Chronic nausea and vomiting: evaluation and treatment

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Nausea is an uneasy feeling in the stomach while vomiting refers to the forceful expulsion of gastric contents. Chronic nausea and vomiting represent a diverse array of disorders defined by 4 weeks or more of symptoms. Chronic nausea and vomiting result from a variety of pathophysiological processes, involving gastrointestinal and non-gastrointestinal causes. The prevalence of chronic nausea and vomiting is unclear, although the epidemiology of specific conditions, such as gastroparesis and cyclic vomiting syndrome, is better understood. The economic impact of chronic nausea and vomiting and effects on quality of life are substantial. The initial diagnostic evaluation involves distinguishing gastrointestinal causes of chronic nausea and vomiting (e.g., gastroparesis, cyclic vomiting syndrome) from non-gastrointestinal causes (e.g., medications, vestibular, and neurologic disorders). After excluding anatomic, mechanical and biochemical causes of chronic nausea and vomiting, gastrointestinal causes can be grouped into two broad categories based on the finding of delayed, or normal, gastric emptying. Non-gastrointestinal disorders can also cause chronic nausea and vomiting. As a validated treatment algorithm for chronic nausea and vomiting does not exist, treatment should be based on a thoughtful discussion of benefits, side effects, and costs. The objective of this monograph is to review the evaluation and treatment of patients with chronic nausea and vomiting, emphasizing common gastrointestinal causes.

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INTRODUCTION

Chronic nausea and vomiting represents a broad array of gastrointestinal and non-gastrointestinal disorders. Nausea, derived from the Greek word *nautia* (seasickness), is defined as a vague, unpleasant feeling of unease with the sensation that vomiting might occur. Nausea, a subjective symptom, is frequently preceded by feelings of anorexia and is often accompanied by objective symptoms of pallor, hypersalivation, diaphoresis, and tachycardia. Vomiting (Latin: *vomere*—to discharge) is characterized by the forceful ejection of gastric contents from the mouth. Distinguishing vomiting from regurgitation and rumination is critical as the evaluation and treatment of these two disorders are markedly different [1]. Regurgitation, a cardinal symptom of gastroesophageal reflux disease, is characterized by the effortless and involuntary movement of gastric contents into the mouth without abdominal wall contractions [2]. Rumination is a voluntary process in which patients effortlessly bring up recently ingested food from the stomach into the mouth, where it is often then chewed again and re-swallowed [3]. Nausea, and the autonomic manifestations typically seen with vomiting, are usually absent with regurgitation and rumination.

Chronic nausea and vomiting is defined by symptom duration of 4 weeks or longer, in contrast to acute nausea and vomiting, generally defined by symptom duration of 7 days or less [1]. This distinction is important, as most cases of acute nausea and vomiting represent a transient medical condition (e.g., a viral gastroenteritis), a self-limited somatic disorder (e.g., musculoskeletal trauma; acute myocardial infarction), or a medication side effect (e.g., chemotherapy, anesthetics, glucagon-like peptide 1-agonists). Similar to other functional gastrointestinal disorders, recent Rome IV guidelines for cyclic vomiting syndrome (CVS), chronic nausea and vomiting syndrome (CNVS), and cannabinoid hyperemesis syndrome (CHS) state that symptoms should be present for more than 6 months and active within the last 3 months [4]. The clinical utility of a longer period of symptom duration (i.e., 3 months vs. 4 weeks) has not been evaluated.

The epidemiology of chronic nausea and vomiting in the community is not well known. A telephone survey of 21,128 adults in the United States documented that nausea and vomiting during the past 3 months was present in 7% of the respondents [5]. There are, however, data on specific disease states that cause chronic nausea and vomiting. The Rochester Epidemiology project estimated a prevalence rate of diagnosed gastroparesis of 9.6 per 100,000 in men and 37.8 per 100,000 in women [6]. This rate is lower than an estimated prevalence of 1.8%, based on a regression model developed from the association of symptoms suggestive of gastroparesis and measured gastric emptying, suggesting that there are many undiagnosed patients with gastroparesis [7]. Recurrent nausea and

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vomiting affects 50–75% of pregnant women [8, 9]; fortunately only 0.5–1% suffer from the more extreme form of nausea and vomiting during pregnancy, hyperemesis gravidarum [10].

Quality of life is reduced in patients with chronic nausea and vomiting, with the best data again derived from studies of gastroparesis [11, 12]. The economic impact of gastroparesis can be substantial, with one study reporting that 11% of patients were disabled due to their gastroparesis symptoms, while another 28.5% reported a loss of yearly income [11]. In the large telephone survey performed by Camilleri and colleagues, nausea and vomiting led to an average 6.6 missed days of work, 9.0 missed leisure days, and 19.7 household days during the past 3 months [5].

PATHOPHYSIOLOGY

Symptoms of nausea and vomiting develop from complicated neuroanatomical pathways that converge on the emetic center ("vomiting" center) located in the dorsal lateral reticular formation of the medulla (see Fig. 1). The emetic center is a collection of closely linked nuclei that coordinate the complex series of events involved in vomiting [13]. Afferent pathways arise from the gastrointestinal tract, oropharynx, heart, musculoskeletal system, and vestibular system (Fig. 1). These afferent pathways, as well as signals from the chemoreceptor trigger zone and cerebral cortex, synapse on the solitary nucleus of vagus, to stimulate the emetic center [14]. One theory suggests that mild stimulation of these pathways leads to nausea, while more intense stimulation leads to vomiting. Efferent pathways from the emetic center are responsible for coordinating the intricate series of events leading to vomiting, which involves the gastrointestinal tract, diaphragm, abdominal wall muscles, and oropharynx [15]. In brief, antral contractions stop and the stomach relaxes, pyloric tone increases, the lower esophageal sphincter relaxes, abdominal wall muscles and the diaphragm contract, and material is propelled upward into the mouth to be ejected. During the final step, respiration briefly ceases, the glottis and vocal cords close, and the soft palate rises, all to prevent aspiration. Key neurotransmitters and hormones involved in this process include histamine, dopamine, serotonin, norepinephrine, acetylcholine, substance P, cortisol, beta-endorphin, and vasopressin [16, 17].

