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REVIEW ARTICLE

Pharmacological treatment of functional dyspepsia: from A to Z

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Abstract

Functional dyspepsia (FD) is a condition characterized by the presence of recurrent upper gastrointestinal tract symptoms without evident organic cause, which frequently overlaps with other disorders of gut-brain interaction and affects the quality of life of those who suffer from it. It is a multifactorial and complex disease that has multiple therapeutic targets. Various drugs can help with symptomatic control and improve quality of life in this disorder, but adequate knowledge is required to optimize their use. The objective of this article is to present an updated review of the pharmacological treatment of FD. A PubMed search was conducted from January 2016 to May 2025, and all relevant publications were included, giving preference to consensus statements, guidelines, systematic reviews, and meta-analyses. This was supplemented with relevant articles from the archives of *Revista de Gastroenterología de México* during the same period. We present a critical review of the pharmacological treatment of FD with emphasis on locally acting drugs, antisecretory agents and acid suppression therapy, prokinetics, neuromodulators, antibiotics, probiotics, and phytopharmaceuticals. We conclude that FD is one of the most frequent digestive disorders and consider that this critical and updated review of its pharmacological treatment is applicable to daily practice.

Keywords: Dyspepsia. Functional dyspepsia. Treatment. Drugs.

Tratamiento farmacológico de la dispepsia funcional: de la A a la Z

Resumen

La dispepsia funcional (DF) es un padecimiento que se caracteriza por la presencia de síntomas recurrentes del tracto gastrointestinal superior sin causa orgánica evidente, que frecuentemente se sobrepone con otros trastornos de la interacción intestino-cerebro y afecta la calidad de vida de quienes la padecen. Es una enfermedad multifactorial y compleja que tiene múltiples blancos terapéuticos. Existen diversos fármacos que pueden ayudar al control sintomático y a mejorar la calidad de vida en este trastorno, pero se requiere un conocimiento adecuado para optimizar su empleo. El objetivo de este artículo es presentar una revisión actualizada del tratamiento farmacológico de la DF. Se realizó una búsqueda en PubMed de enero de 2016 a mayo de 2025 y se incluyeron todas las publicaciones relevantes, dando preferencia a los consensos, las guías, las revisiones sistemáticas y los metaanálisis. Se complementó con los artículos de relevancia de los archivos de *Revista de Gastroenterología de México* en el mismo periodo. Presentamos una revisión crítica del tratamiento farmacológico de la DF con énfasis en los fármacos de acción local, los antisecretores y la terapia contra el ácido, los procinéticos, los neuromoduladores, los antibióticos, los probióticos y los fitofármacos. Concluimos que la DF es uno de los padecimientos digestivos más frecuentes y consideramos que esta revisión crítica y actualizada de su tratamiento farmacológico es de aplicación en la práctica diaria.

Palabras clave: Dispepsia. Dispepsia funcional. Tratamiento. Fármacos.

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Date of reception: 29-05-2025
Date of acceptance: 02-08-2025
DOI: 10.24875/CGME.M25000019
Available online: 04-12-2025
Clín. Gastroenterol. Méx. (Eng). 2025;1(2):151-162
www.clinicasgastroenterologiademexico.com

Introduction

Dyspepsia is a symptom complex that presents with a wide variety of recurrent symptoms originating in the gastroduodenal area, caused by different pathophysiological mechanisms that may coexist in the same patient[1]. This translates clinically into heterogeneous groups of subjects who frequently present with other overlapping disorders of gut-brain interaction, thus requiring differentiated treatments.

In functional dyspepsia (FD), multiple pathophysiological mechanisms have been identified, including altered motility, visceral hypersensitivity, and dietary, genetic, allergic, postinfectious, inflammatory, and psychosocial factors. To date, no universal pathophysiological factor has been established, which explains why there is no single or uniform treatment[1-3].

The objective of treatment in FD is symptomatic control and achievement of improved quality of life. In the following sections, we will discuss the different pharmacological options that may be employed in FD.

Locally acting drugs and histamine H_2-receptor blockers

The evidence supporting the use of antacids, bismuth salts, or sucralfate in FD is of low quality; therefore, they cannot be recommended in this context[2-5]. Although antacids and mucosal protective agents are an economical and widely available option, there is no current quality evidence in FD to support their use.

A systematic review that evaluated the effect of various mucosal protective agents and antacids found no significant difference in favor of the intervention compared with placebo[6]. A randomized study that included a small number of patients treated with bismuth or sucralfate versus placebo for 4 weeks also found no difference in symptomatic relief between groups[7]. Although they are considered safe compounds, they are known not to be free of adverse effects; excessive consumption of bismuth can cause toxicity[8].

The use of histamine H_2 receptor antagonists (H_2RAs) in the treatment of dyspepsia has been evaluated in multiple clinical trials, but recent studies are lacking, as most research with these products was conducted before the development of the Rome criteria[9]. A meta-analysis that included 12 good-quality studies demonstrated that H2RAs achieve symptom control in a greater proportion compared to placebo, with a number needed to treat (NNT) of 7[10]. In recent years, there has been growing interest in duodenal eosinophilia related to postprandial distress syndrome (PDS) as a potential therapeutic target[11-13]. H2RAs stand out in this regard since, in addition to their known effect on gastric acid secretion, their antihistaminic effect has the potential to improve duodenal eosinophilia. At least two studies using ranitidine in combination with loratadine or hydroxyzine demonstrated improvement in duodenal eosinophilia and symptomatic relief[13,14]. Despite this evidence, three aspects must be considered before prescribing them in FD: 1) their effect on symptom control is less than that achieved with proton pump inhibitors (PPIs); 2) they are associated with the development of tachyphylaxis, which limits their prolonged use[15]; and 3) ranitidine was withdrawn from the market due to the presence of a potentially carcinogenic metabolite, although famotidine continues to be marketed in Mexico.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are one of the most widely prescribed pharmacological groups worldwide, and possibly the most commonly used in the management of dyspeptic symptoms. Considering that the organic lesions most frequently detected in patients with uninvestigated dyspepsia are erosive esophagitis and peptic ulcer disease (both of which are amenable to successful treatment with PPIs), and that malignant lesions are rare[16-18], the empirical use of PPIs has been suggested in this group of patients, provided they do not present alarm features[19]. However, this recommendation cannot be fully extrapolated to subjects with FD without first considering various aspects.

A meta-analysis that included seven controlled clinical trials and more than 3,000 patients found that PPIs were more effective than placebo in reducing symptoms in subjects with FD, with an NNT of 14[20], but the stratified analysis demonstrated differential efficacy, being greater in patients with “ulcer-like” and “reflux-like” dyspepsia than in those with “dysmotility-like” dyspepsia (now PDS). Another meta-analysis that included 25 controlled clinical trials and more than 8,000 subjects, which compared the effect of PPIs versus placebo, H2RAs, or prokinetics for the relief of global symptoms and quality of life in patients with FD, demonstrated that PPIs had efficacy similar to low and standard doses, which were more effective than placebo (NNT = 11) and whose effectiveness was slightly greater than or similar to that of H2RAs and slightly greater than that of prokinetics[21]. All evidence suggests that the response to PPI treatment in FD is heterogeneous and

there may be subgroups of patients with FD who experience alterations in acid sensitivity and benefit directly from PPI therapy[22]. A specific example is the patient who presents with overlap of FD and symptoms of reflux disease.

Various consensus statements, guidelines, recommendations, and position papers recognize that the use of PPIs is an effective therapy in FD[2,3,9,11,16,23,24]. The most recent evidence indicates that there are no significant differences among the different types of PPIs, in the use of high or low doses, or in their effectiveness among FD subgroups[24-26]. The working group that recently developed the Good Clinical Practice Recommendations for the Diagnosis and Treatment of Functional Dyspepsia of the Asociación Mexicana de Gastroenterología[3] suggests providing short-term treatment with low-dose PPIs in these patients, provided there is periodic review to avoid the risk of long-term overprescription.

Although they are considered safe drugs, the use of PPIs for prolonged periods is not without adverse events; however, the majority of these adverse events have been described in association studies and causality has only been demonstrated in some cases[27]. Nevertheless, all patients chronically treated with PPIs should be reviewed at regular intervals to assess whether there is truly a need to continue therapy or whether it is possible to reduce the dose, or even discontinue them completely, in order to avoid overprescription and potential risks, and to optimize the cost of therapy[27].

