CLINICAL PRACTICE

Functional Dyspepsia

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

SUMMARY

Functional dyspepsia is a common but serious medical syndrome that can induce weight loss and food aversion and may be associated with increased risks of hospitalization and death. It probably comprises several different and as yet incompletely characterized disorders. Patients with local mucosal microinflammation driven by an aberrant Th2 response may represent an important subgroup. There is overlap with other gastrointestinal syndromes, particularly irritable bowel syndrome and gastroesophageal reflux disease, and patients with overlap have more severe symptoms. There is no approved drug for functional dyspepsia. Treatment is empirical and directed at symptoms and consists of acid suppressants and low-dose tricyclic antidepressants (and other neuromodulators) along with appropriate nutritional and psychological support.

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CME

A 33-year-old woman presents with a 3-year history of epigastric burning pain, nausea, and early satiety after meals. She is increasingly anxious because endoscopy and imaging have not found any underlying cause, and she has not had a response to omeprazole or over-the-counter medications. How would you further evaluate and treat this patient?

THE CLINICAL PROBLEM

Functional dyspepsia is a syndrome of unexplained epigastric pain or burning, postprandial fullness, or meal-restricting early satiety (and often bloating and nausea) in varying combinations. Worldwide, functional dyspepsia is present in 7.2% of adults (10.1% in the United States), affects women 1.6 times as often as men, and is more common in persons younger than 40 years of age.[1] The incidence of functional dyspepsia is estimated to be 3 to 4% per year.[2]

Acute gastrointestinal infections can precipitate functional dyspepsia in at least 10% of cases.[3] Heavy smoking is a strong risk factor for functional dyspepsia.[4] Overall hereditability is weak (5%).[5] Approximately one third of persons with functional dyspepsia have anxiety or depression (or both),[6] a proportion similar to that of persons with organic dyspepsia (i.e., dyspepsia from a known cause — e.g., peptic ulcer or gastroesophageal reflux disease [GERD]) or other chronic disorders.[7] A history of anxiety may confer a predisposition to subsequent functional dyspepsia, but the presence of functional dyspepsia can itself induce subsequent anxiety and depression.[2]

Patients with functional dyspepsia have moderate-to-severe impairments to their quality of life, similar to those seen with other chronic diseases, and in two thirds

of patients the symptoms persist over time, with associated high rates of health care use and high socioeconomic costs.[8-10] A large nationwide study showed an increase in hospitalization, suicide, and death from any cause among patients with functional dyspepsia.[11]

Approximately one third to one half of affected patients meet the symptomatic criteria for both functional dyspepsia and irritable bowel syndrome (IBS).[12] More than 30% of patients with functional dyspepsia have symptoms suggestive of GERD, and more than 40% of patients with GERD have functional dyspepsia symptoms.[13] Overlap is associated with more severe functional dyspepsia symptoms.[12]

CURRENT UNDERSTANDING OF THE PATHOPHYSIOLOGICAL PROCESSES

An understanding of the pathophysiological processes of functional dyspepsia can help the patient contextualize symptoms and manage expectations and enhances trust in the physician. Although several putative factors have been described, differences between healthy controls and patients with functional dyspepsia are not always found because of the heterogeneity of the syndrome, nonuniform approaches to measurement, and a lack of normative standards. Functional dyspepsia is likely to be a collection of different diseases with multiple causes. There is reasonable evidence to suggest that at least a subset of the syndrome may arise from local microinflammation driven by an aberrant immune response by type 2 helper T (Th2) cells (Fig. 1). A modest increase in eosinophils and mast cells has been noted in the duodenum and, less often, in the stomach of patients with functional dyspepsia.[14] Eosinophilic activation and degranulation may be more consistently associated with functional dyspepsia[14] than eosinophil counts alone and correlated with symptoms in one study,[15] as do altered submucosal neuronal responses and gliosis in the duodenum.[16] In such a context, physiological stimuli such as endogenous duodenal acidification may increase gastric hypersensitivity and inhibit postmeal gastric accommodation.[17] Aberrant macrophage activation associated with a loss of interstitial cells of Cajal has also been observed in the myenteric (motor) plexus of the stomach.[10] These changes may underlie some of the observed changes in gastric function and associated symptoms, which include impairment of gastric accommodation (seen in 40% of patients), hypersensitivity to gastric distention (in 40%), and mild delays in gastric emptying (in 30%); however, 30% of patients have none of these.[18]

