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# Motility and Functional Disorders of the Stomach: Diagnosis and Management of Functional Dyspepsia and Gastroparesis

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**Functional dyspepsia and gastroparesis are the most common functional and motility disorders of the stomach. Functional dyspepsia is a heterogeneous syndrome with multiple pathophysiologies that refers to symptoms originating in the gastroduodenal region in the absence of an organic cause. Patients with functional dyspepsia may present with primarily postprandial symptoms including fullness, early satiety, and bloating, while other patients may present with the predominant symptom of epigastric pain. Gastroparesis is a symptomatic chronic disorder characterized by delayed gastric emptying without mechanical obstruction. Although gastroparesis is often caused by diabetes and prior gastric surgery, the underlying cause may not be found in many patients. Clinical manifestation of gastroparesis is variable. Patients present with debilitating nausea and vomiting resulting in weight loss and dehydration. Other patients may present with postprandial symptoms of postprandial fullness, early satiety, and effortless regurgitation. In this review, an update on the underlying mechanisms, clinical features, diagnostic evaluation, and treatment for functional dyspepsia and gastroparesis is provided.**

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## INTRODUCTION

Functional dyspepsia and gastroparesis are the most common functional and motility disorders of the stomach. Functional dyspepsia refers to symptoms originating in the gastroduodenal region. Patients with functional dyspepsia may present with primarily postprandial symptoms consisting of fullness, early satiety, and bloating, while others present with the predominant symptom of epigastric pain. Gastroparesis is a symptomatic chronic disorder characterized by delayed gastric emptying without a mechanical obstruction. Some patients present with debilitating nausea and vomiting resulting in weight loss and dehydration. These patients may have frequent hospitalizations. Other patients with gastroparesis may present postprandial symptoms such as early satiety, postprandial fullness and effortless regurgitation.

There are many similarities and differences between functional dyspepsia and gastroparesis. Functional dyspepsia is a functional disorder with sensory and motility abnormalities, where gastroparesis is primarily a motility disorder. In a subset of patients, there is an overlap in symptoms and delayed gastric emptying. As a consequence, some patients with mild abdominal pain, nausea, postprandial distress, and evidence of delayed emptying are considered to have functional dyspepsia by some clinicians and gastroparesis by others. Both disorders are discussed in this manuscript.

Patients with functional dyspepsia and gastroparesis may have dysfunction of both the proximal and distal regions of the stomach. Impaired gastric accommodation in the proximal stomach may lead to rapid gastric emptying of liquids and dumping symptoms. This may coexist with motor abnormalities of the distal stomach resulting in delayed emptying of solids. The pathophysiologies of functional dyspepsia and gastroparesis are multifactorial. This may explain why there is a poor correlation between delayed gastric emptying and symptoms.

In this review, we will provide an update on the underlying mechanisms, clinical features, diagnostic evaluation, and treatment for functional dyspepsia and gastroparesis.

**Table 1.**
**Alarm features of uninvestigated dyspepsia warranting an upper endoscopy**

- New onset of dyspepsia at age >55 years
- Unexplained weight loss >10%
- Progressive dysphagia
- Gastrointestinal bleeding
- Iron deficiency anemia
- Persistent vomiting
- Previous esophagogastric cancer
- Previous documented peptic ulcer
- Family history of gastrointestinal cancer
- Lymphadenopathy or abdominal mass on exam

## FUNCTIONAL DYSPEPSIA

Symptoms of dyspepsia are very common, occurring in 26% to 34% of the general population in the United States (1,2). It is important to make the distinction between "uninvestigated" and "investigated" dyspepsia. Uninvestigated dyspepsia describes individuals in the community presenting with dyspeptic symptoms before diagnostic testing. Patients with alarm features should undergo upper endoscopy to look for an ulcer or gastric cancer (Table 1) (3). In patients with uninvestigated dyspepsia without alarm features, two strategies are recommended: 1) test and treat for *Helicobacter pylori* using a validated non-invasive test; or 2) an empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4 to 8 weeks (3). The test-and-treat option is preferable in the patient populations with 10% prevalence for *H. pylori,* and empiric trial of PPI is preferable in lower prevalence situations (3). Investigated functional dyspepsia is defined as symptoms originating in the gastroduodenal region, in the absence of organic, systemic, or metabolic disease that would explain the symptoms (4). Usual investigations include a history and physical examination to understand the symptoms and inquire on alarm symptoms, blood tests, and an upper endoscopy. Some patients complain of postprandial symptoms with fullness, early satiety, and bloating, while others have primarily epigastric pain. The precise cause of functional dyspepsia is unclear; it is believed to be a heterogeneous syndrome with multiple underlying mechanisms.

