Functional dyspepsia

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Abstract | Functional dyspepsia is one of the most prevalent functional gastrointestinal disorders. Functional dyspepsia comprises three subtypes with presumed different pathophysiology and aetiology: postprandial distress syndrome (PDS), epigastric pain syndrome (EPS) and a subtype with overlapping PDS and EPS features. Functional dyspepsia symptoms can be caused by disturbed gastric motility (for example, inadequate fundic accommodation or delayed gastric emptying), gastric sensation (for example, sensations associated with hypersensitivity to gas and bloating) or gastric and duodenal inflammation. A genetic predisposition is probable but less evident than in other functional gastrointestinal disorders, such as irritable bowel syndrome (IBS). Psychiatric comorbidity and psychopathological state and trait characteristics could also play a part, although they are not specific to functional dyspepsia and are less pronounced than in IBS. Possible differential diagnoses include *Helicobacter pylori* infection and peptic ulceration. Pharmacological therapy is mostly based on the subtype of functional dyspepsia, such as prokinetic and fundus-relaxing drugs for PDS and acid-suppressive drugs for EPS, whereas centrally active neuromodulators and herbal drugs play a minor part. Psychotherapy is effective only in a small subset of patients, whereas quality of life can be severely affected in nearly all patients. Future therapies might include novel compounds that attempt to treat the underlying gastric and duodenal inflammation.

The disease entity functional dyspepsia — discomfort or pain in the upper abdomen, often related to food intake, but with no obvious organic cause — was introduced during the Rome consensus process for the classification of functional gastrointestinal disorders, which started in 1988. Before this, patients who presented with symptoms that resembled functional dyspepsia often received a diagnosis of non-ulcer dyspepsia, irritable stomach syndrome, chronic idiopathic dyspepsia or essential dyspepsia. Major efforts were made to distinguish functional dyspepsia from structural gastrointestinal diseases (such as gastric ulcer-induced symptoms, duodenal ulcer-induced symptoms and gastro-oesophageal reflux disease) or unexplained nausea and vomiting, to name a few differential diagnoses[1,2], but problems in the classification remain owing to the broad spectrum of functional dyspepsia symptoms. In 1990, the first Rome classification system was published; in 1991, the gastroduodenal criteria separated functional dyspepsia into ulcer-like dyspepsia, dysmotility-like dyspepsia, reflux-like dyspepsia or unspecified functional dyspepsia to account for the fact that although some patients report pain as their predominant symptom, others report postprandial symptoms (for example, fullness, early satiety (the inability to finish normal-sized meals), nausea or bloating), and many patients experience both kinds of symptoms. This distinction was maintained in the subsequent Rome I (1992) and Rome II (1999) classifications. With the Rome III classification (2006), the definition of functional dyspepsia became more-restrictive, and the subtype labels changed to epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) (BOX 1). This distinction was preserved in the Rome IV (2016) classification[3] and is responsible for some of the discrepancies in global epidemiology. *Helicobacter pylori*-associated dyspeptic symptoms are now accepted as a separate entity[4,5]; however, only a minority of patients remain asymptomatic at 6–12 months follow-up after successful eradication therapy, suggesting that *H. pylori* infection was not the primary cause of the dyspeptic symptoms[6,7]. Because gastro-oesophageal reflux disease and functional dyspepsia overlap to some degree[8], patients with functional dyspepsia are often misclassified as having gastro-oesophageal reflux disease[9] and prescribed proton pump inhibitors (PPIs), which are

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standard therapy for gastro-oesophageal reflux disease. Paediatric dyspeptic symptoms are being addressed in a separate classification effort[10]. This Primer covers functional dyspepsia in adults only, although we sporadically refer to paediatric functional dyspepsia when similarities exist.

Epidemiology

The population prevalence of functional dyspepsia is quite variable across the globe, with overall high numbers (10–40%) in Western countries and low numbers (5–30%) in Asia, independent of the respective functional dyspepsia definitions[11]. A large-scale health and nutrition survey from France[12] (which involved >35,000 people) identified that 15% of individuals had suspected functional dyspepsia, 28% had irritable bowel syndrome (IBS) and 6% had both. The population of patients who are affected by both IBS and functional dyspepsia has been reported to range between 10% and 27% in previous studies[13] and to approach 30% in population samples; it could be even higher in specific populations[14,15]. This observation has given rise to the term 'overlap syndrome' (REF. 13), which calls into question the sensitivity and specificity of the Rome criteria, at least for IBS and functional dyspepsia. This argument is also supported by the observation that patients with functional dyspepsia might eventually present with IBS symptoms at follow-up, whereas others with IBS might switch to functional dyspepsia after 2–10 years[16,17]. Functional dyspepsia overlaps not only with IBS and other functional gastrointestinal disorders but also with some somatic diseases and functional non-intestinal diseases, such as fibromyalgia, overactive bladder and chronic pelvic pain[18–21].

The incidence of functional dyspepsia is estimated to be 4–5% over a 10-year period[22,17], with a similar rate of disappearance; disappearance could be due to spontaneous or therapy-induced remission but could also be temporary at the time of assessment[23]. That the prevalence of functional dyspepsia is higher among women than men is well established[24], although in functional dyspepsia this difference is less prominent than in IBS. This correlation could be due to sex-specific biological differences in gastrointestinal function (for example, sex hormone-driven alterations in intestinal motility) or the processing of (visceral) pain in the central nervous system, but also to sex-specific health care behaviour.

Known and presumed risk factors for developing functional dyspepsia are gastrointestinal infections and traveller's diarrhoea[25], antibiotic use[26], intake of NSAIDs[27], childhood abuse[28], early environmental microbial exposure[29] and other early life factors[30], smoking[31], overweight and obesity[32] and perceived stress[33] as well as psychosocial states and traits (for example, anxiety and depression; see Psychosocial factors and brain mechanisms, below). Women have an overall higher probability of developing functional dyspepsia compared with men[34], including post-infectious functional dyspepsia[35]. However, for example, in the case of gastroenteritis, none of these risk factors can currently determine whether the resulting disease will predominantly occur in the upper or lower gastrointestinal tract[36] or in the gastrointestinal tract at all[21]. In the case of gastrointestinal infections, one hypothesis suggests that the extent of intestinal inflammation after the infection can determine the phenotype[37].

The high prevalence of psychiatric comorbidity in functional dyspepsia[18], another shared feature with IBS, has generated the hypothesis of a psychiatric origin of the disease, but long-term data indicate that this cause–effect correlation could go both ways: anxiety can increase the risk of future and new-onset functional dyspepsia[38], and functional dyspepsia without psychiatric comorbidity at baseline can predict higher anxiety and depression scores at follow-up[22]. In an Australian cohort of 1,900 patients with IBS and/or functional dyspepsia, the diagnosis of depression and anxiety preceded that of a functional disorder in one-third of patients, whereas a functional disorder was diagnosed before the mood disorder in the other two-thirds[39]. As a consequence of the low prevalence of primary psychiatric disorder, the use of psychotherapy to manage functional dyspepsia is less often attempted (see Psychotherapy, below) and less effective in general than in IBS[40]. Psychiatric comorbidities that are much more prevalent in functional dyspepsia (in particular in PDS) than in IBS are eating disorders (for example, bulimia or anorexia nervosa)[41,42] and, therefore, it is necessary to first exclude a primary eating disorder in patients who present with functional dyspepsia symptoms and weight loss.

Health economic data indicate that functional dyspepsia has high direct and indirect costs, specifically driven by the high prevalence of comorbidity[18,43], but both organic dyspepsia and functional dyspepsia have similar economic effects[44].

Mechanisms/pathophysiology

Functional dyspepsia is considered a multifactorial disorder in which different pathophysiological mechanisms play a part[45,46], and each one could contribute to all subtypes. Traditionally, functional dyspepsia, in particular PDS, has been associated with disturbances in gastric motor function[47,48]. However, a study showed that gastric physiological disturbances did not correlate with symptoms[49], and delayed gastric emptying presented to a similar extent in PDS, EPS and overlapping groups. Meal ingestion substantially modulates symptoms[50], and genetic factors could also have a role.

H. pylori-related dyspepsia is considered a separate entity. However, other prior gastrointestinal infections have been described as triggers of functional dyspepsia, by impairing gastric accommodation (a vagally mediated reflex that occurs postprandially and results in a reduction of smooth muscle tone; the stomach relaxes and provides a reservoir for the meal), possibly via immune mechanisms[51–53].

Communication between the central nervous system and the enteric nervous system has been recognized for over a century, but the fact that brain–gut communications are bi-directional has only been appreciated more recently[54,55]. Innervation of the gastrointestinal tract regulates secretions, sphincter control, motility, blood flow and enteroendocrine function, and the enteric nervous system also communicates with the intestinal barrier via neuroendocrine and mucosal immune cells[54,56]. We discuss these different putative pathophysiological mechanisms in more detail in the following sections.

Gastroduodenal motility

Altered motility and pathological responses to mechanical and chemical stimuli are common sensorimotor disorders of the gastroduodenum in patients with functional dyspepsia[57] (FIG. 1). There are distinct motility patterns during interdigestive and digestive states. During interdigestive periods, when the gut is empty, cyclic, recurring migrating motor complexes (MMC) move over the gastrointestinal tract fulfilling 'housekeeper' functions. The most characteristic phase of interdigestive motility is phase III, which consists of high-amplitude, propagating contractions moving as a front slowly from the oral to the anal end of the small bowel. Abnormal motility patterns in functional dyspepsia occur in the stomach, pylorus and small intestine during digestive or interdigestive periods as well as during triggered reflex activity[58–62] (FIG. 1). Up to ~30% of symptoms are associated with MMC-like activity, which in these patients is atypical, as it mainly consists of retrograde or non-propagating clustered contractions[62]. The pathological consequences of motility disturbances range from altered gastric emptying and intestinal reflex activity to increased chemosensitivity or mechanosensitivity.

Patients with functional dyspepsia have impaired accommodation of the proximal stomach in response to gastric balloon distension in the fasted state and after meal ingestion[63,64]. This impaired accommodation results in disproportional volume distribution, with a larger than normal antral volume, but smaller fundus volume[65]. The degree of antral distension is related to the severity of functional dyspepsia symptoms[66]. In addition, patients with functional dyspepsia show impaired fundus accommodation in response to duodenal distension[67]. Impaired gastric accommodation is associated with early satiety.