Mast cells appear to be particularly more numerous in patients with IBS overlap, which suggests a common pathophysiological factor.[19] In children with functional dyspepsia, the density of mast cells correlates with symptoms, gastric myoelectrical activity, and altered gastric emptying.[20]

A role for immune dysfunction is supported by the association with atopic and rheumatologic disorders.[21] Systemic immune activation has been reported, with small intestinal homing T cells and cytokines correlating with symptoms and delayed gastric emptying.[22] In a tertiary clinical practice, 26% of patients with functional dyspepsia had two or more markers of a systemic autoimmune disorder, a finding that was particularly common in patients with joint hypermobility and coexisting autonomic dysfunction.[23] Putative antigenic triggers may include foodborne pathogens, environmental allergens, or dysbiosis (or a combination of these) accompanied by changes in duodenal permeability.[24] Noninflammatory causes are less well understood but could include postinfectious alterations in the plasticity of the enteric nervous system and visceral afferents, bile-salt dysregulation, or dietary constituents (e.g., salicylates and histamines).[24,25]

STRATEGIES AND EVIDENCE

DIAGNOSIS

Symptoms alone are insufficient to distinguish functional dyspepsia from other gastrointestinal disorders (Table 1), and appropriate tests should be ordered on the basis of clinical judgment, particularly in the presence of symptoms that arouse concern (Table 2). Weight loss is often considered to be a red flag but is not uncommon, particularly in persons with severe symptoms. Conditioned reflexive behavior may be responsible for food aversion in some cases, but the term "avoidant restrictive food intake disorder" is technically inaccurate in patients with functional dyspepsia and may cause confusion or stigmatization owing to the suggestion that an eating disorder is present.