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## Underlying Mechanisms

Over the years, multiple motor and sensory disturbances have been identified in patients with functional dyspepsia. Four different abnormalities have been postulated to explain the symptoms of functional dyspepsia: impaired fundic accommodation; visceral hypersensitivity; delayed gastric emptying; and *Helicobacter pylori* infection.

Gastric accommodation is a reflex adaptation of the proximal stomach to relax to accommodate the food. This normal reflex is mediated by the vago-vagal pathway and can be induced by many factors, such as eating, antral distension, or duodenal exposure to nutrients. Gastric accommodation can be studied with either a gastric barostat or with specialized scintigraphic procedures to measure gastric volume. The fasting compliance of the fundus is normal in functional dyspepsia, but gastric accommodation after meals is impaired in about one-third of the patients (5). The feedback mechanism of the duodenum is also abnormal. When the duodenum is exposed to acid and lipids, the impairment of gastric accommodation and gastric hypersensitivity may be exaggerated in some patients with functional dyspepsia (6,7)

Visceral hypersensitivity is a heightened conscious perception of visceral stimuli independent of the intensity. It has an important role in many GI disorders, including functional dyspepsia, non-erosive reflux disease, non-cardiac chest pain, and irritable bowel syndrome (IBS). Approximately 30% of patients with functional dyspepsia have gastric hypersensitivity to distension in the fundus (5) and antrum (8,9) most likely due to alteration in the tension mechanoreceptors in the gastric wall. Antral hypersensitivity can be exacerbated by impaired gastric accommodation that can lead to rapid fundic emptying with resultant antral distension.

Delayed gastric emptying is present in 23% to 32% of patients with functional dyspepsia (5,10). However, it is controversial whether delayed gastric emptying is the underlying cause of dyspeptic symptoms. A few studies found that delayed gastric emptying was associated with postprandial fullness and vomiting of functional dyspepsia (11,12), but other studies found no correlation (13–15). Some patients may have rapid emptying of liquids as well as delayed emptying of solids; this may explain in part why there is a lack of correlation between gastric emptying and dyspepsia.

Although the test-and-treat strategy for *H. pylori* is recommended in patients with uninvestigated dyspepsia (3), there is a poor correlation between *H. pylori* and functional dyspepsia. Some studies reported that *H. pylori* infection was associated with epigastric pain (12), but others found no symptom association (5). It is not known how *H. pylori* can cause symptoms in the absence of a peptic ulcer and gastritis. The presence of *H. pylori* does not appear to correlate with the gastric motor or sensory disturbance associated with functional dyspepsia.

## Clinical Features

The average age of the patients with functional dyspepsia is 40-years-old, and approximately two-thirds are females (5,11). Epigastric pain is usually related to meals and can be episodic or persistent. Many patients present with predominant symptoms of postprandial fullness, bloating, early satiety, or epigastric burning. A diagnosis of functional dyspepsia is accurate over time, as only 2% to 8% of patients have a peptic ulcer if endoscopy is repeated later if symptoms exacerbate (16,17). Somatization, depression, and anxiety appear to correlate with symptom severity (20). Stress and abnormal illness behavior may characterize some patients, but studies have not found any significant correlation between psychological factors and health care seeking behavior (21). Severe abdominal pain is probably more important in seeking help than psychological factors (22). Patients have no significant morbidity in long term follow-up (18). However, less than 20% of patients become asymptomatic (19).

A past classification of functional dyspepsia (Rome I) was to divide patients into ulcer-like, dysmotility-like, reflux-like, and non-specific functional dyspepsia. However, subsequent studies found that this classification had little clinical utility because predominant symptoms overlapped and were unstable over time (16,23). Recent studies used factor analysis to identify three to four distinct subgroups of dyspepsia in the general population (24,25) and in patients from tertiary centers (26–28). Based on this data, the

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**Table 2.**
**Rome III diagnostic criteria for postprandial distress and epigastric pain syndromes of functional dyspepsia**

| | *Required Criteria* | *Supportive Criteria* |
|---|---|---|
| Postprandial Distress Syndrome* | One or both of the following:<br>1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week<br>2. Early satiation that prevents finishing a regular meal, at least several times per week | 1. Upper abdominal bloating or postprandial nausea or excessive belching can be present<br>2. Epigastric pain syndrome may coexist |
| Epigastric Pain Syndrome* | All of the following:<br>1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week<br>2. The pain is intermittent<br>3. Not generalized or localized to other abdominal or chest regions<br>4. Not relieved by defecation or passage of flatus<br>5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders | 1. The pain may be of a burning quality but without a retrosternal component<br>2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting<br>3. Postprandial distress syndrome may coexist |

*Fulfilled for last 3 months with symptom onset at least 6 months before diagnosis.
From Tack, et al. *Gastroenterology*, 2006;130:1466 (4).

