Curr Treat Options Gastro (2021) 19:434–442
DOI 10.1007/s11938-021-00349-8

Stomach (P Malfertheiner, Section Editor)

Dyspepsia: Treatment Options Directed to Specific Targets

Gerald Holtmann, MD, PhD, MBA, FRACP, FRCP[1,2,3,*]
Ayesha Shah, FRACP[1,2,3]
Ronen Ben Jacob, MBBS[1,2]
Natasha Koloski, PhD[1,2,3]

Address
[1]Faculty of Medicine and Biomedical Sciences, Translational Research Institute, Department of Gastroenterology & Hepatology, Princess Alexandra Hospital, University of Queensland, Brisbane, QLD, Australia
[2]Department of Gastroenterology & Hepatology, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, QLD, Australia
[*,3]NHMRC Centre for Research Excellence in Digestive Health, Brisbane, Newcastle, Sydney, Melbourne, Australia
Email: g.holtmann@uq.edu.au

Published online: 27 May 2021

This article is part of the Topical Collection on *Stomach*

Keywords Functional gastrointestinal disorders · Functional dyspepsia · Breath tests · Antimicrobial · Tricyclic antidepressant

Abstract

Purpose of review Functional dyspepsia (FD) is a highly prevalent condition affecting up to 12% of the US population. We reviewed the recent medical literature regarding therapeutic interventions and aimed to identify guidance for the most appropriate/effective treatment in patients presenting with FD.

Recent findings There are a variety of therapeutic interventions that have recently demonstrated clinical efficacy in placebo-controlled trials and subsequent systematic reviews and meta-analysis. Pharmacologic interventions include acid inhibition, prokinetics, antimicrobial interventions, and central nervous system acting drugs (with emphasis on tricyclic antidepressant). In addition, available data support the use of specific herbal preparations. However, while treatments may substantially improve symptoms in individual patients, for all effective (pharmacologic and non-pharmacologic) interventions, the gain over placebo is only small consistent with the concept that FD actually is caused by a variety of underlying mechanisms and the occurrence of spontaneous fluctuation of disease activity that may amplify 'placebo responses'.

Summary FD is a condition with a most likely multifaceted pathophysiology. Thus, it is unlikely that a single pharmacologic intervention will provide cure or even symptom relief for a large proportion of patients. While the symptom-based categorisation of FD (postprandial distress syndrome and epigastric pain syndrome) is intuitive, it remains to be

established that the proposed categorisation translates into improved patient outcomes. The main problem is the considerable overlap of various symptom-based disease categories in severely affected patients. Considering the multifaceted pathophysiology of FD, it is likely that for patients with FD manifestations severely affecting quality of life, multiprofessional treatment approaches involving medical, mental health, and other allied health professionals are required.

Introduction

Chronic, unexplained gastrointestinal symptoms (also referred to as functional gastrointestinal disorders (FGID)) are highly prevalent in the population and are amongst the most frequent causes for consultation in primary care and care provided by specialist gastroenterologists [1]. Patients with 'unexplained' symptoms and concomitant alterations of pain associated with bowel habits are labelled as irritable bowel syndrome (IBS). Similarly, patients with upper gastrointestinal/epigastric symptoms that may or may not increase in intensity after a meal are labelled functional dyspepsia (FD) [2]. Patients with FD can be subdivided into patients with epigastric pain syndrome (EPS) or postprandial distress syndrome (PDS) [3]. While the prevalence of symptoms is slightly different in various geographic regions and according to different diagnostic criteria, 12% of the US population report symptoms consistent with functional dyspepsia [4•]. Due to the high prevalence in the population and the subsequent health care utilisation [5, 6, 7••], costs of FGID to patients and society are substantial [8–10].

In recent years, progress has been made to delineate and appreciate the multifaceted disease mechanisms of FGID including FD [11, 12]. Visceral hypersensitivity [13, 14] and abnormal gastric motility [15, 16] are thought to be the physiological abnormalities that directly cause FD symptoms. This has allowed to specify approaches that potentially can improve symptoms. Unfortunately, there is thus far no cure for patients with FD or other FGID. As a consequence, excess health care utilisation continues and this is explained by the poor response to existing treatments [17,18] and the subsequent dissatisfaction of FGID patients with their care [19]. The guiding principles for the management of patients with FD are summarised in Table 1.