Gastroduodenal sensitivity

Gastroduodenal sensitivity to both mechanical and chemical stimuli is altered in functional dyspepsia. Patients with functional dyspepsia show visceral hypersensitivity after distension of the gastric fundus in the fasted state and after meal ingestion[57,68]. The proportion of hypersensitive patients depends on the diagnostic criteria and whether the abnormal sensation is defined as aberrant, allodynia (pain sensitization to normally non-painful stimuli) and/or hyperalgesia (increased sensitivity to painful stimuli). The degree of visceral hypersensitivity correlates with symptom severity[69]. Even patients with normal accommodation report discomfort after gastric distension[70]. Some patients are also hypersensitive to duodenal[61], jejunal[70] or rectal[71] distension, which suggests a more-generalized sensitization in the central and autonomic (vagal, spinal and enteric) nervous systems. Interestingly, gastric hypersensitivity was not observed in patients with IBS[71]. The hypersensitivity to gastric distension in functional dyspepsia improved when the cholinergic tone was reduced by muscarinic receptor blockade, but not when muscle relaxation was induced with the nitric oxide donor nitroglycerine[72], with the exception of one study in which sublingual administration immediately before a meal improved the overall symptom score[73]. These findings demonstrate a major role for upregulated cholinergic pathways (probably enteric) in abnormal sensations but also leave the door open for strategies to increase inhibitory pathways to the muscle.

Functional dyspepsia symptoms after duodenal acid infusion[74] could result from sensitization of transient receptor potential cation channel subfamily V member 1 (TRPV1) or decreased acid clearance from

Box 1 | **Rome IV symptom criteria for functional dyspepsia and its subtypes***

- Symptoms of functional dyspepsia include bothersome postprandial fullness, bothersome early satiety, bothersome epigastric pain and bothersome epigastric burning. Functional dyspepsia is diagnosed if a patient reports having ≥1 of these symptoms for the past 3 months with onset at least 6 months before diagnosis, there is no evidence of structural disease that can account for the symptoms and the patient can be classified as having postprandial distress syndrome (PDS), epigastric pain syndrome (EPS) or both.
- PDS is diagnosed if a patient with symptoms compatible with functional dyspepsia complains of bothersome postprandial fullness and/or bothersome early satiety that are severe enough to interfere with daily activities or to prevent finishing a meal for at least 3 days per week. Other digestive symptoms can coexist with PDS.
- EPS is diagnosed if a patient with symptoms compatible with functional dyspepsia reports bothersome epigastric pain and/or bothersome epigastric burning that are severe enough to interfere with daily activities and occur at least once per week. Other digestive symptoms can coexist with EPS.

*Based on data in REF. 3.

the proximal duodenum owing to a compromised fasting duodenal motor activity[75]. TRPV1 is expressed on vagal and spinal sensory nerve endings in the gut wall and is activated by low pH, high temperature and painful stimuli. Patients with functional dyspepsia have a higher sensitivity to capsaicin[76], an agonist of TRPV1. As a consequence, acute capsaicin application evokes a feeling of warmth and pain, which can be desensitized during prolonged application.

The finding that intraduodenal lipid (but not glucose) infusion sensitizes the stomach to distension in patients with functional dyspepsia, but not in controls[77], suggests a cross-sensitization between mechanosensors and chemosensors and could explain why fatty meals can exaggerate symptoms related to gastric filling. Lipids in the duodenum can provoke symptoms through different possible mechanisms: direct neuronal stimulation, higher lipid sensitivity of enteroendocrine cells or nerves, increased levels of systemic or local cholecystokinin (which is secreted by lipid-activated enteroendocrine cells, stimulates the release of digestive enzymes and bile and induces satiety) and/or increased sensitivity to cholecystokinin involving type A cholecystokinin receptors[78].

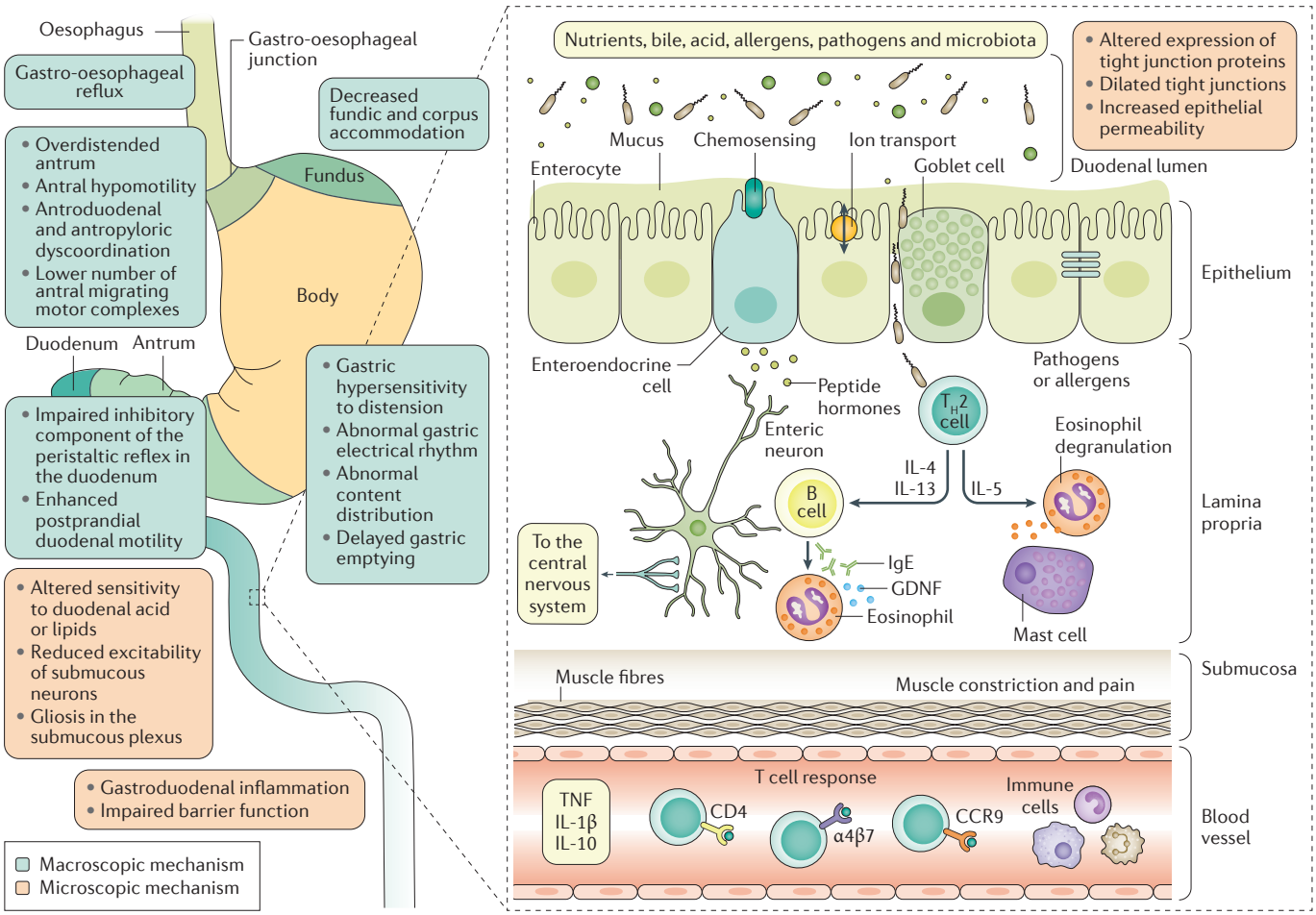

Figure 1 | **Putative mechanisms of functional dyspepsia symptoms at the macroscopic and microscopic level.** Epithelial chemosensors on enteroendocrine cells respond to contents in the lumen (nutrients, bile, acid, allergens, pathogens and microbiota) by releasing peptide hormones (for example, histamine, cholecystokinin and peptide YY), which act on enteric neurons; this boosts the defence of the epithelium via mucus and bicarbonate secretion and stimulation of the immune milieu[247]. However, the number of enteroendocrine cells in the duodenum is significantly lower in patients with functional dyspepsia compared with controls[83], and this alteration could contribute to the impaired function of the mucosal barrier. When the mucosal barrier is dysfunctional, pathogens or allergens can cross the gut epithelium in the duodenum and trigger a T helper 2 (T_H2) cell response that leads to the activation (mediated by eotaxin, which is secreted by mononuclear cells within the lamina propria (not shown)) of resident and newly recruited eosinophils. Eosinophils act as antigen-presenting cells to T_H2 lymphocytes, which express IL-5, a cytokine that subsequently leads to eosinophil degranulation close to nerve fibres, causing muscle contraction and pain[37]. Eosinophils (and glial cells) also release glial cell line-derived neurotrophic factor (GDNF), which was found to be increased in functional dyspepsia and positively correlated with functional dyspepsia symptoms[79] but is also involved in epithelial barrier repair. T_H2 cells also express IL-4 and IL-13, which provide feedback to the stomach and can promote immunoglobulin (Ig) class-switching in B cells and induce the expression of pro-allergic IgE antibodies, which further stimulate eosinophil degranulation and increase epithelial permeability. The pro-inflammatory cytokines tumour necrosis factor (TNF) and IL-1β and the anti-inflammatory cytokine IL-10 can be released by immune cells into the blood and promote, along with small-intestinal-homing T cells (expressing T cell surface glycoprotein CD4, integrin β7 (α4β7) and CC-chemokine receptor type 9 (CCR9)), an anxiety or stress response, which in turn can lead to disordered motility and visceral hypersensitivity in the stomach and duodenum[37,94].

Evidence for sensitization of peripheral nerves is provided by the observation that nociceptor-related genes that encode β-nerve growth factor, glial cell line-derived neurotrophic factor (GDNF)[79] and TRPV1 (REF. 80) are upregulated in duodenal biopsy samples of patients with functional dyspepsia. This finding is consistent with higher levels of GDNF in patients with functional dyspepsia[79]. Both duodenal and gastric biopsy samples showed mast cell hyperplasia and an increased release of histamine and tryptase (which indicates mast cell activation)[81]. Gastric biopsy samples also revealed a closer association between nerves and mast cells[81], and these immune mediators are known to synergistically activate neurons[82]. In the duodenal bulb, the number of chromogranin A (CGA)-positive enteroendocrine cells was reduced in duodenal biopsy samples from patients with functional dyspepsia, mostly in patients with EPS[83]. CGA plays a part in release of mediators from enteroendocrine cells, the activity of nerve and immune cells and the protection against oxidative stress. Reduced CGA expression could disturb homeostasis and, hence, contributing to the development of abnormal sensations in functional dyspepsia.