Rome III Committee of Functional GI Disorders recommends two separate entities to describe functional dyspepsia: postprandial distress syndrome and epigastric pain syndrome (Table 2) (4). Patients may have both components but one should predominate. Future studies are pending to determine if this new classification can identify unique pathophysiology, predict clinical outcome, and direct effective therapy.

## Diagnostic Evaluation

A diagnosis of functional dyspepsia implies that an organic, systemic, or metabolic cause has been excluded. Baseline tests include a complete blood count, a complete metabolic panel, and if indicated amylase and lipase. Ideally, upper endoscopy should be performed to exclude ulcer disease or other mucosal and structural abnormalities. It may be best to perform this during a symptomatic period off acid suppression (4). Further tests should be based on the clinical scenario, severity of symptoms, and treatment response. Additional evaluation, such as an abdominal CT scan, may be needed in patients with alarm features, especially with significant weight loss or clinical concern for cancer. Patients with prominent heartburn should be considered to have gastroesophageal reflux disease (GERD), rather than functional dyspepsia. In patients with prominent retching and vomiting, testing for gastroparesis and mechanical obstruction is appropriate.

Solid phase gastric scintigraphy is widely available to detect delayed gastric emptying, but it is not currently recommended as a routine test for functional dyspepsia (4). As stated earlier, the role of delayed gastric emptying causing dyspepsia is controversial. However, gastric scintigraphy is reasonable in the patient with refractory postprandial distress syndrome. A barium upper GI series and small bowel follow-through is useful if mechanical obstruction is suspected. Abdominal ultrasound is not recommended as

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a routine test without clinical and biochemical evidence for biliary or pancreatic disease. Physiologic testing such as gastric barostat, electrogastrography, water or nutrient load tolerance test are not advocated at this time for routine clinical practice (4).

## Treatment

Patient education and reassurance are essential in functional dyspepsia because of the benign but persistent nature of the disorder. Fatty foods should be avoided. Lipids impair gastric emptying, and lipids in the duodenum may exacerbate impaired gastric accommodation and gastric hypersensitivity. Medications that may cause dyspepsia should be discontinued.

Pharmacologic therapy is the next step for most patients. Efficacy of pharmacologic therapy has been difficult to prove, in part due to the placebo response rate of about 35% in clinical trials (29). Acid suppression is a safe and reasonable first line of therapy. In a meta-analysis of 22 randomized controlled trials (RCT's) with histamine-$_2$ receptor antagonists ($H_2$RA), only five studies have sufficient data to address the resolution of epigastric pain (30). Patients treated with an $H_2$RA are 1.8 times more likely to have a complete relief of epigastric pain. However, the sample sizes were small, and the study quality was suboptimal. Multiple randomized controlled trials (RCTs) of proton pump inhibitors (PPIs) for functional dyspepsia have been performed. In a study of 1,248 subjects, complete symptom relief was achieved in 38% and 36% on omeprazole 20 mg and 10 mg once daily, respectively, compared to 28% on placebo (31). The difference was significant, but the clinical benefit was marginal. Other trials reported a small benefit of a PPI over placebo (32,33), but others reported no benefit (34,35). Patients with coexisting heartburn responded better with a PPI (32,33,36). Patients with predominant postprandial fullness, early satiety, or bloating were unlikely to respond (31,32). Economic analysis suggested that a PPI may be cost-effective despite a small benefit in functional dyspepsia, provided that generic prices of PPI's are used (36).

Very few prokinetic medications are available in the United States. They include anti-dopaminergic agents (metoclopramide), motilin agonist (erythromycin), serotonin agonist (tegaserod), and cholinergic agonists (bethanecol and neostigmine). A meta-analysis of 14 RCT's for functional dyspepsia reported that prokinetics have efficacy over placebo (37). However, the various studies were difficult to interpret as a group, and publication bias was a concern. The role of serotonin (5-HT) in the stomach is complex, with accommodation in the proximal stomach and contraction in the distal stomach. Tegaserod, a $5HT_4$ agonist for chronic constipation and for constipation-predominant IBS, had a small benefit in a RCT in patients with functional dyspepsia and normal gastric emptying (38). Alosetron, a 5-$HT_3$ antagonist for diarrhea-predominant IBS, also showed potential benefit in relieving dyspepsia (39). The use of 5HT agents is reasonable, especially if the patient has coexisting IBS. Various pharmacologic agents have been proposed to improve the impairment of gastric accommodation, but clinical efficacy is unproven. They include sildenafil (phosphodiesterase-5 inhibitor to enhance nitric oxide-induced smooth muscle relaxation), buspirone (5-$HT_{1A}$ agonist), and sumatriptan (5-$HT_{1P}$ agonist).