Potassium-competitive acid blockers

Potassium-competitive acid blockers (P-CABs) are drugs that selectively inhibit the proton pump through reversible blockade of potassium channels[28]. They represent a new pharmaceutical class and offer advantages over PPIs: they are active drugs (not prodrugs), therefore they act rapidly from the first dose, raise intragastric pH above 6 from the first day, and do not require administration before food intake. Tegoprazan was the first P-CAB approved and marketed in Mexico, and currently we also have fexuprazan available[29,30]. Although there are numerous studies on gastroesophageal reflux disease, *Helicobacter pylori* eradication, prophylaxis of gastric lesions, and management of peptic ulcer, the evidence for the use of P-CABs in FD is very limited[31-34]. While P-CABs are a promising option, current evidence is insufficient to recommend their use in FD, and it has even been suggested that they may worsen symptoms such as postprandial fullness and early satiety by reducing gastric emptying[35].

In one study, a small group of patients with FD was treated with vonoprazan (20 mg/day) or placebo for 4 weeks, showing a decrease in symptom intensity in favor of the drug (45% vs. 28%)[31]. Another study compared the efficacy of vonoprazan at a dose of 10 mg daily (n = 48) versus acotiamide at a dose of 100 mg three times daily (n = 37) for 4 weeks, finding that epigastric pain and postprandial distress scores improved significantly in both groups, and the improvement score was similar in both groups[36]. In an open-label, non-comparative study, 173 patients with FD (Rome IV) were treated with tegoprazan (50 mg/day), achieving satisfactory symptom relief at 8 and 4 weeks in 86.7% and 74.6%, respectively; improvement was also observed in quality of life scales, with no serious adverse events related to the drug[37]. In another randomized, double-blind, placebo-controlled study, in which gastric emptying (by scintigraphy) and dyspeptic symptoms (by structured questionnaires) were measured in a group of healthy subjects after receiving tegoprazan (50 mg/day) or placebo (n = 15 per group), no significant objective changes were found in gastric emptying or dyspeptic symptoms[38]. To our knowledge, there is no evidence regarding the utility of fexuprazan (available in Mexico) in FD.

Prokinetics

Alterations in gastric emptying and in fundic receptive relaxation following food intake are recognized mechanisms causing symptoms in FD. For this reason, prokinetics have been used in this disorder. However, the relationship between symptom improvement and gastrointestinal motor functions is controversial, and their long-term efficacy is limited by the side effects of some of them. This group comprises various classes of drugs that improve gastrointestinal motor function by acting through different pathways, and includes dopamine-2 receptor antagonists, acetylcholinesterase inhibitors, motilin agonists, and ghrelin agonists[3]. Because this is a heterogeneous group of drugs and the evidence supporting their use is not uniform, the recommendation for their use in FD is differentiated. We will briefly discuss the utility of prokinetics as a group, and then the evidence for each of the different classes in FD.

A systematic review and meta-analysis that evaluated prokinetics as a group and included 29 studies and more than 10,000 patients demonstrated that these drugs are significantly more effective than placebo in reducing FD symptoms, with a therapeutic gain of 14% over placebo and an NNT of 7[39]. However, this work

has been highly questioned due to the heterogeneity of the included trials and the inherent biases.

Dopamine-2 receptor antagonists (metoclopramide, domperidone, itopride, levosulpiride, and clebopride) reduce symptoms in patients with FD by promoting gastric emptying and increasing gastrointestinal motility.

Metoclopramide, the first D_2 receptor antagonist, is a 5-HT_4 receptor agonist. Its easy passage through the blood-brain barrier is associated with possible irreversible neurological effects, which has generated a warning due to the induction of extrapyramidal symptoms[40,41]. Several trials and a meta-analysis comparing the efficacy of metoclopramide with placebo or with other pharmacological therapies in FD showed significant improvement of symptoms in favor of the drug, highlighting its limitations due to potential adverse effects[40-44].

Domperidone, in addition to peripheral prokinetic properties, has an antiemetic effect. Although few studies have been published, some indicate a significant reduction in dyspepsia symptoms with domperidone compared to placebo, reaching up to 76%, with results similar to metoclopramide but with fewer side effects, although its use is only recommended for short-term treatment[44,45]. A meta-analysis suggested that beneficial effects are achieved at doses of 10-20 mg three times daily, compared to placebo, in the overall rate of dyspeptic symptoms[46]. The effectiveness of domperidone in specific subgroups of FD has not yet been investigated due to the risk of QT interval prolongation and the increased risk of ventricular arrhythmia[40].

Itopride is a D_2 receptor antagonist and cholinesterase inhibitor that promotes gastric contractility, increases lower esophageal sphincter pressure, and accelerates gastric emptying. Four clinical trials reported significant improvement in FD symptoms after 2 to 8 weeks of treatment with itopride, whereas two trials demonstrated no improvement compared to placebo[23,39,40,47]. A study that evaluated the effects of itopride using validated patient-reported measures demonstrated its efficacy especially in those patients with overlapping PDS and epigastric pain syndrome (EPS)[47].

Levosulpiride is a dual-action drug, both prokinetic and neuromodulatory, that acts through dopaminergic pathways controlling gastrointestinal motility, and its serotonergic component (5-HT_4) may also enhance its therapeutic efficacy. Several studies have supported the efficacy of levosulpiride in controlling dyspeptic symptoms such as epigastric pain or discomfort, nausea, abdominal distension, and aerophagia, as well as global symptoms, while also demonstrating a favorable safety profile[48,49]. A systematic review reported that the incidence of adverse events with levosulpiride was 11%, with the majority being mild and rarely resulting in treatment discontinuation. In a randomized trial, levosulpiride showed similar efficacy to cisapride in reducing gastric emptying times[50].

Clebopride is a non-selective benzamide with high affinity for D_2, D_3, and D_4 receptors, which acts as a dopamine receptor antagonist. Although it has proven effective in relieving gastroparesis symptoms, the evidence supporting its effectiveness in FD is limited and has not been updated with recent studies[51].

Among the acetylcholinesterase inhibitors, only acotiamide has extensive evidence in FD, primarily due to its effect as a gastric prokinetic agent. Acotiamide enhances acetylcholine release in the enteric nervous system through muscarinic receptor antagonism and acetylcholinesterase inhibition. It has low affinity for serotonin receptors 5-HT_2, 5-HT_3, and 5-HT_4, and for D2 receptors, compared to other prokinetic agents[52]. In several clinical trials, acotiamide has shown significant improvement in the sensation of fullness, distension, and early satiety compared to placebo[53-55]. However, a meta-analysis that selected only high-quality studies including 1,697 patients demonstrated that, although the improvement in symptoms of FD was greater in individuals treated with acotiamide than in those who received placebo, there was no statistically significant difference (odds ratio [OR]: 1.48; 95% confidence interval [95% CI]: 0.93-2.35)[56].

Motilin receptor agonists are drugs that mimic the action of this neurotransmitter by selectively interacting with its receptor, increasing lower esophageal sphincter pressure, stimulating gastric motility, and improving accommodation. Of this group, only erythromycin, a macrolide antibiotic, has evidence in FD[57]. In a controlled clinical trial conducted in patients with FD and delayed gastric emptying, erythromycin administration did not significantly improve global symptoms and additionally carries a significant risk of tachyphylaxis[58].

Ghrelin agonists stimulate gastric motor function through the vagus nerve and have been associated with motility and appetite regulation. Relamorelin, a ghrelin agonist, has been mentioned as a promising drug in dyspepsia, but the evidence for its use in FD is limited and with contradictory results[59].

Several guidelines recognize that prokinetics are an effective therapy in FD[2,3,9,16,23,24]. Some suggest their use only in patients who remain symptomatic after *H. pylori* eradication or following PPI treatment[23], while others recommend them in a targeted manner for the control of dyspepsia-related symptoms, such as nausea, early

satiety, and postprandial fullness[3,16]. Their acceptance has been influenced by the fact that the evidence supporting their use in FD is heterogeneous and of lower quality compared to other therapeutic options, and that not all are available in all countries[60]. The working group that developed the Good Clinical Practice Recommendations for the Diagnosis and Treatment of Functional Dyspepsia of the Asociación Mexicana de Gastroenterología 2024[3] considered them to be a good therapeutic alternative for FD, especially in our country, where a wide range of prokinetics is available, with a good safety profile if patients are appropriately selected and they are used properly.

