Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Title:
Updated document on the management of functional dyspepsia by the Asociación Española de Neurogastroenterologia y Motilidad (ASENEM) and Sociedad Española de Medicina Familiar y Comunitaria (semFYC)

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DOI: 10.17235/reed.2025.10572/2024
Link: PubMed (Epub ahead of print)

Please cite this article as:
Serra Jordi, Alcalá-González Luis Gerardo, Mendive Juan Manuel, Santander Vaquero Cecilio, Serrano Falcón Blanca. Updated document on the management of functional dyspepsia by the Asociación Española de Neurogastroenterologia y Motilidad (ASENEM) and Sociedad Española de Medicina Familiar y Comunitaria (semFYC) . Rev Esp Enferm Dig 2025. doi: 10.17235/reed.2025.10572/2024.

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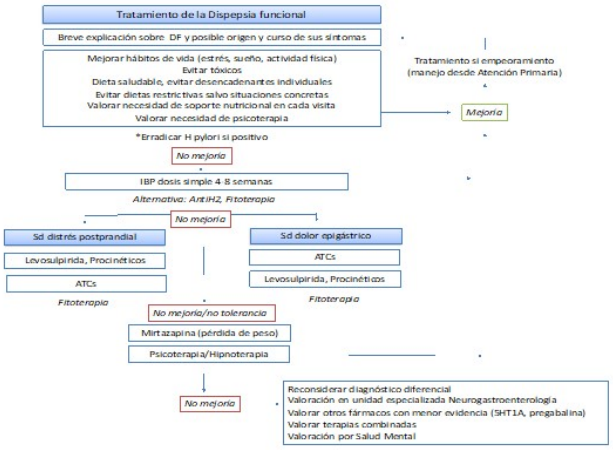
UPDATED DOCUMENT ON THE MANAGEMENT OF FUNCTIONAL DYSPEPSIA BY THE *ASOCIACIÓN ESPAÑOLA DE NEUROGASTROENTEROLOGIA Y MOTILIDAD* (ASENEM) AND *SOCIEDAD ESPAÑOLA DE MEDICINA FAMILIAR Y COMUNITARIA* (semFYC)

EPIGASTRIC PAIN

HEARTBURN

EARLY SATIETY

POSTPRANDIAL FULLNESS



Management of dyspeptic symptoms:
PRIMARY CARE:
1. Assess *Helicobacter pylori* infection
2. PPI or prokinetics
3. Neuromodulators

REFER TO SPECIALIST complex cases with need for further study:
- Endoscopy
- Gastric emptying
- Other special testing

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Updated document on the management of functional dyspepsia by the *Asociación Española de Neurogastroenterologia y Motilidad* (ASENEM) and *Sociedad Española de Medicina Familiar y Comunitaria* (semFYC)

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Funding: Laboratorios Salvat. This document was developed by the Asociación Española de Neurogastroenterologia y Motilidad and the Sociedad Española de Medicina Familiar y Comunitaria. Laboratorios Salvat have not taken part in or influenced in any way the development of the present paper.

Authors´ contributions: Writing-original draft: L. G. A. G., J. M. M., C. S. V., and B. S. F.; writing-review and editing: J. S., and J. S.

Conflicts of interest: JS: research grants from Bayer and Laboratorios Salvat. Consultant/Speaker for Menarini, Casen Recordati, Schwabe, and Norgine. CS: speaker/author in educational courses and/or consultant for Laborie/MMS, Medtronic Covidien AG, Menarini Consumer Healthcare, Doctaforum Medical Marketing S.L., Isomed Pharma S.L., AstraZeneca y Farma de Colombia SAS; has received research funds from AstraZeneca, EsoCap Biotech, Regeneron Pharmaceuticals Inc., Celldex Therapeutics, Adare Pharmaceuticals Inc., International marketing & Communication, S.A, and Dr. Falk Pharma GmbH. JM: consultant for and education activities funded by

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Reckitt-Benkiser. BS-F: Consultant/Speaker for Schwabe. LA-G: no conflicts of interest apply.