Diagnosing and treating for *H. pylori* in patients with functional dyspepsia is controversial. A few RCT's supported the benefit of *H. pylori* eradication (40,41), but many other studies did not (42–50). More importantly, *H. pylori* eradication success did not correlate with treatment success (48,50). A meta-analysis reported a marginal 9% relative benefit with *H. pylori* eradication for functional dyspepsia (51).

Studies on tricyclic antidepressants and serotonin reuptake inhibitors for functional dyspepsia are limited in number. Meta-analysis on the few available RCT's on tricyclic antidepressants reported some efficacy for functional dyspepsia, but the quality of the studies was suboptimal (52). It is reasonable to try these agents in the refractory patient, and many patients may already have depression and anxiety disorders. The benefit of interpersonal psychotherapy and hypnosis for intractable functional dyspepsia has been reported (53,54). However, the efficacy of psychological intervention is unclear because the sample sizes of the existing trials were too small (55).

Patients often try complimentary alternative medicine for functional dyspepsia. Herbal extracts, such as peppermint oil, caraway oil, artichoke leaf abstract,

capsaicin from red chili powder, and celandine, have shown some efficacy in RCT's. The most studied was STW 5 (Iberogast®), a combination product of nine different herbal extracts from bitter candy tuft (*Iberis amara*), peppermint leaves, caraway fruit, angelica root, milk thistle fruit, greater celandine, liquorice root, camomile flowers, and lemon balm leaves (56). Animal studies reported that STW5 has some region-specific effect on gastric motility (57). Meta-analysis of the six RCT's, all from Germany, supported the efficacy and safety of STW5 in functional dyspepsia (56). However, publication bias should be a concern.

## GASTROPARESIS

Gastroparesis is a symptomatic chronic syndrome characterized by delayed gastric emptying without a mechanical obstruction (58). It is the most common true motility disorder of the stomach. The precise prevalence of gastroparesis is unknown. It is frequently overlooked in clinical practice because the symptoms are nonspecific; the diagnosis needs to be entertained in order to obtain the appropriate testing for this disorder. Gastroparesis is often caused by systemic diseases, such as diabetes mellitus, affecting the GI neuromuscular system. However, no underlying etiology can be found in about 40% of patients (59,60), a condition called idiopathic gastroparesis.

### Underlying Mechanisms

Gastroparesis implies a motor disorder resulting in delayed gastric emptying, but many different mechanisms have been identified. In the proximal stomach, impaired gastric accommodation may lead to early filling of the antrum and rapid emptying of liquids, a feature identified in patients with diabetic gastroparesis. The mid-stomach grinds and churns the food to expose them to gastric acid. Hypomotility of the gastric body results in bezoars of undigestible solids. Coordination between antral contraction and pyloric relaxation is essential to grind the foods before presenting to the duodenum. Antral hypomotility and pylorospasms have been described in patients with diabetic and idiopathic gastroparesis. The gastric pacemaker consists of interstitial cells of Cajal to produce the normal 3 cycles-per-minute electrical rhythmic. Bradygastria and tachygastria are found in patients with diabetic and idiopathic gastroparesis.

The potential causes of gastroparesis are numerous (Table 3). Any disease state that affects the GI smooth muscle, vagus nerve, autonomic nervous system, and the enteric nervous system can cause gastroparesis. The most common established causes for gastroparesis are diabetes and postsurgical condition. The pathology of diabetic gastroparesis consists of demyelination of the vagus nerve, loss of parasympathetic and sympathetic fibers, and degeneration of the interstitial cells of Cajal. Postsurgical gastroparesis can result from surgery with or without a vagotomy. Fundoplication can impair vagus nerve function (61). Vagal nerve dysfunction can be investigated by showing a lack of rise of pancreatic polypeptide levels during and after sham feeding. However, in patients with gastroparesis, no underlying etiology can be found in about 40% of patients (59,60), a condition called idiopathic gastroparesis. Viral infection has been suspected in some patients with idiopathic gastroparesis, but the association has been based on history of acute viral-like illness, not by identifying the virus (62).

Central and peripheral autonomic disorders can involve the vagus nerve resulting in gastroparesis. Scleroderma and polymyositis can cause motility problems in different regions of the GI tract, including gastroparesis, secondary achalasia, and chronic intestinal pseudo-obstruction. Paraneoplastic syndrome is caused by cancer cells that express antigens mimicking the neuronal tissues, resulting in an inflammatory neuropathy of the enteric nervous system. Small cell lung cancer is the most common cause of paraneoplastic syndromes, followed by breast, ovarian, Hodgkin's lymphoma, and multiple myeloma (63).