5-HT$_4$ receptor agonists of serotonin

5-HT$_4$ receptor agonists (cisapride, mosapride, prucalopride, tegaserod, velusetrag, and renzapride) release acetylcholine from the myenteric plexus and stimulate smooth muscle contraction, thereby accelerating gastric emptying. The widespread distribution of these serotonin receptors contributes to their involvement in a large number of functions that have not yet been fully studied, including the modulation of visceral pain[61].

Cisapride, one of the first non-selective 5-HT$_4$ receptor agonists used in patients with FD and gastroparesis, demonstrated benefits by accelerating gastric emptying and improving gastric accommodation in healthy subjects. However, its effects on gastrointestinal symptoms are controversial, as some studies show no significant differences due to high placebo responses[62]. Cisapride was withdrawn from the market in the United States due to its arrhythmogenic potential, related to its affinity for the human ether-à-go-go-related gene (HERG) channel[63].

Mosapride is used as a prokinetic agent in Asia, but a controlled trial in Europe did not demonstrate efficacy in FD[64]. In a controlled clinical trial comparing controlled-release mosapride with nortriptyline in patients with FD for 4 weeks, both drugs showed similar efficacy in terms of symptom relief, anxiety control, and improvement in quality of life[65].

Prucalopride is a potent, highly specific agonist of 5-HT$_4$ receptors that has been shown to improve gastric emptying, as well as small intestinal and colonic transit in patients with chronic idiopathic constipation. Studies in healthy volunteers have demonstrated that it can increase gastric emptying, with symptomatic benefits after 120 minutes[66], suggesting potential efficacy in delayed gastric emptying, although large-scale trials have not been conducted in this disorder.

Tegaserod, a partial agonist of 5-HT$_4$ receptors originally developed for irritable bowel syndrome (IBS) with predominant constipation and for functional constipation, demonstrated benefits in the treatment of FD. A randomized, placebo-controlled study showed a 4.6% improvement in days with symptom relief after 6 weeks of treatment compared to placebo; however, although these results were statistically significant, the clinical value is insufficient for its recommendation[67]. Another study in women with FD receiving concomitant PPI treatment for heartburn did not demonstrate statistically significant benefits[68]. Tegaserod was withdrawn from the market in 2008 due to a presumed increase in cardiovascular adverse effects, but the Food and Drug Administration recently approved its reintroduction for women under 65 years of age with IBS with predominant constipation.

Velusetrag and renzapride have not yet been evaluated in patients with FD.

A meta-analysis that included 10 randomized, controlled, placebo-comparative clinical trials evaluating the efficacy of serotonin agonists in the treatment of FD demonstrated high efficacy of these drugs for symptomatic control compared with placebo[69]. However, the selection of studies was highly heterogeneous, including drugs from different classes and patients diagnosed using various criteria, which precludes drawing clear conclusions. Therefore, the evidence supporting the use of serotonin 5-HT$_4$ receptor agonists in FD is limited, and in some cases nonexistent, further constrained by the adverse effects of some of these agents, which does not allow for recommending their use.

5-HT$_{1A}$ receptor agonists of serotonin

5-HT$_{1A}$ agonists induce gastric relaxation and improve FD symptoms in patients with impaired accommodation and hypersensitivity to gastric distension[70]. In a controlled clinical trial in which subjects received buspirone at a dose of 10 mg three times daily for 4 weeks, global and individual symptoms of early satiety, postprandial fullness sensation, and upper abdominal distension improved significantly; however, no improvement was observed in pain or epigastric burning, suggesting it could be more useful in the subgroup of patients with PDS[71]. Conversely, another placebo-controlled comparative clinical trial using increasing doses of buspirone for 2 months showed no significant difference in symptomatic relief, anxiety scales, or quality of life compared to placebo, but the number of patients included was small[72]. A systematic review and meta-analysis that

included 10 studies and 283 patients did not demonstrate that buspirone improved FD symptoms more than placebo, although the studies were small[73].

Tandospirone demonstrated significant improvement in a 4-week placebo-controlled comparative clinical trial in patients with FD conducted in Japan[74]. Another randomized, placebo-controlled comparative study showed that tandospirone effectively improved both gastrointestinal symptoms and anxiety in patients with FD[75]. It has been proposed that these therapeutic effects may be associated with the modulation of brain-derived neurotrophic factor and inflammatory cytokines that were measured.

Although the evidence supporting the use of 5-HT_{1A} receptor agonists in FD is limited compared to other drugs, they may be a therapeutic option in selected cases[3].

Neuromodulators

Neuromodulators are molecules that regulate the activity of ion channels and membrane potentials in neural cells, stimulating or inhibiting, either totally or partially, one or more pre- and postsynaptic serotonergic, muscarinic, cholinergic, or noradrenergic transporters or receptors, with effects on gastrointestinal motility and tone, and on gastric accommodation, with antinociceptive effects or on central pain processing according to the pharmacological group[76-78]. There are eight pharmacological groups and, based on their site of action, they can be classified as central (all except delta ligands) or peripheral (delta ligands)[76,79].

We must recognize that the evidence supporting the use of neuromodulators in FD is not homogeneous. Initial studies and systematic reviews grouped these drugs into a single category, or classified them as antidepressants or anxiolytics, showing heterogeneous results[80]. The improved understanding of disorders of gut-brain interaction has been able to demonstrate that there are important differences between groups, as confirmed by subsequent controlled studies and meta-analyses[80-85]. Considered as a group, neuromodulators have proven to be useful for the treatment of FD, with an NNT of 6[80].

Several studies have demonstrated the utility of tricyclic antidepressants in FD, and they constitute the pharmacological group with the best evidence. Amitriptyline and imipramine have been shown to be superior to placebo and escitalopram in EPS, with an NNT of 6 for symptomatic improvement and 7 for reduction of pain scores[81]. A controlled clinical trial in patients with EPS, which compared the effect of pantoprazole against a low dose of amitriptyline (25 mg at night) for 4 weeks, demonstrated significant improvement of symptoms in the group treated with amitriptyline, although without achieving an impact on psychological stress or anxiety scores[82]. A study that included 107 patients with FD refractory to esomeprazole and domperidone analyzed the effect of imipramine versus placebo, and demonstrated significant improvement in global dyspepsia symptom scores, with an NNT of 4[83]. Although the dose increase of imipramine was gradual, a greater proportion of patients treated with the drug discontinued it due to adverse effects, compared with those who received placebo (18 vs. 8%, respectively), the most common being dry mouth, constipation, and somnolence. A controlled, randomized, comparative clinical study between nortriptyline and duloxetine demonstrated the superiority of nortriptyline in the symptomatic improvement of patients with FD, although duloxetine was more effective in reducing anxiety[84]. The most recent meta-analyses have confirmed the efficacy of tricyclic antidepressants in the treatment of FD with low NNTs[10,80,85].

In contrast, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have not been shown to be superior to placebo, tricyclic antidepressants, or tetracyclic antidepressants for symptomatic control in FD[80,86]. Some guidelines consider these groups as second-line options for pain control when there is intolerance to tricyclic antidepressants, but the evidence is insufficient[87]. Their use may be considered in patients with FD who have anxiety (SSRIs and SNRIs), obsessive-compulsive disorders, or depression (SSRIs).

Among the noradrenergic and serotonergic tetracyclic antidepressants, mirtazapine has proven to be useful in PDS, particularly when associated with weight loss. Mirtazapine was superior to placebo in terms of global improvement, early satiety, quality of life, and gradual weight recovery, apparently related to an effect on fundic relaxation and gastric accommodation[88]. Although mirtazapine did not achieve statistically significant efficacy in the meta-analysis by Ford et al.[80], promising and good-quality evidence has emerged with this drug. A study comparing the effect of mirtazapine versus nortriptyline in FD demonstrated a significant decrease in epigastric pain, belching, bloating, and depression in the group treated with mirtazapine, with no differences found in anxiety[89]. A controlled clinical trial comparing mirtazapine plus traditional treatment versus placebo plus traditional treatment for 8 weeks demonstrated that the administration of mirtazapine significantly improved global dyspepsia symptoms, as

well as individual symptoms (postprandial fullness, early satiety, nausea and vomiting), anxiety and quality of life, and achieved weight gain in patients with FD[90].

