



Gastroduodenal Disorders

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Symptoms that can be attributed to the gastroduodenal region represent one of the main subgroups among functional gastrointestinal disorders. A slightly modified classification into the following 4 categories is proposed: (1) functional dyspepsia, characterized by 1 or more of the following: postprandial fullness, early satiation, epigastric pain, and epigastric burning, which are unexplained after a routine clinical evaluation; and includes 2 subcategories: postprandial distress syndrome that is characterized by meal-induced dyspeptic symptoms and epigastric pain syndrome that does not occur exclusively postprandially; the 2 subgroups can overlap; (2) belching disorders, defined as audible escapes of air from the esophagus or the stomach, are classified into 2 subcategories, depending on the origin of the refluxed gas as detected by intraluminal impedance measurement belching: gastric and supragastric belch; (3) nausea and vomiting disorders, which include 3 subcategories: chronic nausea and vomiting syndrome; cyclic vomiting syndrome; and cannabinoid hyperemesis syndrome; and (4) rumination syndrome.

Keywords: Dyspepsia; Nausea; Vomiting; Belching; Rumination.

At least 20% of the population has chronic symptoms that can be attributed to disorders of gastroduodenal function, and the majority of these people have no evidence of organic causes.¹ Functional gastroduodenal disorders are classified into 4 categories: functional dyspepsia (FD) (comprising postprandial distress syndrome [PDS] and epigastric pain syndrome [EPS]), belching disorders (comprising excessive gastric and supragastric belching), chronic nausea and vomiting disorders (comprising chronic nausea vomiting syndrome [CNVS], cyclic vomiting syndrome [CVS], and cannabinoid hyperemesis syndrome [CHS]), and rumination syndrome.

B1: Functional Dyspepsia

Definition

FD is a medical condition that significantly impacts on the usual activities of a patient and is characterized by one or more of the following symptoms: postprandial fullness,

early satiation, epigastric pain, and epigastric burning that are unexplained after a routine clinical evaluation.¹

Symptom definitions remain somewhat vague, and potentially difficult to interpret by patients, practicing physicians and investigators alike, as documented by the major misunderstandings that characterize many of the therapeutic trials on FD that claim to have been carried out according to the Rome criteria, although better inclusion criteria were obtained when the Rome III definition was adopted.² In order to overcome at least some of these problems, the committee proposed more detailed descriptive definitions of symptoms that should be enriched by pictograms.³

The broad term *functional dyspepsia* comprises patients from the diagnostic categories of PDS, which is characterized by meal-induced dyspeptic symptoms; EPS, which refers to epigastric pain or epigastric burning that does not occur exclusively postprandially, can occur during fasting, and can be even improved by meal ingestion, and overlapping PDS and EPS, which is characterized by meal-induced dyspeptic symptoms and epigastric pain or burning.

Uninvestigated vs Investigated Dyspepsia

From an etiological viewpoint, patients with dyspeptic symptoms can be subdivided into 2 main categories as follows:

1. Those with an organic, systemic, or metabolic cause for the symptoms that can be identified by traditional diagnostic procedures where, if the disease improves or is eliminated, symptoms also improve or resolve (eg, peptic ulcer disease, malignancy, pancreaticobiliary disease, endocrine disorders, or medication use) and is described by the term *secondary dyspepsia*. *Helicobacter pylori*–associated

Abbreviations used in this paper: CHS, cannabinoid hyperemesis syndrome; CNVS, chronic nausea and vomiting syndrome; CVS, cyclic vomiting syndrome; EPS, epigastric pain syndrome; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; LES, lower esophageal sphincter; PDS, postprandial distress syndrome; UES, upper esophageal sphincter.

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dyspepsia is diagnosed in a subset of dyspepsia patients whose symptoms are treated by *H pylori* eradication.

2. Those in whom no identifiable explanation for the symptoms can be identified by traditional diagnostic procedures that are exemplified under the “umbrella” term *functional dyspepsia*.

Epidemiology

Large-scale studies reported a 10%–30% prevalence of FD worldwide.⁴ The reported prevalence of dyspepsia varies considerably in different populations, due to different interpretation and expression of symptoms, diagnostic criteria adopted, environmental factors, and local prevalence of organic diseases, such as peptic ulcer and gastric cancer. Patients with dyspepsia have reduced quality of life and emotional distress because of their symptoms, with heavy economic burdens through direct medical expenses and loss of productivity. Different studies have identified different risk factors for dyspepsia, including female sex, increasing age, high socioeconomic status, decreased degree of urbanization, *H pylori* infection, nonsteroidal anti-inflammatory drug use, low educational level, renting accommodation, absence of central heating, sharing a bed with siblings, and being married. Interestingly, smoking is only marginally associated with dyspepsia, and alcohol and coffee are not.^{4,5}

Gastroduodenal Disorders

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

^aMust fulfill criteria for B1a. PDS and/or B1b. EPS.

^bCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

B1a. Postprandial Distress Syndrome

Diagnostic criteria

Must include one or both of the following at least 3 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)

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

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^a

Must include at least 1 of the following symptoms at least 1 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).

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

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

Justification for Changes to the Criteria

Only minor changes have been introduced after the Rome III criteria,¹ with the purpose of improving the specificity of definitions. FD remains the accepted umbrella term and refers to a patient who fulfills diagnostic criteria for PDS and/or EPS.

This division was originally based on factor analyses of dyspepsia in the general population and FD as defined by Rome II criteria, which identified separate factors of meal-related symptoms and epigastric pain⁶ and has been later supported by endoscopy-driven epidemiological studies.⁷ Importantly, several therapeutic trials on the effects of *H pylori* eradication, antisecretory, and prokinetic agents provide a clinically relevant support to the existence of PDS and EPS as substantially different subsets of dyspepsia, as detailed in the section on therapy.