Artificial intelligence: the authors declare that they did not use artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Recibido: 07/06/2024

Aceptado: 17/06/2024

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ABSTRACT

Functional dyspepsia (FD) is a gut-brain axis disorder characterized by postprandial fullness, early satiety, bloating and/or epigastric pain, which are presumed to originate in the gastroduodenal tract. While the international recommendations in the Rome IV consensus require endoscopy to rule out an organic condition before establishing a diagnosis of FD, international guidelines recommend that, in the absence of risk factors, patient management be initiated at the primary care level by establishing *Helicobacter pylori* infection status, with eradication when positive, followed by empiric therapy with proton pump inhibitors and/or prokinetics, and that endoscopy be reserved for patients refractory to said measures. Second-line therapy includes neuromodulating agents, among which tricyclic antidepressants and atypical antipsychotics such as levosulpiride stand out. The latter has a predominant prokinetic effect, hence it is also used as first-line therapy for patients where early satiety and postprandial fullness predominate. Other therapy alternatives include phytotherapy using STW5 or peppermint/caraway oil, which have shown their superiority over placebo in controlled studies. Concurrently, dietary and lifestyle counseling, as well as psychological interventions such as cognitive-behavioral therapy, when available, may represent a therapeutic alternative worth considering for some patients.

Keywords: Functional dyspepsia. Gastroesophageal reflux disease.

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INTRODUCTION

Functional dyspepsia (FD) is a gut-brain axis disorder characterized by a set of gastrointestinal (GI) symptoms localized in the upper abdomen, commonly associated with food ingestion, in the absence of any identifiable organic cause using standard diagnostic techniques (1). *Common symptoms* in FD include postprandial fullness, early satiety, bloating and/or epigastric pain, which presumably originate in the gastroduodenal tract. On occasion, patients report nausea, vomiting and/or weight loss (2). In order to be considered as FD, these symptoms must occur in a chronic, relapsing manner, first appearing at least 6 months before diagnosis (3). Given its high prevalence and challenging management, FD represents a significant challenge for both the family doctor and gastroenterology specialist. This collaborative paper by the *Asociación Española de Neurogastroenterologia y Motilidad* (ASENEM) and the *Sociedad Española de Medicina Familiar y Comunitaria* (semFYC) provides up-to-date management recommendations from the perspective of both family medicine and gastroenterology specialists.

PATHOPHYSIOLOGICAL MECHANISMS

Although the pathophysiology of FD is not fully elucidated, mechanistic studies have shown the presence of both sensitive and motor gastroduodenal changes, as well as inflammatory activity in the duodenal mucosa, which together contribute to the development of digestive complaints in many of these patients (Fig. 1). Patients with FD display gastric motility changes. It has been documented that patients with FD have delayed gastric emptying (4) and impaired gastric fundic accommodation in response to food ingestion, and this impairment is associated with their early satiety and postprandial fullness complaints (5). However, in real practice, gastric emptying results are not clearly associated with clinical complaints (6), hence its study is not recommended in daily clinical practice. Visceral hypersensitivity is also a significant mechanism. Patients with FD have impaired gastric sensitivity to both physical and chemical stimuli. Using a gastric barostat, up to 30 % of patients with FD have a lower threshold for discomfort during fundus distension (7), this being more prevalent in

patients with more severe epigastric pain and weight loss (7). On the other hand, when assessing the response to acid infusion directly into the stomach, patients with FD also display more intense symptoms versus healthy subjects (8). The severity of digestive complaints in patients with FD is directly related to visceral hypersensitivity level, regardless of any potential psychological comorbidities (9).

In the last few years changes in the intestinal epithelial barrier and local micro-inflammation in the duodenum have also been reported as an additional symptom-associated mechanism in FD (10). Local mast cell activation is directly related to increased psychological stress (11). Furthermore, increased eosinophil infiltration has been shown in the duodenal mucosa of patients with FD when compared to healthy controls (12). Both mast cells and eosinophils play a significant role in allergic inflammatory responses (13), and their increased presence in the duodenal mucosa may suggest some sort of allergic activation at the local level in response to certain stimuli (gastric acid, food, etc.).

MANAGEMENT OF FUNCTIONAL DYSPEPSIA

Diagnostic study of functional dyspepsia

The diagnostic approach to patients with FD starts by taking detailed clinical notes including dietary habits, medical history, use of drugs potentially involved in their symptomatology (NSAIDs, opioids, phosphodiesterase inhibitors, calcium channel blockers, GLP1 agonists, etc.), family history (celiac disease), and physical examination, complemented by *blood testing and an endoscopic study* (gastroscopy with biopsies) to exclude any organic/structural conditions potentially accounting for the patient-reported complaints.

