Functional dyspepsia in adults

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INTRODUCTION

Dyspepsia is a common symptom with an extensive differential diagnosis and a heterogeneous pathophysiology [1]. The prevalence of uninvestigated dyspepsia worldwide is up to 20 percent, especially in females, smokers, and people taking nonsteroidal antiinflammatory agents. The prevalence varies according to the definition used for dyspepsia [2,3]. Dyspepsia can significantly impair quality of life [4]. The proportion of affected people who seek medical care ranges from 14 to 66 percent in various countries and ethnic groups [5]. The majority of patients (75 to 80 percent) with symptoms of dyspepsia are eventually categorized as having functional (idiopathic, nonulcer) dyspepsia. Many authorities regard it as a "disorder of gut-brain interaction" along with irritable bowel syndrome and other symptom-based gastrointestinal disorders [6], but the term "functional" is still commonly used. This topic review will provide an overview of the pathophysiology and treatment of functional dyspepsia.

Our recommendations for the diagnosis and management of functional dyspepsia are largely consistent with the American College of Gastroenterology, Canadian Gastroenterological Association, and American Gastroenterological Association guidelines [7,8], and a European expert consensus [9]. The etiology, general approach to the evaluation, and management of the patient with uninvestigated dyspepsia are presented separately. (See "Approach to the adult with dyspepsia".)

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The prevalence of functional dyspepsia ranges from 5 to 11 percent worldwide [2,3]. The pathophysiology of functional dyspepsia is not well understood. However, several potential mechanisms have been suggested. These mechanisms may differ between subtypes of functional dyspepsia (postprandial distress syndrome and epigastric pain syndrome) [10]. (See 'Diagnostic criteria' below.)

- **Gastric emptying, accommodation, and vagal function** – Functional dyspepsia has been associated with several motility disorders. These include mild delays in gastric emptying, rapid gastric emptying, antral hypomotility, gastric dysrhythmias, impaired gastric accommodation in response to a meal, and abdominal vagal dysfunction [10-13]. However, these findings vary among patients. (See "Gastroparesis: Etiology, clinical manifestations, and diagnosis".)

- **Visceral hypersensitivity** – Visceral hypersensitivity is characterized by a lowered threshold for induction of pain in the presence of normal gastric compliance. Visceral hypersensitivity independent of delayed gastric emptying has been demonstrated in patients with functional dyspepsia [14]. Both mechanoreceptor dysfunction and aberrant processing of afferent input in the spinal cord or brain may play a role in the pathophysiology of visceral hypersensitivity [15]. In one study that included 270 patients with functional dyspepsia, 37 percent had hypersensitivity to gastric distension, and hypersensitive patients reported higher cumulative symptom scores as compared with normosensitive patients [10]. Intraduodenal infusion of dextrose and lipids was also associated with symptoms in patients with functional dyspepsia, and an association of hypersensitivity with higher plasma concentrations of enteral hormones suggested hormonal mediation of the sensitivity [16].

- ***Helicobacter pylori* infection** – The role of *H. pylori* infection in the pathogenesis of functional dyspepsia remains unclear (see "Pathophysiology of and immune response to Helicobacter pylori infection"). Furthermore, only a small minority of patients with functional dyspepsia report symptom improvement after eradication therapy for *H. pylori* [17].

- **Altered gut microbiome** – Alterations in the upper gastrointestinal tract microbiome may result in the development of dyspepsia. This hypothesis is supported by the observation that dyspeptic symptoms are more likely to occur after an episode of gastroenteritis [18-21]. In one study, risk factors for the persistence of dyspepsia eight years after exposure to a waterborne outbreak of bacterial dysentery were female sex, smoking, premorbid irritable bowel syndrome (IBS), anxiety, depression, and >7 days of diarrhea or abdominal cramps during the acute illness [19]. It has been hypothesized that the efficacy of *H. pylori*

therapy in improving symptoms of functional dyspepsia in some patients is due to the impact on the gut microbiome rather than the eradication of *H. pylori* alone [22,23].

- **Duodenal inflammation and immune activation** – Increased eosinophils and mast cells and altered lymphocyte populations, including "gut-homing" lymphocytes, have been reported in the duodenum of patients with functional dyspepsia [24-28]. Structural and functional differences in duodenal submucosal ganglia between patients with functional dyspepsia and controls have also been described [29]. Confocal endomicroscopy has revealed increased epithelial gaps in patients with functional dyspepsia plus reduced transepithelial electrical resistance that was inversely correlated with symptom severity [30]. The proton pump inhibitor pantoprazole reduced duodenal eosinophils, mast cells, mucosal permeability, and symptoms in patients with functional dyspepsia [31]. These findings support the suggestion that luminal factors, such as acid and bile acids, cause low-grade inflammation that impairs mucosal integrity, resulting in abnormal gastrointestinal neuroregulation and symptoms [32].