Gastroduodenal inflammation

Mechanical and chemical hypersensitivity could result from local immune activation. Emerging data have now shifted the focus of the research on the mechanisms of functional dyspepsia from *H. pylori* infection and altered motility to the role of impaired permeability of the epithelial barrier, duodenal eosinophilia and subtle mucosal inflammation in the duodenum[84] (FIG. 1).

Most studies have demonstrated an impairment of epithelial barrier function in the duodenum in both patients and biopsy samples. Investigation during endoscopy revealed increased mucosal permeability in EPS, PDS and functional dyspepsia with concomitant IBS[85]. This finding confirmed earlier studies on biopsy samples that demonstrated decreased transepithelial resistance and increased paracellular permeability together with immune cell infiltration[86]. One study reported larger gaps between adherens of epithelial cells in biopsy samples from patients with functional dyspepsia compared with controls[79], whereas another study described a normal appearance of the epithelial surface[87] and an even higher epithelial resistance (and, therefore, lower permeability) in biopsy samples from patients compared with controls[87]. Acidification of the duodenal lumen stimulates the release of serotonin (also known as 5-hydroxytryptamine (5-HT)) by enteroendocrine cells, which in turn is involved in restoring the ionic balance. Serotonin-induced duodenal ion secretion is reduced in functional dyspepsia[87]. Secretory activity, among others, is maintained by bicarbonate flux into the lumen[88]; thus, the reduced ion secretion could indicate reduced bicarbonate secretion and, therefore, an impaired protection of the mucosa against high acid loads. Acute psychological stress can also increase duodenal mucosal permeability via mast cell activation mediated by corticotropin-releasing hormone[89].

Duodenal eosinophilia occurs in paediatric[90] and adult functional dyspepsia[91] and is probably linked to abnormal submucosal nerve structure and impaired responsiveness of submucosal neurons[92]. Eosinophils and mast cells that degranulate next to enteric neurons provide a mechanism for sensory excitation, which can be perceived by the enteric and central nervous systems[54]. Immune activation can still occur in the absence of eosinophilia; in this case, only the number of degranulated eosinophils is increased[93].

The levels of circulating pro-inflammatory and anti-inflammatory cytokines as well as small-intestinal-homing T cells (FIG. 1) were increased in patients with functional dyspepsia and correlated with symptom intensity and impaired gastric emptying, suggesting that gastric disturbances in functional dyspepsia could, in fact, be secondary to duodenal inflammation[94]. Together with data of increased duodenal eosinophilia[90,91,95,96], these studies have demonstrated that low-grade mucosal inflammation plays a key part in the pathogenesis of functional dyspepsia. Increased $CD4^+$ T helper 2 (T_H2) cell response is a potent producer of key cytokines (IL-4, IL-5 and IL-13) that are involved in recruiting and activating eosinophils and mast cells[97]. Eosinophil and mast cell numbers are increased in the submucosal plexus of the duodenum in patients with functional dyspepsia, and this finding was accompanied by a clear impairment of nerve excitability in the duodenal submucosal plexus — a decreased calcium response to depolarization and electrical stimulation — and could also implicate the central nervous system[54,92]. Blood-borne cytokines from the gut can also signal in the brain, thereby enabling cross-talk between the immune system, brain and gut[54].

Intestinal microbiota

There is contradictory evidence on the role in functional dyspepsia of small-intestinal bacterial overgrowth, a condition in which the bacterial population in the small intestine is greater than the physiological state and composed of species that are typical of the colon microbiota[98,99]. One study has linked the composition of the faecal microbiota to abdominal pain, and enterotypes (that is, types of gut microbiota populations) in which bacteria of the *Prevotella* genus were predominant correlated with less-intense pain[100]. In addition, the abundance of *Prevotella* spp. in the gastric microbiota was inversely associated with the severity of PDS symptoms in a small study[101]. Another small study analysed the composition of the gastric microbiota in patients with functional dyspepsia and reported that Bacteroidetes were more abundant than Proteobacteria compared with healthy controls, and Acidobacteria were absent[102], whereas another study described an altered duodenal microbiota with a predominance of species typically found in the oral microbiota[103]. These results warrant further studies on the role of the microbiota in functional dyspepsia.

Genetic contributions

In one twin study with 3,000 twin pairs[104], genetic modelling showed independent genetic effects in IBS

and gastro-oesophageal reflux disease, but no effect for functional dyspepsia. In this study, the estimates for the genetic variance were 22% for IBS, 13% for gastro-oesophageal reflux disease and 0% for functional dyspepsia. Although this finding might suggest that genetic factors do not play a relevant part in the manifestation of functional dyspepsia, in patients with severe functional dyspepsia (that is, with symptoms that are severe enough to negatively affect the quality of life (QOL)), symptoms of functional dyspepsia very frequently overlap with symptoms of IBS or gastro-oesophageal reflux disease[2,105]. Thus, data analysis that is restricted to patients with symptoms of functional dyspepsia probably only includes a skewed subpopulation that is not representative of the majority of patients. Indeed, other studies[106,107] found an increased risk of functional dyspepsia in relatives of patients with a confirmed diagnosis of functional dyspepsia or symptoms consistent with functional dyspepsia. These results clearly suggest a genetic component that contributes to the manifestation of symptoms in functional dyspepsia.

Various association studies have explored the correlation between functional dyspepsia and specific genotypes potentially related to gastrointestinal motility, sensitivity (including central processing of afferent inputs) or immune responses. Polymorphisms in the gene G protein subunit β3 (*GNB3*) affect a large number of functions, including adrenergic, serotonergic and immune functions[108], all of which are potentially important for the manifestation of functional dyspepsia. After an initial study that revealed an association between a specific *GNB3* genotype and functional dyspepsia on the basis of population-based patient cohorts[109], subsequent studies have confirmed this link[110–112]. Interestingly, some studies found this correlation only in patients without *H. pylori* infection[112] or with specific symptom manifestations, such as EPS[110]. This observation might suggest a specific interaction between *H. pylori* infection and *GNB3*. In a large, placebo-controlled trial[113] (which targeted the effects of treatment with a PPI on dyspeptic symptoms in patients with functional dyspepsia who were also treated with NSAIDs), there was a statistically significant link between a *GNB3* polymorphism and the intensity of dyspeptic symptoms. However, the *GNB3* genotype did not influence the response to therapy[114].

Serotonin plays a crucial part in the regulation of gastrointestinal secretion, motility, perception and central nervous system function[115,116], and several drugs used for treating functional dyspepsia target 5-HT receptors[117] (see below). In one study[118] of polymorphisms in candidate genes for different 5-HT receptors, cholecystokinin receptors and *GNB3* as well as in the promoters of the genes encoding cholecystokinin and the sodium-dependent serotonin transporter, only the role of *GNB3* in functional dyspepsia was confirmed.

Of note, a mutation in *SCN5A* (which encodes a sodium voltage-gated channel) that is associated with congenital long QT syndrome has also been associated with abdominal pain in patients with functional gastrointestinal disorders[119].

Psychosocial factors and brain mechanisms

Psychosocial factors constitute integral components of a biopsychosocial model of functional dyspepsia as a disorder of the brain–gut axis. These factors include both fairly long-lasting alterations in individual psychosocial functioning that result from psychiatric comorbidity or changes in personality (traits) and short-term psychological processes that are induced by momentary emotions or cognition (states)[120,121].

Psychosocial traits. The most prominent psychosocial trait in functional dyspepsia is psychiatric comorbidity. An increased prevalence of anxiety, depression, somatization and high neuroticism is well documented in patients with functional dyspepsia compared with healthy cohorts but could also be higher compared with patients with organic gastrointestinal or non-gastrointestinal disease[120,121,122]; comparison with patients with IBS remains inconclusive. Some evidence supports a higher prevalence of physical and emotional abuse, life event-related stress and dysfunctional coping styles in patients with functional dyspepsia compared with healthy controls[120]. Although psychopathology can be a consequence of chronic gastrointestinal symptom burden[22,39] and predicts health care-seeking behaviour[123] and reduced QOL[124,125] (see below), its role in the aetiology and pathophysiology of functional dyspepsia is unequivocally broader[33,120,121,126]. Several prospective studies[22,38,39,127] support a causal role of anxiety and/or depression in the aetiology, with recent findings suggesting differences according to the functional dyspepsia subgroup[128]. However, bi-directional interactions between chronic symptom burden and psychosocial factors are assumed to occur in all functional gastrointestinal disorders as well as in other medical conditions associated with chronic physical symptoms, especially pain. Furthermore, psychosocial trait factors can negatively affect the clinical course[125] and shape treatment outcomes in functional dyspepsia[129,130]. Finally, different traits reportedly correlate with altered gastric sensorimotor functioning in functional dyspepsia, including gastric sensitivity, accommodation, antral meal retention and gastric emptying[131–134].

