GASTROENTEROLOGY 2006;130:1466–1479

Functional Gastroduodenal Disorders

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A numerically important group of patients with functional gastrointestinal disorders have chronic symptoms that can be attributed to the gastroduodenal region. Based on the consensus opinion of an international panel of clinical investigators who reviewed the available evidence, a classification of the functional gastroduodenal disorders is proposed. Four categories of functional gastroduodenal disorders are distinguished. The first category, functional dyspepsia, groups patients with symptoms thought to originate from the gastroduodenal region, specifically epigastric pain or burning, postprandial fullness, or early satiation. Based on recent evidence and clinical experience, a subgroup classification is proposed for postprandial distress syndrome (early satiation or postprandial fullness) and epigastric pain syndrome (pain or burning in the epigastrium). The second category, belching disorders, comprises aerophagia (troublesome repetitive belching with observed excessive air swallowing) and unspecified belching (no evidence of excessive air swallowing). The third category, nausea and vomiting disorders, comprises chronic idiopathic nausea (frequent bothersome nausea without vomiting), functional vomiting (recurrent vomiting in the absence of self-induced vomiting, or underlying eating disorders, metabolic disorders, drug intake, or psychiatric or central nervous system disorders), and cyclic vomiting syndrome (stereotypical episodes of vomiting with vomiting-free intervals). The rumination syndrome is a fourth category of functional gastroduodenal disorder characterized by effortless regurgitation of recently ingested food into the mouth followed by rechewing and reswallowing or expulsion. The proposed classification requires further research and careful validation but the criteria should be of value for clinical practice; for epidemiological, pathophysiological, and clinical management studies; and for drug development.

A large group of patients with functional gastrointestinal disorders have chronic symptoms that can be attributed to the gastroduodenal region (Table 1). Based on the consensus opinion of an international panel of clinical investigators who reviewed the available evidence, a classification of the functional gastroduodenal disorders into functional dyspepsia (FD) (category B1, comprising postprandial distress syndrome [PDS] and epigastric pain syndrome [EPS]), belching disorders (category B2, comprising aerophagia and unspecified belching), functional nausea and vomiting disorders (category B3, comprising chronic idiopathic nausea [CIN], functional vomiting, and cyclic vomiting syndrome [CVS]), and the rumination syndrome (category B4) is recommended.

B1. Functional Dyspepsia

Definition of Functional Dyspepsia

Many different sets of symptoms have been used synonymously with the term dyspepsia, which has caused confusion. Most patients do not recognize the term dyspepsia, and historically physicians have interpreted the meaning of dyspepsia very variably.

Hence, the committee recommended the following pragmatic definition: FD is defined as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms. These symptoms are listed in Table 2. However, particularly for experimental purposes, the term functional dyspepsia should preferably be replaced by more distinctively defined disorders, for which there is now increasing evidence in the literature. These are the new diagnostic categories of (1) meal-induced dyspeptic symptoms (PDS), and (2) epigastric pain (EPS).

Patients with 1 or more of these symptoms (postprandial fullness, early satiation, or epigastric pain or burning) are referred to as patients with dyspepsia. Previous Rome committees defined dyspepsia as pain or discom-

Abbreviations used in this paper: CIN, chronic idiopathic nausea; EPS, epigastric pain syndrome; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drugs; PDS, postprandial distress syndrome; PPI, proton pump inhibitor.

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0016-5085/06/$32.00
doi:10.1053/j.gastro.2005.11.059

Table 1. Functional Gastrointestinal Disorders

B. Functional gastroduodenal disorders
B1. Functional dyspepsia
B1a. Postprandial distress syndrome
B1b. Epigastric pain syndrome
B2. Belching disorders
B2a. Aerophagia
B2b. Unspecified excessive belching
B3. Nausea and vomiting disorders
B3a. Chronic idiopathic nausea
B3b. Functional vomiting
B3c. Cyclic vomiting syndrome
B4. Rumination syndrome in adults

fort centered in the upper abdomen and excluded reflux symptoms.[1] However, it has remained unsettled whether discomfort is a mild variant of pain or a separate symptom complex.[1,2] Moreover, discomfort comprised a large number of nonpainful symptoms including upper abdominal fullness, early satiety, bloating, or nausea. Bloating is an unpleasant sensation of tightness and should be distinguished from visible distention; usually, this symptom is not well localized and often occurs in IBS so bloating was not considered a cardinal symptom of dyspepsia. Nausea (queasiness or sick sensation or a feeling of the need to vomit) may occur with dyspepsia or IBS but is often from central origin and is also not considered a localizing symptom.[1–4] Whether or not individual symptoms such as upper abdominal fullness or bloating are labeled as pain by the patient may depend on cultural and linguistic factors and possibly education level.[2]

Heartburn has been defined by the esophageal committee. A burning sensation confined to the epigastrium is not considered to be heartburn unless it also radiates retrosternally. In the past, heartburn (as well as acid regurgitation) has often been included as sufficient on its own to define dyspepsia.[3] Heartburn is not considered a symptom that primarily arises from the gastroduodenum, and there is evidence that heartburn has moderate specificity for gastroesophageal reflux disease (GERD).[4,5] Hence, the committee concluded that heartburn is excluded from the definition of dyspepsia even though it may occur simultaneously with gastroduodenal symptoms. Similarly, retrosternal pain suggestive of esophageal disease or of a type embraced by the term noncardiac chest pain is excluded from dyspepsia.

