REVIEW

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Gastroparesis for the nongastroenterologist

ABSTRACT

Gastroparesis is a heterogeneous motility disorder characterized by nausea, vomiting, and postprandial fullness. Its diagnosis requires objective documentation of delayed gastric emptying of solid food and exclusion of mechanical obstruction. Its epidemiology is unclear, and the main causes are diabetes mellitus and idiopathic disease. Cardinal symptoms often co-occur. Management involves nutritional assessment, dietary changes, drug evaluation, glycemic control (for patients with diabetes mellitus), and symptom relief. In this review, we explore challenges nongastroenterologists may encounter and how they can use current recommendations to manage patients with gastroparesis.

KEY POINTS

The diagnosis of gastroparesis requires specific symptoms and objective documentation of delayed gastric emptying of solid food without mechanical obstruction, which should be excluded by upper gastrointestinal endoscopy or imaging studies.

Cardinal symptoms of gastroparesis such as nausea, vomiting, early satiety, postprandial fullness, bloating, belching, and upper abdominal discomfort usually present in clusters or combinations.

Management of gastroparesis aims to improve symptoms and gastric emptying. It includes improving nutritional status through dietary modifications, minimizing or avoiding drugs such as opioids, achieving glycemic control in patients with diabetes, treating underlying causes, and instituting pharmacologic and nonpharmacologic options when indicated.

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Gastroparesis is a chronic motility disorder and a heterogeneous syndrome with significant variability in its symptoms, causes, severity, and response to treatment. It is defined by symptoms such as nausea, vomiting, postprandial fullness, and upper abdominal discomfort; objective documentation of delayed gastric emptying of solid food; and exclusion of mechanical obstruction.[1]

Delayed gastric emptying was first reported in patients with diabetes by Boas[2] in 1925, and the term "gastroparesis diabeticorum" was used by Kassander[3] in 1958 to describe asymptomatic gastric retention in patients with diabetes. Although diabetes mellitus accounts for more than one-third of all cases of gastroparesis,[4] other risk factors include gastrointestinal surgery, medications, and neurologic and autoimmune disorders. Moreover, in many patients no underlying cause is found,[5] making this condition even more variable.

Regardless of the cause and despite advances in understanding of the pathogenesis (which has unresolved questions), gastroparesis poses a challenge in diagnosis and management for gastroenterologists and nongastroenterologists alike.

This review focuses on the most relevant challenges encountered when approaching patients with this condition, current recommendations for diagnosis and treatment, and how nongastroenterologists such as primary care clinicians can use these to help manage patients.

PREVALENCE VARIES IN DIFFERENT STUDIES AND COUNTRIES

A 2023 systematic review reported that the overall standardized prevalence of gastroparesis

ranged widely (from 13.8 to 267.7 per 100,000 adults) in studies from 1994 to 2019.[6] However, many of these studies used a broad definition of gastroparesis ("probable and/or possible gastroparesis") solely based on diagnosis codes and without objective evidence of delayed gastric emptying.

Community-based studies with a strict case definition (objective evidence of delayed gastric emptying, typical symptoms, and absence of mechanical obstruction)[1] appear to offer a more accurate estimate. For instance, 2 US studies using community-based databases reported a prevalence of 21.5 per 100,000 adults[7] and 24.2 per 100,000 adults.[8] In contrast, a study conducted using a community database from the United Kingdom and a strict case definition reported a prevalence of 13.8 per 100,000 persons.[9] Similarly, a study from Israel showed a crude prevalence of 13.6 per 100,000 persons.[10] The incidence has been reported to be around 6.3 per 100,000 person-years in the United States[8] and 1.9 per 100,000 person-years in the United Kingdom.[9]

The difference in prevalence in different studies and countries can be attributed to several factors. First, epidemiologic studies classify gastroparesis inconsistently: some rely solely on diagnosis codes while others consider specific diagnostic criteria. Second, the diagnosis of gastroparesis may vary among regions and countries, influenced in part by differences in the methodology of gastric emptying studies and variations in clinical practice.[6] Lastly, diabetes mellitus is a major contributor to gastroparesis, and its prevalence is notably higher in the United States (11.6%)[11] than in the United Kingdom (7%)[12] and Israel (2.6%),[13] potentially contributing to the overall higher prevalence of gastroparesis in the United States.