Psychosocial states. The effects of negative mood[135,136], acute stress[137], placebo manipulations[138], hypnosis[139] or distraction[140] on oesophageal and gastric sensorimotor functions and visceral pain perception are well documented in healthy individuals. Although evidence remains scarce, emotional states and cognitive factors can modulate the pathophysiology and treatment of functional dyspepsia and could be altered in patients, in particular those with hypersensitivity. For example, state anxiety at the time of testing was associated with impaired gastric accommodation[133] and correlated negatively with gastric discomfort and pain thresholds as well as gastric compliance in patients with hypersensitive functional dyspepsia[141]. Mental stress reduced antral motility in healthy individuals, but not in patients with functional dyspepsia[142,143]. The neurobiological mechanisms underlying these effects remain

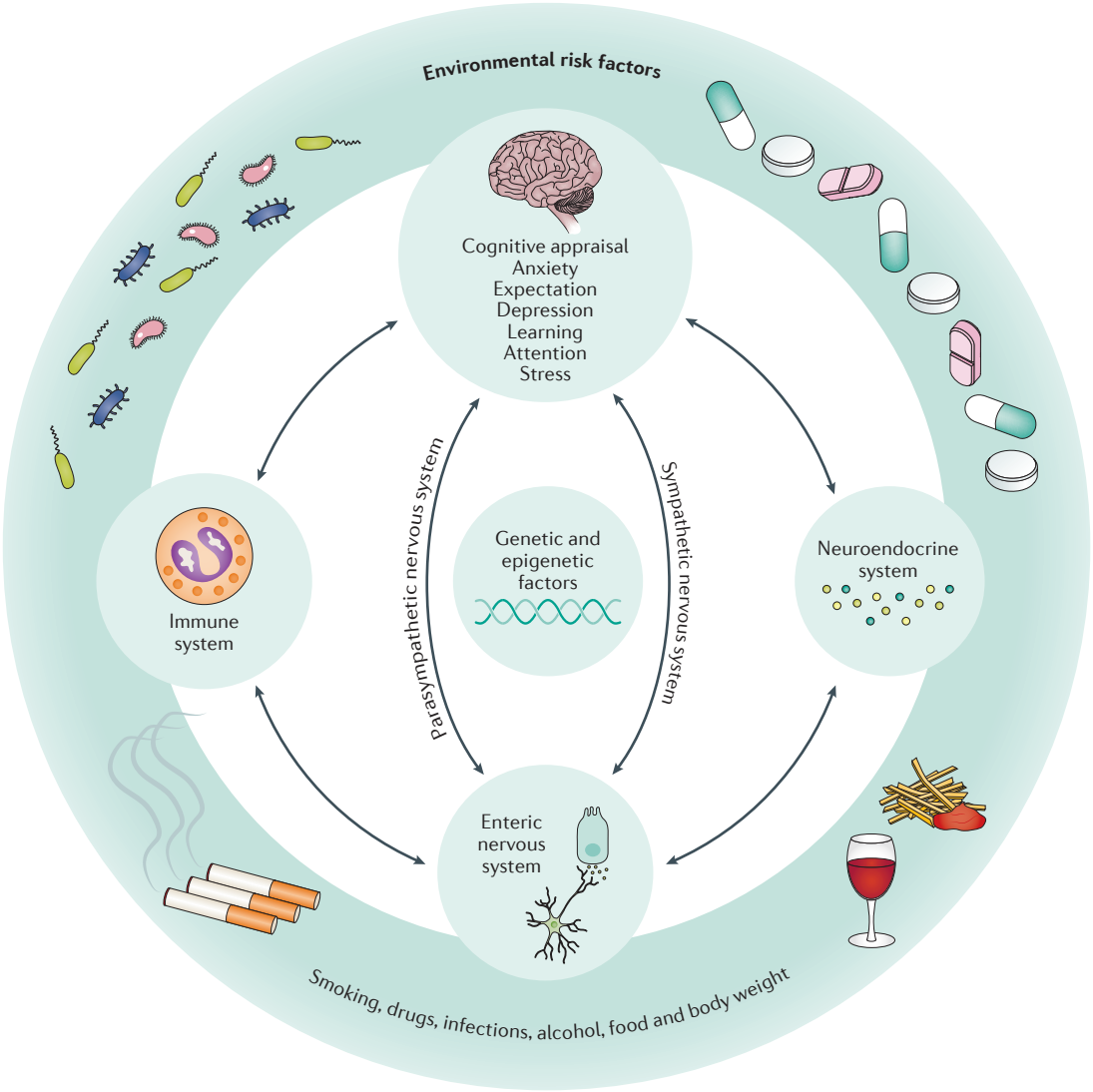

Figure 2 | **Proposed model for the interaction of factors involved in the generation of functional dyspepsia symptoms.** Different polymorphisms in genes involved in serotoninergic, adrenergic and immune functions have been explored and point to modulating effects on the different brain–gut and gut–brain pathways in the neuroendocrine and immune systems and the autonomic nervous system (including the sympathetic, parasympathetic and enteric nervous systems), although there are inconsistencies. These inconsistencies probably reflect differences in the inclusion criteria of patients with functional dyspepsia and controls, as well as differences in functional dyspepsia subtypes, geographical and ethnic variations and environmental factors, but could also reflect inadequate sample sizes. Nevertheless, genetic and epigenetic studies will help to pave the way for a paradigm shift of functional dyspepsia from a condition that is poorly defined by symptoms and functional abnormalities of uncertain aetiology and relevance to a disease that manifests because of the interaction of endogenous and exogenous (risk) factors. Genetic and epigenetic data potentially provide a conceptual framework that explains the individual susceptibility to developing functional dyspepsia in response to environmental challenges, for example, after an infectious or inflammatory intestinal event.

incompletely understood, especially in patients, but probably involve top-down neuroendocrine and autonomic pathways and could include mast cell-dependent effects on the permeability of the gastrointestinal epithelium[89,144,145] (FIG. 2).

Central nervous system mechanisms. Both trait and state psychosocial factors modulate the processing of visceral signals in the central nervous system and shape how symptoms are perceived and reported[146]. Visceral signals that originate from the upper gastrointestinal tract reach the brainstem and higher cortical areas via well-defined ascending pathways[144,145]. Multiple subcortical and cortical brain regions are dynamically involved in the conscious experience of aversive visceral sensations, which encompasses not only sensory-discriminative but also emotional, motivational and cognitive aspects. Brain imaging studies using functional MRI (fMRI), PET or other emerging imaging technologies[147] have identified alterations in several interconnected brain networks, including sensorimotor, emotional arousal and salience networks, in patients with functional

Box 2 | **Alarm symptoms***

- New-onset dyspepsia at >55 years of age
- Overt gastrointestinal bleeding, for example, melena (dark tarry stools) or haematemesis (vomiting blood)
- Dysphagia (difficulty swallowing), especially if progressive, or odynophagia (pain when swallowing)
- Persistent vomiting
- Unintentional weight loss
- Family history of gastric or oesophageal cancer
- Palpable abdominal or epigastric mass or abdominal adenopathy
- Evidence of iron-deficiency anaemia

*Based on data in REF. 37.

gastrointestinal disorders[145,148]. In patients with functional dyspepsia, altered neural activation in response to gastric distension or sham distension has been documented[149], which supports altered processing not only during noxious visceral stimulation but also during anticipation. Compared with healthy individuals, patients with functional dyspepsia also reveal alterations in the functional connectivity of brain regions at rest[149] and different structural brain measures, including regional grey matter volume and white matter microstructure[150–153]. Finally, emerging evidence supports alterations in central neurotransmitter systems, including the serotoninergic and endocannabinoid systems, in functional dyspepsia[154–156]. Of note, to date no study has compared functional dyspepsia with other functional gastrointestinal disorders or with psychiatric control groups. Thus, the specificity of brain alterations to functional dyspepsia is unclear. Although some measures of aberrant brain function or structure consistently correlate with gastrointestinal symptoms and/or visceral hypersensitivity, others are at least in part explained by psychiatric comorbidity. Psychological state factors, such as anxiety during scanning[157], also contribute to group differences. Overall, the number of brain imaging studies on evoked neural activation in patients with functional dyspepsia is currently too small to apply much-needed meta-analytical approaches that would allow researchers to assess the reliability, consistency and specificity of functional alterations in specific brain regions or networks and to define the contribution of psychosocial trait and state factors to dynamic alterations in the central processing of visceral signals.

Inflammation of the gastric and duodenal wall can not only sensitize the local gut wall but also result in spinal neural upregulation, that is, dorsal horn neurons become hypersensitive even to physiological stimuli and exhibit allodynia. Preliminary evidence for such central sensitization is provided by the observation that gastric distension activates the somatosensory and ventrolateral prefrontal cortex, but not the pregenual anterior cingulate[157]. Such a response pattern would suggest that arousal and anxiety have a role in perturbing pain modulation.

Finally, in patients with functional dyspepsia, the reduced stress-induced decrease in antral motility could be associated with decreased vagal tone, rather than increased sympathetic tone[142]. The reduced antinociceptive role of the vagus nerve[158], together with corticosterone-induced increased excitability of dorsal root ganglion neurons, as observed in rats[159], could be the underlying mechanism for stress-related gastric hypersensitivity.

Diagnosis, screening and prevention

Diagnostic criteria

As defined by Rome IV, functional dyspepsia is a medical condition that has substantial effects on the well-being of those affected[3]. Three main diagnostic categories are defined based on the predominant symptoms: PDS, characterized by meal-induced dyspeptic symptoms (such as postprandial fullness and early satiety, 69% of patients with functional dyspepsia), EPS (7%), in which epigastric pain or epigastric burning that do not exclusively occur after a meal are the main symptoms, and overlapping PDS and EPS (25%), characterized by meal-induced dyspeptic symptoms combined with epigastric pain or burning[160] (BOX 1). The classification into PDS, EPS or overlapping PDS and EPS is relevant to further determine the clinical management.

Clinical features and physical examination

The diagnosis of functional dyspepsia is based on clinical symptom definitions, recently reformulated and refined in the Rome IV criteria[3]. Patient history and clinical examination should search for alarm symptoms (BOX 2). In particular, patients with functional dyspepsia, especially more-severe cases referred to tertiary centres, could present with substantial weight loss. A large study in Belgium indicated that 16% of 636 patients with functional dyspepsia reported weight loss of >10 kg (REF. 161). Thus, when collecting the patient's medical history, clinicians should pay particular attention to this sign. Apart from epigastric discomfort upon palpation of the abdomen, physical examination does not generally reveal valuable diagnostic information in patients with functional dyspepsia. Palpation of an abdominal mass obviously prompts further diagnostic work-up. However, symptom definitions remain mostly vague and cannot reliably distinguish between organic and functional dyspepsia[37] (BOX 3; FIG. 3). Thus, in clinical practice, physicians should consider upper endoscopy to rule out organic causes of dyspepsia, especially in case of risk factors or alarm symptoms (BOX 2). The diagnostic value of ultrasonography imaging is less clear, unless the patient has features suggesting biliary pathology. As upper endoscopy is negative in >70% of patients presenting with dyspepsia (whether organic or functional), it is important to complement endoscopy with cross-sectional imaging (such as ultrasonography), particularly in patients with weight loss, to look for carcinoma, cholelithiasis (gallstones) or chronic pancreatitis. If an organic, systemic or metabolic cause is found and symptoms improve or resolve with targeted treatment, these patients are referred to as having secondary dyspepsia,

which includes patients who show long-term improvement after *H. pylori* eradication. If no identifiable explanation for the dyspeptic symptoms can be found, the patient is diagnosed with functional dyspepsia[3]. Other digestive symptoms (such as those from gastro-oesophageal reflux disease or IBS) can coexist with functional dyspepsia. Although patients with functional dyspepsia can experience vomiting, persistent vomiting suggests another underlying disorder and should prompt the physician to initiate further investigations to exclude an organic or metabolic cause. Similarly, pain that seems to be of biliary origin (that is, an intense, dull discomfort located in the right upper quadrant, epigastrium or (less often) substernal area that can radiate to the back (in particular the right shoulder blade)) should also be considered indicative of a condition other than functional dyspepsia.