ETIOLOGY

The etiology of chronic nausea and vomiting is diverse and not limited solely to the gastrointestinal tract. As outlined below, one of the first steps in the evaluation of a patient with chronic nausea and vomiting is to exclude common non-gastrointestinal causes, such as medications, chronic renal insufficiency, cardiac disorders, vestibular disorders, neurologic disorders, and mechanical processes (see Tables 1 and 2). This is important, because symptoms of nausea and vomiting may resolve if the underlying disorder is treated appropriately (e.g., an offending medication is stopped; cardiac ischemia improves; an inner ear condition is treated).

Gastrointestinal causes of chronic nausea and vomiting should be categorized as gastroparesis or an alternative disorder (see Table 1). This strategy may be controversial to some providers; however, it is grounded in the fact that the vast majority of research in this field has focused on the diagnosis and treatment of gastroparesis [18]. Vomiting immediately after eating may indicate anatomic or neuromuscular dysfunction of the esophagus (e.g., severe esophagitis, an esophageal stricture, achalasia, Zenker's diverticulum). Patients with functional dyspepsia (FD) frequently report

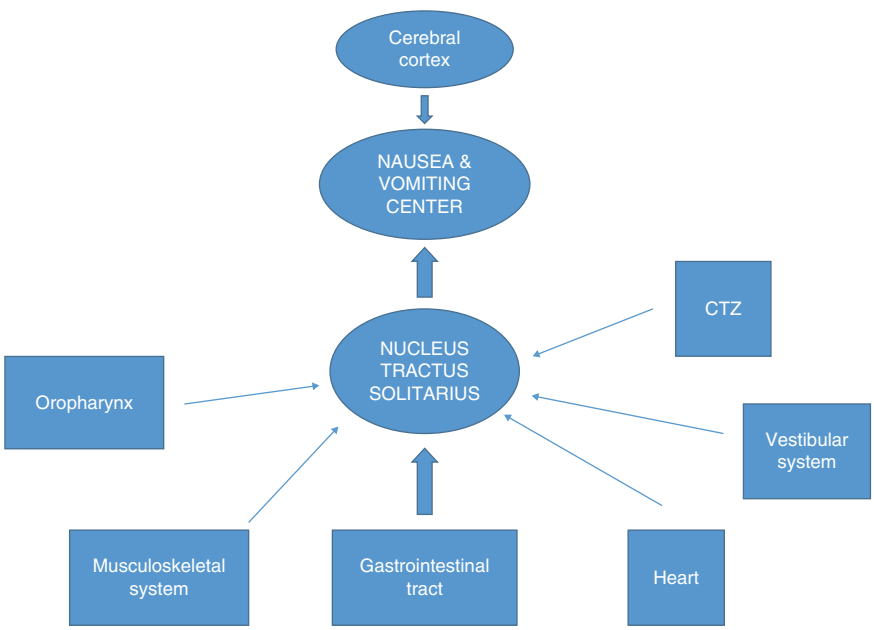

Fig. 1 Afferent pathways involved in nausea and vomiting

Table 1 Common causes of chronic nausea and vomiting

Gastroparesis
Functional dyspepsia
Cyclic vomiting syndrome (CVS)
Cannabinoid hyperemesis syndrome (CHS)
Chronic nausea and vomiting syndrome (CNVS)
Anatomic causes (gastric outlet obstruction, intermittent partial bowel obstruction, extrinsic compression of the GI tract, stenosis from ischemia, radiation or Crohn's disease)
Chronic pancreatitis
Hepatobiliary disorders (acute and chronic hepatitis; infiltrative disorders; partial biliary obstruction)
Endocrine disorders (diabetes, hyperglycemia)
Chronic intestinal pseudo-obstruction (primary or secondary)
Vascular disorders (median arcuate ligament syndrome, SMA syndrome, chronic ischemia)
Connective tissue disorders (scleroderma, SLE)
Renal insufficiency
Vestibular disorders (labyrinthitis, Meniere's disease, motion sickness, chronic otitis media)
Esophageal disorders (achalasia, Zenker's diverticulum)
Medications (opioids, antibiotics, antiarrhythmics, anticonvulsants)
Neurologic disorders (Parkinson's disease, seizure disorders, migraine headaches)
Cardiac disorders (ischemia, congestive heart failure)
Eating disorders (anorexia, bulimia)
Psychogenic causes (anxiety, depression, conversion disorder, learned behaviors)
Miscellaneous (alcohol abuse, post-vagotomy)

Table 2 Uncommon causes of chronic nausea and vomiting

Endocrine disorders (hyperthyroidism, Addison's disease, hyponatremia, hyperparathyroidism, hypercalcemia)
Paraneoplastic syndromes
Radiation-induced
CNS disorders (aneurysm, tumor, hydrocephalus, meningitis, pseudotumor cerebri)
Nervous system disorders (severe neuropathy, demyelinating disorders, autonomic nervous system disorders)
Renal and urologic disorders (nephrolithiasis, obstruction)
Severe constipation
Retroperitoneal and mesenteric pathology
Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
Miscellaneous (acute intermittent porphyria, Familial Mediterranean Fever, angioedema, glaucoma, toxins/poisons, mitochondrial disorders, ion channel disorders, food allergies, and intolerances)

nausea, especially in the post-prandial period; vomiting as the predominant symptom is less common [19–21]. CVS is characterized by recurrent, stereotypical, self-limited episodes of nausea and vomiting, sometimes associated with autonomic symptoms such as sweating or fainting, and separated by symptom-free intervals [22]. A history of migraine headaches is common in CVS patients; rapid gastric emptying is found in some [4, 22]. The diagnosis of CHS can be made in some patients presenting with CVS based on a history of chronic excessive use of cannabis; patients often describe compulsive bathing or showering during acute episodes [23]. Resolution of symptoms with cessation of cannabis use confirms the diagnosis.

PPIs with efficient healing of antro-pyloric inflammation and ulceration has led to a decrease in severe gastritis and gastric outlet obstruction (GOO) as a cause of chronic nausea and vomiting. Intermittent, partial bowel obstruction needs to be excluded (see evaluation section below), especially in patients with prior abdominal surgery. A careful history and appropriate testing can identify chronic pancreatitis and hepatobiliary disorders as causes of chronic nausea and vomiting [24, 25]. Chronic intestinal pseudo-obstruction (primary or secondary), connective tissue disorders [26, 27], vascular disorders, such as median arcuate ligament syndrome (MALS) and superior mesenteric artery syndrome (SMA syndrome) should be considered if other causes cannot be identified [28].