- **The hypothalamic-pituitary-adrenal (HPA) axis and stress** – Patients with functional gastrointestinal disorders who experience mental stress can have increased activation of the amygdala and dysregulation of the HPA axis [33]. In healthy subjects, acute stress increases salivary cortisol levels and intestinal permeability [34]. In patients with functional dyspepsia, especially those with the epigastric pain subtype, magnetic resonance imaging of the brain revealed functional abnormalities in areas that process afferent signals [35].

- **Psychosocial dysfunction** – Functional dyspepsia has been associated with generalized anxiety disorder, somatization, and major depression [36-38]. There is also a higher prevalence of functional gastrointestinal disorders in patients with a self-reported history of childhood abuse [39-41]. In patients with the prototypical functional gastrointestinal disorder, IBS, a history of adverse early life events was related to HPA hyper-responsiveness to a visceral stressor [42]. A long-term follow-up study revealed initial trait anxiety was independently correlated with symptoms and quality of life; depression, anxiety, and comorbid functional somatic symptoms (IBS and chronic fatigue) were cross-sectionally associated with dyspepsia symptoms at follow-up [43]. The importance of psychosocial factors is further evident from an analysis of a large number of patients with functional dyspepsia that assessed gastrointestinal symptoms, psychological comorbidity, and extra-intestinal symptoms. The subjects clustered into four groups, two of which were characterized by high psychological burden [44].

CLINICAL MANIFESTATIONS

Patients with functional dyspepsia usually describe postprandial fullness, early satiety, bloating and/or epigastric pain/burning. Postprandial fullness is the most intense symptom in patients with meal-induced symptoms [45]. Symptoms may be severe enough to limit usual activities. Some patients may have nausea, vomiting, or heartburn, however, these symptoms are usually infrequent.

DIAGNOSIS

Overview of diagnostic approach — Functional dyspepsia is suspected in patients with a clinical history of postprandial fullness, early satiety, or epigastric pain/burning. A clinical diagnosis of functional dyspepsia requires the fulfillment of symptom-based diagnostic criteria and an evaluation to exclude other causes of dyspepsia. This evaluation consists of a history (eg, dietary, medical, surgical, family, and medications/supplements), physical examination, laboratory studies, and endoscopic evaluation to exclude organic/structural disease to explain the symptoms (algorithm 1). An approach to the evaluation of a patient with dyspepsia is discussed in detail separately. (See "Approach to the adult with dyspepsia", section on 'Initial evaluation' and "Approach to the adult with dyspepsia", section on 'Diagnostic strategies and initial management'.)

Diagnostic criteria — Symptom-based criteria have been proposed to standardize the diagnosis of functional dyspepsia.

- **Rome IV criteria for functional dyspepsia** – According to the Rome IV criteria, functional dyspepsia is defined as the presence of one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain or epigastric burning, and no evidence of structural disease (including at upper endoscopy) to explain the symptoms (table 1) [46].

  While patients with these symptoms and a negative diagnostic evaluation likely have functional dyspepsia, according to the Rome IV guidelines, the criteria should be fulfilled for the last three months with symptom onset at least six months before diagnosis. Criteria for symptom frequency and duration are particularly useful in defining patient eligibility for research, but clinician judgement may allow diagnosis in practice without rigid adherence to them.

- **Functional dyspepsia subtypes** – Two subtypes of functional dyspepsia are recognized based on the predominant symptoms. However, overlap between these subtypes is common [10,47].

- Postprandial distress syndrome is characterized by bothersome postprandial fullness and/or early satiation (table 1).
- Epigastric pain syndrome is characterized by bothersome epigastric pain or burning that is not exclusively postprandial (table 1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of functional dyspepsia includes other organic causes of dyspepsia (table 2). Although there are several organic causes for dyspepsia, the main causes are peptic ulcer disease, gastritis, gastroesophageal reflux, and medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]). An underlying gastric malignancy is a rare cause of dyspepsia in North America. Functional dyspepsia is differentiated from these by clinical assessment, laboratory testing, and upper endoscopy. (See "Approach to the adult with dyspepsia", section on 'Dyspepsia secondary to organic disease'.)