Gas-related symptoms

Patients with functional dyspepsia frequently complain of excessive gas in the gut[162] (BOX 4), which can manifest as eructation (belching), sensation of excessive abdominal pressure (bloating), abdominal rumbling (borborygmi), abdominal girth increment (distension) and/or excessive flatulence. It is not clear whether these symptoms truly belong to the functional dyspepsia syndrome spectrum or whether they reflect the frequent overlap between functional dyspepsia and IBS. Symptom assessments and focus groups show that upper abdominal bloating is an important functional dyspepsia symptom; however, the role of flatulence is not as clear, and it could be considered a lower gut symptom.

Repetitive eructation. Epigastric fullness is often misinterpreted by patients as excessive gas in the stomach. In an attempt to release this gas, these patients inadvertently swallow air, which accumulates in the hypopharynx or the stomach and is finally released by belching with a sense of relief[163], thereby reinforcing the patients' conviction. The correlation between belching and epigastric fullness is supported by the fact that belching was more frequently reported by patients with functional dyspepsia with hypersensitivity to gastric distension[164]. Functional dyspepsia-associated belching usually resolves, or at least improves, with a clear pathophysiological explanation of the symptoms, and such oesophageal belching (also called aerophagia) has been removed from the Rome IV definition of functional dyspepsia.

Abdominal bloating. An experimental gas challenge test (high-rate exogenous gas infusion directly into the jejunum) has shown that patients with functional dyspepsia who complain of bloating have impaired handling of intestinal gas, that is, gas retention, abdominal symptoms or both[165]. However, studies using abdominal CT and MRI scanning in clinical conditions could not correlate abdominal symptoms with excessive intestinal gas in these patients, as in the majority of the patients the volume and distribution of intestinal gas were within the normal ranges[166,167]. Hence, the perception of abdominal bloating could be related to a poor tolerance of normal gut content.

Abdominal distension. A large proportion of patients with functional dyspepsia report visible abdominal distension after meals and attribute the distension to gas production in response to some offending foods[168]. Visible distension is frequently associated with a bloating sensation, but the reverse is not the rule. Patients who complain of postprandial distension indeed develop an increment in girth during the distension episodes compared with basal conditions, but the volume of gastrointestinal gas is by and large within the normal range[167]. Furthermore, this abnormal distension is produced by a paradoxical diaphragmatic contraction, which is associated with a relaxation of the anterior abdominal wall[169]. The abdominal walls can actively adapt to changes in the abdominal content and volume by modulating their muscle tone. In healthy individuals, an increase in the abdominal content is accommodated by relaxation and ascent of the diaphragm, intercostal muscle contraction and only minimal protrusion of the anterior wall. In patients with functional dyspepsia, the paradoxical response of the diaphragm and abdominal walls can be experimentally induced by ingestion of a challenge meal, for example, a mixed-nutrient liquid containing polyethylene glycol administered orally at 50 ml per min for as long as it is tolerated[168]. Interestingly, abdominal distension triggered by meal ingestion can be improved using behavioural techniques, for example, teaching the patients to control the activity of abdominothoracic muscles and correct the postural tone of the muscles; these data suggest that abdominal distension is a somatic manifestation of functional gastrointestinal disorders[170]. In these patients, the perception of gut symptoms triggers a conditioned somatic response with an abnormal postural tone of the abdominothoracic muscles that leads to distension. Although distension is generally considered a symptom of IBS, but not functional dyspepsia, assessments of patients with functional dyspepsia and especially focus groups indicate that it is an important functional dyspepsia symptom.

Box 3 | **Possible differential diagnoses of functional dyspepsia***

- Peptic ulcer disease (with or without infection with *Helicobacter pylori*)
- Gastro-oesophageal cancer
- Gallstones, sphincter of Oddi dysfunction, biliary dyskinesia or gallbladder cancer
- Drug-induced adverse effects (for example, NSAIDs, iron supplements, calcium antagonists, angiotensin-converting enzyme inhibitors, methylxanthines and glucocorticoids)
- Chronic pancreatitis or pancreatic cancer
- Parasitic infections (for example, *Giardia intestinalis* (also known as *Giardia lamblia*), *Strongyloides* spp. and *Anisakis* spp.)
- Hepatocellular carcinoma
- Chronic mesenteric ischaemia
- Crohn's disease
- Infiltrative diseases (for example, eosinophilic gastroenteritis and sarcoidosis)

*Based on data in REF. 37.

Laboratory tests

If an organic disease, which should be suspected particularly in the presence of alarm symptoms, has been excluded (mainly via upper endoscopy), additional testing in functional dyspepsia has limited added diagnostic value. If the prevalence of *H. pylori* is at least 10% (as it is in specific, at-risk populations such as, for example, elderly people and physicians)[171], it is recommended to test for *H. pylori* infection with either ^{13}C-urea breath-testing or stool antigen testing. This approach could also be considered as a first-line strategy, especially as these tests are non-invasive and accurate. However, the subgroup of patients with functional dyspepsia who have *H. pylori* infection is expected to become progressively smaller, as the prevalence of *H. pylori* infection is steadily declining, and only a small fraction of patients respond with persistent symptomatic improvement after *H. pylori* eradication.

Because delayed gastric emptying is considered a pathophysiological mechanism of functional dyspepsia[172,173], some experts advocate the assessment of this parameter in the diagnostic work-up. However, the correlation between gastric emptying and dyspeptic symptoms is still unclear, and treatment of delayed of gastric emptying with prokinetic drugs poorly correlates with symptomatic improvement[174]. Moreover, gastric emptying measurement is expensive and not widely available as a well-standardized test. Quantification of gastric emptying is, therefore, not advocated in the standard clinical management of functional dyspepsia[3]. Gastric emptying could be assessed by ultrasonography, but this approach requires expertise and is time-consuming; thus, it should be considered as a research tool only. Similar considerations apply for functional tests that assess gastric accommodation or hypersensitivity.

Management

Dietary adjustments and *H. pylori* eradication (in those who are infected) can be applied for the management of all patients with functional dyspepsia. When initiating pharmacotherapy, it is recommended to choose the agents on the basis of the Rome IV subdivision of functional dyspepsia in EPS, PDS and the overlapping group, to specifically treat the predominant symptoms of each subtype (FIG. 4; TABLE 1).

H. pylori *eradication*

H. pylori eradication treatment is advocated in all guidelines for patients with functional dyspepsia who are infected, as it has the potential to improve symptoms and control the risk of developing peptic ulcers and gastric cancer[5,175,176]. Symptom improvement in response to eradication occurs after 6–12 months and is more evident in patients with EPS than in patients

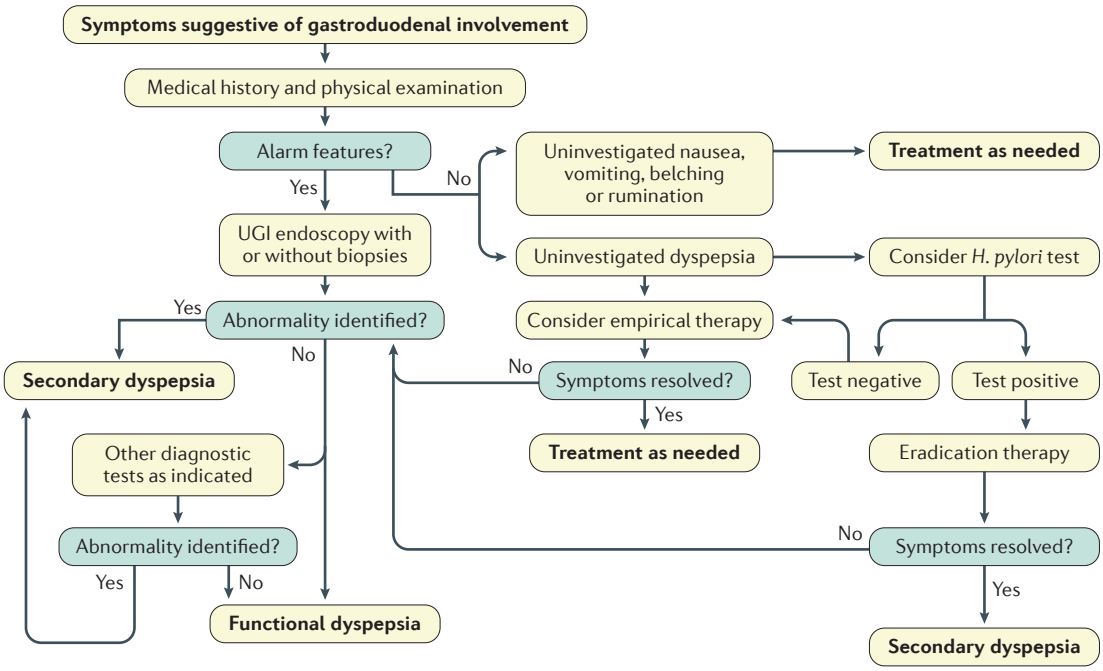

Figure 3 | **Diagnostic algorithm in functional dyspepsia.** Patients who present with symptoms suggestive of gastrointestinal involvement should receive physical examination and the physician should take an accurate medical history. If alarm features (BOX 2) are present, patients should undergo upper gastrointestinal (UGI) endoscopy. In the absence of alarm features, the physician should consider testing for *Helicobacter pylori* in high prevalence regions or start empirical treatment based on the predominant symptom profile. If symptoms persist, the physician should re-evaluate and consider further diagnostic steps, including UGI endoscopy (with or without concomitant biopsies or *H. pylori* testing) and ultrasonography of the abdomen, in particular if the patient has severe, intermittent episodes of pain. If no abnormalities are detected, the patient is diagnosed with functional dyspepsia and should be treated with an alternative treatment. If abnormalities are identified, the patient is diagnosed with secondary dyspepsia and should be treated accordingly. Adapted with permission from REF. 3, Elsevier.

with PDS[177]. The beneficial effect was most prominent in studies from Asia (possibly reflecting different pathogenicity features of *H. pylori* in Asia compared with western countries), and the number needed to treat (the number of patients in a clinical trial who need to be treated for one of them to benefit compared with a control condition) was estimated to be as high as 14 (REF. 53). Based on the Kyoto global consensus report, *H. pylori*-positive functional dyspepsia with a sustained response (>6–12 months) to eradication therapy is now referred to as *H. pylori*-associated dyspepsia and not functional dyspepsia[43].