Pathophysiological studies investigating the effect of meal ingestion on symptom generation have demonstrated that, in dyspeptic patients, not only postprandial fullness and satiety, but also epigastric pain/burning and nausea may increase after meal ingestion (Figure 1).⁸ Thus, the definition of PDS was slightly modified by acknowledging that, beyond postprandial fullness and early satiety that occur postprandially by definition, other digestive symptoms including epigastric pain and epigastric burning, can be perceived by the patient as

being induced or worsened by a meal. Epigastric bloating, belching, and nausea can be present in both PDS and EPS and should be considered as possible adjunctive features of the 2 subgroups. Vomiting, on the other hand, is unusual and should prompt the search for other diagnoses.

Although relief of fullness or pain by the passage of stool or gas likely indicates a lower gut symptom origin, there is insufficient evidence to include this requirement in the criteria. The Committee has confirmed that heartburn is excluded from the definition of dyspepsia, even though it can often occur simultaneously with gastroduodenal symptoms, perhaps because of overlapping pathophysiology.⁹ Typical biliary pain is quite distinctive, being severe or very severe, episodic, and unpredictable, and can clinically be distinguished from EPS by appropriate history taking and physical examination.

Other minor changes were introduced to more precisely define the minimal thresholds for frequency and severity of each individual symptom, primarily for scientific purposes, but data still need to be collected to define thresholds based on the frequency and/or severity of symptoms that impair quality of life. Severity should be at least sufficient to identify symptoms as “bothersome,” which should be clinically defined as “severe enough to impact on usual activities.” For research purposes “bothersome” can be semi-quantitatively defined as ≥ 2 in a 5-point adjectival scale linked to the effect exerted by symptoms on usual activities (ie, severe enough to at least distracting from usual activities).¹⁰ Frequency of symptoms was not detailed in the Rome III Criteria. It is proposed to introduce a minimal frequency to distinguish those with disease based on symptom thresholds obtained from normal subjects for the Rome IV consensus. Thus, cutoffs for frequencies of symptoms and syndromes were based on data indicating no more than 5% of the normal population would experience each symptom this frequently.¹¹

Pathophysiology

The pathophysiology of FD is likely complex and multifactorial (Figure 2), and not completely elucidated.

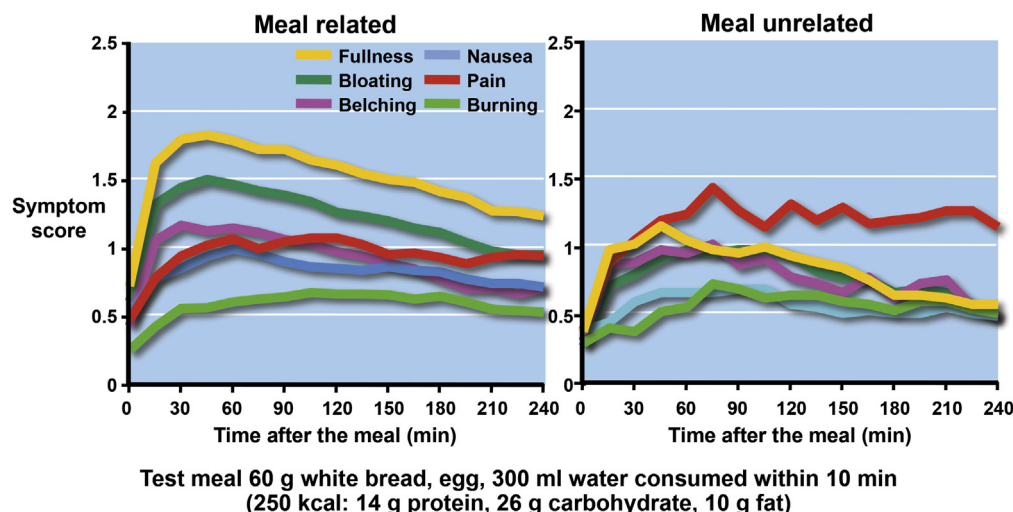


Figure 1. Postprandial symptom severity in 218 patients with functional dyspepsia. Symptoms were defined as meal-related if their severity increased within 30 minutes after meal ingestion.

Gastroduodenal motor and sensory dysfunction, as well as impaired mucosal integrity, low-grade immune activation, and dysregulation of the gut–brain axis have all been implicated.¹²

Gastric emptying. Gastric emptying is delayed in a sizable fraction (estimates vary from about 25% to 35%) of unselected FD patients, while rapid gastric emptying is uncommon probably occurring in under 5% of cases.¹³ Correlation between gastric emptying and dyspeptic symptoms remains unsettled. Severely delayed gastric emptying in patients diagnosed as gastroparesis is associated with more vomiting and loss of appetite, but can be asymptomatic.¹³

Impaired gastric accommodation. Gastric accommodation is controlled by a vago-vagal reflex triggered by meal ingestion and mediated by the activation of nitrergic nerves in the gastric wall. Abnormal distribution of food in the stomach, with antral pooling of chyme and decreased proximal reservoir content, has long been known to occur.¹⁴ A reduced gastric relaxatory response to ingestion of a meal has been seen in about one-third of FD patients observed, and it appears to be more likely in post-infection dyspepsia.¹⁵ The potential relation between impaired gastric accommodation and dyspeptic symptoms also remains unclear.