Azapirones with 5-HT_1 receptor antagonist effects have demonstrated utility in PDS (buspirone) and in EPS (tandospirone)[10]. Furthermore, their effect appears to extend beyond their action on gastric motility, as they have been shown to reduce anxiety scores in subjects with FD[73,75].

Among atypical antipsychotics, levosulpiride and sulpiride have the best evidence in the treatment of FD. Both drugs have a dual action, as they are not only D_2 receptor antagonists and partial D_3 agonists, but also 5-HT_1 agonists and 5-HT_2 antagonists, thus acting as prokinetics and neuromodulators. In the meta-analysis by Ford et al.[80], the atypical antipsychotic group showed a risk of symptom persistence below unity (relative risk: 0.50; 95% CI: 0.37-0.67), with an NNT of 3 and a number needed to harm of 21. Anticonvulsants do not have clinical studies in FD.

Delta ligands belong to the neurolytics group, but they have also been classified as peripheral-acting neuromodulators with anxiolytic activity. Pregabalin and gabapentin have been evaluated in case series, open-label studies, and controlled clinical trials comparing them against placebo and in combination with omeprazole, demonstrating overall improvement, as well as improvement in perception and symptom scores[91-93].

Certain neuromodulators appear to have an effect on more than one mechanism associated with pain, including gastroduodenal and visceral hypersensitivity, alterations in central pain processing, and gastric accommodation. The effect is cumulative over 6 to 8 weeks, after which maximum clinical benefit is achieved, which may be limited by the presence of adverse effects that can occur from the initiation of treatment; therefore, they should be used at gradually escalating doses according to tolerability. The selection of the drug should consider various factors, such as demonstrated effectiveness, associated psychological comorbidity, undesirable effects, and tolerability.

Probiotics and rifaximin

Recent evidence suggests that microbiota imbalance is involved in the development of FD[94]. Dysbiosis and alterations of the mucosal barrier contribute to low-grade inflammation and sensory dysfunction, generating dyspeptic symptoms that are modified by environmental factors such as diet and drug consumption, especially gastric acid secretion inhibitors[95-97]. In recent years, there has been growing interest in modulating the microbiota as a therapeutic target in FD, and for this purpose, probiotics and rifaximin have been used. Probiotics have been evaluated in multiple cohort studies and controlled clinical trials using specific strains and combinations, either exclusively or in association with conventional treatments such as prokinetics and antisecretory agents[98,99]. Some probiotics have demonstrated certain physiological or symptomatic benefit, but the study design and lack of clarity in their mechanisms of action prevent obtaining solid and reproducible conclusions. The efficacy of prebiotics and probiotics was studied in a meta-analysis that included exclusively controlled clinical trials[100]. The investigators concluded that the use of probiotics was not associated with significant improvement in FD symptoms (RR: 1.13; 95% CI: 0.99-1.28; p = 0.67). Careful analysis of these studies shows heterogeneity, with significant differences in strain, dose, and treatment duration, as well as in patient subgroups, clinical outcomes, and definitions of improvement, which prevents reaching quality conclusions.

The potential utility of rifaximin, a synthetic and non-absorbable antibiotic, in FD has been explored in several studies. A controlled, comparative clinical trial demonstrated that administration of the antibiotic (400 mg, three times daily, for 2 weeks) achieved global relief of dyspeptic symptoms in a significantly higher proportion of subjects compared with placebo (78% vs. 52%; p = 0.02), as well as improvement in belching and postprandial distension at 4 weeks, primarily in women[101]. Although the number of patients included was relatively small, a relevant aspect of this study was that subjects with suggestive symptoms or diagnosis of IBS were actively excluded, so that the overlap of FD with IBS did not influence the results. Another controlled clinical trial compared the effectiveness of rifaximin, mosapride, and the combination of both in the treatment of bacterial overgrowth in subjects with FD[102]. Rifaximin reduced exhaled gases and relieved some symptoms, but the small number of subjects studied, the overlap with IBS, the high dropout rate, and the lack of a placebo group make the results difficult to interpret. Another small open-label study in which 21 patients with FD (with and without IBS) were treated consecutively with 550 mg of rifaximin, twice daily for 10 days, demonstrated significant relief in the symptom scale scores used, without finding apparent influence of the presence of IBS on the results[103]; however, the obvious limitations of the study limit its interpretation.

Therefore, the potential of probiotics and rifaximin is undeniable, especially in those patients who present

Table 1. Drugs for the treatment of functional dyspepsia recommended by the Asociación Mexicana de Gastroenterología[3]

Group	Available drugs	Therapeutic action	Observations
Proton pump inhibitors	Omeprazole Pantoprazole Lansoprazole Esomeprazole Rabeprazole Ilaprazole Isomers and magnesium formulations	Inhibition of acid secretion	There are no significant differences in the effectiveness of different drugs in FD The response is heterogeneous Overprescription should be avoided
Dopamine 2 receptor antagonists	Metoclopramide Domperidone Itopride Levosulpiride* Clebopride	They increase lower esophageal sphincter tone, promote gastric emptying, and enhance gastrointestinal motility	Antiemetic effect (metoclopramide, domperidone) Risk of extrapyramidal symptoms (metoclopramide), QT interval prolongation and increased risk of ventricular arrhythmia (domperidone) Extended-release formulations are available in Mexico (metoclopramide and domperidone) that have not been evaluated in FD Levosulpiride has dual action: prokinetic and neuromodulatory
5-HT_4 receptor Agonists	Cisapride Mosapride Prucalopride	They promote gastric emptying, accelerate small intestinal and colonic transit	Caution due to arrhythmogenic potential (cisapride) May be useful in patients with overlapping FD and constipation
Acetylcholinesterase inhibitors	Acotiamide	Gastric prokinetic	Recommended, but with weak and developing evidence
Tricyclic neuromodulators	Amitriptyline Imipramine Nortriptyline†	They decrease gastrointestinal motility and produce visceral analgesic effects	Effective at low doses, limited by side effects (somnolence, dry mouth, constipation)
Tetracyclic noradrenergic and serotonergic neuromodulators	Mirtazapine	It increases gastric emptying and modulates pain perception	Effective in PDS, particularly when associated with weight loss Stimulates appetite Causes drowsiness
Peripheral neuromodulators (delta ligands)	Gabapentin Pregabalin	Visceral analgesics	Anxiolytics, cause drowsiness Potential for abuse Use with caution in renal insufficiency
Phytopharmaceuticals	STW-5 Peppermint DA-9701‡	Antispasmodics: probable analgesic effect and effect on gastric accommodation	Multipurpose drugs, potentially useful in patients with overlap of FD and IBS DA-9701 has non-inferiority studies compared with itopride and pantoprazole

*Levosulpiride has a dual action: prokinetic and neuromodulatory (atypical antipsychotic).
†Nortriptyline is only available in Mexico in combination with fluphenazine.
‡DA-9701 is not mentioned in the recommendations of the Asociación Mexicana de Gastroenterología, but it is included in this table due to its availability in Mexico.
FD: functional dyspepsia; PDS: postprandial distress syndrome; IBS: irritable bowel syndrome.

overlap with IBS, but more and better studies are required before recommending their use in the treatment of FD.

Herbal compounds and phytopharmaceuticals

In recent years, there has been an increase in published studies on the potential utility of herbal products in some disorders of the gut-brain interaction, primarily in FD[104,105]. The majority of these herbal products are multi-component preparations with a wide variety of effects on gastrointestinal function, which until now have lacked high-quality evidence regarding their efficacy[106-108]. Formal research in herbal medicine has also been resumed through phytopharmacology, which focuses on the study of standardized extracts of medicinal plants. Phytopharmaceuticals are preparations whose active substance contains the extract of a specific plant or a combination of various plants, roots, and

vegetables, and their mechanism of action is known. For example, Rikkunshito (composed of eight herbs and roots) reduces dyspeptic symptoms by promoting adaptive relaxation and increasing gastric emptying. A recent meta-analysis that included 5,475 patients demonstrated greater efficacy of Rikkunshito compared to Western treatment and placebo in significantly reducing the dyspepsia symptom scale and improving gastric emptying[109].

