Functional Dyspepsia: A Review of the Symptoms, Evaluation, and Treatment Options

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Abstract: The community prevalence of dyspepsia ranges from 20% to 40%, and dyspepsia accounts for 3% to 5% of primary care visits. Dyspepsia symptoms include epigastric pain, epigastric burning, postprandial fullness, early satiety, epigastric bloating, nausea, and belching. Functional dyspepsia is diagnosed when an organic etiology for the symptoms is not identified. Diagnostic symptom-based criteria are defined by Rome IV. Functional dyspepsia is further subclassified into postprandial distress syndrome and epigastric pain syndrome based on the predominance of postprandial bloating and fullness vs epigastric pain. Evaluation of functional dyspepsia is driven by patient age and the presence of red-flag symptoms, such as patients over age 60 years or those with anemia undergoing evaluation with esophagogastroduodenoscopy. *Helicobacter pylori* infection should be excluded in all patients. Treatment options include proton pump inhibitors, neuromodulators, and prokinetics; however, the evidence supporting these therapies is weak, and the response rate is less than robust.

Keywords
Epigastric pain, epigastric burning, early satiety, postprandial fullness, nausea, *Helicobacter pylori*, peptic ulcer disease

The diagnosis and treatment of functional dyspepsia is often clinically challenging due to factors such as the heterogeneity of upper gastrointestinal symptoms and the generalized poor response to currently available treatment options. This article defines functional dyspepsia, discusses known and proposed pathophysiologic mechanisms, and outlines a recommended approach to the evaluation and treatment of the disorder.

Definition and Clinical Presentation

Dyspepsia symptoms include a constellation of upper gastrointestinal complaints, such as belching, postprandial fullness, early satiety, epigastric pain, and epigastric burning. Functional dyspepsia is diagnosed when an organic etiology for the symptoms is not identified. The disorder is defined by Rome IV criteria and subclassified into