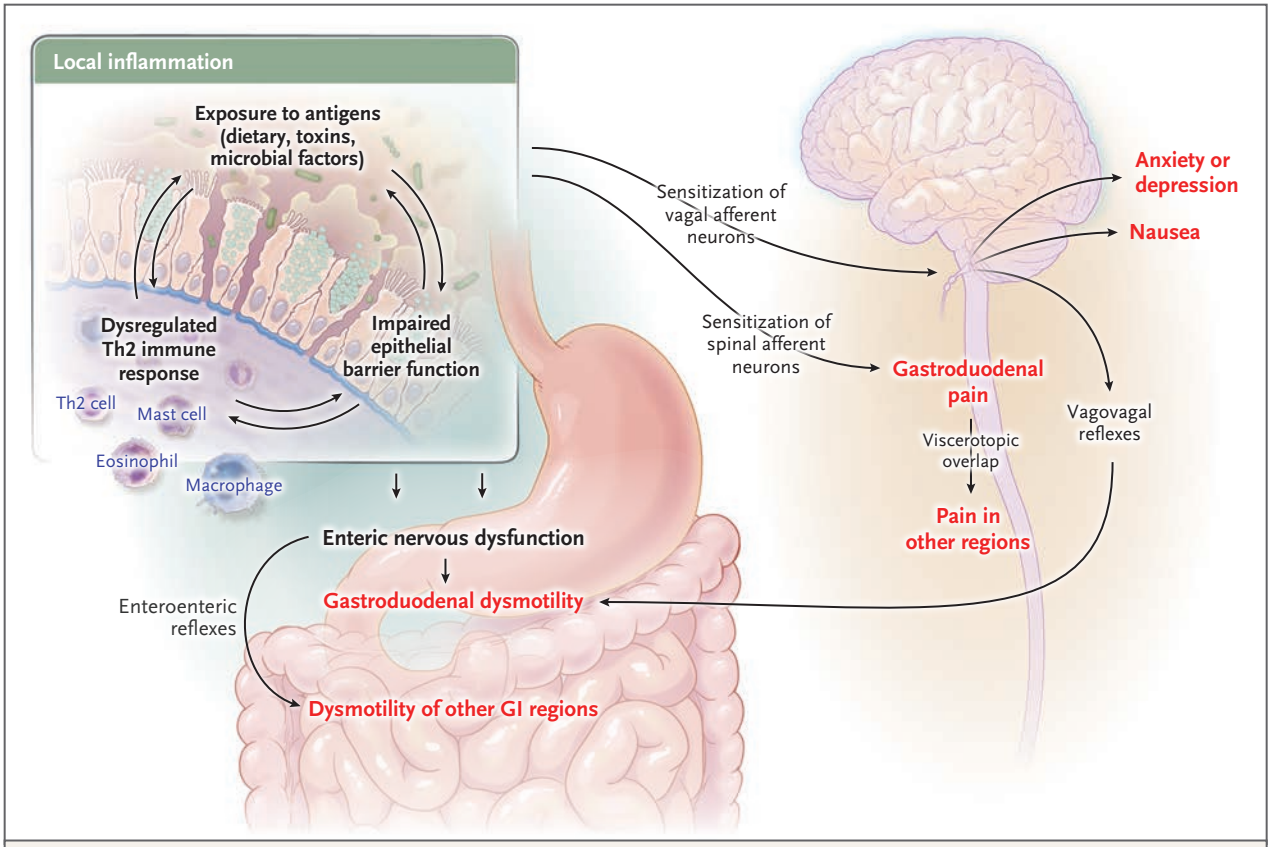

Figure 1. Proposed Pathophysiological Model of Functional Dyspepsia.

Local gastroduodenal inflammation triggered by luminal antigens leads to a dysregulated immune response by type 2 helper T (Th2) cells and activation of eosinophils, mast cells, and macrophages. The resulting impairment of the epithelial barrier function may further facilitate antigen penetration and perpetuate the microinflammation. These changes drive enteric nervous dysfunction, leading to dysmotility of the gastroduodenal region and other regions of the gut. The changes also result in the sensitization of vagal and spinal afferent pathways, leading to pain felt in the epigastrium (as well as other regions of the gut), nausea, and changes in affect. This conceptual model is probably applicable only to a subgroup of patients with functional dyspepsia rather than all persons who meet symptomatic criteria for this disorder. GI denotes gastrointestinal.

Lack of an association between symptoms and meals should raise questions about the diagnosis. Testing and treatment for *Heliobacter pylori* infection is recommended because a substantial minority of patients with such infection will have symptom resolution at 12 months (relative risk of unresolved symptoms, 0.91; 95% confidence interval [CI], 0.88 to 0.94).[27] Systematic reviews indicate that among patients in the Western hemisphere who have symptoms, esophagogastroduodenoscopy shows erosive esophagitis in 25% of the patients and peptic ulcer in 6%, with esophageal or gastric cancer seen in less than 0.4%.[29] An argument can therefore be made for empirical treatment with proton-pump inhibitors, reserving esophagogastroduodenoscopy for patients with symptoms that arouse concern. However, given the persistent nature of symptoms and associated anxiety, most patients eventually undergo esophagogastroduodenoscopy. Patients who have prominent nausea, vomiting, and weight loss should have a formal evaluation of solid-food gastric emptying to assess the presence and severity of gastroparesis.

TREATMENT

There is no approved drug for the treatment of functional dyspepsia, and practitioners rely on empirical treatment that is directed at symptoms, often with unsatisfactory results. Given the limit-

Table 1. Differential Diagnosis of Symptoms Associated with Functional Dyspepsia.

