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Functional dyspepsia: How to manage the burn and the bloat

ABSTRACT

Functional dyspepsia is defined as persistent symptoms of postprandial bloating, early satiety, or pain in the center of the upper abdomen, without findings on upper endoscopy such as peptic ulcer disease to explain these symptoms. It is common, affecting up to 30% of the global population, but it often goes undiagnosed for years. There are 2 subtypes: epigastric pain syndrome (burning and pain) and postprandial distress syndrome (bloating and satiety). The authors discuss how to diagnose and treat both subtypes.

KEY POINTS

The pathophysiology of functional dyspepsia is poorly understood, but there are clear associations with visceral hypersensitivity and disruptions of normal gastroduodenal motility, and a number of proposed mechanisms.

No treatment carries an approved indication for functional dyspepsia, but agents of several classes are used off-label.

Clinical guidelines recommend starting proton pump inhibitor therapy in patients with functional dyspepsia who test negative for *Helicobacter pylori* or who continue to have dyspeptic symptoms after *H pylori* eradication.

A 41-year-old woman reported having epigastric fullness and bloating with meals for more than 10 years, but denied having heartburn, regurgitation, dysphagia, or weight loss. She underwent upper endoscopy 5 years before, and her esophagus, stomach, and duodenum appeared normal. Biopsies of the gastric antrum and gastric corpus were negative for *Helicobacter pylori*, and biopsies of the duodenum were normal. She had tried 2 different proton pump inhibitors without success.

TWO CATEGORIES

Dyspepsia refers to a group of symptoms in the upper region of the gastrointestinal tract. Functional dyspepsia (ie, not due to an identifiable abnormality) can be divided into 2 categories:

- Postprandial distress syndrome (fullness or early satiety after meals)
- Epigastric pain syndrome (epigastric burning or pain).¹

While many patients and clinicians assume that dyspeptic symptoms indicate peptic ulcer disease, recent studies have found that up to 85% of patients with dyspeptic symptoms have normal findings on upper endoscopy.²

The global prevalence of functional dyspepsia ranges between 10% and 30%.³ Risk factors include female sex, high socioeconomic status, older age, living in a rural location, using nonsteroidal inflammatory drugs, and being married. Smoking is weakly associated with functional dyspepsia, whereas coffee and alcohol consumption have no known association with it.^{1,3}

■ FUNCTIONAL DYSPEPSIA VS IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is a disorder of recurring abdominal pain combined with bowel movement changes (constipation, diarrhea, or both). It is similar to functional dyspepsia in many ways: symptoms are related to diet, there are often psychiatric comorbidities, and treatments are similar. Hence, irritable bowel syndrome is often misdiagnosed as functional dyspepsia. However, functional dyspepsia refers to symptoms in the upper abdomen, whereas irritable bowel symptoms present in the lower abdomen and are connected to changes in bowel habits.⁴

The 2 conditions can overlap. A 2022 study from Australia found that 45% of patients with functional dyspepsia also met the criteria for irritable bowel syndrome.⁵ A careful discussion with the patient is required to tease out specific symptoms of functional dyspepsia and irritable bowel syndrome so that they are treated optimally.

■ PATHOPHYSIOLOGY

The pathophysiology of functional dyspepsia, like that of all disorders of gut-brain interaction, is poorly understood. However, there are clear associations with visceral hypersensitivity, disruptions of normal gastroduodenal motility, or both. Potential mechanisms include the following:

Delayed gastric emptying can be found in 25% to 35% of patients with functional dyspepsia.^{1,6} However, some patients with functional dyspepsia actually have rapid gastric emptying.⁷

Abnormal gastric accommodation. Normally, gastric accommodation is modulated by food consumption triggering the vagovagal response and nitrergic nerve excitement in the gastric wall. This process is often impaired in patients with functional dyspepsia, who may experience uneven gastric food distribution, antral pooling of chyme, and reduced proximal reservoir content. After eating, up to a third of patients with functional dyspepsia have impaired gastric accommodation.^{1,8}

Hypersensitivity in response to chemical and mechanical stimulation in the upper bowel and stomach is common in cases of functional dyspepsia, and this hypersensitivity is suspected to occur in response to stimuli such as lipids and intraluminal acid.¹

H pylori infection can retrospectively be presumed to be the cause of functional dyspepsia if the symptoms resolve after the organism is eradicated. However, eradicating *H pylori* does not guarantee that dyspepsia will

go away: in various studies, between 7 and 15 patients needed to undergo *H pylori* eradication for 1 case of functional dyspepsia to be resolved.^{9,10}