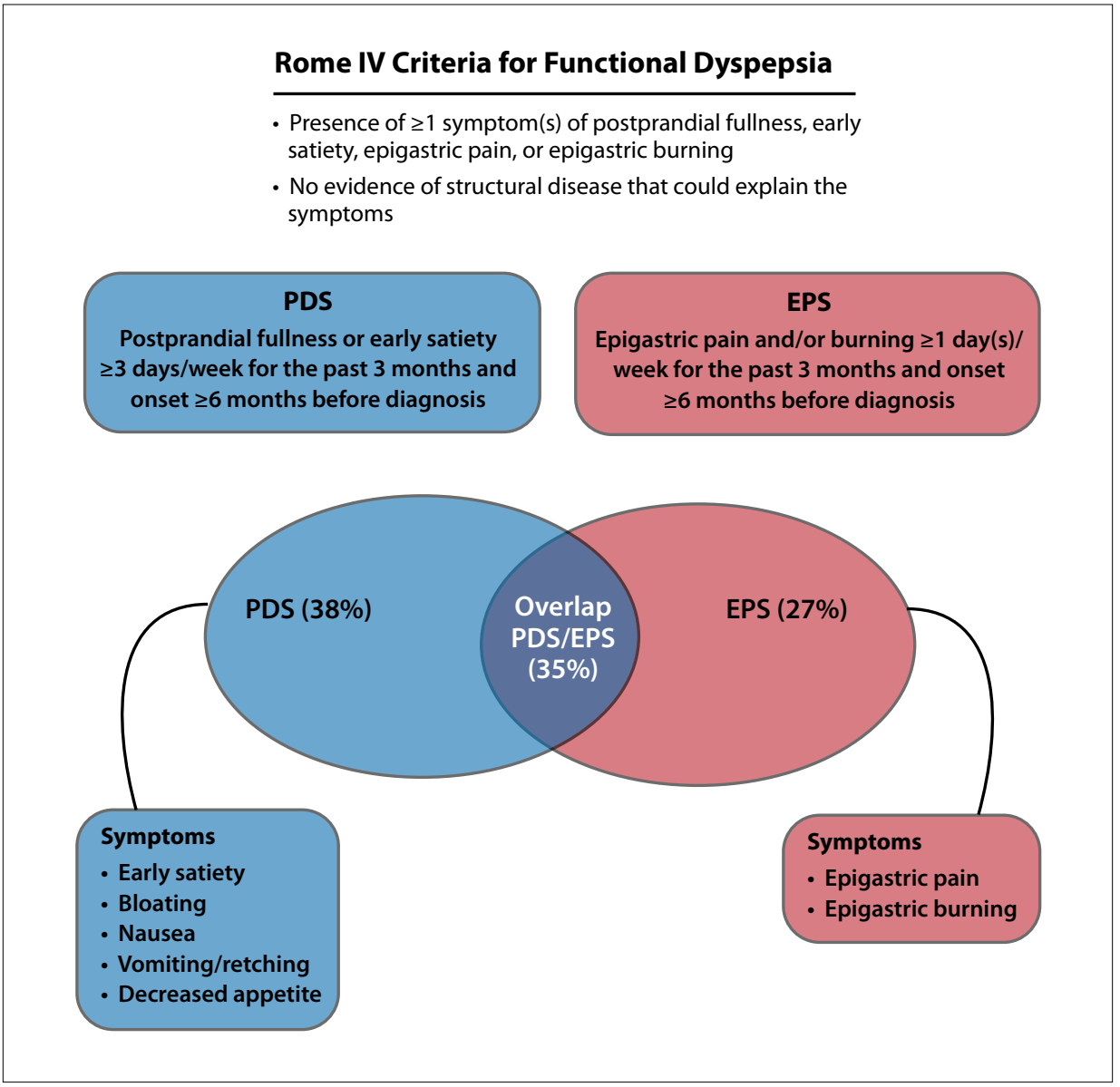

Figure 1. Rome IV criteria for functional dyspepsia and its subclassifications.

EPS, epigastric pain syndrome; PDS, postprandial distress syndrome.

postprandial distress syndrome and epigastric pain syndrome (Figure 1).[1] Of patients with functional dyspepsia, approximately 38% are classified with postprandial distress syndrome, 27% are classified with epigastric pain syndrome, and 35% meet criteria for both.[2] Dyspepsia patients often report a range of upper gastrointestinal symptoms,[3] and this complex presentation is further complicated by the fact that patients use terms such as heartburn or indigestion to describe epigastric pain or burning. Despite the Rome IV definition, diagnosis of functional dyspepsia often remains challenging due to the inherent heterogeneity in symptoms as well as the significant overlap in symptoms with other disorders, such as gastroparesis, irritable bowel syndrome, and gastroesophageal reflux disease. One study demonstrated that more than 50% of patients with functional dyspepsia with a normal pH study reported heartburn and regurgitation.[4] In a study published by the National Institutes of Health Gastroparesis Clinical Research Consortium, patients with functional dyspepsia and idiopathic gastroparesis were essentially clinically indistinguishable. Other studies have demonstrated that more than 25% of patients who

were diagnosed with functional dyspepsia had delayed gastric emptying,[5] and 86% of patients with idiopathic gastroparesis met functional dyspepsia symptom criteria.[6] There is growing support for the thought that functional dyspepsia and gastroparesis share pathophysiologic mechanisms and represent a spectrum of disorders driven by duodenogastric neuromuscular dysfunction. Thus, it is crucial to complete a thorough history and physical examination of the patient when working to identify the most likely etiology of the patient's symptoms. For example, predominant nausea and vomiting symptoms point toward gastroparesis, and predominant postprandial right upper quadrant pain places a pancreaticobiliary etiology higher on the differential diagnosis.

Epidemiology of Dyspepsia

The community prevalence of dyspepsia is typically quoted in the range of 20% to 40%, and the disorder accounts for 3% to 5% of primary care visits.[7-12] Of patients with investigated dyspepsia, approximately 70% have negative endoscopic studies and approximately 50% to 60% are subsequently classified as functional dyspepsia.[12,13] Admittedly, estimating the prevalence of functional dyspepsia is challenging due to variable diagnostic criteria used in prevalence studies, the overlap in symptoms with other disorders, and inconsistent interpretation of dyspepsia symptoms. Risk factors include female sex, increasing age, *Helicobacter pylori* infection, high socioeconomic status, smoking, and nonsteroidal anti-inflammatory drug use.

Etiology of Functional Dyspepsia

The etiology of dyspepsia has been poorly defined; however, numerous pathophysiologic mechanisms, most of which are directed at gastroduodenal pathways, have been proposed to explain the disorder. Many mechanisms are currently being investigated as potential causes of functional dyspepsia symptoms. Given the number of potentially unidentified etiologies for dyspepsia symptoms and the association of the word functional with a lack of an organic cause for symptoms, we cautiously use the term functional dyspepsia to describe dyspepsia symptoms without an identified organic etiology.