Gastric and duodenal hypersensitivity to distention, acid, and other intraluminal stimuli. Hypersensitivity to mechanical stimulation of the stomach and upper small bowel is frequent in FD patients, but underlying mechanisms of the putative relationship between fasting gastric hypersensitivity and dyspeptic symptoms remain unsettled. FD patients may show hypersensitivity to chemical stimuli, such as intraluminal acid and lipids,¹⁶ but evidence provided so far is not conclusive. Independent of acid-related effects, proton pump inhibitors may reduce duodenal eosinophils and H₂ blockers may work via antihistamine effects (via mast cell recruitment in a subset of patients with functional dyspepsia).¹⁷

***Helicobacter pylori* infection.** *H. pylori* infection is considered a possible cause of FD symptoms if successful eradication leads to sustained resolution of all cardinal symptoms, as reviewed recently.¹⁸ Both acid secretion and hormonal status can be affected to some extent with *H. pylori* eradication therapy, and restoration of these changes may explain, in part, the beneficial effect of eradication on dyspeptic symptoms, although this hypothesis needs to be confirmed. In fact, antibiotic therapies can affect dyspeptic symptoms by mechanisms other than *H. pylori* eradication, including prevention of unrecognized peptic ulcers or modification of intestinal microbiota.

Duodenal low-grade inflammation, mucosal permeability, and food antigens. The mucosal barrier serves as the first line of defense against pathogens and noxious substances in the lumen.¹² Duodenal eosinophilia has been reported in FD patients and is apparently related to early satiety.¹⁹ Infections, stress, duodenal acid exposure, smoking, and food allergy have all been implicated in the pathogenesis of duodenal mucosal inflammatory and permeability changes.

Environmental exposures. Acute infection can trigger upper gastrointestinal symptoms in 10%–20% of infected individuals,^{12,20} although post-infectious dyspepsia can be short-lived compared with post-infection IBS.²¹ Features of the infective agents and genetic predisposition of infected individuals likely modulate the probability of developing post-infectious digestive syndromes.

Psychosocial factors. The association between dyspepsia and psychiatric disorders, especially anxiety, depression, and neuroticism is commonly recognized.²² A meta-analysis confirmed an association between anxiety, depression, and FD.²³ Also, physical and emotional abuse in adulthood and difficulty in coping with life events might be involved. Whether FD is more prevalent in patients presenting with psychiatric disorders or is characterized by a higher prevalence of anxiety and depression than organic dyspepsia is unclear. A bidirectional relationship probably

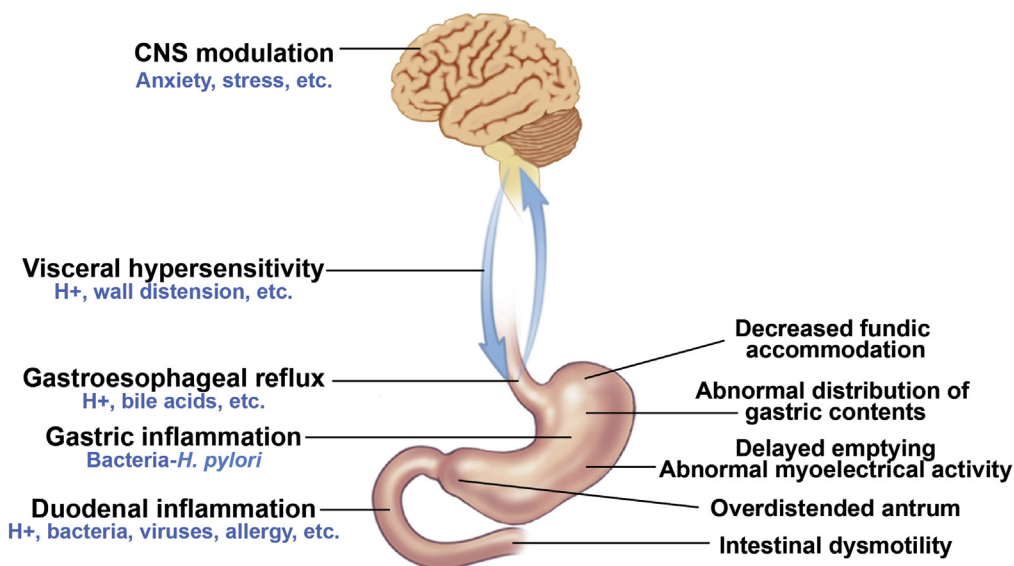


Figure 2. Putative pathophysiological mechanisms of functional dyspepsia. CNS, central nervous system.

exists between gut and psyche because patients with functional gastrointestinal disorders are more prone to develop psychological problems, and vice versa.²⁴ Neuroimaging studies suggest that symptom perception can be influenced by cognition and emotion.

Clinical Evaluation

Management strategy of un-investigated dyspepsia should be based on history taking, including alarm features and iatrogenic causes, treatment of overlapping gastroesophageal reflux disease (GERD), *H pylori* “test and treat,” especially in high-prevalence regions, while prompt endoscopy should be performed in all patients with alarm features (Figure 3). If FD is diagnosed, patients should be divided into PDS and/or EPS and treated accordingly (Figure 4).

Treatment

Treatment of dyspepsia has been reviewed recently.²⁵ Reassurance, education, lifestyle, and dietary recommendations (more frequent, smaller meals and avoiding meals with high fat content) are frequently recommended to FD patients, but they have not been studied systematically. Avoidance of nonsteroidal anti-inflammatory drugs, coffee, alcohol, and smoking is commonly recommended and seems sensible, although not of established value.

There is evidence of a small but statistically significant benefit in eradicating *H pylori* in patients with chronic dyspepsia, with a number needed to treat of 14. Dyspeptic symptom can be attributed to *H pylori* gastritis, termed by *H pylori*–associated dyspepsia, if successful eradication is followed by long-term sustained (6 months or longer) remission.^{26,27} Economic analyses suggest that *H pylori* eradication is the most cost-effective approach for infected dyspeptic patients compared with alternative medical therapies that need to be taken long term. It is unclear

whether *H pylori* eradication therapy has a different efficacy in different FD subgroups.

Proton pump inhibitors and H2RAs are regarded as effective treatment for FD, based on several controlled trials with a therapeutic gain over placebo of 10%–15%, although the effect of overlapping or misdiagnosed GERD cannot be ruled out. Proton pump inhibitors are ineffective in relieving PDS symptoms.