Dietary management

The majority of patients with functional dyspepsia report that meal ingestion induces their typical symptoms, and dietary factors are increasingly recognized to play an important part in the generation of symptoms in functional dyspepsia. The division of functional dyspepsia into EPS and PDS[46] as part of the Rome III criteria formally acknowledged for the first time that functional dyspepsia (in particular PDS) is, at least in part, a disorder related to food ingestion *per se*, in which symptoms can be induced by specific foods or food components; that is, it is not simply a postprandial gastrointestinal motility disorder. Indeed, approximately two-thirds of patients report symptoms within 15–45 min of food ingestion[50,178]. Nevertheless, an understanding of how dietary factors induce dyspeptic symptoms and effective treatment strategies remain elusive.

Dietary patterns. Many patients with functional dyspepsia report early satiety and that, in particular, fatty foods trigger their typical symptoms; these observations could suggest that patients with functional dyspepsia might have reduced overall energy intake and body weight. However, both parameters vary substantially between patients[179,180]; the contribution of overweight to functional dyspepsia symptoms warrants consideration[32]. Although no major differences in meal size or frequency, energy intake or macronutrient consumption were observed between patients with functional dyspepsia and healthy controls, some studies have found that patients with functional dyspepsia tend to consume slightly smaller numbers of full meals and greater numbers of smaller meals and snacks[178,180–182] and have slightly lower mean energy and fat intakes[178] (although some patients have much larger intakes than healthy controls[178,183]).

Evidence indicates that overall meal-associated symptoms, fullness and bloating are correlated with energy and fat intakes[178], and in a population-based study, snacking (greater meal frequency) was associated with lower odds of postprandial fullness and early satiety[184]. It is possible (but this possibility has not been investigated yet) that differences in the timing of symptom onset after meal ingestion could relate primarily either to gastric distension (and, therefore, could occur more immediately) or to specific food components (for example, spices, gluten or fat, among others). Symptoms caused by specific foods could occur somewhat later, as gastric emptying, digestion and small-intestinal exposure would be needed. Thus, considering the temporal relationship between food ingestion and symptom onset could help to distinguish the primary cause of symptoms. However, it is important to recognize that, particularly in the case of lipids, symptoms could occur promptly after ingestion[185], as only very small amounts of fat might be required to induce marked symptoms in hypersensitive patients. Moreover, it seems that symptoms of fullness, bloating or nausea all occur within a similarly wide time frame after meal ingestion[178]. Much more research is required to delineate the relationship between temporal occurrence of functional dyspepsia symptoms and specific food components.

Food intolerances and potential underlying mechanisms. In addition to fatty foods, a range of other foods or food groups are frequently associated with functional dyspepsia symptoms by patients[179–182,186,187] (FIG. 5), but how they could contribute to the pathophysiological mechanisms of functional dyspepsia is under investigation. This diversity illustrates the challenges that researchers and clinicians face in their effort to identify causal links between specific dietary factors and dyspeptic symptoms, underlying mechanisms and potential interventions. Early satiety and intolerance of fatty foods could be related to gastrointestinal hypersensitivities to distension and/or small-intestinal fat[186]. Fermentable carbohydrates (namely, fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)) are poorly absorbed and have been shown to induce symptoms in IBS[188], and gluten intolerance, even in the absence of coeliac disease, needs to be considered. Dairy or lactose intolerances and hypersensitivity to sour, acid-secreting or irritant foods (for example, citrus, spices, coffee or alcohol) could also play a part. Protein-rich foods (such as meats) can contain hidden fat, not readily identified by patients. Specific immune responses to food proteins are also a possibility[86].

Box 4 | The role of intestinal gas

The amount of gas within the gut is determined by a complex and finely regulated homeostasis that involves the production, consumption and diffusion of gas between the intestinal lumen and the blood[235]. The total volume of intraluminal gas under normal conditions is 100–200 ml, evenly distributed in the different gut compartments: stomach, small bowel and ascending, transverse, descending and pelvic colon; accordingly, the largest pool of gas is located within the colon.
Gas input results from swallowing, chemical reactions, diffusion from blood and bacterial fermentation.
Gas output is achieved by eructation, adsorption into the blood, bacterial consumption and anal evacuation.
In humans, the stomach contains a small chamber of gas, which is introduced during swallowing, and the excess is eliminated by belching or passage into the intestine.
A role for gastric gas in functional dyspepsia has not been established.

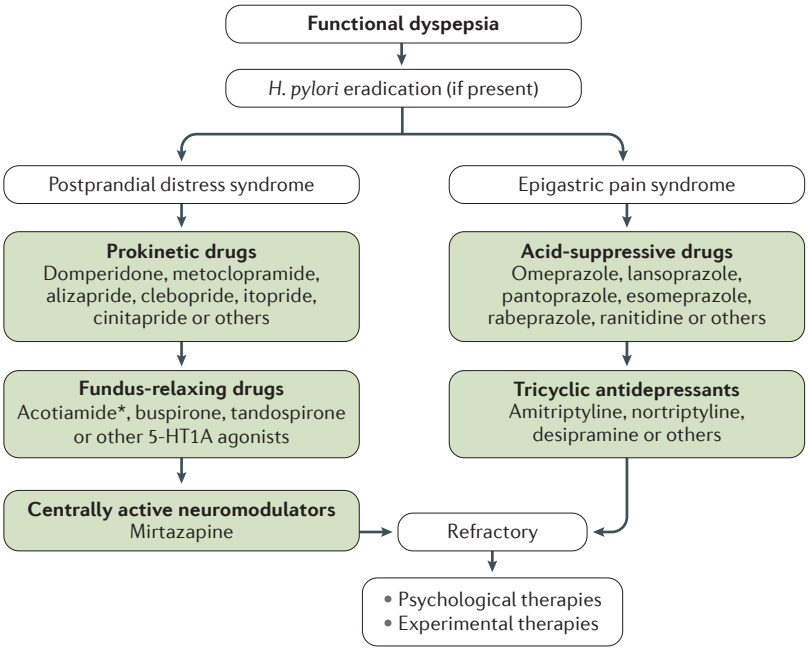

Figure 4 | **Treatment algorithm in functional dyspepsia.** On the basis of recent literature[3,175], with the exception of *Helicobacter pylori* eradication, the preferred treatment options depend on the subtype of functional dyspepsia (epigastric pain syndrome or postprandial distress syndrome; in patients with overlapping features, treatment should address the most prevalent symptoms)[3,175]. Although pharmacological therapy is considered in a large proportion of patients, drugs with established efficacy are lacking for patients with functional dyspepsia as a group[3,175]. The only approved drug for functional dyspepsia is acotiamide. However, several drugs could provide symptom control in subsets of patients, a finding that probably reflects the heterogeneous nature of the condition. This heterogeneity, the lack of objective biomarkers and the paucity of well-validated end points in clinical trials hamper effective drug development for functional dyspepsia. *If available. 5-HT1A, 5-hydroxytryptamine receptor 1A.

Dietary challenge studies and therapeutic interventions. Although some patients adjust their dietary habits in an attempt to alleviate symptoms[178,180], many patients do not[180–183], despite identifying certain foods as symptom triggers. With the exception of dietary fat[146,185,189], studies that applied blind challenge tests produced inconsistent outcomes[190,191], and causal links between specific foods and the induction of symptoms remain to be established. This is a highly challenging undertaking, given that functional dyspepsia is a multifactorial disorder with multiple dietary factors implicated and potential additional effects from cognitive factors[146,192]. Thus, future studies should systematically evaluate the role of specific trigger foods in large patient cohorts, thereby enabling meaningful subgrouping of patients, which also takes into account the possible underlying mechanisms. The outcomes of such studies could then help to design dietary intervention studies, which, if successful, could form the basis for new dietary treatment approaches that are cost-effective and largely devoid of major adverse effects.

Pharmacological treatment of PDS

Prokinetic drugs. The drugs in this heterogeneous class stimulate gastric smooth muscle contractions, are widely used in functional dyspepsia and have been proposed as first-line therapies for PDS[193]. Prokinetics (TABLE 1) include 5-HT receptor 4 (5-HT4) agonists, D(2) dopamine receptor antagonists and motilin receptor agonists, such as erythromycin. Evidence in the literature for their symptomatic benefit is often limited, and there are few high-quality studies[193].

Fundus-relaxing drugs. Impaired gastric accommodation can be targeted by 5-HT1A agonists and the muscarinic auto-receptor antagonist and acetylcholinesterase inhibitor acotiamide[193]. Studies have shown symptomatic benefit in PDS of the 5-HT1A agonists buspirone and tandospirone[194,195] (in particular for symptoms of early satiety, whereas no relationship between symptom improvement and the patient's anxiety status was observed) and acotiamide[196], a finding that led to the approval of acotiamide for functional dyspepsia treatment in Japan and India.

Centrally acting neuromodulators. Many, often small, studies have evaluated centrally acting neuromodulators in functional dyspepsia. The rationale is based on the frequent presence of psychiatric comorbidity as well as the hypothesis that visceral hypersensitivity contributes to symptom generation and could respond to centrally acting neuromodulators. These drugs are probably most effective for EPS (see below). However, through their effects on gastrointestinal motility, they could also exert therapeutic effects in PDS, as described for 5-HT1A agonists that act on gastric accommodation. The antidepressant mirtazapine, when taken at a low dose in the evening, has also shown efficacy for the treatment of early satiety and nausea in patients with functional dyspepsia with weight loss who had no clinically relevant depression or anxiety comorbidity[197].