Uninvestigated versus investigated dyspepsia. Especially when considering epidemiological data, it is important to distinguish the subjects with dyspeptic symptoms who have not been investigated from patients with a diagnostic label after investigation, with or without an identified causal abnormality.

Organic versus idiopathic dyspepsia. From an etiological viewpoint, patients with dyspeptic symptoms can be subdivided into 2 main categories:

1. Those with an identified organic or metabolic cause for the symptoms where, if the disease improves or is eliminated, symptoms also improve or resolve (eg, peptic ulcer disease, GERD with or without esophagitis, malignancy, pancreaticobiliary disease, or medication use).
2. Those with no identifiable explanation for the symptoms. In some of these patients, an identifiable pathophysiological or microbiologic abnormality of uncertain clinical relevance (eg, *Helicobacter pylori* gastritis) may be present, which is not thought to explain the symptoms. Others have abnormal motor or sensory dysfunction (eg, altered gastric emptying, fundic dysaccommodation, or gastroduodenal hypersensitivity) of uncertain significance. This broad group of patients with idiopathic dyspepsia has previously been referred to as nonulcer dyspepsia, essential dyspepsia, idiopathic dyspepsia, or FD. FD is currently the most recognized term in the literature.

Epidemiology

Approximately 20% to 30% of people in the community each year report chronic or recurrent dyspeptic symptoms.[6,7] Although these data represent uninvestigated dyspepsia and often also included heartburn, an organic cause is found in only a minority of dyspeptic subjects who

Table 2. Dyspeptic symptoms and their definitions

Symptom	Definition
Epigastric pain	Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome without being interpreted by the patient as pain.
Epigastric burning	Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Burning refers to an unpleasant subjective sensation of heat.
Postprandial fullness	An unpleasant sensation like the prolonged persistence of food in the stomach
Early satiation	A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished. Previously, the term "early satiety" was used, but satiation is the correct term for the disappearance of the sensation of appetite during food ingestion.

are investigated, and hence it is reasonable to assume that the majority would have functional dyspepsia.[8,9] Based on prospective studies of subjects who report dyspeptic symptoms for the first time, the incidence is approximately 1% per year.[7,10] The majority of patients with unexplained dyspeptic symptoms continue to be symptomatic over the long-term despite periods of remission.[11] Approximately, 1 in 2 subjects is estimated to seek health care for their dyspeptic symptoms at some time in their life.[12] Pain severity and anxiety (including fear of serious disease) appear to be factors associated with consulting behavior.[12,13]

Heterogeneity of FD Symptoms: Subgroups

It seems likely that chronic unexplained dyspepsia includes different types of patients with distinct underlying pathophysiologies who require different management approaches. However, it has been particularly difficult to identify these subgroups reliably. Subclasses based on symptom clusters have been proposed.[6,14] In clinical practice, however, this classification showed great overlap between subclasses, limiting its value.[7,15]

Identifying the predominant symptom was shown to distinguish subgroups with different demographic and symptomatic properties and with some relationship to putative pathophysiological mechanisms like delayed gastric emptying and presence of *H pylori*.[15] Thus, the Rome II committee proposed a subdivision according to the predominant symptom being pain or discomfort, but this subdivision has also been criticized because of the difficulty distinguishing pain from discomfort, the lack of an accepted definition of the term predominant, number of patients who do not fit into one of the subgroups, and especially the lack of stability, even over short time periods.[4,7,16]

A different approach was based on attempts to identify pathophysiology-based subgroups. Thus, associations were shown between symptom patterns and delayed gastric emptying,[17–19] impaired fundic accommodation,[20] and visceral hypersensitivity.[21] However, the association of these pathophysiological mechanisms with symptoms has not been confirmed in other studies.[22–24]

Diagnostic Criteria

The committee proposed to define FD at 2 levels. A general, more umbrella definition of FD, to be used mainly for clinical purposes, and although further research on more specific definitions is ongoing, is provided under category B1. However, particularly for pathophysiological and therapeutic research purposes, newly defined entities of (1) meal-induced dyspeptic symptoms (PDS, defined under category B1a), and (2) epigastric pain (EPS, defined under category B1b), should be used operatively.

