Functional (Non-Ulcer) Dyspepsia and Gastroparesis—Differentiating These Conditions and Practical Management Approaches

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Because of the limited therapeutic options, management of patients with functional dyspepsia can be remarkably difficult. This review considers the current state of the art for patients who present with unexplained dyspepsia, and outlines a practical management approach for clinicians.


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Many patients present with troublesome epigastric pain or epigastric burning, feelings of fullness or inability to finish a normal meal (early satiation), and nausea.1,2 After appropriate endoscopic and baseline screening blood tests, there is often no obvious structural cause found. The diagnostic labels applied to such patients vary markedly,1,2 although data on this topic are scant. Many of these patients are labeled as having gastroesophageal reflux disease (GERD) if there is even a whiff of heartburn in the history, and this label is still used if there is subsequently no objective evidence of pathologic acid reflux on formal esophageal pH testing.3 Others diagnose these patients as having gastroparesis if gastric emptying is even slightly slowed.4 Still others will diagnose these patients as having dyspepsia, or, less often, non-ulcer dyspepsia (NUD) or functional dyspepsia (FD). But gastric emptying is slow in about one-third of patients with a diagnosis of functional dyspepsia.5-7 If gastric emptying is slow, should these patients really be labeled with gastroparesis, or is functional dyspepsia a more appropriate diagnosis? No wonder so many
Functional Dyspepsia and Gastroparesis

physicians feel bewildered and confused when such patients present to them! This review considers the current state of the art for patients who present with unexplained dyspepsia, and outlines a practical management approach for clinicians.

The Birth of Functional Dyspepsia

Typical duodenal ulcer symptoms were well described early in the 20th century, and looking at the historical literature, it appears that Walter Alvarez, a gastroenterologist at the Mayo Clinic in Rochester, MN, first used the term functional dyspepsia in 1917. He subsequently coined the term nervous dyspepsia for patients with this condition in 1943, which he considered likely to have a psychological (or hysterical) basis. Skeptics might argue that we have made little progress since the time of Alvarez, although hints about the underlying pathogenesis of functional dyspepsia have emerged that are likely to change management paradigms in the future.

Rome Criteria for Functional Dyspepsia

Current consensus-based criteria for dyspepsia recognize this syndrome as comprised of 4 cardinal symptoms: early satiation or inability to finish a normal meal, postprandial heaviness or fullness, epigastric pain, and epigastric burning. To diagnose functional dyspepsia, patients must have at least 1 of these symptoms on a chronic or recurrent basis (for at least 6 months) and there must be no obvious structural explanation after an appropriate evaluation including esophagogastroduodenoscopy.

Most patients who present with functional dyspepsia, however, have multiple upper gastrointestinal complaints. They will also often report typical heartburn (retrosternal burning or painful sensation that rises up toward the throat) as well as bloating and nausea. Indeed, the features that clinically distinguish nonerosive reflux disease (NERD) from functional dyspepsia remain poorly defined in the current literature; many patients with NERD confirmed by abnormal esophageal pH testing also complain of early satiety, fullness, epigastric pain, and nausea, and it seems likely NERD and functional dyspepsia represent the ends of an overlapping pathophysiological spectrum. Currently, the diagnostic criteria distinguishing NERD from functional dyspepsia rests on which symptoms are reported as predominant or most frequent; if the symptoms predominantly appear to be arising from the epigastric region rather than retrosternally or elsewhere, then a label of functional dyspepsia is recommended, although the utility of such criteria remains controversial.

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The current definition for gastroparesis overlaps with the criteria for functional dyspepsia. The consensus definition refers to patients who present with nausea, vomiting, bloating, epigastric pain, or fullness, where these symptoms are explained by slow gastric emptying. However, on careful reflection it is clear that this is a very vague definition that will misclassify a number of patients. Indeed, there is no methodology currently available to ascertain whether the actual symptoms are really driven by slow gastric emptying or other causes.

Does My Patient Have Gastroparesis or Functional Dyspepsia?