The mean age of patients with gastroparesis has been reported as between 45.4 and 58.9 years, and the proportion who are White from 46.7% to 90.1%.[6] In several reports, most patients (63.7% to 76.4%) were female,[6] with an age-adjusted female-to-male ratio of 3.9:1.[8] Although this female predominance has been attributed to factors such as sex hormones, it has not been accurately described or researched.[6]

The mortality rate is higher in patients with gastroparesis than in the general population, the most common causes of death being cardiovascular disease, respiratory failure, and malignancy, although some studies reported that inpatient mortality rates have been falling over time.[6]

The most common comorbidities also differ among regions and countries. For instance, in the United States the most common comorbidities were hypertension, smoking history, obesity, chronic pulmonary disease, and cerebrovascular disease, regardless of the cause of gastroparesis, while in the United Kingdom chronic pulmonary disease was most common, followed by renal disease and malignancy.[7,9]

DIABETES AND OTHER CAUSES

Diabetes and idiopathic disease are the most common causes of gastroparesis. However, the etiology differs among studies and populations.

A large national claims database study from the United States (N = 82,574,650) reported diabetes mellitus as the most common cause, involving 57.4% of all cases, with type 2 diabetes (51.7%) being more prevalent than type 1 (5.7%).[7] Second was surgery (15%), mostly esophageal, gastric, and duodenal surgeries, although there are anecdotal cases involving cardiothoracic surgery, mainly vagus nerve resection.[7] Third (11.8%) were drugs that can impair gastric emptying (opioids, anticholinergic agents, calcium channel blockers, glucagon-like peptide 1 [GLP-1] receptor agonists, cyclosporine). Unknown causes came fourth (11.3%).[7] Other causes such as autoimmune diseases (scleroderma, systemic lupus erythematosus), hypothyroidism, Parkinson disease, cerebral palsy, and multiple sclerosis account for less than 5% of all cases.

Other studies had different findings. For instance, another US study found that the most common causes were idiopathic (49.4%), diabetes mellitus (25.3%), drugs (22.9%), and surgery (7.2%).[8] In another large population-based study in the United States (N = 43,827,910), diabetes was the most common cause (71.7%), followed by idiopathic (28.3%).[14] However, the investigators relied solely on diagnosis codes from medical records for gastroparesis classification.

Interestingly, the etiology varies in other countries and regions. For instance, in the UK study, idiopathic disease was the most common cause of gastroparesis (39.4%), followed by diabetes (37.5%)[9]; in the study in Israel,[10] diabetes accounted for 17.2% of all cases and the rest (82.8%) were classified as idiopathic (the authors excluded cases due to other causes).

Differences in the etiology of gastroparesis across countries can be partly explained by differences in the prevalence of diabetes mellitus, which is probably the most common cause where its prevalence is higher. Additionally, in some studies, the differentiation of the etiology is poor, with subgroup analyses that classify all nondiabetic gastroparesis cases (postsurgical, drug-induced) as idiopathic.[6]

Evidence regarding certain risk factors or causes of gastroparesis lacks consensus. For example, hypothyroidism has been reported to be associated with 4.0% of cases.[7] Some studies suggest hypothyroidism may affect esophageal and gastric motor activity, leading to upper gastrointestinal symptoms that can be improved with thyroid hormone replacement.[15,16] However, a group of experts from European gastroenterology societies could not reach consensus on hypothyroidism as a cause of gastroparesis.[5] Similarly, this group did not reach consensus on whether viral infections can cause gastroparesis.[5] Nonetheless, gastroparesis has been (rarely) associated with viruses such as Epstein-Barr, norovirus, herpes, and cytomegalovirus, and viral illness has been linked to poor prognosis if there is evidence of autonomic dysfunction, such as postural hypotension.[4]

Recent findings highlight that gastrointestinal motility disorders presenting with gastroparesis symptoms can occur in patients with generalized autoimmune dysautonomia.[17] Several antibodies have been associated with autoimmune disorders that manifest gastroparesis-like symptoms, including antibodies targeting ganglionic nicotinic acetylcholine receptors containing alpha 3 subunits or antibodies against calcium channels.[17]

For instance, autoimmune gastrointestinal dysmotility is a limited form of autoimmune dysautonomia that can occur as an idiopathic or paraneoplastic phenomenon. It has various presentations: hypermotility or hypomotility, such as colonic inertia, pyloric obstruction, anal spasm, and gastroparesis.[17] It is believed that an unknown number of "idiopathic" gastroparesis cases may fall within this category, leading to consideration of immunotherapy as a treatment option.[17] However, stronger evidence regarding the immune profiles and response to immunotherapy of this group of patients is needed. The latest American College of Gastroenterology guideline does not recommend routine clinical use of autoimmune therapy in the management of gastroparesis.[1]

GASTROPARESIS OFTEN PERSISTS DESPITE TREATMENT

More than two-thirds of patients receiving treatment for gastroparesis do not have significant symptom improvement during 1 year of follow-up.[18,19]

Gastroparesis is associated with increased emergency department visits and hospitalizations due to exacerbation of symptoms such as vomiting, electrolyte abnormalities, abdominal pain, and malnutrition. Higher healthcare resource utilization has been shown within 2 years of gastroparesis diagnosis.[10]

