Current and Emerging Therapeutic Options for Gastroparesis

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Abstract: Gastroparesis is a complex, debilitating dysmotility disorder with challenging symptom management. A diagnosis of gastroparesis is based on objectively delayed gastric emptying in the absence of mechanical obstruction. Given the limited efficacy of treatment options and serious side effects, significant research continues for therapeutic options for gastroparesis. Promising investigational pharmacologic therapies include relamorelin, prucalopride, and aprepitant. A novel endoscopic therapy is gastric peroral endoscopic pyloromyotomy, which is associated with improved gastric emptying. This article reviews both current and emerging therapeutic options for gastroparesis, including dietary modification and pharmacologic, electrical stimulation, endoscopic, and surgical therapies. Further research and novel treatment options are needed to address the substantial morbidity of gastroparesis.

Gastroparesis is defined as a syndrome of objectively delayed gastric emptying in the absence of mechanical obstruction. Cardinal symptoms include early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain.[1] Etiologies of gastroparesis include idiopathic causes, diabetes, postoperative causes, neuromuscular disease, collagen vascular disease, medications, and pseudo-obstruction. Idiopathic gastroparesis is the most common form, whereas diabetes accounts for approximately one-third of all cases of gastroparesis.[2] Other causes of nausea, vomiting, and postprandial distress symptoms (eg, early satiety, postprandial fullness, and epigastric pain) are excluded by standard endoscopy, routine laboratory studies, and computed tomography of the abdomen and head.[3] Patients with gastroparesis can have chronic constipation, which also needs to be ruled out prior to a diagnosis of gastroparesis. Gastric emptying scintigraphy (Figure 1) is the standard procedure for evaluating the rate of gastric emptying and establishing the diagnosis of gastroparesis.[4] Delayed gastric emptying is defined as gastric retention of more than 10% of gastric contents at 4 hours and/or more than 60% at 2 hours when using a standard low-fat meal

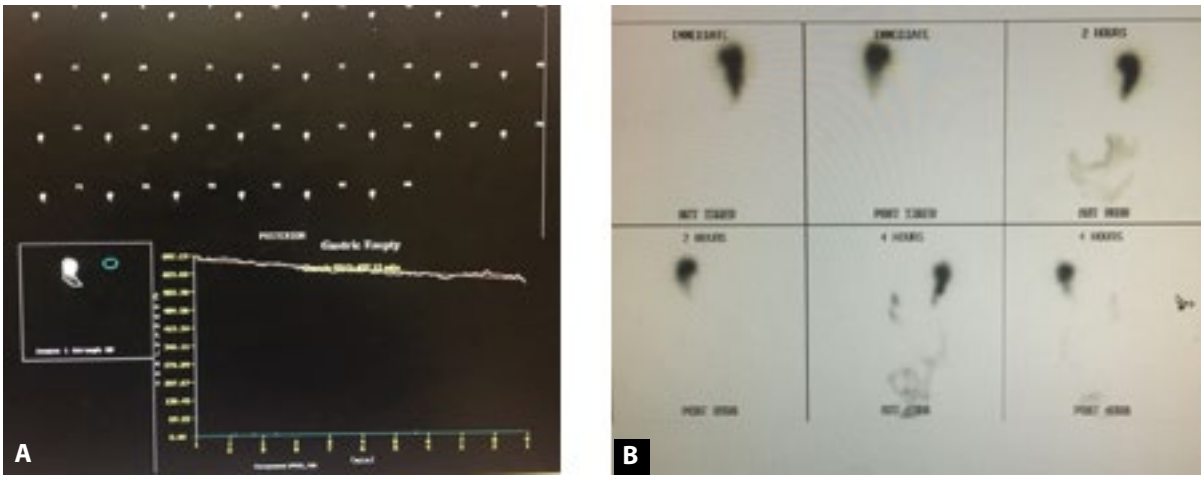

Figure 1. Data (**A**) and image (**B**) acquisition of gastric emptying scintigraphy. During this study, the geometric mean of radiotracer activity was 74,277 counts at 2 hours, which corresponds with a 72% retention rate. At 4 hours, the geometric mean of radiotracer activity was 56,188 counts, which corresponds with a 55.1% retention rate and is delayed compared with normal gastric emptying.