One of the confusing areas in this field is differentiating who has gastroparesis from who has functional dyspepsia. A patient presents to your office with early satiety and fullness but denies nausea or vomiting; endoscopy is normal but gastric scintigraphy shows mildly slowed gastric emptying. Does this patient have functional dyspepsia or gastroparesis?

Applying the Rome criteria to patients who present in clinical practice, around 30% to 40% will have slow gastric emptying on gastric scintigraphy, although the abnormalities are often mild or at most moderate. Gastric emptying is more likely to be slower in women compared with men who present with functional dyspepsia. Whereas some studies have found a clear association between symptoms and slow gastric emptying in functional dyspepsia, large multicenter studies have failed to demonstrate any clear link. This has led a number of authorities to suggest that gastric emptying, although a marker of abnormality in functional dyspepsia, is unlikely to explain the underlying symptoms. There is also a small group of patients (about 5%) with functional dyspepsia who have accelerated gastric emptying on scintigraphy, which may change management.

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by slow gastric emptying. In clinical practice, gastroparesis is relatively rare if the definition is restricted to include those with chronic vomiting and/or weight loss associated with significant slowing of gastric emptying. These patients require a somewhat different management plan than patients with functional dyspepsia, which suggests that differentiating the conditions is important. It is a pity that gastroparesis experts have failed to recognize the serious shortcomings of the current published definitions.

Pathophysiological Abnormalities Identified in Functional Dyspepsia

In addition to alterations of gastric emptying, other gastroduodenal abnormalities have been identified in subsets of patients with functional dyspepsia and may represent disease markers. Gastric accommodation is impaired in approximately 40% of patients with functional dyspepsia who have been diagnosed with this condition in tertiary referral centers. Unfortunately, it is unknown whether a high prevalence of fundic abnormality also occurs in primary care or in the general population. There is some evidence that failure of fundic accommodation induces early satiety and weight loss in patients with functional dyspepsia. Some cases appear to occur after acute infectious gastroenteritis, similar to postinfectious irritable bowel syndrome.

Another abnormality that has been identified in functional dyspepsia is gastric hypersensitivity. This finding was based on balloon distention experiments comparing sensation in patients with functional dyspepsia with controls. Other data suggest hypersensitivity also occurs in the duodenum of patients with functional dyspepsia. Some of these patients also have evidence of vagal dysfunction. Postprandial pain, belching, fullness, and weight loss have been linked to the presence of gastric hypersensitivity, although these observations need to be more broadly confirmed.

Other duodenal abnormalities have also been identified in subsets of patients. Based on intraduodenal infusions of acid, there appears to be acid retention in the duodenum in some patients with this condition secondary to motor disturbances in the upper small intestine. There may also be reflex abnormalities in some patients; for example, acid infusion into the duodenum is associated with less meal-induced relaxation of the gastric fundus in patients with functional dyspepsia. Finally, eosinophilic infiltration and degranulation has been observed in a case-control study of patients with functional dyspepsia. Notably, the eosinophilic infiltration was subtle and required quantification histology to identify an abnormality, and whether this occurs in other populations remains to be confirmed.

Diagnosis of Functional Dyspepsia

Traditionally, a diagnosis of functional dyspepsia has been one of exclusion. Patients with typical symptoms first undergo esophagogastroduodenoscopy, which, if normal, leads clinicians to apply this label. Because this has been a diagnosis of exclusion, many other diagnostic labels have been misapplied to these patients. Heartburn is a common coexisting symptom, in part because reflux symptoms are very common in the general community and perhaps because reflux disease is part of the disease continuum. Notably, gastroesophageal reflux disease is part of the disease continuum. Notably, gastroesophageal reflux disease has been diagnosed with this condition.

There is a growing body of evidence that patients with functional dyspepsia have a greater symptomatic response to food ingestion than those who do not have this condition. A polymorphism of the G protein (GNδ3) is linked to functional dyspepsia. Initial evidence suggested that a particular polymorphism (the homozygous CC type) was linked to functional dyspepsia although other work has implied the TT polymorphism. However, genetic testing currently has neither diagnostic nor prognostic value.