Gastroparesis predominantly affects women, who are more likely to have idiopathic gastroparesis with more severe symptoms of postprandial fullness, early satiety, bloating, and upper abdominal pain, and are less likely to improve after 48 weeks of follow-up.[18,19]

Some predictors of improvement over 48 weeks include age 50 and older, moderate or severe gastroparesis (> 20% gastric retention at 4 hours), and onset of gastroparesis following an infectious prodrome. Predictors associated with lack of improvement include being overweight or obese, severe abdominal pain, concomitant gastroesophageal reflux (eg, pyrosis, dysphagia, chest pain, chronic cough), and depression.[18,19]

Gastroparesis in patients with type 1 diabetes mellitus is associated with higher hemoglobin A1c levels, longer duration of gastrointestinal symptoms, greater gastric retention, and more hospitalizations due to gastroparesis. Patients with type 2 diabetes mellitus and gastroparesis are older and heavier and have more comorbidities. More than 40% of patients with type 2 diabetes who require insulin therapy have delayed gastric emptying.[18]

Improvement in glycemic control is associated with a decreased incidence of microvascular complications, and it is expected to be associated with a lower incidence of diabetic gastroparesis.[4] Indeed, diabetic gastroparesis seems to be associated with poor glycemic control and vascular and neurogenic complications.[20] But once delayed gastric emptying is established, it may persist for up to 25 years despite improved glycemic control.[21]

GASTRIC EMPTYING IS COMPLEX, AND SO IS GASTROPARESIS

In diabetic and idiopathic gastroparesis, the main alterations that lead to delayed gastric emptying and symptoms are impaired accommodation of the gastric fundus and body, antral hypomotility, impaired pyloric relaxation, and dysmotility in the small intestine.[18]

Emptying a meal from the stomach into the small bowel requires complex coordination involving the fundus, antrum, and pylorus. Swallowing induces relaxation of the gastric fundus, allowing it to accommodate the food. Then, steady increases in fundic tone propel gastric contents toward the pylorus, where phasic contractions facilitate the grinding of digestible solids.[18] The antral contractions are regulated by the interstitial cells of Cajal, generating a basal electrical rhythm. This process reduces digestible solids to particles 2 mm or smaller, forming the chyme. Small bowel function is also crucial to complete gastric emptying, as emptying

requires coordination between the antrum and pylorus, and inhibitory signals from the small bowel modulate emptying rates based on chyme composition.[18]

Fewer inhibitory neurons expressing nitric oxide synthase (nitrergic neurons) may play an important role in impaired accommodation and pyloric relaxation.[4,18] The interstitial cells of Cajal and cells positive for platelet-derived growth factor receptor-alpha (fibroblast-like) in the gastric smooth muscle layer are considered the pacemakers that convey the stimulation from extrinsic vagal fibers and intrinsic enteric nerves to the gastric smooth muscle cells (multicellular electrical syncytium), resulting in coordinated contractions towards the antropyloric region.[4] Reduced numbers of interstitial cells of Cajal and fibroblast-like cells and altered expression of smooth muscle cell contractile protein have been found in patients with gastroparesis, and this may explain the antral hypomotility that interferes with peristalsis, trituration, and gastric emptying.[4]

Immune alterations seem to play an important role in the mechanism of injury. Injury and loss of the interstitial cells of Cajal, smooth muscle cells, and fibroblast-like cells, comprising the electrical syncytium of the gut, have been associated with reduced numbers of anti-inflammatory M2 macrophages, which mediate cell repair.[4,18] Losing M2 macrophages reduces the protection of neural tissue from oxidative stress and inflammation—both involved in diseases such as diabetes mellitus.[4]

NAUSEA, VOMITING, EARLY SATIETY

The main symptoms of gastroparesis are nausea, vomiting, early satiety, postprandial fullness, bloating, belching, and upper abdominal discomfort.[4] These cardinal symptoms are usually present in clusters or combinations, eg, abdominal pain with early satiety and heartburn; heartburn with bloating, early satiety, nausea, and vomiting; and regurgitation with bloating, nausea, and vomiting.[4,22]

Severe early satiety and postprandial fullness are reported by 50% to 60% of patients, and 95% experience nausea, which is the predominant symptom in 29% of cases.[18] Nausea is related to food intake in at least three-quarters of patients; in 40% of cases, nausea lasts most of the day.[18]

Vomiting and early satiety are often the initial symptoms in diabetic gastroparesis. Patients with diabetic gastroparesis may experience greater nausea and longer periods of vomiting than those with idiopathic gastroparesis.[18,23]

Abdominal pain is often the initial presentation of idiopathic gastroparesis.[23] Two-thirds of patients report it, and it is associated with nonacute onset of gastroparesis, bowel disturbances, and opiate and antiemetic use. In addition, patients in whom pain is the predominant symptom have greater impairment in quality of life than those in whom nausea and vomiting predominate.[18]

Bloating is more significant in women, individuals who are overweight, and those using probiotics, regardless of the etiology.