Images provided by the George Washington University Medical Center Department of Radiology.

(Figure 1).[5] Other modalities to assess gastric emptying include wireless motility capsule testing and ^{13}C-breath testing.[6,7] This article reviews both current and emerging therapeutic options for gastroparesis, including dietary modification and pharmacologic, electrical stimulation, endoscopic, and surgical therapies.

Dietary Modification

A gastroparesis diet includes liquid and solid foods that are easy for the stomach to mix and empty.[3] Liquid nutrient intake should be increased, and fat and fiber intake should be minimized, as liquid emptying is often preserved in patients with gastroparesis, whereas fat and fiber tend to slow emptying. With respect to nausea, low-fat meals are better tolerated than high-fat meals, and liquid meals are better tolerated than solid meals.[8] Foods that provoke gastroparesis symptoms are generally fatty, acidic, spicy, and roughage-based; foods that are tolerable are typically bland, sweet, salty, and starchy.[9] Small meals consumed 4 to 5 times daily are recommended because the stomach may only empty a given number of calories in a fixed period of time.[10] Glycemic control in diabetic patients is important for managing diabetic gastroparesis symptoms, as acute hyperglycemia has been shown in experimental clinical studies to worsen gastric emptying or inhibit antral contractility.[11,12] However, the benefit of long-term improvement of good glycemic control on the normalization of gastric emptying and the relief of symptoms in diabetic patients has not been established.[13]

Pharmacologic Therapies

Prokinetic agents increase the rate of gastric emptying and decrease symptoms in patients with gastroparesis. Metoclopramide, a dopamine-2 receptor antagonist, is approved by the US Food and Drug Administration (FDA) for the treatment of gastroparesis. However, it carries a black box warning, as it is generally not well-tolerated and chronic use (>12 weeks) may lead to extrapyramidal side effects and potential irreversible tardive dyskinesia, which has been reported in a small percentage of case reports.[14,15] Domperidone is a peripherally acting dopamine-2 antagonist that decreases nausea, corrects gastric dysrhythmias, and increases gastric emptying rates.[16] Although widely available globally, domperidone currently can only be obtained in the United States through an FDA Investigational New Drug Application due to risks of cardiac arrthythmias.[1] Erythromycin, a macrolide antibiotic and motilin-like molecule, increases gastric emptying by stimulating strong phase III migrating motor complex contractions. It is effective via both oral and intravenous routes, but tachyphylaxis limits long-term efficacy. Additionally, there is a theoretical concern about inducing *Clostridium difficile*–toxin colitis.[17,18]

Antiemetic agents are used to control nausea and vomiting in gastroparesis patients. Ondansetron and granisetron are 5-hydroxytryptamine (HT) 3 receptor antagonists that are often prescribed for these symptoms. Other commonly used antiemetic agents are phenothiazines (eg, prochlorperazine) and antihistamines (eg, promethazine, dimenhydrinate, and cyclizine).

However, no controlled trials have been performed on these agents in the setting of patients with gastric neuromuscular disorders.[1]

Antianxiety benzodiazepine agents, such as lorazepam and alprazolam, reduce nausea in some patients.[19] Amitriptyline and nortriptyline are tricyclic antidepressants that reduce symptoms of nausea and vomiting as well as abdominal pain in patients with diabetic and idiopathic gastroparesis.[20,21] The doses of tricyclic antidepressants used in patients with gastroparesis are lower than those used to treat depression.[20] Mirtazapine is an antidepressant with a multifactorial mechanism of action involving antagonism of central and peripheral presynaptic α_2 adrenergic receptors as well as actions on several subtypes of the 5-HT serotonin receptor and the H1 histamine receptor. Mirtazapine has been shown to improve nausea and vomiting in patients with gastroparesis in documented case reports and in a small-scale uncontrolled study.[22,23] The recommended dosage and common adverse effects of these medications are summarized in the Table.