Most clinical guidelines [20] recommend treatment with acid inhibitory drugs such as proton pump inhibitors and *H. pylori* eradication therapy if *H. pylori* is present. However, there is limited evidence that acid secretion is increased in FD patients [21], and while antimicrobial therapy initiated to eradicate *H. pylori* results in some studies in small improvements of symptoms [22•], it still remains questionable if the *H. pylori* prevalence is increased in patients with FD [23]. Many pathophysiologic studies now point towards the role of the duodenum for the control and coordination of gastroduodenal function [11, 24]. Disturbed duodenal mucosal integrity or low-grade mucosal inflammation [25••] have been associated with altered neuronal signalling [26] and systemic immune activation [27], and these alterations may be causally linked to alterations of gastric motor function [27] and ultimately to dyspeptic symptoms. The role of various luminal factors including bile acid [28], or specific dietary antigens [29•] in increasing the duodenal barrier defects [30] are implicated although causal relationships remain to be proven. On the other hand, the density of microbial colonisation of the duodenum is linked to the severity of meal-related symptoms [31••].

One of the potentially game-changing observations for our current concept of FGID is the link between symptoms and increased duodenal eosinophils and mast cells [32]. This has triggered speculations about potential pharmacologic treatments targeting eosinophils [33]. However, until results from appropriately designed clinical trials are available, the link between mucosal inflammation and symptoms simply might be an association and not necessarily causal.

While there is a strong focus on treatments that target GI function, it is important to acknowledge the relationship between FGIDs and psychological morbidity and the fact that this relationship is bidirectional, where in some patients, symptoms are driven by psychological issues (brain-gut), while in others, psychological health is affected by GI symptoms (gut-brain) [34, 35]. The role

Table 1. Management principles in functional dyspepsia

1. Determine the expectations and communicate realistic goals to the patient
2. Ensure that the diagnosis is established and address any diagnostic ambiguity. Confirm or establish, a positive clinical diagnosis based on the history and physical examination. Communicate this clearly to the patient.
3. Avoid repetitive, low value testing without clinical indication.
4. Empower patient to manage their symptoms by life-style interventions.
5. Explore dietary modification (small meals, low-fat diet, small meals, split ingestion of solids and liquids, identify and avoid foods that precipitate symptoms).
6. Explore specific diets (e.g. FODMAP, gluten-free diet)
7. Prescribe medications targeting the main symptoms. Define when medication can be discontinued (avoid permanent medical therapy) and treat on demand.
8. Consider cognitive behavioural therapy for severe cases.
9. Develop follow-up plan.

of brain-gut and gut-brain interactions should be examined whether patient subtyping based upon psychological comorbidities can predict response to treatments targeting brain-gut vs. gut-brain disease.

Recent findings

Targeting diet

Worldwide the market for gluten-free products is growing rapidly and producers market these products with the claim that gluten-free products are helpful in managing digestive disorders. A recent systematic review and meta-analysis [29•] revealed that wheat-containing foods were implicated in the induction of FD symptoms in six studies. On the other hand, recent studies exploring gluten-free diets and gluten exposure in patients reporting intolerance to gluten in the absence of celiac disease revealed inconclusive results [36]. There was no clear association between symptoms and the dose of gluten, with higher doses of gluten appeared to be better tolerated as compared to the small doses of gluten [36]. This may suggest that gluten is not the (sole) culprit for digestive symptoms after consumption of wheat or similar grains. Indeed, a systematic review [37••] revealed that the prevalence of non-celiac gluten sensitivity (NCGS) after gluten re-challenge is low, and the percentage of relapse after a gluten- or a placebo-challenge is similar. While this argues against the use of gluten-free or gluten-restricted diets for the treatment of FD, this may not rule out that other ingredients of wheat or similar grains such as Amylase-Trypsin-Inhibitors that can be targeted may cause symptoms in FD and other FGID [38•]. Furthermore, other foods reported as inducing symptoms were high in either natural food chemicals or high in fermentable carbohydrates. The consumption of caffeine was associated with FD in four studies, while the association with alcohol was not inconclusive [29•].