Pharmacological treatment of EPS

Acid-suppressive drugs. Inhibition of acid secretion is the most frequently used first-line treatment in functional dyspepsia. Response rates are highest (up to 45%[198]) in patients with concomitant heartburn, a finding that suggests that gastro-oesophageal reflux disease is the primary indication[198]. Meta-analyses show significant benefit of PPIs, which are more effective than histamine H2 receptor antagonists after 4–8 weeks of standard therapy. As this analysis did not find dose-related improvements with dose escalation, increasing PPI doses in non-responding patients with functional dyspepsia does not seem to be warranted[198]. Patients with EPS are more likely to respond than patients with PDS[199].

Centrally acting neuromodulators. Centrally acting neuromodulators are overall superior to placebo in improving functional dyspepsia, and this effect could occur in the absence of major depressive or anxiety comorbidity[200]. However, the benefit was limited to antipsychotics (D(2) dopamine receptor antagonists) and tricyclic antidepressants (which are particularly effective in EPS[201]). Selective serotonin reuptake inhibitors and serotonin–noradrenalin reuptake inhibitors seem to have no beneficial effects, based on available studies[178,201].

Formal evidence of an effect of central neuromodulators on visceral hypersensitivity in functional dyspepsia is only available for levosulpiride[202] (TABLE 1).

Other therapies

Herbal therapies. Traditional herbal therapies often lack a clearly identified mechanism of action but have shown beneficial effects in clinical trials; however, these trials often had inconsistent methodological quality. The herbal drug preparation STW 5 (a composition of garden angelica root, milk thistle fruits, caraway fruits, greater celandine, bitter candy tuft, liquorice root, chamomile flowers, balm leaves and peppermint leaves) is one of the best-studied compounds. A meta-analysis that included the data of three randomized controlled trials showed that STW 5 decreased the severity of the most bothersome gastrointestinal symptoms compared with placebo without inducing serious adverse events[203]. In healthy volunteers, STW 5 enhanced gastric accommodation[204] and antral phasic contractions. Of note, one randomized clinical trial reported that STW 5 had an efficacy equivalent to that of a prokinetic drug (cisapride)[205]. Whether a combination of STW 5 with other drugs will be useful warrants investigation.

Rikkunshito, a Japanese Kampo herbal medicine, has also been studied in functional dyspepsia. Two placebo-controlled studies showed efficacy in improving symptoms such as epigastric pain[206] and postprandial fullness or early satiety[207]. This effect is associated with improved gastric accommodation and emptying and increased plasma levels of the appetite-regulating hormone ghrelin, which stimulates food intake and gastric motility[208,209].

Table 1 | **Summary of pharmacological therapies for patients with functional dyspepsia**

Drug or drug class	Mechanism of action	Target symptoms	Advantages	Adverse effects
Prokinetic agents				
Metoclopramide	5-HT receptor 4 agonist; D(2) dopamine receptor antagonist	Nausea, postprandial fullness and other PDS symptoms	Increases gastric motility	Extrapyramidal effects (movement disorders), including tardive dyskinesia and hyperprolactinaemia
Domperidone	D(2) dopamine receptor antagonist	Mainly nausea and PDS symptoms	Less frequent extrapyramidal effects compared with metoclopramide	QT interval prolongation
Alizapride	D(2) dopamine receptor antagonist	Mainly nausea and PDS symptoms	Comparable to domperidone	Extrapyramidal effects and hyperprolactinaemia
Clebopride	5-HT receptor 4 agonist, 5-HT receptor 3 antagonist; D(2) dopamine receptor antagonist	PDS symptoms and nausea	Increases gastric motility	Extrapyramidal effects and hyperprolactinaemia
Cinitapride	5-HT receptor 4 and 5-HT receptor 1 agonist; 5-HT receptor 2 and D(2) dopamine receptor antagonist	PDS symptoms	Increases gastric motility	Extrapyramidal effects
Itopride	Acetylcholinesterase inhibitor; D(2) dopamine receptor antagonist	Nausea and PDS symptoms	Additional effect on gastro-oesophageal reflux adverse events	Hyperprolactinaemia
Fundus-relaxing drugs				
Acotiamide	Acetylcholinesterase inhibitor; muscarinic auto-receptor antagonist	PDS symptoms	Improves accommodation and gastric emptying	Comparable to placebo
Buspirone	5-HT receptor 1A agonist	Early satiety and other PDS symptoms	Improves accommodation	Sedation and dizziness
Tandospirone	5-HT receptor 1A agonist	Early satiety and other PDS symptoms	Anxiolytic; probably also improves accommodation	Sedation and dizziness
Acid-suppressive drugs				
Proton pump inhibitors	Irreversible H^+/K^+ ATPase blockers	EPS symptoms, at standard doses	Can manage coexisting heartburn	Generally well tolerated
Centrally active neuromodulators				
Tricyclic antidepressants	Serotonin and noradrenaline reuptake inhibitor; muscarinic receptor antagonist; variable individual affinities for other receptors	EPS symptoms	Can decrease visceral sensitivity and improve comorbid anxiety and depression	Sedation, anticholinergic effects and weight gain
Levosulpiride	D(2) dopamine receptor antagonism	Nausea and EPS symptoms	Decreased sensitivity to gastric distension	Extrapyramidal effects, sedation, dizziness and hyperprolactinaemia
Mirtazapine	5-HT receptor 2, α2A adrenergic receptor, histamine H1 receptor and 5-HT receptor 3 antagonist	Early satiety, weight loss, nausea and other PDS symptoms	Allows weight regain	Sedation and weight gain

5-HT, 5-hydroxytryptamine; EPS, epigastric pain syndrome; PDS, postprandial distress syndrome.

Psychotherapy. In contrast to IBS, psychotherapy has rarely been tested in functional dyspepsia and has not been shown to be effective: only four controlled trials[210–213] were published until 2002 and an updated 2011 Cochrane analysis was withdrawn for unknown reasons. Three additional trials[214–216] were performed since the first Cochrane review, and all seven trials together covered the entire spectrum of psychotherapy options, but each technique was tested only in a single, small study (TABLE 2). Moreover, the patients included had a variety of functional dyspepsia symptoms and illness durations.

In all seven studies, the patients who received psychotherapy demonstrated some improvements with respect to gastrointestinal symptoms compared with the patients under standard medical care. These patients had better total symptom scores, reduced symptom severity and improved QOL, and the symptoms of their comorbid psychiatric conditions (such as anxiety, depression and somatization) also improved[211,215]. It is not clear whether the improvements in psychiatric symptoms are secondary to the alleviation of gastrointestinal symptoms or vice versa. However, most follow-up studies could not detect any differences between the two patient groups[216]. Additional limitations to the use of psychotherapy in functional dyspepsia are the lack of studies that directly compare different psychological approaches, focus on high-risk groups of patients (that is, who have a substantial psychiatric comorbidity) or focus on sex-related and culture-related issues that are involved in the development and course of functional dyspepsia as well as the lack of independent replication of findings (for example, for hypnotherapy).

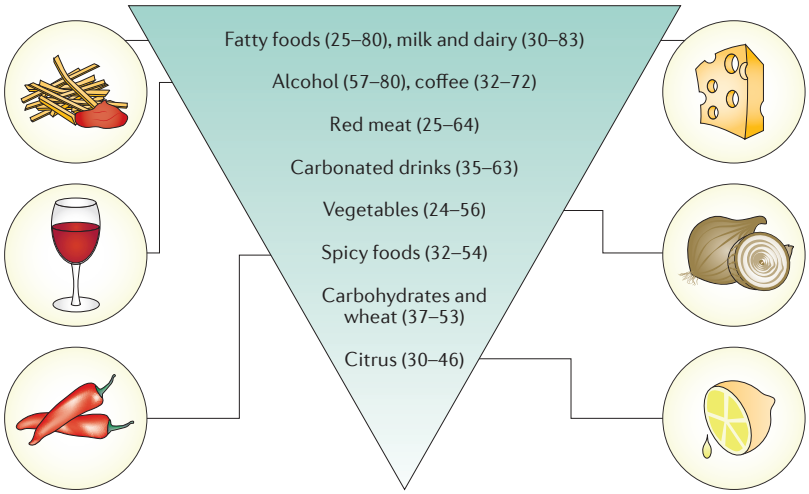

Figure 5 | **Foods and food groups frequently associated with symptom induction or exacerbation in functional dyspepsia.** Offending foods reported by patients with functional dyspepsia include fatty food (for example, fried food[179–181,187,191]), alcohol[179,180], dairy products[179,181], coffee[179–181], red meat[179,181], carbonated drinks[179–181,187], vegetables (including onion, cabbage, capsicum (peppers) and legumes[179–181,187]), spicy foods[180,181,187], carbohydrate-containing and wheat-containing foods (including pasta, bread, pastry, banana, sweets and cakes[179–181]) and citrus fruit, fruit juices and pickles[179–181]. Values in parentheses indicate the percentage of patients who report that specific food in association with symptoms.

Nevertheless, this poor empirical evidence could also indicate that — unlike in IBS[40] — either psychiatric comorbidity in functional dyspepsia is of secondary nature and waxes and wanes with functional dyspepsia symptom fluctuation (a hypothesis that contradicts some epidemiological findings, for example REFS 22,39) or the underlying causes of functional dyspepsia are predominantly, if not exclusively, peripheral in nature and, therefore, unresponsive to centrally targeted interventions, including psychotherapy.

