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Management of functional dyspepsia: a clinical practice review

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Authors' Contributions

1. Hanna Naliuka was the originator of the study idea and led the conceptualization of the review. She conducted the bibliographic work, including reference searching, screening, and verification of bibliographic details. She supervised the integration of all sections, drafted the chapters on treatment strategy and the conclusion, and was responsible for creating the table and corresponding figures for these sections. She performed the final content check of the complete manuscript and assumed responsibility for correspondence.
2. Ewa Byjoś drafted the sections on epidemiology, risk factors, and diagnosis. She also conducted bibliographic work, including reference searching, screening, and verification of bibliographic details.
3. Kamila Milewska drafted the chapter on acid suppression therapy (PPIs, H2RAs, and older agents), including efficacy estimates, safety considerations, and guideline positioning, and contributed to tables related to acid-suppressive treatments.
4. Karolina Bury drafted the chapter on prokinetic agents, including comparative efficacy, dosing, adverse effects, and clinical positioning, and prepared the corresponding summary table of oral prokinetics.
5. Katarzyna Fabiś drafted the chapter on neuromodulators, summarizing mechanisms, phenotype-guided indications, evidence from randomized trials, and tolerability, and developed the neuromodulator evidence table.
6. Katarzyna Młynarczyk drafted the chapter on Helicobacter pylori–associated dyspepsia and eradication therapy, including evidence synthesis (RR/NNT), resistance-driven regimen selection, and the comparative summary table of eradication regimens.
7. Mateusz Zbylut drafted the chapter on probiotics and microbiota-targeted therapies, including strain-specific evidence, clinical endpoints, mechanistic findings, and safety.
8. Patrycja Mateja drafted the chapter on dietary interventions, including low-FODMAP, low-fat, and gluten-free approaches, and summarized key trials and outcomes relevant to phenotype-based dietary counseling.
9. Sylwia Buczek drafted the chapter on acupuncture, summarizing proposed mechanisms, evidence from meta-analyses and network meta-analyses, durability of effect, and safety.
10. Weronika Mstowska drafted the chapter on herbal therapies (including STW 5-II, rikkunshito, and peppermint–caraway combinations), focusing on efficacy, limitations of the evidence, and safety considerations.

Abstract

Introduction and purpose:

Functional dyspepsia (FD) is a common disorder of gut–brain interaction characterized by chronic upper gastrointestinal symptoms without structural disease. Its heterogeneous mechanisms and limited treatment efficacy remain major clinical challenges. This review summarizes evidence published between 2020 and 2025 on adult FD management and proposes a practical, phenotype-guided therapeutic approach for everyday clinical practice.

State of knowledge:

All patients with dyspeptic symptoms should undergo testing for *Helicobacter pylori*, with eradication therapy recommended for all infected individuals to identify H. pylori–associated dyspepsia and prevent misclassification as FD. In confirmed FD, proton pump inhibitors

represent first-line pharmacotherapy, providing modest but clinically relevant symptom improvement. H_2-receptor antagonists may be used as second-line or on-demand therapy. In patients with postprandial distress syndrome, prokinetic agents are preferred. However, safety concerns limit long-term use of metoclopramide and domperidone, whereas itopride and cinitapride offer more favourable efficacy–tolerability profiles. For epigastric pain–predominant FD or treatment-refractory disease, low-dose tricyclic antidepressants show the strongest evidence among neuromodulators, while SSRIs and SNRIs are not recommended. Selected adjunctive therapies offer additional benefit with good short-term safety.

Summary:

Management of FD should be systematic, stepwise and phenotype-driven, combining pharmacological therapy and evidence-based adjunctive interventions. Although treatment effects are modest, individualized combination strategies can achieve meaningful and sustained symptom improvement in many patients.

Keywords: Functional dyspepsia; H. pylori–associated dyspepsia; Pharmacologic therapy; Non-pharmacologic therapy; Management strategies.

Introduction

Functional dyspepsia (FD) is one of the most common disorders of gut–brain interaction (DGBI). [1–3]. FD is associated with impaired quality of life, high health-care utilization, and substantial economic costs, which in the United States have been estimated to exceed 18 billion dollars annually [2].

In response to its clinical and societal burden, international societies have published guidelines to standardize the diagnosis and management. The Japanese Society of Gastroenterology (JSGE) issued its first FD guideline in 2014 and updated it in 2021 to refine diagnostic and therapeutic strategies [4]. More recently, the 2022 British Society of Gastroenterology (BSG) guideline incorporated Rome IV criteria and recommended a stepwise approach, including *Helicobacter pylori* eradication, acid suppression, prokinetics, and neuromodulators [1,2]. Similar consensus efforts across Europe, North America, and other regions emphasize the heterogeneity of FD and the unmet need for more effective therapies [5].

This review summarizes current evidence (2020-2025) on therapeutic strategies and guideline-based management of FD.

Epidemiology

Functional dyspepsia is highly prevalent worldwide, with a global pooled prevalence of 7–16% depending on methodology [2,3]. Population surveys relying on symptoms rather than endoscopy suggest that up to one in five adults experience dyspeptic symptoms [2,6]. Endoscopy-based population studies show that only about 20% of individuals with dyspeptic symptoms have organic pathology, whereas the majority have no endoscopic or imaging changes and are therefore classified as having functional dyspepsia [2].

Data based on Rome IV criteria provide the most reliable estimates. Large internet surveys conducted in the US, UK, and Canada report a pooled prevalence of approximately 10%, with higher rates in the US (12%) than in the UK or Canada (8%) [2,3,5]. Across Europe, the overall point prevalence of FD was 8.78%, ranging from 17.68% in Norway to 3.68% in Denmark, with a prevalence of 8.3% reported in Poland [30, 31].

Risk Factors

Current evidence suggests that the development of functional dyspepsia is multifactorial, involving biological, psychosocial, and environmental determinants, although the strength of individual contributions is generally modest [2,5].

Epidemiological studies consistently show that FD is more common among women, with a reported female-to-male ratio of approximately 1.3–1.5:1. Prevalence typically peaks between the fourth and fifth decades of life and gradually decreases in older adults [2,29]. Ethnic variation has also been observed; for instance, higher prevalence has been reported among Indian and Malay populations compared with Chinese cohorts in Malaysia [2]. Socioeconomic determinants may contribute as well, with lower socioeconomic status linked to increased FD risk, although findings across studies remain heterogeneous [29].

Psychological factors play an important role in the pathophysiology of FD, reinforcing the relevance of the brain–gut axis. Anxiety and depression are frequently associated with the disorder, and longitudinal analyses indicate a bidirectional relationship—patients with pre-existing psychological comorbidities exhibit a higher likelihood of developing FD, while persistent dyspeptic symptoms may subsequently trigger or exacerbate mood disturbances [2,5,35]. In a Swedish population study, individuals with anxiety demonstrated an up to eightfold higher risk of FD compared with controls, underscoring the clinical relevance of psychological burden in this patient population [2].

Infection-related mechanisms represent another well-established etiological pathway. Post-infectious FD (PI-FD) is increasingly recognized, and meta-analytic evidence indicates that acute gastroenteritis—particularly caused by agents such as norovirus, *Salmonella* spp., or *Giardia lamblia*—can increase the likelihood of persistent dyspeptic symptoms threefold [2,33]. The role of *Helicobacter pylori* is more nuanced. Although infection is frequently observed in individuals with dyspepsia, only a subset demonstrates meaningful clinical improvement after eradication therapy. Patients whose symptoms resolve following eradication are categorized as having *H. pylori-associated dyspepsia*, whereas persistence of symptoms despite successful treatment supports the diagnosis of FD [2,33].