Gut microbiome dysbiosis. Numerous studies have found a strong link between gut microbiome dysbiosis and functional dyspepsia, as the biological barrier and immune functions of the intestinal mucosa are disrupted. The microbiota in the gastrointestinal tract and mouth have been shown to be imbalanced in patients with functional dyspepsia, and small intestinal bacterial overgrowth has been associated with functional dyspepsia. Damage to the intestinal mucosal barrier increases its permeability and thereby decreases its ability to block noxious substances. Additionally, studies have found microinflammatory cell infiltration in the duodenum of more than 40% of patients with functional dyspepsia.^{11,12}

Environmental factors. Eosinophilia in the duodenum and a correlation with early satiety have been observed in patients with functional dyspepsia. Changes in permeability and inflammation in the duodenal mucosal lining have been associated with stress, food allergies, smoking, infection, and acid exposure.¹

Psychological component. A relationship between psychiatric disease, anxiety, depression, and functional dyspepsia has been confirmed, and a relationship between functional dyspepsia and neuroticism is often acknowledged.¹ Troubles managing life affairs and experiencing emotional and physical abuse as an adult may contribute to functional dyspepsia. Because having a functional gastrointestinal disease makes a patient more susceptible to psychological issues, the relationship is probably bidirectional.

■ CRITERIA FOR DIAGNOSIS

The Rome Foundation is a global initiative that creates guidelines for diagnosing and treating functional gastrointestinal conditions. The Rome criteria were initially developed for research, but more recent iterations have also focused on clinical care. The most recent update, Rome IV,^{1,13} was released in 2016. The Rome IV criteria for functional dyspepsia are as follows:

- Patients must present with symptoms of postprandial fullness, epigastric burning, epigastric pain, or early satiation; for **postprandial distress syndrome**, patients must experience postprandial fullness affecting daily activities or early satiation affecting their ability to consume a normal-size meal at least 3 days each week; for **epigastric pain syndrome**, patients must experience epigastric pain or burning, or both, affecting daily activities at least 1 day each week

- There should be no sign of a structural problem (including at upper endoscopy) that could be correlated with symptoms
- Symptoms must be present for at least 6 months, and diagnostic criteria must be met for 3 months.^{1,13}

Regarding testing, current guidelines suggest upper endoscopy for patients age 60 and older to rule out malignancy. However, routine upper endoscopy to rule out malignancy is not recommended for patients under age 60, as their risk of cancer is less than 1% even if they have alarm features.¹⁰ For patients younger than 60, noninvasive testing for *H pylori* such as stool antigen assay is recommended.^{10,14}

■ SYMPTOMS CAN WAX AND WANE

Although symptoms of functional dyspepsia can be managed, it is a lifelong medical condition that can wax and wane over time. The aim of treatment is to improve quality of life by decreasing or eliminating symptoms. Patients can often reduce the dosage or even stop treatments once their symptoms resolve. It is, however, reasonable to expect symptom exacerbations throughout the life span, especially in response to stress or triggers, which may require patients to restart treatment.¹⁵ Importantly, functional dyspepsia has not been shown to affect long-term survival.¹⁶

■ TREATMENTS ARE ALL OFF-LABEL

Currently, no therapy for functional dyspepsia has US Food and Drug Administration approval. All the agents listed below are used off-label for treating this condition.

Antisecretory agents

Famotidine is a histamine-2 receptor antagonist used to decrease the production of stomach acid in patients with duodenal and gastric ulcers, gastroesophageal reflux disease, and erosive esophagitis. Famotidine twice daily was found to be more effective than the prokinetic medication mosapride and the antianxiety medication tandospirone in a study in patients with functional dyspepsia.¹⁷ No specific subtype of functional dyspepsia was reported to respond better to famotidine.¹⁷

Tachyphylaxis develops rapidly in response to histamine-2 receptor antagonists, which may limit their long-term use in functional dyspepsia.¹⁸

Proton pump inhibitors are often used to treat symptoms of acid reflux and gastroesophageal reflux disease. They work by irreversibly inhibiting the hydrogen-potassium adenosine triphosphatase proton pump in

the parietal cell membrane on the luminal surface of the stomach.¹⁹

Clinical guidelines recommend starting proton pump inhibitor therapy in patients with functional dyspepsia who test negative for *H pylori* or who continue to have dyspeptic symptoms after *H pylori* eradication.¹⁰ Meta-analyses have found proton pump inhibitors to be better than placebo and possibly slightly better than histamine-2 receptor agonists and prokinetics.^{10,20} Subgroup analysis suggested that more patients responded to proton pump inhibitors if their symptoms were related to heartburn.¹⁰ On the other hand, there was no difference in efficacy according to functional dyspepsia subtype, ie, whether patients had epigastric pain syndrome or postprandial distress syndrome, and therefore experts do not recommend using the type of symptom to guide treatment choice.²¹