Symptom-based criteria have been suggested for a standardized diagnosis of FD. According to the *Rome IV criteria* (3) FD is defined as the presence of one or more of the following complaints: postprandial fullness, early satiety, epigastric pain or heartburn, and no evidence of structural conditions (blood workup and oral panendoscopy). The criteria must have been met for the previous three months, with symptom onset at least 6 months before diagnosis. These symptom frequency and duration criteria are recommended to facilitate research studies; however, they are

not strictly necessary for a diagnosis in daily clinical practice.

Two FD subtypes are recognized according to the symptoms that predominate; however, both subtypes commonly overlap:

1. *Postprandial distress syndrome* is characterized by postprandial fullness after a standard meal, *at least 3 days a week,* and/or early satiety precluding completion of a standard meal, at least 3 days a week. Postprandial belching and nausea may be associated.
2. *Epigastric pain syndrome* is characterized by epigastric pain and/or severe heartburn, *at least once a week*, with a negative impact on daily activity. Meals may induce or alleviate this. It is not generalized to the whole abdomen or the chest, is not suggestive of a biliary condition, and is not relieved by defecation.

Endoscopy is mandatory for establishing a firm diagnosis of FD (1). Infection with H. pylori *must be ruled out or eradicated,* as it is a known cause of dyspepsia. Currently, some authors also recommend duodenal biopsy to rule out celiac disease and giardiasis, but no definite consensus exists in this regard. Anyway, from a pragmatic perspective, in the primary care setting a diagnostic-therapeutic approach is used that may initially exclude endoscopy under the conditions described below.

Other diagnostic tests recommended on a case-by-case basis by the NICE Guidelines (14) to actively rule out FD include:

1. Serology for celiac disease (transglutaminase antibody test) in patients with FD and irritable bowel syndrome (IBS)-related complaints.
2. Abdominal ultrasound if epigastric pain has been present for less than 1 year and biliary colic features are associated (localized/radiating to the right hypochondrium).
3. Abdominal CT scan if weight loss is present and symptom onset develops at over 60 years of age, to rule out pancreatic cancer.

The various diagnostic tests for FD are used at different clinical practice levels, depending on availability and ease of access *(primary care, gastroenterology) (15).*

The *differential diagnosis* of FD includes other organic causes of dyspepsia such as peptic ulcer, gastroesophageal reflux disease, drugs, and gastric tumors. Furthermore, FD may often overlap with other disorders:

- *IBS:* over 60 % of patients with FD may have symptoms of IBS, another gut-brain axis disorder, and overlap may be more likely when symptoms are severe.
- *Gastroesophageal reflux disease (GERD):* the presence of retrosternal pyrosis and regurgitation suggests GERD, and both diagnoses overlap in 30 % of patients.
- *Gastroparesis:* objective delayed gastric emptying in the absence of mechanical obstruction, with mainly nausea, vomiting, early satiety, postprandial fullness, and/or abdominal pain symptoms. Motility testing is not recommended routinely as part of the diagnostic workup of FD. The indication of gastric emptying scintigraphy is made for patients with FD experiencing mainly severe nausea and vomiting, as well as empiric therapy failure (16).

Initial management in primary care

FD represents a diagnostic, therapeutic challenge in the primary care setting because of its high prevalence and the difficulties often associated with the therapy regimens necessary to relieve its manifestations. Patient acquaintance and longitudinal health care are important. Both primary care characteristics may help efficiently manage this health issue. Thus, a history of fibromyalgia or anxiety in a patient with suspected FD may help in our clinical assessment (3,17).

In the presence of clinical characteristics suggestive of FD, current European clinical practice guidelines establish that an endoscopic study is not necessary for all patients in the primary care setting, but may be reserved for patients with symptom onset at 55 or more years of age (over 60 years in American guidelines), or for those presenting with an alarm sign (3,14,15) (Table 1).

General recommendations: lifestyle

Anamnesis is the primary diagnostic, therapeutic tool in a patient with dyspepsia (3,14,15). In fact, a large part of the problems associated with symptomatology have to do with unhealthy lifestyles, including dietary and nutritional aspects as well as physical activity and exercise. Obesity and overweight also have a negative impact, and are definitely present in many patients with dyspepsia.