EVALUATION OF THE PATIENT WITH CHRONIC NAUSEA AND VOMITING

Given the diverse causes of chronic nausea and vomiting, many of which are not due to a gastrointestinal cause, an orderly approach to the evaluation of patients is required.

History

Patient history forms the framework for diagnostic evaluation. Categories of clinical conditions that cause chronic nausea and vomiting should be considered (Table 3) [29]. Understanding the patient's symptoms (especially vomiting) is important (Table 4) [30]. Symptom characteristics and associated symptoms often tend to suggest a diagnosis (Table 5). Two medications are particularly associated with nausea and vomiting: opiates and cannabis. Opiates can cause nausea and vomiting both directly or indirectly though delaying gastric emptying. With the legalization of cannabinoid use in many states, a history of cannabis use and relationship to the timing of emesis in relation to use or withdrawal of the cannabinoid should be sought.

Physical examination

A careful physical examination may help determine the underlying cause of chronic nausea and vomiting and can also assess untoward consequences of chronic nausea and vomiting. Well-designed prospective studies evaluating the sensitivity and specificity of physical exam findings in patients with chronic nausea and vomiting, even in the more common conditions of gastroparesis or CVS, are unfortunately lacking. Signs of weight loss and dehydration should be sought. A postural decrease in blood pressure and an increase in pulse rate with standing suggest significant dehydration; a decrease in blood pressure without any change in pulse rate suggests autonomic neuropathy.

Table 3 Categories of chronic nausea and vomiting with some specific causes

Gastrointestinal disorders	
Mucosal inflammation	Peptic ulcer disease
Mechanical obstruction	Gastric outlet obstruction
	Small intestinal obstruction
Motility disorders	Gastroparesis
	Gastroparesis—like syndrome
	Chronic intestinal pseudoobstruction
Medications and toxins	Marijuana—Cannabinoid hyperemesis
	Opiate analgesis
	NSAIDs
	Anticholinergic agents
	Estrogen/progesterone
	Lubiprostone
	Amylin analogs
	Chemotherapy
	Digitalis
Metabolic/endocrine causes	Pregnancy
	Diabetes (gastroparesis, DKA)
	Uremia
	Adrenal insufficiency
	Thyroid disorders
CNS disorders	Migraine headache
	Cyclic vomiting syndrome
	Mass lesion; brain tumors
	Pseudotumor cerebri
Psychiatric disease	Anorexia, bulimia
	Conditioned vomiting

Modified from Koch [29]

Table 4 Vomiting and similar symptoms: definitions

Nausea	Feeling sick to your stomach as if going to vomit or throw up
	An unpleasant sensation of the imminent need to vomit
	A sensation that may or may not ultimately lead to the act of vomiting
Vomiting	Forceful oral expulsion of gastric contents;
	Associated with contraction of the abdominal musculature
Retching	Heaving as if to vomit, but nothing comes up
	Spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents, referred to as "dry heaves"
Regurgitation	Food brought back into the mouth without abdominal and diaphragmatic muscular activity that characterizes vomiting
Rumination	Chewing and swallowing of regurgitated food that has come back into the mouth through a voluntary increase in abdominal pressure within minutes of eating or during eating

Modified from Quigley et al. [30]

Examination may detect jaundice, lymphadenopathy, abdominal masses, or fecal occult blood as well as reveal systemic features suggestive of thyrotoxicosis or Addison's disease. Auscultation may demonstrate increased bowel sounds in obstruction or absent bowel sounds in ileus. A succussion splash detected by listening over the epigastrium while shifting the abdomen side to side suggests gastroparesis or GOO. One small study identified a succussion splash in nearly half of patients with pyloric obstruction [31]. Tenderness in the mid-epigastrium raises the possibility of a peptic ulcer; tenderness in the right upper quadrant suggests biliary tract disease or a loaded right colon in patients with constipation who may present with chronic nausea or vomiting [32].

Extremities may show changes suggestive of scleroderma such as Raynaud's phenomenon, and telangiectasia or peripheral neuropathy. Fingernails may show findings of self-induced vomiting. Loss of dental enamel may indicate recurrent vomiting, as in bulimia, gastroparesis, or consequences of reflux disease.

Brief neurologic examination includes assessing cranial nerves (including checking for external ocular movements which may suggest mitochondrial cytopathy, pupillary responses to light which may be absent in diabetics with neuropathy, or nystagmus which may suggest a central nervous system [CNS] disease) and observing the patient's gait. Cranial nerve abnormalities and/or long tract signs suggest a CNS cause. Brainstem tumors, although rare, may present with vomiting and may be accompanied by long tract or cranial nerve signs, although these are often absent and autonomic dysfunction may be the only neurological manifestation [33]. Chronic vestibular dysfunction was present in 26% of patients with chronic nausea and vomiting presenting to a gastroenterologist [34].

Blood tests

Goals of blood tests are to help identify an underlying cause and assess consequences of vomiting. Basic laboratory testing includes a complete blood count, complete metabolic panel, thyroid stimulating hormone (TSH), and in diabetics, glycosylated hemoglobin (HbA1c). Severe vomiting, resulting in loss of fluid and electrolytes, may lead to dehydration and a hypokalemic metabolic alkalosis, caused in part by loss of gastric hydrochloric acid in the vomitus. Laboratory tests may provide clues to other systemic disorders; for example, hyponatremia may raise suspicion of Addison's disease. In women, a pregnancy test is usually obtained, not only to assess whether pregnancy might be the cause of symptoms, but also prior to performing radiologic studies. Serum drug levels may indicate toxicity among patients taking digoxin, theophylline, or salicylates or recreational drug use (opiates, cannabis).