Symptoms and Other Potential Causes	Relevant Symptoms	Tests to Rule Out Other Causes
Early satiety (fullness)		
Gastric cancer	Unexplained weight loss; chronic untreated *Heliobacter pylori* infection; age >60 yr; risk factors related to geographic location, ethnic group, and others	Upper endoscopy
Gastroparesis	Recurrent or frequent vomiting or severe nausea	Gastric emptying test
Epigastric pain		
Peptic ulcer	*H. pylori* infection, use of nonsteroidal antiinflammatory medication	Upper endoscopy
Gallstone disease	Crescendo–decrescendo episodic pain lasting ≥30 min, often severe	Ultrasound of the gallbladder and bile ducts
Anterior cutaneous nerve entrapment syndrome or chronic abdominal-wall pain	Point tenderness	Carnett's sign (pressure on the point of tenderness before and after the patient tenses the abdominal wall reveals increased tenderness on tensing)
Chronic pancreatitis	Risk factors (e.g., alcohol use, genetic predisposition), steatorrhea	Pancreatic imaging
Epigastric burning		
Gastroesophageal reflux	Heartburn, regurgitation	Upper endoscopy, pH testing
Bloating		
Celiac disease	Family history, diarrhea, unexplained iron deficiency	Celiac serologic testing
Small intestinal bacterial overgrowth	Long-term use of proton-pump inhibitor, dysmotility of the small intestines	Breath test, duodenal aspirate for bacteria, empirical treatment with antibiotics

ed efficacy of drugs that are recommended under national and international guidelines (see below), the consideration of therapies for which evidence is insufficient may be reasonable in refractory cases (Table 3).

DIET

In most patients with functional dyspepsia, symptoms are meal-related, generally reaching a peak within an hour after eating. The effectiveness of simple dietary advice (i.e., small low-fat meals and avoidance of carbonated drinks to limit gastric distention), although seemingly rational, has not been borne out in a randomized trial.[33] Low-FODMAP (fructans, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diets have not been shown to reduce symptoms any more than traditional dietary advice.[34] IgE-mediated (classical) food allergy is generally not mistaken for functional dyspepsia, and screening for IgG-mediated reactivity to food antigens is not recommended.[25] Diets that exclude specific antigens such as gluten or the six-food (milk, wheat, eggs, soy, peanuts or tree nuts, and fish or shellfish) elimination diet have yet to be tested rigorously but may be reasonable options for patients with refractory symptoms.[35]

ACID SUPPRESSANTS

Acid-inhibition pharmacotherapy is considered to be first-line treatment in functional dyspepsia. However, the benefits of this approach are modest at best, even in patients who have a response. In a meta-analysis of 16 trials of proton-pump inhibitors that involved 6017 patients, a reduction in symptoms was observed (relative risk of no improvement vs. control, 0.86; 95% CI, 0.78 to 0.95).[27] Treatment with histamine H_2–receptor antagonists is also superior to placebo, as shown in a network meta-analysis (relative risk of no improvement, 0.81; 95% CI, 0.73 to 0.90).[28] How these drugs work is unclear, because basal-acid

Table 2. Clinical Features Prompting Further Evaluation.*

Evidence of gastrointestinal bleeding (e.g., hematemesis, melena, and bright-red blood from the rectum)
New-onset symptoms in patients 60 years of age or older (in the United States)
Iron-deficiency anemia
Unexplained weight loss (>10% of body weight)
Progressive dysphagia or odynophagia
Persistent vomiting
Long-term use of aspirin or nonsteroidal antiinflammatory drugs
Strong family history of gastrointestinal cancer (especially esophagogastric)
History of upper gastrointestinal cancer
Lymphadenopathy or abdominal mass

* These symptoms and features may indicate a higher risk of peptic-ulcer disease or upper gastrointestinal cancer,[26] prompting further evaluation with esophagogastroduodenoscopy.

production is not increased in functional dyspepsia. Intraduodenal-acid infusion may induce nausea in some patients,[36] and acid can activate sensory neurons through pH-responsive receptors, such as TRPV1, which may be sensitized in patients with functional dyspepsia.[37] In addition, proton-pump inhibitors are known to reduce gut eosinophils, and H_2 blockers may also inhibit activation of nociceptive receptors by histamine released by mast cells and by bacterial breakdown of dietary histidine.[25]