- **Gastroesophageal reflux disease** – The most common symptoms of gastroesophageal reflux disease are retrosternal burning pain and regurgitation. Dyspepsia symptoms can coexist with heartburn, but in patients with functional dyspepsia, epigastric pain, and fullness are the predominant symptoms [48].
- **Gastroparesis** – Gastroparesis is less prevalent than functional dyspepsia, but overlaps with it, as gastric emptying may be slow and symptoms of dyspepsia occur in both disorders [49,50]. Patients with functional dyspepsia may have nausea. However, in patients with gastroparesis, vomiting, rather than abdominal pain or epigastric fullness, is generally the predominant symptom.
- **Irritable bowel syndrome** – More than 60 percent of patients with functional dyspepsia may have overlapping IBS symptoms [8,46,51], and the overlap may be more likely when the symptoms of either disorder are severe [52]. Rather than epigastric pain associated with functional dyspepsia, IBS is characterized by abdominal pain or discomfort associated with a change in stool form or frequency. As compared with patients with IBS alone, patients with both IBS and functional dyspepsia had increased bloating and abdominal pain after a lactulose-nutrient challenge test [53].

MANAGEMENT

The management of patients with functional dyspepsia is controversial and alleviates symptoms in only a small proportion of patients (algorithm 1) [46,54].

Initial approach — Patients with functional dyspepsia should be tested and treated for *Helicobacter* pylori. We treat patients with functional dyspepsia who test negative for *H. pylori* and those with persistent symptoms four weeks after eradication of *H. pylori* with a proton pump inhibitor (PPI). A Cochrane systematic review revealed 14 patients needed to be treated to cure one case of dyspepsia [17]. (See 'Helicobacter pylori test and treat' below and 'Proton pump inhibitors' below and 'Subsequent approach' below.)

Helicobacter pylori test and treat — The diagnosis of *H. pylori* should be made with a test for active infection (stool antigen assay or urea breath test) if testing was not performed at the time of upper endoscopy performed for evaluation of dyspepsia (algorithm 1). Serologic testing should not be performed due to the low positive predictive value. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Approach to diagnostic testing' and "Approach to the adult with dyspepsia", section on 'Diagnostic strategies and initial management'.)

H. pylori eradication may improve dyspeptic symptoms by altering acid secretion or modification of intestinal microbiota [55,56]. It also has the benefit of preventing unrecognized peptic ulcers associated with *H. pylori*. (See "Treatment regimens for Helicobacter pylori in adults" and 'Epidemiology and pathophysiology' above.)

Proton pump inhibitors — PPIs appear to be moderately effective in the treatment of some patients with functional dyspepsia. In a systematic review of 18 randomized controlled trials, PPIs were more effective than placebo in relieving overall dyspepsia symptoms (RR 0.88, 95% CI 0.82-0.94) with a NNT of 11 [57]. Low- and standard-dose PPIs had similar effectiveness. Twice daily PPI use has not been shown to be better than once daily use. PPIs may exert their beneficial effect by reducing duodenal eosinophils, mast cells, and mucosal permeability [31]. In patients with functional dyspepsia who respond to PPI therapy, attempts should be made to discontinue PPIs every 6 to 12 months to minimize long-term risk of therapy.

H2-receptor antagonists — In a meta-analysis of 12 trials with a total of 2183 patients, H2RAs were associated with a 23 percent reduction in symptoms compared with placebo (relative risk reduction [RRR] 23 percent, 95% CI 8-35 percent) with an NNT of 7 [58]. In the systematic review of PPI therapy for functional dyspepsia, only two studies compared the efficacy of PPIs with H2AAs, and no difference was evident [57]. However, the quality of most trials included was poor, and there was significant heterogeneity among studies. Another limitation of these

studies is that patients with gastroesophageal reflux disease may have been misclassified as having functional dyspepsia.

Subsequent approach

Antidepressants — In patients with functional dyspepsia whose symptoms do not improve after eight weeks of PPI therapy, we initiate a therapeutic trial with a tricyclic antidepressant (TCA). For patients with a partial clinical response to a PPI, a TCA can be initiated as combination therapy. For patients who fail to improve on a PPI, the PPI should be stopped and a TCA initiated.