Gastric Neuromuscular Dysfunction

Gastric neuromuscular dysfunction, including delayed gastric emptying, impaired gastric fundus relaxation with blunting of postprandial accommodation, and altered gastric mechanosensitivity, has been of particular interest in this area. Up to 70% of patients with functional dyspepsia have abnormal antroduodenal manometry results,[14] and approximately 40% have impaired gastric accommodation.[15] Research has also demonstrated impaired gastric emptying in patients with functional dyspepsia[5]; however, there is significant debate regarding whether functional dyspepsia and gastroparesis are separate entities or if they are part of a spectrum of gastric neuromuscular dysfunction disorders. This debate is largely driven by evidence showing that patients with symptoms suggestive of gastroparesis (eg, early satiety, nausea, vomiting, and postprandial fullness) in the setting of a normal gastric emptying study are clinically indistinguishable from patients with the same symptoms and impaired gastric emptying.[16] Impaired gastric accommodation has also been associated with increased transient lower esophageal sphincter relaxations, and the increased occurrence of these relaxations has been proposed as an explanation of the overlap between dyspepsia and gastroesophageal reflux disease symptoms within this patient population.[17]

Duodenal Acid Exposure, Dysmotility, and Inflammation

There is preliminary evidence concerning the presence of increased postprandial duodenal acid exposure in functional dyspepsia patients with prominent nausea symptoms.[18] In addition, duodenal motility and bolus clearance impairment have been induced by instilling acid into the duodenum, raising concern that duodenal acid–driven pathology may contribute to dyspepsia symptoms in a subset of patients.

There is growing evidence regarding the role of duodenal inflammation and duodenal eosinophilia in functional dyspepsia. Duodenal inflammation, and in particular duodenal eosinophilia, has been seen in up to 40% of patients with functional dyspepsia.[19-21] A mean eosinophil count of 49 eosinophils per high-power field was associated with a diagnosis of functional dyspepsia in one study[19]; however, data are lacking regarding normative values. The cause of duodenal eosinophilia is unknown, but increased duodenal permeability, mast cell disorders, and smoking are proposed to be contributing factors.

The phenomenon of postinfectious irritable bowel syndrome due to bowel inflammation has been expanded to include postinfectious dyspepsia as a potential cause of functional dyspepsia.[22] A systematic review and meta-analysis of 19 studies demonstrated a mean prevalence of functional dyspepsia after acute gastroenteritis at approximately 10%, with an odds ratio for development of postinfectious functional dyspepsia of 2.54 (95% CI, 1.76-3.65).[22] Norovirus is the most common cause of gastroenteritis, and, although inflammation is a proposed mechanism for dyspepsia symptoms, norovirus has also been shown to alter gastric motility.[23] Bacterial pathogens,

Table. Alarm Features

• Unintentional weight loss
• New or progressive dysphagia
• Odynophagia
• Persistent vomiting
• Unexplained iron deficiency anemia
• Palpable mass or lymphadenopathy
• Family history of upper gastrointestinal malignancy
• Childhood spent in a country with high risk for gastrointestinal malignancy (eg, Southeast Asia, parts of South America)

including *Escherichia coli* O157, *Salmonella*, *Campylobacter*, and *Giardia lamblia*, have also been proposed to cause functional dyspepsia.[22]

Psychological Distress

Psychological distress has been associated with dyspepsia, with research showing both that distress and anxiety can precede symptoms and that symptoms can induce distress and anxiety. Thus, a bidirectional gut-brain pathway mechanism has been proposed.[2]