B1. Diagnostic Criteria* for Functional Dyspepsia

Must include

1. ***One or more*** **of:**
   - **a. Bothersome postprandial fullness**
   - **b. Early satiation**
   - **c. Epigastric pain**
   - **d. Epigastric burning**

   AND
2. **No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms**

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

B1a. Diagnostic Criteria* for Postprandial Distress Syndrome

Must include *one or both* of the following:

1. **Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week**
2. **Early satiation that prevents finishing a regular meal, at least several times per week**

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criteria

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present
2. EPS may coexist

B1b. Diagnostic Criteria* for Epigastric Pain Syndrome

Must include *all* of the following:

1. **Pain or burning localized to the epigastrium of at least moderate severity at least once per week**
2. **The pain is intermittent**
3. **Not generalized or localized to other abdominal or chest regions**
4. **Not relieved by defecation or passage of flatus**
5. **Not fulfilling criteria for gallbladder and sphincter of Oddi disorders**

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criteria

1. The pain may be of a burning quality but without a retrosternal component
2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
3. Postprandial distress syndrome may coexist

Overlap with GERD and IBS. Heartburn, considered an esophageal symptom, as well as dyspepsia are extremely common, and some overlap between both is likely. The Rome II definition proposed to exclude patients with predominant heartburn from the dyspepsia spectrum,[1] but recent studies have shown that the predominant symptom approach does not reliably identify all patients with GERD.[25–28] In general, overlap of GERD with PDS or EPS is probably frequent and needs to be carefully considered in both clinical practice and experimental trials. The committee recommends that the presence of frequent and typical reflux symptoms should lead to a provisional diagnosis of GERD.[29] In clinical practice and for clinical trials, recognition of frequent heartburn may be improved by a simple descriptive questionnaire.[26,27] The presence of heartburn does not exclude a diagnosis of PDS or EPS if dyspepsia persists despite a trial of adequate acid suppression therapy.

Overlap between dyspeptic symptoms and IBS is also commonly observed, and overlap between IBS on one hand and PDS or EPS on the other hand is likely to occur. The presence of IBS does not exclude the diagnosis of any of these functional gastroduodenal disorders because coexisting IBS was found to have a minor impact on symptom pattern and putative pathophysiological mechanisms in FD.[30]

Rationale for Changes in Criteria From Rome II

The rationale for the proposed new classification was based on the inadequacy of prior approaches such as the predominant symptom, the results of factor analysis in tertiary care and in the general population, clinical experience, and new observations in the peer-reviewed literature. Previously, all patients without definite structural or biochemical explanation for dyspeptic symptoms were considered to have functional dyspepsia. The committee agreed that there is a lack of uniform interpretation and acceptance of the term FD at different levels of practice, in different countries and with regulatory authorities. Despite the Rome II recommendations, several recent large studies included heartburn and even acid regurgitation as "typical symptoms of dyspepsia."[25,28,31]

There is also increasing evidence for the existence of different entities within the "dyspepsia symptom complex." There is no single symptom that is present in all patients with FD, and there is considerable variation in the symptom pattern between patients.[32] Factor analysis studies in the general population and in patients with idiopathic dyspeptic symptoms[7,33–40] have failed to support the existence of FD as a homogeneous condition. Pathophysiological studies have provided evidence for heterogeneity of putative underlying pathophysiological mechanisms, and the association of symptoms with mechanisms is better for certain symptoms than for the overall dyspepsia symptom complex.[17–21,32] Moreover, there is evidence for different response to therapy for different subgroups in therapeutic studies in functional dyspepsia.[28,31]

In clinical practice, in the absence of medication approved for functional dyspepsia, therapy is usually directed toward individual symptoms (eg, symptomatic treatment of nausea), rather than the full symptom complex. In many clinical trials, different therapeutic responses for different symptoms seem expected because strategies are used to enrich the patient population for certain symptom profiles.[31,41–43] Based on these limitations, the committee proposes to focus the notion of FD into more distinctively defined disorders.

Factor analysis studies in the general population and in patients with idiopathic dyspeptic symptoms generally conclude that dyspeptic symptoms comprise 3 or 4 different symptom groupings[33–40] (Table 3). By definition, certain symptoms such as early satiation or postprandial fullness are related to the ingestion of a meal. The factor analysis studies have uniformly identified a separate factor of meal-related symptoms.[7,33–40] Systematic studies revealed that symptoms are induced or worsened by meal ingestion in the majority of, but not all, patients with dyspeptic symptoms.[37,44] The committee considers a distinction between meal-induced symptoms and meal-unrelated symptoms to be both pathophysiologically and clinically relevant. Other consistently found symptom groupings include an epigastric pain factor and a nausea factor (with or without vomiting)[33–40] (Table 3). In some studies, belching also appears as a separate symptom group.[34,38]

Clinical Evaluation

The management of the patient with uninvestigated dyspeptic symptoms should not be confused with the approach to the patient whose dyspepsia has been investigated.