We begin with a TCA at a low dose (eg, amitriptyline 10 mg, nortriptyline 10 mg, or desipramine 25 mg at night). The dose may be increased at one- to two-week intervals. A dose of 20 to 30 mg is adequate in many patients, and we do not exceed a dose of 50 mg in most patients. Higher doses may not be more effective than lower doses and may be associated with daytime sedation and other anticholinergic side effects. We usually continue the TCA for 8 to 12 weeks before stopping, if it is ineffective. If the patient responds, we usually continue the drug for appropriately six months and then consider slowly tapering the medication off. The TCA can be resumed if dyspepsia recurs. While some clinicians prefer to use trazodone rather than amitriptyline or desipramine, there are few clinical data to support its use. Low dose TCAs may also improve associated symptoms of insomnia and fibromyalgia in patients with functional dyspepsia [59].

The TCA amitriptyline is beneficial for some patients. In a large trial, adequate relief was obtained by 53 percent of patients taking amitriptyline 50 mg once daily versus 40 percent of patients taking placebo [60]. A network meta-analysis revealed TCAs ranked second for efficacy (relative risk [RR] of remaining symptomatic 0.71, 95% CI 0.58-0.87) and first when only low risk of bias trials were included. Most of the trials that assessed TCAs studied patients who were refractory to other drugs analyzed in the network [61]. The drug did not delay gastric emptying and improved accommodation and postprandial bloating, but the exact mechanism of action remains unknown [62].

Mirtazapine has also demonstrated benefit in patients with functional dyspepsia and unintentional weight loss that may be due to a central mechanism of action [63-65]. We usually begin with a low dose (eg, mirtazapine 7.5 mg one hour before bedtime) and slowly increase the dose; most patients need 30 to 45 mg daily. In 34 patients with >10 percent weight loss randomized to mirtazapine 15 mg per day or placebo for eight weeks, mirtazapine reduced global symptoms of dyspepsia, early satiation, and gastrointestinal-specific anxiety. In addition, patients treated with mirtazapine reported improved nutrient tolerance and quality of life and

weight gain [63]. In another study in which 60 patients with functional dyspepsia and >5 percent weight loss randomized to mirtazapine 30 mg per day, paroxetine 20 mg per day or conventional (acid inhibitor or prokinetic) therapy for eight weeks, mirtazapine reduced dyspepsia and depression and resulted in weight gain compared with the other two groups [64]. Mirtazapine-associated drowsiness was common in both studies.

Prokinetic agents — We reserve the use of prokinetics (eg, metoclopramide 5 to 10 mg three times daily one-half an hour before meals and at night for four weeks), to patients in whom other therapies have failed and limit their duration to four weeks before discontinuing treatment [8]. If symptoms recur, we repeat a course of therapy, recognizing that up to 30 percent of patients may have side effects, most of which are generally mild and resolve with cessation of therapy [8].

In a systematic review and meta-analysis that included 29 trials of six different prokinetics (cisapride, acotiamide, itopride, tegaserod, mosapride, and ABT-229) in patients with functional dyspepsia, overall, global symptom improvement was greater with prokinetics as compared with placebo (40 versus 26 percent, respectively) [66]. However, the quality of evidence to support the use of these agents was low. The use of prokinetics was not associated with an improvement in quality of life. All agents were well tolerated over a short term except cisapride. As few studies have related efficacy of treatment to gastric emptying, it has no role in directing therapy. Notably, no eligible studies assessed metoclopramide or domperidone, the only agents available in North America, in functional dyspepsia. Methodologic difficulties, including the frequent overlap of functional dyspepsia with gastroesophageal reflux disease, lack of validated endpoints, and presence of delayed gastric emptying in only a minority of patients [13] complicate designing studies of prokinetics [67].

If postprandial nausea is a predominant symptom, trials of other antiemetic agents can be employed (eg, promethazine, prochlorperazine, meclizine), although data from clinical trials are lacking.

THERAPIES WITH LIMITED OR UNCLEAR ROLE

- **Psychotherapy** – We reserve psychotherapy for motivated patients who associate symptoms with stressors and in patients who fail initial empiric medical therapy. The psychological factors associated with functional dyspepsia suggest that psychological therapy could help some patients. A systematic review of four trials (relaxation therapy and hypnosis, psychodrama, psychotherapy, and cognitive-behavioral therapy) suggested therapy could be beneficial for one year, but methodological deficiencies led to

uncertainty about the results [68]. (See "Overview of psychotherapies", section on 'Cognitive and behavioral therapies'.)