DIAGNOSIS REQUIRES SYMPTOMS PLUS STUDIES

The diagnosis of gastroparesis requires 3 criteria:

- Symptoms of gastroparesis
- Exclusion of mechanical obstruction such as pyloric stenosis with esophagogastroduodenoscopy or a radiographic study
- Evidence of delayed gastric emptying of solids.

There are currently 2 gold-standard tests to document delayed gastric emptying: gastric emptying scintigraphy and the stable isotope gastric-emptying breath test.

Gastric emptying scintigraphy

Gastric emptying scintigraphy measures gastric emptying of a solid meal using an egg or protein-based (western-style) or rice-based (Asian-style) meal containing a radioisotope, usually technetium Tc 99m. A gamma camera is used to scan the gastric area (anteroposterior view) at baseline and 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after the meal. Normally, more than 90% of the solid meal should be emptied at 3 hours. Retention of more than 10% at 4 hours is considered diagnostic for delayed gastric emptying.[1] The assessment of severity based on gastric emptying scintigraphy is as follows[24]:

- Grade 1 (mild): 11% to 20% retention at 4 hours
- Grade 2 (moderate): 21% to 35% retention
- Grade 3 (severe): 36% to 50% retention
- Grade 4 (very severe): > 50% retention.

While this reporting method is the most commonly used, the results can be presented in other ways such as half-time of emptying or rate of emptying (percent per minute), and the test may be conducted under varied protocols. This lack of standardization complicates the clinical utility of the test and poses a challenge for physicians and patients, particularly when interpreting tests from different institutions.[24] A unified protocol that can be implemented in all institutions and nuclear medicine facilities would be optimal.

The test has other limitations. Radiation exposure limits its use in pregnant or breastfeeding women; patients with severe symptoms or allergies may not tolerate a solid

meal; and special equipment and rooms are needed.[4,18] Hyperglycemia can delay gastric emptying and thus confound the test; hence, the test should not be done if the fasting blood glucose level is above 200 mg/dL.[4]

Medications that affect gastric emptying should be withheld before the test (**Table 1**).[25] This includes marijuana (the time frame is unknown).

Glucagon-like peptide-1 (GLP-1) receptor agonists and gastric inhibitory polypeptide receptor agonists, commonly used for managing diabetes mellitus and obesity, are associated with nausea and vomiting attributed to delayed gastric emptying. However, there are no clear guidelines on how long to withhold these medications before a gastric emptying test. While the American Society of Anesthesiologists advises skipping 1 weekly dose of GLP-1 receptor agonists before endoscopy, the American Gastroenterological Association at this time does not endorse this recommendation and suggests tailoring the approach for each patient based on the indication for the GLP-1 agonist and clinical symptoms before endoscopy.[26] While not officially recommended for gastric emptying scintigraphy, the guidelines above may serve as a reference for clinicians ordering the test. The decision to withhold GLP-1 agonists before gastric emptying scintigraphy seems to be based on institutional guidelines and clinician experience.

TABLE 1
Medications to discontinue 48 to 72 hours before gastric emptying scintigraphy

Prokinetics
Metoclopramide, cisapride, domperidone, erythromycin

Anticholinergics, antispasmodics
Dicyclomine, donnatal, hyoscyamine, glycopyrrolate

Opioids
Meperidine, codeine, morphine, oxycodone

Laxatives
Any laxative (discontinue 24 hours before)

Gastric acid suppressants, aluminum-containing antacids
Aluminum hydroxide

Calcium channel blockers
Amlodipine, nifedipine

Agents that may affect gastric emptying
Atropine, benzodiazepines, octreotide, progesterone, theophylline, phenylamine

Adapted from reference 25.