Prokinetic drugs exert a significant benefit for prokinetics over placebo, with a relative risk reduction of 33% and number needed to treat of 6, but these results were mainly driven by studies using cisapride and domperidone, and concerns were raised about publication bias. Pure prokinetic treatments without central antiemetic effects (eg, erythromycin, azithromycin, ABT 229) unphysiologically accelerate gastric emptying by inducing a fasting type of gastroduodenal motility in the postprandial period and may be less effective than therapies with combined prokinetic and antiemetic action. Itopride is a novel prokinetic agent that works by antagonizing dopamine D2-receptors and inhibiting acetylcholinesterase, and has been shown to improve postprandial fullness and early satiety with a low rate of adverse reactions.

Botulinum toxin pyloric injections are not superior to placebo on gastroparesis and dyspeptic symptoms. In uncontrolled series, gastric electrical stimulation reduces vomiting without influencing gastric emptying.

Acotiamide (Z-338) is a novel compound with fundus-relaxing and gastroprokinetic properties, based on a pro-cholinergic effect that improves dyspeptic symptoms over placebo, with a number needed to treat of 6. Notably, the drug benefited PDS but not EPS. Other potentially effective fundic relaxants include 5-HT_{1A} receptor agonists tandospirone and buspirone, 5HT_{1B/D} receptor agonist sumatriptan and the herbal product STW-5 and rikkunshito.

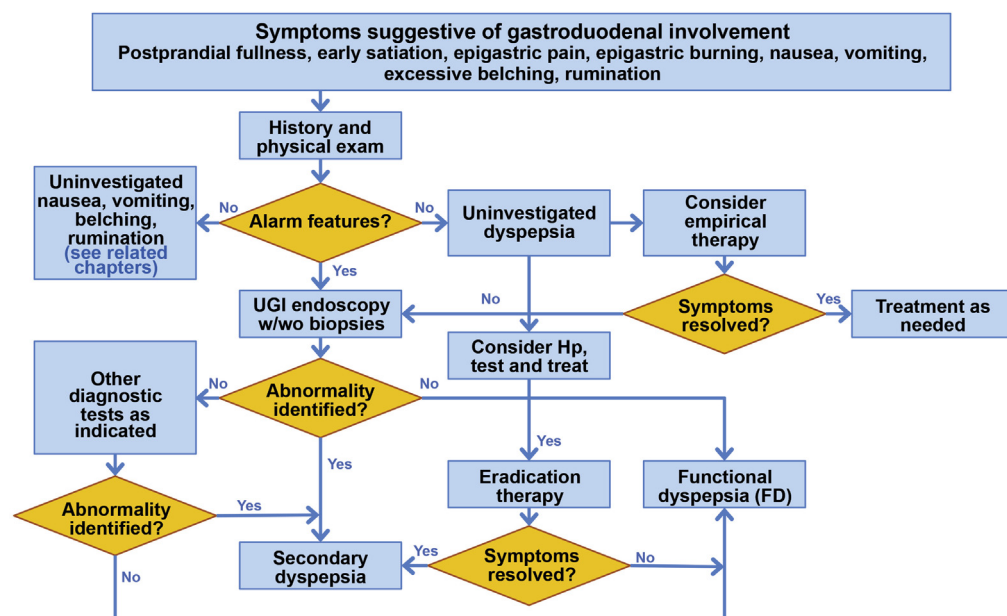


Figure 3. Clinical management of patients complaining of symptoms that can be attributed to disorders of gastroduodenal functions (see text for details).

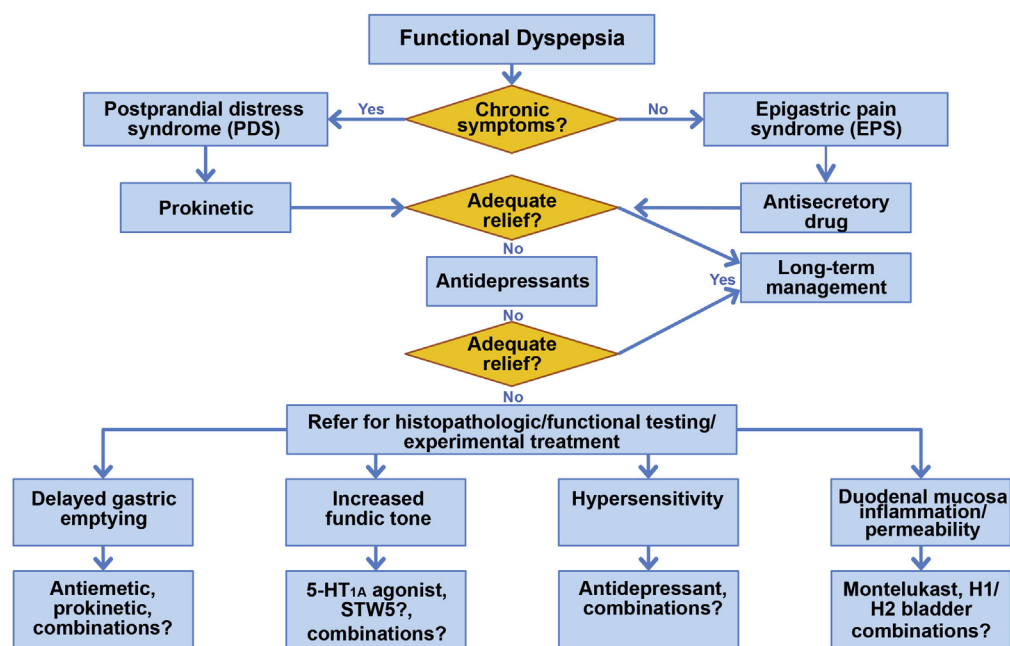


Figure 4. Clinical management of patients affected by functional dyspepsia (see text for details).