Lifestyle-related factors may further influence FD risk or symptom severity. Smoking, elevated body mass index (BMI), and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have each been associated with higher FD prevalence in observational cohorts [2,27]. Dietary behaviors have also gained increasing research attention, as many patients report symptom exacerbation in relation to specific foods. High-fat meals, spicy foods such as chili, and fermentable carbohydrates appear particularly likely to provoke discomfort, suggesting potential roles for altered gastric motility, visceral hypersensitivity, or luminal fermentation pathways [18,34,35].

Diagnosis

Functional dyspepsia (FD) is a distinct subtype of dyspepsia whose definition has evolved substantially in recent years. Dyspepsia itself is regarded as a symptom complex rather than a diagnosis, encompassing upper gastrointestinal complaints such as postprandial fullness, epigastric pain or burning, and early satiety, irrespective of etiology [2,4].

FD is diagnosed only when dyspeptic symptoms occur in the absence of identifiable structural or biochemical abnormalities capable of explaining them [2,4,5]. According to the Rome IV criteria, FD requires at least one cardinal symptom—troublesome postprandial fullness, early satiation, epigastric pain, or non-radiating epigastric burning—present for at least three months, with symptom onset at least six months before diagnosis [4,5]. Rome IV also recognizes Helicobacter pylori–associated dyspepsia as a separate entity, defined by sustained symptom resolution within 6–12 months after confirmed eradication. Persistent symptoms after eradication support a diagnosis of FD [2,4,6].

Two clinical subtypes of FD are recognized: postprandial distress syndrome (PDS), characterized by meal-related symptoms such as postprandial fullness and early satiety occurring at least three days per week, and epigastric pain syndrome (EPS), defined by

epigastric pain or burning that may occur independently of food intake and occurs at least one day per week [1,2,5].
Population-based studies indicate that PDS predominates (60–66%), EPS accounts for 15–20%, and the remainder exhibit overlapping features [2,29,31].
Testing for H. pylori is a central component of the diagnostic workup. UEG/ESNM and the 2023 Indonesian Consensus recommend a test-and-treat strategy for all dyspeptic patients, particularly in regions with moderate to high prevalence, using non-invasive testing or assessment during endoscopy [5,6]. A 2022 meta-analysis by Ford et al. demonstrated that H. pylori eradication provides meaningful symptom improvement in a subset of FD patients [33]. Non-invasive testing is especially cost-effective in younger patients without alarm features, whereas upper gastrointestinal endoscopy with concurrent H. pylori testing is preferred in patients aged ≥60 years or in those presenting with alarm symptoms, including unintended weight loss, persistent vomiting, gastrointestinal bleeding, dysphagia, or a family history of gastrointestinal malignancy [2,7].

Helicobacter pylori
Helicobacter pylori–associated dyspepsia constitutes a clinical entity distinct from functional dyspepsia. Although only approximately 5% of dyspepsia cases in the general population are attributable to H. pylori infection [1] and the bacterium is not necessarily the direct cause of all reported symptoms, current international guidelines consistently support eradication therapy as the initial management strategy in patients with dyspepsia who test positive for H. pylori [1,5,7]. This recommendation specifically targets H. pylori–associated dyspepsia and should not be interpreted as treatment for FD in H. pylori–negative individuals.
An updated systematic review and meta-analysis demonstrated that H. pylori eradication provides a statistically significant, though clinically modest, benefit in dyspeptic patients. The most recent analysis by Ford et al. [33], pooling 29 randomized controlled trials and 6,781 H. pylori–positive FD patients, showed a 9% relative reduction in the risk of persistent symptoms compared with placebo or antisecretory therapy (relative risk (RR) 0.91, 95% confidence interval (CI) 0.88–0.94), corresponding to a number needed to treat (NNT) of 14. Earlier summaries, including the UEG/ESNM consensus report [5] and the Lancet review [2], reported similar improvements of 9–10%, confirming the consistency of this therapeutic effect across trials. Benefits encompass reductions in global dyspeptic symptom severity, epigastric pain, and postprandial distress, along with higher rates of complete symptom resolution [2,5,33]. Overall, these findings indicate that while the individual benefit is moderate, the population-level effect is meaningful, reproducible, and clinically relevant.
The choice of eradication regimen is largely driven by local and regional antibiotic resistance patterns. Rising resistance to clarithromycin, metronidazole, and levofloxacin has markedly reduced the efficacy of traditional proton pump inhibitor-based triple therapy, and in settings where clarithromycin resistance exceeds about 15%, bismuth-based quadruple therapy is recommended as the preferred first-line option [6,44]. The commonly used eradication regimens, including their drug components, doses, and recommended treatment durations, are summarized in Table 1.

Table 1. Recommended H. pylori eradication regimens, drug doses, and treatment duration based on contemporary randomized trials and international guidelines

Regimen	Drugs and Doses	Duration	Guideline Position
Vonoprazan–amoxicillin dual therapy	• Vonoprazan **20 mg** BID • Amoxicillin **750 mg TID** or **1 g** BID	**10–14 days**	**Preferred first-line option**; supported by RCTs and meta-analyses showing high eradication rates, good tolerability, and favorable safety, including in clarithromycin-resistant strains.
Vonoprazan–amoxicillin–clarithromycin triple therapy	• Vonoprazan **20 mg** BID • Amoxicillin **1 g** BID • Clarithromycin **500 mg** BID	**14 days**	**First-line option** in regions with low clarithromycin resistance; demonstrates higher eradication rates than PPI-based triple therapy.
PPI-based triple therapy (clarithromycin triple)	• PPI BID • Amoxicillin **1 g** BID • Clarithromycin **500 mg** BID	**14 days**	**Alternative first-line option** in regions with low clarithromycin resistance, with declining efficacy in many regions.
Bismuth-based quadruple therapy	• PPI BID • Bismuth subcitrate or subsalicylate **120–300 mg QID** • Tetracycline **500 mg QID** • Metronidazole **400–500 mg TID - QID**	**10–14 days**	Recommended first-line therapy in regions with high or unknown clarithromycin resistance; robust efficacy but higher adverse event rates.
Non-bismuth concomitant therapy	• PPI BID • Amoxicillin **1 g** BID • Clarithromycin **500 mg** BID • Metronidazole **500 mg** BID	**10–14 days**	**Acceptable first-line alternative** in selected regions; effectiveness depends on local resistance patterns and adherence.
Levofloxacin triple therapy (second-line option)	• PPI BID • Amoxicillin **1 g BID** • Levofloxacin **500 mg OD**	**10–14 days**	**Second-line (rescue) therapy** after first-line failure; limited by increasing fluoroquinolone resistance and safety concerns.

***PPI** - proton pump inhibitor, **OD** - once daily, **BID** - twice daily, **TID** – three times daily, **QID** – four times daily*

More recently, potassium-competitive acid blockers (P-CABs) such as vonoprazan have emerged as an alternative acid-suppressive backbone for eradication regimens. Unlike proton pump inhibitors, vonoprazan produces rapid, potent, and sustained 24-hour inhibition of gastric acid secretion, independent of parietal cell activation, resulting in a more stable intragastric pH that may enhance the activity of amoxicillin and macrolides [6,36].

In a large randomized trial conducted in the United States and Europe, vonoprazan-based triple and dual therapy achieved eradication rates of 81% and 77%, respectively, compared with 69% for lansoprazole-based triple therapy; among patients with clarithromycin-resistant strains, eradication rates were 66–70% versus 32% [40]. A randomized trial in treatment-naïve Chinese patients confirmed these observations, reporting eradication rates of 96% with vonoprazan–amoxicillin dual therapy and 96% with vonoprazan–amoxicillin–clarithromycin triple therapy, compared with 92% for bismuth-based quadruple therapy [41]. Additional randomized studies and meta-analytic data further support the high eradication rates and robust performance of vonoprazan–amoxicillin dual therapy as a first-line treatment option [42–43,45].