Possible long-term adverse effects of proton pump inhibitors include hip fracture, electrolyte imbalances, dementia, pneumonia, and *Clostridioides difficile* infection. However, experts have concluded that these associations are probably not causal and that even if they were, the number needed to harm would be more than 1,000 in most cases.¹⁰ A 3-year randomized double-blind trial found pantoprazole was not associated with any adverse event, with the possible exception of an increased risk of enteric infection.²² Patients should stop the drug if there is no response after taking the standard dose for 8 weeks, and should try to withdraw from the drug within 6 to 12 months, regardless of the response.

Neuromodulators

Antidepressant and antianxiety medications are often used to treat irritable bowel syndrome, but their efficacy in treating functional dyspepsia is less well known. These medications may improve central analgesic function, improve sleep, normalize orocecal transit, and augment gastric accommodation, all of which are hypothesized to help alleviate functional dyspepsia symptoms.^{23–26}

Buspirone is a serotonin 5-HT_{1A} receptor agonist. In a study in 17 patients with functional dyspepsia, buspirone 10 mg before meals was found to augment fundic accommodation and improve postprandial fullness, bloating, and early satiety.²³

Buspirone may also have a role in treating functional dyspepsia in patients with rapid gastric emptying. In 1 reported case, early satiety, nausea, vomiting, and diarrhea all improved within 1 week of starting buspirone 10 mg 3 times a day before meals.²⁴

Mirtazapine. The antidepressant mirtazapine is an antagonist to histamine-1 receptor, serotonin receptors

5-HT_{2C} and 5-HT₃, and the A₂ adrenergic receptor. Mirtazapine has been studied in patients with symptoms of functional dyspepsia and associated weight loss, as the drug is associated with weight gain and its antagonist activity on the 5-HT₃ receptor specifically is associated with nausea suppression. One study reported a mean weight gain of nearly 4 kg in patients with functional dyspepsia after 8 weeks of treatment with mirtazapine 15 mg daily, along with improvements in early satiety, nausea, quality of life, meal volume tolerance, and gastrointestinal-specific anxiety.²⁵

Tricyclic antidepressants. Amitriptyline is a tricyclic antidepressant used most commonly to treat major depressive disorder, pain disorders, migraine, headaches, and fibromyalgia.

The Antidepressant Therapy for Functional Dyspepsia trial²⁶ measured the benefits of amitriptyline and the selective serotonin reuptake inhibitor escitalopram in patients with functional dyspepsia who were not on antidepressants and did not present with depression. Patients were given amitriptyline 50 mg, escitalopram 10 mg, or placebo for 10 weeks. The patients on amitriptyline had a higher response rate (53%) than those on escitalopram (38%) or placebo (40%, $P = .05$), leading to the conclusion that amitriptyline has therapeutic benefit in functional dyspepsia while escitalopram does not. In the subset of patients with ulcer-like symptoms, the response rate for those receiving amitriptyline was 67%, compared with 39% with placebo and 27% with escitalopram. In patients who had normal gastric emptying, amitriptyline significantly improved abdominal pain, suggesting that tricyclic antidepressants could be used for patients with pain-leading symptoms. Amitriptyline and citalopram did not improve the symptom of satiety compared with placebo, and patients with delayed gastric emptying were less likely to benefit.²⁶

Gabapentin is a gamma-aminobutyric acid analog anticonvulsant medication used to treat neuropathic pain and seizures.²⁷ There is also evidence that it has therapeutic effects on visceral hypersensitivity. An open-label trial indicated that gabapentin could help in treating functional dyspepsia.²⁷ Patients were started on gabapentin 25 to 100 mg at bedtime, which was increased at 2-week intervals to 300 mg 3 times per day. They reported significant improvement in postprandial fullness, upper and lower abdominal pain, heartburn, nausea, and vomiting, while no change in bloating was noted.²⁷

Although gabapentin significantly reduced functional dyspepsia symptoms, more studies are needed to establish it as a treatment.

Pregabalin is a gabapentinoid neuromodulator currently used to manage partial-onset seizures, postherpetic

neuralgia, pain induced by impairment to the nerves due to spinal cord injury or diabetes, and fibromyalgia. It works within the central nervous system, acting on voltage-gated calcium channels.

