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Gastroduodenal Disorders

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Symptoms that can be attributed to the gastroduodenal area are classified into 5 categories: (1) functional dyspepsia, with 2 subcategories that can overlap: postprandial distress syndrome, with meal-induced symptoms of postprandial fullness or early satiation and epigastric pain syndrome, with epigastric pain or burning that does not occur exclusively postprandially; (2) nausea and vomiting disorders, which include 3 subcategories: chronic nausea vomiting syndrome; cyclic vomiting syndrome; and cannabinoid hyperemesis syndrome; (3) excessive belching disorders, defined as audible escapes of air from the esophagus or the stomach and classified into 2 subcategories depending on the origin of the refluxed gas: gastric or supragastric belching; (4) inability to belch syndrome, a new category defined by the self-reported inability to belch; and (5) rumination syndrome, defined by the repetitive, effortless regurgitation of recently ingested food into the mouth, followed by the reswallowing or expulsion of the food bolus.

Keywords: Dyspepsia; Nausea; Belching; Rumination.

The Rome Foundation Global Epidemiology Study (RFGES) for disorders of gut–brain interaction (DGBI) found that 10.6% of the general population had symptoms consistent with a gastroduodenal disorder.[1] The Rome V classification categorize these disorders into functional dyspepsia (FD), subcategorized into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS); chronic nausea and vomiting disorders, subcategorized into chronic nausea and vomiting syndrome (CNVS); cyclic vomiting syndrome (CVS), and cannabinoid hyperemesis syndrome (CHS); excessive belching disorders, subcategorized into excessive gastric and supragastric belching, the new category of inability to belch syndrome; and finally, rumination syndrome.

B1. Functional Dyspepsia

Definition

Patients with dyspeptic symptoms (bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning) are classified as having secondary dyspepsia if a structural, systemic, or metabolic disease can be identified, or as FD if diagnostic procedures identify no explanation for the symptoms. The specifier categories PDS and EPS should be used guided by symptoms profile.

Epidemiology

The RFGES for DGBI reported a prevalence of 7.2% (95% confidence interval, 7.0–7.4) for FD symptoms.[1]

Justification for Change in Criteria

Although FD remains the umbrella term, the subgroups terminology PDS or EPS, or both, should preferentially be used.

In PDS, bothersome postprandial fullness or early satiation, or both, remain the cardinal symptoms. Other symptoms triggered or worsened by the ingestion of a meal (eg, epigastric pain or burning, epigastric bloating, nausea, and excessive belching) may coexist and are part of the same diagnostic entity. The Rome IV criteria for EPS stated that epigastric pain may occur after meals (postprandial epigastric pain) or independently from meals, resulting in considerable overlap with PDS. This issue was set to be solved in the current criteria by specifying that postprandial epigastric pain in the presence of PDS symptoms

Abbreviations used in this paper: **5-HT, 5-hydroxytryptamine receptor; CBT, cognitive behavioral therapy; CHS, cannabinoid hyperemesis syndrome; CNVS, chronic nausea and vomiting syndrome; CVS, cyclic vomiting syndrome; D, dopamine; DGBI, disorders of gut–brain interaction; EPS, epigastric pain syndrome; FD, functional dyspepsia; GE, gastric emptying; GERD, gastroesophageal reflux disease; GI, gastrointestinal; *H pylori*, *Helicobacter pylori*; NNT, numbers needed to treat; PDS, postprandial distress syndrome; PPI, proton pump inhibitor; RFGES, Rome Foundation Global Epidemiology Study; TCA, tricyclic antidepressant; THC, tetrahydrocannabinol; TLESR, transient relaxation of the lower esophageal sphincter; TRPV1, transient receptor potential cation channel, subfamily V, member 1; UES, upper esophageal sphincter.**

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B1. Diagnostic Criteria[a] for Functional Dyspepsia[b]

1. One or more of the following:
   a. Bothersome postprandial fullness
   b. Bothersome early satiation
   c. Bothersome epigastric pain
   d. Bothersome epigastric burning
2. No evidence of structural, systemic, or metabolic disease that is likely to explain the symptoms

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
[b]Must fulfill criteria for postprandial distress syndrome or epigastric pain syndrome, or both.

B1b. Diagnostic Criteria for Epigastric[a] Pain Syndrome

1. One or both of the following symptoms[b] at least 1 day per week:
   a. Bothersome epigastric pain (ie, severe enough to affect usual activities)
   b. Bothersome epigastric burning (ie, severe enough to affect usual activities)
2. Both 1a and 1b can be induced or worsened postprandially, or occur independently from meal ingestion.[c]
3. PDS criteria are not fulfilled.
4. Predominant nausea or persisting vomiting, or both, excludes the diagnosis of EPS.[d]
5. Heartburn is not a gastroduodenal symptom but often coexists.
6. No evidence of structural, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations.

[a]Limited to the central part of the abdomen above the navel.
[b]When epigastric pain or burning, or both, are consistently relieved by bowel movements, consider a bowel disorder.
[c]Provisional criteria for postprandial EPS: Epigastric pain or epigastric burning starts or gets worse after meals in ≥50% of the times. Provisional criteria for meal-unrelated EPS: Epigastric pain or epigastric burning starts or gets worse after meals in <50% of the times.
[d]Consider a diagnosis of CNVS or gastroparesis.

should be characterized as PDS and not EPS. Moreover, a recent study showed that meal-related epigastric pain in PDS can respond to therapy with a prokinetic agent and that patients with PDS, with or without postprandial epigastric pain, may show similar benefit,[2] suggesting that a similar treatment approach can be used in these patient populations.

The relation of the symptoms with the meal should be straightforward, and meal-related symptoms have been shown to emerge or worsen within the first 2 hours after meal ingestion.[3] Symptoms occurring or worsening later than 2 hours could be suggested to have a different pathophysiological background.[4] The updated symptom prevalence in PDS is based on patient focus group interviews revealing bothersomeness of PDS symptoms when present 2 days/week. Because nausea or vomiting, or both, may coexist with FD, nausea that is mainly postprandial and in the presence of PDS is part of PDS. When predominant nausea or recurrent vomiting is reported, especially in the absence of bothersome PDS symptoms, a diagnosis of CNVS or gastroparesis should be considered.[5–7]

B1a. Diagnostic Criteria for Postprandial[a] Distress Syndrome

1. Must include *one or both* of the following at least 2 days per week:
   a. Bothersome postprandial fullness (ie, severe enough to impact usual activities)
   b. Bothersome early satiation (ie, severe enough to prevent finishing a regular-sized meal)
2. In the presence of 1a or 1b, or both, other bothersome symptoms (ie, postprandial epigastric pain or burning, postprandial nausea, postprandial upper abdominal bloating, or postprandial excessive belching) that are elicited or worsened by food ingestion are part of PDS.
3. Predominant nausea and/or persisting vomiting excludes the diagnosis of PDS.[b]
4. Heartburn is not a gastroduodenal symptom but often coexists.
5. No evidence of structural, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations.

[a]Postprandial means symptoms that are triggered within 2 hours of meal intake.
[b]Consider a diagnosis of CNVS or gastroparesis.

The cardinal symptoms of EPS should be clearly localized to the central/upper part of the abdomen (above the navel) to avoid misdiagnosing heartburn or bowel disorders in this category. If the epigastric pain or burning is relieved by bowel movements, a bowel disorder should be considered. Also in EPS, nausea and vomiting can coexist; however, in the presence of predominant nausea or recurrent vomiting the diagnosis of CNVS or gastroparesis should be considered.

In the absence of PDS symptoms, not all epigastric pain is unrelated to a meal. Recent observations in 4 cohorts involving more than 1300 FD patients, of whom 21% had EPS according to Rome IV criteria, showed that most reported epigastric pain unrelated to meals, but a substantial proportion reported epigastric pain triggered or worsened by the ingestion of a meal.[8] As a result, the committee acknowledges that the group of patients with EPS, in the absence of PDS, could be further subdivided into meal-related EPS and meal-unrelated EPS. This subdivision requires further research to better characterize these patients, their underlying pathophysiology, and treatment approach and to this end provisional criteria have been developed.

A PDS or EPS diagnosis is only confirmed with certainty by excluding structural, systemic, or metabolic diseases that are likely to explain the symptoms. On the other hand, the yield of endoscopy is low in patients with typical symptoms and in the absence of alarm or risk factors.[9] Hence, for standard clinical practice, routine laboratory investigations, including testing for *Helicobacter pylori* (*H pylori*) should suffice, and upper endoscopy is not compulsory in patients without risk or alarm symptoms. For research purposes, it is strictly necessary to confirm the diagnosis by normal findings on an upper endoscopy.