Safety data from multiple randomized trials and large real-world cohorts indicate that vonoprazan-based regimens are at least as well tolerated as, and in several studies better tolerated than, bismuth-based quadruple therapy and conventional proton pump inhibitors-based regimens [40–46]. The most commonly reported adverse events include diarrhea, nausea, abdominal discomfort, dysgeusia, and headache, and their frequency varies by regimen. Across randomized trials of vonoprazan–amoxicillin dual therapy, overall adverse event rates generally fall in the range of 15–40%, whereas bismuth-based quadruple therapy is consistently associated with higher rates, often 30–70%, depending on the specific regimen and treatment duration [40–43,45–46].

Serious adverse events and treatment discontinuations remain uncommon across all regimens, and vonoprazan–amoxicillin dual therapy appears to offer a particularly favorable balance between eradication efficacy, treatment duration, and tolerability compared with other currently available eradication options [40–43,45–46].

Acid suppression therapy

Although functional dyspepsia is not traditionally considered an acid-driven disorder, experimental and clinical evidence indicates that a subset of patients demonstrates impaired duodenal acid clearance and increased acid sensitivity, supporting the use of acid-suppressive therapies [2,5,10,37]. **A summary of current evidence and practical recommendations related to acid suppression therapy is provided in Table 2.**

Table 2. Summary of evidence on acid suppression therapy in functional dyspepsia

Therapy Class	Evidence of Efficacy	Typical Regimen / Duration	Key Findings	Safety Profile	Guideline Position
PPIs	Moderate benefit	Standard-dose once daily; 4–8 weeks (e.g., omeprazole 20–40 mg, pantoprazole 40 mg, esomeprazole 20–40 mg)	Effective regardless of FD subtype (PDS/EPS); no difference between doses or individual agents	Well tolerated; mild GI and CNS side effects; potential increased risk of CDI with prolonged use	First-line therapy
H2RAs	Moderate benefit	Ranitidine 150 mg BID, famotidine 20 mg BID, nizatidine 150 mg BID, cimetidine 400 mg QID	Efficacy limited by tachyphylaxis after 1–2 weeks	Generally well tolerated	Second-line or optional therapy
Antacids, sucralfate, alginates, bismuth compounds	No consistent benefit over placebo	Various formulations	Lack of reproducible symptom improvement in RCTs	Generally safe	Not recommended

RCTs *– randomized controlled trials,* ***PPIs*** *– proton pump inhibitors,* ***FD*** *– functional dyspepsia,* ***PDS*** *– postprandial distress syndrome,* ***EPS*** *– epigastric pain syndrome,* ***CDI*** *– Clostridioides difficile infection,* ***H2RAs*** *– histamine-2 receptor antagonists,* ***GI*** *– gastrointestinal,* ***CNS*** *– central nervous system*

Proton pump inhibitors

Proton pump inhibitors (PPIs) represent the best-studied class in FD. A systematic review and network meta-analysis including over 6000 patients showed a statistically significant but modest benefit versus placebo, with a relative risk of persistent symptoms of 0.88 (95% CI 0.82–0.94) and a number needed to treat (NNT) of approximately 11, meaning that around 9–

10% of patients obtain a true clinical benefit beyond placebo [5,8,27]. Treatment durations in clinical trials ranged from 4 to 8 weeks, using standard once-daily doses such as omeprazole 20–40 mg, lansoprazole 30 mg, pantoprazole 40 mg, esomeprazole 20–40 mg, or rabeprazole 20 mg [5,8,27]. No clinically relevant differences in efficacy have been demonstrated between individual PPIs or between low-, standard- or high-dose regimens [5,8,27]. Accordingly, international and European guidelines recommend a 4–8-week course of standard-dose PPI as first-line therapy, particularly in H. pylori-negative patients with FD or in those who remain symptomatic after successful eradication [4–6,27].

In studies and meta-analyses that have reported outcomes according to Rome III subtypes, data do not demonstrate robust, reproducible differences in PPI efficacy between postprandial distress syndrome and epigastric pain syndrome. In routine practice, an empirical trial of PPI therapy is therefore considered appropriate in most patients with FD, irrespective of formal Rome subtype [2,5,8,27].

PPIs are generally well tolerated, and in randomized controlled trials, overall adverse event rates are typically similar to those observed with placebo [2,5,8,27,46]. Discontinuation due to side effects occurs in <1–3% of cases [2,5,8,27]. Common mild reactions include headache, abdominal pain, nausea, diarrhea, vomiting and flatulence, typically reported in 1–7% of patients [27,46,48,50]. However, concerns have been raised regarding potential infectious complications. In a nationwide Danish self-controlled case series including 3,583 episodes of community-associated *Clostridioides difficile* infection (CDI) in adults, current PPI use was associated with an adjusted incidence rate ratio (IRR) of 2.03 (95% CI 1.74–2.36) compared with periods of nonuse, with elevated risk persisting 0–6 months after cessation (IRR 1.54, 95% CI 1.31–1.80) and 6–12 months after cessation (IRR 1.24, 95% CI 1.00–1.53) [51]. These findings support prudent prescribing and periodic reassessment of the indication, particularly in patients at high baseline risk of *Clostridioides difficile* infection.

Histamine-2 receptor antagonists

Histamine-2 receptor antagonists (H2RAs) demonstrate moderate efficacy in the treatment of dyspeptic symptoms. Meta-analyses and clinical reviews report relative risk (RR) estimates ranging from 0.75 to 0.85, corresponding to a 15–25% reduction in persistent symptoms compared with placebo [8,27]. Commonly evaluated regimens include ranitidine 150 mg twice daily, famotidine 20 mg twice daily, nizatidine 150 mg twice daily, and cimetidine 400 mg administered multiple times daily [8,27,49].

A major limitation of H2RAs is the rapid development of tachyphylaxis, defined as a progressive reduction in pharmacological response during continuous drug exposure. In the case of H2RAs, tachyphylaxis typically emerges within 1–2 weeks of uninterrupted therapy and is thought to result from adaptive upregulation of histamine-mediated acid secretion and reduced receptor responsiveness. As a consequence, sustained acid suppression diminishes over time, leading to a marked attenuation of clinical efficacy and limiting the usefulness of H2RAs for long-term symptom control [27,48,49].

Network meta-analyses indicate that although H2RAs are superior to placebo, their overall effectiveness is modest and generally inferior to that of several prokinetic agents and neuromodulators [8,14,27]. Accordingly, current clinical guidelines position H2RAs as second-line or adjunctive therapy, primarily for short-term or intermittent (“on-demand”) use in patients for whom proton pump inhibitors are unsuitable [1,4,5,27].

Older agents

Older acid-neutralising or mucosal-protective agents such as antacids, sucralfate, alginates and bismuth preparations have not demonstrated consistent benefit over placebo in randomized trials and are therefore not recommended as first-line pharmacotherapy for FD in contemporary guidelines [2,5,8,27,39].

Summary

Acid suppression remains a core pharmacologic strategy in FD. PPIs provide modest but clinically meaningful symptom improvement when used as a time-limited 4–8-week course and remain the preferred first-line therapy due to the strength of supporting evidence and safety profile [2,5,8,27]. H2RAs may serve as an alternative or adjunct, particularly for intermittent use, but tachyphylaxis limits their long-term effectiveness and supports their role as secondary therapy [7,8,27,48].