### Clinical Features

Clinical manifestation of gastroparesis is variable. Symptoms may be chronic or episodic. Some patients present with vomiting-predominant symptoms of nausea, retching, and vomiting, resulting in dehydration, weight loss, and hospitalization. Others may present with regurgitation-predominant symptoms similar to GERD, but effortless regurgitation of undigested foods

**Table 3.**
**Potential causes of gastroparesis**

**Endocrine diseases**
- Diabetes
- Hypothyroidism
- Renal failure

**Post-surgical**
- Procedures with vagotomy
  - Partial or complete gastrectomy
  - Esophagectomy
- Procedures without vagotomy
  - Fundoplication
  - Bariatric surgery
  - Heart-lung transplant

**Neuromuscular diseases**
- Multiple sclerosis
- Chronic idiopathic demyelinating polyneuropathy
- Myotonic dystrophy

**Connective tissue diseases**
- Scleroderma
- Mixed connective tissue disorder
- Polymyositis
- Dermatomyositis

**Autonomic diseases**
- Central
  - Parkinson
  - Multiple system atrophy
  - Lewy body disease
  - Brainstem diseases
- Peripheral
  - Idiopathic dysautonomia
  - Amyloidosis
  - Vitamin $B_{12}$ deficiency
  - Mitochondrial disorder
  - Porphyria

**Paraneoplastic syndrome**
- Small cell lung cancer
- Multiple myeloma
- Breast cancer
- Lymphomas

**Medications**
Opiates
Anticholinergics
Tricyclic antidepressants
Calcium channel blockers
Parkinson medications (L-dopa)

**Infection**
- Virus
  - Epstein-Barr
  - Cytomegalovirus
  - Herpes simplex
  - Norwalk virus
  - Rotavirus
- Parasites
  - Trypanosoma cruzi (Chagas disease)

should suggest gastroparesis. Postprandial symptoms may be prominent, with or without vomiting. Epigastric pain is commonly reported by patients, but it should not be the predominant symptom in gastroparesis. A diagnosis of epigastric pain syndrome of functional dyspepsia may be more appropriate in these patients.

In general, the symptoms suggesting gastroparesis include nausea, vomiting, early satiety, and postprandial fullness. Gastroparesis is diagnosed when symptoms are associated with objective measurement of delayed gastric emptying. The symptoms of gastroparesis may be quantitated by a symptom questionnaire, the Gastroparesis Cardinal Symptom Index (GCSI), developed and validated in university-based clinical practices for quantifying symptoms in gastroparesis. The GCSI consists of nine symptoms that are graded by the patient from none to severe (Table 4). The GCSI can be divided into three subscales (postprandial fullness/early satiety, nausea/vomiting, and bloating) and represents a subset of the longer Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM).

The clinical outcome of gastroparesis depends on the underlying cause and clinical manifestation. Delayed gastric emptying can be found in 40% to 65% of unselected individuals with diabetes (64,65), but many of them have minimal or no GI symptoms. In the symptomatic patients with diabetic gastroparesis, mortality is not increased (66,67), but morbidity is significant in the vomiting patients with dehydration, hospitalizations, and weight loss. A vicious cycle may occur when gastroparesis leads to poorly controlled diabetes, and subsequent hyperglycemia exacerbates delayed gastric emptying. Some diabetic patients may have poor glucose control after meals with minimal or no GI symptoms. In patients with an identifiable cause for gastroparesis, such as diabetes, vagotomy, and sclero-

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**Table 4.**
**The Gastroparesis Cardinal Symptom Index**

1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)
2. Retching (heaving as if to vomit, but nothing comes up)
3. Vomiting
4. Stomach fullness
5. Not able to finish a normal-sized meal
6. Feeling excessively full after meals
7. Loss of appetite
8. Bloating (feeling like you need to loosen your clothes)
9. Stomach or belly visibly larger

Each symptom is graded by the patient on a 0 to 5 scale: 0=none; 1= very mild, 2=mild, 3=moderate, 4=severe, 5=very severe.
From Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack *J. Aliment Pharm Ther,* 2003;18:141.

derma, symptoms are likely to be chronic and persistent. In post-viral gastroparesis, symptoms may improve over time (62). The clinical outcome of idiopathic gastroparesis is unpredictable, probably due to the heterogeneous pathophysiology and clinical manifestation of this patient population.