Patients With Uninvestigated Dyspeptic Symptoms

Evidence-based analysis[45] suggests the following 6-point management strategy for primary care physicians first seeing patients with dyspepsia:

1. Gather clinical evidence that symptoms most likely arise in the upper gastrointestinal tract.
2. Exclude alarm features (eg, unexplained weight loss, recurrent vomiting, progressive dysphagia, and gas-

Table 3. Factor Analysis Studies of Dyspeptic Symptoms in the General Population and in Tertiary Care Functional Dyspepsia Patients

Study	Setting	Symptom groupings
Westbrook, 2002[55]	Dyspepsia questionnaire in random population sample (n = 2300)	3 dyspeptic symptom factors: an epigastric pain factor, an early satiation/postprandial fullness factor, and a nausea factor. In addition, a heartburn/regurgitation factor
Fischler, 2003[56]	Dyspepsia questionnaire in 438 tertiary care patients with idiopathic dyspeptic symptoms	4 dyspeptic symptom factors: an epigastric pain factor, a postprandial fullness/bloating factor, a nausea/vomiting/satiation factor, and a belching factor
Tack, 2003[57]	Dyspepsia questionnaire in 636 tertiary care patients with idiopathic dyspeptic symptoms	3 dyspeptic symptom factors: an epigastric pain/burning/belching factor, a postprandial fullness/bloating/early satiation factor, and a nausea/vomiting/satiation factor
Jones, 2003[58]	Dyspepsia questionnaire in random population sample (n = 888)	3 dyspeptic symptom factors: an epigastric pain factor, a postprandial fullness/early satiation factor, and a nausea/vomiting factor
Kwan, 2003[59]	Rome II questionnaire in 1012 functional gastrointestinal patients	3 dyspeptic symptom factors: an epigastric pain/discomfort factor, a postprandial fullness/early satiation/bloating factor, and a nausea/vomiting factor
Whitehead, 2003[60]	Rome II questionnaire in 1041 functional gastrointestinal patients	4 dyspeptic symptom factors: 2 epigastric pain factors, a nausea/vomiting/early satiation factor, and an upper abdominal bloating factor
Camilleri, 2005[61]	Telephone survey in random population US sample (n = 21,128)	3 dyspeptic symptom factors: an epigastric pain/bloating/postprandial fullness factor, an early satiation/postprandial fullness/loss of appetite factor, and a nausea factor. In addition, a heartburn/regurgitation factor
Piessevaux, 2005[62]	Face-to-face interview of general population sample (n = 2025)	4 dyspeptic symptom factors: an epigastric pain factor, a postprandial fullness/early satiation factor, a nausea factor, and a belching factor

trointestinal blood loss), which are less common in general practice and which have a low positive predictive value for organic disease when present but which should still prompt investigation to exclude serious disease.[29,46]

3. Exclude ingestion of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs).[47]
4. In the presence of typical reflux symptoms, a provisional diagnosis of GERD should be made.[29] Physicians may initially prescribe proton pump inhibitors (PPIs) empirically in patients who also have heartburn but should take into account that these drugs may be less effective in FD without heartburn.[25,28] If EPS or PDS symptoms persist despite an adequate PPI trial, GERD is an unlikely explanation.
5. Noninvasive testing of *H pylori* infection, followed by eradication ("test and treat") is a cost-effective approach that decreases the number of endoscopies.[48–51] This strategy is indicated for the patient with no alarm features.[52] Test and treat is recommended as this strategy will cure most underlying peptic ulcer disease and prevent future gastroduodenal disease, although many infected patients with functional dyspepsia will not gain symptomatic benefit.[53,54] In those who fail treatment despite Hp eradication, a trial of PPI therapy is a reasonable next step. The yield of this approach is therefore highest in places with a high prevalence of *H pylori*–related peptic ulcer disease. Test and treat effectiveness decreases in case of a low prevalence, which makes false-positive testing more likely.
6. Prompt endoscopy is recommended in patients with alarm symptoms or patients over a threshold age (45–55 years, depending on health care access and incidence of malignant disease). Current evidence indicates that endoscopy first may be more cost-effective in older patients, that Hp testing followed by endoscopy in Hp-positive patients may not be cost-effective, and that many patients with negative *H pylori* tests will still need to undergo endoscopy because of alarm features or age.[55,56]

Patients With Functional Dyspepsia

The available data in the literature are based on functional dyspepsia; no data are available on diagnostic approaches to the categories EPS or PDS as defined by the Rome III committee. Performance of an upper endoscopy during a symptomatic period off acid-suppressant therapy is essential to identify functional dyspepsia appropriately by excluding other important structural diseases. It is recommended that biopsies be routinely obtained at the time of endoscopy to detect *H pylori* infection and, in view of the association of *H pylori* with peptic ulcer disease and dyspepsia, eradication is recommended in all positive cases.[53,54,57]

A barium meal study is less sensitive and specific than upper endoscopy, and hence it is not generally recommended. Ultrasonography is not recommended as a routine clinical test because the yield is low in the absence of symptoms or clinical features or biochemical tests suggestive of biliary tract or pancreatic disease.[58] Barium x-ray study of the small bowel is only useful in case of suspected mechanical obstruction.