Diagnostic Evaluation

By definition, functional dyspepsia is diagnosed in the absence of an organic etiology for the dyspepsia symptoms. As outlined previously, patients with functional dyspepsia report a range of symptoms that can vary greatly in severity, and symptoms are not a reliable way to differentiate organic from functional dyspepsia. Thus, the goal of evaluation is to rule out organic etiologies for the patient's symptoms. Evaluation is based on patient age, presence of alarm features, severity of symptoms, risk of malignancy, and physical examination findings. Esophagogastroduodenoscopy (EGD) is recommended in patients age 60 years or older or in any patient with more than 1 alarm feature (Table), a rapidly progressive alarm feature, clinically significant weight loss (typically >5% of baseline body weight), or overt gastrointestinal bleeding. EGD with gastric biopsies is recommended in any patient age 60 years or older with dyspepsia due to the increased risk of cancer in this age group. In order to ensure detection of *H pylori* infection, gastric biopsies should be obtained from the lesser curvature of the antrum, greater curvature of the antrum, lesser curvature of the body, greater curvature of the body, and incisura angularis.[24] Duodenal biopsies should be obtained in immunosuppressed patients, particularly bone marrow transplant patients, to exclude graft vs host disease or infection. Additionally, given increasing evidence of duodenal pathology driving functional dyspepsia symptoms, an argument can be made to obtain duodenal biopsies in all patients undergoing EGD for evaluation of dyspepsia.

Patients under age 60 years without alarm features should undergo *H pylori* testing via stool antigen testing or urea breath test, followed by treatment and eradication confirmation if testing is positive for active infection. It is important to ensure that patients undergoing testing do not take a proton pump inhibitor (PPI) for 4 weeks prior to testing, as PPI use can cause a false-negative test result.

EGD performed for dyspepsia evaluation identifies peptic ulcer disease in approximately 10% of cases, erosive esophagitis in 6%, and gastroesophageal malignancy in less than 1%.[7,13] Thus, EGD evaluation is unrevealing in a majority of cases. If evaluation via EGD is nondiagnostic, further evaluation should be based on the patient's severity of symptoms and risk factors. Gastric emptying testing should be considered in patients with prominent nausea or vomiting, particularly if gastroparesis risk factors are present (eg, diabetes, evidence of connective tissue disorder, or evidence of more diffuse gastrointestinal dysmotility). Celiac disease should be ruled out in patients with dyspepsia, via either duodenal biopsies or anti-tissue transglutaminase immunoglobulin A antibody serology testing. Medications should also be reviewed, as dyspepsia symptoms can be induced by nonsteroidal anti-inflammatory drugs; bisphosphonate; or antibiotic, neuropsychiatric, antidiabetic, or antihypertensive medication use. The patient's diet should also be reviewed for potential triggers, including alcohol or caffeine use.

Despite the increasing number of patients undergoing bariatric surgery, there is limited evidence regarding the prevalence of dyspepsia or the recommended diagnostic evaluation of dyspepsia symptoms in these patients. Bariatric surgery is intended to limit oral intake by inducing symptoms of dyspepsia such as early satiety and postprandial fullness. However, there is a growing awareness of dyspepsia symptoms in this patient population that can occur many years after the initial surgery and in the setting of a normal EGD. In patients with complaints that exceed expected postsurgical symptoms, EGD with gastric pouch and jejunal biopsies is reasonable to rule out *H pylori* infection, marginal ulcers, or stricture formation. An upper gastrointestinal series with small bowel follow-through may also be helpful to rule out mechanical obstruction. In a study of over 700 gastric bypass patients, 3.8% developed small bowel obstruction and complained of abdominal pain, bloating, and nausea.[25] Small intestinal bacterial overgrowth should also be considered in this patient population prior to a diagnosis of functional dyspepsia.

Treatment

Helicobacter pylori *Eradication*

Although *H pylori*–associated dyspepsia is not technically considered under the umbrella of functional dyspepsia, *H pylori* infection should be treated and confirmation of eradication should be performed if clinically indicated. *H pylori* infection is identified in approximately 5% of dyspepsia cases.[26] A meta-analysis found that the relative risk of persistent symptoms after therapy was 0.90 (95% CI, 0.86-0.94) and the number needed to treat (NNT) was 15.[27] A trial evaluating improvement in specific dyspepsia symptoms following *H pylori* therapy demonstrated improvement in epigastric pain and burning, but not early satiety or postprandial fullness.[28] Another study suggested that female sex is a risk factor for persistent dyspepsia symptoms despite *H pylori* eradication.[29]

Acid-Reducing Therapy

PPI therapy is considered first-line therapy for functional dyspepsia. However, studies have shown PPI therapy to be effective in treating functional dyspepsia in only 14% of patients.[30,31] A meta-analysis of 10 randomized, controlled trials (RCTs) demonstrated a relative risk of persistent symptoms despite PPI therapy of 0.87 (95% CI, 0.08-0.96) and a NNT of 10.[32] The same meta-analysis also evaluated H_2-receptor antagonists and demonstrated a relative risk of 0.77 (95% CI, 0.65-0.92) and a NNT of 7. The quality of the studies of the H_2-receptor antagonists was lower, and many of the trials used in the meta-analysis were performed prior to Rome III classification.