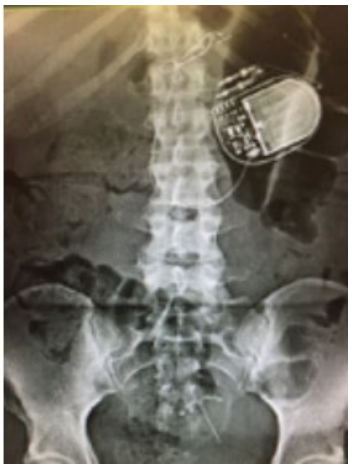

Figure 2. Radiographic image of a patient with an implanted gastric pacer.

Image provided by the George Washington University Medical Center Department of Radiology.

Investigational Therapies

Relamorelin is a synthetic pentapeptide ghrelin receptor agonist that has been shown to accelerate gastric emptying of solids in patients with type 2 diabetes and documented delayed gastric emptying.[24] The highly selective serotonin 5-HT4 receptor agonist prucalopride has been shown to stimulate gut motility in vitro and in vivo.[25] Currently, prucalopride is approved in a number of Western European countries and in Canada for the management of chronic constipation, and it has the potential to treat symptoms of gastroparesis and delayed gastric emptying.[26] Aprepitant, a neurokinin-1 receptor antagonist, is approved in the United States for nausea and vomiting associated with surgery and cancer chemotherapy. It may have some utility in treating refractory nausea caused by gastroparesis.[27] Long-term aprepitant treatment also proved to be effective in alleviating severe symptoms of gastroparesis that had failed to respond to conventional first-line medical treatments in case reports.[27,28]

Electrical Stimulation Therapies

Continuous high-frequency/low-energy gastric electrical stimulation significantly decreases vomiting frequency and gastrointestinal symptoms, and improves quality of life in patients with severe gastroparesis.[29,30] Gastric electrical stimulation is delivered via electrodes that are implanted in the muscle wall of the antrum and connected to a neurostimulator in an abdominal wall pocket (Figure 2).[29] Gastric pacing uses high-frequency gastric stimulation to entrain the normal, slow-wave rhythm of 3 gastric peristaltic contractions in patients with gastroparesis in order to improve gastric emptying.[31] However, the invasive nature of this intervention limits its application.[32] Approximately 20% of patients experience complications from gastric pacer implants, such as infections, migration, and erosion of the stimulation device; stomach wall perforation; pain due to adhesive bands from pacing wires connected to the abdominal wall; dislodgment; breakage; and erosion of leads into the small bowel (Figure 3).[33]

Acupuncture uses tips of thin, stainless steel needles on specific points (called acupoints) through the skin. Conventional acupuncture involves manipulation of the inserted needles by hand, such as lifting, thrusting, twisting, twirling, or other complex combinations. Acustimulation, or electroacupuncture, is a modification of this technique that stimulates acupuncture points with mild electrical stimulation, and has shown to reduce the dyspeptic symptoms of diabetic gastroparesis and accelerate solid gastric emptying in a single-blinded, randomized trial.[34] Electrical stimulation of acupuncture points enhances the regularity of gastric myoelectrical activity.[35]

Endoscopic Therapies

Botulinum Toxin Injection

Botulinum toxin injection has been shown to be effective in treating disorders of smooth muscle hypertonicity in the gastrointestinal tract. Endoscopic intrasphincteric injection of the pylorus with botulinum toxin significantly improves symptoms and solid gastric emptying in