NEUROMODULATORS

Tricyclic antidepressants are considered first-line therapy in this category and act on pain principally by inhibiting monoamine uptake in the spinal cord; however, many of these drugs are also potent antagonists of the histamine H_1 and, to a lesser extent, H_2 receptors. A meta-analysis showed that tricyclic antidepressants reduced symptoms of functional dyspepsia, with a relative risk of no improvement of 0.74 and number needed to treat of six to reduce symptoms in one patient.[38] Results of the Functional Dyspepsia Treatment Trial showed significant superiority of low-dose amitriptyline over placebo in achieving prespecified "adequate relief" for the last 5 weeks of the 10-week trial (53% with amitriptyline vs. 40% with placebo, P=0.05). The effect appeared to be greatest in participants with epigastric pain (relative risk, 1.34; 95% CI, 1.02 to 1.59). In contrast, the response obtained with escitalopram (a selective serotonin-reuptake inhibitor) did not differ from that obtained with placebo.[39] The benefit of amitriptyline was independent of changes in depression or anxiety scores.

The benefits of tricyclic antidepressants may not generalizable to other neuromodulators. The serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine has been shown to be ineffective.[40] Duloxetine (another SNRI but a more potent inhibitor of norepinephrine uptake) was less effective than nortriptyline at 3 months.[30] Mirtazapine (an atypical tetracyclic antidepressant that also antagonizes histamine H_1 receptors and serotonin 5-hydroxytryptamine [5-HT] type 3 receptors) also has shown efficacy in functional dyspepsia and may be best suited for patients with prominent nausea and clinically significant weight loss.[41] The gabapentinoid agent pregabalin was superior to placebo, with 71% patients reporting adequate relief at week 8 (as compared with 45% with placebo [P=0.03]); however, side effects (including dizziness) were common, and without an active comparator, inferences cannot be made about relative effectiveness.[31]

AGENTS THAT AFFECT GASTROINTESTINAL MOTILITY

The rationale for administering drugs that affect gastrointestinal motility is to improve gastric emptying or gastric accommodation. Metoclopramide, a dopamine D_2-receptor antagonist, has not been studied in functional dyspepsia, and although a few studies have suggested efficacy of domperidone (another dopamine D_2-receptor antagonist), the quality of the trials is very low.[42] Azapirones such as buspirone and tandospirone are serotonin-receptor partial agonists targeting the 5-HT 1A agonists that relax the gastric fundus and, theoretically, improve early satiety (buspirone may also reduce nausea because of dopamine D_2-receptor antagonism); however, a meta-analysis only showed a reduction in bloating, with no overall benefit.[32]

IMMUNOMODULATING TREATMENTS

A randomized, controlled trial of montelukast, a cysteinyl leukotriene antagonist, in children with duodenal eosinophilia and dyspeptic symptoms showed a significant effect in reducing pain as compared with placebo (62% vs. 32%, P<0.02), and the effect appeared to be even greater (84%)

