremonini F, *et al*. Effects of asimadoline, a kappa-opioid agonist, on satiation and postprandial symptoms in health. *Aliment Pharmacol Ther* 2003; **18**: 507–14.

122 Stanghellini V, De Ponti F, De Giorgio R, Barbara G, Tosetti C, Corinaldesi R. New developments in the treatment of functional dyspepsia. *Drugs* 2003; **63**: 869–92.

123 Holzer P. Acid-sensitive ion channels in gastrointestinal function. *Curr Opin Pharmacol* 2003; **3**: 618–25.

124 Honore P, Mikusa J, Bianchi B, *et al*. TNP-ATP, a potent P2X3 receptor antagonist, blocks acetic acid-induced abdominal constriction in mice: comparison with reference analgesics. *Pain* 2002; **96**: 99–105.

125 Ide Y, Maehara Y, Tsukahara S, Kitahata LM, Collins JG. The effects of an intrathecal NMDA antagonist (AP5) on the behavioral changes induced by colorectal inflammation with turpentine in rats. *Life Sci* 1997; **60**: 1359–63.

126 Kuiken SD, Lei A, Tytgat GN, Holman R, Boeckxstaens GE. Effect of the low-affinity, noncompetitive N-methyl-D-aspartate receptor antagonist dextromethorphan on visceral perception in healthy volunteers. *Aliment Pharmacol Ther* 2002; **16**: 1955–62.

127 Kawabata A. Gastrointestinal functions of proteinase-activated receptors. *Life Sci* 2003; **74**: 247–54.

128 Kawabata A, Kinoshita M, Nishikawa H, *et al*. The protease-activated receptor-2 agonist induces gastric mucus secretion and mucosal cytoprotection. *J Clin Invest* 2001; **107**: 1443–50.

129 Ward SM, Bayguinov J, Won KJ, Grundy D, Berthoud HR. Distribution of the vanilloid receptor (VR1) in the gastrointestinal tract. *J Comp Neurol* 2003; **465**: 121–35.

130 Holzer P. Gastrointestinal afferents as targets of novel drugs for the treatment of functional bowel disorders and visceral pain. *Eur J Pharmacol* 2001; **429**: 177–93.

131 Foxx-Orenstein A, Camilleri M, Stephens D, Burton D. Effect of a somatostatin analogue on gastric motor and sensory functions in healthy humans. *Gut* 2003; **52**: 1555–61.

132 Mearadji B, Straathof JW, Biemond I, Lamers CB, Masclee AA. Effects of somatostatin on proximal gastric motor function and visceral perception. *Aliment Pharmacol Ther* 1998; **12**: 1163–9.

133 Mertz H, Walsh JH, Sytnik B, Mayer EA. The effect of octreotide on human gastric compliance and sensory perception. *Neurogastroenterol Motil* 1995; **7**: 175–85.

134 Feinle C, Rades T, Otto B, Fried M. Fat digestion modulates gastrointestinal sensations induced by gastric distention and duodenal lipid in humans. *Gastroenterology* 2001; **120**: 1100–7.

135 Holzer P, Holzer-Petsche U. Tachykinin receptors in the gut: physiological and pathological implications. *Curr Opin Pharmacol* 2001; **1**: 583–90.

136 Monnikes H, Tebbe JJ, Hildebrandt M, *et al*. Role of stress in functional gastrointestinal disorders. Evidence for stress-induced alterations in gastrointestinal motility and sensitivity. *Dig Dis* 2001; **19**: 201–11.

137 Liddle RA, Morita ET, Conrad CK, Williams JA. Regulation of gastric emptying in humans by cholecystokinin. *J Clin Invest* 1986; **77**: 992–6.

138 Moran TH, McHugh PR. Cholecystokinin suppresses food intake by inhibiting gastric emptying. *Am J Physiol* 1982; **242**: R491–7.

139 Chua AS, Keeling PW, Dinan TG. Role of cholecystokinin and central serotonergic receptors in functional dyspepsia. *World J Gastroenterol* 2006; **12**: 1329–35.

140 Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, *et al*. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003; **97**: 3090–8.

141 Chawla SP, Grunberg SM, Gralla RJ, *et al*. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 2003; **97**: 2290–300.

142 Hill R. NK1 (substance P) receptor antagonists – why are they not analgesic in humans? *Trends Pharmacol Sci* 2000; **21**: 244–6.

143 Sanger GJ. Neurokinin NK1 and NK3 receptors as targets for drugs to treat gastrointestinal motility disorders and pain. *Br J Pharmacol* 2004; **141**: 1303–12.

144 Dinan TG, Quigley EM, Ahmed SM, *et al*. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? *Gastroenterology* 2006; **130**: 304–11.

145 Tache Y. Cyclic vomiting syndrome: the corticotropin-releasing-factor hypothesis. *Dig Dis Sci* 1999; **44** (Suppl. 8): 79S–86S.

146 Chen CY, Inui A, Asakawa A, *et al*. Des-acyl ghrelin acts by CRF type 2 receptors to disrupt fasted stomach motility in conscious rats. *Gastroenterology* 2005; **129**: 8–25.

147 Luckey A, Wang L, Jamieson PM, *et al*. Corticotropin-releasing factor receptor 1-deficient mice do not develop postoperative gastric ileus. *Gastroenterology* 2003; **125**: 654–9.

148 Talley NJ, Van Zanten SV, Saez LR, *et al*. A dose-ranging, placebo-controlled, randomized trial of alosetron in patients with functional dyspepsia. *Aliment Pharmacol Ther* 2001; **15**: 525–37.

149 De Ponti F. Pharmacology of serotonin: what a clinician should know. *Gut* 2004; **53**: 1520–35.

150 Tack J, Talley NJ, Camilleri M, *et al*. Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466–79.