A motivational interview centered on identifying aspects amenable to improvement to be incorporated into day-to-day living may represent a highly positive therapeutic approach.

Inividuals should be capable themselves of identifying their change needs and the steps thereto within a collaborative, shared decision-making strategy.

Specific treatment of dyspepsia

Currently, in our setting, the clinical management of patients with dyspeptic complaints and no alarm signs should start by establishing the status of infection with *Helicobacter pylori* as first step, as shown in figure 2 (3).

If the infection is established, whether through breath testing or fecal antigen testing, eradication therapy should be attempted using the most effective regimen available at the time and place. If *Helicobacter pylori* testing yields a negative result, in the absence of alarm signs, the guidelines suggest administering a trial of proton pump inhibitors (PPIs) for 4 to 8 weeks as first step (Fig. 2).

In case of poor response to this treatment, the next therapy level includes prokinetic agents; however, particularly in patients with predominant epigastric pain, consideration may also be given to moving on directly to tricyclic antidepressants (amitriptyline) for 8-12 weeks.

Having arrived at this point, it is befitting to consider how several studies have suggested that, in contrast to patients with the epigastric pain syndrome subtype of FD (who usually respond better to PPIs and antidepressants), patients with postprandial distress syndrome may respond better to prokinetics. Therefore, the timing of prokinetic therapy onset should be individualized for each patient (18).

When prokinetics are used, a very common occurrence in primary care, comparative meta-analyses have shown a superior benefit of levosulpiride, an atypical antipsychotic (see below) with prokinetic action, versus commonly used classic prokinetics such as domperidone, metoclopramide or cinitapride (19,20). Before prescription, it should be considered that these drugs act on dopaminergic receptors, hence they are contraindicated in patients with Parkinson's disease, established neuroleptic-related tardive dyskinesia, and epilepsy. Domperidone has been associated with an increased

risk of severe ventricular arrhythmias, especially is patients older than 60 years, and is therefore contraindicated in patients known to have prolonged cardiac conduction intervals (particularly QT) and patients with significant electrolyte imbalances or underlying heart disease, including congestive heart failure.

Treatment of difficult-to-control functional dyspepsia

FD symptoms may persist beyond hygienic-dietary measures, *Helicobacter pylori* eradication and PPIs, which are the recommended first-line treatments (1), and also after treatment with prokinetic agents. In this scenario, other therapeutic strategies must be considered, always ensuring a correct differential diagnosis, that life habits were improved, and that the need for psychotherapy and nutritional support was evaluated (Fig. 2).

Neuromodulators

Neuromodulators or psychoactive drugs are useful for the treatment of gut-brain axis disorders; they have been accepted in the IBS setting (21,22), but evidence for FD is sparser. A recently reported systematic review of FD medications (18) concluded that neuromodulators are effective in the management of FD, albeit with notable heterogeneity among the various studies reported thus far. Benefits are limited to tricyclic antidepressants (TCAs), antipsychotics, pregabalin and mirtazapine.

TCAs: amitriptyline and imipramine at 10-50 mg once a day have demonstrated their superiority over placebo for the control of dyspeptic symptoms in 5 clinical trials, 4 of them in patients refractory to other treatments (PPIs, prokinetics) (23-26). Because of this, combined with the adverse effects of prokinetics and low evidence for their role in FD, the US-Canadian guideline recommends using TCAs before prokinetics in both FD subtypes (16).

Amitriptyline seems to induce a greater response in the epigastric pain subtype of FD, compared to delayed gastric emptying cases (1,18), and has proven superior to escitalopram in this clinical context (25). Given its effectiveness in other functional disorders, it may be useful when bowel symptoms are associated, but further studies are needed to establish its position in the

therapeutic algorithm for overlap syndromes (18).

However, TCAs are not free from adverse effects, which may limit long-term treatment (27) (Table 2), not to mention the reluctance of some patients to receive antidepressants. In order to increase adherence, the indication and treatment objectives, as well as the time to effect (1-8 weeks), should be discussed with the patient; also, gradual dose titration from 10 mg to 50 mg once daily may be used to improve tolerance (14).