A gastric-emptying study (eg, scintigraphy, ^{13}C-octanoic acid, or ultrasonography) is not currently recommended as a routine clinical test because the results uncommonly alter management. Recent studies have shown that less than 25% of patients with FD have delayed gastric emptying, even when considering exclusively the Rome II subgroup of dysmotility-like dyspepsia.[19,24,31] Inconsistent correlations have been shown between symptoms and abnormalities of gastric function assessed by gastric barostat or electrogastrography.[31] None of these tests can be advocated in routine clinical practice.

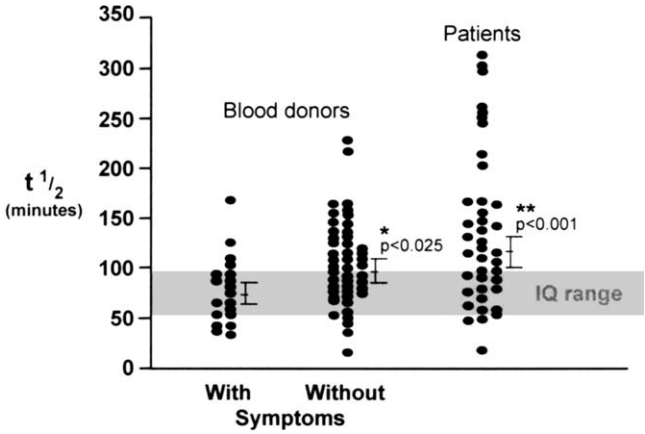

Figure 1. Prevalence of gastric emptying in the community: blood donors without and with dyspepsia, and patients with documented functional dyspepsia. Gastric emptying was significantly slower in healthy blood donors with symptoms versus those without, and was slower in patients with functional dyspepsia compared with healthy asymptomatic blood donors. (Reprinted from Haag et al. Gut 2004; 53:1445–1451).

Physiologic Features

The available data in the literature are based on FD patients as a group; no data are available on the physiological features of the categories EPS or PDS as newly defined by the Rome III committee.

Little is known about the influence of nutrient intake in the etiology of FD.[59] Neither smoking, alcohol, or NSAIDs are considered to be risk factors for FD.[60] However, patients with FD are more likely to develop symptoms when treated with NSAIDs.[61] Basal gastric acid secretion is within normal limits in patients with FD,[62] but acid-related symptoms (perhaps through gastric or duodenal hypersensitivity, see later) may arise in a subgroup of patients.

The role of *H pylori* infection in FD has been controversial, but recent meta-analyses suggest a small benefit from *H pylori* eradication in infected patients. No consistent disturbances of motor or sensory function of the upper gut have been reported in *H pylori*–infected individuals.[32,63]

There are several lines of evidence that gastrointestinal motility is abnormal in a proportion of patients with FD. The contribution of motor abnormalities to symptom generation is incompletely established. Impaired (typically delayed) gastric emptying of solids is the most widely studied motility disorder in dyspepsia.[32] Figure 1 shows that gastric emptying is slower in patients with FD compared with healthy controls. The delay in gastric emptying may be more common among patients with fullness, nausea, and vomiting and in females, but this is controversial.[17–19,32] Several studies show that the accommodation or volume response of the stomach after a meal is reduced in ~40% of patients with functional dyspepsia.[20,32] Other disturbances of upper gut motility are postprandial antral hypomotility,[32,64] reduced frequency of interdigestive migrating motor complexes,[65] impaired duodenal motor responses to acid and nutrient infusion,[66] and excess of phasic contractions of the fundus after the meal.[67] Several studies have documented the presence of gastric dysrhythmias especially in the postprandial period in patients with FD.[33,68]

Evidence of gastric hypersensitivity in a subset of functional dyspepsia is well documented in the literature.[21,32,69] The brain centers involved in sensation of gastric stimuli like distention have been documented in health,[70,71] and full reports of the brain centers involved in functional dyspepsia are awaited. Altered intestinal sensitivity has been observed in response to balloon distention or in response to duodenal acid or lipid infusion.[72–74] A subset of dyspeptic patients has spontaneously increased duodenal acid exposure, and this is associated with higher symptom intensity.[75] The role of altered parasympathetic and sympathetic activity, of altered secretion of gastrointestinal hormones, and of G-protein polymorphisms requires further study.[63,76,77]

Psychological Features

In dyspepsia, there is evidence of an association with psychopathological factors, and comorbidity with psychiatric disorders, especially anxiety disorders, is high.[12,13,32,78,79] It is still unclear whether these psychopathological factors determine health care–seeking behavior, whether they play a key role in the pathophysiology of the dyspepsia symptom complex, or whether they reflect a common predisposition for functional and psychological disorders. Abnormalities of several psychosocial dimensions were found to be associated

with epigastric pain and with hypersensitivity to gastric distention in FD.[34]

Treatment

The available data in the literature apply to FD patients as a group; no data are available on treatment approaches to the categories EPS or PDS as newly defined by the Rome III committee. Evaluation of pharmacotherapy in FD is confounded by high placebo response rates from 20% to 60%.[80] Reassurance and explanation represent the first management step and may be sufficient in many patients. Stopping smoking and ceasing consumption of coffee, alcohol, or NSAIDs is commonly recommended, but there is no convincing evidence of efficacy.[60] Although it seems plausible to recommend taking several small low-fat meals per day, this has not been formally investigated.

