STATE-OF-THE-ART REVIEW

Functional gastroduodenal disorders

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Abstract

Functional gastroduodenal disorders are chronic, heterogeneous conditions experienced by adults worldwide. The Rome III consensus recognizes four syndromes: functional dyspepsia, belching disorders, nausea and vomiting disorders and ruminating syndrome. Considerable advances have occurred in the field of functional gastroduodenal disorders. This review provides an overview of the definitions, epidemiology, clinical features, investigations and treatments of some of these disorders. Functional dyspepsia is divided into post-prandial distress syndrome (PDS) and epigastric pain syndrome (EPS). The prevalence of functional dyspepsia is about 11–20% in the western world. Dysfunctional gastrointestinal motility and hypersensitivity are involved in the generation of symptoms in some patients. Several classes of drugs are used to treat patients with functional dyspepsia, and the increasing understanding of pathophysiology will greatly affect future treatment regimens. Belching disorders may have either a behavioural or a physiological background, and therefore behavioural and speech therapies show promise, but definitive studies are required. The effect of fundoplication and drugs, such as a selective gamma-aminobutyric acid agonist baclofen, on belching await confirmatory studies on their usefulness. Mechanisms of functional nausea and vomiting are poorly understood, and their treatment currently focuses on pharmacological and non-pharmacological therapies, including antidepressants and psychological approaches.

Introduction

Functional gastroduodenal disorders in adults are a heterogeneous group of conditions that occur worldwide. They are responsible for significant reduction in quality of life in sufferers and impose a substantial economic burden on society and health care systems. The Rome III committee has classified four syndromes: functional dyspepsia, belching disorders, nausea and vomiting disorders and the ruminating syndrome, which all relate to the gastroduodenum and are chronic disorders. Functional dyspepsia occurs with no underlying cause that explains the dyspeptic symptoms experienced, hence it is a diagnosis of exclusion. Belching is a normal event related to swallowing. It can become problematic when it persists for long periods or recurs frequently, and it is then characterized as a belching disorder. Nausea and vomiting occur with many medical conditions, but occur less often in the absence of any identifiable cause, when it is described as a ‘functional’ nausea and vomiting disorder. Rumination is the regurgitation of food to the mouth, rechewing and swallowing or expelling. It is a rare and poorly studied syndrome and is not discussed further in this review.

Almost a decade has passed since Rome III updated the definition of functional gastroduodenal disorders. During this time, improvements have occurred in the understanding of epidemiology, pathophysiology and treatment of such disorders, although much work is still to be done. We present an updated review of functional dyspepsia, belching disorders, and nausea and vomiting disorders.

Functional dyspepsia

Definition

Functional dyspepsia (Table 1) refers to chronic epigastric symptoms that remain unexplained after standard investigations have been reported
as normal. Chronicity in this case refers to a period of at least 6 months with recurrent symptoms.

Rome III defines functional dyspepsia on the basis of four main symptoms: post-prandial fullness, early satiation, epigastric pain and burning. Factor analysis studies, clinical experience and research have suggested that these symptoms could be grouped into two distinguishable but overlapping syndromes: post-prandial distress syndrome (PDS), encompassing post-prandial fullness and early satiation symptoms, and epigastric pain syndrome (EPS), with symptoms of epigastric pain and burning.

There have been changes to the definition of functional dyspepsia proposed by the Rome III committee compared with previous definitions. Key symptoms were reduced from eight to four and discomfort was excluded from the definition. These changes aimed to increase the specificity of the criteria in identifying gastroduodenal symptoms.

Despite changes to the definition, it is argued that the Rome III criteria are not superior to previous definitions in identifying functional dyspepsia. Moreover, the exclusion of heartburn from the definition did not successfully reduce the cases of oesophagitis being identified during upper gastrointestinal endoscopy, suggesting that the new criteria are not effective in discriminating organic from functional causes of dyspepsia.

Considering the prevalent overlap between gastro-oesophageal reflux disease (GORD) and dyspepsia, it is a criticism that the separation of heartburn (one of the symptoms of GORD) and functional dyspepsia is artificial and might not be possible. However, the Rome committee excludes heartburn from the definition of functional dyspepsia because it is not a symptom of the gastroduodenum.