As previously mentioned, there is emerging evidence and growing interest in the association between duodenal acid exposure, duodenal eosinophilia, and dyspepsia symptoms. The effect of PPI therapy on suppression of duodenal eosinophilia was evaluated in a case-control study of 20 functional dyspepsia patients and demonstrated lower descending duodenum (ie, D2) eosinophil counts in patients taking PPIs compared to patients not taking PPIs (P=.03); however, no difference between the groups was noted in the duodenal bulb (ie, D1) eosinophil counts or gastric biopsies.[33] One hypothesized mechanism by which PPI therapy improves dyspeptic symptoms includes signal transducer and activator of transcription 6 blockade–induced anti-inflammatory effects. Bismuth, sucralfate, and calcium carbonate have not shown benefit in treating functional dyspepsia.[34]

Neuromodulators

If PPI therapy is ineffective or provides inadequate relief, guidelines by the American College of Gastroenterology and the Canadian Association of Gastroenterology recommend a trial of a neuromodulator medication targeting gastric hypersensitivity. A systematic review and meta-analysis of 13 RCTs demonstrated a relative risk of functional dyspepsia symptoms not improving with psychotropic drugs vs placebo of 0.78 (95% CI, 0.68-0.91) and a NNT of 6.[35] Following the systematic review,[35] an RCT was published that compared the tricyclic antidepressant medication imipramine vs placebo for functional dyspepsia symptoms refractory to treatment with a PPI and domperidone.[36] Relief of global dyspepsia symptoms at 3 months was 63% in the imipramine group vs 36% in the placebo group. However, 18% of patients in the imipramine group discontinued therapy secondary to negative side effects compared to 8% in the placebo arm. Another study comparing nortriptyline to placebo in Asian patients with functional dyspepsia, which was published after the previously mentioned systematic review, did not demonstrate superiority to placebo.[37] Studies evaluating selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have not demonstrated symptom benefit.[38,39] The efficacy of sertraline and venlafaxine for the treatment of functional dyspepsia patients was tested in 2 RCTs, and both studies demonstrated no difference in outcomes between treatment and placebo groups.[39,40] An RCT was then performed comparing amitriptyline, escitalopram, and placebo in patients with functional dyspepsia. The amitriptyline group demonstrated improved dyspepsia symptoms compared to placebo, but the escitalopram group did not demonstrate similar benefit. Both antidepressant treatments increased gastric accommodation, but neither resulted in a subsequent increase in maximal tolerated volume of the nutrient drink test.[41] Functional dyspepsia subsets that showed the best response to amitriptyline included patients with ulcer-like symptoms and patients with normal gastric emptying. Therapy with mirtazapine promoted greater improvement in dyspepsia symptoms and weight gain compared to paroxetine or conventional therapy among patients with functional dyspepsia with weight loss in a separate study.[42]

Prokinetics and Fundus-Relaxing Therapies

The effectiveness of prokinetic agents to treat functional dyspepsia is unclear. The potential benefit of prokinetics was supported by a meta-analysis that demonstrated benefit with cisapride, domperidone, and itopride therapies.[32] However, 2 subsequent phase 3 trials evaluating the efficacy of itopride did not show benefit over placebo.[43] Cisapride was afterward removed from the market due to the risk of cardiac events. Routine use of metoclopramide in the functional dyspepsia population is typically avoided due to the lack of evidence and the potential neurologic side effects. Although domperidone has a cleaner neurologic side-effect profile, the risk of QT

interval prolongation, lack of approval by the US Food and Drug Administration, and paucity of evidence demonstrating efficacy in the functional dyspepsia population often preclude routine use of the medication.