Acid suppression is safe and remains first-line therapy in the absence of *H pylori* infection; an adequate trial of therapy should be given and stepped up if unsuccessful initially. Patients with dyspepsia often take antacids, although there is no proof of efficacy.[81] A Cochrane meta-analysis evaluating the efficacy of H_2-receptor antagonists in functional dyspepsia reported a significant benefit over placebo with a number needed to treat of 8.[82] However, these trials were relatively small and heterogeneous and often misclassified reflux disease as functional dyspepsia, which may account for much of the benefit. A meta-analysis of controlled, randomized trials with PPIs in functional dyspepsia reported that this class of agents was superior to placebo with a number needed to treat of 7.[83] Much of this benefit may be explained by unrecognized GERD.[26,31,83] Furthermore, epigastric pain, but not meal-related symptoms, seems to respond to a PPI.[28,31,83] There is no evidence that high-dose PPI therapy is beneficial over standard dosing, but an empiric trial of high-dose PPI in practice may be considered in difficult cases.

A Cochrane meta-analysis reported an 8% pooled relative-risk reduction with eradication of *H pylori* compared with placebo at 12 months of follow-up.[53] The number needed to treat was calculated to be 17. Because *H pylori* eradication can induce sustained remission in a small minority of patients, this should be routinely considered once the benefit and risks have been carefully discussed with the patient.

Gastroprokinetic drugs like metoclopramide, domperidone, and cisapride appear efficacious in functional dyspepsia compared with placebo but have been poorly studied.[82,84] Publication bias may also account in part for some of the positive meta-analyses in the literature.[82] Cisapride has been withdrawn from most markets in the world because of rare fatal arrhythmias. The macrolide antibiotic erythromycin acts on the motilin receptor to increase gastric emptying rate in patients with diabetic and idiopathic gastroparesis,[85,86] but its side effects and tachyphylaxis limit its clinical utility. ABT-229, a synthetic motilin-like prokinetic drug without antibacterial activity, was of no significant benefit in functional dyspepsia over placebo, possibly because the drug impairs fundic relaxation.[41] Several other approaches to FD, including fundus-relaxing drugs, new prokinetics, selective serotonin reuptake inhibitors, and visceral analgesic drugs are currently under investigation.[87–89]

The value of antidepressants in FD is not established. In 1 crossover trial of 7 patients, amitryptiline in low doses improved symptoms but not visceral hypersensitivity or sleep.[90] Limited promising data are available on psychotherapy or hypnotherapy,[91,92] but more studies are needed.

B2. Belching Disorders

Air swallowing during eating and drinking is a normal physiological event and so is venting of the ingested air during transient relaxations of the lower esophageal sphincter.[93] Hence, belching can only be considered a disorder when it becomes troublesome. The committee distinguishes aerophagia from unspecified excessive belching.

B2a. Diagnostic Criteria* for Aerophagia

Must include *all* of the following:

1. **Troublesome repetitive belching at least several times a week**
2. **Air swallowing that is objectively observed or measured**

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

B2b. Diagnostic Criteria* for Unspecified Excessive Belching

Must include *all* of the following:

1. **Troublesome repetitive belching at least several times a week**
2. **No evidence that excessive air swallowing underlies the symptom**

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

Justification for Changes to the Criteria

In the previous Rome II classification, aerophagia was described as an unusual disorder with excessive belching due to air swallowing. The committee decided

to expand the category based on consensus that excessive belching is a presenting symptom and based on recent evidence, obtained with intraluminal impedance measurement of air transport in the esophagus,[93] which confirms that different mechanisms of excessive belching occur.[94] Belching is usually an unconscious act, and the motility patterns of belching are quite similar to those found in gastroesophageal reflux.[93] A recent study performed by using intraluminal impedance measurement in aerophagia patients revealed swallowing of air that enters the esophagus very rapidly and is expulsed almost immediately in the oral direction.[94] This phenomenon of "supragastric belching," clearly distinct from "gastric" belching, is not accompanied by transient relaxation of the lower esophageal sphincter and is only observed in aerophagia.[94]

Clinical Evaluation

A positive diagnosis is based on a careful history and observation of air swallowing. In typical cases, no investigation is required. Excessive belching may also accompany GERD, and in difficult cases, pH monitoring or empirical acid suppressive therapy may be considered.[95] Belching is also often reported in dyspepsia in which it does not respond to acid suppressive therapy.[95] In FD, belching is associated with hypersensitivity to gastric distention,[21,32,34] which supports the concept that belching is induced to relieve upper abdominal discomfort. Rumination can usually be distinguished by the history and observation. It may be important to screen for psychiatric disease, but there is no evidence of excess psychopathology in aerophagia or in functional dyspepsia with symptoms of belching.[34]

Treatment

Explanation of the symptoms and reassurance are important. The habit can sometimes be inhibited by showing 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 often recommended but has not been rigorously tested. Behavioral therapy seems helpful in some cases, but clinical trials are lacking. Studies investigating drug therapy specifically in aerophagia are also lacking.