Psychotropic drugs, especially antidepressants, are often used as second-line drugs in functional gastrointestinal disorders. A systematic review²⁴ suggested that psychotropic drug therapy in FD is associated with a significant symptom improvement over placebo, but most trials were small and of poor quality; often used levosulpiride, which also bears prokinetic properties; and often recruited in psychiatric rather than gastroenterological settings. A multicenter placebo-controlled trial recently carried out in North America comparing selective serotonin reuptake inhibitors and tricyclics showed no effect and poor tolerance of the former, while low-dose amitriptyline showed some advantages over placebo, although confined to epigastric pain with no signal in PDS cases or in those with delayed gastric emptying.²⁸

Psychological therapies are advocated as rescue therapy for FD symptoms that are severe and not responding to

pharmacotherapy. Available controlled trials suggested clinical benefit, but lacked convincing evidence because of small sample sizes and poorly matched treatment groups.

The concept that a subset of FD cases is mediated by intestinal inflammation via eosinophils with or without mast cells is intriguing, and both the anti-asthma drug montelukast, a cystLT receptor antagonist that stabilizes eosinophils, and histamine H₁ antagonist represent promising approaches but require rigorous testing. The use of herbal medicines in FD also still needs scientific support.

B2: Belching Disorders

Definition

Belching is defined as an audible escape of air from the esophagus or the stomach into the pharynx. It occurs commonly and can only be considered a disorder when it is excessive and becomes troublesome. Depending on the origin of the refluxed gas, belching is classified into 2 types: the gastric belch and the supragastric belch.

Epidemiology

The epidemiology of excessive belching in the general population remains to be carefully defined; however, it is not encountered uncommonly in the clinical setting.

Diagnostic Criteria

The previous Rome III consensus focused on aerophagia as a mechanism of belching disorders, based on the observation of the occurrence of excessive air swallowing.¹ Studies using intraluminal impedance measurement of air transport in the esophagus have demonstrated that different mechanisms of excessive belching occur.²⁹

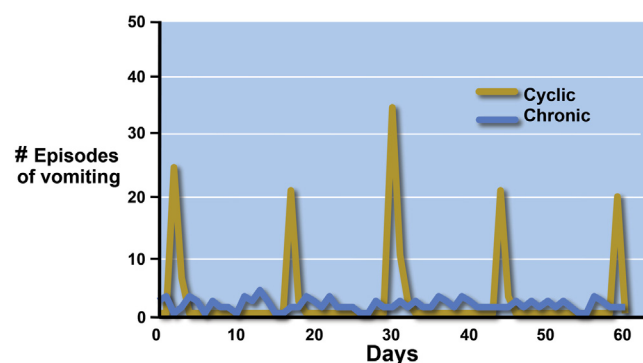


Figure 5. Frequency of vomiting episodes over time in cyclic and chronic vomiting syndromes, the former being characterized by stereotypical, brief (less than 1 week) episodes of intense vomiting with acute onset that are separated by periods of at least 1 week in the absence of vomiting.

Belching activity follows a distinct pattern, characterized by rapid antegrade and retrograde flow of air in the esophagus that usually does not reach the stomach. This phenomenon of “supragastric belching” is not accompanied by the transient relaxation of the lower esophageal sphincter (LES), as is observed in gastric belching.²⁸ Supragastric belching is defined as a behavior in which the eructated air does not originate from the stomach, but is sucked or injected into the esophagus from the pharynx and expelled immediately after, through the oral route, in the absence of excessive air swallowing. Belching is a frequent manifestation of GERD due to both gastric and supragastric belching.

B2. Diagnostic Criteria^a for Belching Disorders

Must include all of the following:

Bothersome (ie, severe enough to impact on usual activities) belching from the esophagus or stomach more than 3 days a week

B2a: Excessive supragastric belching (from esophagus)

B2b: Excessive gastric belching (from stomach).

Supportive remarks

- Supragastric belching is supported by observing frequent, repetitive belching
- Gastric belching has no established clinical correlate
- Objective intraluminal impedance measurement can be used to distinguish supragastric from gastric belching.

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Justification for Change in Criteria

The current Rome IV committee clearly distinguished such excessive supragastric belching from gastric belching, but both remained within the category of gastroduodenal disorders because of the common presenting symptom. Because not all cases with belching arise from swallowing air, aerophagia is a confusing term when applied to excessive belching, and is now considered historical. Most importantly, supragastric belching can be objectively distinguished from gastric belching by high-resolution manometry and impedance.³⁰

Pathophysiology

Physiological features. Air swallowing is normal. Through esophageal peristalsis and LES relaxation, this air is transported to the stomach along with the rest of the bolus. The ingested air accumulates in the proximal stomach. A physiologic venting system is present to protect the stomach against extreme dilatation: LES relaxes in response to distension of the stomach due to the gas, and this is followed by relaxation of the upper esophageal sphincter

(UES). In the majority of patients, supragastric belches are initiated by the creation of subatmospheric pressure in the thoracic cavity by movement of the diaphragm in the aboral direction, similar to deep inspiration, whereas gastric belches occur while the LES is relaxed and intrathoracic pressure is slightly elevated. UES relaxation occurs in both supragastric and gastric belches; during supragastric belches, UES relaxation precedes the onset of the antegrade airflow, and during gastric belches, UES relaxation occurs after the onset of the retrograde esophageal airflow.³⁰

Psychological features. Supragastric belching stops during speaking, distraction, and sleeping. It significantly impairs health-related quality of life and is associated with stressful events and a high prevalence of anxiety disorders. Excessive belching can also occur in patients with obsessive compulsive disorder, bulimia nervosa, and encephalitis.^{31,32}

Clinical Evaluation

Diagnosis is based on a careful history evaluation. Observation of air swallowing provides supportive information. Patients who complain of isolated excessive belching are more likely to suffer from excessive uncontrolled supragastric belching, and from episodes of frequent belching in which they may belch up to 20 times per minute. If symptoms are troublesome and the technology is available, esophageal impedance/manometry will provide useful information to guide therapy.