Several phytopharmaceuticals have been commercialized and have been available for clinical use for several years. One of those with the largest number of studies is STW-5, a compound of nine herbs and roots of German origin that has been shown to improve FD symptoms by producing fundic relaxation and promoting gastric emptying. Several clinical studies, controlled and comparative against placebo, as well as meta-analyses, have evaluated STW-5 in patients with FD and have confirmed its efficacy in symptom control after 4-8 weeks of use, with a good safety profile[110-113]. This phytopharmaceutical has been described as "multipurpose," as it also has evidence regarding its effectiveness in the treatment of IBS, making it a practical alternative in patients with overlapping FD and IBS[114-117].

Peppermint oil (Mentha piperita), whose active principle is menthol, has antispasmodic properties due to its capacity to block calcium channels in intestinal smooth muscle, although evidence exists for other possible mechanisms of action, such as modulation of visceral and central sensitivity, and antioxidant, antiparasitic, antifungal, microbiota-modulating, and direct anti-inflammatory effects[118,119]. A meta-analysis that included five controlled clinical trials with 578 patients evaluated the utility of the combination of peppermint oil and caraway oil in the treatment of FD, demonstrating significant relief in global symptoms and epigastric pain (NNT = 3 for both endpoints), with good tolerability and without serious adverse effects[120]. Since it has demonstrated a good clinical effect in IBS[121], it could be a good therapeutic option for those patients with overlapping FD and IBS[117].

DA-9701 is a phytopharmaceutical formulated with ethanolic extracts of *Pharbitidis* (derived from the seeds of *Pharbitis nil Choisy*) and *Corydalis* tuber (derived from the roots of *Corydalis yanhusuo*)[122]. These two herbs have been commonly used in traditional Chinese, Korean, and Japanese medicine for abdominal and gynecological symptoms. Preclinical studies showed favorable effects on gastric emptying and accommodation, colonic motility, and visceral sensitivity. Clinical studies have demonstrated that it is not inferior to other conventional treatments for FD. A multicenter, randomized, controlled study with 462 Korean patients with FD (Rome II) showed that the effect of 30 mg of DA-9701 three times daily on FD symptoms was similar to that of 50 mg of itopride hydrochloride three times daily (37% with DA-9701 and 36% with itopride at 4 weeks)[123]. Another Korean multicenter, randomized, double-blind study that included 389 patients with FD (Rome III) showed that the effect of 30 mg of DA-9701 three times daily on global FD symptoms was similar to that of 40 mg of pantoprazole once daily (60.5% with DA-9701 and 65.6% with pantoprazole at 4 weeks)[124].

Conclusions

FD is one of the most frequent digestive disorders in the general population. It is a complex disorder with multiple pathophysiological factors and diverse therapeutic options. Appropriate knowledge of the different pharmacological alternatives is highly relevant to achieve the therapeutic objectives that this disorder imposes in daily practice. Table 1 summarizes the recommended pharmacological options for the treatment of FD available in Mexico[3].

Funding

The authors declare that they have not received funding for this study.

Conflicts of interest

O. Gómez-Escudero is a speaker for Faes Pharma, Carnot, and Pometis laboratories. R. Carmona-Sánchez and D. Carmona-Guerrero declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments have been conducted on human subjects or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor does it require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