Table. Treatment Options for Gastroparesis

Treatment Options	Recommended Dosage	Adverse Effects and Disadvantages
Diet Modification		
Gastroparesis diet	NA	NA
Pharmacologic Therapies		
Prokinetic Agents		
Metoclopramide	5-20 mg before meals and at bedtime	Extrapyramidal side effects and potential irreversible tardive dyskinesia
Domperidone	10-20 mg before meals and at bedtime	Cardiac arrhythmias. Available only in the United States through an FDA Investigational New Drug Application.
Erythromycin	125-250 mg 4 times daily	Tachyphylaxis
Antiemetic Agents		
Ondansetron	4-8 mg 2-4 times daily, orally or intravenously	Liver enzyme abnormalities
Granisetron	2 mg once daily or 3.1 mg/24-hr patch	Liver enzyme abnormalities
Prochlorperazine	5-10 mg 3 times daily	Drowsiness
Promethazine	25 mg twice daily	Drowsiness
Dimenhydrinate	50 mg 4 times daily	Drowsiness
Cyclizine	50 mg 4 times daily	Drowsiness
Antianxiety Agents		
Lorazepam	0.5-1 mg 4 times daily	Addictive potential
Alprazolam	0.25-0.5 mg 3 times daily	Addictive potential
Antidepressant Agents		
Amitriptyline	25-100 mg at bedtime	Anticholinergic effects
Nortriptyline	10-75 mg at bedtime	Anticholinergic effects
Mirtazapine	15 mg at bedtime	Weight gain
Investigational Therapies		
Relamorelin	NA	Not yet available
Prucalopride	NA	Not yet available
Aprepitant	NA	Not yet available
Electrical Stimulation Therapies		
Gastric pacing	3 cpm, 300 microseconds, 4 mÅ	Invasive procedure. Risk of serious complications such as infection, migration, and erosion of the device.
Acustimulation	NA	NA
Endoscopic Therapies		
Botulinum toxin injection	25-50 units per quadrant	No randomized, controlled trials to prove efficacy
Gastric peroral endoscopic pyloromyotomy	NA	Investigational
Gastrostomy tube	NA	Not good for feeding due to delayed gastric emptying
Jejunostomy tube	NA	Cannot vent stomach
Surgical Therapy		
Laparoscopic pyloroplasty	NA	Invasive therapy

FDA, US Food and Drug Administration; NA, not applicable.

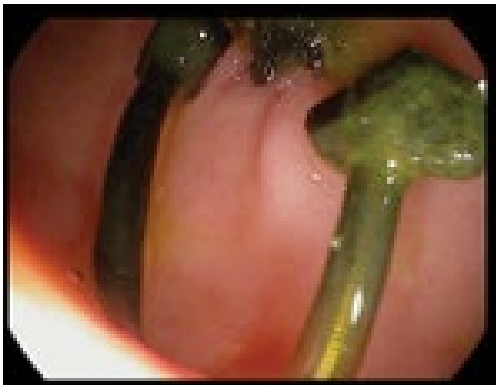

Figure 3. Endoscopic image of gastric pacer wires eroding into the stomach of a patient with gastroparesis who had a gastric pacer implanted 6 years prior. The erosion, a complication of gastric pacer placement, was revealed through esophagogastroduodenostomy evaluation. The patient presented with acute abdominal pain.

Image provided by the George Washington University Medical Center Division of Gastroenterology and Liver Diseases.

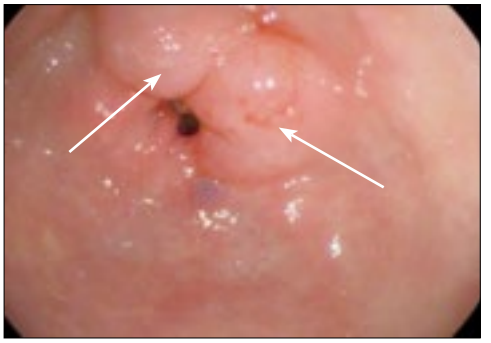

Figure 4. Endoscopic image of the gastric antrum following intrapyloric injection of botulinum toxin. The injection sites are marked by arrows.