Pregabalin has been studied to determine its potential benefit on reducing visceral hypersensitivity in patients with functional dyspepsia who did not respond to proton pump inhibitors.²⁸ Patients reported significant improvement in some symptoms, particularly epigastric burning and pain and the feeling of regurgitating acid. However, postprandial fullness, nausea, bloating, and early satiety did not improve with pregabalin.²⁸

Prokinetic therapy

Prokinetic drugs have shown success in treating functional dyspepsia. The prokinetic drug metoclopramide has antidopaminergic and cholinergic actions. Its antidopaminergic properties are primarily responsible for its antiemetic effect.

In a randomized, double-blind trial, metoclopramide improved symptoms in 83% of patients in the subgroup with regurgitation or heartburn compared with 89% with cisapride, the comparator treatment.²⁹ In patients with epigastric symptoms, the response rates were 72% with metoclopramide vs 86% with cisapride. However, 2 weeks after treatment stopped, the response rates dropped to 39% in the metoclopramide group vs 71% in the cisapride group.²⁹

Use of metoclopramide is limited by adverse effects including tardive dyskinesia, and expert recommendations advise caution when using it for functional dyspepsia.¹⁰

Antibiotics

Rifaximin, an antibiotic commonly used to treat diarrhea associated with irritable bowel syndrome, has been shown to reduce global dyspeptic symptoms, postprandial bloating and satiety, and belching in patients with functional dyspepsia.³⁰

A study by Tan et al³⁰ in 2017 postulated a relationship between gut dysbiosis and functional dyspepsia symptoms. Rifaximin has been shown to improve bloating and pain symptoms in patients with irritable bowel syndrome, 2 symptoms common in patients with functional dyspepsia. It has also been shown to decrease gut inflammation and visceral hyperalgesia (contributors to functional dyspepsia), and to act as an antibiotic. After 8 weeks, 78% of patients who had received rifaximin 400 mg 3 times a day for 2 weeks had global dyspepsia symptom relief, compared with 52% with placebo ($P = .02$), and this trend was more apparent in female patients.³⁰

Complementary and alternative medicine

STW 5 is a preparation consisting of extracts of 9 herbs: chamomile flower, celandine herb, caraway fruit, milk thistle fruit, licorice root, balm leaf, peppermint herb, angelica root, and bitter candytuft. It has demonstrated effects on hypertension and gastric motility and has antioxidative, anti-inflammatory, antacid, and gastroprotective properties. Particularly, the extract from bitter candytuft (*Iberis amara*) has shown promising effects on intestinal motility.³¹ In a randomized, double-blind trial, patients receiving STW 5 (20 drops before meals) improved by 6.9 points on the 40-point Gastrointestinal Symptom Score after 8 weeks, compared with 5.9 points with placebo ($P < .05$).³¹

Caraway oil and L-menthol (COLM-SST) is a preparation of caraway oil 25 mg and L-menthol 20.75 mg. In a randomized trial, 2 capsules of COLM-SST twice daily provided relief of functional dyspepsia symptoms within 24 hours compared with placebo.³² Patients experiencing more extreme symptoms had a stronger response. At 24 hours after the start of treatment, patients who received COLM-SST had a statistically significant decrease in postprandial distress symptoms of heaviness, pressure sensations, and fullness. Epigastric pain symptoms also improved, but the difference was not statistically significant. After 28 days of treatment, however, none of these reductions were statistically significant.³²

Capsaicin, an active component of red peppers, can be a treatment for functional dyspepsia symptoms, as it desensitizes visceral nociceptive C-type fibers. Bortolotti et al³³ found that symptoms decreased by 60% in patients taking red pepper powder daily, compared with 30% with placebo. Symptoms actually increased the first day patients took red pepper powder, but subsequently there were statistically significant reductions in general symptom score, epigastric pain, nausea, and epigastric fullness, and a borderline significant reduction in early satiety. There were no statistically significant differences in bloating, epigastric burning, or burping or belching.³³ The dosage used in the study was 500 mg before breakfast and 1,000 mg before lunch and dinner.³³

Acupuncture. In a study in patients with functional dyspepsia, acupuncture in 4 specific areas (stomach meridian-specific acupoints, stomach meridian-nonspecific acupoints, transport and alarm acupoints, and gallbladder meridian-specific acupoints) 5 times a week for 1 month resulted in significant symptom improvement compared with sham acupuncture.³⁴ Patients with postprandial distress syndrome had a