Acotiamide, an acetylcholinesterase inhibitor, has been available in Japan since 2013 and has initiated the approval process in North America and European countries. Studies evaluating the efficacy of acotiamide have shown symptom improvement in patients with postprandial distress syndrome, as well as improvement in gastric emptying time and gastric accommodation.[44-49]

Buspirone, a $5HT_{1A}$ agonist, has been shown to improve dyspepsia symptoms and gastric accommodation in an RCT that included patients with functional dyspepsia.[50] Another RCT evaluated a different $5HT_{1A}$ agonist, tandospirone, in functional dyspepsia; the tandospirone group demonstrated greater improvement in abdominal pain and discomfort scores compared to placebo.[51]

Rifaximin

Eighty-six patients with functional dyspepsia with a negative glucose hydrogen breath test were randomized to treatment with either a 2-week course of rifaximin 400 mg 3 times daily or placebo.[52] At 8 weeks, 78% of patients in the rifaximin group had adequate relief of global dyspeptic symptoms compared to 52% of patients in the placebo group (P=.02).

Psychological Therapies

Fifty-eight patients with functional dyspepsia were randomized to either medical therapy alone or with psychotherapy, with great improvement in dyspepsia-related quality-of-life scores in the combination therapy group.[50] Despite psychological pathology being a proposed mechanism of functional dyspepsia and preliminary evidence supporting the use of psychotherapy treatments,[53] there is limited research evaluating the efficacy of psychological treatments. Research in this area is likely inhibited by the lack of insurance coverage for psychological services, shortage of gastroenterology-specialized psychologists, and variability in psychological therapies.

Complementary and Alternative Medicine

There is a paucity of evidence regarding the efficacy of complementary and alternative medicine (CAM) therapies for the treatment of functional dyspepsia. However, it is estimated that approximately 50% of patients with functional dyspepsia try CAM therapies for symptom relief.[54] This is not unexpected given the limited efficacy of the aforementioned pharmacologic therapies.

Herbal therapies, such as peppermint and ginger, have been proposed to treat dyspepsia.[55] Despite moderate symptom relief demonstrated in several reports, some studies have had high placebo response rates and many were of low quality.[55] STW5 (Iberogast, Bayer) and FDgard (IM HealthScience) are 2 commercially available herbal remedies. STW5 is an oral liquid derived from 9 herb extracts that has been suggested to relieve functional dyspepsia symptoms and has been shown to enhance gastric fundus relaxation.[56] FDgard is a capsule formulation of caraway oil and peppermint oil.

Capsaicin is a chili pepper extract that has been used in topical creams as an analgesic. Although capsaicin-containing foods are often avoided by dyspepsia patients, as such foods can elicit a sensation of burning, capsaicin therapy with increasing dose titration has been shown to improve upper gastrointestinal symptoms in functional dyspepsia patients.[57]

Rikkunshito (TJ-43, Tsumura and Co), a kampo herbal medicine, is primarily used in Japan for treatment of dyspepsia symptoms. Preliminary studies have suggested that rikkunshito promotes gastric accommodation and expedites gastric emptying time.[58-60] Three RCTs have also demonstrated that the medicine improves dyspepsia symptoms, including abdominal pain, postprandial fullness, and bloating.[61-63]

A meta-analysis of 24 RCTs evaluating the efficacy of acupuncture for the treatment of functional dyspepsia reported improvement in functional dyspepsia symptoms and health-related quality of life.[64]

Although there is some evidence regarding the positive benefits of CAM treatment options for functional dyspepsia, patients and providers should be aware that most of these therapies are considered dietary supplements and are not subject to regulation by the US Food and Drug Administration. There is also a case report of STW5-induced acute liver failure,[65] which highlights the need for additional safety and efficacy studies evaluating these therapies.

Therapy Recommendations

The currently identified therapies are largely lackluster. This is likely due to numerous potential etiologies driving dyspepsia symptoms, as well as ill-defined underlying mechanisms and targets for therapeutic intervention. Once *H pylori* infection is ruled out or managed, treatment with a PPI is recommended. If antisecretory therapy is ineffective, neuromodulator therapy, prokinetics, and fundus-relaxing therapies should be considered.

Our suggested approach to treatment is shown in Figure 2. We recommend *H pylori* testing in all patients with dyspepsia. If *H pylori* testing is negative and criteria for an EGD are not met (age >60 years or red-flag symptoms present), we recommend a 4-week trial of a moderate-dose PPI (eg, omeprazole 40 mg daily). If symptoms are not resolved with PPI therapy, we recommend consideration