**Epidemiology**

Epidemiological studies do not always investigate patients with a definite diagnosis of functional dyspepsia. Patients presenting with dyspeptic symptoms that have not been thoroughly examined (and undergone upper endoscopy) are said to have uninvestigated dyspepsia. Therefore, uninvestigated dyspepsia includes patients with organic and functional dyspepsia. However, since the majority of patients with dyspepsia have no endoscopic findings, this broader classification provides a rough estimation of functional dyspepsia epidemiology.

Functional dyspepsia and its subdivisions EPS and PDS seem to have a heterogeneous distribution around the world. The prevalence of functional dyspepsia in the western world ranges from 11% to 20%. The annual global incidence rate is estimated to be between 1% and 6% and seems to be

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Diagnostic criteria for functional dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1. Diagnostic criteria* for functional dyspepsia</td>
<td>Must include:</td>
</tr>
<tr>
<td>1. <strong>One or more</strong> of the following:</td>
<td>■ Bothersome post-prandial fullness</td>
</tr>
<tr>
<td>■ Early satiation</td>
<td>■ Epigastric pain</td>
</tr>
<tr>
<td>■ Epigastric burning</td>
<td>AND</td>
</tr>
<tr>
<td>2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms</td>
<td></td>
</tr>
<tr>
<td><em><em>B1a. Diagnostic criteria</em> for post-prandial distress syndrome</em>*</td>
<td>Must include <strong>one or both</strong> of the following:</td>
</tr>
<tr>
<td>■ Bothersome post-prandial fullness, occurring after ordinary-sized meals, at least several times per week</td>
<td>■ Early satiation that prevents finishing a regular meal, at least several times per week</td>
</tr>
<tr>
<td><strong>Supportive criteria:</strong></td>
<td></td>
</tr>
<tr>
<td>■ Upper abdominal bloating or postprandial nausea or excessive belching can be present</td>
<td>■ Epigastric pain syndrome may coexist</td>
</tr>
<tr>
<td><em><em>B1b. Diagnostic criteria</em> for epigastric pain syndrome</em>*</td>
<td>Must include <strong>all</strong> of the following:</td>
</tr>
<tr>
<td>■ Pain or burning localized to the epigastrium of at least moderate severity, at least once per week</td>
<td>■ The pain is intermittent</td>
</tr>
<tr>
<td>■ Not generalized or localized to other abdominal or chest regions</td>
<td>■ Not relieved by defecation or passage of flatus</td>
</tr>
<tr>
<td>■ Not fulfilling criteria for gallbladder and sphincter of Oddi disorders</td>
<td><strong>Supportive criteria:</strong></td>
</tr>
<tr>
<td>■ The pain may be of a burning quality, but without a retrosternal component</td>
<td>■ The pain is commonly induced or relieved by ingestion of a meal, but may occur while fasting</td>
</tr>
<tr>
<td>■ Post-prandial distress syndrome may coexist</td>
<td></td>
</tr>
</tbody>
</table>

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

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balanced by the number of patients who stop experiencing symptoms each year, contributing to a relatively stable prevalence over the years.\textsuperscript{2}

A study evaluated the population of two Italian villages and found that 15\% had dyspepsia, while 11\% had functional dyspepsia because there were no endoscopic findings to explain the symptoms. Of those with functional dyspepsia, 67\% had PDS, 48\% had EPS and 16\% had both. The overlap between the two subtypes of functional dyspepsia was smaller than expected by chance, hence is consistent with the division proposed by the Rome III criteria. Unemployment, divorce, smoking and irritable bowel syndrome were linked with functional dyspepsia.\textsuperscript{7}

Another study on the Chinese population concluded that a younger age (mean 44 years), use of non-steroidal anti-inflammatory drugs (NSAIDs), anxiety and irritable bowel syndrome are risk factors for functional dyspepsia. Other factors were linked to PDS alone but not with EPS, consistent with the division of EPS and PDS proposed by the Rome committee.\textsuperscript{9}

While most epidemiological data gathered via questionnaires in the United States of America and Europe have found a distinct separation between PDS and EPS, there are some studies that have reported a significant overlap between these syndromes.\textsuperscript{5} The reasons for such discrepancies are likely to be related to patient selection and methods used, but it is reasonable to consider that, overall, the evidence points towards the division of functional dyspepsia as proposed by the Rome III criteria.