Prokinetics

When patients with functional dyspepsia fail to respond to proton pump inhibitors, prokinetics represent an important therapeutic alternative [6,11,14]. A subset of patients with FD demonstrates abnormalities in gastric motility, impaired fundal accommodation, and hypersensitivity to gastric distension, providing the rationale for using prokinetic agents in therapy [1,2,8]. These drugs enhance gastroduodenal motility and gastric accommodation, thereby potentially alleviating postprandial distress syndrome and symptoms such as early satiation and fullness.

Pooled analyses report a relative risk (RR) of persistent symptoms of 0.81 (95% CI 0.74–0.89), corresponding to an approximately 19% relative reduction in the likelihood of ongoing symptoms compared with placebo, although the overall quality of evidence is low and between-study heterogeneity is substantial [2,5]. A subsequent meta-analysis confirmed a statistically significant but more modest benefit, showing a smaller reduction in treatment failure, with an RR of no symptom improvement of 0.89 (95% CI 0.84–0.95), equivalent to an 11% relative reduction in the risk of persistent symptoms compared with placebo [8]. It should be noted, however, that many of the earlier trials involved cisapride, which was later withdrawn from the market due to its association with QT prolongation and sudden cardiac death [2,5].

Current therapeutic options include dopamine D_2 receptor antagonists (e.g. domperidone, metoclopramide), serotonin 5-HT_4 receptor agonists (e.g. cinitapride), and acetylcholinesterase inhibitors (e.g. itopride, acotiamide) [3,8,14]. A concise comparison of the main oral prokinetics, including dosing, relative efficacy, adverse effects, and key clinical considerations, is presented in Table 3.

Table 3. Summary of oral prokinetics used in functional dyspepsia

Drug	**Typical dosing**	**Efficacy vs placebo**	**Main adverse effects**	**Key conclusions**
Metoclopramide	5–10 mg, 3–4×/day;	**High efficacy**	High neurological risk: EPS, akathisia, restlessness, tardive dyskinesia	Effective but limited to **short-term** use due to safety concerns
Domperidone	10 mg, 3×/day	**Moderate–high efficacy**	QTc prolongation, arrhythmias, hyperprolactinaemia	Useful alternative; avoid in patients with **cardiac risk**
Itopride	50 mg, 3×/day before meals	**Moderate efficacy**	Mild GI symptoms or rash; low CNS penetration; no QT prolongation	Good **efficacy–safety balance**; suitable for longer use
Cinitapride	1 mg, 3×/day	**High efficacy**;	Generally mild adverse events	Strong option; limited by **restricted access**
Acotiamide	100 mg, 3×/day	**Low–modest efficacy**;	Very well tolerated; mild GI adverse events	Consider in PDS; overall **modest** therapeutic effect

EPS - extrapyramidal symptoms, GI – gastrointestinal, CNS - central nervous system, PDS - postprandial distress syndrome

Metoclopramide

A network meta-analysis revealed that metoclopramide outperformed placebo in terms of overall efficacy rate (odds ratio [OR] 5.68, 95% CI 2.98–11.10), as well as domperidone (OR 2.29, 95% CI 1.16–4.63), itopride (OR 2.77, 95% CI 1.41–5.59), and acotiamide (OR 2.63, 95% CI 1.33–5.36) , while showing comparable efficacy to cinitapride (OR 1.62, 95% CI 0.75–3.53) [14]. The use of metoclopramide in FD is limited to short-term treatment due to safety concerns. Meta-analyses have confirmed a high incidence of neurological adverse events, including extrapyramidal symptoms (akathisia up to 22–36%, dystonia, parkinsonism), restlessness (15%), and tardive dyskinesia (≈2%), as well as a sevenfold increased risk of restlessness compared with placebo [13]. Because of these risks, long-term use of metoclopramide is not recommended in FD.

Domperidone

Domperidone, another dopamine D_2 receptor antagonist, avoids central nervous system penetration and thus has fewer neurological side effects than metoclopramide [13,14,52]. A multicenter randomized, double-blind, placebo-controlled pilot study conducted in 2023 evaluated the efficacy of domperidone for the treatment of Chinese patients with FD. Participants (n = 160) were randomized to receive domperidone 10 mg or matching placebo tablets three times daily for 14 days. The overall treatment effect response rate after 2-week therapy was higher for domperidone compared with placebo (60.7% vs 46.0%; RR 1.318, 95% CI 0.972–1.787; corresponding OR ≈ 1.15) [11]. An updated network meta-analysis from 2023 showed higher efficacy of domperidone compared with placebo (OR 2.47, 95% CI 1.87–3.29) [14]. These studies support the effectiveness of domperidone in the treatment of FD; however, its use is limited by cardiovascular safety concerns (QTc prolongation, arrhythmias, chest pain) and endocrine effects such as hyperprolactinaemia, galactorrhoea, and breast tenderness, which were reported in up to 96% of patients in small studies [13,14], and are also discussed in recent consensus documents [5]. Domperidone was also associated with a higher risk of total adverse events compared with cinitapride (OR 1.85, 95% CI 1.05–3.32) [14].

Itopride

Itopride is widely used in several countries, including Poland and other European and Asian regions, where it is considered a well-established prokinetic agent with a favourable balance between efficacy and safety [47,52]. It acts as a dopamine D_2 receptor antagonist and acetylcholinesterase inhibitor, thereby enhancing upper gastrointestinal motility and gastric accommodation [5,47]. Several randomized trials and network meta-analyses have demonstrated that prokinetic agents, including itopride, are more effective than placebo in improving global functional dyspepsia symptoms [8,14]. Accordingly, itopride may be considered in both EPS and PDS, particularly in patients with a higher overall symptom burden [2,5,8,14]. Compared with domperidone, which has been associated with an increased risk of cardiac and neurological adverse events [13,52], itopride shows a more favourable safety profile, with adverse events typically limited to mild gastrointestinal discomfort or rash and a low likelihood of clinically significant central nervous system effects [47,52]. Importantly, pharmacological data indicate no clinically relevant QT prolongation, supporting its use as a potentially safer long-term prokinetic option [47]. The recommended therapeutic regimen for adults is 50 mg three times daily (150 mg/day total dose) administered before meals, which has been shown to optimize both efficacy and tolerability [47].

Cinitapride

Cinitapride is a newer prokinetic agent with combined 5-HT_4 agonist and dopamine D_2 antagonist activity, resulting in enhanced upper gastrointestinal motility [14]. In a recent network meta-analysis, cinitapride demonstrated significantly greater overall efficacy compared with placebo (OR 3.52, 95% CI 2.01–6.24) [14]. Its pharmacological profile and

favourable efficacy ranking position it among the more promising prokinetic options for FD; however, its clinical use remains limited by restricted regional availability [52].

Acotiamide

The efficacy of acotiamide in functional dyspepsia versus placebo has been evaluated in a separate systematic review and meta-analysis [12]. The improvement in symptoms of FD after treatment was higher in patients treated with acotiamide than placebo, although the difference did not reach statistical significance (OR 1.48, 95% CI 0.93–2.35) [12,14].

Summary

Prokinetic agents constitute an important therapeutic option in the management of functional dyspepsia, particularly in patients who do not respond to PPIs. Evidence from multiple meta-analyses and network analyses consistently supports their superiority over placebo, with metoclopramide and cinitapride ranking highest in terms of efficacy [13,14]. However, the long-term use of metoclopramide is limited by neurological adverse events, while domperidone, although effective, carries risks of cardiovascular and endocrine complications [5,13,14]. By contrast, itopride demonstrates a more favourable balance between efficacy and safety and remains a recommended option in countries where it is available, including Poland and several Asian and Eastern European regions [2,5,8,47,52]. Cinitapride appears highly effective with a safer profile, yet its availability is geographically restricted [14,52]. Acotiamide may provide modest benefit, although results remain less consistent [12,14]. Taken together, these findings underscore the therapeutic potential of prokinetics in FD, while highlighting the importance of tailoring drug choice to both efficacy and safety considerations as well as local availability.