Table 5 Features of some important causes of nausea and vomiting

Vomiting or regurgitation	
Forceful expulsion	Vomiting from the stomach
Passive regurgitation	Esophageal disorders such as GERD, achalasia, and rumination syndrome
Initial onset, progression, and duration of symptoms	
Insidious onset of nausea:	Gastroparesis, a medication-related side effect, metabolic disorders, pregnancy, gastroesophageal reflux disease
Description of the vomitus	
Regurgitation of undigested food	Esophageal disorders—achalasia, esophageal stricture, Zenker's diverticulum
Vomiting of partially digested food several hours after a meal	Gastroparesis or gastric outlet obstruction
Bilious vomiting	Small bowel obstruction
Feculent or putrid odor to vomitus	Bacterial degradation of stagnant intestinal contents, a feature of intestinal obstruction
Timing and description of vomiting	
Vomiting in am before breakfast	Pregnancy, uremia, alcohol ingestion, increased intracranial pressure
Projectile vomiting, without nausea	Increased intracranial pressure
Nausea and vomiting an hour after meal	Gastroparesis or gastric outlet obstruction
Vomiting during or soon after meal	Rumination, anorexia nervosa or bulimia
Episodes of severe unrelenting vomiting	Cyclic vomiting syndrome, Cannabinoid Hyperemesis
Conditioned vomiting	The original symptoms of "organic" origin are reinforced by short-term benefits of initial therapy, and the now chronic symptoms represent a learned behavior
Associated symptoms	
Early satiety, postprandial abdominal fullness/bloating	Gastroparesis
Abdominal pain	Biliary or pancreatic disorder
Pain is prominent, severe, and colicky; may improve after vomiting	Small bowel obstruction
Weight loss	Malignancy, gastroparesis and gastric outlet obstruction
CNS symptoms—headache, vertigo, focal neurologic deficits	Central cause of nausea and vomiting
	Vomiting as the only manifestation of a brainstem tumor is rare

Diagnostic evaluation

Diagnostic tests should be directed primarily by the history and examination (Table **6**) [1, 30, 31]. If symptoms suggest obstruction (abdominal pain relieved by vomiting), supine and upright abdominal radiographs are obtained; however, these can be normal or show nonspecific changes in 22% of patients with partial small bowel obstruction [35]. Chronic nausea and vomiting that develops shortly after eating may represent an esophageal motility disorder such as achalasia. If upper endoscopy excludes an anatomic or structural disorder, then high resolution esophageal manometry should be performed.

Mucosal disorders of the stomach and/or duodenum, such as peptic ulcer disease and GOO, are most accurately diagnosed by esophagogastroduodenoscopy (EGD) during which mucosal biopsies can be obtained for *Helicobacter pylori* and celiac disease. Retained food in the stomach after an overnight fast without evidence of obstruction suggests, but is not diagnostic of, gastroparesis. A retrospective study correlating retained food in the stomach found during upper endoscopy with delayed gastric emptying measured by 4-h solid phase scintigraphy demonstrated a sensitivity of 0.27 and specificity of 0.83 [36]. EGD is more sensitive and more specific for detection of mucosal lesions than radiographic testing [37, 38], although double-contrast barium techniques are more sensitive than single-contrast studies [38–40]. No published studies have reported on the utility of transaxial imaging (CT, or MRI) for diagnosing gastroparesis.

Several radiographic techniques are available to visualize the small intestine; pathological disorders of the small bowel may retard gastric emptying and present with clinical features of gastroparesis. Small bowel follow-through (SBFT) examination can be used to evaluate for a high-grade obstruction and also provides an assessment of the terminal ileum but may fail to detect low-grade obstruction and smaller mucosal lesions [40, 41]. Dedicated small bowel evaluations are performed with CT enterography or MR enterography for detection and localization of intestinal obstruction and may identify abdominal masses and pancreatic, hepatobiliary, or retroperitoneal pathology [41–44] as well as small bowel dilatation, obstruction or diverticula. Abdominal ultrasonography may provide information on gallbladder, pancreatic, or hepatobiliary disorders. Prospective studies with video capsule endoscopy have been applied in the evaluation of chronic nausea and vomiting in specialized centers (and specific

Table 6 Tests to evaluate patients with chronic nausea and vomiting

Tests for obstruction and mucosal abnormalities	
Abdominal X-ray	May suggest obstruction, CIIP;
	May be performed on day of clinical evaluation
Upper GI radiographic series	May reveal obstructive or mucosal lesions of upper GI tract
(and SBFT)	SBFT may suggest superior mesenteric artery syndrome in some patients
Abdominal CT	Detect and diagnose cause of obstruction;
	Also examines other intra-abdominal organs
Upper endoscopy	Examination of esophageal, gastric and duodenal mucosa;
	Mucosal biopsies possible
GI motility tests	
Gastric emptying tests	Quantifies gastric emptying of solids and/or liquids
Scintigraphy	
Breath test	
Wireless motility capsule	
Specialized tests of gastric function	
Antroduodenal manometry	Measures intraluminal pressure changes;
	Detects abnormal motor patterns suggestive of myopathy, neuropathy, obstruction. May be helpful when it shows entirely normal findings.
Electrogastrography (EGG)	Evaluates for gastric dysrhythmias; indirect measure of gastric motility
Gastric accommodation and sensation tests	
Gastric barostat	
Gastric mucosal labeling with —SPECT imaging	
Abdominal MRI	
Intragastric meal distribution during scintigraphy	
Drink tests (water load, nutrient satiety test)	
CNS imaging	Evaluates for CNS lesions
Head CT	
Head MRI	

Modified from Quigley et al. [30]

physiological criteria based on image analysis have been proposed [45, 46]).

Tests of gastric motor function. If neither obstruction nor mucosal disease is evident, an underlying motility disorder such as gastroparesis should be considered. The diagnosis of gastroparesis is based on compatible symptoms, delayed gastric emptying, and the absence of obstruction and mucosal disease. There are three tests to evaluate for gastric emptying: scintigraphy, breath testing, wireless motility capsule.

Gastric emptying scintigraphy offers a noninvasive, physiologic means to assess gastric motor function [47, 48]. The patient ingests a radiolabeled meal; emptying from the stomach is monitored over time by serial images using a gamma camera. Solid-phase meals are more sensitive than liquid meals in detecting gastroparesis because normal emptying of liquids is often preserved until gastroparesis is advanced [49]. For solid-phase gastric emptying studies, extending gastric emptying to four hours detects more patients with delayed gastric emptying [50, 51]. Nausea and vomiting were more frequently observed in patients with delayed gastric emptying compared to those with normal or accelerated gastric emptying [52]. Nausea is present in essentially all patients with gastroparesis irrespective of cause and associates with decreased quality of life. Vomiting occurs more often in diabetic than idiopathic gastroparesis [53]. There are patients with nausea and vomiting with normal gastric emptying presenting similarly as gastroparesis; this is categorized as Gastroparesis-Like Syndrome or Chronic Unexplained Nausea and Vomiting [54]. In the Rome IV criteria, CNVS includes bothersome nausea, occurring at least 1 day per week and/or one or more vomiting episodes per week [4].