Treatment

Supragastric belching. There is little evidence on the treatment of patients with supragastric belching. Reassurance and explanation of the symptoms as well as the mechanism of belching are important.³³ The habit can occasionally be inhibited by demonstrating chest expansion and air ingestion as the patient belches. Dietary modification (avoiding sucking candies or chewing gum, eating slowly and encouraging small swallows, and avoiding carbonated beverages) is traditionally recommended. When patients with FD or GERD complain of excessive belching, it seems reasonable to treat the other symptoms first. Successful treatment of excessive belching by speech therapy performed by a well-informed speech therapist, biofeedback, and diaphragmatic breathing training, is reported in an open-label study, demonstrating that speech therapy performed by a well-informed speech therapist can lead to a significant reduction in symptoms,³⁴ but appropriate studies are needed. When there is a suspicion that excessive belching is secondary to a psychiatric disorder, the patient should be referred for an evaluation by a psychiatrist. The treatment of associated psychiatric disease or employment of stress-reduction techniques may theoretically be beneficial.

Gastric belching. Acute and severe episodes are rare and occur mainly in mentally disabled patients and can result in volvulus of organs, as well as obstruction and breathing difficulties, because of increased abdominal pressure. In this case, a nasogastric tube to relieve gastric air appears to be reasonable treatment, and sedatives may

help to reduce repetitive air swallowing. Patients with chronic gastric belching should avoid carbonated beverages and eat slowly. Treatment with speech therapy to reduce air swallowing seems reasonable. Diaphragmatic breathing may be helpful. Baclofen, a γ -aminobutyric acid-B receptor agonist that reduces the frequency of transient LES relaxations and suppresses swallowing rate through a presumed central mechanism of action, may decrease both gastric and supragastric belching events.³⁵ Surface tension-reducing drugs, such as dimethicone and simethicone, might prevent gas formation in the intestines and alleviate symptoms as well, but there is no consistent evidence to support their use.

B3: Nausea and Vomiting Disorders

Definitions

Nausea is a subjective symptom and can be defined as an unpleasant sensation of the imminent need to vomit typically experienced in the epigastrium or throat. Vomiting refers to the forceful oral expulsion of gastrointestinal contents associated with contraction of the abdominal and chest wall muscles.

Epidemiology

Nausea is less prevalent than epigastric pain or meal-related symptoms in the community.³⁶ Unexplained chronic nausea is often associated with other gastroduodenal symptoms. Unexplained vomiting occurring at least once monthly is distinct from occasional vomiting reported with FD, and is believed to be rare, occurring in approximately 2% of women and 3% of men.³⁶ The prevalence of CNVS is unknown.

CVS is estimated to cause symptoms in 3%–14% of adults referred for unexplained nausea and vomiting.³⁷ CVS presents in young adults across all races and in both sexes. Adult patients present to emergency departments a median of 15 times before diagnosis 5–6 years after symptom onset.³⁷ CVS may be linked to the menses (catamenial CVS), precipitated by pregnancy, or associated with diabetes mellitus. Common precipitants of CVS episodes include stress, sleep deprivation, infections, foods, motion sickness, and medications. Most patients show gradual symptom reductions over time. However, some adults progress to daily nausea and vomiting without asymptomatic intervals.

CHS resolves with cessation of marijuana smoking. One-third of patients with presumed CVS report marijuana use. Cannabinoid use is more often reported in CVS compared with chronic functional vomiting. CHS typically occurs in males with prolonged daily cannabis use (3–5 times daily) over at least 2 years. As with CVS, delays in CHS diagnosis and numerous emergency department visits before diagnosis are typical.³⁷

B3. Diagnostic Criteria^a for Nausea and Vomiting Disorders

B3a: Chronic Nausea and Vomiting Syndrome (CNVS)

Must include all of the following:

1. Bothersome (ie, severe enough to impact on usual activities) nausea, occurring at least 1 day per week and/or 1 or more vomiting episodes per week
2. Self-induced vomiting, eating disorders, regurgitation, or rumination are excluded
3. No evidence of organic, systemic, or metabolic diseases that is likely to explain the symptoms on routine investigations (including at upper endoscopy).

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

B3b: Cyclic Vomiting Syndrome (CVS)

Must include all of the following:

Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)

1. At least 3 discrete episodes in the prior year and 2 episodes in the past 6 months, occurring at least 1 week apart
2. Absence of vomiting between episodes, but other milder symptoms can be present between cycles

Supportive remarks:

- History or family history of migraine headaches

B3c: Cannabinoid Hyperemesis Syndrome (CHS)

Diagnostic criteria^a

Must include all of the following:

1. Stereotypical episodic vomiting resembling cyclic vomiting syndrome (CVS) in terms of onset, duration, and frequency
2. Presentation after prolonged excessive cannabis use
3. Relief of vomiting episodes by sustained cessation of cannabis use

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

Supportive remarks:

- May be associated with pathologic bathing behavior (prolonged hot baths or showers).

Justification for Change in Criteria

The previous separate sections were merged into a single entity entitled Chronic Nausea and Vomiting

Syndrome due to a paucity of data delineating differences in diagnostic approach and management of 2 symptoms that are frequently associated. Chronic nausea can present in the absence of vomiting. Vomiting in the absence of nausea might prompt suspicion of an organic central nervous system disease. Nausea may be meal-related or unrelated, suggesting potential pathogenic heterogeneity. Minor changes to the CVS criteria were made to acknowledge the observation that some affected adult patients report inter-episodic symptoms other than vomiting, and being free of vomiting for at least a week between episodes was a distinguishing feature in adults (Figure 5). CHS is distinct from CVS, as it exhibits different epidemiology and has specific bathing behavior and therapy.