B3. Nausea and Vomiting Disorders

Definition

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 gastric or intestinal content associated with contraction of the abdominal and chest wall muscles. Vomiting must be distinguished from regurgitation and rumination.

B3a. Diagnostic Criteria* for Chronic Idiopathic Nausea

Must include *all* of the following:

1. **Bothersome nausea, occurring at least several times per week**
2. **Not usually associated with vomiting**
3. **Absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea**

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

B3b. Diagnostic Criteria* for Functional Vomiting

Must include *all* of the following:

1. **On average, 1 or more episodes of vomiting per week**
2. **Absence of criteria for an eating disorder, rumination, or major psychiatric disease according to DSM-IV**
3. **Absence of self-induced vomiting and chronic cannabinoid use and absence of abnormalities in the central nervous system or metabolic diseases to explain the recurrent vomiting**

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

B3c. Diagnostic Criteria* for Cyclic Vomiting Syndrome

Must include *all* of the following:

1. **Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)**
2. **Three or more discrete episodes in the prior year**
3. **Absence of nausea and vomiting between episodes**

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criterion

History or family history of migraine headaches.

Rationale for changes in criteria. After review of the available literature, a new category, CIN was added.

In the Rome II criteria, nausea was considered a symptom of motility-like dyspepsia,[1] but the committee decided to revise this on the basis of factor analysis data, on clinical experience that persistent nausea is often of central or psychological origin, and on the lack of responsiveness of this symptom to empiric therapy.

The committee slightly modified the previous definition of functional vomiting based on the setting of threshold frequencies and on the recognition of cannabinoid use as a mechanism. A new category, cyclical vomiting in adults, was added based on expert opinion and a better appreciation that those with stereotypical attacks of cyclical vomiting differ from those with functional vomiting.

Clinical Features

Nausea is a common symptom, and the differential diagnosis is wide. The committee recognized a group of patients exist who have frequent unexplained nausea with little or no vomiting. The mechanisms remain unknown.

In children, the syndrome of cyclical vomiting is well described (See "Childhood Functional Gastrointestinal Disorders: Neonate/Toddler" on page 1519 in this issue). Although it is rare, adults may develop cyclical vomiting in middle age, and both men and women are affected.[96,97] Only 1 in 4 adults had a history of migraine headaches. Adults have a mean of 4 cycles of vomiting per year, with a mean duration of 6 days (range, 1–21) and an average symptom-free interval of 3 months (range, 0.5–6).[96,97]

The mechanisms underlying functional and cyclic vomiting remain unknown. Major depression has been linked to habitual postprandial and irregular vomiting, whereas conversion disorder may explain some cases of continuous vomiting.[98] In cyclical vomiting in adults, psychiatric disease appears to be uncommon, with the largest adult series suggesting only 20% having anxiety or another psychiatric disorder.[98]

Clinical Evaluation

The differential diagnosis of recurrent nausea or vomiting is extensive. Many drugs, including cannabinoid use, may cause nausea and vomiting.[99,100] In patients with a history of "vomiting," rumination and eating disorders need to be excluded by careful clinical evaluation.

It is particularly important to exclude intestinal obstruction, gastroparesis, and intestinal pseudo-obstruction as well metabolic and central nervous system disease (eg, brainstem lesions on magnetic resonance imaging) in adults presenting with recurrent unexplained vomiting.[99] An upper endoscopy and a small bowel x-ray or computed tomography enterography are performed to exclude gastroduodenal disease and small bowel obstruction. Biochemical testing is also essential to exclude electrolyte abnormalities, hypercalcemia, hypothyroidism, and Addison's disease. If these tests are normal, then it is reasonable to consider gastric-emptying evaluation or gastrointestinal manometry. The use of electrogastography is not widely accepted, although gastric dysrhythmias may be recorded in some patients with unexplained nausea and vomiting with normal gastric emptying.[101]

Treatment

The treatment of chronic idiopathic nausea is not defined. Antinausea drugs provide limited benefit empirically. Commonly used antinauseants like prochlorperazine, diphenhydrinate, and cyclizine promethazine have not been systematically studied in unexplained nausea and have many side effects. Modest symptom improvement has been shown with the 5-hydroxytryptamine$_3$ antagonists ondansetron and alosetron over placebo in functional dyspepsia, but nausea has not been specifically studied.[42,89] Low-dose tricyclic antidepressant therapy may be helpful anecdotally.

In functional vomiting, management of nutritional status and psychosocial support is important. The role of dietary and pharmacological therapy, both frequently used, has not been specifically tested. There is also no evidence that medications are particularly useful in this group, although anecdotal reports suggest that tricyclic antidepressants are helpful.[97,100] Antiemetic drugs can be tried but are often of little value. Data are lacking on the value of behavioral or psychotherapy.