The *wireless motility capsule* is an ingestible capsule that measures pH, pressure, and temperature using miniaturized wire-

less sensor technology. The gastric residence time of the wireless motility capsule has a high correlation (85%) with the time for 90% emptying (T-90%) measured by gastric emptying scintigraphy, suggesting that the gastric residence time of the wireless motility capsule represents a time near the end of emptying of a solid meal [55, 56]. Wireless motility capsule not only measures gastric emptying, but also assesses small bowel and colonic transit [57].

Stable isotope breath tests use ^{13}C bound to a digestible substance. After ingestion and stomach emptying, ^{13}C-octanoate or ^{13}C-spirulina is absorbed in the small intestine and metabolized to $^{13}CO_2$, which is then expired from the lungs with the rate-limiting step being gastric emptying. Breath testing simultaneous with scintigraphy had 89% sensitivity for identifying delayed gastric emptying [58].

Several specialized tests are performed at select centers to assess gastric motor function. Antroduodenal manometry assesses for gastric and/or small intestinal motility disturbances and provides information on myopathic or neuropathic dysfunction, and, at times can show patterns suggesting partial obstruction [48]. A normal antroduodenal motility study is helpful because manometry helps to exclude dysmotility as a cause of symptoms. Electrogastrography may identify dysrhythmias or a failure of the gastric electrical signal to increase postprandially [59]. Rhythm abnormalities may be unrelated to impaired emptying. Gastric accommodation can be measured using with either a barostat or using single photon emission computed tomography (SPECT) gastric imaging after administration of intravenous ^{99m}Tc pertechnetate, or MRI. These tests are available at only a few specialized motility centers. Abnormalities of gastric accommodation and visceral hypersensitivity appear to correlate with fullness rather than nausea or vomiting [60, 61]. Among almost 1300 patients presenting to a tertiary center with upper gastrointestinal symptoms, about a quarter had abnormal (mostly delayed) gastric emptying, a quarter impaired gastric accommodation, a quarter both abnormal gastric emptying and accommodation, and a quarter normal on both tests [52].

Evaluation for central disorders. It is rare for an adult patient with vomiting related to an intracranial lesion not to have neurologic symptoms, most commonly headache, or neurologic signs, such as cranial nerve findings, long tract signs, or papilledema [62, 63]. Because objective neurologic findings may occasionally be absent in patients with intracranial lesions, an imaging study can be considered in those with unexplained chronic nausea and vomiting; magnetic resonance imaging provides superior visualization of the posterior fossa [64, 65].

Autonomic testing

Autonomic function testing (e.g., heart rate response to deep breathing at a defined rate and to the Valsalva maneuver, and blood pressure change with posture), or at least an EKG with measurement of the variation in the R–R interval, are useful tests to assess for presence of extrinsic neural cause of the gastroparesis, e.g., in patients with diabetes.

Evaluation for eating disorders

When an underlying cause has not been identified after a careful history, physical examination, and testing (as noted above), patients with persistent symptoms of nausea and vomiting should be evaluated for an eating disorder (e.g., anorexia or bulimia). Patients at high risk include: young women; competitive athletes; those with a first degree family member with an eating disorder; and those with significant anxiety, depression, body image disorders or sexual orientation/gender expression disorders. Patients who fail repeated courses of empiric therapy for chronic nausea and vomiting (see treatment section below) with a negative diagnostic evaluation should also be evaluated for an eating disorder. This is especially important when considering further treatment options so as to avoid inappropriate institution of treatments, such as enteric feedings in an individual with an eating disorder.

Role of sham feeding tests

Vagal integrity is essential for a food-related rise in serum pancreatic polypeptide levels, and sham feeding protocols are used at some academic centers to assess gastroparesis patients for vagal nerve dysfunction [66]. In one small prospective study, an impaired pancreatic polypeptide response suggestive of vagal nerve dysfunction was identified in patients with diabetic and post-surgical gastroparesis, but not idiopathic gastroparesis [66].

MANAGEMENT

The management of chronic nausea and vomiting, with a few exceptions (see below), is generally similar to that of gastroparesis apart from the use of prokinetics and pyloric interventions. The overall management of such patients is shown in Fig. **2**, and selected therapy can be guided by the degree of retardation of gastric emptying and response to therapy.

General measures

A. *Concomitant medications*: Medications that decrease gastrointestinal motility should be discontinued, such as opioids (including tramadol and tapentadol), dopamine agonists, calcium channel blockers, α2-adrenergic agonists, and muscarinic cholinergic antagonists. In patients with diabetic gastroparesis, pramlintide and GLP-1 analogs (e.g., exenatide) should be avoided, as they decrease gastric emptying [67]. Nonsteroidal anti-inflammatory agents and aspirin products should ideally be stopped in those patients with esophagitis, gastritis and/or peptic ulcer disease identified on endoscopy.
B. *Glycemic control*: There is conflicting evidence whether long-term glycemic control improves gastric emptying and symptoms of gastroparesis [68, 69]. However, acute hyperglycemia can slow gastric emptying [70].
C. *Diet and oral nutrition*: Poor oral intake may result in deficiencies in calories, vitamins and minerals [71]. Daily caloric requirement (kcal) can be estimated by the formula: 25 * weight in kg [72]. The stomach empties at a rate of up to ~2.5 kcal/min [73]. Patients with gastroparesis should consume small, frequent meals, low in fat and fiber, since high fat and non-digestible fiber may delay gastric emptying [18, 71]. Blenderized solids or nutrient liquids can be used, since gastric emptying of liquids is usually preserved in