## Diagnostic Evaluation

The recommended evaluation of patients suspected with gastroparesis is provided in Table 5 (58). The extent of tests should be based on symptom severity and response to treatment. For example, the workup can be minimal in the patient with type-1 diabetes or history of vagotomy. More extensive evaluation is often needed for idiopathic gastroparesis associated with severe vomiting. A detailed history, review of systems, and physical exam are essential to look for the potential causes of gastroparesis (Table 3). Paraneoplastic syndrome should be considered in the older patients presenting with gastroparesis and in patients at risk for lung and breast cancers. Mechanical obstruction and other causes of nausea and vomiting should be identified. Upper endoscopy is often performed, and the presence of undigestible solids in the stomach despite an overnight fast supports the diagnosis for gastroparesis. However, repeating endoscopies in patients with established gastroparesis should be avoided.

**Table 5.**
**Recommended evaluation of patients suspected to have gastroparesis**

1. Initial investigation
   - A. History and physical examination
   - B. Blood tests
     - – Complete blood count
     - – Complete metabolic profile, including glucose, potassium, creatinine, total protein, albumin, calcium
     - – Amylase, if abdominal pain is significant symptom
     - – Pregnancy test, if appropriate
   - C. Abdominal obstruction series, if vomiting or pain is acute or severe
2. Evaluate for organic disorders
   - A. Upper endoscopy to evaluate for mechanical obstruction or mucosal lesions
     Alternative: upper GI series or small bowel follow-through
   - B. Biliary ultrasonography if abdominal pain is a significant symptom
3. Evaluate for delayed gastric emptying
   - A. Solid-phase gastric emptying test
   - B. Screen for secondary causes of gastroparesis
     - – Thyroid function tests (thyroid-stimulating hormone)
     - – Rheumatologic serologies (antinuclear antibody, scleroderma antibody [Scl70])
     - – Glycosylated hemoglobin ($HbA_{1C}$)
4. Treatment trial with prokinetic agent and/or antiemetic agent
5. If no clinical response, consider further investigation
   - A. Electrogastrography
   - B. Antroduodenal manometry
   - C. Small bowel evaluation with enteroclysis or small bowel follow-through
   - D. Further laboratory tests, if indicated
     - – ANNA, tissue transglutaminase antibody

Modified from Parkman, et al. *Gastroenterology*, 2004;127:1592 (58).

The presence of delayed gastric emptying should be confirmed. Solid phase gastric scintigraphy is widely available. An international scintigraphy standard has been established with a $^{99m}$Tc-sulfur colloid-labeled egg sandwich meal (68). Spot images are

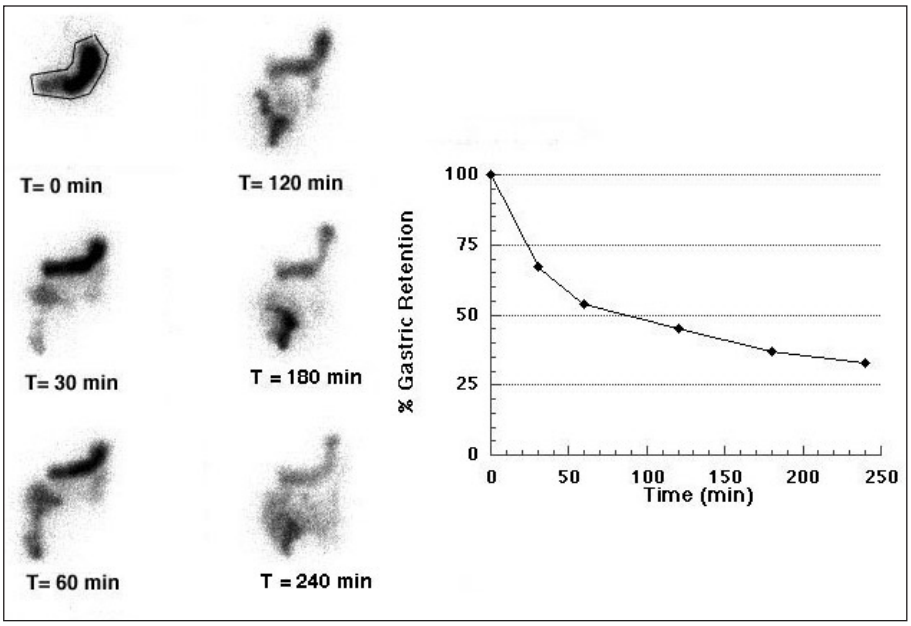


**Figure 1.** Gastric emptying scintigraphy test demonstrating gastroparesis. Scintigraphic images are obtained at 0, 30, 60,120,180, 240 minutes after meal ingestion of scrambled egg sandwich labeled with $^{99m}$Tc sulfur colloid and water. A region of interest is drawn around the entire stomach for all images acquired (shown here for the anterior image at T = 0). The geometric mean of gastric counts is determined for each imaging time. After correction for radionuclide decay, mean gastric counts at each imaging time are expressed as a percent of the maximal geometric mean counts at time zero. The percent gastric retention for solids was 45% at 2 hours after meal ingestion which is at the upper limit of normal but 31% at 4 hours after meal ingestion which is moderately elevated.