Targeting gastrointestinal motility

Abnormal gastric accommodation and alterations of gastric emptying are considered by many to play a key role for the manifestation of symptoms in FD patients. Thus, prokinetics are widely used in many countries for the treatment of FD. Interestingly the most recent systematic review and meta-analysis [39] concluded that due to low, or very low, quality of evidence, it was impossible to determine whether prokinetics are effective in the treatment of functional dyspepsia. This might be more a reflection of the constantly changing disease definitions and refinements of trial requirements rather than lack of clinical evidence.

While delayed gastric emptying might be the cause of symptoms in some patients, others may experience symptoms due to accelerated gastric emptying. In a recent elegant study by Brandler et al, the naturally occurring hormone secretin delayed gastric emptying of solids without affecting gastric accommodation, satiation, or other upper gastrointestinal hormones, or postprandial symptoms [40]. Based upon this, it is speculated that in FD patients with rapid gastric emptying (an estimated 20% of FD patients), stimulation of the secretin receptor could be of benefit.

Peppermint oil is a calcium channel blocker and thus may modulate smooth muscle contraction of the gastrointestinal tract. A recently published randomised controlled trial observed in FD patients a significant gain over placebo for a combination of peppermint oil and caraway [41•]. Similarly, a recent systematic review demonstrated that peppermint oil is also beneficial in IBS patients [42••]. These data are now complemented by a systematic review of peppermint oil in combination with caraway as a treatment for patients with FD [43]. While it might be speculated that effects of peppermint oil are mediated by effects on the smooth muscles (e.g. causing fundic relaxation and delaying gastric emptying), there are now data suggesting that peppermint (Mentha piperita) — an essential oil with high levels of menthol/menthone and characteristic in vitro cholinergic inhibitory, calcium regulatory, and GABAA/nicotinic receptor binding properties — modulated performance in cognitive tasks [44•]. Thus, it might be speculated that peppermint oil also has central nervous system (CNS) effects that contribute to the clinical effects.

Targeting gastric acid secretion

For many years, acid inhibition primarily with proton pump inhibitors (PPI) has been considered as one of the pillars of FD therapy. Indeed, the most recent systematic review and meta-analysis [45] provide further evidence that '…PPIs are effective for the treatment of FD, independent of the dose and duration of treatment as compared to placebo..'. PPIs may be slightly more effective than prokinetics for the treatment of FD; however, the evidence is scarce. However, it remains open if PPI are superior to prokinetics since trials directly comparing PPIs and prokinetics are difficult to interpret as they are potentially at risk of bias. In addition, there is emerging evidence that therapy with PPI may alter the microbial colonisation in the small intestine and increases the risk of small intestinal bacterial overgrowth [46•] and may result in IBS-type symptoms.

Targeting mucosal inflammation

Micro-inflammation in the form of local immune cell infiltration, particularly eosinophils and mast cells, has been observed in patients with FD [47] and might be linked to the manifestation of the gastrointestinal symptoms. While it is speculated that this inflammation is a reflection of an auto-immune process and treatments that specifically target this immune process might be beneficial have been speculated [33], a recent study was not able to identify a link between eosinophils and FD but duodenal eosinophils were associated with *H. pylori* [48].

Targeting the gastrointestinal microbiome

For many years, antibiotic therapy has been used in patients with FD for the eradication of gastric *H. pylori* infections. While this antimicrobial approach is widely used in patients with FD with concomitant *H. pylori* infection, systematic reviews and meta-analysis reveal only a small (but statistically significant) benefit [22•]. While epidemiologic studies have questioned the role of *H. pylori* for the manifestation of symptoms in otherwise health subjects (e.g. blood donors) [23], the effect of antimicrobial therapy also could occur unrelated to *H. pylori*. Indeed, antimicrobial therapy in FD patients without *H. pylori* utilising the non-absorbable antibiotic rifaximin improves symptoms in patients with fFD [49••].

While recent data suggest that the density of bacterial colonisation in the small intestine is linked to meal-related symptoms and the response to a standardised nutrient challenge [31••, 50•], the effect of antimicrobial therapy utilising the non-absorbable antibiotic rifaximin might be mediated by a reduction of the bacterial load of the duodenum/small intestine. However, thus far, the effect of antimicrobial therapy on visceral sensory functions has not been studied.