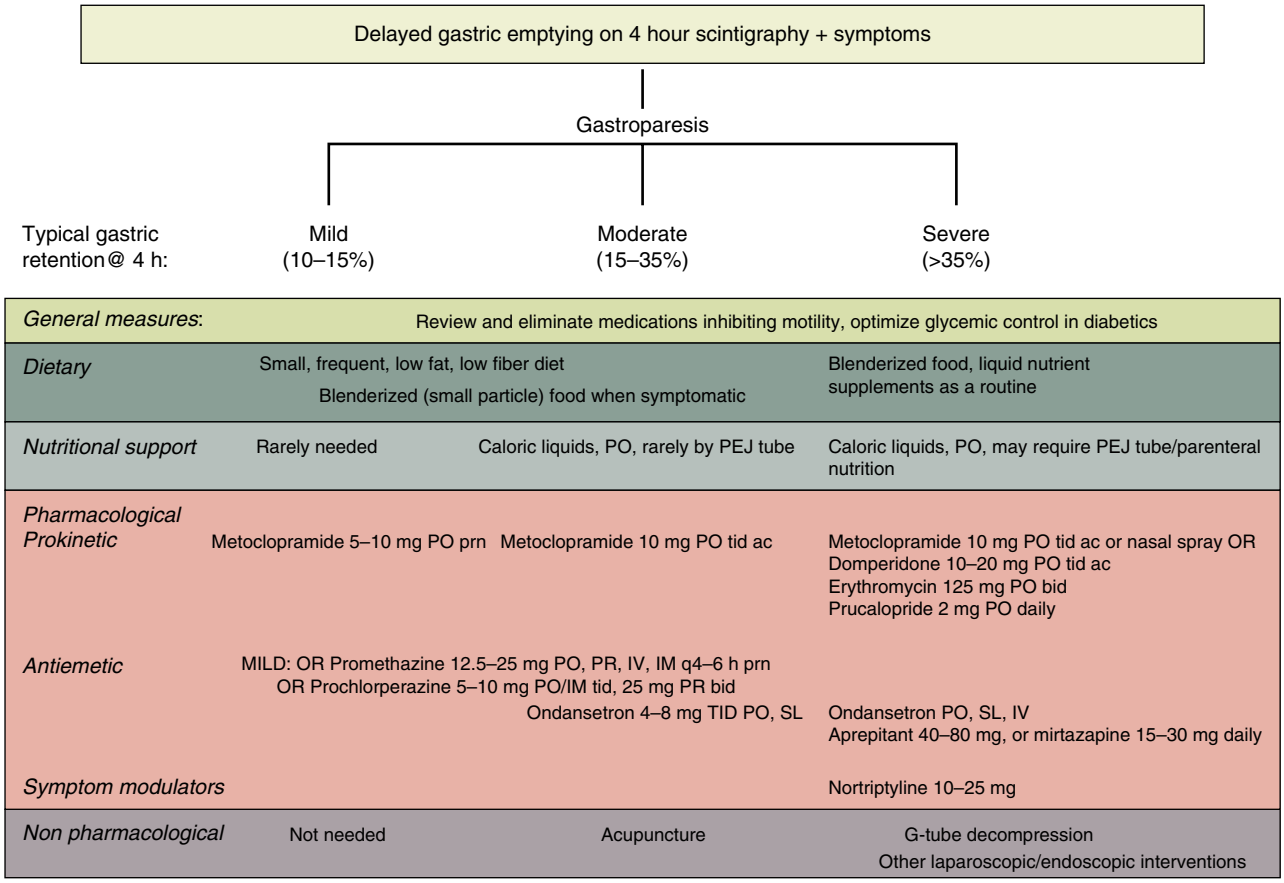

Fig. 2 Summary of treatment strategy for patients with gastroparesis

gastroparesis [18]. In diabetic gastroparesis, patients on a small particle diet (compared to standard diet) had decreased symptoms of gastroparesis and anxiety, but abdominal pain was not affected [74]. A liquid multivitamin should also be prescribed [71].

Poor tolerance of liquids is predictive of poor outcome with oral nutrition [71] and necessitates enteral nutrition.

D. *Smoking and alcohol*: Smoking and alcohol can delay gastrointestinal transit and should be avoided [75, 76].
E. *Enteral nutrition*: As long as small bowel function is normal, jejunal feeding improves symptoms and reduces hospitalizations while maintaining nutrition [77, 78]. Enteral feeding is preferred over parenteral nutrition due to lower potential for complications and cost, and greater ease of delivery [18].

Medications. There is a need for robust clinical appraisal of all therapies, including medications, in patients with chronic nausea and vomiting with normal gastric emptying and in those with gastroparesis. The following section will focus on broad categories of agents used to treat chronic nausea and vomiting, with the caveat that most of the data used to support clinical decision making is from studies of either gastroparesis or FD. As mentioned previously, a few special categories exist. For example, the occasional patient who suffers from chronic nausea and vomiting due to severe gastritis, esophagitis or peptic ulcer disease identified on endoscopy, should receive a proton pump inhibitor (PPI) with follow-up at 8–12 weeks. Achalasia and other esophageal motility disorders (see Table 1) may present with chronic nausea and vomiting, as can chronic intestinal pseudo-obstruction. Treatment for these conditions is individualized and include Heller myotomy, peroral endoscopic myotomy (POEM), or in the case of CIP, pyridostigmine. Data from large, prospective, randomized controlled trials using nausea and vomiting as the primary outcome for these disorders is not available. Patients with chronic nausea and vomiting may benefit from using either liquid (e.g., granisetron, or promethazine or metoclopramide) or oral dissolving (e.g., ondansetron, or metoclopramide) or transdermal (e.g., scopolamine patch) formulations of their anti-emetic medications in order to maximize absorption and optimize pharmacokinetics.

1. *Prokinetics* promote aborad movement of luminal contents through increased contractility of the gastrointestinal tract. In a systematic analysis of prokinetics in gastroparesis, erythromycin was the most effective on gastric emptying, while both erythromycin and domperidone improved overall symptoms [79]. A recent Bayesian network meta-analysis of treatment of the related condition, FD, suggests that metoclopramide, trimebutine, mosapride, and domperidone showed better efficacy than itopride or acotiamide [80]; however,

there is possible publication bias or other small study effects in appraisal of prokinetics for non-ulcer dyspepsia [81].