**Clinical features**

**Symptoms**

The dyspepsia symptom complex involves more symptoms than the four key symptoms of functional dyspepsia as defined by the Rome III committee.\textsuperscript{10} Studies in tertiary care settings have addressed their prevalence. The most frequent symptom is post-prandial fullness, followed by upper abdominal bloating, epigastric pain and early satiation. Less often, patients also experience belching, epigastric burning, nausea and vomiting.\textsuperscript{5}

Patients may have difficulty in understanding and identifying dyspeptic symptoms. For this reason, new strategies for assessing dyspeptic patients are being evaluated, such as the use of pictograms. These pictograms are a symbolic representation of the symptoms using pictures and short descriptions and their ease of understanding has been beneficial for clinical evaluation of dyspepsia.\textsuperscript{11}

**Pathophysiology**

Understanding of the underlying causes of functional dyspepsia as a whole or of its sub classifications PDS and EPS is a developing area. There is evidence that dysfunctional gastrointestinal motility (delayed gastric emptying, impaired fundal accommodation) and gastric hypersensitivity play roles in different subsets of patients with functional dyspepsia.\textsuperscript{2,12} Some pathophysiological findings seem to support the different natures of PDS and EPS, as impaired gastric accommodation and raised duodenal eosinophil count have been linked to PDS rather than EPS.\textsuperscript{5}

In terms of correlation with symptoms, the stomach seems to participate more in symptoms of post-prandial fullness, bloating and belching, since these symptoms ameliorate when food is emptied from the stomach.\textsuperscript{13} The involvement of the small intestine in the generation of symptoms in dyspeptic patients has gained strength lately because of findings of increased duodenal sensitivity to lipids and acid and of low-grade duodenal inflammation.\textsuperscript{14} Hence, it is speculated that the small intestine is involved in pain-related sensations. The prevalent uncertainties regarding the pathophysiology of functional dyspepsia have a direct impact on limiting the development of effective therapies. More research on this topic will bring clear benefits to the dyspeptic population.

**Investigation**

It is essential that patients who present to health care with uninvestigated dyspeptic symptoms receive clinical confirmation that the symptoms are indeed located in the upper gastrointestinal tract.\textsuperscript{2} Establishing the onset of symptoms is also crucial, since functional dyspepsia is a chronic, recurring disease. Alarm features for malignancy (such as dysphagia, significant weight loss) must be investigated following a thorough medical history and physical examination.\textsuperscript{15,16} If an alarm feature is present,\textsuperscript{2} endoscopy should be performed. Recent studies, however, have found that alarm symptoms do not predict gastric and oesophageal cancer appropriately. Hence, there is the suggestion that thresholds for further investigations should be lower.\textsuperscript{10}
Since peptic ulcer disease and GORD are the most common causes of organic dyspepsia, it is reasonable to determine the use of NSAIDs, the presence of infection by Helicobacter pylori and reflux symptoms. H. pylori infection assessment is usually performed through non-invasive methods and usually leads to a ‘test-and-treat’ strategy if results are positive. This strategy is effective in areas where H. pylori infection is prevalent.

Functional dyspepsia is a diagnosis of exclusion, and thus can be confirmed only after negative endoscopic findings. However, indication of endoscopy is a debatable topic. Although upper endoscopy sheds light on diagnosis (either organic or functional), evidence that endoscopic findings are present in only up to one-third of dyspeptic patients is in accordance with some international guidelines that reserve this procedure for patients with alarm features.

**Treatment**

Establishing an effective treatment for functional dyspepsia is a difficult task, considering the current gaps in its pathophysiology. In order to increase therapeutic success, the treatment of functional dyspepsia should be individualized, be directed to the patient’s complaints and take side-effects into account.