Antipsychotics: sulpiride and levosulpiride rank second in the classification of FD treatment effectiveness (18) after TCAs when only studies with low publication bias are considered. In addition, they have demonstrated their effectiveness to control FD symptoms completely with no more adverse effects than placebo. The most common dosages and adverse events are listed in table 2 (28).

Mirtazapine, at 15 mg daily, has proven superior to placebo in patients with FD and weight loss (excluding anxiety) for improving early satiety, weight gain, and tolerable daily intake, but not dyspectic complaints overall (3).

The neuromodulators most commonly used in our setting for the treatment of FD are summarized in table 2.

Phytotherapy

Plant-derived products represent an increasingly demanded treatment alternative, but their huge variety and the scarce or nil scientific evidence supporting their effectiveness and safety limit their use. Table 2 lists the options with evidence for FD (32).

STW5: according to the results of a recent meta-analysis this combination of herbs improves the global and cardinal symptoms of FD after treatment for 4 and 8 weeks, with no differences in side effects versus placebo (33). It has proven effective in patients with IBS (Rome IV) (34) and may be a good alternative in cases with gas-related complaints (35).

A preparation containing a combination of *peppermint oil and caraway oil* has been shown to be effective for epigastric pain relief and overall improvement

in FD according to a recent meta-analysis (36), with a good safety profile. Furthermore, it improves other FD symptoms such as early satiety and bloating (37), and seems to alleviate IBS-specific intestinal complaints (36).

Others: Rikunshito, Zhizhu Kuanzhong, not available in our setting. *Curcuma longa* has demonstrated superiority over omeprazole in improving symptoms (38).

Phytotherapy has not been included in the treatment algorithms of major international clinical guidelines for FD (1,14,16), even though it may represent a safe treatment alternative in view of the above-mentioned evidence. Quality studies are needed to assess its role in the treatment scheme for FD and FD-IBS overlap, a scenario where it may play a promising role given its actions on multiple targets/mechanisms (32).

Psychological interventions

Their use is based on the social and psychological factors that may accompany FD complaints, and on the psychiatric comorbidities commonly associated with these conditions**.** The US-Canadian guideline (16) reviewed 13 trial including psychotherapy, most commonly cognitive-behavioral therapy (CBT), and found significant benefits in terms of psychological, digestive symptoms and quality of life versus the control arm in the management of FD. Other less-studied interventions include interpersonal psychodynamic therapy, relational conflict therapy, stress management, and hypnotherapy, all with good results but in need for more supportive evidence (14). Heterogeneity in study design does not allow clear conclusions regarding the therapy of choice, which must be selected according to site availability and patient comorbidity.

CONCLUSIONS

FD is a highly prevalent chronic disorder and a common cause of visits to both primary care and specialist gastroenterology clinics. According to the stringent criteria laid down by the Rome consensus on gut-brain axis disorders, the diagnosis of FD requires frequent symptoms (epigastric pain or heartburn at least one day a week, or early

satiety or postprandial fullness at least three days a week) that interfered with patient activities for the past 3 months, and with symptom onset at least 6 months earlier. Furthermore, standard upper endoscopy is required to rule out any organic condition as symptom cause. However, in daily clinical practice and because of its high prevalence, international guidelines advise that patient management may be initiated in primary care without the need for upper GI endoscopy except in late-onset cases or in patients presenting with alarm symptoms. Thus, in the primary care setting, it is recommended that testing to exclude *Helicobacter pylori* infection be first performed, and that treatment be then started with proton pump inhibitors. In unresponsive cases, and primarily in patients with predominant postprandial distress, prokinetic agents may be considered as first choice. Should the patient fail to respond to these measures, the next step involves the indication of neuromodulators or phytotherapy. At this point, we believe that patient reassessment is the best course of action and, when not done before, consideration should be given to ordering an upper GI endoscopy and blood workup including celiac disease markers. In patients with severe nausea or vomiting and conditions predisposing to gastroparesis, including diabetes *mellitus* or surgical procedures apt to damage the vagus nerve, ruling out impaired gastric emptying using isotope studies should be considered. In general, most of these patients may be managed in primary care, but in cases refractory to second-line therapies or when serious or complex underlying diseases are suspected that require specific studies, it is recommended that patients be referred to a specialist clinic for a more specific assessment including appropriate testing according to clinical suspicion, as well as a dietary and psychological appraisal to exclude eating disorders potentially manifesting with dyspeptic complaints.