- **Fundic relaxant drugs** – There is limited evidence that relaxing the gastric fundus may improve early satiation and postprandial fullness. In a small randomized trial, buspirone (10 mg, three times daily for four weeks) as compared with placebo increased gastric accommodation and reduced the overall severity of symptoms of dyspepsia, despite slowing gastric emptying of liquids [69]. In another study that included 32 patients with functional dyspepsia refractory to PPIs and/or domperidone, buspirone improved gastric emptying measured by ^{13}C-octanoic breath test and reduced early satiation [70].

- **Antinociceptive agents** – It is hypothesized that antinociceptive agents (eg, carbamazepine, tramadol, or pregabalin) may impact the central processing of pain, thereby decreasing visceral hypersensitivity that has been associated with functional dyspepsia. A post hoc analysis of data obtained from six randomized controlled trials in patients with generalized anxiety disorder and prominent gastrointestinal symptoms showed that pregabalin was significantly more effective than placebo in treating both anxiety and gastrointestinal symptoms [71]. In a placebo-controlled trial of pregabalin in patients with irritable bowel syndrome reduced pain, but adequate relief did not differ from the placebo group [72]. However, results of trials in functional dyspepsia are needed. We do not routinely use of tramadol for the treatment of functional gastrointestinal disorders due to the potential for addiction.

- **Complementary and alternative medicine** – Several complementary and alternative medicine approaches to functional dyspepsia have been described. However, further studies are needed before they can be recommended [73,74]. A systematic review of several low quality studies involving herbal and natural products, acupuncture, and homeopathy suggested a benefit from peppermint oil and STW5, a European multiherbal preparation that includes peppermint and caraway [75]. STW5 may improve symptoms of functional dyspepsia by stimulating gastric fundic relaxation and antral motility [76]. An eight-week placebo-controlled trial of STW5 found statistically significant but marginal symptomatic improvement [77]. A study in 95 patients with FD (Rome III criteria) found that a combination of L-menthol and caraway oil improved postprandial FD symptoms in some patients [78].

- **Dietary modification** – The postprandial timing of symptoms suggests improvement could be obtained through dietary modification. However, a population case-control study failed to find an association between various foods and functional gastrointestinal disorders [79]. The multifactorial nature of functional dyspepsia and difficulty of

conducting controlled dietary studies has markedly limited information useful to practice. Possibly, dieticians could help some patients through individualized approaches [80].

ADDITIONAL EVALUATION OF PERSISTENT SYMPTOMS

Patients with functional dyspepsia who have persistent symptoms of dyspepsia may require additional testing for an alternate diagnosis. We perform a gastric emptying study to evaluate for gastroparesis in selected patients with refractory functional dyspepsia who have persistent nausea and vomiting or risk factors for delayed gastric emptying (eg, diabetes mellitus). However, it is important that a significant overlap exists between dyspepsia and gastroparesis [49,50]; and treatment directed at accelerating delayed gastric emptying in these patients may not necessarily improve symptoms. (See "Gastroparesis: Etiology, clinical manifestations, and diagnosis", section on 'Evaluation' and "Treatment of gastroparesis".)

PROGNOSIS

Functional dyspepsia has a chronic disease course with symptoms that vary in severity over time [51]. Patients may be asymptomatic for periods of time and have periodic symptomatic relapses. In two population-based studies of the natural history of functional dyspepsia, over a follow-up of 10 to 12 years approximately 15 to 20 percent of individuals had persistent symptoms and 40 to 52 percent had symptom resolution [81]. In 30 to 35 percent of patients symptoms fluctuated over time and patients met criteria for another functional gastrointestinal disorder.

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Dyspepsia".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Stomach ache and stomach upset (The Basics)")
- Beyond the Basics topics (see "Patient education: Upset stomach (functional dyspepsia) in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The prevalence of functional dyspepsia is up to 20 percent worldwide. The pathophysiology of functional dyspepsia is not well understood. Several potential mechanisms have been suggested. (See 'Epidemiology and pathophysiology' above.)
- Patients with functional dyspepsia describe postprandial fullness, early satiety, and/or epigastric pain/ burning. Nausea, vomiting, or heartburn are less frequent. (See 'Epidemiology and pathophysiology' above and 'Clinical manifestations' above.)
- A clinical diagnosis of functional dyspepsia requires the fulfillment of symptom-based diagnostic criteria and an evaluation to exclude other causes of dyspepsia (algorithm 1 and table 1). This evaluation consists of a history, physical examination, laboratory studies, and endoscopic evaluation to exclude organic/structural disease underlying the symptoms. The evaluation of a patient with dyspepsia to establish the cause is discussed in detail, separately. (See "Approach to the adult with dyspepsia".)
- Non-invasive testing for active *Helicobacter pylori (H. pylori*) infection should be performed in patients with functional dyspepsia if gastric biopsies were not obtained for *H. pylori* on upper endoscopy (algorithm 1). We suggest treatment for *H. pylori* in patients with functional dyspepsia who test positive for an infection (**Grade 2A**). (See "Treatment regimens for Helicobacter pylori in adults".)
- We suggest a four- to eight-week trial of a once daily proton pump inhibitor (PPI) in patients with functional dyspepsia and no evidence of *H. pylori* and patients with persistent symptoms after eradication of *H. pylori* (**Grade 2A**). (See 'Proton pump inhibitors' above.)