Neuromodulators

The use of neuromodulators in functional dyspepsia has received increasing interest because the disorder is characterized by altered visceral pain perception and dysregulated communication between the gastrointestinal tract and the central nervous system [2,5,8,15]. Neuromodulators are thought to reduce visceral pain sensitivity by enhancing descending inhibitory pathways and dampening central pain amplification in limbic and cortical networks [8,15]. In addition, some neuromodulators influence gastrointestinal motor and sensory function, including gastric accommodation and sensitivity to distension, which may contribute to symptom relief in selected patient phenotypes [2,3,5,8]. They are generally recommended in patients with functional dyspepsia—either in those without Helicobacter pylori infection or in those with symptoms persisting after successful eradication—and particularly in individuals who do not respond to acid suppression or prokinetic therapy [2,5,8,9,15]. A comparative overview of the efficacy, dosing, and preferred clinical indications of neuromodulators evaluated in randomized controlled trials is presented in Table 4.

Table 4. Efficacy of neuromodulators versus placebo in randomized controlled trials, with preferred FD phenotype

Agent	Dose	Drug outcome	Placebo outcome	Duration	Preferred phenotype / clinical use
Amitriptyline	10–25 mg at bedtime	**~53% adequate relief**	**40%**	12 weeks	**EPS (best evidence), pain-predominant FD**
Imipramine	25–50 mg once daily	**~63% responders**	**36% responders**	12 weeks	**EPS; pain-predominant FD**
Escitalopram	10 mg once daily	**~38% adequate relief**	**40%**	12 weeks	**Not effective**
Sertraline	50 mg once daily	**No improvement**	—	8 weeks	**Not effective**

Venlafaxine	75 mg once daily	**No significant symptom improvement**	—	8 weeks	**Not effective; high AE burden**
Mirtazapine	15 mg at bedtime	**~55–60% improvement**	**20–25%**	8 weeks	**PDS with early satiation, poor nutrient tolerance, weight loss**
Levosulpiride	25 mg three times daily	**~60–70% global improvement**	**20–30%**	4–8 weeks	**PDS / dysmotility (fullness, early satiation)**

***FD** – functional dyspepsia, **EPS** – epigastric pain syndrome, **PDS** – postprandial distress syndrome, **AE** – adverse events*

Tricyclic antidepressants (TCAs)

TCAs (e.g. amitriptyline, imipramine, nortriptyline) are the most extensively studied neuromodulators in FD and remain the only antidepressant class with consistent evidence of benefit.

In the largest randomized controlled trial (292 patients), amitriptyline increased adequate global symptom relief from around 40% with placebo to about 53% with amitriptyline, with the benefit driven mainly by improvements in epigastric pain and upper abdominal discomfort [5,8,15].

Typical FD regimens employ low doses of 10–25 mg at night, titrated up to 50 mg as tolerated for 8–12 weeks, to optimize efficacy while limiting adverse effects [2,3,5,8].

Low-dose imipramine (25–50 mg nightly) has also demonstrated efficacy in a controlled trial of 107 patients with refractory FD. Smaller studies of amitriptyline and nortriptyline further support reductions in epigastric pain and global symptom burden, particularly in EPS-predominant patients [3,5,8].

Adverse events—including drowsiness, dry mouth, constipation, urinary retention, and weight gain—are common, and may lead to treatment discontinuation in roughly 10–20% of patients in clinical trials [2,5,8,15].

Evidence for TCA efficacy is strongest in EPS and in patients whose symptoms persist after PPI therapy or H. pylori eradication, whereas data in pure PDS remain more limited. In North American guidelines (ACG/CAG), TCAs are recommended as the preferred neuromodulators once first-line therapy has failed. In contrast, European (UEG/ESNM) and Spanish (ASENEM/semFYC) guidelines also place TCAs as second-line options but list them alongside several other neuromodulators considered broadly equivalent, with selection guided by symptom pattern, comorbidities, tolerability, and local availability [2,5,9].

SSRIs and SNRIs

In contrast to TCAs, selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs) have not shown consistent benefit in FD. In the multicenter RCT mentioned above, escitalopram 10 mg daily for 12 weeks did not improve global dyspepsia symptoms compared with placebo [5,8,15]. A pilot RCT of sertraline 50 mg daily was also negative [5,8,15].

In a double-blind RCT of 160 FD patients, venlafaxine given for 8 weeks at 75 mg/day (below the standard antidepressant/anxiolytic therapeutic range) failed to significantly improve dyspepsia severity, quality of life, or anxiety/depression scores. Adverse events were common, and 25–35% of patients discontinued treatment because of intolerability—most frequently nausea (≈23%), insomnia (≈18%), increased anxiety (≈12–15%), and hypertension (≈8%)

[5,8,15]. These side effects occurred at substantially higher rates than in the placebo group, contributing to the lack of therapeutic benefit.

Mirtazapine

Mirtazapine is a tetracyclic antidepressant that antagonises α_2-adrenergic and 5-HT_2/5-HT_3 receptors and has antihistaminic, appetite-stimulating effects, making it useful in FD patients with early satiation and weight loss [5,8].

In a randomized placebo-controlled study of 34 FD patients with weight loss, mirtazapine 15 mg nightly for 8 weeks produced clinically meaningful improvements: early satiation improved in ~55–60% of patients (vs ~20–25% with placebo), nutrient tolerance increased by ~25–30%, mean weight gain was +2.2–2.8 kg and visceral anxiety decreased significantly [5,8,15]. Global dyspepsia scores showed improvement at week 4 but the effect attenuated by week 8 [5].

A second trial of 60 FD patients with weight loss and comorbid depression demonstrated that mirtazapine 30 mg/day improved dyspeptic symptoms in about 50–60% of patients and produced significant weight gain (~2–3 kg) [5].

Adverse effects were generally mild to moderate and reflected the known pharmacology of mirtazapine: sedation and somnolence (≈30–40%), increased appetite (≈20–35%), and weight gain (≈15–25%) [5,8]. These rates are consistent with both FD trials and broader safety data for mirtazapine in psychiatric indications.

Antipsychotics (sulpiride, levosulpiride)

Antipsychotic neuromodulators used in FD—primarily sulpiride and levosulpiride—are dopamine D_2-receptor antagonists with both central and peripheral actions. Peripherally, they enhance gastric emptying and may improve gastric accommodation. Centrally, they modulate nausea and visceral perception [5,8,12,15].

Doses and treatment duration used in RCTs were typically: levosulpiride 25 mg three times daily for 4–8 weeks, sulpiride 100–150 mg/day (usually 50 mg TID) for 2–6 weeks.

Older RCTs (each including 40–120 patients) demonstrated that levosulpiride improved global dyspepsia symptoms in 60–70% of patients, compared with 20–30% with placebo. The benefit was especially pronounced in dysmotility-like FD and PDS, with improvements in postprandial fullness, early satiation, and upper abdominal discomfort [5,8,15].

Some studies also showed accelerated gastric emptying in ~25–40% of treated patients, consistent with its prokinetic profile [5,8,15].