In summary, FD is a highly prevalent disorder that in most cases may be managed in the primary care setting, but a group of patients with more severe, challenging symptoms such as nausea, vomiting or weight loss will require an in-depth study by a gastroenterologist, and often a multidisciplinary evaluation including a dietitian and a psychologist.

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Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Table 1. Alarm signs in patients with dyspepsia

Dysphagia or odynophagia
Unexplained iron-deficiency anemia
Long-standing vomiting
Palpable mass or lymphadenopathies
Family history of upper gastrointestinal neoplasms

Authors' own work.

Table 2. Treatment options most commonly used for difficult-to-control dyspepsia (neuromodulators and phytotherapy)

Drug class	Prototype drug	Dyspepsia subtype of choice *	Recommended dosage	Common adverse effects	Special precautions
Neuromodulators					
Tricyclic antidepressants (TCAs)	Amitriptyline	- EPS - Optional in PPDS - FCD/IBS-D overlap	10-75 mg/day, preferably in single evening dose	Constipation, mucosal dryness, urinary retention, and somnolence	Avoid in poorly controlled constipation
Antipsychotics (D2 antagonists and 5-HT4 agonists)	Levosulpiride	- EPS - PPDS	25 mg every 8 hours (before meals)	Breast tenderness, gynecomastia or galactorrhea (increased prolactin levels). Neuroleptic effects such as somnolence and sedation are uncommon at the recommended dosage	Dementia, prior stroke, concurrent use of other neuroleptics, elevated QT interval

Noradrenergic and specific serotoninergic antidepressants	Mirtazapine	- Early satiety - Weight loss	15-30 mg daily, preferably in single evening dose	Increased appetite, increased weight, somnolence, headache, dry mouth	Liver failure, kidney failure, DM (adjust insulin dose), epilepsy
Phytotherapy (over-the-counter drugs)					
STW5: hydroethanolic extracts of wild candytuft, angelica root, chamomile flower, caraway fruit, milk thistle fruit, balm leaf, peppermint herb, celandine herb, liquorice root		- PPDS - EPS - Overlap with intestinal symptoms	20 drops before each meal	Toxic hepatitis cases have been reported	Avoid associating hepatotoxic drugs
Peppermint and caraway oil: peppermint essential oil and caraway essential oil (90/50 mg)		- EPS - PPDS - Overlap with intestinal symptoms	1 capsule twice a day (before meals)	Heartburn, nausea, belching	Avoid in biliary conditions. Avoid in association with PPIs (gastro-resistant, enteric release)

Authors' own work. EPS: epigastric pain syndrome; PPDS: postprandial distress syndrome; CFD: chronic functional diarrhea; IBS-D: irritable bowel syndrome-diarrhea; DM: diabetes *mellitus*; PPI: proton pump inhibitor.

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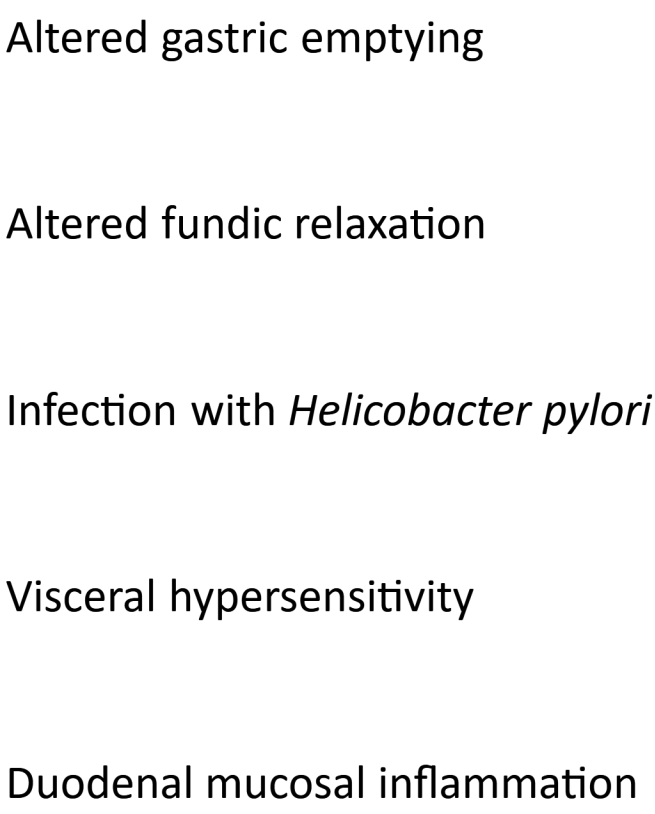

Figure 1. Pathophysiological mechanisms involved in functional dyspepsia.