An explanation of the condition, as well as of the therapeutic options, is crucial in functional dyspepsia. General measures such as avoidance of identified triggers, smoking cessation and discontinuation of NSAIDs should be implemented, and may be sufficient for relieving symptoms. As an alternative or in addition to a drug-based therapy, psychotherapeutic options have shown positive results in treating dyspeptic patients. The most successful psychological approaches to functional dyspepsia are cognitive–behavioural therapy, which has been shown to improve dyspeptic symptoms, and hypnotherapy, which has reduced the need for medication and consultations.

Non-invasive investigation and treatment of H. pylori infection is encouraged in areas of high prevalence, as described above. Further therapies include:

- Empirical treatment with a proton-pump inhibitor (PPI) can relieve symptoms in up to one-third of patients with functional dyspepsia and is present in primary care guidelines for managing dyspepsia.

- The use of prokinetics may be effective in a subset of patients, mostly in those with PDS symptoms.

- Switching between PPI and prokinetics, as well as a combining therapy, may be attempted in order to alleviate symptoms.

- Tricyclic antidepressants are an option for patients who fail to respond to antisecretory therapy or H. pylori eradication.

Novel drugs are under evaluation for functional dyspepsia. Acotiamide (Acofide®, Zeria Pharmaceutical Co. Ltd, Saitama, Japan), an acetylcholine enhancer, is already in use in Japan. Preliminary findings show a benefit for patients belonging to the PDS subgroup of functional dyspepsia. Despite optimistic results, there is urgent need for more successful therapies that can improve the quality of life of patients with functional dyspepsia as a whole.

**Belching disorders**

**Definition**

Belching is defined as an oral expulsion of a gas bolus from the upper gastrointestinal tract. Whenever eating or drinking, an amount of air will be swallowed. Belching is a normal physiological event that occurs from time to time, and post-prandial venting is normal within a frequency of three to four belches per hour. However, some people experience excessive belching, which can be troublesome for themselves and their surroundings.

Generally, there are two types of belching:

- Gastric belching, which occurs when the accumulation of swallowed air in the stomach triggers a response mediated by the vagal nerve, called transient lower oesophageal sphincter relaxation (TLOSR). This vagovagal reflex is initiated by a distension of the proximal stomach.

- Supragastric belching, when the swallowed air almost never reaches the stomach. It is seen as a behavioural peculiarity, as the rate at which supragastric belching occurs is influenced by attention and distraction. In supragastric belching, two mechanisms are used: air is sucked in and creates a negative intrathoracic pressure (air sucking) or an increase of pharyngeal pressure (air pushing) occurs, before the influx of air. Supragastric belching can be divided into subgroups: aerophagia and unspecified excessive belching.
Aerophagia is a psychological condition in which the patient experiences belching because of swallowing excessive amounts of air. The process involves expanding the thorax and lowering the diaphragm against a closed glottis. Often the belch is audible. Patients with aerophagia can belch up to 20 times per minute. People who belch excessively will in most cases suffer from supragastric belches. Supragastric belching can elicit regurgitation in patients suffering from rumination syndrome, as well as inducing reflux. Excessive belching is divided into different subgroups depending on the aetiology of the belching (Table 2).

**Epidemiology**
The prevalence of excessive belching remains unknown. However, differences in ethnic distribution have been described, hence the variation in prevalence between an Asian and a western population. Only 1% of the Asian population met the Rome II criteria, compared with 6% of the western population.

There is a high prevalence of comorbid anxiety disorders in patients with excessive belching, and symptoms are reported to increase during stressful events. Furthermore, excessive belching is described in patients with obsessive–compulsive disorder and bulimia nervosa. It is also described in conditions causing abdominal discomfort such as peptic ulcer, pancreatitis, angina pectoris and cholecystolithiasis. Up to 70% of patients with GORD report belching, and troublesome belching is reported in 40–49% of the patients with GORD.