Pathophysiology

FD is a heterogeneous and multifactorial disorder for which many pathophysiological mechanisms have been implicated in symptom generation (Figure 1). PDS is better studied than EPS, but to what extent the pathophysiology of the subgroups differs remains unclear.[10]

Disordered motility. Impaired gastric accommodation is found in up to 40% of FD patients,[11] and this could lead to an altered distribution of a meal toward the distal stomach.[12] Impaired gastric accommodation in FD is associated to early satiation, postprandial fullness, and unintentional weight loss.[13] Delayed gastric emptying (GE) is reported in ∼30% of patients with FD and has been associated to more severe upper gastrointestinal (GI) symptoms, especially postprandial fullness, nausea, and vomiting.[7]

In up to 30% of patients with FD, increased visceral sensitivity has been reported.[14] Initially, visceral hypersensitivity was correlated to epigastric pain, suggesting a relation to EPS,[13] but it has also been shown to be associated to meal-related symptom severity in FD.[15] Chemical stimuli, such as luminal acidity,[16] nutrients,[17] and lipids,[18] can have an impact on visceral sensitivity. Altered gut peptide release in FD may be implicated in pathways that affect gastroduodenal motility.[19]

Duodenal alterations. Duodenal barrier alterations have been linked to increased mucosal permeability and increased immune activation in patients with FD.[20–22] A meta-analysis highlighted higher counts of duodenal esoinophils and mast cells in FD and more pronounced in postinfection FD, but with no differences between FD subtypes.[23] A reduction in duodenal eosinophil counts by budesonide treatment was correlated with a reduction in symptoms of postprandial fullness and early satiation.[24] The use of proton pump inhibitors (PPI) in FD patients has also shown a relation between the decrease of eosinophil and mast cell counts, improved barrier function, and decreased symptom severity.[25]

Altered microbiota. The microbiome of duodenal biopsy specimens showed differences in the relative abundances of the bacterial phyla of Firmicutes, Fusobacteriota, and Patescibacteria in patients with FD compared with control individuals, although overlapping irritable bowel syndrome and PPI use are potential confounders.[26]

Bile salt composition. The ratio between fasting primary and secondary bile salts was decreased in FD compared with healthy individuals,[27] with bile salt concentration correlating with impaired duodenal permeability. Also, the expression of the vitamin D receptor, which is a bile acid sensor with an essential role in bile acid homeostasis, was increased in FD. Another study found an inverse correlation between GE rate and the concentration of duodenal bile salts.[28]

Adverse reactions to nutrients. Most patients with FD report symptoms to be triggered or aggravated by the ingestion of food. Elimination of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols in an FD cohort showed a beneficial effect on symptoms and improvement of intraepithelial flux across the duodenal mucosa.[29] Confocal laser endomicroscopy has enabled the observation that food can induce acute immune reactions, including eosinophils in the duodenal mucosa in DGBI, including FD.[30–32] A beneficial effect of the 6-food elimination diet was also reported in FD.[33]

Neuronal dysfunction. Studies have shown a relationship between the presence of low-grade inflammation and neuroimmune dysregulation. Immune cells (mainly mast cells) showed closer proximity to duodenal submucosal nerve endings in patients with FD compared with healthy individuals, and this was correlated with increasing numbers of GI symptoms and the presence of epigastric pain.[34] Also, the number of eosinophils and mast cells in the submucous plexus in patients with FD was correlated to submucosal neuronal structural and functional damage.[35]

Stress. There are indications of a dysregulated duodenal hypothalamic–pituitary–adrenal axis signaling in FD.[36]

Altered brain processing of visceral signaling. Studies have found clear associations between psychological comorbidities and FD.[37–39] Symptom severity and weight loss in FD have been associated with psychosocial factors and somatisation,[40] and a history of abuse was associated with alterations in gastric sensorimotor function and PDS symptoms.[41] Patients with FD tend to experience life events as more stressful.[38] The interaction between FD symptoms with psychological comorbidities has been shown to occur bidirectionally over time.[42]

Genetics. FD has a weak heritability.[43] Meta-analysis of studies has not found any association to FD with specific single nucleotide polymorphisms,[44] and there are inconsistencies between findings for candidate genes.[45]

Pathogenic microorganisms. Acute gastroenteritis caused by bacteria, viruses, and parasites increases the risk for developing FD.[46] Postinfection onset is associated with weight loss and early satiety.[47] A meta-analysis of case-control studies also showed increased numbers of duodenal eosinophils in postinfection FD compared with controls and patients with FD without any history of infection.[23]

***Helicobacter pylori* infection.** *H pylori* gastritis with endoscopically and histologically distinguishable characteristic findings, such as described in the Kyoto classification

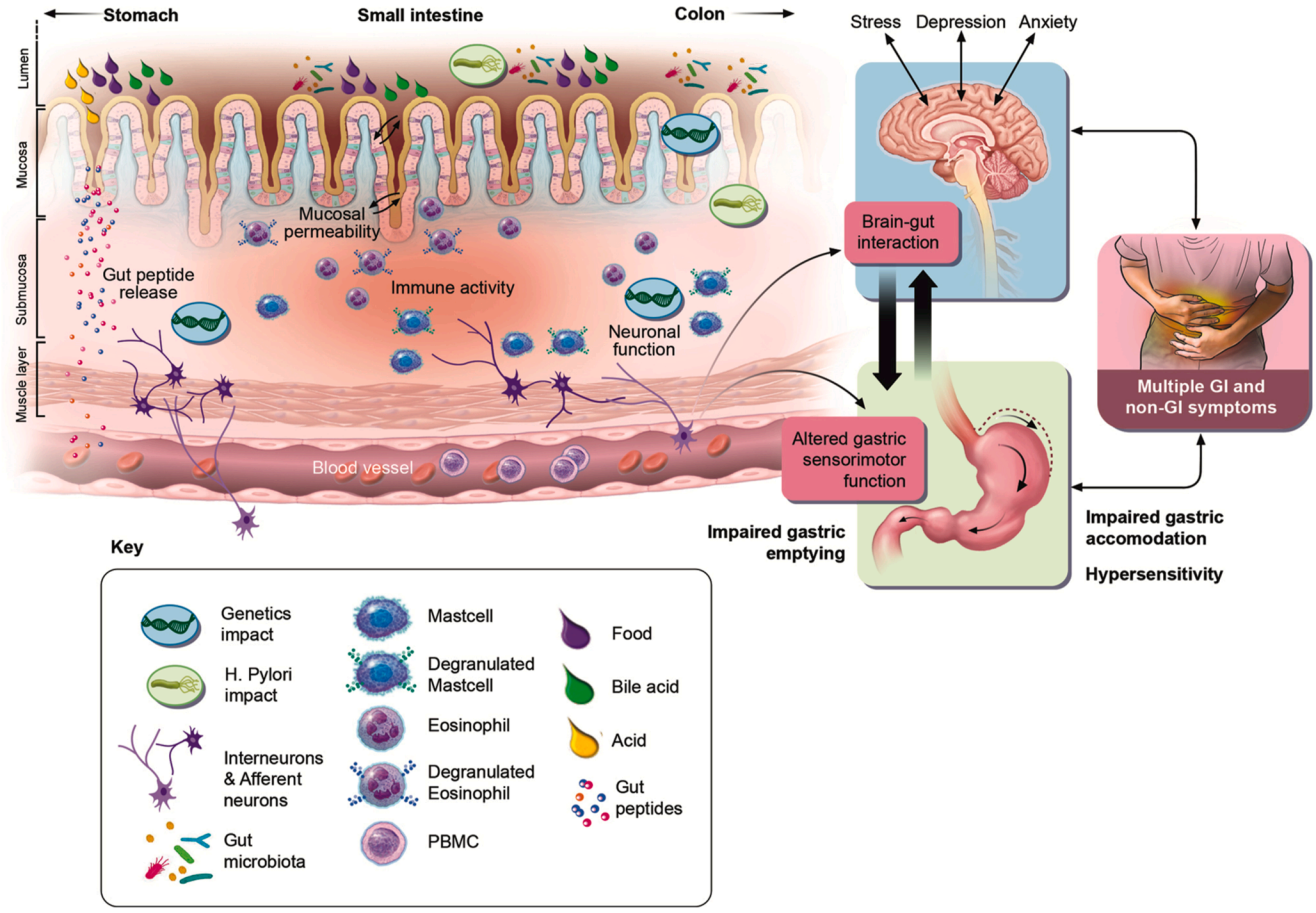

Figure 1. The pathophysiology of FD is heterogeneous and multifactorial. Different pathways have been described to be implicated in the generation of symptoms. The figure indicates one possible pathway where different triggers, such as food, *Helicobacter pylori* infection, genetics, acid, microbiome, bile acids composition, and others, could play a role that might have some level of impact and affect the duodenal barrier function. Increased barrier permeability to luminal factors might lead to an altered immune reaction where the number and activation of immune cells, such as eosinophils and mast cells, can be involved. The presence of this low-grade inflammation could lead to a neuroimmune dysregulation affecting GI motility, sensitivity, and brain–gut perceptions leading to symptoms. In addition, external factors could play a role affecting the brain–gut interaction also triggering GI alterations and symptoms. PBMC, peripheral blood mononuclear cell.

of gastritis,[48] should be considered an organic disease. In individuals with FD symptoms, *H pylori* eradication therapy is effective in ∼30%, with numbers needed to treat (NNT) at 15.[49] If symptom remission remains for half a year or longer after eradication, the symptoms of dyspepsia are considered as due to *H pylori* infection, and the condition is diagnosed as *H pylori*–associated dyspepsia.