A network meta-analysis identified antipsychotics as one of the most efficacious neuromodulator classes for reducing persistent FD symptoms, although the evidence base remains limited by small sample sizes and low methodological quality [5,15]. The Spanish guideline specifically highlights levosulpiride as a neuromodulator with predominantly prokinetic action, recommending it as a first-line or early-line therapy when postprandial fullness and early satiation are dominant symptoms [9].

Safety reporting in FD trials was limited, but available data indicate that adverse effects of sulpiride and levosulpiride are usually mild. The most frequently reported are somnolence/sedation and fatigue. Based on broader clinical experience (outside FD), these drugs may also cause hyperprolactinaemia (≈10–15%), weight gain (≈5–10%), and infrequent extrapyramidal symptoms (<5%); however, exact rates in FD-specific studies remain uncertain due to incomplete reporting [8–10,15].

Summary

Among the available agents, tricyclic antidepressants have the strongest and most consistent evidence, improving dyspepsia symptoms. Their benefit is most evident in EPS, though adverse effects may limit tolerability. In contrast, SSRIs and SNRIs have not demonstrated meaningful symptom improvement and are associated with higher rates of adverse events, and therefore are not recommended.

Mirtazapine shows benefit in selected patients with early satiation, poor nutrient tolerance, and

weight loss, improving satiation, nutrient capacity, and appetite, although evidence remains based on small trials. Antipsychotic neuromodulators such as sulpiride and levosulpiride may be useful in PDS or dysmotility-predominant FD due to prokinetic effects, but data quality is low and safety concerns limit routine use.

Probiotics

Disturbances in the upper gastrointestinal microbiota have been implicated in the pathophysiology of functional dyspepsia, and several clinical studies have evaluated whether microbiota-targeted therapies can improve symptoms [26,27].

Bifidobacterium animalis subsp. lactis BL-99

A larger multicenter randomized controlled trial evaluated Bifidobacterium animalis subsp. lactis BL-99 in 200 adults with FD, who were assigned to placebo, a positive control (rabeprazole 10 mg/day), or low- or high-dose BL-99 for 8 weeks [25]. The primary outcome, the clinical response rate (CRR; >0.5-point reduction in the composite FD symptom score), was highest in the high-dose BL-99 group (~90%), followed by rabeprazole (~70%) and placebo (~58%). Symptom improvement was observed in both FD subtypes. Short-term follow-up indicated that benefits of high-dose BL-99 persisted for up to two weeks after treatment discontinuation. Treatment was well tolerated; only mild gastrointestinal adverse events occurred (2–4%), none requiring discontinuation [25].

Spore-Forming Bacillus Strains

In a randomized, double-blind, placebo-controlled exploratory trial using a spore-forming probiotic formulation containing Bacillus coagulans MY01 and Bacillus subtilis MY02, significant clinical benefit was demonstrated in adults with FD (n = 68) [24]. The primary benefit consisted of higher responder rates—defined as a ≥0.7-point reduction in the PDS subscore of the Leuven Postprandial Distress Scale—with 48% of probiotic-treated versus 20% of placebo-treated patients meeting the endpoint (RR 1.95, 95% CI 1.07–4.11). Symptom improvement was driven mainly by reductions in postprandial fullness and early satiety. The safety profile was favourable, with adverse events occurring in 16% of probiotic-treated versus 33% of placebo-treated participants, predominantly mild gastrointestinal complaints [24].

Lactobacillus, Bifidobacterium, Streptococcus, Bacillus subtilis, and Bacillus licheniformis

A systematic review and meta-analysis of five RCTs (n=409) assessed the efficacy and safety of probiotics and prebiotics in FD [26]. "Global improvement," defined as patient-reported improvement or resolution of dyspeptic symptoms, was more common with probiotics than with placebo (RR 1.15, 95% CI 1.01–1.30), and corresponding to approximately a 15% relative improvement in symptom response. The included studies evaluated strains of Lactobacillus, Bifidobacterium, Streptococcus, Bacillus subtilis, and Bacillus licheniformis, but given the limited number of trials, strain-specific comparative analyses were not feasible. Adverse events were uncommon and similar to placebo (RR 0.27, 95% CI 0.07–1.05), with no severe or treatment-limiting events reported [26].

Summary

Current evidence suggests that probiotics may provide symptom relief in FD, with the most consistent benefits observed for Bifidobacterium animalis subsp. lactis BL-99 and for spore-forming Bacillus species. However, the available studies are limited in number and size, and further large, well-designed trials are needed to confirm these findings [24–26].

Acupuncture

Acupuncture alleviates functional dyspepsia by modulating autonomic balance (activating vagal afferent pathways), gut–brain axis activity (including HPA function), serotonin signaling, gastrointestinal hormones (ghrelin, motilin, cholecystokinin), and inflammatory responses, thereby improving gastric motility, accommodation, and visceral sensitivity [17,28].

Acupuncture has been extensively investigated as a therapeutic option for functional dyspepsia, with multiple meta-analyses and network meta-analyses confirming its potential benefits. A Bayesian network meta-analysis of 26 RCTs involving 2,950 participants demonstrated that acupuncture—either alone or combined with conventional Western medicine (CWM)—effectively reduced early satiation, postprandial fullness, epigastric pain, and epigastric burning [16]. Among the evaluated modalities, manual acupuncture (MA), electroacupuncture (EA), moxibustion (Mox), warm needling (WN), and acupoint catgut embedding (ACE) were included. MA and MA-based combinations frequently ranked among the most effective treatments [16]. MA involves manual manipulation of needles. EA uses low-frequency electrical stimulation. Mox applies thermal stimulation. WN combines heat with needling. ACE embeds absorbable sutures to prolong acupoint stimulation [16].

A meta-analysis of 61 RCTs showed that in 13 RCTs including patients with FD, acupuncture monotherapy was superior to standard pharmacotherapy—mainly prokinetic agents and acid-suppressive drugs (76–82% vs. 70–76%; RR 1.08, 95% CI 1.03–1.14). The strongest effects were observed for meal-related symptoms, such as early satiation and postprandial fullness. True acupuncture also outperformed sham acupuncture - superficial needling at non-acupoints or blunt needles (49–60% vs. 29–36%; RR 1.69, 95% CI 1.37–2.08). When used as adjunctive therapy to pharmacotherapy, acupuncture significantly increased response rates compared with pharmacotherapy alone (92–97% vs. 74–78%; RR 1.25, 95% CI 1.21–1.30) [17].

A 2024 dose–response meta-analysis demonstrated that acupuncture efficacy follows a non-linear curve, with optimal therapeutic effects occurring after approximately 10–24 treatment sessions, after which the clinical benefit gradually declines despite additional sessions [32].

Across all analyses, acupuncture was associated with minimal and self-limiting adverse events such as transient swelling, ecchymosis, mild hematoma, or needle-related discomfort; rare systemic reactions resolved spontaneously, and no serious adverse events were reported [16–17].

Summary

Overall, acupuncture has demonstrated consistent efficacy in functional dyspepsia across multiple meta-analyses, outperforming standard pharmacotherapy and sham acupuncture, particularly for meal-related symptoms. Manual acupuncture and MA-based combinations ranking among the most effective modalities. Therapeutic benefits are optimized after approximately 10–24 sessions and are achieved with a favorable safety profile, as adverse events are rare, mild, and self-limiting. However, substantial variability in treatment protocols highlights the need for large, standardized, multicenter RCTs.

Diet

Dietary modifications are increasingly recognized as a relevant component of non-pharmacological management in functional dyspepsia, as a substantial proportion of patients report postprandial symptom exacerbation.