**Clinical features**

**Symptoms**

Excessive belching has been shown to impair quality of life for patients. The greatest burden on quality of life in patients with excessive belching is the effect on areas such as social functioning, mental health, vitality, bodily pain and general health. In patients suffering from excessive belching, the most severe symptoms reported are epigastric fullness and discomfort. A per-patient analysis has revealed that belches that coincide with liquid reflux events are even more symptomatic than isolated belches. In addition, it is reported that symptoms of regurgitation and heartburn are more severe in patients with severe belching.

**Investigation**

When examining patients, a variety of methods can be used to achieve the correct diagnosis. Initially, a thorough patient history is taken and an objective examination performed. Different tests can be performed:

- **Intraluminal impedance monitoring** is used to detect air in the oesophagus and to differentiate gas and liquid reflux. Impedance monitoring can support the diagnosis of aerophagia and, when suspected, it is considered the gold standard for diagnosis.

- **Manometry** is used to measure motility in the oesophagus as well as measuring the pressure in the lower oesophageal sphincter (LOS), and can detect episodes of transient LOS relaxation events.

- **pH monitoring** can be performed in addition to manometry to measure the pH of the refluxate and to help determine if belching is associated with GORD.

- **Questionnaires (symptom markers)** are used to count frequency and evaluate severity of the belches.

- **Radiography** can detect air in the intestine.

Patients with aerophagia can be mistakenly thought to suffer from ileus because of accumulation of air in the small intestine, and it is important to note that these patients should not undergo laparotomy.

Intraluminal impedance monitoring is a method to detect air passage in the oesophagus, in the antegrade and retrograde directions. This method

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**TABLE 2** Diagnostic criteria for belching disorders

<table>
<thead>
<tr>
<th>B2. Belching disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>B2a. Diagnostic criteria</em> for aerophagia</em>* Must include all of the following:</td>
</tr>
<tr>
<td>- Troublesome repetitive belching at least several times a week</td>
</tr>
<tr>
<td>- Air swallowing that is objectively observed or measured</td>
</tr>
<tr>
<td><em><em>B2b. Diagnostic criteria</em> for unspecified excessive belching</em>* Must include all of the following:</td>
</tr>
<tr>
<td>- Troublesome repetitive belching at least several times a week</td>
</tr>
<tr>
<td>- No evidence that excessive air swallowing underlies the symptom</td>
</tr>
</tbody>
</table>

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

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makes it possible to identify air swallows and belches during the same period, and can characterize the belch by distinguishing between supragastric and gastric belches. Using impedance measurements, a supragastric belch is defined as an increase in impedance (equal to or over 1000 ohms) moving in an antegrade direction followed by a return to baseline, and then the increase in impedance moves from distal to proximal impedance recording channels. Supragastric belches are related to reflux when a supragastric belch occurs immediately or <1 second following the onset of reflux or during the reflux episode when it occurs approximately 10 seconds after the start of the episode. This method can also differentiate between liquid- and gas-related reflux.

**Treatment**
The treatment must be specialized in accordance with the type of belch. The following types of treatment have been acknowledged:

- **Speech therapy** has been investigated as a treatment for supragastric belching. Hemmink *et al.* found that 6 out of 11 patients in the study benefited greatly from speech therapy and that four patients had modest improvements. Only one patient was reported to experience an increase in symptoms. This supports the hypothesis that speech therapy is beneficial in well-motivated patients with excessive supragastric belching. The study has its limitations because of a small sample size and a significant dropout from the speech therapy, which was caused by travel time, etc. Speech therapy focuses on awareness and regaining control of supragastric belching and normalizing breathing patterns.

- **Behavioural therapy** has also been suggested as an optional beneficial treatment. The therapy focuses on making patients aware of the behaviour and furthermore explains how the behaviour affects the mechanism of excessive belching. The mechanism of excessive belching occurs by closing the glottis at rest (non-speech), accompanied by tight closing of the mouth. When this mechanism is understood, the patients are trained in refraining from it and achieve normal fluent breathing. Behavioural therapy has been shown to reduce the symptoms of excessive belching if the belching is an isolated symptom.