Targeting the gastrointestinal microbiome cannot only be achieved by antibiotic therapy, but prebiotics or probiotics may also alter the gastrointestinal microbiome. A recent systematic review and meta-analysis examined the available data on the efficacy of prebiotics and probiotics for FD [51•]. Five RCTs were suitable for inclusion and the relative risk of FD symptoms improving with probiotics or probiotics vs placebo was 1.15 (95% CI 1.01–1.30). Thus, the authors concluded that probiotics and prebiotics appeared effective treatments for FD while no firm conclusion in relation to individual species and strains could be drawn.

Acupuncture as treatment for functional dyspepsia

Acupuncture or electroacupuncture (EA) is used for the treatment of patients with FD. Analysing eight studies that explored effects of acupuncture and EA on gastric motility, gastric accommodation, mental status, gastrointestinal hormones, central and autonomic functions, symptoms, and quality of life, the authors concluded that the data support the potential use of acupuncture and EA. However, the authors of the systematic review and meta-analysis [52] acknowledged that high-quality studies with well-planned designs are lacking and thus more credible evidence is required before acupuncture can be accepted as a routine treatment for FD.

Herbal therapies

Herbal therapies are frequently used in some regions of the world while the efficacy of herbal medicines for FGID including IBS and FD is still controversial and there considerable differences in regulatory approaches taken in different jurisdictions to ensure safety and efficiency of herbal preparations used for the treatment of patient with FD and other FGID [53]. Regarding efficacy, a recent systematic review with meta-analysis [54] explored the efficacy of a variety of herbal therapies in a variety of FGIDs and identified 49 trials. Subgroup analysis found that herbal therapies were better than placebo in alleviating symptoms for FD (RR = 1.50, 95% CI 1.32–1.69).

Targeting the CNS

In systematic reviews and meta-analyses, tricyclic antidepressant (TCA) but not serotonin reuptake inhibitors (SSRI) are effective for the treatment of FD [55], but antidepressants were also associated with more adverse events compared with placebo. While TCA improve dyspeptic symptoms, a recent publication reveals that the symptom response to a standardised nutrient challenge is improved while gastric emptying remains unchanged [56••]. Interestingly, the beneficial effects of low-dose TCA occur even in patients not responding to PPI or prokinetics [57].

Summary

While in recent years progress has been made to delineate and appreciate the multifaceted disease mechanisms of FD [11, 12], there is as yet no cure for patients with these conditions. As a consequence, treatment is applied in a trial-and-error fashion and excess health care utilisation continues to be high as a consequence of poor response to existing treatments [17,18], resulting in dissatisfaction of FD patients with their care [19]. Patients with FD are categorised into patients with EPS and PDS. However, there is very little evidence that this categorisation has translated in improved patient outcomes. The main reason for this might be that patients with severe manifestations of FD present with an overlap of FD and IBS [58•] and an overlap of PDS and EPS. Moreover, subtyping FD patients by brain-gut and gut-brain order of incidence may also offer better treatment responses.

To meet patient's needs, systematic approaches are required to translate the knowledge of the multifaceted pathophysiology into targeted interventions to control symptoms and ultimately cure patients affected by FD and similar FGID. To achieve real progress, it is most likely insufficient to simply assess the effect of a specific treatment on symptoms or quality of life. It is rather required to simultaneously study whenever possible the influence of a specific treatment on relevant disease mechanisms that cause symptoms and the symptom response. Thus, if we acknowledge that visceral sensory function may play a role for the manifestation of symptoms, visceral sensory function testing should be routinely incorporated into clinical studies that explore treatment effects.

As FD is a condition with a multifaceted pathophysiology, it is extremely unlikely that a single treatment will be the solution for large cohorts of patients. Instead it is to be expected that integrated research and clinical care approaches driven by multiprofessional teams involving medical, mental health, and other

allied health specialists are required to address the thus far unmet patient needs and initial results of these treatment approaches are promising [59, 60].