Pathophysiology

Physiologic defects associated with CNVS, CVS, and CHS are incompletely characterized. No correlation has been established between abnormal gastric emptying or fundic accommodation and CNVS, CVS, and CHS. Autonomic neural disorders are found in CVS, including complex regional pain syndrome, postural orthostatic tachycardia syndrome, orthostatic pulse and blood pressure changes, impaired parasympathetic responses to deep breathing, and abnormal sympathetic skin responses.³⁸

Psychological dysfunction presents in some patients with nausea and vomiting disorders. Although psychiatric diagnoses, including major depression and conversion disorder, have been described in different emetic profiles, a correlation has not been confirmed. CVS attacks share features with migraines, including episodic attacks, intervening well periods, stereotypic onset, and associated pallor, hypersensitivity, and fatigue.

The pathophysiology of CHS is poorly understood. Some cannabinoids have antiemetic actions, and others may contribute to recurrent vomiting, their effects also depending on doses.³⁹

Masses occupying intracranial space, such as tumors of the third ventricle; inner ear diseases, such as vestibular neuronitis; and medication other than cannabinoids, such as opiates, are all possible causes of secondary intermittent vomiting with or without associated nausea. Food allergies and intolerances may elicit a presentation similar to CVS. Gene mutations and mitochondrial DNA polymorphisms have been described in CVS patients.⁴⁰

Clinical Evaluation

Symptom profiles. CNVS is primarily distinguished from CVS by distinct temporal characteristics. CVS typically comprises 4 phases: (1) a pre-emetic period with pallor, diaphoresis, and nausea; (2) intense emesis up to 30 episodes daily, often with associated epigastric or diffuse abdominal pain and/or diarrhea; (3) a recovery phase with gradual symptom resolution of nausea and vomiting; and (4) an interepisodic period without vomiting. CVS attacks are generally longer and more frequent in adults than in children.⁴¹ Similarly, CHS is divided into

prodromal, hyperemetic, and recovery phases. Hot baths or showers during attacks provide relief of the hyperemetic phase.

Differential diagnosis. The differential diagnosis of recurrent vomiting is extensive. Gastroparesis, intestinal pseudo-obstruction, mechanical obstruction, and some metabolic and central nervous system diseases present with recurrent nausea and/or vomiting. Rumination syndrome presents with effortless regurgitation of undigested food, often with re-swallowing or spitting within minutes of eating, which can be mistaken for vomiting. Although there is no associated nausea, weight loss can occur. Patients with bulimia nervosa may have self-induced vomiting associated with binge episodes. Several rare conditions have presentations that mimic CVS, including acute intermittent porphyria (which also has associated neurologic symptoms) and disorders of fatty acid oxidation.

Diagnostic testing

Performance of diagnostic testing is dictated by the clinical presentation. Those with bilious vomiting, abdominal tenderness, abnormal neurologic findings, or a worsening pattern of vomiting episodes warrant more aggressive investigation.⁴² Biochemical testing can exclude electrolyte and acid–base abnormalities, hypercalcemia, hypothyroidism, and Addison's disease. Drug screening may be considered if CHS is a possibility but is denied. Upper endoscopy, small bowel radiography, or computed tomography or magnetic resonance enterography can evaluate for gastroduodenal disease and small bowel obstruction. Computed tomography head is necessary to exclude space-occupying lesions. If these tests are normal, the clinician can consider a gastric-emptying evaluation. If severe symptoms persist, antroduodenal manometry can assess for enteric neuropathy or myopathy, but a normal manometric recording is most helpful. Esophageal pH testing can be considered to exclude vomiting as an atypical presentation of GERD.

Consideration of rare conditions is warranted in some CVS patients, including urine measurements of amino-levalulinic acid and porphobilinogen, plasma ammonia levels, plasma amino acid, and urine organic acid quantification.⁴²

Treatment

Chronic nausea vomiting syndrome. Limited investigation has focused on treatment of what is now called CNVS. Agents with antiemetic capabilities have been developed in several drug classes, including histamine H₁ antagonists, muscarinic M₁ antagonists, dopamine D₂ antagonists, serotonin 5-HT₃ antagonists, neurokinin NK₁ antagonists, and cannabinoids.⁴³ 5-HT₃ antagonists exhibit superior control of vomiting compared with nausea. Uncontrolled series of patients with presumed functional causes of nausea and vomiting report significant benefits by tricyclic antidepressant agents, gastric electrical stimulation, and cognitive and social skills training. Pain negatively

impacts symptom reductions, while gastric emptying rates do not predict responses. Notably, a noradrenergic and specific serotonergic antidepressant mirtazapine is often used clinically to treat patients with nausea, and recently has shown benefit in patients with dyspeptic symptoms associated with weight loss.

Cyclic vomiting syndrome. Therapies for acute CVS attacks include supportive care and aggressive medication regimens. Intravenous hydration with 10% dextrose with potassium replenishment as needed associated with antiemetics (especially serotonin 5-HT₃ antagonists) may provide substantial benefit in some cases.⁴² Acute vomiting episodes requiring emergency department or inpatient care can benefit from additional induction of sedation with intravenous benzodiazepines. Opiate agents or nonsteroidal anti-inflammatory drugs may be needed for control of pain associated with CVS flares; some benefits of parenteral ketorolac also have been described. Anecdotal success has been noted with antimigraine serotonin 5-HT_{1B,1D} agonists (eg, sumatriptan), especially in children with personal or family histories of migraines, but these drugs can be considered also in adults in the absence of such histories. Tricyclic agents exhibit efficacy for preventing recurrent CVS attacks, with poor responses being related to co-existent psychiatric disease, marijuana or opiate use, and poorly controlled migraines. Anticonvulsant drugs (eg, phenobarbital, phenytoin, carbamazepine, topiramate, and valproate) can be offered to individuals with CVS who fail tricyclic prophylaxis. Other classes with prophylactic effects in CVS include anticonvulsant drugs, β -blockers, cyproheptadine, and over-the-counter mitochondrial stabilizers (eg, L-carnitine and co-enzyme Q10), alone or in combinations. In a retrospective report, 75% of 20 CVS patients unable to take or respond to tricyclics exhibited benefits taking either zonisamide or levetiracetam over 9 months, with a mean 62% reduction in vomiting episodes.