2. *Dopamine receptor antagonists*: Dopamine inhibits gastrointestinal motility through D2 receptors [82]. Dopamine receptor antagonists theoretically accelerate gastric emptying. Metoclopramide is the only FDA approved medication for gastroparesis; it targets both D1 and D2 dopamine receptors [18, 82] with peripheral gastrointestinal prokinetic and central antiemetic effects [82]. It should be started at the lowest possible dose (5 mg, 15 min before meals and at bedtime) and then titrated to a maximum of 40 mg/day. Metoclopramide is available as a tablet, orally disintegrating, liquid, and injectable form [83]. Metoclopramide nasal spray decreased symptoms in women (but not in men) with diabetic gastroparesis [84]. Side effects of metoclopramide include akathisia, restlessness, insomnia, and agitation that are treatable with diphenhydramine and resolve with cessation of the drug [83]. Major side effects include tardive dyskinesia (FDA black box warning), depression, and prolongation of QTc [85]. The precise risk of irreversible tardive dyskinesia is unclear [86]. Unless patients have therapeutic benefits that outweigh potential risks, metoclopramide should not be used for more than 12 weeks [18].
   Domperidone, another oral D2 receptor antagonist (10 mg, t.i.d. before meals), is as efficacious as metoclopramide [18] but may cause prolonged QTc, cardiac arrhythmias, and sudden cardiac death [87]. It is not FDA approved and can only be prescribed through FDA's expanded access to investigational drugs [85], if the corrected QTc is <450 ms for males and <470 ms for females [https://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm490128.pdf]. The European Medicines Agency recommends domperidone should not be used for more than one week at a time. In a recent prospective cohort study in patients with refractory gastroparesis symptoms, improvement was noted in 68% of patients [88], with better responses in those with normal gastric emptying or <30% retention at 4 h.
   Drug interactions (based on CYP450-2D6 or CYP450-3A4) can occur with certain antiemetics and antidepressants, often co-prescribed for treatment of gastroparesis [18], and these potential interactions should be reviewed carefully with the patient.
3. *Motilin receptor agonists*: Macrolide antibiotics are motilin receptor agonists that stimulate enteric cholinergic neurons and smooth muscle directly [89]. Erythromycin and azithromycin stimulate gastric emptying and antral pressure activity [90]; however, both are associated with tachyphylaxis caused by down regulation of the motilin receptor at ~2 weeks after initiation of therapy [91].
4. *5-HT$_4$ receptor agonists* release acetylcholine from myenteric neurons, resulting in smooth muscle contractions and accelerated gastric emptying. Prucalopride, a highly selective 5-HT$_4$ receptor agonist with no effects on hERG channel, significantly increased gastric emptying and improved symptoms and quality of life in patients with idiopathic gastroparesis [92] without cardiac effects. Prucalopride is not available in the U.S. Velusetrag is undergoing clinical trials in patients with gastroparesis (ClinicalTrials.gov Identifier: NCT02267525). It accelerates gastric emptying after six consecutive days of treatment in healthy subjects [93].
5. *Ghrelin receptor agonists*: Ghrelin, a 28-amino acid peptide produced in the stomach, increases food intake [94]. Ghrelin administration increased gastric emptying and improved meal-related symptoms in patients with idiopathic gastroparesis [30].

Relamorelin, a pentapeptide ghrelin receptor agonist, accelerated gastric emptying of solids in diabetic patients [85, 95, 96] and increased antral contractions without affecting gastric accommodation [97]. Relamorelin also significantly accelerated gastric emptying and decreased symptoms associated with diabetic gastroparesis [98, 99].

Antiemetics

Antiemetics are required for management of nausea and vomiting. Commonly prescribed agents include *phenothiazines* (e.g., prochlorperazine), *antihistamines* (e.g., promethazine), or *5-HT$_3$ receptor antagonists* (e.g., ondansetron). Transdermal scopolamine improves symptoms in some patients with chronic nausea and vomiting, although prospective controlled studies are lacking, and some patients note side effects of visual changes and a dry mouth. Scopolamine competitively inhibits muscarinic receptors for acetylcholine, and exerts central sedative, antiemetic and amnestic effects. The main indication is motion sickness and it may retard gastric emptying by its antimuscarinic effects, and should be avoided in patients with gastroparesis.

Cannabinoids are also approved for chemotherapy-induced nausea and vomiting (CINV). Cannabis is used by patients who report relief of symptoms and increase in appetite. However, CHS may occur with chronic cannabis use, characterized by cyclic episodes of nausea and vomiting (mimicking CVS), and frequent hot bathing [100].

The *neurokinin-1 receptor antagonist*, aprepitant, acts centrally by counteracting the activity of substance P [101]. It is widely used in combination with other agents for CINV [102]. In a controlled trial of 125 patients with symptoms of gastroparesis, there was overall symptom relief with aprepitant compared to placebo, with no significant adverse effects [103]. In two case reports [104, 105], aprepitant successfully treated nausea and vomiting in patients with gastroparesis. Aprepitant did not delay gastric emptying, but it enhanced gastric accommodation and volume to satiation in healthy subjects [106].

Aside from their benefits in treating visceral pain (see following section), low dose tricyclic antidepressants (TCAs) have shown some benefit in functional nausea and vomiting [107], including diabetic patients [108].

Pain management

Abdominal pain is reported by 90% of patients with gastroparesis [18], and may contribute to symptoms of nausea and vomit-

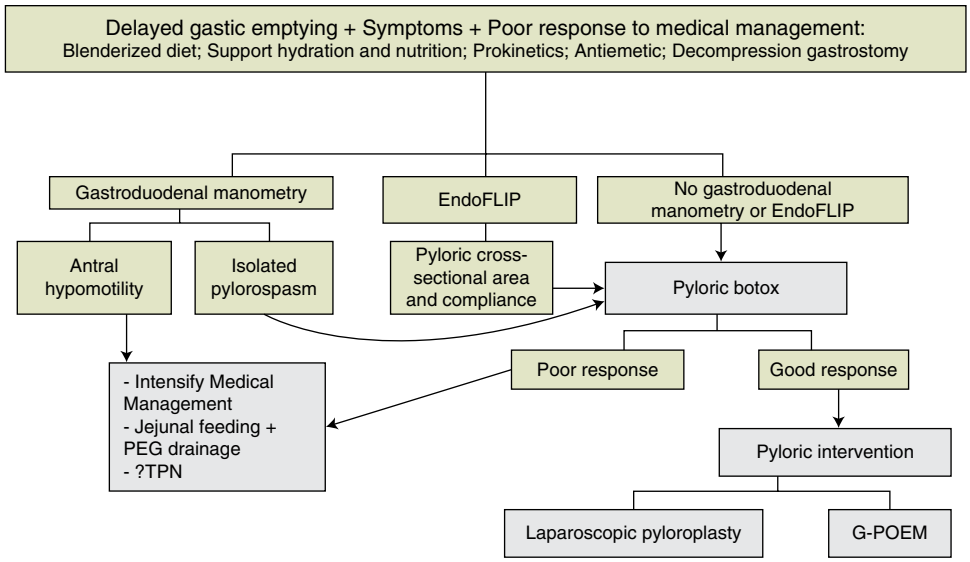

Fig. 3 Proposed algorithm for introduction of pyloric interventions for management of gastroparesis unresponsive to medical management