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Koloski NA, Talley NJ, Boyce PM. Epidemiology and health care seeking in the functional GI disorders: a population-based study. Am J Gastroenterol. 2002;97:2290–9.
2. Tack J, Drossman DA. What's new in Rome IV? Neurogastroenterol Motil. 2017;29.
3. Talley NJ, Walker MM, Holtmann G. Functional dyspepsia. Curr Opin Gastroenterol. 2016;32:467–73.
4.• Aziz I, Palsson OS, Törnblom H, et al. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study. Lancet Gastroenterol Hepatol. 2018;3:252–62

Epidemiologic FD data utilising the current Rome criteria.

5. Koloski N, Jones M, Walker MM, et al. Population based study: atopy and autoimmune diseases are associated with functional dyspepsia and irritable bowel syndrome, independent of psychological distress. Aliment Pharmacol Ther. 2019;49:546–55.
6. Boyce PM, Talley NJ, Burke C, et al. Epidemiology of the functional gastrointestinal disorders diagnosed according to Rome II criteria: an Australian population-based study. Intern Med J. 2006;36:28–36.
7.•• Sperber AD, Bangdiwala SI, Drossman DA, et al. worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. Gastroenterology. 2020;

Epidemiologic and disease burden data utilising the current Rome criteria.

8. Cash BD, Sullivan D, Barghout V. Total cost of IBS: Employer and managed care perspective. Am J Manag Care. 2005;1.
9. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. Health Qual Life Outcomes. 2017;15:35.
10. Buono JL, Mathur K, Averitt AJ, et al. Economic Burden of irritable bowel syndrome with diarrhea: retrospective analysis of a U.S. commercially insured population. J Manag Care Spec Pharm. 2017;23:453–60.
11. Enck P, Azpiroz F, Boeckxstaens G, et al. Functional dyspepsia. Nat Rev Dis Primers. 2017;3:17081.
12. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2016;1:133–46.
13. Holtmann G, Goebell H, Talley NJ. Gastrointestinal sensory function in functional dyspepsia. Gastroenterology. 1995;109:331.
14. Holtmann G, Gschossmann J, Buenger L, et al. Do changes in visceral sensory function determine the development of dyspepsia during treatment with aspirin? Gastroenterology. 2002;123:1451–8.
15. Bisschops R, Tack J. Dysaccommodation of the stomach: therapeutic nirvana? Neurogastroenterol Motil. 2007;19:85–93.
16. Park SY, Acosta A, Camilleri M, et al. Gastric motor dysfunction in patients with functional gastroduodenal symptoms. Am J Gastroenterol. 2017;112:1689–99.
17. Talley NJ, Holtmann G, Walker MM. Therapeutic strategies for functional dyspepsia and irritable bowel syndrome based on pathophysiology. J Gastroenterol. 2015;50:601–13.
18. Chey WD, Maneerattaporn M, Saad R. Pharmacologic and complementary and alternative medicine therapies for irritable bowel syndrome. Gut Liver. 2011;5:253–66.
19. Linedale EC, Shahzad MA, Kellie AR, et al. Referrals to a tertiary hospital: a window into clinical management issues in functional gastrointestinal disorders. JGH Open. 2017;1:84–91.
20. Moayyedi P, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017;112:988–1013.
21. Nyrén O. Secretory abnormalities in functional dyspepsia. Scand J Gastroenterol Suppl. 1991;182:25–8.
22.• Du LJ, Chen BR, Kim JJ, et al. Helicobacter pylori eradication therapy for functional dyspepsia: systematic review and meta-analysis. World J Gastroenterol. 2016;22:3486–95

Most recent systematic review and meta-analysis on the effects of H. pylroi eradication in FD.