Table 3. Treatments to Consider in Functional Dyspepsia.*

Drug Class	Pathophysiological Target	Examples	Relative Strength of Evidence
Acid suppressants	Acid-induced reflexes triggered by enteric and sensory neurons	Proton-pump inhibitor, H2RA	Symptom abatement with standard dose of PPI: relative risk of no improvement, 0.86 (95% CI, 0.78 to 0.95)[27] Symptom abatement with H2RA: relative risk of no improvement, 0.81 (95% CI, 0.73 to 0.90)[28]
Neuromodulators	Increased or aberrant signaling by afferent neurons to the CNS	Tricyclic antidepressants, duloxetine, mirtazapine, pregabalin, gabapentin	Symptom abatement with low-dose tricyclic antidepressant: relative risk of no improvement, 0.75 (95% CI, 0.62 to 0.90)[27] No placebo-controlled trials of duloxetine; not as efficacious as nortriptyline for functional dyspepsia symptoms but better with regard to anxiety, depression, and quality of life[30] Pregabalin: relative risk of no improvement with pregabalin, 0.53 (95% CI, 0.29 to 0.96)[31]
Motility agents†	Delayed gastric emptying, decreased gastric accommodation	Metoclopramide, domperidone, prucalopride, buspirone	Controlled trials of metoclopramide, domperidone, and prucalopride are lacking; buspirone (three small trials of 4-wk duration) led to nonsignificant improvement in functional dyspepsia and gastroparesis symptoms vs. placebo (standardized mean difference, –0.14; 95% CI, –0.44 to 0.17; P=0.39); with regard to individual symptoms, buspirone reduced only the severity of bloating more than placebo[32]
Th2 response modulators	Eosinophil and mast-cell activation	Montelukast, mast-cell antagonists (H1RA, H2RA, ketotifen)	Evidence limited to children only[32]; no evidence for mast-cell antagonists
Agents affecting the microbiota	Dysbiosis	*Bacillus coagulans* and *B. subtilis* combination, rifaximin	Limited evidence: single trials, small numbers, and short-term results
Over-the-counter remedies	Miscellaneous	Peppermint-oil preparations	Limited evidence: few trials, small numbers, and short-term results

* CNS denotes central nervous system, H1RA histamine H_1–receptor antagonist, H2RA histamine H_2–receptor antagonist, and Th2 type 2 helper T.
† Shown are agents that are available in the United States.

in patients with more than 20 eosinophils per high-powered field.[43] Patients with systemic autoimmune markers may be considered for immunomodulatory therapy,[23] although controlled trials are lacking.

PSYCHOLOGICAL SUPPORT AND INTERVENTIONS

Recognition and treatment of uncontrolled anxiety and depression are important in all cases. In refractory functional dyspepsia, it is also important to consider psychological therapies as an adjunct for helping patients cope with their symptoms and perhaps attenuate the severity of symptoms. Studies support the use of cognitive behavioral therapy, mindfulness-based stress reduction, and hypnotherapy in functional dyspepsia, and benefits may last up to 12 months.[42] However, the evidence from these trials is considered to be very low because of heterogeneous interventions, methods, and outcomes; inability to conduct the trials in a blinded manner; and lack of correction for uncontrolled anxiety and depression.[27]

OTHER TREATMENTS

Administration of a combination of *Bacillus coagulans* and *B. subtilis* for 8 weeks resulted in a significantly higher proportion of patients with a clinical response than placebo (48% vs. 20%, P=0.03) and a decrease in Th17 signaling markers in the blood.[44] Patients given the antibiotic agent rifaximin for 2 weeks were also more likely to report greater relief than patients who received placebo (78% vs. 52%, P=0.02).[45]

Table 4. Professional Society Guidelines and Consensus Statements on Approaches to Patients with Symptoms of Functional Dyspepsia.*

Group	*H. pylori* Testing	Prompt EGD	PPIs	Tricyclic Antidepressant Agents	Prokinetic Agents	Psychological Therapy	Complementary or Alternative Medicine
ACG and CAG[42]	Test all patients and treat	Patients >60 yr of age or who have symptoms that arouse concern	First-line therapy	Second-line therapy	Third-line therapy	In the case of failure of medical treatment	Not recommended
UEG and ESNM[49]	Test all patients and treat	Mandatory for diagnosis but can be deferred in primary care in absence of alarm features	Endorsed	No consensus	No consensus	No consensus	No consensus
BSG[27]	Test all patients and treat	Reserved for patients with risk factors	First-line therapy	Second-line therapy	Recommended drugs not available in the United States	In the case of failure of medical treatment or for other considerations (e.g., weight loss)	No statement

* ACG denotes American College of Gastroenterology, BSG British Society of Gastroenterology, CAG Canadian Association of Gastroenterology, EGD esophagogastroduodenoscopy, ESNM European Society of Neurogastroenterology, PPI proton-pump inhibitor, and UEG United European Gastroenterology.