Image provided by the George Washington University Medical Center Division of Gastroenterology and Liver Diseases.

patients with gastroparesis (Figure 4).[36,37] A subgroup of gastroparesis patients may require an increased dose of botulinum toxin. A retrospective analysis of a large population of gastroparesis patients undergoing intrapyloric botulinum toxin injection found that the patients who are most likely to respond to an increase in botulinum toxin doses included women; patients younger than 50 years; patients with nondiabetic, nonpostoperative gastroparesis; and, possibly, patients without retained food or opiate use or with severely delayed gastric emptying.[38] Patients with diabetic or idiopathic gastroparesis who are refractory to medical therapy also show improvement in symptoms with botulinum toxin injection therapy. The improvement is maintained at a mean duration of 6 weeks.[38,39] Patients who had a positive response to the first dose continue to respond to repeat injections, and retreatment is often required.[37]

Gastric Peroral Endoscopic Pyloromyotomy

Gastric peroral endoscopic pyloromyotomy (G-POEM) is a novel endoscopic technique with emerging data that have demonstrated not only symptomatic improvement, but also improved gastric emptying in up to 70% of patients.[40,41] Endoscopy is performed first, followed by myotomy of the inner circular and oblique muscle bundles located 2 to 5 cm proximal to the pylorus on the anterior wall of the stomach, preserving the longitudinal muscle layers with larger vessels in the submucosa. Endoscopic pyloromyotomy is then performed by dissecting the pylorus until deeper layers become evident, with full separation of the pyloric ring.[42] In a small reported case series, G-POEM has been noted to significantly improve Gastroparesis Cardinal Symptom Index scores in treated patients.[43] G-POEM has the potential to emerge as an alternative, less-invasive treatment for refractory gastroparesis.

Gastrostomy and Jejunostomy Tube Placement

Percutaneous insertion of a gastrostomy tube through the abdominal wall where it is in close contact with the stomach can be performed safely with endoscope-assisted transillumination techniques. Although placement of a percutaneous endoscopic gastrostomy tube does not treat the underlying gastric neuromuscular disorder, it may allow for intermittent venting for decompression of gastric contents, preventing frequent vomiting episodes and improving quality of life.[44,45] Jejunostomy tubes (J-tubes) are used for enteral nutrition that is needed to provide basic caloric support for patients with severe nausea and vomiting who are not able to maintain nutrition with oral intake. J-tubes can be placed directly into the small intestine and can be placed either percutaneously, laparoscopically, or surgically via laparotomy. Most patients have improved overall health following J-tube placement.[46]

Surgical Therapy

Laparoscopic pyloroplasty is a procedure in which an incision is made extending from the antrum to the duodenum. A retrospective study demonstrated that this procedure improved or normalized gastric emptying in nearly 90% of patients with gastroparesis with very low morbidity.[47] Another retrospective study

reported significantly improved symptoms of nausea, vomiting, bloating, and abdominal pain after undergoing laparoscopic pyloroplasty.[48]

Summary

Gastroparesis is a difficult-to-treat syndrome that has a significant impact on quality of life and is characterized by chronic dyspeptic symptoms and delayed gastric emptying. Metoclopramide is currently the only drug approved by the FDA for the treatment of gastroparesis, yet numerous other treatment options are available and utilized by physicians. Pharmacologic therapies are limited by significant side effects, including extrapyramidal effects (with metoclopramide) and tachyphylaxis (with erythromycin). Domperidone has shown promising clinical data; however, it is only available via the FDA Investigational New Drug protocol due to cardiac risks. Electrical stimulation and gastric pacing have been used, with small studies noting improved symptoms and gastric emptying. Botulinum toxin injection into the pylorus, an endoscopic therapy, has shown some efficacy in small trials. Given the limitations of the available therapies and continued morbidity of gastroparesis, novel treatment options have been investigated. New medications such as relamorelin or aprepitant may be promising. Novel endoscopic treatment options such as G-POEM have shown some efficacy in small trials. Further investigation is warranted to identify new and effective treatment options.

The authors have no relevant conflicts of interest to disclose.

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