- We suggest a tricyclic antidepressant drug for patients with persistent symptoms after an eight-week trial of a PPI (**Grade 2C**). We start with a low dose (eg, amitriptyline 10 mg at bedtime, nortriptyline 10 mg at bedtime, or desipramine 25 mg at bedtime) and gradually increase the dose as tolerated. (See 'Antidepressants' above.)

- We suggest the use of prokinetics in patients in whom eradication of *H. pylori* and a trial of proton pump inhibitor and tricyclic antidepressant has failed (**Grade 2C**). In such patients, we generally limit a trial of metoclopramide to 5 to 10 mg three times daily one-half an hour before meals and at night for about four weeks. The risk of side effects, including tardive dyskinesia, increase with the cumulative dose and duration of treatment. We refer motivated patients who fail medical therapy and patients who associate symptoms with stressors for psychotherapy. (See 'Prokinetic agents' above.)

- Functional dyspepsia has a chronic disease course with symptoms that vary in severity over time. Patients may be asymptomatic for periods of time followed by symptomatic relapses. (See 'Prognosis' above.)

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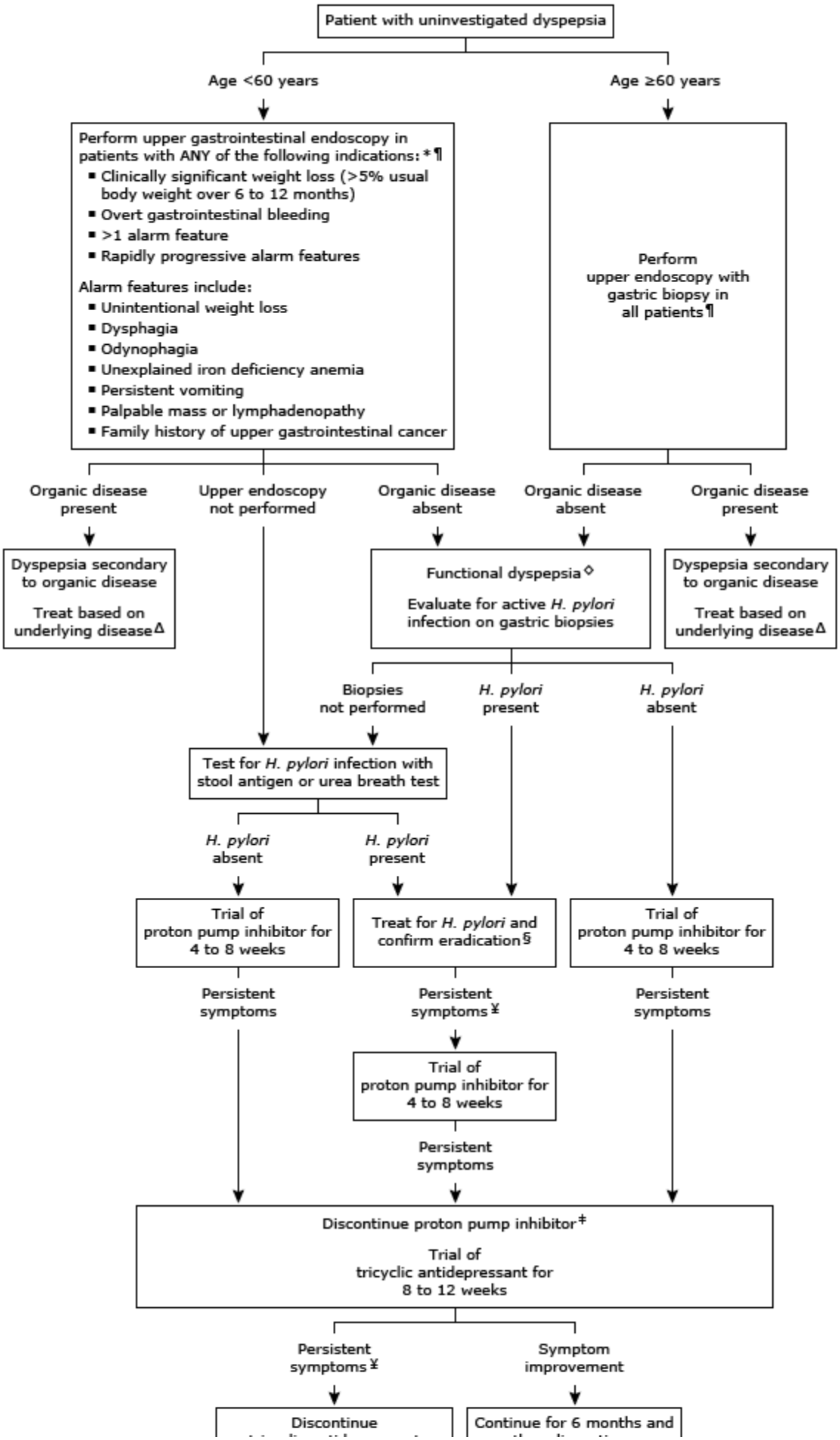
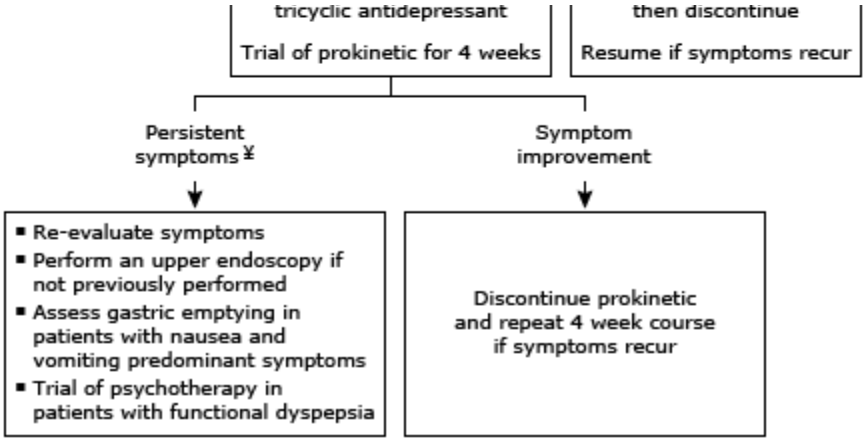
Topic 19 Version 41.0