23. Holtmann G, Goebell H, Holtmann M, et al. Dyspepsia in healthy blood donors. Pattern of symptoms and

association with Helicobacter pylori. Dig Dis Sci. 1994;39:1090–8.
24. Holtmann G, Shah A, Morrison M. Pathophysiology of functional gastrointestinal disorders: a holistic overview. Dig Dis. 2017;35(Suppl 1):5–13.
25.•• Walker MM, Talley NJ. The role of duodenal inflammation in functional dyspepsia. J Clin Gastroenterol. 2017;51:12–8
Mucosal inflammation reflected by increased eosinophils disease mechanism in FD.
26. Feinle-Bisset C. Upper gastrointestinal sensitivity to meal-related signals in adult humans - relevance to appetite regulation and gut symptoms in health, obesity and functional dyspepsia. Physiol Behav. 2016;162:69–82.
27. Liebregts T, Adam B, Bredack C, et al. Small bowel homing T cells are associated with symptoms and delayed gastric emptying in functional dyspepsia. Am J Gastroenterol. 2011;106:1089–98.
28. Beeckmans D, Riethorst D, Augustijns P, et al. Altered duodenal bile salt concentration and receptor expression in functional dyspepsia. United European Gastroenterol J. 2018;6:1347–55.
29.• Duncanson KR, Talley NJ, Walker MM, et al. Food and functional dyspepsia: a systematic review. J Hum Nutr Diet. 2018;31:390–407
Comprehensive review of the potential role of varies dietary factors for the manifestation of FD. Provides a conceptual framework for dietary interventions.
30. Xu C, Gu K, Yasen Y, et al. Efficacy and safety of celecoxib therapy in osteoarthritis: a meta-analysis of randomized controlled trials. Medicine (Baltimore). 2016;95:e3585.
31.•• Zhong L, Shanahan ER, Raj A, et al. Dyspepsia and the microbiome: time to focus on the small intestine. Gut. 2017;66:1168–9
First clinical study that explored symptoms and the density of bacterial colonisation in the duodenum.
32. Walker MM, Warwick A, Ung C, et al. The role of eosinophils and mast cells in intestinal functional disease. Curr Gastroenterol Rep. 2011;13:323–30.
33. Hua S, Cook D, Walker MM, et al. Pharmacological treatment of eosinophilic gastrointestinal disorders. Expert Rev Clin Pharmacol. 2016;9:1195–209.
34. Koloski NA, Jones M, Talley NJ. Evidence that independent gut-to-brain and brain-to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: a 1-year population-based prospective study. Aliment Pharmacol Ther. 2016;44:592–600.
35. Koloski NA, Jones M, Kalantar J, et al. The brain–gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. Gut. 2012;61:1284–90.
36. Roncoroni L, Bascuñán KA, Vecchi M, et al. Exposure to different amounts of dietary gluten in patients with non-celiac gluten sensitivity (NCGS): an exploratory study. Nutrients. 2019;11.
37.•• Lionetti E, Pulvirenti A, Vallorani M, et al. Re-challenge studies in non-celiac gluten sensitivity: a systematic review and meta-analysis. Front Physiol. 2017;8:621
The data suggest that factors other than just gluten play a role for the now highly prevalent NCWS.
38.• Calasso M, Francavilla R, Cristofori F, et al. New protocol for production of reduced-gluten wheat bread and pasta and clinical effect in patients with irritable bowel syndrome: a randomised, double-blind, crossover study. Nutrients. 2018;10:1873
Practical guidance for specific dietary interventions.
39. Pittayanon R, Yuan Y, Bollegala NP, et al. Prokinetics for functional dyspepsia. Cochrane Database Syst Rev. 2018;10:Cd009431.
40. Brandler J, Miller LJ, Wang XJ, et al. Secretin effects on gastric functions, hormones and symptoms in functional dyspepsia and health: randomized crossover trial. Am J Physiol Gastrointest Liver Physiol. 2020;318:G635–g645.
41.• Rich G, Shah A, Koloski N, et al. A randomized placebo-controlled trial on the effects of Menthacarin, a proprietary peppermint- and caraway-oil-preparation, on symptoms and quality of life in patients with functional dyspepsia. Neurogastroenterol Motil. 2017;29
Prospective randomised trial testing the effect of a fixed combination with peppermint-oil on FD symptoms.
42.•• Alammar N, Wang L, Saberi B, et al. The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. BMC Complement Altern Med. 2019;19:–21
Systematic review support the conclusion that treatment with peppermint oil provides benefits in FGID patients.
43. Li J, Lv L, Zhang J, et al. A combination of peppermint oil and caraway oil for the treatment of functional dyspepsia: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2019;2019:7654947.
44.• Kennedy D, Okello E, Chazot P, et al. Volatile terpenes and brain function: investigation of the cognitive and mood effects of Mentha × Piperita L. essential oil with in vitro properties relevant to central nervous system function. Nutrients. 2018;10:1029
Peppermint oil acts as a smooth muscle relaxant. This study suggests that peppermint oil also has CNS effects that may contribute to the clinical effects.
45. Pinto-Sanchez MI, Yuan Y, Hassan A, et al. Proton pump inhibitors for functional dyspepsia. Cochrane Database Syst Rev. 2017;11:Cd011194.
46.• Shah A, Talley NJ, Jones M, et al. Small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis of case-control studies. Am J Gastroenterol. 2020;115:190–201
Alterations of bacterial colonisation of the small intestine are linked to FGID. However, there are also considerable methodological challenges that may impact the ability to interpret the available data.
47. Du L, Chen B, Kim JJ, et al. Micro-inflammation in functional dyspepsia: a systematic review and meta-analysis. Neurogastroenterol Motil. 2018;30:e13304.