Patients with cyclical vomiting syndrome may require hospital admission and supportive care during severe bouts. Empiric treatments of antimigraine medications have been used with anecdotal reports of success, and a trial of antimigraine medications is worthwhile, especially when there is a family history of migraine headaches. There are anecdotal reports on the use of beta-blockers, tricyclic antidepressants, cyproheptadine, ketorolac, and several others.[96,97,102]

B4. Rumination Syndrome

Rumination syndrome is a condition characterized by the repetitive, effortless regurgitation of recently ingested food into the mouth followed by rechewing and reswallowing or expulsion.[103] Although initially described in infants and the developmentally disabled (reference to pediatric chapter), it is now widely recognized that rumination syndrome occurs in males and females of all ages and cognitive abilities.[103,104] In general, rumination is more common in females than males.

Epidemiology

The epidemiology of rumination syndrome in the adult general population remains to be carefully defined, but clinical impression suggests it is rare.

B4. Diagnostic Criteria* for Rumination Syndrome

Must include *both* 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**

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criteria

1. Regurgitation events are usually not preceded by nausea
2. Cessation of the process when the regurgitated material becomes acidic
3. Regurgitant contains recognizable food with a pleasant taste

Clinical Evaluation

Rumination syndrome is a probably underappreciated condition in adults who are often misdiagnosed as having vomiting secondary to gastroparesis or gastroesophageal reflux or anorexia or bulimia nervosa. Clinical experience suggests that many individuals with rumination have additional symptoms including nausea, heartburn, abdominal discomfort, diarrhea, and/or constipation. Weight loss can also be a prominent feature of rumination syndrome, particularly in the adolescent population.[103,104] Typical clinical features include the following:

1. Repetitive regurgitation of gastric contents beginning within minutes of the start of a meal; this is to be contrasted with the typical history of vomiting in the later postprandial period in patients with gastroparesis.
2. Episodes often last 1–2 hours.
3. The regurgitant consists of partially recognizable food, which often has a pleasant taste according to the patients.
4. The regurgitation is effortless or preceded by a sensation of belching immediately before the regurgitation or arrival of food in the pharynx.
5. Regurgitation may be preceded by brisk voluntary contraction of the abdominis rectus.
6. There is usually lack of retching or nausea preceding the regurgitation.
7. Patients make a conscious decision regarding the regurgitant once it is present in the oropharynx. The choice may depend on the social situation at the time. Rumination is typically a "meal-in, meal-out, day-in, day-out" behavior.

An association between rumination and bulimia nervosa has been described,[105] although bulimic patients tend to expel rather than reswallow food and may self-induce vomiting. Pathophysiological mechanisms involved in rumination syndrome remain somewhat unclear, although all observations suggest some adaptation of the belch reflex that overcomes the resistance to retrograde flow provided by the lower esophageal sphincter.[105,106] Many patients have evidence of "pathological gastroesophageal reflux" because pH monitoring shows $>4\%$ time with intraesophageal pH below 4. However, careful study shows that this is typically in the first hour after a meal and that the time that esophageal pH is <4 may be paradoxically low because food buffers the gastric acid during the postprandial period when repetitive regurgitation occurs.

Treatment

Reassurance, explanation, and behavioral therapy are currently the mainstays of treatment in adolescents and adults of normal intelligence with rumination syndrome. PPIs are frequently used to suppress heartburn and to protect the esophageal mucosa while therapy is instituted. The preferred behavioral treatment for rumination syndrome consists of habit reversal by using diaphragmatic breathing techniques to compete with the urge to regurgitate.[107] Treatment of rumination in bulimics has been reported to be less successful.

Future Research

Rome III Definitions for Gastroduodenal Disorders

The relationship of the newly defined disorders (PDS, EPS, CIN, and CVS) to each other, to pathophysiological mechanisms, and to response to therapy needs to be assessed. The epidemiology of these disorders will also need to be studied carefully.

Mechanisms of Symptom Production

The goal should be that the field moves to therapy based on identified mechanisms. This requires more ex-

tensive understanding of the physiological mechanisms causing symptoms.

Diagnostic Issues

There is a great need for validated noninvasive diagnostic methods to help the clinician evaluate the etiology of symptoms and to target appropriate treatment. The pros and cons of the nutrient drink test need to be more thoroughly understood.

Therapeutic Issues

There is a need for further development of validated endpoints that may serve as biomarkers in the development of novel treatment approaches. Medications affecting the putative pathophysiological mechanisms require further development. Combination therapies need to be tested, to either enhance correction of underlying single pathophysiology, or to correct more than one pathophysiology. The peripheral and central effects of selective serotonin reuptake inhibitor, tricyclic antidepressants, and selective noradrenaline reuptake inhibitors in health and dyspepsia require thorough characterization. Appropriate pharmacoeconomic studies are also needed to test the true value of available and future therapies.

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Received January 31, 2005. Accepted November 3, 2005.

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