References

1. Stanghellini V, Chan FKL, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92.
2. Carmona-Sánchez R, Gómez-Escudero O, Zavala-Solares M, Bielsa-Fernández MV, Coss-Adame E, Hernández-Guerrero AI, et al. Mexican consensus on dyspepsia. Rev Gastroenterol Mex.2017;82:309-27.
3. Carmona-Sánchez R, Vázquez-Elizondo G, Rodríguez-Leal MA, Gómez-Escudero O, Bielsa-Fernández MV, Coss-Adame E, et al. Recomendaciones de buena práctica clínica en el diagnóstico y tratamiento de la dispepsia funcional. Revisión de expertos de la Asociación Mexicana de Gastroenterología. Rev Gastroenterol Mex. 2025; 90: 227-51
4. Gudjónsson H, Oddsson E, Björnsson S, Gunnlaugsson O, Theodors A, Jónasson TA, et al. Efficacy of sucralfate in treatment of non-ulcer dyspepsia. A double-blind placebo-controlled study. Scand J Gastroenterol. 1993;28:969-72.
5. Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. Lancet. 2020;396:1689-702.
6. Moayyedi P, Soo S, Deeks J, Forman D, Harris A, Innes M, et al. Systematic review: antacids, H2-receptor antagonists, prokinetics, bismuth and sucralfate therapy for non-ulcer dyspepsia. Aliment Pharmacol Ther. 2003;17:1215-27.
7. Kumar M, Yachha SK, Aggarwal R, Shukla S, Pandey R, Prasad KN, et al. Healing of chronic antral gastritis: effect of sucralfate and colloidal bismuth subcitrate. Indian J Gastroenterol. 1996;15:90-3.
8. Gonçalves A, Matias M, Salvador JAR, Silvestre S. Bioactive bismuth compounds: is their toxicity a barrier to therapeutic use? Int J Mol Sci. 2024;25:1600.
9. Black CJ, Paine PA, Agrawal A, Aziz I, Eugenicos MP, Houghton LA, et al. British Society of Gastroenterology guidelines on the management of functional dyspepsia. Gut. 2022;711:1697-723.
10. Ford AC, Moayyedi P, Black CJ, Yuan Y, Veettil SK, Mahadeva S, et al. Systematic review and network meta-analysis: efficacy of drugs for functional dyspepsia. Aliment Pharmacol Ther. 2021;53:8-21.
11. Gwee KA, Lee YY, Suzuki H, Chand Ghoshal U, Holtmann G, Bai T, et al. Asia-Pacific guidelines for managing functional dyspepsia overlapping with other gastrointestinal symptoms. J Gastroenterol Hepatol. 2023;38:197-209.
12. Friesen CA, Neilan NA, Schurman JV, Taylor DL, Kearns GL, Abdel-Rahman SM. Montelukast in the treatment of duodenal eosinophilia in children with dyspepsia: effect on eosinophil density and activation in relation to pharmacokinetics. BMC Gastroenterol. 2009; 9: 32.
13. Potter MDE, Goodsall TM, Walker MM, Talley NJ. Dual histamine blockade for the treatment of adult functional dyspepsia: a single centre experience. Gut. 2020;69:966.
14. Friesen CA, Sandridge L, Andre L, Roberts CC, Abdel-Rahman SM. Mucosal eosinophilia and response to H1/H2 antagonist and cromolyn therapy in pediatric dyspepsia. Clin Pediatr (Phila). 2006;45:143-47.
15. Gillen D, McColl KE. Problems related to acid rebound and tachyphylaxis. Best Pract Res Clin Gastroenterol. 2001;15:487-95.
16. Oh JH, Kwo JG, Jung HK, Tae CH, Song KH, Kang SJ, et al. Clinical practice guidelines for functional dyspepsia in Korea. J Neurogastroenterol Motil. 2020;26:29-50.
17. Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2010;8:830-7.
18. Nasseri-Moghaddam S, Mousavian AH, Kasaeian A, Kanno T, Yuan Y, Ford AC, et al. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Updated systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2023;21:1739-49.e2.
19. Wang WH, Huang JQ, Zheng GF, Xia HH, Wong WM, Liu XG, et al. Effects of proton-pump inhibitors on functional dyspepsia: a meta-analysis of randomized placebo-controlled trials. Clin Gastroenterol Hepatol. 2007;5:178-85.
20. Pinto-Sanchez MI, Yuan Y, Hassan A, Bercik P, Moayyedi P. Proton pump inhibitors for functional dyspepsia. Cochrane Database Syst Rev. 2017;11:CD011194.
21. Sud R, Pebbili KK, Desai SA, Bhagat S, Rathod R, Mane A, et al. Dyspepsia – the Indian perspective: a cross-sectional study on demographics and treatment patterns of dyspepsia from across India (Power 1.0 study). J Assoc Physicians India. 2023;71:11-2.
22. Samsom M, Verhagen MA, vanBerge Henegouwen GP, Smout AJ. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. Gastroenterology. 1999;116:515-20.
23. Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG Clinical Guideline: Management of dyspepsia. Am J Gastroenterol. 2017;112:988-1030.
24. Wauters L, Dickman R, Drug V, Mulak A, Serra J, Enck P, et al. United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia. United European Gastroenterol J. 2021;9:307-31.
25. Iwakiri R, Tominaga K, Furuta K, Masuyama H, Kanke K, Naagahara A, et al. Randomized clinical trial: rabeprazole improves symptoms in patients with functional dyspepsia in Japan. Aliment Pharmacol Ther. 2013;38:729-40.
26. Chuah KH, Loo QY, Hian WX, Khoo XH, Panirsheeluam S, Jubri NBM, et al. Clinical trial: treatment of functional dyspepsia according to subtype compared with empirical proton pump inhibitor. Aliment Pharmacol Ther. 2025;61:258-67.
27. Valdovinos-García LR, Villar-Cávez AS, Huert-Iga FM, Amieva-Balmori M, Arenas-Martínez JS, Bernal-Reyes R, et al. Good clinical practice recommendations for proton pump inhibitor prescription and deprescription. A review by experts from the AMG. Rev Gastroenterol Mex. 2025; 90:111-30.
28. Abdel-Aziz Y, Metz DC, Howden CW. Review article: potassium-competitive acid blockers for the treatment of acid-related disorders. Aliment Pharmacol Ther. 2021;53:794-809.
29. Akiyama J, Hosaka H, Kuribayashi S, Moriyasu S, Hisada Y, Okubo H, et al. Efficacy of vonoprazan, a novel potassium-competitive acid blocker, in patients with proton pump inhibitor-refractory acid reflux. Digestion. 2020;101:174-83.
30. Anik AH, Proma FA, Saha P, Sarker S. Tegoprazan as a new remedy for gastrointestinal diseases in comparison with its therapeutic predecessors: a mini review. Curr Drug Res Rev. 2023 Apr 28. doi: 10.2174/2589977515666230428140741. Online ahead of print.
31. Asaoka D, Nagahara A, Hojo M, Matsumoto K, Ueyama H, Matsumoto K, et al. Efficacy of a potassium-competitive acid blocker for improving symptoms in patients with reflux esophagitis, non-erosive reflux disease, and functional dyspepsia. Biomed Rep. 2017;6:175-80.
32. Scarpignato C, Hunt RH. Potassium-competitive acid blockers: current clinical use and future developments. Curr Gastroenterol Rep. 2024;26:273-93.
33. Huh CW, Youn YH, Jung DH, Cha RR, Kim YJ, Jung K, et al. Efficacy of tegoprazan in patients with functional dyspepsia: a prospective, multicenter, single-arm study. J Neurogastroenterol Motil. 2024;30:313-21.
34. Abbasi A, Siddiqui SA, Ram B, Khan JUA, Sheikh K, Ali A, et al. Real-world evidence to evaluate the efficacy and safety of vonoprazan in gastrointestinal disorders in the Pakistani population. Cureus. 2023;15:e48994.
35. Takahashi N, Tegoprazan TY. A novel potassium-competitive acid blocker to control gastric acid secretion and motility. J Pharmacol Exp Ther. 2018;364:275-86.
36. Shinozaki S, Osawa H, Hayashi Y, Miura Y, Sakamoto H, Yano T, et al. Vonoprazan therapy is as effective for functional dyspepsia without heartburn as acotiamide therapy. J Gastrointest Liver Dis. 2023;32:23-9.
37. Huh CW, Youn YH, Jung DH, Cha RR, Kim YJ, Jung KJ, et al. Efficacy of tegoprazan in patients with functional dyspepsia: a prospective, multicenter, single-arm study. J Neurogastroenterol Motil. 2024;30:313-21.
38. Lim HS, Yoon HJ, Jung HK, Hong JT, Yoo MY, Jeong ES. Effects of tegoprazan, potassium-competitive acid blocker, on the gastric emptying and postprandial symptoms in healthy humans. Dig Dis Sci. 2025;70:1091-8.
39. Pittayanon R, Yuan Y, Bollegala NP, Khanna R, Lacy BE, Andrews CN, et al. Prokinetics for functional dyspepsia: a systematic review and meta-analysis of randomized control trials. Am J Gastroenterol. 2019; 114:233-43.
40. Masuy I, Van Oudenhove L, Tack J. Review article: treatment options for functional dyspepsia. Aliment Pharmacol Ther. 2019;49:1134-72.
41. Banani SJ, Lankarani KB, Taghavi A, Bagheri MH, Sefidbakht S, Geramizadeh B. Comparison of metoclopramide oral tablets and solution in treatment of dysmotility-like dyspepsia. Am J Health Syst Pharm. 2008;65:1057-61.
42. Qi Q, Wang N, Liu H, Li Y. Prokinetics for the treatment of functional dyspepsia: an updated systematic review and network meta-analysis. BMC Gastroenterol. 2023;23:370.
43. Alizadeh-Naeeni M, Saberi-Firoozi M, Pourkhajeh A, Taheri H, Malekzadeh R, Derakhshan MH, et al. Effect of Helicobacter pylori eradication or of ranitidine plus metoclopramide on Helicobacter pylori-positive functional dyspepsia. A randomized, controlled follow-up study. Digestion. 2002;66:92-8.
44. Singh H, Bala R, Kaur K. Efficacy and tolerability of levosulipride, domperidone and metoclopramide in patients with non-ulcer functional dyspepsia: a comparative analysis. J Clin Diagn Res. 2015;9:Fc09-12.
45. Arts E, Anthoni H, de Roy G, D'Hollander J, Verhaegen H. Domperidone in the treatment of dyspepsia: a double-blind placebo-controlled study. J Int Med Res. 1979;7:158-61.
46. Veldhuyzen van Zanten SJ, Jones MJ, Verlinden M, Talley NJ. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. Am J Gastroenterol. 2001;96:689-96.
47. Carbone F, Vandenberghe A, Holvoet L, Piessevaux H, Arts J, Caenepeel P, et al. A double-blind randomized, multicenter, placebo-controlled study of itopride in functional dyspepsia postprandial distress syndrome. Neurogastroenterol Motil. 2022;34:e14337.
48. Macarri G, Biasi L, Brunelli E, Marucci L, Svegliati Baroni G. L-sulpiride versus metoclopramide in functional dyspepsia: a randomized double-blind study. Minerva Med. 1992;83:295-8.