- **Laparoscopic Nissen fundoplication (LNF)** is an option to treat GORD, but has an effect on belching as well. Broeders *et al.* aimed to investigate the effect of LNF on weakly acidic reflux, gastric and supragastric belching. They found that the number of gastric belches was significantly reduced. Another study by Broeders *et al.* compared the effects of a 270-degree laparoscopic posterior fundoplication and 360-degree LNF. They found that a LNF will cause a greater reduction in gastric belching, but patients can experience increased bloating and flatulence. There was less bloating and flatulence after the laparoscopic posterior fundoplication than after the LNF. In addition, the reduction in gastric belching was substituted by an increase in supragastric belches. In some patients LNF led to an increase in the frequency of supragastric belches, in an attempt to vent air from the stomach. Before surgery, the majority of supragastric belches were not reflux associated and these doubled after LNF. By contrast, post-LNF reflux-associated supragastric belches were abolished.

- **Baclofen**, a selective gamma-aminobutyric acid agonist (GABA-B), has been shown to increase the LOS pressure and thereby reduce TLOSRs. GABA-B receptors are expressed in neurons of the motor nucleus of the vagal nerve and nucleus tractus solitarius. GABA-B receptors play a central role in TLOSRs. The peripheral activation of GABA-B receptors inhibit distension-related TLOSRs. TLOSRs are seen as a major cause of gastric belches and are therefore an interesting target. Cossentino *et al.* showed that patients receiving baclofen had significantly less belching (*p* = 0.038). Multiple studies have shown that baclofen increases LOS pressure and reduces the number of TLOSRs. This strengthens the results concerning the effect of this drug. Moreover, it is said that baclofen affects the primary vagal afferents by reducing the mechanosensitivity of the proximal stomach after gastric distension, which may also help reduce induction of TLOSRs. It is also found that baclofen reduces swallow frequency, which may be useful in patients with supragastric belching and especially aerophagia. To evaluate the usefulness of treatment with baclofen in patients with aerophagia, additional studies must be performed.
correlate with a reduction in flow events. This suggests that there must be other mechanisms responsible for improvements in belching beside Baclofen. This study by Blondeau et al. has its limitations: lack of blinding, possible recruitment bias and difficulties in differentiating symptoms of belching and rumination in the patients studied.

**Nausea and vomiting disorders**

**Definition**

Nausea and vomiting are common symptoms. Nausea is, at best, considered an unpleasant, painless and subjective feeling of wanting to vomit. It is a common symptom and the differential diagnoses are numerous (Table 3). Nausea may be caused by both organic and functional disease. The diagnosis of functional nausea relies on ruling out any organic disease, hence screening for gastrointestinal, metabolic and other systemic diseases is required before the diagnosis can be made (Table 1).

Vomiting, on the other hand, is a forceful oral expulsion of gastric or intestinal contents, secondary to a series of motor and autonomic responses leading to contraction of the abdominal and chest wall muscles. It is key to distinguish vomiting from rumination and regurgitation. In regurgitation the food is brought back into the mouth without nausea, abdominal and chest muscle contraction. In rumination syndrome the food is voluntarily regurgitated repeatedly. The food tastes like it has not been eaten. Rumination often occurs within minutes of a meal and is almost always repetitive.

**TABLE 3** Differential diagnosis of nausea and vomiting (modified from Anderson and Strayer)

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Adhesion</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Oesophageal motility disorders</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>Incarcerated hernia</td>
</tr>
<tr>
<td>Gastritis</td>
<td>Intestinal obstruction</td>
</tr>
<tr>
<td>GORD</td>
<td>Mesenteric ischaemia</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Peritonitis</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>Cerebrovascular event</td>
</tr>
<tr>
<td>Motion sickness</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Benign positional vertigo</td>
<td>Ménière disease</td>
</tr>
<tr>
<td></td>
<td>Closed head injury</td>
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<tr>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Pseudotumour cerebri</td>
</tr>
<tr>
<td></td>
<td>Seizure disorder</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Parathyroid disorders</td>
</tr>
<tr>
<td>Uraemia</td>
<td>Adrenal disorders</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Thyroid disorders</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>Brain abscess</td>
</tr>
<tr>
<td>Foodborne illness</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Bacterial gastroenteritis</td>
<td>Pneumonia</td>
</tr>
<tr>
<td><strong>Medications and toxins</strong></td>
<td></td>
</tr>
<tr>
<td>Antibiotics, anticonvulsants, arsenic, antiarrhythmic, digoxin, oestrogens, NSAIDs, opiates, ethanol overdosed and withdrawal, pesticides, organophosphates, rimon, chemotherapeutics, radiation therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction, nephrolithiasis, pain, acute glaucoma, psychiatric disorder</td>
<td></td>
</tr>
</tbody>
</table>
Chronic idiopathic nausea (CIN), functional vomiting and cyclic vomiting syndrome (CVS) are defined in the Rome III criteria (Table 4), and include the exclusion of any psychiatric diagnoses as well as organic disease.