TABLE 1
Effect of various treatments on functional dyspepsia

| Treatment ^a | Effect on postprandial distress ^b | Effect on epigastric pain ^b |
|---|--|--|
| Antisecretory agents | | |
| Famotidine ¹⁷ | ++ | ++ |
| Proton pump inhibitors ^{10,20} | ++ | ++ |
| Neuromodulators | | |
| Buspirone ^{23,24} | ++ | 0 |
| Mirtazapine ²⁵ | ++ | 0 |
| Amitriptyline ²⁶ | 0 | ++ |
| Escitalopram ²⁶ | 0 | + |
| Gabapentin ²⁷ | + | NA |
| Pregabalin ²⁸ | ++ | ++ |
| Prokinetic therapy | | |
| Metoclopramide ²⁹ | ++ | ++ |
| Antibiotics | | |
| Rifaximin ³⁰ | ++ | ++ |
| Complementary and alternative medicine | | |
| STW 5 ³¹ | NA | NA |
| Caraway and L-menthol ³² | ++ | ++ |
| Capsaicin ³³ | ++ | ++ |
| Acupuncture ³⁴ | + | + |
| Hypnotherapy ³⁵ | NA | + |

^aAll treatments are off-label. No treatment for functional dyspepsia has yet been approved by the US Food and Drug Administration.

^bQualitative estimates of effect are based on experience and the studies summarized in the text: 0 = no effect, + = some effect, ++ = moderate effect, +++ = strong effect.

NA = information not available

stronger response to acupuncture, particularly stomach meridian-specific acupoints, than patients with epigastric pain syndrome. There were statistically significant decreases in postprandial fullness, early satiety, and quality of life, but no statistically significant decreases in epigastric burning and epigastric pain.³⁴

Hypnotherapy. Hypnosis induces a conscious state with focused attention, decreased awareness peripherally, and increased susceptibility to external suggestion. Neuroimaging studies show changes in brain activity in networks of the prefrontal cortices, thalamus, anterior cingulate, and basal ganglia associated with hypnosis.³⁵

Popa et al³⁵ performed a systematic review of 4 studies of hypnotherapy for functional dyspepsia. One study found that 1 session of hypnosis was more effective than cisapride in alleviating epigastric pain, abdominal discomfort, epigastric fullness, and gastric emptying. Another study showed hypnotherapy was more effective than ranitidine 300 mg/day. A third study reported that 80% of patients had improvements in pain frequency and severity with hypnotherapy, compared with 23% of control patients.³⁵ Further randomized controlled trials are needed to definitively determine the efficacy of hypnotherapy in treating functional dyspepsia.

■ GENERAL MANAGEMENT PRINCIPLES

In our practice, we follow the recommendations of the Rome Committee and the American College of Gastroenterology guidelines in diagnosis and treatment of functional dyspepsia. In particular, the American College of Gastroenterology guidelines do not recommend upper endoscopy in patients under age 60, as their risk of cancer is less than 1%, even with alarm symptoms.¹⁰ If *H pylori* testing or upper endoscopy is negative, patients can be diagnosed with functional dyspepsia per the Rome IV criteria.

Our general practice is to treat with a proton pump inhibitor for 2 months. If symptoms respond, then we taper off the medication or reduce it to the lowest effective dose. If dyspepsia does not respond to a proton pump inhibitor, we use an individualized approach, discussing the agents listed above and summarized in **Table 1**.^{10,17,20,23–35}

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■ CASE FOLLOW-UP: IMPROVEMENT WITH BUSPIRONE

The 41-year-old patient in the introductory scenario was diagnosed with functional dyspepsia (postprandial distress subtype) and given information about the disease. She started taking buspirone 10 mg 15 to 30 minutes before meals, and her postprandial bloating improved significantly. The proton pump inhibitor she had been taking was then discontinued without worsening her symptoms. A plan was made to continue therapy for 12 months, then reassess the need for buspirone.

■ EDUCATIONAL SOURCES

A thorough understanding of functional dyspepsia is vital for healthcare professionals and patients. Two patient sources of information about functional dyspepsia are:

- American College of Gastroenterology (<https://gi.org/topics/dyspepsia/>, also available in Spanish)
- Cleveland Clinic (my.clevelandclinic.org/health/diseases/22248-functional-dyspepsia).

Additionally, the American College of Gastroenterology Patient Care Committee, in conjunction with its patient-education partner Gastro Girl (gastrogirl.com), has prepared a free podcast for patients and clinicians about functional dyspepsia (www.youtube.com/watch?v=7ggCB8VJHHA).

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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