Cannabinoid hyperemesis syndrome. CHS should be managed by withdrawal of marijuana, but many patients are unwilling to follow this advice. Tricyclic agents may also be used in an attempt to abort attacks

B4: Rumination Syndrome

Definition

In human patients, rumination syndrome is characterized by the repetitive, effortless regurgitation of recently ingested food into the mouth followed by rechewing and reswallowing or expulsion of the food bolus.

Epidemiology

Although initially described in infants and the developmentally disabled, it is now known that rumination syndrome occurs in males and females of all ages and cognitive function. The epidemiology of adult rumination syndrome is not well characterized. In a large database of patients with unexplained nausea and vomiting, 3.3% of women and 3.5% of men satisfied Rome III criteria for rumination syndrome.⁴⁴

B4. Diagnostic Criteria^a for Rumination Syndrome

Must include all of the following:

1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing
2. Regurgitation is not preceded by retching.

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive remarks:

- Effortless regurgitation events are usually not preceded by nausea
- Regurgitant contains recognizable food that might have a pleasant taste
- The process tends to cease when the regurgitated material becomes acidic.

Justification for Change in Criteria

The criteria for rumination are essentially unchanged but effortless regurgitation is emphasized as a major diagnostic point in the supportive remarks. Rumination is a heterogeneous syndrome that can present with an acid-tasting regurgitant that should not lead to a misdiagnosis of GERD. Supportive remarks are based on clinical experience, but lack scientific support.

Pathophysiology

Physiological features. Different mechanisms for the rumination events have been proposed, including simultaneous LES relaxations occurring during episodes of increased intra-abdominal pressure and voluntary relaxation of the diaphragmatic crura that permits the normal postprandial gastric pressure increase to exceed the barrier pressure provided by the LES.⁴⁵

Many patients show evidence of “pathological gastroesophageal reflux” on ambulatory pH testing or show macroscopic or microscopic damage to the lower esophagus on endoscopy. However, rapid pH oscillations are most prominent in the first postprandial hour and result from regurgitation and reswallowing of food. Conversely, nocturnal esophageal pH usually is normal. “Rumination waves” characterized by simultaneous contractions in all recording sites soon after meal ingestion can be recorded by antroduodenal manometry. Rumination events are identified on combined impedance and high-resolution manometry, as elevations in intragastric pressure before or concurrently with oral esophageal fluid propulsion that are generally nonacidic. Upper esophageal sphincter relaxes during all rumination events, suggesting potential participation of this structure as well.⁴⁶

Psychological features. Psychological dysfunction can be related to some cases of rumination syndrome. Stressful life events can be identified around the time of symptom onset in some patients.⁴⁷ Rumination can be associated with bulimia nervosa, although bulimics with rumination more commonly expel rather than reswallow meal residues.

Clinical Evaluation

Symptom profiles. Rumination syndrome most often presents with the clinical features reported here. Symptoms can be present with every meal, including liquids, which often are better tolerated in conditions with true vomiting. In contrast to most patients, a subset reports that the regurgitant is sour or bitter tasting and that the behavior does not stop when the regurgitant becomes “acidic.” Many individuals with rumination report additional symptoms, including nausea, heartburn, abdominal discomfort, diarrhea, and/or constipation. Weight loss can be prominent, particularly in adolescents.

Differential diagnosis. Discriminating rumination syndrome from regurgitation in GERD can sometimes be challenging, especially in those with associated heartburn. Rumination is contrasted to emetic conditions, such as gastroparesis, in which vomiting typically occurs later in the postprandial period, the food residue is not recognizable, and there is preceding nausea and/or retching. Given the female predominance of rumination and the frequent development of weight loss, patients are often misdiagnosed with bulimia or anorexia nervosa. Achalasia generally presents with dysphagia, which is not typical of the rumination syndrome, and its diagnosis requires esophageal manometric testing.

Diagnostic testing. Combined esophageal impedance/high-resolution manometry or antroduodenal manometry can provide typical findings that confirm the diagnosis in selected cases. Recent proposed impedance/high-resolution manometry criteria for rumination included reflux events extending to the proximal esophagus that are closely associated with abdominal pressure increases >30 mm Hg.⁴⁸

Treatment

Treatment of rumination syndrome has been reviewed recently.⁴⁹ Lifestyle, medication, surgical, and behavioral therapies have been offered for rumination syndrome with varying degrees of success. Gum chewing has anecdotal benefits in children with rumination. Proton pump inhibitors suppress heartburn and protect the esophageal mucosa during regurgitations, however, such drugs can prolong rumination by blunting the intragastric meal acidification that normally serves to terminate events. The γ -aminobutyric acid agonist baclofen may elicit reductions in rumination, possibly by blunting transient LES relaxations, but data are insufficient to support the clinical application of the drug. Most prokinetics induce relatively minor LES increases and levosupiride was used as part of

a multidisciplinary program due to its antidepressant effects.

The mainstay of treatment for rumination syndrome involves behavioral modification. For most patients, this consists of habit reversal using diaphragmatic breathing techniques to compete with the urge to regurgitate because rumination and the breathing technique cannot proceed at the same time.⁵⁰ Nissen fundoplication has been proposed in nonresponders, but data are insufficient.

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Conflicts of interest

The authors disclose no conflicts.