The stable isotope gastric-emptying breath test

The stable isotope gastric-emptying breath test involves the patient ingesting a meal containing a carbon 13-labeled substrate such as *Arthrospira (Spirulina) platensis* (edible blue-green algae) or octanoic acid (a medium-chain fatty acid).[27] Then, breath samples are taken to calculate the carbon 13 carbon dioxide excretion rate for approximately 4 hours, usually at 45, 90, 120, 180, and 240 minutes. At any time point, the carbon 13 carbon dioxide excretion is proportional to the rate of gastric emptying, so that increasing excretion means increasing rates of gastric emptying. Patients with delayed gastric emptying will have carbon 13 carbon dioxide excretion rates lower than references values.[27]

This test is relatively easy to perform. It can be done in the office or at the bedside and does not require elaborate detection equipment. Because it does not involve radiation exposure, it is safer than scintigraphy, which is especially important in pregnant or breastfeeding women and children.[28] On the other hand, it may be inaccurate in patients with malabsorption or liver or lung diseases.[1,27] Physical activity influences carbon dioxide production, and hence, measurements of the breath test. Therefore, it is recommended that patients be at rest through the entire test.[27]

Other tests

American College of Gastroenterology guidelines[1] recommend against using whole-gut motility tests such as the radiopaque marker test as well as the wireless motility capsule to measure gastric emptying. The main reason that the radiopaque marker and the nondigestible wireless motility capsule are not recommended is that they do not empty with the solid food from the stomach and hence may give a false-positive result of delayed gastric emptying.[5] There is evidence that the capsule empties during phase III of the migrating motor complex, similar to a nondigestible solid, which occurs after digestion of solid food.[29]

Electrogastrography may complement the identification of pathophysiologic mechanisms in gastric function, as it reveals distinct patterns and electrical waves associated with specific motility disorders such as gastroparesis, functional dyspepsia, and cyclic vomiting. However, the clinical significance of this information remains unclear,[1] and as a result, it is not routinely requested. More research will help to clarify its role in clinical practice.

TABLE 2
Differential diagnosis of gastroparesis

Disorder	Clinical presentation and differentiation from gastroparesis	Treatment
Functional dyspepsia	Less nausea and vomiting Often indistinguishable	*Helicobacter pylori* eradication, proton pump inhibitors, tricyclic antidepressants, prokinetics, consider psychotherapy[29]
Rumination syndrome	Effortless and repetitive regurgitation of ingested food	Behavioral modification: deep-breathing exercises, diaphragmatic breathing
Cyclic vomiting syndrome	Absence of symptoms between vomiting episodes Compulsive hot bathing or showering Strong association with personal or family history of migraines	Acute attacks: ondansetron, triptans, aprepitant Prophylaxis: tricyclic antidepressant, topiramate, aprepitant, zonisamide, levetiracetam
Cannabinoid hyperemesis syndrome	Absence of symptoms between vomiting episodes Compulsive hot bathing or showering Cannabis use Gastric emptying scintigraphy might be normal	Benzodiazepines, tricyclic antidepressants, haloperidol, droperidol, promethazine, prochlorperazine, ondansetron, corticosteroids, capsaicin Cannabis cessation
Anorexia or bulimia	Binge and purge behavior (bulimia), and severe caloric restriction (anorexia)	Psychotherapy, selective serotonin reuptake inhibitors
Anxiety disorder toward food (avoidant restrictive food intake disorder)	Immediate postprandial nausea and vomiting when patients see the food or put it in their mouth	Cognitive behavioral therapy, cyproheptadine
Narcotic bowel syndrome	Chronic or intermittent colicky abdominal pain that worsens when the narcotic effect wears off Constipation is common	Clonidine, benzodiazepines, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, laxatives, methylnaltrexone

Based on information from references 30–32.

CONSIDER OTHER FACTORS, DISORDERS

During the assessment, it is important to consider manageable factors that could explain gastroparesis symptoms. This includes reviewing the patient's medical history, assessing medications that may affect gastric emptying (eg, opioids, GLP-1 receptor agonists), and obtaining thyroid function tests. In addition, sensory or motor disorders of the upper gastrointestinal tract may have similar symptoms as gastroparesis.

Some functional gastrointestinal disorders can have a clinical presentation similar to that of gastroparesis. Hence, it is important to properly differentiate among them (**Table 2**).[30–32] Functional dyspepsia, rumination syndrome, cyclic vomiting syndrome, and others should be considered in the differential diagnosis.

Functional dyspepsia can be indistinguishable from gastroparesis.[30] It is defined by similar symptoms, eg, early satiety, postprandial fullness, bloating, and epigastric discomfort or pain, and approximately 25% to 35% of patients may have delayed gastric emptying.[4] Two categories or subtypes are recognized: epigastric pain syndrome and postprandial distress syndrome, with postprandial distress syndrome having more similarities to symptoms of gastroparesis.[30]

Distinguishing between functional dyspepsia and gastroparesis is important, since functional dyspepsia has different treatments and a better prognosis.[1]

Rumination syndrome presents with effortless, repetitive regurgitation, chewing, and reswallowing, or spitting out previously digested food.[4,30] It can be

diagnosed with combined high-resolution manometry–impedance monitoring, revealing a pattern of low-pressure gastric straining followed by regurgitation.[31] Treatment of rumination syndrome is also different, with education and behavioral modification (diaphragmatic and deep-breathing exercises).[30,31]

