Update on the Evaluation and Management of Functional Dyspepsia

RYAN A. LOYD, MD, and DAVID A. McCLELLAN, MD, Texas A&M Health Science Center College of Medicine, Bryan, Texas

Dyspepsia affects up to 40 percent of adults each year and is often diagnosed as functional (nonulcer) dyspepsia. The defining symptoms are postprandial fullness, early satiation, or epigastric pain or burning in the absence of causative structural disease. These symptoms may coexist with symptoms of functional gastrointestinal disorders, such as gastroesophageal reflux and irritable bowel syndrome, as well as anxiety and depression. The history and physical examination can help identify other possible causes of the symptoms. Warning signs of serious disease, such as cancer, are unintended weight loss, progressive dysphagia, persistent vomiting, evidence of gastrointestinal bleeding, and a family history of cancer. In these cases, more extensive laboratory investigation, imaging, and endoscopy should be considered as clinically indicated. During the initial evaluation, a test-and-treat strategy to identify and eradicate *Helicobacter pylori* infection is more effective than empiric treatment and more cost-effective than initial endoscopy. Eradication of *H. pylori* helps one out of 15 patients with functional dyspepsia diagnosed by endoscopy, but may not be cost-effective. Treatment options that may be beneficial for functional dyspepsia include histamine H$_2$ blockers, proton pump inhibitors, and prokinetic agents. Although psychotropic medications and psychological interventions have no proven benefit in patients with functional dyspepsia, they are appropriate for treating common psychiatric comorbidities. (*Am Fam Physician*. 2011;83(5):547-552. Copyright © 2011 American Academy of Family Physicians.)

Patient information: A handout on dyspepsia, written by the authors of this article, is provided on page 554.
motility-related symptoms, such as bloating, early satiation, nausea, and vomiting. Studies have documented altered gastric motility (e.g., gastroparesis, gastric dysrhythmias, abnormal fundus accumulation, pyloric sphincter dysfunction) in up to 80 percent of patients with functional dyspepsia. However, the degree of dysmotility does not correlate with symptoms. Because many patients with functional dyspepsia have burning pain that is indistinguishable from ulcer-related dyspepsia, the relationship between functional dyspepsia and acid secretion is unclear. One study demonstrated a lower pH level in the duodenum of patients with functional dyspepsia compared with those in the control group, although the pH level did not correlate with symptoms. The role of Helicobacter pylori infection in functional dyspepsia has also been investigated. Large population studies have shown an increased incidence of H. pylori infection in patients with functional dyspepsia; however, given the high incidence of both conditions in the general population and the minimal response to treatment, the significance of the association is unclear.

In spite of this uncertainty, testing for and treating H. pylori infection have become integral to the diagnostic management of functional dyspepsia.

### Diagnostic Approach

Functional dyspepsia is a diagnosis of exclusion; therefore, physicians should focus on excluding serious or specifically treatable diseases, without spending too much time investigating symptoms. Dyspepsia has a broad and diverse differential diagnosis (Table 2), including functional dyspepsia, peptic ulcer disease, reflux esophagitis, and gastric or esophageal malignancy. Functional dyspepsia is the most prevalent diagnosis, making up 70 percent of dyspepsia cases.

The physician should perform a detailed history and physical examination at the initial presentation, noting any findings that point to a diagnosis other than...
Functional dyspepsia (e.g., right upper-quadrant pain with cholelithiasis, exercise association with coronary artery disease, radiation to the back with pancreatitis). Table 3 includes medications and other agents commonly associated with dyspepsia. Because the differential diagnosis is broad, the workup can range from empiric therapy to extensive laboratory and imaging studies. Figure 1 is an algorithm for the evaluation and treatment of patients with dyspepsia.5,19

History and physical examination alone have low sensitivity and specificity for predicting which patients with dyspepsia will have organic disease discovered on esophagogastroduodenoscopy.15,20 Because of this inaccuracy, the high incidence of normal endoscopic findings, and the very low incidence of malignancy, it is desirable to try empiric treatment before invasive and expensive diagnostic testing.

Several strategies have been suggested for initial management of uninvestigated dyspepsia, including a trial of acid suppressants, a test-and-treat approach (for H. pylori infection), and early endoscopy. A Cochrane review found that in the absence of warning signs for serious disease, a test-and-treat strategy is effective and cheaper than initial endoscopy.21 Initial endoscopy has been shown to provide a small reduction in the risk of recurrent dyspepsia symptoms; however, physicians need to weigh the cost of endoscopy against patient preference for early reassurance and symptom reduction.21 The Cochrane review showed the test-and-treat strategy to be slightly more effective than empiric acid suppressants, although the comparative cost-effectiveness of these strategies has not been established.21 Physicians can diagnose H. pylori infection with non-invasive tests, such as serologic, stool antigen, or urea breath tests. Serologic testing is the most common because of its wide availability and low cost, although urea breath testing is more accurate.22