Clinical Evaluation

The diagnostic algorithm for FD is described in Figure 2. The management strategy should be guided by the patient's history. In the absence of alarm features, unnecessary drugs and supplements that could be responsible for dyspepsia should be discontinued before proceeding to further diagnostic testing. The *H pylori* status should be determined in every patient with dyspeptic symptoms.[7,50–52] Routine laboratory testing, including celiac disease serology, is not recommended due to a low diagnostic yield,[53] and no international consensus recommends the routine use of duodenal biopsies.[7,50–52] In standard clinical practice, uninvestigated dyspepsia can be managed without upper endoscopy if there are no alarm features.[7,50–52] In patients presenting with alarm features and when dyspeptic symptoms are investigated for a clinical or mechanistic trial, an upper endoscopy is mandatory.

The evidence does not support routine imaging in the diagnostic workup for symptoms compatible with FD.[7,50,52] However, it is important to consider additional testing in individuals who have abnormal findings on clinical examination or when treatment has failed on a case-by-case basis. It is generally accepted that the introduction of motility studies in the routine diagnosis of FD is not recommended.[7,50–52]

Treatment

Treatment of FD is a stepwise process. The evidence in support of diet as a therapeutic strategy in FD is low, but it is reasonable to advise frequent small-size meals and avoiding

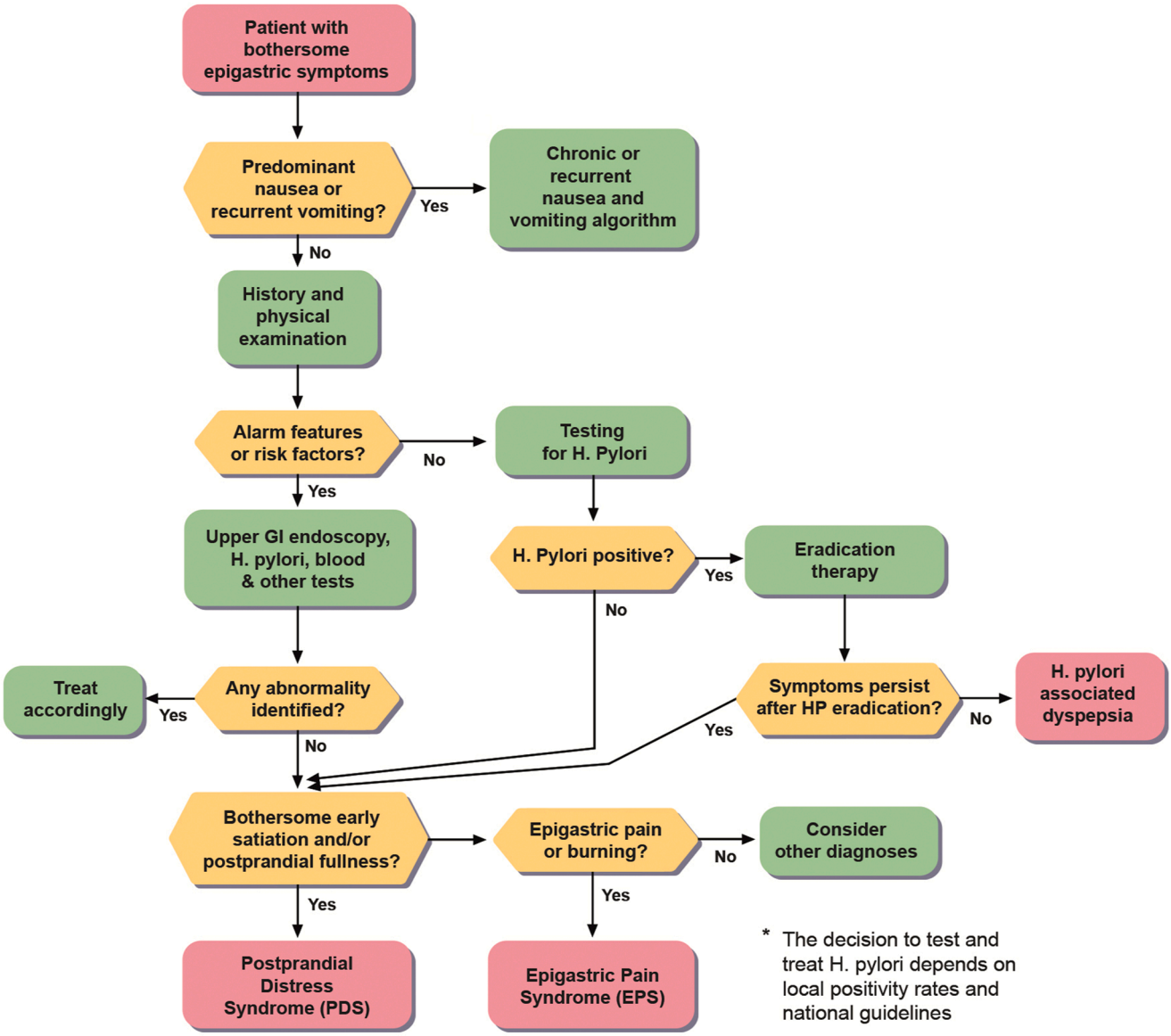

Figure 2. Diagnostic approach to dyspeptic symptoms. HP, *Helicobacter pylori*.

high-fat food items. *H pylori* can be considered the cause of FD symptoms if eradication is associated with sustained symptom benefit.[48,54,55] PPIs are generally the recommended first-line treatment for patients with FD who remain symptomatic after eradication of *H pylori* or who are negative for *H pylori*.[7,51,52,56] A standard once-daily dose of PPI during 4 to 8 weeks with discontinuation of therapy in case of insufficient improvement is advised, without a dose-escalation strategy.[52,57] PPIs are more effective than placebo in the reduction of global symptoms of FD with a NNT of 11.[58] Notably, in most studies of PPI, FD was defined as epigastric pain or burning, and gastroesophageal reflux disease (GERD) was not invariably excluded. The evidence supporting PPI in either FD subgroup is limited, no data are available in the large EPS-PDS overlap group,[59] and PPI may be less effective in relieving PDS symptoms.[60]

Histamine 2 receptor blockers in FD have a NNT of 7, but the quality of studies is low, and inclusion of patients with GERD is likely.[61] Nevertheless, most guidelines suggest PPI and not histamine 2 receptor blockers as the first-line therapy, except for the National Institute for Health and Care Excellence guidelines, which propose both options.[57]

Prokinetics. Prokinetics are a heterogeneous class of agents with either mainly antiemetic properties, such as dopamine D2 (D2) antagonists, or prokinetic activities through 5-hydroxytryptamine receptor 4 (5-HT_4) agonism, cholinesterase inhibition, or other modes of action. A meta-analysis demonstrated a significant effect of prokinetics in reducing dyspeptic symptoms, with an NNT of 12 when cisapride was excluded.[62] Among 5-HT_4 agonists, tegaserod showed some benefit in female patients with FD.[63] Itopride, a combined D2 antagonist and cholinesterase inhibitor, reported significantly more responders to treatment based on a global efficacy measure and with the Leuven post-prandial distress scale in patients with overlapping PDS-

EPS according to the Rome III definition.[2] Acotiamide, a cholinesterase inhibitor and antagonist at presynaptic M1 and M2 muscarinic receptors, enhances gastric accommodation and GE rate, is well-tolerated and most effective for PDS.[64,65]

Neuromodulators. Centrally acting neuromodulators appear to be an effective treatment for FD with an NNT of 6. However, this beneficial effect appeared to be limited to tricyclic antidepressants (TCA) and antipsychotics, such as levosulpiride, which also exerts prokinetic activity.[66] The longest duration of therapy identified was 12 weeks. The longer-term efficacy of neuromodulators in FD is unknown.[66] The number of adverse events and adverse events leading to withdrawal were both significantly higher among those taking psychotropic drugs.[66] The effects on pain of amitriptyline have been suggested to be potentially more useful in EPS.[67] The results of 2 studies of selective serotonin reuptake inhibitors in FD were negative.[67,68]

Mirtazapine can improve early satiation scores, and nutrient tolerance compared with placebo, which was associated with significant recovery of weight loss, improvement of quality of life and a GI-specific anxiety score,[69] and improvement of FD symptoms.[70] Tandospirone citrate, a 5-HT_{1A} agonist, has been shown to improve the abdominal symptom score,[71] the overall severity of dyspeptic symptoms, and individual symptoms of postprandial fullness, early satiation, and upper abdominal bloating.[72] It also significantly increased gastric accommodation and delayed GE of liquids.[72] A meta-analysis showed that patients with FD treated with 5-HT_4 or 5-HT_{1A} agonists had significantly greater improvement of symptoms compared with placebo-treated patients.[73]