**Epidemiology**

Updated studies on the prevalence of CIN, functional vomiting and CVS are lacking. Studies on the prevalence of CVS have shown that it affects all ages, both sexes and any ethnicity. Population studies among school children found a 1.9% prevalence of CVS. The median age at onset was 4.8 years. In adults the mean age at onset of CVS has been reported to be 30 years (study conducted on 14- to 58-year olds). The average duration of each episode was 6 days.

In general, nausea and vomiting significantly affect quality of life. As other causes of vomiting and nausea are taken into account, the medical costs and loss of worker productivity are considerable.

**Clinical features**

**Symptoms**

The symptoms of nausea are the unpleasant, painless sensation that may potentially lead to vomiting, i.e. forceful expulsion of stomach contents. Acute symptoms are often attributed to inflammatory, infectious or iatrogenic causes. However, chronic nausea and vomiting are typically a pathological response to many different conditions. A thorough history, clinical examination and investigations may help in detecting the cause.

**Pathophysiology**

The vomiting centre is located in the medulla oblongata and includes the nucleus of the tractus solitarius and reticular formation. It is a group of loosely organized neurons in the medulla which receive signals from the nucleus tractus solitarius and the chemoreceptor trigger zone. When triggered, signals descend through the motor pathways within the 5th, 7th, 9th, 10th and 12th cranial nerves to the upper gastrointestinal tract. The ‘vomiting centre’ can be activated by irritants or indirectly by inputs from the gastrointestinal tract, cerebral cortex and thalamus, vestibular region and chemoreceptor trigger zone. The chemoreceptor trigger zone lies between the floor of the fourth ventricle and the medulla. It is unlike other brain centres as it is not protected by the blood–brain barrier.

Vomiting starts with a period of antiperistalsis, in which rhythmic contractions occur up the digestive tract instead of downwards. The antiperistalsis pushes the contents of the lower small intestine up into the duodenum and thereafter to the stomach. It all happens within a few minutes. Distension within the upper portions of the gastrointestinal tract triggers afferent impulses to the vomiting centre, where the actual act of

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TABLE 4 Diagnostic criteria for nausea and vomiting disorders

<table>
<thead>
<tr>
<th>B3a. Diagnostic criteria* for chronic idiopathic nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must include all of the following:</td>
</tr>
<tr>
<td>▪ Bothersome nausea occurring at least several times per week</td>
</tr>
<tr>
<td>▪ Not usually associated with vomiting</td>
</tr>
<tr>
<td>▪ Absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea</td>
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</tbody>
</table>

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<thead>
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<th>B3b. Diagnostic criteria* for functional vomiting</th>
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<td>Must include all of the following:</td>
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<td>▪ On average one or more episodes of vomiting per week</td>
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<td>▪ Absence of criteria for an eating disorder, rumination, or major psychiatric disease according to DSM-IV</td>
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<td>▪ 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</td>
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<th>B3c. Diagnostic criteria for cyclic vomiting syndrome</th>
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<td>Must include all of the following:</td>
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<td>▪ Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)</td>
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<td>▪ Three or more discrete episodes in the prior year</td>
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<td>▪ Absence of nausea and vomiting between episodes</td>
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Supportive criterion:

| ▪ History or family history of migraine headaches |

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

DSM-IV, classification according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

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vomiting is generated. The actual vomit begins with intrinsic contractions of the duodenum and stomach; meanwhile, the LOS relaxes and vomitus enters the oesophagus. Finally, the chest and abdominal muscles contract and expel the vomitus into the mouth. The mechanism of explaining functional and cyclic vomiting is partly unknown. There could be peripheral, central or combined abnormalities. Major depression has been diagnosed in patients suffering from these conditions; however, a study from the Mayo Clinic found that psychiatric diagnoses were similarly distributed in patients with chronic unexplained vomiting and organic disease controls.