48. Leite C, Mazzoleni LE, Uchoa DM, et al. Association of duodenal eosinophilic infiltrate with Helicobacter pylori infection, but not with functional dyspepsia. Arq Gastroenterol. 2020;57:74–8.
49.•• Tan VP, Liu KS, Lam FY, et al. Randomised clinical trial: rifaximin versus placebo for the treatment of functional dyspepsia. Aliment Pharmacol Ther. 2017;45:767–76
First prospective randomised, blinded trial that demonstrated a beneficial effect of antimicrobial therapy in H. pylori negative subjects.
50.• Shah A, Talley NJ, Koloski N, et al. Duodenal bacterial load as determined by quantitative polymerase chain reaction in asymptomatic controls, functional gastrointestinal disorders and inflammatory bowel disease. Aliment Pharmacol Ther. 2020;52:155–67
Novel methodology to quantify bacterial load in the small intestine to guide antimicrobial therapy.
51.• Zhang J, Wu HM, Wang X, et al. Efficacy of prebiotics and probiotics for functional dyspepsia: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99:e19107
Most recent comprehensive Ssystematic review and meta-analysis of prebiotics- and probiotics in FD.
52. Zhang J, Liu Y, Huang X, et al. Efficacy comparison of different acupuncture treatments for functional dyspepsia: a systematic review with network meta-analysis. Evid Based Complement Alternat Med. 2020;2020:3872919.
53. Holtmann G, Schrenk D, Madisch A, et al. Use of evidence-based herbal medicines for patients with functional gastrointestinal disorders: a conceptional framework for risk-benefit assessment and regulatory approaches. Dig Dis. 2020;38:269–79.
54. Tan N, Gwee KA, Tack J, et al. Herbal medicine in the treatment of functional gastrointestinal disorders: a systematic review with meta-analysis. J Gastroenterol Hepatol. 2020;35:544–56.
55. Lu Y, Chen M, Huang Z, et al. Antidepressants in the treatment of functional dyspepsia: a systematic review and meta-analysis. PLoS One. 2016;11:e0157798.
56.•• Lacy BE, Saito YA, Camilleri M, et al. Effects of antidepressants on gastric function in patients with functional dyspepsia. Am J Gastroenterol. 2018;113:216–24
Elegant, large clinical study linking gut function (gastric emptying) and symptom improvement in FD during treatment with tricyclic antidepressant.
57. Cheong PK, Ford AC, Cheung CKY, et al. Low-dose imipramine for refractory functional dyspepsia: a randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2018;3:837–44.
58.• von Wulffen M, Talley NJ, Hammer J, et al. Overlap of irritable bowel syndrome and functional dyspepsia in the clinical setting: prevalence and risk factors. Dig Dis Sci. 2019;64:480–6
In the routine clinical setting, patients with severe manifestations of FGID overlap of FD and IBS is the norm. In contrast, patients with mild manifestation may present with FD or IBS.
59. Mikocka-Walus AA, Turnbull D, Holtmann G, et al. An integrated model of care for inflammatory bowel disease sufferers in Australia: development and the effects of its implementation. Inflamm Bowel Dis. 2012;18:1573–81.
60. Haag S, Senf W, Tagay S, et al. Is there a benefit from intensified medical and psychological interventions in patients with functional dyspepsia not responding to conventional therapy? Aliment Pharmacol Ther. 2007;25:973–86.

Publisher's Note