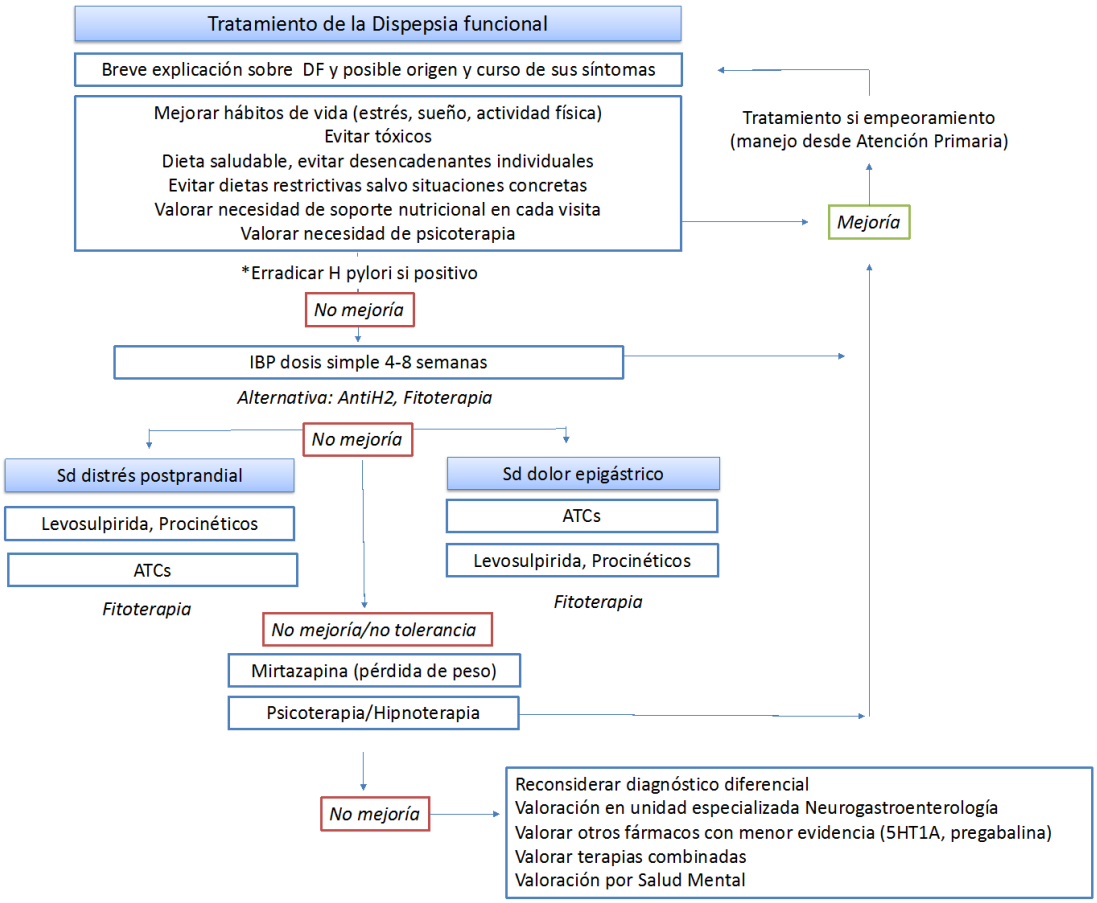

Figure 2. Functional dyspepsia management algorithm. Starting with dietary and lifestyle counseling, treatment ensues by establishing *Helicobacter pylori* infection status and pursuing its eradication when present. Otherwise, treatment is initiated with proton pump inhibitors, albeit prokinetics may be alternatively used for patients with postprandial distress syndrome. Treatment with neuromodulators is recommended when symptoms persist. Phytotherapy and psychological interventions should also be considered for these patients. TCA: tricyclic antidepressant.