Herbal therapies. The herbal combination drugs STW 5 and STW 5-II, as well as the combination of peppermint oil and caraway oil, have shown to be superior compared with placebo in the treatment of FD.[74–80] The Japanese herbal KAMPO preparation Rikkunshito has also shown efficacy and safety in FD.[81] ZhiZhu KuangZhong has shown a symptom reducing effect in PDS,[82] and Biling Weitong granules therapy was superior to placebo in reducing epigastric pain severity in EPS.[83]

Probiotics. Higher rates of improvement for PDS—but not EPS—symptoms were reported with daily intake of *Lactobacillus gasseri* OLL2716 (LG21) for 3 months,[84] and the combination of *Bacillus subtilis* and *Bacillus coagulans* strains was effective for the key individual symptoms of FD.[85] A review summarizes the effects of probiotics in FD.[86]

Psychological and behavioral therapies. Among the various psychotherapy options for FD,[87] at least 4 studies on cognitive behavioral therapy (CBT) have shown positive short-term effects on FD symptoms,[88] with sustained efficacy after 6 months of follow-up in 1 study.[89] Positive results of hypnotherapy in FD were reported in 1 small randomized controlled study.[90]

Acupuncture. Meta-analyses of numerous low-quality randomized controlled trials suggest manual and electric acupuncture as being effective in the treatment of FD.[91] Selection bias, performing bias, reporting bias, and attrition bias remain major concerns when interpreting the findings.

Proposed Management Algorithm

On the basis of the literature summary above and clinical experience, the Gastroduodenal Committee proposes the algorithm in Figure 3 for the treatment of PDS. Dietary and lifestyle advice precedes pharmacotherapy. Clinical experience and availability of therapeutic agents in different parts of the world decides whether PPI, first-line prokinetic agents, or herbal preparations with an established efficacy and safety profile can be used as first-line therapy. In terms of herbal preparations, STW 5, STW 5-II, rikkunshito, peppermint oil/caraway oil, or some of the better studied Chinese herbal medicines can be considered. In case of insufficient response to a first-line approach, endoscopy and other tests are recommended if not yet performed. Neuromodulators are recommended as second-line therapies. In case of refractory early satiation, a 5-HT_{1A} agonist, such as tandospirone[71] or buspirone,[72] can be considered. In case of weight loss, mirtazapine[69] is an option, whereas TCA may show some efficacy for postprandial fullness.[67]

In PDS patients who are nonresponders to these different treatment steps, a GE test can be considered. If this shows significant delay in GE, second-line prokinetic agents (eg, prucalopride, levo-sulpiride) can be considered. These patients can be referred to as having PDS with delayed GE. The term gastroparesis is reserved for those with predominant nausea or recurrent vomiting.[5,6]

Also in EPS, dietary and lifestyle advice precedes pharmacotherapy (Figure 4). Clinical experience and availability of therapeutic agents in different parts of the world decides whether PPI or herbal preparations with an established efficacy and safety profile can be used as first-line therapy. In case of insufficient response to a first-line approach, endoscopy and other tests are recommended, if not yet performed. Neuromodulators, more specifically TCA, are recommended as second-line therapies.[67] In both EPS and PDS, nutritional support is recommended in patients with refractory symptoms inducing weight loss or feeding restrictions.

B2. Nausea and Vomiting Disorders

Definition

Nausea is the unpleasant sensation of the impending need to vomit. Vomiting is the forceful oral expulsion of GI contents from the mouth and is distinguished from regurgitation, which is effortless passage of recently digested food into the mouth. The diagnostic approach to chronic or recurrent nausea or vomiting, or both, is proposed in Figure 5.

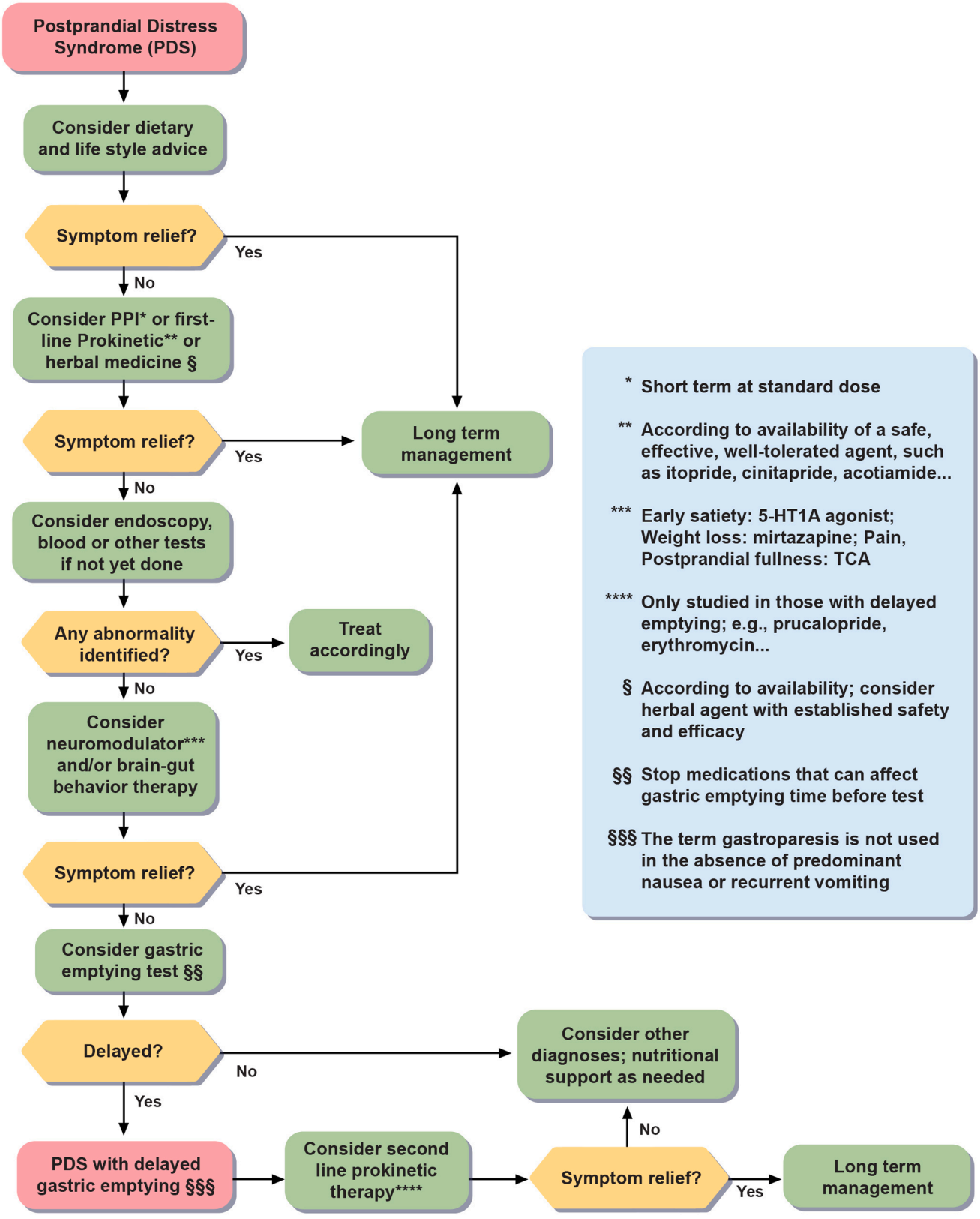

Figure 3. Treatment of PDS. Agent availability and local regulations will impact choices.