GRAPHICS

Approach to the evaluation and management of dyspepsia in adults


Patient with uninvestigated dyspepsia
Age <60 years
Age ≥60 years
Perform upper gastrointestinal endoscopy in patients with ANY of the following indications: *¶
Clinically significant weight loss (>5% usual body weight over 6 to 12 months)
Overt gastrointestinal bleeding
>1 alarm feature
Rapidly progressive alarm features
Alarm features include:
Unintentional weight loss
Dysphagia
Odynophagia
Unexplained iron deficiency anemia
Persistent vomiting
Palpable mass or lymphadenopathy
Family history of upper gastrointestinal cancer
Perform upper endoscopy with gastric biopsy in all patients ¶
Organic disease present
Upper endoscopy not performed
Organic disease absent
Organic disease absent
Organic disease present
Dyspepsia secondary to organic disease
Treat based on underlying disease Δ
Functional dyspepsia ◊
Evaluate for active H. pylori infection on gastric biopsies
Dyspepsia secondary to organic disease
Treat based on underlying disease Δ
Biopsies not performed
H. pylori present
H. pylori absent
Test for H. pylori infection with stool antigen or urea breath test
H. pylori absent
H. pylori present
Trial of proton pump inhibitor for 4 to 8 weeks
Treat for H. pylori and confirm eradication §
Trial of proton pump inhibitor for 4 to 8 weeks
Persistent symptoms
Persistent symptoms ¥
Persistent symptoms
Trial of proton pump inhibitor for 4 to 8 weeks
Persistent symptoms
Discontinue proton pump inhibitor ‡
Trial of tricyclic antidepressant for 8 to 12 weeks
Persistent symptoms ¥
Symptom improvement
Discontinue
Continue for 6 months and



H. pylori: *Helicobacter pylori*.

* Gastric mucosal biopsies should be obtained at the time of upper gastrointestinal endoscopy to rule out infection with *H. pylori*.

¶ Additional evaluation may be required based on symptoms (eg, abdominal imaging in patients with concurrent jaundice or pain suggestive of a biliary/pancreatic source).