Over-the-counter products (e.g., menthol) have shown some efficacy over placebo, as have herbal preparations, but the safety of herbal preparations remains a concern.[27] Acupuncture (manual or electrical) is often used, but the quality of evidence is very poor, and the results of an analysis of sham stimulation suggest that at least some of the benefits may be placebo-driven.[46] Transcutaneous vagal-nerve stimulation is potentially effective, and one such device has been approved for use for functional abdominal pain in adolescent and young adult patients (11 to 21 years of age) who have IBS and functional dyspepsia, with modest amelioration of symptoms shown in a randomized, controlled trial.[47]

AREAS OF UNCERTAINTY

The distinction between functional dyspepsia and gastroparesis is evolving. In a prospective study, patients with functional dyspepsia and patients with idiopathic gastroparesis had identical symptom profiles and disease severity and had similar outcomes at 48 weeks.[10] The same study also showed the lability of gastric emptying, with close to 40% of the patients in each group crossing over into the other category on the basis of a second emptying study conducted approximately 1 year later; however, the patients' symptoms remained stable despite this change in classification. Full-thickness biopsies of the stomach showed identical pathological changes in the myenteric plexi in both groups, a finding suggesting that functional dyspepsia and gastroparesis may be part of the same spectrum of neurogastrointestinal disorders and should be considered together in trials of new treatments for common symptoms such as nausea. However, patients with persistent and severe delays in gastric emptying (e.g., >35% retention 4 hours after a solid meal) may need more-aggressive therapeutic approaches, including tight glycemic control and pyloromyotomy in some cases. In addition, cases involving patients with diabetes and gastroduodenal symptoms (regardless of the results of gastric-emptying studies) may represent a pathophysiological profile different from that of idiopathic diseases.

It is clear that traditional explanations (e.g., acid–peptic factors, dysmotility) and symptom-based phenoptypes have not been helpful in advancing our understanding of functional dys-

Table 5. Treatment Approach in Patients with Refractory Symptoms of Functional Dyspepsia.*

Treatable conditions to consider
Small intestinal bacterial overgrowth
Suspect with IBS-like symptoms and prominent gas, bloating particularly with long-standing use of proton-pump inhibitors
Consider appropriate testing, treatment for small intestinal bacterial overgrowth, or both
Food-driven immune responses
Consider if patient has strong history of atopy, prominent eosinophils on mucosal biopsy, or evidence of mast-cell activation
Autoimmune or autoinflammatory disease
Consider if patient has history of known autoimmune syndromes (hypothyroidism, sicca symptoms, etc.) particularly with autonomic symptoms or joint hypermobility
Treatment of symptoms
Pain
Low-dose naltrexone
Milnacipran or levomilnacipran
Zonisamide or lacosamide
Valproate
Lamotrigine
Oxcarbazepine or carbamazepine
Quetiapine
Food-driven immune response
Elimination diet
H1RA and H2RA combinations
Ketotifen
Montelukast
Nausea
Antihistamines — promethazine, diphenhydramine
Anticholinergics — meclizine, scopolamine
NK1 receptor antagonists — aprepitant
Cannabinoids — dronabinol
Zonisamide or lacosamide
Antipsychotics — prochlorperazine, haloperidol, quetiapine, olanzapine
Autoimmune or inflammatory disease — work with rheumatologist to consider appropriate immunomodulator therapy
Supportive treatments
Cognitive behavioral therapy, hypnotherapy, and others
Control of anxiety and depression, if present
Transcutaneous vagal-nerve stimulation

* Considerable controversy exists among experts regarding the approach to patients with refractory functional dyspepsia. Shown is a suggested clinical approach to the treatment of such patients; this approach is recommended for use in collaboration with a pain specialist, clinical psychologist or psychiatrist, rheumatologist, and nutritionist. The drug therapies shown represent off-label use and target symptoms of functional dyspepsia and are not intended to treat a neuropsychiatric condition. The risk–benefit balance, including potential side effects and drug interactions, should be considered; some patients may receive combination therapy, but polypharmacy should be avoided. IBS denotes irritable bowel syndrome, and NK1 neurokinin-1.