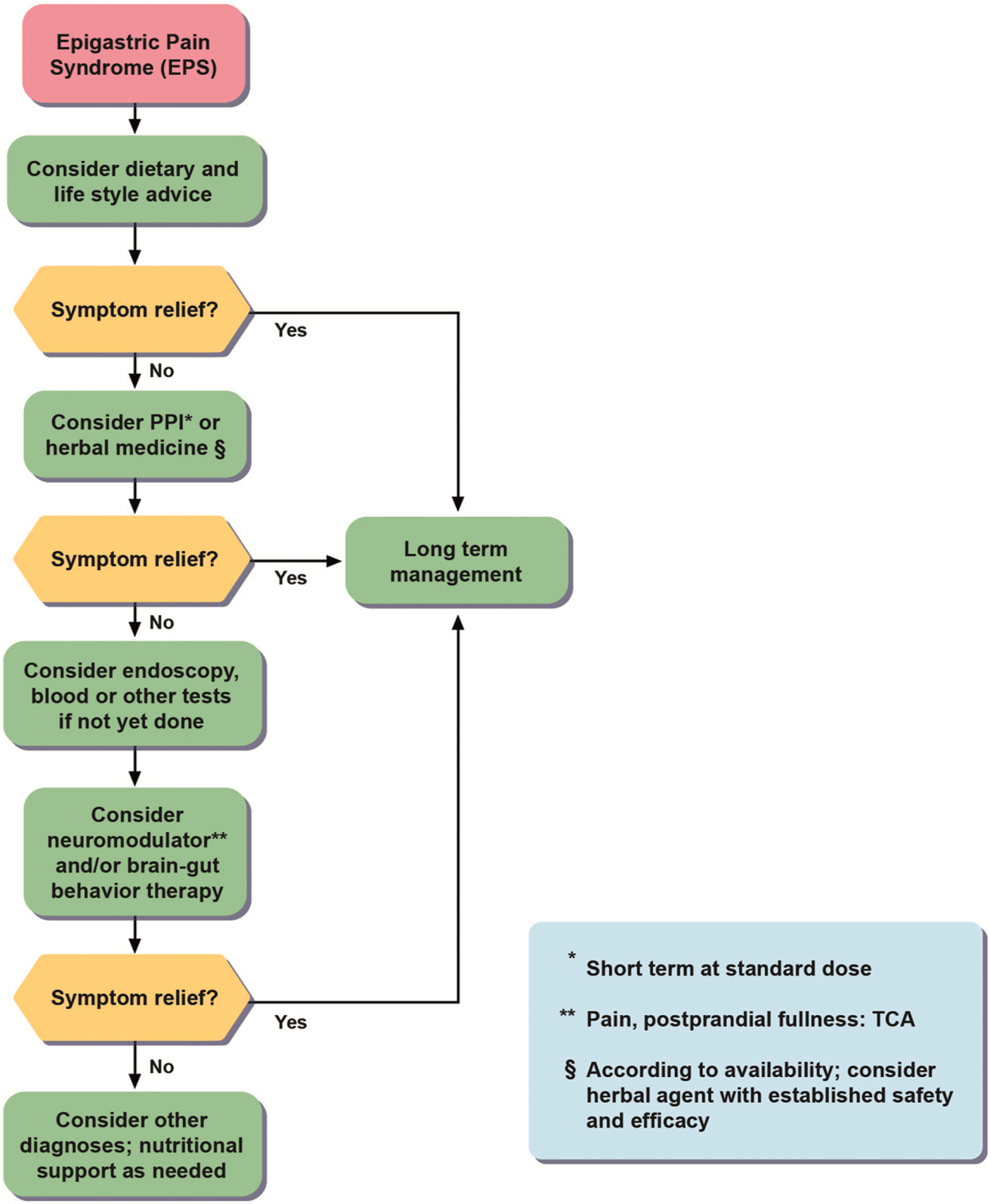

Figure 4. Treatment of EPS. Agent availability and local regulations will impact choices.

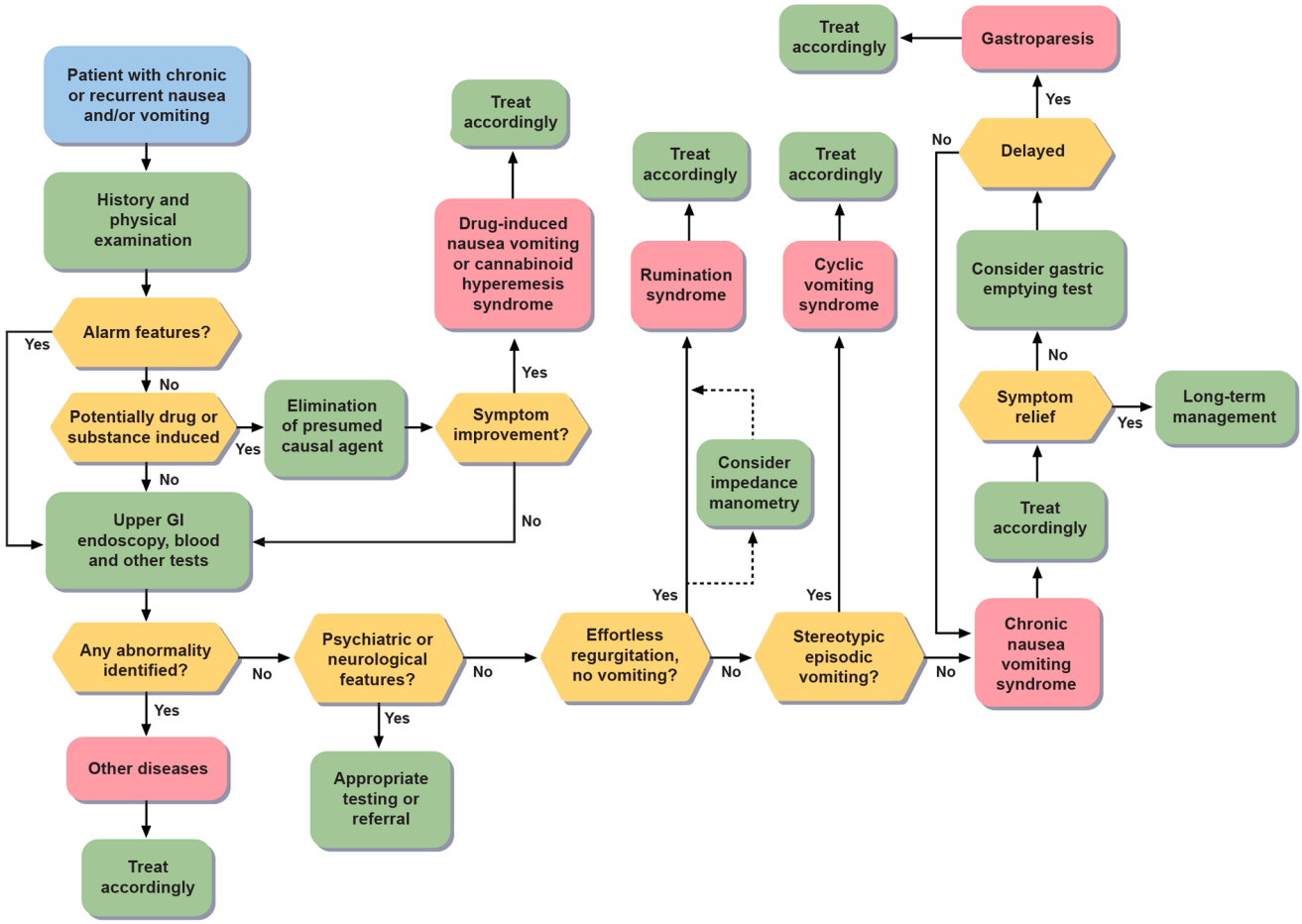

Figure 5. Diagnostic approach to chronic or recurrent nausea or vomiting, or both.

Justification for Change in Criteria

For CNVS, symptom frequency was changed to ≥2 nausea days weekly, with or without ≥1 weekly vomiting episodes. PDS symptoms should be questioned when evaluating for CNVS and a PDS diagnosis is conferred if such symptoms are dominant. Delayed GE with symptoms satisfying CNVS criteria should prompt diagnosis of gastroparesis. Minor changes were made to CVS criteria to acknowledge that some patients experience minor vomiting during interepisodic phases. CHS criteria were updated to quantify cannabis-use profiles and durations of abstinence for diagnosis.

B2a. Chronic Nausea Vomiting Syndrome

Epidemiology

Unexplained vomiting at least once monthly is reported by 2% to 3% of individuals, and nausea at least weekly is experienced by 3%. In the RFGES,[1] nausea without vomiting was reported by 1.9% of responders (unpublished data) which was more common in women and in those aged <40 years. A Rome IV survey calculated a CNVS prevalence of 0.8% to 1.2%, which was associated with irritable bowel syndrome in 41% and FD in 55% and reduced quality of life.[92]

Pathophysiology

CNVS pathophysiology is multifactorial. The insular cortex, amygdala, putamen, pons, and other cortical regions contribute to nausea perception, whereas the dorsal vagal complex and other vagal pathways regulate vomiting. Most studies report poor correlations of delayed GE to severity of nausea and vomiting. One study found symptoms in patients with FD and normal GE were nearly identical to those with gastroparesis and delayed GE.[93] GE was labile, with more than one-third of patients switching GE rate group at 48 weeks of follow-up. However, in a review restricting GE analyses only to optimal methods, delayed GE correlated with nausea, vomiting, early satiety/fullness, and abdominal pain, with odds ratios ranging from 1.5 to 2.[94] Likewise, histopathologic findings from full-thickness gastric specimens relate poorly to GE, with similar reductions in gastric interstitial cell of Cajal populations in those with delayed vs normal GE.

Clinical Evaluation

Differential diagnosis includes gastroparesis, mechanical obstruction, metabolic disorders, autoimmune disease, infiltrative disorders, psychiatric illnesses, intracranial masses, inner ear disease, and medications. The role of chronic cannabis use as a cause of CNVS is controversial.