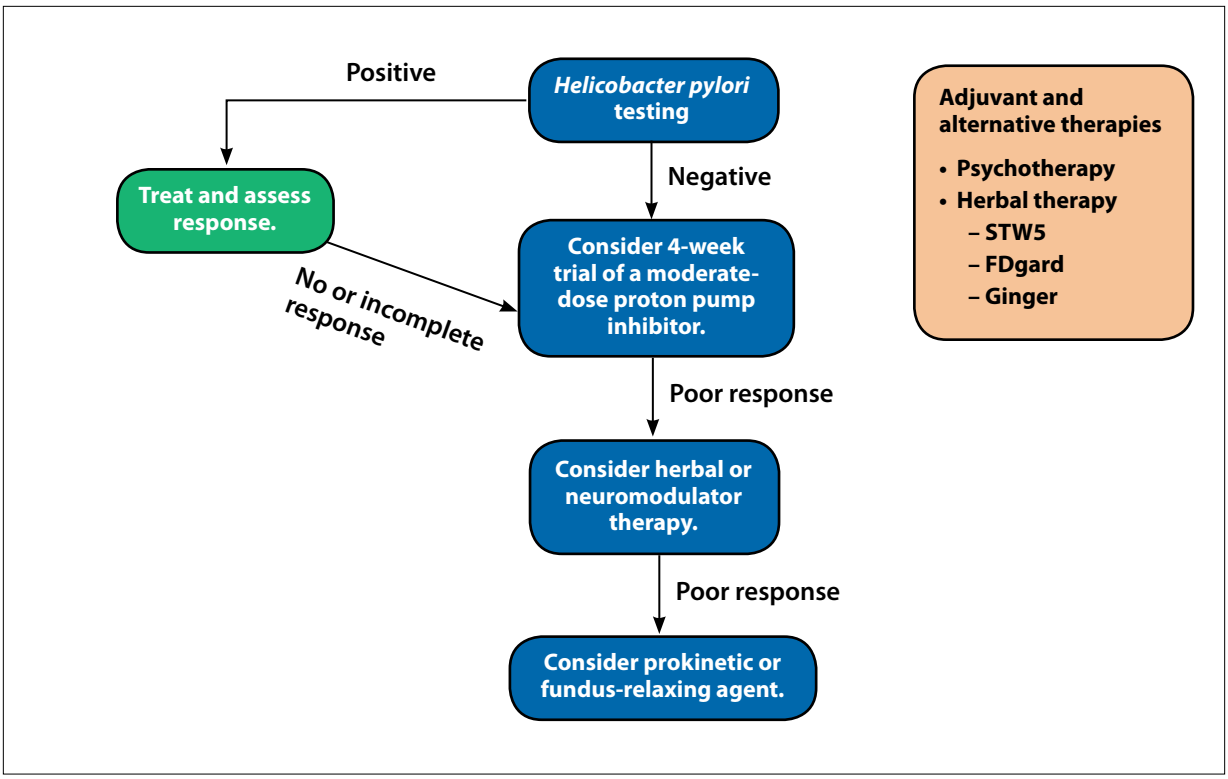

Figure 2. Functional dyspepsia treatment algorithm.

of herbal (FDgard or STW5) or neuromodulator therapy. Tricyclic antidepressants are typically our first-line neuromodulator agents, with amitriptyline or nortriptyline being used most frequently. We start amitriptyline or nortriptyline 10 mg at night, with a dose increase of 10 mg every 1 to 2 weeks as tolerated to a dose of 50 mg. It may take 4 to 6 weeks of therapy to notice a benefit in symptoms, and patients should be educated on the expected timeline to prevent premature cessation of treatment. Amitriptyline has more robust anticholinergic side effects and is less desirable in elderly patients or patients with constipation. If tricyclic therapy is ineffective or if there is significant nausea, we recommend a trial of buspirone or mirtazapine. Buspirone is dosed 5 mg 3 times daily with meals and can be increased to 10 mg 3 times daily with meals after 2 weeks. Mirtazapine is typically started at a dose of 7.5 to 15 mg at night and increased by 15 mg every 2 weeks as tolerated to a dose of 30 to 45 mg at night. As with tricyclic therapy, the maximal effect of mirtazapine can take 4 to 6 weeks to appreciate.

Summary

Functional dyspepsia is a clinically challenging diagnosis due to the heterogeneous spectrum of upper gastrointestinal complaints, overlap in symptoms with other diagnoses, poorly defined pathophysiology, and lackluster treatment options. As the scientific community continues to elucidate causative mechanisms and effective treatment options, clinicians should focus on obtaining a thorough patient history and targeting therapy based on the symptom profile and possible contributing or underlying pathophysiologic process.

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