49. Arienti V, Corazza GR, Sorge M, Boriani F, Ugenti F, Biagi F, et al. The effects of levosulpiride on gastric and gallbladder emptying in functional dyspepsia. Aliment Pharmacol Ther. 1994;8:631-8.
50. Corazza GR, Tonini M. Levosulpiride for dyspepsia and emesis: a review of its pharmacology, efficacy and tolerability. Clin Drug Invest. 2000;19:151-62.
51. Sabbatini F, Minieri M, Manzi G, Piai G, D'Angelo V, Mazzacca G. Clinical efficacy and safety of cisapride and clebopride in the management of chronic functional dyspepsia: a double-blind, randomized study. Ital J Gastroenterol. 1991;23:1-4.
52. Ogishima M, Kaibara M, Ueki S, Kurimoto T, Taniyama K. Z-338 facilitates acetylcholine release from enteric neurons due to blockade of muscarinic autoreceptors in guinea pig stomach. J Pharmacol Exp Ther. 2000;294:33-7.
53. Sterne JA, Savović J, Page MJ, Elbers RG, Bleencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019:366:l4898.
54. Kusunoki H, Haruma K, Manabe N, Imamura H, Kamada T, Shiotani A, et al. Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: randomized controlled study evaluation by real-time ultrasonography. Neurogastroenterol Motil. 2012;24:540-5, e250-1.
55. Xiao G, Xie X, Fan J, Deng J, Tan S, Guo Q, et al. Efficacy and safety of acotiamide for the treatment of functional dyspepsia: systematic review and meta-analysis. ScientificWorldJournal. 2014;2014:541950.
56. Shrestha DB, Budhathoki P, Subedi P, Khadka M, Karki P, Sedhai YR, et al. Acotiamide and functional dyspepsia: a systematic review and meta-analysis. Cureus. 2021;13:e20532.
57. Peeters TL, Matthijs G, Depoortere I, Cachet T, Hoogmartens J, Vantrappen G. Erythromycin is a motilin receptor agonist. Am J Physiol. 1989;257:G470-4.
58. Arts J, Caenepeel P, Verbeke K, Tack J. Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. Gut. 2005;54:455-60.
59. Zatorski H, Mosinska P, Storr M, Fichna J. Relamorelin and other ghrelin receptor agonists – future options for gastroparesis, functional dyspepsia and proton pump inhibitors-resistant non-erosive reflux disease. J Physiol Pharmacol. 2017;68:797-805.
60. Bor A, Kalkan IH, Savarino E, Rao S, Tack K, Pasricha J, et al. Prokinetics-safety and efficacy: The European Society of Neurogastroenterology and Motility/The American Neurogastroenterology and Motility Society expert review Neurogastroenterol Motil. 2024;36:e14774.
61. Sgambato V. The serotonin 4 receptor subtype: a target of particular interest, especially for brain disorders. Int J Mol Sci. 2024;25:5245.
62. Zala AV, Walker MM, Talley NJ. Emerging drugs for functional dyspepsia. Expert Opin Emerg Drugs. 2015;20:221-33.
63. Tack J, Camilleri M, Chang L, Chey WD, Galligan JJ, Lacy BE, et al. Systematic review: cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. Aliment Pharmacol Ther. 2012;35:745-67.
64. Tack J, Masuy I, Van Den Houte K, Wauters L, Schol J, Vanuytsel Y, et al. Drugs under development for the treatment of functional dyspepsia and related disorders. Expert Opin Investig Drugs. 2019;28:871-89.
65. Tae CH, Cha RR, Oh JH, Gweon TG, Park JK, Bang KB, et al. Clinical trial: Efficacy of mosapride controlled-release and nortriptyline in patients with functional dyspepsia: a multicenter, double-placebo, double-blinded, randomized controlled, parallel clinical study. J Neurogastroenterol Motil. 2024;30:106-15.
66. Nennstiel S, Bajbouj M, Schmid RM, Becker V. Prucalopride reduces the number of reflux episodes and improves subjective symptoms in gastroesophageal reflux disease: a case series. J Med Case Rep. 2014;8:34.
67. Vakil N, Laine L, Talley NJ, Zakko SF, Chey WD, Kralstein J, et al. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. Am J Gastroenterol. 2008;103:1906-19.
68. Vakil N, Kianifard F, Bottoli I. Exploratory study of tegaserod for dyspepsia in women receiving PPIs for heartburn. Arch Drug Inf. 2008;1:79-88.
69. Jin M, Mo Y, Ye K, Chen M, Liu Y, He C. Efficacy of serotonin receptor agonists in the treatment of functional dyspepsia: a meta-analysis. Arch Med Sci. 2019;15:23-32.
70. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology. 1998;115:1346-52.
71. Tack J, Janssen P, Masaoka T, Farré R, Van Oudenhove L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. Clin Gastroenterol Hepatol. 2012;10:1239-45.
72. Taghvaei T, Elyasi F, Rahbar Z, Neyestani F. Effectiveness of buspirone in patients with functional dyspepsia: a randomized, double-blind, placebo-controlled study. Middle East J Dig Dis. 2021;13:302-13.
73. Mohamedali Z, Amarasinghe G, Hopkins CWP, Moulton CD. Effect of buspirone on upper gastrointestinal disorders of gut-brain interaction: a systematic review and meta-analysis. J Neurogastroenterol Motil. 2025;31:18-27.
74. Miwa H, Nagahara A, Tominaga K, Yokoyama T, Sawada Y, Inoue K, et al. Efficacy of the 5-HT1A agonist tandospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. Am J Gastroenterol. 2009;104:2779-87.
75. Liu L, Yang W, Lu Y, Wang J, Zheng Y, Gu S. Clinical efficacy of tandospirone on functional dyspepsia patients with anxiety: a randomized, placebo-controlled study. Dig Dis Sci. 2023;68:521-8.
76. Gómez-Escudero O, Remes-Troche JM, Coss-Adame E, García-Zermeño K, Aquino-Matus J, Jiménez-Pavón J, et al. Recomendaciones de buena práctica clínica para el uso de neuromoduladores en gastroenterología: revisión conjunta de expertos de la Asociación Mexicana de Gastroenterología (AMG) y Asociación Mexicana de Neurogastroenterología y Motilidad (AMNM). Rev Gastroenterol Mex. 2025;90:252-87.
77. Keefer L, Drossman DA, Guthrie E, Simrén M, Tillisch K, Olden K, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016;150:1408-19.
78. Drossman DA, Tack J, Ford AC, Szigethy E, Törnblom H, Van Oudenhove L. Neuromodulators for functional gastrointestinal disorders (disorders of gut-brain interaction): a Rome Foundation Working Team Report. Gastroenterology. 2018;154:1140-71.
79. Gómez-Escudero O, Aquino-Matus J, Valdovinos-García LR. Neuromoduladores: lo que el gastroenterólogo debe saber. En: Gómez-Escudero O, Velarde-Ruiz Velasco JA, Coss-Adame E, editores. Clínicas Mexicanas de Gastroenterología, Farmacología I. México: AMS; 2024. p. 179-203.
80. Ford AC, Luthra P, Tack J, Boeckxstaens GE, Moayyedi P, Talley NJ. Efficacy of psychotropic drugs in functional dyspepsia: systematic review and meta-analysis. Gut. 2017;66:411-20.
81. Talley NJ, Locke GR, Saito YA, Almazar AE, Bouras EP, Howden CW, et al. Effect of amitriptyline and escitalopram on functional dyspepsia: a multicenter, randomized controlled study. Gastroenterology. 2015;149:340-9.e2.
82. Liu J, Jia L, Jiang SM, Zhou WC, Liu Y, Xu J. Effects of low-dose amitriptyline on epigastric pain syndrome in functional dyspepsia patients. Dig Dis Sci. 2021;66:521-5.
83. Cheong PK, Ford AC, Cheung CKY, Ching JYL, Chan Y, Sung JJY, et al. Low-dose imipramine for refractory functional dyspepsia: a randomized, double-blind placebo-controlled trial. Lancet Gastroenterol Hepatol. 2018;3:837-44.
84. Banihashem SS, Mofatioshieh SM, Rastegar R, Sadeghi A. Comparing the efficacy of duloxetine and nortriptyline in alleviating the symptoms of functional dyspepsia – a randomized clinical trial. Front Psychiatry. 2024;14:1297231.
85. Zhou W, Li X, Huang Y, Xu X, Liu Y, Wang J, et al. Comparative efficacy and acceptability of psychotropic drugs for functional dyspepsia in adults: a systematic review and network meta-analysis. Medicine (Baltimore). 2021;100:e26046.
86. Lacy BE, Saito YA, Camilleri M, Bouras E, DiBaise JK, Herrick LM, et al. Effects of antidepressants on gastric function in patients with functional dyspepsia. Am J Gastroenterol. 2018;113:216-24.
87. Drossman DA, Tack J, Ford AC, Szigethy E, Törnblom H, Van Oudenhove L. Neuromodulators for functional gastrointestinal disorders (disorders of gut-brain interaction): a Rome Foundation Working Team Report. Clin Gastroenterol Hepatol. 2018;154:1140-71.
88. Tack J, Ly HG, Carbone F, Vanheel H, Vanuytsel T, Holvoet L, et al. Efficacy of mirtazapine in patients with functional dyspepsia and weight loss. Clin Gastroenterol Hepatol. 2016;14:385-92.
89. Jamshidfar N, Hamdieh M, Eslami P, Batebi S, Sadeghi A, Rastegar R, et al. Comparison of the potency of nortriptyline and mirtazapine on gastrointestinal symptoms, the level of anxiety and depression in patients with functional dyspepsia. Gastroenterol Hepatol Bed Bench. 2023;16:468-77.
90. Cao L, Li G, Cao J, Li F, Han W. Randomized clinical trial: the effects of mirtazapine in functional dyspepsia patients. Ther Adv Gastroenterol. 2025;18:17562848241311129.
91. Kotikula I, Thinrungroj N, Pinyopornpanish K, Kijdamrongthum P, Leerapun A, Chitapanarux T, et al. Randomised clinical trial: the effects of pregabalin vs placebo on functional dyspepsia. Aliment Pharmacol Ther. 2021;54:1026-32.
92. Shafigh-Ardestani MH, Karami-Horestani M, Emami B, Arjmandpour A. Evaluating the effect of oral gabapentin on the improvement of gastrointestinal symptoms in patients with functional dyspepsia resistant to conventional treatments. Adv Biomed Res. 2019:8:53.
93. Staller K, Thurler AH, Reynolds JS, Dimisko LR, McGovern R, Skarbinski KF, et al. Gabapentin improves symptoms of functional dyspepsia in a retrospective, open-label cohort study. J Clin Gastroenterol. 2019;53:379-84.
94. Marasco G, Fiocca M, Cremon C, Colecchia L, Maida M, Dajti E, et al. Therapeutic role of probiotics for the treatment of dyspepsia: a review of the literature. Neurogastroenterol Motil. 2025:e70057.
95. Brown G, Hoedt EC, Keely S, Shah A, Walker MM, Holtmann G, et al. Role of the duodenal microbiota in functional dyspepsia. Neurogastroenterol Motil. 2022;34:e14372.
96. Wauters L, Tito RY, Ceulemans M, Lambaerts M, Accarie A, Rymenans L, et al. Duodenal dysbiosis and relation to the efficacy of proton pump inhibitors in functional dyspepsia. Int J Mol Sci. 2021;22:13609.
97. Shanahan ER, Kang S, Staudacher H, Shah A, Do A, Burns G, et al. Alterations to the duodenal microbiota are linked to gastric emptying and symptoms in functional dyspepsia. Gut. 2023;72:929-38.
98. Tziatzios G, Gkolfakis P, Leite G, Mathur R, Damoraki G, Giamarellos-Bourboulis EJ, et al. Probiotics in functional dyspepsia. Microorganisms. 2023;11:351.