B2a. Diagnostic Criteria[a] for Chronic Nausea Vomiting Syndrome

Must include *all* of the following:

1. Bothersome (ie, severe enough to affect usual activities) nausea occurring at least 2 days per week with or without 1 or more vomiting episodes per week.
2. Self-induced vomiting, eating disorders, regurgitation, or rumination are excluded as a cause of vomiting.
3. No evidence of structural, systemic, or metabolic diseases that is likely to explain the symptoms on routine investigations.
4. Symptoms predominantly due to PDS exclude the diagnosis.
5. Predominant nausea or persistent vomiting associated with delayed GE should prompt a diagnosis of gastroparesis.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Diagnostic testing for chronic nausea, with or without vomiting, is dictated by the clinical presentation. Bilious vomiting, abdominal tenderness, abnormal neurologic findings, or worsening vomiting warrants evaluation. Blood work excludes electrolyte abnormalities and metabolic disorders. Endoscopy or imaging tests evaluate for organic disease. Specialized tests of GI function are offered in selected settings.

Treatment

There has been scant investigation on CNVS treatment. Antagonists of H_1, D_2, 5-HT_3, and neurokinin 1 receptors and agonists of cannabinoid CB_1 receptors exhibit antiemetic action. Other therapies, including TCA and psychological measures, show benefits in some patients with chronic nausea and vomiting. There are limited data supporting use of ginger, herbal remedies, and electroacupuncture.

B2b. Cyclic Vomiting Syndrome

Epidemiology

In a Rome IV survey, CVS prevalence was 1.4% and was greater in the United States vs Canada and the United Kingdom.[92] In Japan, CVS prevalence is lower (0.05 cases/1000 population). CVS begins at a mean age of 32 years and appears to be more common in women.

Pathophysiology

CVS occurs in isolation or in association with GI, neurohumoral, autonomic, or genetic factors. Rapid GE is found in 40% to 80% of CVS patients between vomiting episodes, and delayed GE has been described in 27%. Autonomic abnormalities and sympathetic dysfunction are prevalent in CVS.[95] CVS patients often report personal or family histories of migraines. CVS flares in some women begin before menstruation (catamenial CVS). Some CVS patients exhibit maternal inheritance, suggesting mitochondrial DNA abnormalities. Polymorphisms of cannabinoid and μ-opioid receptor genes, as well as single-nucleotide mitochondrial DNA polymorphisms (*16159T* and *3010A*) and calcium channel gene type-2 ryanodine receptor mutations, are associated with CVS.[96,97] Endocannabinoid-related lipids and salivary cortisol are elevated during emetic episodes. Triggers of flares include psychological stress and catastrophizing, physiologic stressors (infection, altered food intake, exercise, and impaired sleep) and food (cheese, cured meats, chocolate, and monosodium glutamate). Of adults with CVS, 78% screen positive for depression, and 84% are positive for anxiety.[98]

Clinical Evaluation

Four phases of CVS are characterized. A prodrome of nausea, abdominal pain, fatigue, and weakness is the initial presentation, which can be stereotypical in timing. This is followed within minutes to hours by a 3- to 6-day emetic phase with unrelenting vomiting >8 times hourly on average.[95,99] Nearly two-thirds of patients report abdominal pain and diarrhea during this phase.

As emesis wanes, a recovery phase lasting up to 1 week follows, with persistence of nausea, lightheadedness, and meal intolerance in some but not all patients. Patients then enter an interepisodic phase lasting weeks to months. Up to 63% of CVS patients have milder nausea, dyspepsia, and intermittent vomiting between attacks.[100] Fluid loss, electrolyte abnormalities, and hematemesis may occur acutely, and dental enamel damage is seen with repeated attacks. Compulsive hot bathing behavior is reported by 48% of CVS patients who do not use cannabis.

As with CNVS, diagnostic testing is performed only to exclude other causes of chronic nausea and vomiting and with negligible yield.

Treatment

Abortive treatment may not be feasible if the prodrome is short. After emesis starts, nonoral treatments are most likely to be beneficial. The 5-HT_3 antagonist ondansetron is commonly used for CVS attacks, but without trials of this

B2b. Diagnostic Criteria for Cyclic Vomiting Syndrome

Must include *all* of the following:

1. Stereotypical episodes of repetitive vomiting regarding onset (acute) and duration (up to 10 days).
2. At least 3 discrete episodes in the prior year and 2 episodes in the past 6 months occurring at least 1 week apart.
3. Milder symptoms including nausea and isolated vomiting can be present between cycles.

Supportive Remark
History or family history of migraine headaches can be present.

drug in specifically CVS.[101] Neurokinin 1 antagonists (aprepitant, fosaprepitant) reduce emesis frequency and hospitalizations in refractory patients. Sedating agents, including benzodiazepines and H_1 antagonists, are often beneficial adjunct to antiemetics. Intranasal or injectable triptans may reduce vomiting and abdominal pain, especially with family histories of migraines.

Preventive treatment by TCA produced improvements in 69% of CVS patients.[102] Poor responses to TCA were observed in those with migraines, psychological illness, and cannabis or opioid use. CVS attacks and health care use were reduced in 65% of patients treated with the anticonvulsant topiramate.[103] Similarly, patients refractory to TCA showed 50% fewer CVS attacks on zonisamide or levetiracetam. Mitochondrial supplements (coenzyme Q10, L-carnitine, and riboflavin) show some prophylactic efficacy in CVS. Psychological therapy with CBT is advocated for some patients. An integrative health care model including mediation plus care coordination elicited superior outcomes.

B2c. Cannabinoid Hyperemesis Syndrome

Epidemiology

CHS presents with episodic vomiting but differs from CVS by virtue of its development after prolonged cannabis use. Whether CHS should be considered a subtype of CVS or a distinct entity is debated.[104] CHS as a distinct diagnosis is advocated because its pathophysiology and treatment differ from CVS. However, up to 80% of CVS patients use cannabis to relieve vomiting or abdominal pain during acute attacks and likely do not have CHS. The overall prevalence of CHS is estimated at 0.12% but is 0.4% in United States populations.[92]

Cannabis use among CVS patients increased 10-fold from 2005 to 2014. CHS is reported in 18% of CVS patients overall and in 39% of CVS patients who are cannabis users.[92] CHS is more common in men, with a median age of diagnosis of 28 years and a >4 year delay in diagnoses in 40% of patients.[105] In one review, 22% of CHS patients used cannabis products >11 years, 17% for 6 to 10 years, and 36% for 2 to 5 years.[106] Cannabis use was at least daily in 61% of patients and weekly in 19%. CHS diagnoses doubled from 2000 to 2015, likely due to use of cannabis products higher in δ-9-tetrahydrocannabinol (THC) content.

Pathophysiology

Mechanisms for symptom induction in CHS are likely multifactorial. THC is believed to contribute to both antiemetic and proemetic actions of cannabis. It is postulated that CHS may result from down-regulation, desensitization, or internalization of CB_1 receptors in the hypothalamic–pituitary–adrenal axis and sympathetic nervous system.[107] Changes in transient receptor potential cation channel, subfamily V, member 1 (TRPV1) receptor function also may be prominent in CHS.[108] Among patients with CHS, 59% screen positive for anxiety and 68% are positive for depression.

Clinical Evaluation

As with CVS, CHS exhibits 4 phases. Acute emetic phases of CHS last from a few hours to 1 week, with vomiting >20 times daily in association with abdominal pain, diarrhea, and autonomic symptoms. One review showed up to 18% of cases were not characterized as exhibiting episodic emesis, raising the possibility that not all CHS cases mimic CVS.[109] Extreme compulsive bathing behaviors are prevalent in CHS and are reported by 92% of patients to reduce vomiting and pain during attacks.[110]

One review reported factors associated with CHS diagnosis included cannabis use >1 year, daily cannabis use, at least weekly cannabis use, symptom resolution with cannabis abstinence, compulsive bathing to relieve symptoms, male sex, and age <50 years.[106] Confirming symptom resolution after cannabis cessation has been a roadblock to accurately diagnosing CHS in many cases. One analysis found only 19% of patients were able to abstain from cannabis for >4 weeks.[109] Cannabis metabolites persist ≥1 month, and cannabis-induced brain impairments may endure longer; thus, cannabis cessation >6 months or ≥3 typical CHS cycles is currently proposed for CHS diagnosis. Diagnostic testing is rarely indicated in the absence of complications (eg, hemorrhage). Urine drug testing for THC metabolites is considered for patients who do not admit to cannabis use, but no metabolite profile is specific for CHS.

Treatment

Several reports confirm that cannabis cessation leads to CHS resolution and that resuming cannabis use promotes symptom resurgence.[106,111,112] CBT may help reduce cannabis dependence in CHS.

B2c. Diagnostic Criteria for Cannabinoid Hyperemesis Syndrome

Must include *all* of the following:

1. Stereotypical episodic vomiting resembling cyclic vomiting syndrome in onset, duration, and frequency.
2. Presentation after prolonged (1 year) and excessive (≥4 days per week or ≥15 doses per week, or both) cannabis use.
3. Relief of vomiting episodes by sustained (at least 6 months or 3 typical emetic cycles) cessation of cannabis use.

Supportive Remark
May be associated with pathologic bathing behavior *(prolonged hot baths or showers)*.