KEY POINTS

FUNCTIONAL DYSPEPSIA

- Functional dyspepsia is a common but serious medical syndrome that can induce weight loss and food aversion and may be associated with increased risks of hospitalization and death.
- The syndrome probably comprises several different and as yet incompletely characterized disorders; local microinflammation driven by an aberrant response by type 2 helper T cells may represent an important subset of cases.
- Functional dyspepsia can overlap with other gastrointestinal syndromes, particularly irritable bowel syndrome and gastroesophageal reflux disorder, and persons with such overlap have more severe symptoms.
- There is no approved drug therapy; treatment is empirical and directed at symptoms, consisting of acid suppressants and low-dose tricyclic antidepressants (and other neuromodulators), along with appropriate nutritional and psychological support.

pepsia. An alternative and testable hypothesis formed on the basis of an atopic model is shown in Figure 1 and can theoretically explain most of the diverse pathophysiological abnormalities described above. These hypotheses can be tested in clinical trials, and we strongly encourage the adoption of standard protocols to evaluate Th2 markers in endoscopic biopsies (e.g., eosinophils or mast cells) to classify patients according to pathologic endophenotypes. Such an approach can also provide a firmer foundation for the testing of immune modulators, including monteleukast, macrophage inhibitors, and others, including biologic agents — all of which are potential treatments in need of additional research.

The term "functional dyspepsia" has persisted as an umbrella label and conveys a sense of diagnostic certainty about a heterogenous group of illnesses, potentially masking as yet incompletely characterized causes, such as a microinflammatory neurogastrointestinal illness. We believe that functional dyspepsia should no longer be considered "functional" (indicating a lack of organic pathologic features). The trend toward the use of other broad labels such as "disorder of gut–brain interaction" is also potentially problematic because it is nonspecific, may distract scientific attention away from the root cause, and may be considered dismissive or stigmatizing by patients.[48] Finally, the term "dyspepsia," as widely understood, does not correspond to the seriousness of this condition. Fresh nomenclature is therefore needed to facilitate new guidelines for research and treatment. One proposed term is gastroduodenal neuromuscular disorder, which can be further parsed into subtypes as our understanding of these conditions evolves.

GUIDELINES

Major aspects of the approach to functional dyspepsia that were considered in current guidelines or consensus statements by North American and international professional societies are summarized in Table 4. The recommendations presented in this review are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

In the case of the patient in the vignette, we would prescribe low-dose amitriptyline, nortriptyline, or imipramine (e.g., at a dose of 10 mg taken at night and adjusted to a range of 25 to 50 mg), with ondansetron (at a dose of 4 mg as needed) prescribed for nausea. If the patient does not have a response and pain remains prominent, we would recommend a trial of pregabalin (up to 50 mg taken three times daily for 4 to 6 weeks); an alternative would be duloxetine (at a dose of 30 to 60 mg daily). If nausea is bothersome, especially if associated with weight loss, we would prescribe mirtazapine, often beginning at very low doses (e.g., 3.75 to 7.5 mg taken at night) and increasing in weekly increments to a range of 30 to 45 mg a day. Patients taking this drug must be cautioned about the potential for excessive weight gain; many patients may not be willing to assume this risk.

In patients who have refractory symptoms, we recommend further diagnostic testing and therapeutic interventions that assume a neuropathic origin of the symptoms but are entirely empirical, may have clinically significant adverse effects, and are best delivered in the setting of an integrated and experienced multidisciplinary care clinic (Table 5). In a survey, nearly half of patients with functional dyspepsia would accept an effective therapy even when the trade-off was a 13% risk of sudden death.[50] Nevertheless, patients must be informed partners in these trial-and-error approaches, and clinical trials are needed to guide best practice and to develop new and more effective treatments.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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