ing. In the largest controlled trial of nortriptyline in patients with idiopathic gastroparesis, there was no benefit on composite or individual symptoms [109]. Mirtazapine helped ameliorate symptoms, especially nausea and vomiting, in individual reports of diabetic or non-diabetic gastroparesis [110–113]. Although data from controlled trials is not available, low-dose gabapentin may improve visceral pain in some patients and also improve symptoms of nausea. Abdominal pain that is thought to result from severe gastritis or antro-pyloric ulcerations should be treated with a PPI. Opioids should be avoided, given their potential to decrease gastric motility and to worsen nausea.

Pyloric and other surgical interventions

Pylorospasm has been observed in patients with gastroparesis [114]; it is conceivable that endoscopic (BOTOX injection or POEM) or surgical interventions (pyloroplasty) could be beneficial in these patients [85]; however, formal sham-controlled trials are necessary. Success of pyloric intervention may be predicated by preservation of antral motor activity and ability to triturate solids [115]. An algorithm for selection of patients for pyloric interventions such as G-POEM or laparoscopic pyloroplasty is summarized in Fig. 3; assessment of pyloric cross-sectional area and compliance with Endo FLIP may help select patients for consideration of pyloric interventions such as gastric POEM.

When evaluating patients with chronic nausea and vomiting, mechanical and/or anatomical causes may be identified (see Table 3). These should be corrected surgically, as indicated. Surgical options for patients with gastroparesis are limited and should be approached cautiously [3, 78, 85]. The rare gastroparesis patient with persistent symptoms of nausea and vomiting resistant to all standard and experimental therapy may benefit from total gastrectomy, however, this experience was predominantly based on patients with prior vagotomy or partial gastrectomy performed for peptic ulceration [116] and well-designed, prospective trials in patients without prior gastric surgery do not exist.

Gastric electrical stimulation (GES)

GES is FDA-approved as a humanitarian exemption device in refractory diabetic and idiopathic gastroparesis. There is limited controlled trial evidence of efficacy [117, 118]. GES does not normalize gastric emptying. In a large database of patients with GES and continued pharmacological therapies [119], 75% had improvement in symptoms.

Complementary and alternative therapy

A number of complementary and alternative therapies (CAM) are used to treat symptoms of chronic nausea and vomiting (regardless of the underlying cause), although data from large, randomized, placebo-controlled trials is lacking for most agents. The most commonly used CAM therapies are briefly described.

Electroacupuncture [120–122] or osteopathic manipulative treatment [123] are used by some patients; however, efficacy is based mostly on individual reports.

Ginger, in a variety of forms (e.g., powder, oils, tea, candied, crystallized, pickled) has been used for centuries to treat nausea and vomiting; the precise mechanism of action of its antiemetic function is unknown. Most studies have focused on the use of ginger to treat nausea and vomiting in pregnancy or due to chemotherapy; large prospective trials for nausea and vomiting secondary to gastrointestinal disorders are lacking. A recent systematic review of 12 studies involving 1278 pregnant women found that ginger (in a variety of forms and doses) was more effective than placebo at relieving symptoms of nausea and vomiting [124]. Ginger is considered safe with few adverse effects; the recommended dose in studies of pregnant women is approximately 1000 mg/day. A systematic review of ginger in CINV found that ginger, when used as a supplement to other anti-emetic agents, provided some further relief of symptoms, although differences in preparation and dosing make the results difficult to interpret [125].

Iberogast is a liquid that contains nine distinct herbal products. It has been available in Europe for more than 40 years and is widely used to treat symptoms of irritable bowel syndrome and FD. Pro-

spective, randomized, controlled trials evaluating the efficacy and safety in patients with chronic nausea and vomiting (of any cause) have not been published, and thus a definitive recommendation cannot be made about its use.

Caraway oil and peppermint oil are often used by patients to improve symptoms of dyspepsia or IBS. Both agents are considered safe, however data from prospective, randomized, controlled trials in patients with nausea and vomiting due to a gastrointestinal cause are lacking.

Hypnotherapy is considered safe and efficacious for a number of medical and psychological disorders. A systematic review evaluating the efficacy of hypnotherapy for the treatment of nausea and vomiting related to chemotherapy found some benefits, however, five of the six studies were performed in children [126]. No data is available from studies involving patients with chronic nausea and vomiting of gastrointestinal origin.

CONCLUSION

Chronic nausea and vomiting is a common problem that develops for a diverse array of reasons, both gastrointestinal and non-gastrointestinal in nature. At the initial encounter with a patient referred for chronic nausea and vomiting, clinicians need to act as a skillful detective; teasing out key characteristics of the history is essential and will eliminate unnecessary testing and inappropriate medications. After excluding a structural or organic cause for symptoms of nausea and vomiting, identifying the patient with delayed gastric emptying is useful, as it frequently influences therapy. Early initiation of therapy is important as it may minimize complications of chronic nausea and vomiting (e.g., hypochloremic alkalosis, hypokalemia, malnutrition, Mallory-Weiss tear, Boerhaave's syndrome). Medical therapy should be individualized based on previous trials, and a careful discussion with the patient regarding risks, benefits and costs. Combination therapy is useful for many patients, although prospective studies evaluating this are not available. Novel pharmacotherapy with prucalopride and relamorelin are promising, and endoscopic or laparoscopic interventions may change the landscape of therapy for gastroparesis [127, 128].

CONFLICT OF INTEREST

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