Among abortive therapies, cutaneous capsaicin, a TRPV1 agonist, shortens CHS episodes and decreases therapy requirements in several reports.[113–115] Likewise, hot showers activate skin TRPV1 thermoreceptors providing a plausible mechanism for their benefit in CHS. The parenteral D_2 antagonists haloperidol and droperidol show efficacy in aborting CHS episodes in uncontrolled series and a controlled trial.[116,117] Benzodiazepines (lorazepam, alprazolam) provide relief in small series.

CHS responds poorly to preventive TCA therapy. One small series of patients with CHS described effective prophylaxis with olanzapine.[118]

B3. Excessive Belching Disorders

Definition

Belching (eructation, ructus) can be defined as the audible escape of gaseous material from the esophagus or the stomach into the pharynx. There are 2 distinct types of belches: the gastric belch and the supragastric belch. Belching is a disorder only when it is excessive and when it is experienced as bothersome. This applies to both type of belches.[119–121]

Epidemiology

In the RFGES, the overall prevalence of Rome IV belching disorders was 1%.[1] In referred patients with upper GI symptoms, the prevalence is several times higher.[122]

Pathophysiology

Gastric belching. Gastric belching is a physiological reflex that is triggered by distension of the proximal stomach and results in a transient relaxation of the lower esophageal sphincter (TLESR). Rapid distension of the esophagus by a large volume of gas is then followed by relaxation of the upper esophageal sphincter (UES). Gaseous distension of the stomach can be caused by air swallowing, by ingestion of a source of carbon dioxide, and as a side effect of mechanical inflation (eg, respirator or sleep apnea equipment).

Supragastric belching. In the case of supragastric belching, the eructated air does not originate from the stomach but is either sucked or, less commonly, injected into the esophagus from the pharynx and then expelled immediately thereafter.[123] Supragastric belching is not accompanied by a TLESR. Occasional supragastric belching occurs in most healthy individuals. Patients with excessive supragastric belching have more belching events but do not swallow more air than gastric belchers.[124]

In patients with excessive supragastric belching, health-related quality of life is significantly impaired, primarily because of impairments in social function and vitality.[125] These patients have a high prevalence of anxiety disorders, and their symptoms are aggravated during stressful events. Distraction reduces the frequency of belching, whereas drawing attention to their belching behavior generally results in an increase in belching frequency.[126]

Excessive belching and gastroesophageal reflux disease. Belching is one of the most frequently reported symptoms in patients with GERD, after heartburn and regurgitation.[127] In part, excessive belching in patients with GERD can be explained by a higher incidence of air swallows and a higher frequency of gastric belching,[126] but in a study of patients who met the Rome IV criteria for excessive belching compared with patients with GERD, the most common type of belching in both groups was supragastric (93% vs 87% of belches, respectively).[128]

Several groups have described a temporal relationship between supragastric belches and reflux events, which can be explained as the individual's response to an unpleasant sensation. Acid-suppressive treatment has been shown to diminish the incidence of these belches.[129] The opposite sequence (supragastric belch first, reflux second) is also found more often than expected by chance.[122,129–131] This observation has prompted the hypothesis that supragastric belches can provoke reflux, at least in a subset of patients.[129,132] This hypothesis is supported by the observation that treatment of supragastric belching with CBT reduces acid reflux.[133]

Clinical evaluation. Patients who present with excessive belching are more likely to be affected by supragastric than by gastric belching, especially when the frequency of belching is very high (eg, 10–20 times per minute). If symptoms are troublesome, especially in case of diagnostic uncertainty, esophageal manometry-impedance testing with prolonged registration, often after a meal challenge, or 24-hour ambulatory pH-impedance monitoring can confirm the diagnosis. There are no solid data on the upper limit of normal of gastric belches, but for excessive supragastric belches. the upper limit was defined as >13 per 24 hours.[122] In patients with gastric belching, a plain abdominal radiograph may show gaseous distension of stomach and bowel loops, but the sensitivity and specificity of this approach are uncertain.

B3. Diagnostic Criteria[a] for Belching Disorders

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

B3a. Supragastric Belching (From Esophagus) and
B3b. Gastric Belching (From Stomach)

Supportive Criteria

1. Supragastric belching is strongly supported by observing frequent, repetitive belching.
2. Supragastric belching can be interrupted by maneuvers or distraction.
3. Excessive gastric belching has no defining clinical correlate.
4. Intraluminal esophageal impedance measurement (with or without concomitant manometry) allows objective differentiation of supragastric from gastric belches.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Excessive supragastric belching can be mistaken for hiccups when the patient is not observed during an episode of repetitive belching. In these cases, a smartphone video recording of the abnormal behavior can provide clarity. Hiccups are not associated with abnormal air transports in the esophagus.

Treatment

Irrespective of belching mechanism. Because the mechanisms involved in excessive gastric and supragastric belching are totally different, treating these 2 disorders differently seems logical. However, "dual goal" therapeutic options should also be considered, primarily because the diagnostic techniques that allow objective differentiation between the 2 belching subtypes are not universally available. Reassurance and explanation of the symptoms and the mechanism of belching are important. Some physicians demonstrate that they can belch intentionally themselves, or that the patient's belching is interrupted by biting on a pencil between the teeth, which might help to convince the patient that this is learned behavior.

Gastric belching. Dietary modification, such as avoiding sucking candies or chewing gum, eating slowly, encouraging small swallows, and avoiding carbonated beverages, is often recommended but has not been rigorously tested. In contrast to popular belief, gum chewing was found to have no effect on supragastric and gastric belching.[134] Several behavioral treatment strategies aiming to reduce air swallowing have been described. Whether speech therapy, CBT, or diaphragmatic breathing should be preferred is unclear. There is no evidence to support the use of surface tension-reducing drugs, such as dimethicone and simethicone.

Supragastric belching. Several treatments that have in common the aim of modification of the patient's behavior have been described as successful. Speech therapy provided by a dedicated and well-informed speech therapist led to an 83% positive symptom response rate.[135] The first step of this therapy consisted of making the patient aware of the behavior that causes the air to be brought into the esophagus. This was accompanied by various speech therapy exercises, including abdominal breathing and open-mouth breathing.

Several studies have shown that dedicated CBT not only has a positive effect on subjective symptoms but also reduces the incidence of objectively measured supragastric belches.[136] Diaphragmatic breathing training may be used to treat excessive supragastric belching.[137–139] Drugs that reduce surface tension, such as dimethicone and simethicone, are not likely to be useful in patients with excessive supragastric belching.

B4. Inability to Belch Syndrome

Definition

Inability to belch syndrome, also known as retrograde cricopharyngeal dysfunction, is a relatively newly recognized disorder characterized by self-reported inability to belch.[140–145] The underlying mechanism is ineffective relaxation of the UES in response to gastroesophageal gas reflux. Presenting symptoms, besides the inability to belch, can include bloating, flatulence, gurgling noises from the chest or lower neck, chest pain, or epigastric pain.[140–145] The contribution of the UES to the pathophysiology of the syndrome is confirmed by case series reporting symptomatic benefit of injecting botulinum toxin into the UES.[145–150]

Epidemiology

The epidemiology of the inability to belch syndrome has not been studied. Clinically, the condition is probably under-diagnosed due to its recent emergence and lack of clinician awareness. On the other hand, the syndrome may also be over-diagnosed because, thus far, most patients are self-referred, and objective confirmation of UES dysfunction is rarely performed.[151]

Pathophysiology

In health, injection of boluses of air into the mid-esophagus leads to UES relaxation, suggesting that it is the gaseous distention of the esophagus that triggers UES relaxation rather than it being a "programmed" component of a TLESR underlying a belching event.[140,152] The larger the volume of air injected, the greater the likelihood of eliciting UES relaxation and the more prolonged the period of relaxation. In patients with the inability to belch syndrome, gas injection fails to elicit UES relaxation and rather leads to impedance/manometric patterns of common cavity pressurization, oscillations of air load in the esophagus, and secondary peristalsis clearing the air into the stomach. The same events can be observed during high-resolution impedance manometry using carbonated water swallows as a provocative test.[140,142,145,152]

B4. Diagnostic Criteria[a] for Inability to Belch Syndrome

1. Bothersome inability, or impaired ability to belch at least 3 days per week.
2. No evidence of underlying major esophageal disease/dysfunction that explains the symptom (eg, achalasia, fundoplication, esophagogastric junction outflow obstruction, GERD).

Supportive Criteria

1. The following associated symptoms can be present:
   a. Chest pain
   b. Gurgling noises in the chest
   c. Bloating
   d. Flatulence
   e. Epigastric pain
2. Esophageal impedance manometry findings are supportive in the diagnosis (air entrapment/oscillations, gas reflux episodes not followed by adequate UES relaxation).