99. Koga Y. Microbiota in the stomach and application of probiotics to gastroduodenal diseases. World J Gastroenterol. 2022;28:6702-15.
100. Zhang J, Wu HM, Wang X, Xie J, Li X, Ma J, et al. Efficacy of prebiotics and probiotics for functional dyspepsia: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99:e19107.
101. Tan VP, Liu KS, Lam FY, Hung IF, Yuen MF, Leung WK. Randomized clinical trial: rifaximin versus placebo for the treatment of functional dyspepsia. Aliment Pharmacol Ther. 2017;45:767-76.
102. Kim YJ, Jo IH, Paik CN, Lee JM. Efficacies of prokinetics and rifaximin on the positivity of a glucose breath test in patients with functional dyspepsia: a randomized trial. Rev Esp Enferm Dig. 2023;115:121-7.
103. Shah A, Gurusamy SR, Hansen T, Callaghan G, Talley NJ, Koloski N, et al. Concomitant irritable bowel syndrome does not influence the response to antimicrobial therapy in patients with functional dyspepsia. Dig Dis Sci. 2022;67:2299-309.
104. Carmona-Sánchez RI, Carmona-Guerrero DI. Terapias herbales. En: Gómez-Escudero O, Velarde-Ruiz Velasco JA, Coss-Adame E, editores. Clínicas Mexicanas de Gastroenterología, Farmacología I. México: AMS; 2024. p. 223-35.
105. Báez G, Vargas C, Arancibia M, Papuzinski C, Franco JV. Non-Chinese herbal medicines for functional dyspepsia. Cochrane Database Syst Rev. 2023;(6):CD013323.
106. Qiu J, Grana J. Herbal medicines for functional dyspepsia. Am Fam Physician. 2024; 109: 313-314.
107. Kim YS, Kim JW, Ha NY, Kim J, Ryu HS. Herbal therapies in functional gastrointestinal disorders: a narrative review and clinical implication. Front Psychiatry. 2020;11:1-15.
108. Tan N, Gwee KA, Tack J, Zhang M, Li Y, Chen M, et al. Herbal medicine in the treatment of functional gastrointestinal disorders: a systematic review with meta-analysis. J Gastroenterol Hepatol. 2019;35:544-56.
109. Ko SJ, Park J, Kim MJ, Kim J, Park JW. Effects of the herbal medicine Rikkunshito, for functional dyspepsia: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2021;36:64-74.
110. Braden B, Caspary W, Borner N, Vinson B, Schneider AR. Clinical effects of STW 5 (Iberogast) are not based on acceleration of gastric emptying in patients with functional dyspepsia and gastroparesis. J Neurogastroenterol Motil. 2009;21:632-8, e25.
111. Báez G, Vargas C, Arancibia M, Papuzinski C, Franco JV. Non-Chinese herbal medicines for functional dyspepsia. Cochrane Database Syst Rev. 2023;(6):CD013323.
112. Andresen V, Shah A, Fink C, Rabini S, Wargenau M, Holtmann G. Efficacy and safety of STW 5-II for functional dyspepsia treatment: a patient data-based meta-analysis. Digestion. 2024;105:166-74.
113. Vinson B, Fink C, Wargenau M, Talley NJ, Holtmann G. Double-blind, randomized, 8-week multicenter study of the efficacy and safety of STW 5-II versus placebo in functional dyspepsia. JGH Open. 2024; 8:e13054.
114. Malfertheiner P. STW 5 (Iberogast) therapy in gastrointestinal functional disorders. Dig Dis. 2017;35(Suppl 1):25-9.
115. Kim YS, Kim JW, Ha NY, Kim J, Ryu HS. Herbal therapies in functional gastrointestinal disorders: a narrative review and clinical implication. Front Psychiatry. 2020;11:601.
116. Allescher HD, Burgell R, Malfertheiner P, Mearin F. Multi-target treatment for irritable bowel syndrome with STW 5: pharmacological modes of action. J Gastrointestin Liver Dis. 2020;29:227-33.
117. Remes-Troche JM, Coss-Adame E, Schmulson M, García-Zermeño K, Amieva-Blamori M, Carmona-Sánchez R, et al. Pharmacologic treatment of irritable bowel syndrome. Position statement of the Asociación Mexicana de Gastroenterología, 2024. Rev Gastroenterol Mex. 2025; 90:77-110.
118. Scarpellini E, Broeders B, Schol J, Santori P, Addarii M, Boccuto L, et al. The use of peppermint oil in gastroenterology. Curr Pharm Des. 2023;29:576-83.
119. Chumpitazi BP, Kearns GL, Shulman RJ. Review article: The physiological effects and safety of peppermint oil and its efficacy in irritable bowel syndrome and other functional disorders. Aliment Pharmacol Ther. 2018;47:738-52.
120. Li J, Lv L, Zhang J, Xu L, Zeng E, Zhang Z, 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.
121. Alammar N, Wang L, Saberi B, Nanavati J, Holtmann G, Shinohara RT, 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.
122. Kim YS, Kim JW, Ha NY, Kim J, Ryu HS. Herbal therapies in functional gastrointestinal disorders: a narrative review and clinical implication. Front Psychiatry. 2020;11:601.
123. Choi MG, Rhee PL, Park H, Lee OY, Lee KJ, Choi SC, et al. Randomized, controlled, multi-center trial: comparing the safety and efficacy of DA-9701 and itopride hydrochloride in patients with functional dyspepsia. J Neurogastroenterol Motil. 2015;21:414-22.
124. Jung HK, Lee KJ, Choi MG, Park H, Lee JS, Rhee PL, et al. Efficacy of DA-9701 (Motilitone) in functional dyspepsia compared to pantoprazole: a multicenter, randomized, double-blind, non-inferiority study. J Neurogastroenterol Motil. 2016;22:254-63.