In patients 55 years or younger, the American Gastroenterological Association (AGA) identifies several warning signs that should trigger an early, aggressive workup (e.g., unintended weight loss, progressive dysphagia, persistent vomiting, evidence of GI bleeding, family history of cancer).2 The AGA recommends proceeding directly to endoscopy in patients with warning signs and in those older than 55 years; however, there has been debate about a lower cutoff age of 35 to 45 years in men.23 Although it is not addressed in

### Table 2. Differential Diagnosis of Dyspepsia

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Approximate prevalence*</th>
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<tbody>
<tr>
<td>Functional (nonulcer) dyspepsia</td>
<td>Up to 70 percent</td>
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<tr>
<td>Peptic ulcer disease</td>
<td>15 to 25 percent</td>
</tr>
<tr>
<td>Reflux esophagitis</td>
<td>5 to 15 percent</td>
</tr>
<tr>
<td>Gastric or esophageal cancer</td>
<td>&lt; 2 percent</td>
</tr>
<tr>
<td>Abdominal cancer, especially pancreatic cancer</td>
<td>Rare</td>
</tr>
<tr>
<td>Biliary tract disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Carbohydrate malabsorption (lactose, sorbitol, fructose, mannitol)</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Infiltrative diseases of the stomach (Crohn disease, sarcoidosis)</td>
<td>Rare</td>
</tr>
<tr>
<td>Intestinal parasites (Giardia species, Strongyloides species)</td>
<td>Rare</td>
</tr>
<tr>
<td>Ischemic bowel disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Medication effects (Table 3)</td>
<td>Rare</td>
</tr>
<tr>
<td>Metabolic disturbances (hypercalcemia, hyperkalemia)</td>
<td>Rare</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease)</td>
<td>Rare</td>
</tr>
</tbody>
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*—Based on the occurrence of the disorders in patients with dyspepsia who are evaluated with endoscopy.

Information from references 15 through 18.

### Table 3. Agents Commonly Associated with Dyspepsia

<table>
<thead>
<tr>
<th>Acarbose (Precose)</th>
<th>Metformin (Glucophage)</th>
</tr>
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<tbody>
<tr>
<td>Alcohol</td>
<td>Miglitol (Glyset)</td>
</tr>
<tr>
<td>Antibiotics, oral (e.g., erythromycin)</td>
<td>Nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Opiates</td>
</tr>
<tr>
<td>Corticosteroids (e.g., prednisone)</td>
<td>Orlistat (Xenical)</td>
</tr>
<tr>
<td>Herbs (e.g., garlic, ginkgo, saw palmetto, feverfew, chaste tree berry, white willow)</td>
<td>Potassium chloride</td>
</tr>
<tr>
<td>Iron</td>
<td>Theophylline</td>
</tr>
</tbody>
</table>

the AGA guidelines, an initial complete blood count may be appropriate to screen for anemia. The AGA guidelines do not address laboratory testing and imaging; however, it is reasonable to consider these approaches in patients with negative esophagastroduodenoscopy findings and warning signs, or if the treatment course is unsuccessful.

**Treatment**

Treatment of functional dyspepsia can be frustrating for physicians and patients because few treatment options have proven effective. Patients will need continued reassurance and support from their physicians. Treatment is generally aimed at one of the presumed underlying etiologies of functional dyspepsia.

**Gastric Acid Suppression**

Gastric acid suppressants have been studied extensively in the treatment of functional dyspepsia. Although their benefit in patients with ulcer-related dyspepsia or gastroesophageal reflux disease is considerable, the benefit in patients with functional dyspepsia is less clear. Antacids, sucralfate (Carafate), and misoprostol (Cytotec) have been evaluated in limited studies without evidence of benefit.

Bismuth salts showed some benefit compared with placebo in a meta-analysis; however, the studies that showed benefit were not well designed and involved only patients with *H. pylori* infection, with intent to eradicate the infection. Because of the questionable benefit and long-term risk of neurotoxicity, bismuth salts cannot be recommended as first-line agents for functional dyspepsia.

Histamine H$_2$ blockers are more promising agents for treating functional dyspepsia and have been evaluated in multiple trials. A meta-analysis concluded that H$_2$ blockers significantly improve symptoms; however, there was evidence of some publication bias, and the effect may have been overestimated, especially in comparison with proton pump inhibitors. Studies of proton pump inhibitors have shown a statistically significant improvement in symptoms of functional dyspepsia compared with placebo. These studies were of better quality than those investigating H$_2$ blockers, making it difficult to compare relative effectiveness. Given the small benefit of gastric acid suppressants and the commonly chronic nature of functional dyspepsia symptoms, physicians must consider the cost and long-term safety profile of the medication chosen for initial treatment.

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**Figure 1. Algorithm for the evaluation and management of dyspepsia.**


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A search was completed in PubMed and the Cochrane Database of Systematic Reviews using the following keywords: nonulcer/dyspepsia ± cause, evaluation, treatment, and Helicobacter pylori.

Data Sources: A search was completed in PubMed and the Cochrane Database of Systematic Reviews using the following keywords: nonulcer/dyspepsia ± cause, evaluation, treatment, and Helicobacter pylori. Search date: April 1, 2010.

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REFERENCES
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