obtained immediately after eating, and at 1, 2 and 4 hours after the test meal (Figure 1). The upper limits of normal (95th percentile) for gastric retention are 60% and 10% at 2 and 4 hours, respectively. This 4-hour method is more sensitive and specific than the T-50% emptying time extrapolated from images every 10 to 15 minutes for less than 2 hours. If a patient has a normal T-50% emptying time and there is a high suspicion for gastroparesis, scintigraphy should be repeated using the 4-hour method (69). However, severity of delayed gastric emptying does not correlate with symptom severity or clinical manifestation.

Office-based gastric emptying tests are being developed. Breath test can be performed using non-radioactive isotope, such as $^{13}$C-octanoate, $^{13}$C-acetate, or $^{13}$C-Spirulina platensis algae, bound to a solid test meal. During the gastric emptying of solids, the isotope is absorbed in the duodenum and metabolized to $^{13}CO_2$, which is measured sequentially from expelled breath samples. The sensitive and specificity of the breath test for gastroparesis is 67%–100% and 73%–80%, respectively (70–72), using scintigraphy as a standard. However, the accuracy of breath test in patients with lung disease and small bowel malabsorption are unknown. The SmartPill wireless capsule has been developed to measure the pH and pressure of the GI lumen. A rapid change from an acidic to alkaline pH represents the transit of the capsule from the stomach to the duodenum, which defines the capsule gastric residence time. This gastric residence time is a measurement of the late phase of gastric emptying of undigestible solids, and it has a good correlation with T-90% emptying time by scintigraphy (73). Using 240 minutes as a cut-off, the sensitivity and specificity of the gastric residence time for gastroparesis is 85% and 72%, respectively. Furthermore, this wireless capsule can also measure the whole gut transit time simultaneously.

Further evaluation is often needed in patients with refractory symptoms, especially in idiopathic gastroparesis. Tests should determine the underlying cause and the extent of GI neuromuscular disturbance. Electrogastrography is complementary to gastric scintigraphy in patients with unexplained nausea and vomiting, but the clinical role of EGG remains unclear (74). Antroduodenal manometry may detect pylorospasm or small bowel motility disturbances. Other tests, such as anti-neuronal nuclear antibody for paraneoplastic syndrome, tissue transglutaminase antibody for celiac spruce, enteroclysis for small bowel diseases, autonomic testing for autonomic neuropathy, or surgical full-thickness biopsy for enteric neuromuscular diseases, may be needed depending on the clinical situation.

## Treatment

Dietary and lifestyle modification for gastroparesis includes eating smaller and more frequent meals, relying on liquid nutrient, and limiting fatty foods. Undigestible fibers and foods such as salads, raw vegetable, and red meat should be avoided.

Medical treatment for gastroparesis involves the use of prokinetic agents to speed up the emptying of the stomach and the use of antiemetic agents to reduce nausea and vomiting.

Antiemetic medications are frequently used to reduce nausea and vomiting associated with gastroparesis. However, there is very limited literature on the use of antiemetic agents in gastroparesis. Antiemetic medications reduce vomiting by action on a diverse range of receptor subtypes in the peripheral and central nervous systems. When considering antiemetic drug use in gastroparesis, the clinician should take into account factors such as side effects, interactions with other medications, and cost. The most commonly prescribed traditional antiemetic drugs include promethazine and prochlorperazine. Serotonin 5-$HT_3$ receptor antagonists, such as ondansetron, are tried and have efficacy in chemotherapy-induced emesis, post-operative emesis, and radiation therapy-induced vomiting. The 5-$HT_3$ antagonists are expensive for routine administration and there is little published data on their efficacy in gastroparesis.

Prokinetic medications in the United States are very limited in number. Metoclopramide is a central and peripheral dopamine receptor antagonist with antiemetic and prokinetic benefits. It is available in oral, liquid, and intravenous formulations. Chronic use of metoclopramide, however, is limited by its common central nervous system (CNS) adverse effects. If used chronically, patients should be informed of possible adverse effects; this discussion should be documented in the patient record. Domperidone is a peripheral dopamine receptor antagonist, and it does not readily cross the blood brain barrier. Domperidone can be used at a higher dosage than metoclopramide with much less CNS adverse effects. Domperidone is effective for diabetic gastroparesis in RCT's (75). However, it is not available in the United States, but it can be obtained with an Investigational New Drug Application through the FDA (76). Cardiac electrophysiologic adverse effect of domperidone has been described in animals, but the safety in humans is supported by clinical trials (75).