Cyclic vomiting syndrome (associated with a personal or family history of migraines) and **cannabinoid hyperemesis syndrome** (associated with heavy cannabis use) should be considered in the differential diagnosis. Both present with episodic attacks of severe nausea and vomiting, usually associated with dehydration and electrolyte imbalance.[4,31]

Eating disorders such as anorexia and bulimia nervosa should be considered because a low body mass index is associated with delays in gastric emptying and disturbed gastric functioning. Treatment involves psychotherapy and nutrition enforcement, but not prokinetics.[31]

Anxiety disorder toward food, also known as avoidant restrictive food intake disorder, can mimic gastroparesis. However, patients with this disorder have immediate nausea and vomiting as soon as they see food (before eating), while those with gastroparesis have delayed symptoms (20 to 30 minutes after eating). This condition is treated with psychotherapy and neuromodulators.[30]

Narcotic bowel syndrome can be considered in the differential diagnosis, since it is characterized by a progressive and somewhat paradoxical increase in abdominal pain (accompanied by bloating and nausea) despite continued or escalating doses of opioids.[31,32]

Conditions that present with constipation as the predominant syndrome should also be considered. In this case, upper gastrointestinal symptoms and delayed gastric emptying may be the result of constipation, and the symptoms improve when it resolves.[30]

MANAGEMENT: A COMPREHENSIVE STRATEGY

A comprehensive strategy for managing gastroparesis includes optimizing nutritional status (balance between nutrients acquired from food and beverages and their use by the body for essential functions), improving gastric emptying, reversing iatrogenic causes, and achieving glycemic control in patients with diabetes.[1,18,33] It is crucial to avoid medications that exacerbate the gastric emptying delay, such as opioids and GLP-1 receptor agonists. The different strategies for management are summarized in **Table 3**.

Diet and nutrition

The first-line approach is to educate patients on a small-particle diet.[34] This consists of foods with a small particle size or those that can be processed into small particles (eg, soups, smoothies, apple sauce). Foods that are initially not in a small-particle form such as corn, peas, and onions should be avoided, but these foods can be included when they are processed to smoothie consistency.[34]

A registry study found that only one-third of patients with gastroparesis had received nutritional counseling, and just 2% adhered to dietary recommendations for patients with gastroparesis.[35] Even though obesity is increasingly prevalent among patients with gastroparesis, 64% of patients in the registry reported consuming calorie-deficient diets, leading to various vitamin and mineral deficiencies.[35] Consequently, it is important to include a thorough assessment of caloric intake and provide dedicated nutritional counseling for these patients.

In cases of severe gastroparesis despite medical and nutritional interventions, it may be necessary to consider inserting a jejunal feeding tube to bypass the stomach and deliver the formula directly into the small bowel.[33,36] The preferred approach involves placing feeding tubes directly into the jejunum, by either endoscopy or laparoscopy, instead of using percutaneous endoscopic gastrostomy tubes.[33] It is crucial to allow for a gradual adaptation period, incrementally increasing the infusion rate over a few days until the desired feeding rate is achieved.[33,36] Prolonged use of enteric tubes is typically regarded as safe, but there can be infrequent complications such as clogging, dislodgment, malfunction, tip migration, and site infections.[36]

Patients with severe gastroparesis frequently need hospitalization to address their condition, including intravenous hydration to correct metabolic imbalances, nasoenteric decompression, and temporary parenteral nutrition for those experiencing significant weight loss and difficulties with oral intake.[18,33] Total parenteral nutrition can be considered for advanced cases of gastroparesis; however, reinstating oral intake is generally recommended when feasible to reduce the risk of complications such as central-line infections.[1,33]

Prokinetic medications

Pharmacologic therapy of gastroparesis involves prokinetics, antiemetics, and neuromodulators. Prokinetics act by stimulating nonsphincteric muscle contractility. They are classified into different pharmacologic classes, including dopamine (D2) receptor antagonists, serotonin (5-hydroxytryptamine 4 [5-HT4]) receptor agonists, cholinesterase inhibitors, motilin-like agents, and ghrelin-like agents, although many drugs have multiple mechanisms of action.[18,33]

Metoclopramide is the only US Food and Drug Administration (FDA)–approved medication for