Δ Refer to UpToDate topic reviews.

◇ Patients with continued symptoms of dyspepsia for 3 months with symptom onset at least 6 months before diagnosis and no evidence of structural disease to explain the symptoms should be diagnosed and treated as functional dyspepsia.

§ Eradication of *H. pylori* infection can be confirmed with a urea breath test, stool antigen testing, or upper endoscopy-based testing performed 4 weeks after completion of antibiotic therapy. The choice of test depends on the need for an upper endoscopy (eg, follow-up of bleeding peptic ulcer) and local availability. *H. pylori* serology should not be used to confirm eradication of *H. pylori*. Refer to UpToDate topic on diagnostic tests for *H. pylori*.

¥ Allow 8 to 12 weeks before reassessing symptomatic response.

‡ For patients with a partial clinical response to a proton pump inhibitor, a tricyclic antidepressant can be initiated as combination therapy with a proton pump inhibitor.

Graphic 115195 Version 3.0

Rome IV Criteria for Functional Dyspepsia

B1. Functional dyspepsia*
Diagnostic criteria¶
1. One or more of the following:
a. Bothersome postprandial fullness
b. Bothersome early satiation
c. Bothersome epigastric pain
d. Bothersome epigastric burning
AND
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms
B1a. Postprandial distress syndrome
Diagnostic criteria¶
Must include one or both of the following at least three days per week:
1. Bothersome postprandial fullness (ie, severe enough to impact on usual activities)
2. Bothersome early satiation (ie, severe enough to prevent finishing a regular-size meal)
No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)
Supportive remarks
▪ Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
▪ Vomiting warrants consideration of another disorder
▪ Heartburn is not a dyspeptic symptom but may often coexist
▪ Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
Other individual digestive symptoms or groups of symptoms, eg, from gastroesophageal reflux disease and the irritable bowel syndrome may coexist with PDS
B1b. Epigastric pain syndrome
Diagnostic criteria¶
Must include at least one of the following symptoms at least one day a week:

1. Bothersome epigastric pain (ie, severe enough to impact on usual activities)
AND/OR
2. Bothersome epigastric burning (ie, severe enough to impact on usual activities)
No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)
Supportive remarks
1. Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting
2. Postprandial epigastric bloating, belching, and nausea can also be present
3. Persistent vomiting likely suggests another disorder
4. Heartburn is not a dyspeptic symptom but may often coexist
5. The pain does not fulfill biliary pain criteria
6. Symptoms that are relieved by evacuation of feces or gas generally should not be considered as part of dyspepsia
Other digestive symptoms (such as from gastroesophageal reflux disease and the irritable bowel syndrome) may coexist with EPS

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

* Must fulfill criteria for PDS and/or EPS.

¶ Criteria fulfilled for the last three months with symptom onset at least six months before diagnosis.

Original table modified for this publication. Stanghellini V, Chan FKL, Hasler WL, et al. Gastroduodenal disorder. Gastroenterology 2016; 150:1380. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 108003 Version 1.0

Differential diagnosis of dyspepsia

Diagnosis
Functional dyspepsia
Dyspepsia caused by structural or biochemical disease
Peptic ulcer disease
Helicobacter pylori gastritis
Gastroesophageal reflux disease (GERD)
Biliary pain
Chronic abdominal wall pain
Gastric or esophageal cancer
Gastroparesis
Pancreatitis
Carbohydrate malabsorption
Medications (including potassium supplements, digitalis, iron, theophylline, oral antibiotics [especially ampicillin and erythromycin], nonsteroidal antiinflammatory drugs [NSAIDs], glucocorticoids, niacin, gemfibrozil, narcotics, colchicine, quinidine, estrogens, levodopa)
Infiltrative diseases of the stomach (eg, Crohn disease, sarcoidosis)
Metabolic disturbances (hypercalcemia, hyperkalemia)
Hepatocellular carcinoma
Ischemic bowel disease, celiac artery compression syndrome, superior mesenteric artery syndrome
Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease)
Intestinal parasites (*Giardia*, *Strongyloides*)
Abdominal cancer, especially pancreatic cancer

Adapted from:

1. *Talley NJ, Silverstein MD, Agreus L, et al. American Gastroenterological Association (AGA) technical review: evaluation of dyspepsia. Gastroenterology 1998; 114:582.*
2. *Fisher RS, Parkman HP. Management of nonulcer dyspepsia. N Engl J Med 1998; 339:1376.*

Graphic 90590 Version 11.0

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Conflict of interest policy

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