Complementary and alternative therapies. Data on alternative therapies are also sparse. One complementary strategy is acupuncture. A meta-analysis of the data of two randomized controlled trials ($n = 58$) reported an improvement in QOL in patients who received acupuncture ($n = 58$) compared with those who received sham acupuncture (stimulation at non-defined points)[217]; however, in one study, symptoms were specifically reduced in the treatment group only[218], whereas in the other study, both groups reported alleviated symptoms[219]. Another meta-analysis that also included randomized controlled trials of low quality (because allocation concealment was inadequate in most studies, blinding was not rigorously applied or possible, or incomplete data were not thoroughly described) indicated a reduction in functional dyspepsia symptoms and an improvement in QOL after acupuncture compared with sham acupuncture[220]. Moreover, acupuncture might be superior to standard pharmacological treatment in alleviating early satiety and postprandial fullness[220]. Nonetheless, the authors acknowledged the need for randomized controlled trials of high methodological quality[220]. Lastly, traditional Chinese medicine has also been tested in functional dyspepsia as part of the 'liver–stomach disharmony syndrome'. A meta-analysis that included the data of 12 randomized controlled trials (involving ~1,000 patients overall) indicated that traditional Chinese medicine was more beneficial than prokinetic agents[221]. However, the poor methodological quality of these studies and the multitude of agents applied (for example, radix paeoniae, radix bupleuri, radix glycyrrhizae, rhizoma cyperi, fructus aurantii immaturus, fructus aurantii, *Citrus medica* var. *sarcodactylis* and pericarpium citri reticulatae) prevent from drawing any definitive conclusions.

Quality of life

The severity of functional dyspepsia symptoms (from mild to severe) does not reliably correlate with any specific biomarker. Thus, it is difficult to understand the day-to-day burden of functional dyspepsia on patients or their responsiveness to treatment. One way of understanding disease burden is to systematically assess QOL across multiple domains (for example, physical, mental and social).

The QOL of patients with functional dyspepsia can be assessed with generic or disease-specific measures. The most widely used generic measure, the Short Form 36-Item Health Survey (SF-36)[222], assesses eight dimensions of health: physical functioning, social functioning,

Table 2 | **Psychological therapies for functional dyspepsia**

Psychological treatment approach (reference)	Randomized controlled trial design (*n*; dropout rate)	Main findings
Group therapy with focus on relaxation techniques (Bates *et al.*[210])	Three arms, two control conditions and treatment (8 × 90-minute sessions) over 3 months (94; 48%)	• At the end of treatment: significantly decreased self-recorded pain intensity and number of pain occasions in the treatment arm compared with the control arms • At 1-year follow-up: no differences between treatment and control
Cognitive psychotherapy (Haug *et al.*[211])	Two arms, control (no treatment) and treatment (10 × 45–50-minute sessions) over 4 months (100; 14%)	• At 1-year follow-up: improvement in dyspeptic and psychological parameters in both arms. Greater reduction of dyspeptic symptoms, nausea, heartburn, diarrhoea and constipation and better scores on 'target complaints' (defined by the patients themselves, for example, anxiety, life stress or interpersonal problems) in the treatment arm compared with the control arm
Psychodynamic interpersonal psychotherapy (Hamilton *et al.*[212])	Two arms, control (supportive therapy) and treatment (7 sessions: the first 3 hours long, then 6 × 50-minute sessions) over 4 months (73; 19%)	• At the end of treatment: significantly better total symptom scores in both gastroenterologist's and patient's reports in the treatment arm compared with controls • At 1-year follow-up: similar symptomatic scores
Hypnotherapy (Calvert *et al.*[213])	Three arms, two control conditions (supportive therapy plus placebo medication or medical treatment alone) and treatment (12 × 30-minute sessions) over 4 months (126; 16%)	• At the end of treatment: symptom scores and QOL improved more in the treatment arm than in both control groups • At 1-year follow-up: improved symptoms in the treatment arm compared with both control groups
Flexibility coping psychotherapy (Cheng *et al.*[214])	Two arms, control (supportive psychotherapy) and treatment (6 × biweekly 60-minute sessions) over 3 months (75; 15%)	• At 1-year follow-up: participants in both arms showed improvements in coping flexibility and reductions in self-rated dyspeptic symptom severity. The self-rated dyspeptic symptom severity of the treatment arm was comparable with that of a healthy community sample
Core conflictual relationship theme-based psychoanalytic psychotherapy (Faramarzi *et al.*[215])	Two arms, control (standard medication) and treatment (standard medication plus psychotherapy with weekly 50-minute sessions) over 4 months (49; 12%)	• At the end of treatment: improved gastrointestinal symptoms, including heartburn, nausea, fullness, bloating, upper abdominal pain and lower abdominal pain in the treatment arm • At 1-year follow-up: improvement of depression, anxiety, somatization, interpersonal sensitivity, paranoid ideation and total symptom scores in the treatment but not the control arm
Cognitive behavioural therapy, with focus on coping (Orive *et al.*[216])	Two arms, control (medical therapy alone) and treatment (medical therapy plus psychotherapy with 8 × 50-minute group sessions and 2 × 50-minute individual sessions) over 10 weeks (76; 19%)	• At the end of treatment: better dyspepsia-related QOL and Glasgow Dyspepsia Severity Score in the treatment arm compared with the control arm • At 6-month follow-up: as at the end of treatment

QOL, quality of life.

role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, pain and self-rated health. Numerous studies have compared the QOL of patients with functional dyspepsia with that of patients with other medical conditions or healthy controls[223]. Data have yielded inconclusive findings, which is, to some extent, understandable, given the variations in methodology, approach, clinical samples, investigative teams and rigour. Some studies show no difference in QOL dimensions between patients with functional dyspepsia and controls[224], whereas others show significant QOL impairment in patients with functional dyspepsia[225]. Generic QOL measures are designed to facilitate comparison of disease burden across groups by focusing on dimensions common across diseases (BOX 5). Studies that used the Psychological General Well-Being Index, for example, found that the QOL among patients with functional dyspepsia was lower than that of patients without functional dyspepsia and comparable to that of patients with mild heart failure and postmenopausal women[226]. These conclusions should be interpreted judiciously, because any observed QOL impairment based on generic measures could be due, at least in part, to comorbidities and not necessarily to functional dyspepsia alone. In addition, generic measures are less sensitive for detecting smaller changes that would still be important to clinicians and outcome researchers because they do not assess sources of QOL that are specific to a given disease. This limitation has led to the development of QOL measures that are specific to functional dyspepsia, which take into account the specific aspects of the disease that are most meaningful to patients, including, for example, dietary problems, which are not featured in generic measures.

The more-narrow focus of functional dyspepsia-specific QOL measures makes it impossible to compare QOL scores of patients with functional dyspepsia with those of patients with other conditions or healthy controls, but these measures permit a more-precise characterization of disease burden. An example of this approach is the validated Nepean Dyspepsia Index[227], (and its abbreviated version[228]), which has been evaluated for clinically meaningful differences[229]. Finally, somatization[132] (multiple, stress-related symptoms of unknown origin) has been indicated as the most important risk factor for impaired QOL in patients with severe functional dyspepsia. A lifetime history of abuse and current depression influence QOL, but their effect is mediated by somatization[132,230].

Box 5 | **QOL instruments for functional dyspepsia**

Generic QOL measures

- Short Form 36-Item Health Survey (SF-36)[236] and Short Form 12-Item Health Survey[237]
- The Psychological General Well-Being Index (PGWBI)[238]
- EuroQol (EQ-5D)[239]
- General Health Questionnaire (GHQ-30)[240]
- Self-reporting Questionnaire (SRQ-20)[241]

Disease-specific QOL measures

- Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL)[242]
- Functional Digestive Disorders Quality of Life Questionnaire (FDDQL)[243]
- Nepean Dyspepsia Index (NDI)[227]
- Impact on day-to-day activity scale[224]
- Glasgow Dyspepsia Severity Score[244]
- Quality of Life in Reflux and Dyspepsia Questionnaire (QOLRAD)[245]
- Gastrointestinal Quality of Life Index (GIQLI)[246]

QOL, quality of life.

Outlook

Substantial progress has been made in our understanding of functional dyspepsia, and changes in therapeutic approaches will probably follow. The Rome IV consensus criteria, supported by the available evidence, determined that PDS and EPS are distinct entities, despite the overlap in clinical practice[3], and accumulating epidemiological and pathophysiological data support these conclusions[49,231].

Functional dyspepsia has traditionally been thought of as a motility or acid-related disorder, and these concepts have driven therapeutic interventions (prokinetics or acid-suppressive drugs, respectively) and randomized controlled trials, but this concept is now considered overly simplistic[3]. *H. pylori* infection plays a causal part in functional dyspepsia[3]. In patients with functional dyspepsia with slow gastric emptying or impaired fundic accommodation, it is conceivable that neuronal or muscle diseases — in addition to a preceding or concomitant infection or on their own — could explain the pathogenesis and acute onset[232]. Most excitingly, new information documenting subtle duodenal inflammation (notably, duodenal eosinophilia in a subset of patients with PDS), increased duodenal mucosal permeability, a disturbed duodenal microbiota, impaired enteric nervous system reflexes and evidence of systemic alterations (for example, increased levels of circulating cytokines and small-intestinal T cells) have shifted interest from the stomach to the upper small intestine[103].

As these new insights have accumulated, a new comprehensive disease model that integrates these apparently disparate observations has emerged, and the hypotheses presented are testable[37]. The model proposes that in individuals who are genetically predisposed, acute enteric infections or food antigens (for example, wheat) damage the intestinal barrier, thereby setting off an immune-mediated T_H2 cell response that activates the recruitment of eosinophils and, in some cases, release of mast cell mediators. This localized response, in turn, could further damage the intestinal barrier and result in a systemic immune response that could also induce extra-intestinal symptoms, such as anxiety or fatigue. In other cases, the activation of stress hormonal pathways might account for intestinal immune activation. As the antro-pyloro-duodenal region is a master regulator of the gastric functions that control the amounts of chyme (the semi-liquid mass of partly digested food) that reach the upper intestine, gastrointestinal dysfunction could in some cases be a secondary disturbance. However, there is also evidence that changes in mechanosensitivity and chemosensitivity are not triggered by infection or immune activation, and increased nociception could occur independently of immune activation. Thus, it is conceivable that functional dyspepsia could be further classified into different diseases based on different pathological mechanisms.

New treatment options are emerging based on these concepts, including anti-inflammatory drugs (at least in paediatric functional dyspepsia, montelukast (a cysteinyl leukotriene receptor 1 antagonist) has yielded promising results)[233] and non-absorbable antibiotics, such as rifaximin[234]. New data support the role of low-dose tricyclic antidepressants in functional dyspepsia, although the mechanism of action is unclear[200]. Although a role of the gut microbiota in functional dyspepsia is emerging, clinical studies to test this concept with therapeutics such as well-defined and specific probiotics have yet to be performed. It is a very exciting time in this field of research, as new answers seem at hand as our understanding intensifies.

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