Erythromycin is a motilin agonist, and it induces the migratory motor complex-like contraction in the antrum that propels undigestible solids out of the stomach. Erythromycin is given orally in a liquid solution or intravenously at small doses, such as 100 to 125 mg t.i.d. When tolerance develops and symptoms recur, erythromycin should be discontinued and restarted at a later date. Erythromycin is a potent prokinetic, but data on clinical efficacy are limited by lack of RCT's. A review of patient's concurrent medications is essential when prescribing erythromycin. In a study from a state Medicaid database, the adjusted rate of cardiac sudden death in patients who were using erythromycin was twice as high as those who were not (77). This cardiac risk may be increased further if the patient is taking medications that inhibit CYP3A liver enzyme, such as ketoconazole, fluconazole, diltiazem, verapamil, cimetidine, or clarithromycin.

Endoscopic injection of botulinum toxin into the pylorus is based on the hypothesis that lowering the pyloric resistance should improve gastric emptying and symptoms of gastroparesis. Classically, botulinum toxin inhibits release of acetylcholine from cholinergic nerves whereas at higher doses it may also inhibit the pyloric smooth muscle. The response rate of botulinum toxin treatment was only 43% in a retrospective review of 63 patients with gastroparesis, and it lasted about 5 months (78). Botulinum toxin injection appears to be safe, but enthusiasm should be guarded until randomized controlled trials are reported. Multiple botulinum toxin injections should be avoided because it may delay definitive treatment for gastroparesis.

Gastric electrical stimulation is an emerging therapy for severe gastroparesis. A subcutaneous electrical generator is surgically implanted with two electrical leads in the wall of the antrum. The proposed mechanism of the current high-frequency, low-energy electrical stimulation is to stimulate the afferent vagal pathways to the CNS and subsequent stimulation of the vagal efferent pathway. In the only published controlled trial, 33 patients with severe gastroparesis were randomized in a double-blind crossover phase with

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stimulator on or off for 1-month, followed by an unblinded phase with stimulator on for 12 months (79). Vomiting frequency was significantly reduced during the stimulator on versus off in the randomized period and during the unblinded phase. Symptom severity and quality of life also improved. Some patients may require higher stimulation energy if symptoms persist (80). Interestingly, symptom improvement does not parallel improvement in gastric emptying, implying that the gastric electric stimulator's mechanism to improve symptoms may not be from improving gastric emptying. Patient selection is important. Indication of gastric electrical stimulation is refractory nausea and vomiting from severe gastroparesis. Patients with type 1 diabetic gastroparesis are likely to respond (81,82). Idiopathic gastroparesis, frequent use of opiates, and prominent abdominal pain appear to be predictors of poor response. Gastric stimulation should be avoided in the patients with postprandial distress without vomiting or nausea. Patients with refractory idiopathic gastroparesis should be evaluated carefully to detect any underlying cause and the extent of motility disturbance, before undergoing gastric electrical stimulation.

In patients with multiple episodes of dehydration and marked weight loss, jejunal feeding with an isoosmolar, low-fat formula may be needed. A trial of nasoduodenal or nasojejunal feeding for 48 to 72 hours should be undertaken to test the small bowel function before surgically placing a permanent jejunostomy tube. Percutaneous endoscopic gastrostomy should be avoided; it may exacerbate gastroparesis or cause significant scaring to make future placement of electrical stimulator more difficult.

## CONCLUSIONS

Functional dyspepsia is a heterogeneous syndrome with multiple mechanisms, such as impaired gastric accommodation, gastric hypersensitivity, and delayed gastric emptying. Long term prognosis of functional dyspepsia is good, but symptoms remain chronic in the majority of patients. Reassuring and educating the patient are important for patient management. Excessive diagnostic testing should be avoided. Treatment with gastric acid suppressants, such as a proton pump inhibitors, is a reasonable approach. Prokinetic agents, *Helicobacter pylori* eradication, and psychological intervention may be considered in the patient with refractory symptoms.

Gastroparesis is often caused by systemic disease such as diabetes affecting the GI neuromuscular system or prior gastric surgery with vagotomy. However, the underlying cause cannot be found in about 40% of patients, a condition called idiopathic gastroparesis. Clinical manifestations are variable. Gastric emptying scintigraphy is used to diagnose gastroparesis and the 4-hour method is preferred. New office-based tests for measuring gastric emptying are becoming available. Further evaluation and aggressive treatment may be needed in the patients with severe nausea and vomiting. Dietary modification and prokinetic medications can be effective. Studies continue on the efficacy of gastric electrical stimulation in patients with refractory vomiting from severe gastroparesis. ■

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