Low-FODMAP diet

Among these approaches, the low-FODMAP diet has received the most attention. FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols) are present in foods such as wheat products, onions, garlic, legumes, several fruits (e.g., apples, pears, mangoes), and lactose-containing dairy, while naturally low-FODMAP foods include items such as rice, bananas, grapes, strawberries, carrots, zucchini, and hard cheeses [19]. Mechanistic studies suggest that poor absorption and rapid fermentation of FODMAPs increase luminal gas production and osmotic load, which may stimulate visceral mechanoreceptors and chemoreceptors involved in symptoms such as bloating and abdominal discomfort [20].

Observational evidence supports the relevance of dietary triggers in FD: in a cohort study including 384 patients, various foods such as pasta, pickled products, carbonated beverages, red

peppers, and oily dishes provoked symptoms in 39–52% of individuals, whereas other commonly consumed foods alleviated symptoms in 22–34% [18]. These findings illustrate that dietary components - including fermentable carbohydrates, fats, and spices—may contribute to symptom generation in FD.

In a prospective, single-blind randomized controlled trial enrolling 105 individuals, clinically significant improvement (≥50% reduction in SF-NDI score) was observed in 66.7% of patients following a low-FODMAP diet, compared with 56.9% of those receiving standard dietary advice [53]. Consistent findings were reported in an observational study involving patients with FD and overlapping IBS, where 50% of participants adhering to low-FODMAP guidance achieved ≥30% symptom reduction, compared with 16% receiving standard dietary advice [54].

Low-fat diet

The role of low-fat dietary patterns has been assessed mainly within the framework of traditional dietary advice. In a randomized controlled trial including 53 participants with postprandial distress syndrome, a four-week intervention aimed at reducing consumption of fatty and highly processed foods led to "adequate relief" in 39% of patients, compared with 33% among those who received only diagnostic explanation without dietary guidance [55]. Observational data further indicate that high-fat foods—including fried items, sausages, and high-fat meats—are frequently reported symptom triggers and commonly associated with postprandial fullness, bloating, early satiety, upper abdominal discomfort, epigastric pain, and, in many cases, nausea [18].

Gluten-free diet

Evidence regarding gluten-free diets in FD remains inconsistent. However, available data suggest a subgroup of individuals with sensitivity to wheat or gluten. In a double-blind, placebo-controlled crossover trial of 11 patients, approximately one-third to nearly half achieved ≥30% symptom improvement after a four-week gluten-free intervention, although the small sample size limited identification of a specific dietary trigger [56]. Systematic analyses indicate that among patients with refractory FD, 35% respond to a gluten-free diet, with 18.5% experiencing symptom recurrence during gluten rechallenge, supporting the presence of non-celiac wheat or gluten sensitivity [20]. Observational studies further show that many individuals self-report wheat or gluten sensitivity, with gluten-containing foods frequently identified as symptom triggers [18].

Summary

Available evidence suggests that dietary interventions can play a meaningful role in alleviating symptoms of functional dyspepsia. The strongest body of evidence supports the low-FODMAP diet, particularly among individuals with predominant postprandial distress and heightened sensitivity to fermentable carbohydrates. Low-fat dietary strategies provide moderate yet clinically relevant benefits, especially in patients who report symptom exacerbation following fatty meals. By contrast, gluten-free dietary interventions appear beneficial only for a limited subset of patients with confirmed or suspected wheat/gluten sensitivity. These findings highlight the need for a personalized dietary approach in FD, tailored to symptom patterns and dietary tolerances.

Herbal therapies

Herbal therapies represent a growing field of interest in the management of functional dyspepsia.

STW 5-II

One of the most extensively studied remedies is STW 5-II, a multi-herbal preparation derived from nine medicinal plants. In a recent multicenter, randomized, double-blind trial including 272 patients with FD, 8 weeks of treatment with STW 5-II resulted in a significantly higher responder rate compared with placebo (61.2% vs. 45.1%), particularly for early satiety and reduced appetite [21]. Improvements in gastrointestinal symptom scores and quality of life were

observed, while tolerability was high and adverse event rates were comparable to placebo, with no treatment-related serious adverse events [21]. Earlier trials of STW 5 (Iberogast) had suggested similar efficacy, but high placebo response rates, short treatment duration, and heterogeneous endpoints limit the generalizability of the overall evidence [22,23].

Rikkunshito

Rikkunshito (RKT), a Japanese Kampo formula, has demonstrated therapeutic benefits in functional dyspepsia, particularly in patients with postprandial distress syndrome, by improving postprandial fullness and early satiety [57]. Randomized controlled trials suggest that its effects may be mediated through enhancement of gastric accommodation, modulation of gastric motility, and—most notably—promotion and sensitization of ghrelin signaling [58]. RKT may also attenuate visceral hypersensitivity and modulate serotonergic and stress-related pathways [59] which may explain emerging evidence of reductions in anxiety symptoms and its potential usefulness in patients with coexisting psychological burden [57]. Used either alone or as an adjunct to standard therapy, RKT may represent a promising option for FD. However, current evidence is limited by small sample sizes and short follow-up durations [57].

Peppermint oil

Peppermint oil, especially in combination with caraway oil (e.g., enteric-coated formulations such as Menthacarin), has also been investigated in FD. RCTs and meta-analyses indicate that peppermint-caraway combinations reduce upper abdominal pain and discomfort and improve disease-specific quality of life, likely through antispasmodic, carminative, and visceral analgesic mechanisms [22,23]. Evidence for peppermint oil monotherapy in FD remains limited, highlighting the need for more robust FD-specific data [23].

Summary

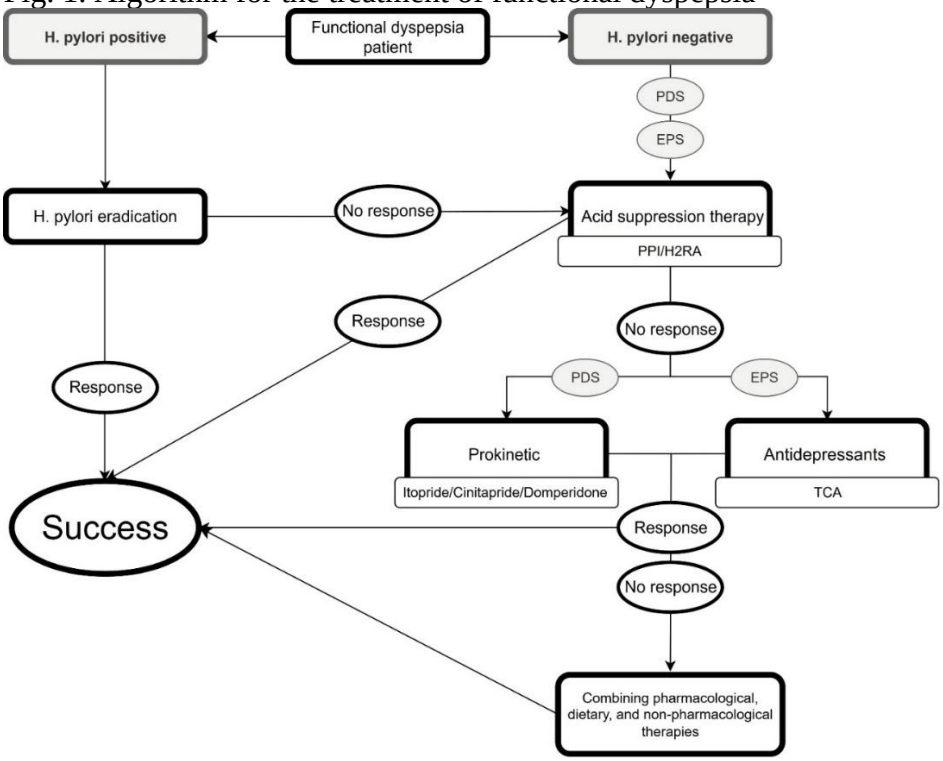
Recent narrative and systematic reviews stress that, while herbal medicines (including STW 5-II, rikkunshito, and peppermint-based formulations) are promising complementary options for FD, wider adoption into treatment algorithms should await further rigorously designed, standardized, multicenter trials with adequate safety monitoring and careful assessment of potential toxicity and herb–drug interactions [22,23,57–59].