TABLE 3
Management strategies for gastroparesis

Exclude iatrogenic causes (eg, opioids, surgery, glucagon-like peptide 1 receptor agonists)		
Diet modification Small-particle diet to improve symptom relief and facilitate gastric emptying		
Pharmacologic therapy		
	Dosage	**Side effects**
Prokinetics		
Metoclopramide[a]	10 mg 3 times a day, 30 minutes before meals, for a maximum of 3 months, or 70-µL spray 30 minutes before meals and at bedtime for 2–8 weeks	Extrapyramidal symptoms (1%–25%, higher in elderly and young), tardive dyskinesia (around 0.1% per 1,000 patient-years)
Erythromycin	250 mg 3 times a day for 1 to 2 weeks	Tachyphylaxis after 4 weeks
Domperidone[b]	10 mg 3 times a day	QTc interval prolongation (6%)
Antiemetics		
5-HT3 receptor antagonists (granisetron, ondansetron)	Same dosage as that used to manage nausea or emesis, or as needed per patient	QTc interval prolongation, second-degree heart block (< 1%)
Neurokinin antagonists (aprepitant, tradipitant)	Aprepitant dose tested in clinical trials is 125 mg once daily	Fatigue, constipation (> 10%)
Neuromodulators		
Levosulpiride	Start with minimum effective dose	Sedation, hypotension, dyskinesia
Buspirone	Start with minimum effective dose	Dizziness, drowsiness
Mirtazapine	Start with minimum effective dose	Somnolence, xerostomia, weight gain
Haloperidol	Start with minimum effective dose	Extrapyramidal symptoms
Nonpharmacologic therapies Gastric electrical stimulation ("gastric pacemaker"), acupuncture		
Pyloric interventions		
Endoscopic functional luminal imaging probe	Used to evaluate pyloric function and predict treatment outcomes following gastric peroral endoscopic myotomy	
Intrapyloric injection of botulinum toxin	Not recommended	
Laparoscopic (Heineke-Mikulicz) pyloroplasty	Safe and enhances gastric emptying with short-term improvement in symptoms	
Gastric peroral endoscopic myotomy	Improves gastric emptying and is equivalent to laparoscopic pyloroplasty	

[a]Only medication approved by US Food and Drug Administration (FDA) for gastroparesis; nasal spray is FDA-approved for diabetic gastroparesis.
[b]Available through the FDA's program for expanded access to investigational drugs.

gastroparesis management. It works by blocking D2 receptors and partly activating 5-HT4 receptors, exerting both prokinetic and central antiemetic effects. Initially it enhances gastric emptying of liquids in diabetic gastroparesis, but its symptomatic efficacy is likely secondary to its central antiemetic effect.

Long-term use is limited due to decreasing effectiveness and the risk of central nervous system side effects, including reversible involuntary movements and irreversible tardive dyskinesia. Recent data show a risk of tardive dyskinesia of around 0.1% per 1,000 patient-years.[37] Typically, metoclopramide is prescribed at 10 mg 3 times a day, taken 30 minutes before meals, for a maximum of 3 months.[1,18,33]

Metoclopramide is also FDA-approved as a nasal spray for diabetic gastroparesis, offering several advantages such as faster and predictable absorption and better symptom control than the oral preparation. As with the oral preparation, extending treatment with the nasal spray longer than 12 weeks should be avoided.[38]

Erythromycin is a motilin agonist and enhances gastric emptying when taken orally at a dosage of 250 mg 3 times a day for 1 to 2 weeks. However, its prokinetic effects are restricted by tachyphylaxis after 4 weeks.[33]

Domperidone, another D2 antagonist, is as effective as metoclopramide for relief of symptoms, and it does not cross the blood-brain barrier in sufficient quantity to cause the neurologic side effects seen with metoclopramide.[18,39] It is typically prescribed at a dosage of 10 mg 3 times a day. However, it should be used with caution, as it causes relative prolongation of the QTc interval.[18] Domperidone is available for prescription through the FDA's program for expanded access to investigational drugs.[1,39]

Prucalopride, a 5-HT4 receptor agonist used to treat chronic constipation, recently has been shown to also exert a gastrokinetic effect and to improve symptoms in a relatively small number of patients with idiopathic gastroparesis.[40]

Several experimental medications are currently in development for the treatment of gastroparesis. These include felcisetrag (a 5-HT4 agonist), tradipitant (a neurokinin-1 antagonist), relamorelin (a ghrelin agonist), and trazpiroben (a dopamine D2/D3 receptor antagonist).[33]

Antiemetic medications

5-HT3 receptor antagonists such as granisetron and ondansetron are known for their effectiveness in managing chemotherapy-induced nausea and vomiting. They reduce nausea without affecting gastric compliance or postprandial accommodation and can be considered for patients with dysmotility disorders primarily characterized by nausea and vomiting.[18,33]

Neurokinin antagonists like aprepitant and tradipitant have been shown to alleviate nausea.[33]

Although both **marijuana and dronabinol** can slow gastric emptying, many patients still turn to THC (tetrahydrocannabinol), found in marijuana, for relief from their nausea.[33]