Management of Functional Dyspepsia

Management is strongly influenced by symptom severity, the type of symptoms the patient is experiencing, and the presence of comorbid conditions.
Patients who predominantly complain of epigastric pain or epigastric burning need to be managed differently from those who predominantly complain of early satiation or bothersome postprandial fullness.

Helicobacter pylori Testing and Treatment

There is evidence that *H. pylori* infection is linked to functional dyspepsia. A number of randomized, controlled trials, when pooled, suggest a very small but significant benefit of *H. pylori* eradication in this setting.

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However, there is one notable concern about the literature, and that is these trials all failed to randomize patients who were *H. pylori* negative as a control group. Therefore, although *H. pylori* eradication treatment may be beneficial, it is not certain whether this is related to eradication of the bacteria or some other nonspecific effect of eradication therapy (such as an alteration of the enteric flora). Despite this concern, the current guidelines recommend *H. pylori* testing and treatment regardless of symptom pattern in functional dyspepsia. In clinical practice, however, most patients who present with functional dyspepsia are *H. pylori* negative.

Acid Suppression

There is evidence that both H2 receptor antagonists and proton-pump inhibitors (PPIs) will improve symptoms of functional dyspepsia, but only a minority respond. The most robust evidence is with PPIs. On pooling the data, it appears that those with epigastric pain or epigastric burning are more likely to respond to PPI than placebo. On the other hand, those with early satiation or postprandial fullness are not more likely to respond than those receiving placebo. Antacids, bismuth, and sucralfate appear no better than placebo in functional dyspepsia based on the available evidence.

Prokinetics

Work on prokinetics in functional dyspepsia has largely revolved around cisapride, which is not approved for this indication. There are few data on the efficacy of metoclopramide or domperidone in functional dyspepsia.

Antidepressants

There are very limited data on the use of antidepressants in functional dyspepsia. Tricyclics may have a benefit, although the evidence is extremely limited and only amitriptyline has been studied. Venlafaxine did not appear to provide any benefit in a recent trial of patients with functional dyspepsia. Currently, the National Institutes of Health is funding a randomized, controlled trial of amitriptyline, escitalopram, and placebo in functional dyspepsia at 7 sites around the United States (Mayo Clinic Florida, Mayo Clinic Rochester, Mayo Clinic Scottsdale, Dartmouth-Hitchcock Medical Center, Northwestern University [Chicago], St. Louis University Medical School, and Baylor College of Medicine). The trial is also assessing pharmacogenomics to determine whether therapy can be individualized more effectively. Finally, the study is assessing the role of pathophysiological biomarkers and response. You can refer patients to this trial by sending an e-mail to mcjdysepsia@mayo.edu.

How Does Management of Functional Dyspepsia Differ From Gastroparesis?

In true gastroparesis, management revolves around symptom control, typically using a combination of prokinetic and antinausea drugs, tight glucose control if the patient is diabetic, and appropriate nutritional support. If these approaches fail, management remains very difficult. Gastric electrical stimulation does provide symptom relief for those with recurrent vomiting, but does not help other symptoms. Surgery has a very limited role. Postinfectious gastroparesis may reverse after a period, but many cases continue and the disease has a measurable mortality.
Functional Dyspepsia and Gastroparesis

Summary of Management
In patients presenting with chronic unexplained dyspepsia, it is important to rule out gastroesophageal reflux and other diseases such as irritable bowel syndrome or chronic constipation. It is then useful to subdivide patients into those who clinically have predominantly epigastric pain or burning versus those with meal-related symptoms, although there is a clear group of about one-third of patients who have both. *H. pylori* should be treated if present. Acid suppression may benefit those with epigastric pain, and an H2 blocker can be tried if PPI fails. Patients with meal-related symptoms may respond to dietary advice (small frequent meals with low fat content) and prokinetic therapy, but the options unfortunately are limited. In those who fail, fundic relaxation drugs including tizanidine may offer a benefit, but good data are lacking. Fast gastric emptying is uncommon but may respond to an anticholinergic. Antidepressants probably have a role although the evidence is remarkably limited. Because of the limited therapeutic options, management of patients with functional dyspepsia remains difficult.

References
Functional Dyspepsia and Gastroparesis