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Clinical Evaluation

To date, the diagnosis of the inability to belch syndrome is made clinically by the presence of patient-reported inability to belch together with any of the associated symptoms described above. In a small prospective open label study, high-resolution impedance manometry with belch provocation using carbonated water swallows showed promise as a diagnostic tool.[142] The diagnostic yield of this approach was confirmed in a larger patient cohort, and this was compared with control patients (without symptoms suggestive of the syndrome) and healthy volunteers.[153] This analysis confirmed the high prevalence and specificity of manometric abnormalities in retrograde cricopharyngeal dysfunction patients. Moreover, the manometric abnormalities were largely eliminated or improved with botulinum toxin injection.[145]

Although high-resolution impedance manometry with ingestion of a carbonated drink can help confirm the diagnosis, its value in the presence of typical suggestive symptoms remains to be determined.

Treatment

The currently best-established treatment approach consists of injection of 50 to 100 IU of botulinum toxin in the UES, mainly performed by ear-nose-throat specialists who targeted their injection to the UES by knowledge of anatomical landmarks or during confirmatory electromyography.[145–149] In the absence of a sham-controlled trial, the precise responder rate to and the long-term outcome of botulinum toxin injection is unclear, but clinical effects seem to last $\geq$6 months in most patients, and sustained remission also seems to occur.[143,147] There are occasional reports of hypnosis and surgery (cricopharyngeal myotomy) for inability to belch syndrome.[143,147,154,155]

B5. Rumination Syndrome

Definition

The rumination syndrome is characterized by the repetitive, seemingly effortless regurgitation of recently ingested food into the mouth, followed by the rechewing and reswallowing or expulsion of the food bolus. Rumination syndrome may be misdiagnosed as GERD, gastroparesis, unexplained vomiting, or an eating disorder.

Epidemiology

Rumination syndrome occurs in males and females of all ages and levels of cognitive function.[156,157] In the RFGES, the overall prevalence of rumination syndrome was 3.1%. It was more common in women than in men (54.5% vs 45.5%), and the mean age was 44.5 years.[158] Not surprisingly, the prevalence of rumination syndrome in patients presenting for evaluation of gastric symptoms can be higher, up to 12.8%.[159]

Justification for Change in Criteria

A new supportive remark was added to underline that an objective diagnostic technique (esophageal impedance monitoring with concurrent manometry) is available to distinguish rumination from other conditions (such as GERD). The observation that rumination events are usually not preceded by nausea was removed from the supportive criteria and added to the second diagnostic criterion because the committee felt that this characteristic is of diagnostic relevance. A supportive criterion was added to help differentiate reflux disease from rumination.

Pathophysiology

Most rumination events begin with an intra-abdominal pressure elevation that is brought about by voluntary abdominal contraction that leads to movement of gastric contents into the esophagus.[156,160–165] Which other mechanisms ruminators use to overcome the antireflux barrier is not completely clear. A subset also has rumination events in which gastric contents enter the esophagus before abdominal straining begins. This has been called secondary rumination.[161,166] It is likely that the patient in these cases perceives a spontaneous episode of gastroesophageal reflux and then produces the abdominal strain in response to it. A third type of rumination event is immediately preceded by a supragastric belch.[161,166] Delayed GE, increased gastric perception, and duodenal eosinophilia have been suggested as pathophysiological factors in rumination, but their relative roles are still uncertain. Stressful life events can be identified near the time of symptom onset in some patients,[167] and an association of rumination with bulimia nervosa has been described.[156,168]

B5. Diagnostic Criteria[a] for Rumination Syndrome

Must include *all* of the following:

1. Recurrent, seemingly effortless regurgitation of recently ingested food into the mouth, with subsequent oral expulsion or swallowing.
2. Regurgitation is not preceded by retching or nausea.

Supportive Criteria

1. The regurgitated material contains recognizable food that might have a pleasant taste.
2. The process tends to cease when the regurgitated material becomes acidic.
3. The presence of heartburn may help to differentiate regurgitation in the context of gastroesophageal reflux disease from rumination.
4. Combined manometry and impedance monitoring can be used to establish an objective diagnosis of rumination.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Clinical Evaluation

Symptom profile. In most cases, the presence of typical features suffices for establishing a diagnosis. The most important of these features are (1) repetitive, seemingly effortless regurgitation, (2) absence of retching and usually also of nausea, (3) starting within minutes after a meal and lasting for 1 to 2 hours, and (4) subsequent spitting out or reswallowing of the regurgitated material.

Many patients with rumination report additional symptoms, including nausea, heartburn, abdominal discomfort, diarrhea, or constipation. Weight loss can be prominent in ruminators, particularly in adolescents.[156,161,169–171] The additional symptoms and signs can lead to a considerable diagnostic delay.[156]

Differential diagnosis. Differentiating rumination from vomiting is essential. In rumination, the regurgitation process usually seems effortless, but some effort in the form of increasing intra-abdominal pressure is made. Absence of preceding nausea and absence of retching are important clues in the differentiation from vomiting.

Differentiating rumination syndrome from regurgitation in the context of GERD can be challenging, particularly in patients with associated heartburn.[172] Rumination must also be differentiated from emetic conditions such as gastroparesis. In the latter, vomiting typically occurs later in the postprandial period, and there is preceding nausea or retching. Patients with rumination are often misdiagnosed with bulimia or anorexia nervosa. This is not surprising given the female predominance in rumination and the frequent development of weight loss.[168,173] Rumination and eating disorders may also coexist.[174]

Diagnostic Testing

In equivocal cases, additional evaluation can be warranted, and for this, combined esophageal pH-impedance monitoring and manometry are the gold standard. This must be performed after a meal because rumination is a postprandial phenomenon. When only pH-impedance monitoring is used, differentiating rumination from reflux is almost impossible because the technique does not provide information on abdominal pressure peaks that are characteristic of rumination.[175] However, ruminating patients have more early postprandial nonacid reflux episodes and a higher postprandial Symptom Index than patients with typical GERD.[176] Proximal regurgitation events in patients with rumination are driven by an abdominal pressure peak >30 mm Hg[160] and a gastrosphincteric pressure gradient immediately before the suspected reflux episode of 2 mm Hg.[177] Evidence of pathologic gastroesophageal reflux upon ambulatory pH testing or presence of esophagitis upon endoscopy do not exclude rumination syndrome.

Treatment

An accurate diagnosis can be therapeutic by itself,[178] but additional treatment is required in most cases. The most important element of treatment for rumination syndrome involves behavioral modification, the most frequently used method.[179] This behavioral approach eliminates rumination in 30% to 66% of patients and reduces its occurrence in 20% to 55% of case series.[172] Diaphragmatic breathing may also be effective in secondary rumination.[123,180] Biofeedback can be used to enhance the efficiency of diaphragmatic breathing, either by showing the patient the manometric images[181] or by using electromyography of abdominal and intercostal muscles.[182]

Baclofen, a known inhibitor of TLESRs, was shown to reduce the number of postprandial rumination episodes more than placebo.[183] PPIs suppress heartburn and protect the esophageal mucosa during regurgitation, but such drugs can prolong rumination by blunting the intragastric meal acidification that normally serves to terminate events.[172] Finally, Nissen fundoplication produced improvements in rumination in a small series of patients who were unresponsive to behavioral approaches.[184]

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Conflicts of interest
These authors disclose the following: Hans Törnblom has received personal fees for giving scientific advice to Cinclus Pharma, Dr. Falk Pharma GmbH, Medifactia, PRO.MED.CS, and Purpose Pharma, and has served on the speaker bureau for Enterra Medical, Medifactia, and Viatris. Hidekazu Suzuki has received honorarium from Astellas Pharmaceutical Company, Otsuka Pharmaceutical Company, Ltd, and Takeda Pharmaceutical Company, Ltd. Jan Tack has received personal fees for giving scientific advice to Aclipse, Adare, AlfaSigma, Clasado, Danone, Enterra, Falk, FitForMe, Ironwood, Kyowa Kirin, Menarini, Promed, Ricordati, Takeda, Truvion, Tsumura, and Zealand Pharmaceuticals, has served on the speaker bureau for Abbott, BioCodex, Mayoly, Menarini, ProMed, Reckitt-Benckiser, Schwabe, Takeda, Thai Meiji, and Truvion Pharmaceuticals, and owns shares of Lys Medical and Agastra. Nicholas J. Talley received personal fees for giving scientific advice to Anatara Life Sciences, ADSSI, Brown University, the Agency for Healthcare Research and Quality, Biocodex, Microba, and Comvita Manuka Honey. Licensing Questionnaires Nepean Dyspepsia Index (NDI) 1998 to MAPI Research Trust, Licensing Questionnaires Talley Bowel Disease Questionnaires licensed to Mayo/Talley, "Diagnostic marker for functional gastrointestinal disorders" US Provisional Patent ID US20240272175A1, "Methods and compositions for treating age-related neurodegenerative disease associated with dysbiosis" US Patent No. 63/537,725, **"**Compositions and methods for the treatment of oesophageal disorders" Australian Provisional Patent ID 2025902002, and "Performance of a biomarker panel for irritable bowel syndrome" Patent ID WO2012158831A1. Vincenzo Stanghellini acted as a consultant for Alfasigma, Bayer, and GE Healthcare and as a speaker for Bayer, Bromatech, and Falck. The remaining authors disclose no conflicts.

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