Investigation
Investigations have been undertaken to determine the underlying cause and to define any derangements that may result from the loss of electrolytes and fluid during vomiting. The list of differential diagnosis of recurrent vomiting or nausea is extensive (Table 3), but can be caused by gastrointestinal disorders such as gastroparesis. Gastroparesis is a motility disorder in which the food is unable to move through the gastrointestinal tract, which can result in nausea and vomiting. Patients with GORD, peptic ulcer disease, irritable bowel syndrome and dyspepsia may have nausea and vomiting. Many drugs can also cause nausea. Drug abuse is a recognized cause of nausea and vomiting, including cannabinoids and marijuana, which have been associated with CVS. This reinforces the importance of taking a detailed and thorough patient history and examination.

In patients with unexplained vomiting the following investigations may be considered:

- Blood tests for metabolic profile, erythrocyte sedimentation and pregnancy.
- If the patient has abdominal pain pancreatic enzyme should be measured.
- Additional tests could include supine and upright abdominal radiography if small bowel obstruction is suspected.
- Gastric emptying tests may be considered. Interestingly, a study on patients with CVS demonstrated that a subset of patients may have accelerated gastric rather than delayed emptying.

- In functional nausea exclusion of GORD is necessary as it is easily treated.

Treatment
The treatment of CIN is not well defined and there is no internationally agreed consensus; therefore, treatment is usually empirical and includes:

- Antiemetic drugs, which act as antagonists at receptor sites within the vomiting centre and associated regions. One of these antagonists is a dopamine receptor antagonist, for example domperidone. Domperidone has both prokinetic and antinausea properties. Domperidone, however, has recently been investigated by the European Medicines Agency, owing to concerns about increased risk of cardiac adverse effects including QTc prolongation, torsade de pointes, serious ventricular arrhythmia and sudden cardiac death.

- 5-Hydroxytryptamine3 antagonists, such as ondansetron, are expensive and have adverse events, such as prolonging the QTc interval, increasing the risk for ventricular arrhythmias.

- Herbal and alternative medicine remedies, such as ginger, are accepted for the treatment of nausea. They have been found to be effective for gastric slow-wave dysrhythmias.

When considering treatment of vomiting, it is useful to separate CVS from functional vomiting (Table 1). CVS can sometimes require hospital admission for intravenous antiemetic therapy and intravenous fluids. For prevention of the attacks of vomiting, tricyclic antidepressant treatment has been found useful in some studies. One study with 24 patients presenting with CVS demonstrated that receiving amitriptyline for at least 3 months decreased symptoms in 93% of patients and achieved full remission in 26%, although 13 of the total 31 were using marijuana, which is, as mentioned, a proposed contributor to CVS.

In patients with functional vomiting, tricyclic antidepressants have been found useful, although these are anecdotal reports and have not been proven using large randomized prospective studies. The treatment of functional vomiting remains difficult. Training in cognitive and social skills has been found to be helpful in some studies and can help to suppress the urge to vomit. In these patients it is of great importance to focus on nutritional status and psychological support.
Conclusion

Chronic idiopathic nausea, functional vomiting and CVS are complex conditions which are incompletely and poorly understood. The diagnosis should be made with caution, and differential diagnoses (Table 1) are important to exclude to avoid mistreatment. When diagnosed, the treatment remains empirical for all patients. The treatment focuses on antiemetics and tricyclic antidepressants, although alternative treatments, such as cognitive behavioural therapy, could be worth considering. Additional studies, which investigate the epidemiology, mechanism and treatment, are needed.

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