Treatment strategy

Management of functional dyspepsia should follow a structured, stepwise, and phenotype-guided strategy. Figure 1 summarizes the proposed treatment pathways, integrating current guideline recommendations and the evidence reviewed in this paper.

The first—and obligatory—step in any patient presenting with dyspeptic symptoms is testing for *Helicobacter pylori*. This is essential both to identify *H. pylori*–associated dyspepsia and to avoid misclassifying these patients as having FD. All patients who test positive should receive eradication therapy (Table 1) as initial management, regardless of endoscopic findings, followed by reassessment of symptoms. The choice of regimen should be guided by local resistance patterns: in regions with high clarithromycin resistance, bismuth-based quadruple therapy remains the recommended first-line option, whereas vonoprazan–amoxicillin dual therapy or vonoprazan-based triple therapy offers high eradication rates with a favourable tolerability profile and lower adverse event rates compared with many bismuth-based regimens. In this framework, eradication therapy is the cornerstone of *H. pylori*–associated dyspepsia, while patients who remain symptomatic despite successful eradication—or who are *H. pylori*-negative—are managed as FD.

Fig. 1. Algorithm for the treatment of functional dyspepsia



PDS – postprandial distress syndrome, EPS – epigastric pain syndrome, PPI – proton pump inhibitor, H2RA – histamine-2 receptor antagonist, TCA – tricyclic antidepressant

In confirmed FD (*H. pylori*–negative or post-eradication with persistent symptoms), first-line pharmacological therapy consists of proton pump inhibitors (Table 2). PPIs provide a modest but clinically relevant benefit over placebo, with no major differences between individual agents or dosing strategies. They are particularly appropriate in patients with overlapping acid-related symptoms or duodenal inflammatory changes, and are generally well tolerated, although long-term use should be periodically reassessed in view of potential infectious complications (e.g., *Clostridioides difficile*). H_2-receptor antagonists may be considered as second-line or "on-demand" therapy when PPIs are contraindicated or poorly tolerated, but their efficacy is lower and subject to rapid tachyphylaxis, limiting their role in chronic management.

For patients who remain symptomatic after PPI therapy, the next step is guided by clinical phenotype. In postprandial distress syndrome or motility-predominant FD (postprandial fullness, early satiation, meal-related bloating), prokinetic agents are preferred (Table 3). As a class, prokinetics reduce persistent symptoms compared with placebo. Network meta-analyses rank metoclopramide and cinitapride among the most efficacious drugs. However, long-term metoclopramide use is constrained by a high risk of neurological adverse events, so it should be limited to short-term therapy. Domperidone is effective but restricted by cardiovascular and endocrine safety concerns. Itopride—widely used in Poland and several European and Asian countries—offers a more favourable balance between efficacy and safety, with no clinically relevant QT prolongation and mostly mild adverse events, making it suitable for longer-term use where available. Cinitapride appears highly effective and comparatively safe but remains geographically limited. Acotiamide may provide additional benefit in some patients, although results are less consistent.

In epigastric pain syndrome, or in patients with persistent symptoms despite PPIs and prokinetics, neuromodulators constitute the next therapeutic step (Table 4). Low-dose tricyclic antidepressants (e.g., amitriptyline, imipramine) have the strongest and most consistent

evidence, improving global dyspepsia and particularly epigastric pain, while also enhancing gastric accommodation. Their use is best suited to pain-predominant phenotypes and to patients who remain symptomatic after *H. pylori* eradication and PPI therapy. Mirtazapine is particularly useful in patients with early satiation, reduced nutrient tolerance, and weight loss, where it improves satiation, nutrient capacity, body weight, and visceral anxiety. Antipsychotic neuromodulators such as levosulpiride may be considered in selected patients with PDS or dysmotility-predominant FD, but limited and low-quality evidence, along with safety considerations, justify restricting their use to second- or third-line settings. In contrast, SSRIs and SNRIs have not demonstrated meaningful benefit and are associated with higher discontinuation rates due to adverse events. Therefore, they are not recommended for routine FD treatment.

Beyond pharmacological therapy, adjunctive and non-pharmacological modalities play an important role, particularly in patients with persistent symptom burden or those preferring integrative approaches. Probiotics—especially spore-forming *Bacillus* species and *Bifidobacterium animalis* subsp. *lactis* BL-99—have demonstrated modest but reproducible improvements in global symptoms, with responder rates approaching or exceeding those of standard pharmacotherapy in some trials and an excellent safety profile. These preparations may be particularly attractive in patients with suspected microbiota alterations and prominent postprandial or fermentation-type symptoms. Acupuncture has consistently shown superiority over sham procedures and, in some analyses, over pharmacotherapy, reducing early satiation, postprandial fullness, epigastric pain, and burning, with benefits persisting for months after treatment and minimal adverse events. It is therefore a reasonable option, especially in PDS and in patients favouring non-pharmacological treatment.

Dietary interventions should be individualized rather than universally prescribed. The strongest evidence supports the low-FODMAP diet, particularly in patients with PDS, bloating, and IBS overlap. Low-fat dietary patterns provide moderate benefit in those reporting symptom exacerbation after fatty or highly processed meals. Gluten-free dietary strategies appear useful in a smaller subgroup with suspected non-coeliac wheat or gluten sensitivity, including some patients with refractory FD.

Herbal therapies—most notably STW 5-II, rikkunshito, and peppermint–caraway oil combinations—represent promising complementary options. STW 5-II has demonstrated improvements in early satiation, appetite, and quality of life. Rikkunshito improves postprandial fullness and early satiety, may reduce anxiety, and exerts multifactorial effects on gastric accommodation, motility, and ghrelin signalling. Peppermint–caraway preparations reduce upper abdominal pain and discomfort and improve disease-specific quality of life. However, heterogeneity of formulations, small sample sizes, and limited long-term safety data mean that these agents should currently be used as adjuncts within a structured treatment plan rather than as standalone first-line therapies.

Conclusion

Functional dyspepsia remains a highly prevalent disorder of gut–brain interaction with a substantial impact on quality of life and healthcare utilization. Although no single therapy provides symptom relief for all patients, advances in scientific understanding and clinical research have significantly expanded the range of evidence-based treatment options. As a result, an increasing proportion of patients are now able to achieve meaningful symptom improvement, enhanced daily functioning, and better overall quality of life.

The proposed treatment strategy emphasizes: (1) systematic identification and eradication of H. pylori in all dyspeptic patients; (2) stepwise, phenotype-guided pharmacotherapy with PPIs, prokinetics, and neuromodulators; and (3) integration of evidence-based adjunctive options such as probiotics, acupuncture, personalized dietary modification, and selected herbal

preparations. Importantly, combining pharmacologic therapy with adjunctive, individualized non-pharmacologic interventions may provide superior symptom control compared with either strategy alone. Throughout treatment, shared decision-making, regular reassessment of therapeutic response, and careful consideration of safety, comorbidities, and patient preferences remain essential.

Nevertheless, further high-quality research is needed to refine treatment pathways and move beyond symptom-based management toward mechanism-driven strategies tailored to patient-specific phenotypes. Such progress is expected to support more effective personalized care and improve long-term outcomes for individuals living with functional dyspepsia.

Disclosure Section

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