Neuromodulators

Levosulpiride, an antipsychotic agent, promotes gastric emptying through its dual action as an antidopaminergic and a 5-HT4 agonist.[41]

Buspirone, an anxiolytic medication acting as a 5-HT1A agonist, enhances gastric accommodation and alleviates postprandial symptoms independently of its anxiolytic properties.[42]

Mirtazapine, an antidepressant with central adrenergic and serotonergic effects, has been shown to improve symptoms of nausea, vomiting, and loss of appetite.[43]

Haloperidol, given intravenously, has demonstrated efficacy in reducing abdominal pain and nausea in severely ill patients with gastroparesis in the emergency department.[44]

Tricyclic antidepressants have generated conflicting data in the context of gastroparesis treatment due to their anticholinergic effects, which could potentially lead to delayed gastric emptying. Notably, nortriptyline demonstrated no discernible difference compared with placebo in patients with idiopathic gastroparesis.[45]

Nonpharmacologic therapy

Gastric electrical stimulation has demonstrated a reduction in the frequency of vomiting, although its mechanism of action remains unclear.[1,18]

Acupuncture, as a stand-alone treatment or when combined with prokinetic drugs, may offer benefits for symptom management in those with diabetic gastroparesis.

Herbal therapies such as rikkunshito or STW5 are not recommended for the treatment of gastroparesis.[1]

Brain-gut therapies such as hypnotherapy and cognitive behavioral therapy are widely used in gastrointestinal disorders in which pain and nausea and vomiting are primary symptoms, such as functional dyspepsia, irritable bowel syndrome, and rumination syndrome. While it is intuitive to consider their applicability to gastroparesis, evidence supporting their role in gastroparesis treatment is limited. However, given their primary use in patients with anxiety and depression—common comorbidities in gastroparesis—they likely play an important role in gastroparesis management in some patients.[46]

Pyloric interventions

Both diagnostic (endoscopic functional luminal imaging probe) and therapeutic pyloric interventions

(intrapyloric injection of botulinum toxin and pyloromyotomy) are available for gastroparesis. They are indicated in cases of refractory gastroparesis not responding to conservative therapy.

Endoscopic functional luminal imaging probe is an innovative diagnostic method employed to evaluate pyloric function and predict treatment outcomes after peroral pyloromyotomy, also known as gastric peroral endoscopic myotomy (G-POEM).[1]

Intrapyloric injection of botulinum toxin was initially applied for achalasia and subsequently extended to gastroparesis. However, based on randomized controlled trials, this intervention has not shown symptom improvement and is not recommended for patients with gastroparesis.[1,33]

Laparoscopic (Heineke-Mikulicz) pyloroplasty involves creating a longitudinal incision across the pylorus, followed by a transverse closure. This surgical approach results in the division of both the longitudinal and circular muscle layers. Laparoscopic pyloroplasty is considered a relatively safe procedure and has been shown to enhance gastric emptying while bringing about short-term improvements in symptoms such as nausea, vomiting, bloating, and abdominal pain.[1,18,33,47]

G-POEM is a novel endoscopic procedure that divides the pylorus from the mucosal surface and presumably cuts predominantly the circular muscle layer while maintaining the longitudinal muscle to avoid perforation.[33] G-POEM has been proven effective in treating gastroparesis, leading to improved gastric emptying. It has demonstrated superiority over gastric electrical stimulation for gastroparesis in terms of duration of clinical response (time from the procedure to clinical recurrence, with recurrence defined as symptoms refractory to medical treatment requiring hospitalization along with Gastroparesis Cardinal Symptom Index score ≥ 3 for 6 months),[48] and has shown results equivalent to surgical pyloroplasty in patients with medically refractory gastroparesis.[49]

TAKE-HOME POINTS

- Primary care clinicians continue to be crucial in providing first-line treatment for patients with mild to moderate gastroparesis, particularly those with obesity or overweight and diabetes mellitus. This includes offering ongoing education and counseling on dietary changes to effectively manage symptoms.
- To assess the risk of diabetic gastroparesis and ensure optimal glycemic control, continuous glucose monitoring can provide valuable insights. Further studies examining the associations between glucose metrics derived from continuous glucose monitoring and diabetic gastroparesis are warranted.
- A better understanding of the etiology of idiopathic gastroparesis is needed.
- A meticulous medical history and relevant workup are needed to accurately diagnose idiopathic gastroparesis. Also, autoimmune disorders associated with neuronal antibodies such as autoimmune gastrointestinal dysmotility should be suspected in patients with dysautonomic manifestations. This requires referral to a gastroenterologist trained in motility disorders. Strong evidence is needed before considering immunotherapy for patients with autoimmune gastrointestinal dysmotility.

DISCLOSURES

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