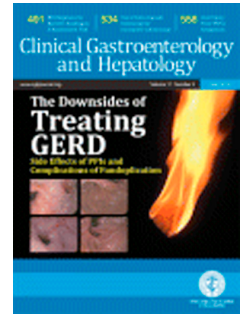


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AGA Clinical Practice Update on Management of Medically Refractory
Gastroparesis: Expert Review

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**AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis:
Expert Review**

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Abbreviations and acronyms: FD: functional dyspepsia; FDA: food and drug administration; RCT: randomized clinical trial; GCSI: gastroparesis cardinal symptom index; 5-HT₃: 5-hydroxytryptamine₃; NK-1: neurokinin-1; TCA: tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; GABA: gamma amino butyric acid; GES: gastric electrical stimulation; FLIP: functional lumen imaging probe; G-POEM: gastric per-oral endoscopic myotomy; G-POP: gastric per-oral pyloroplasty

ABSTRACT

Description: Delayed gastric emptying on objective testing defines gastroparesis, but symptoms overlap with functional dyspepsia, and do not correlate well with gastric emptying delay. This review outlines a strategy for defining, diagnosing and managing refractory gastroparesis.

Methods: The Best Practice Advice statements presented here were developed from review of existing literature combined with expert opinion to provide practical advice. Since this was not a systematic review, formal rating of the quality of evidence or strength of recommendations was not performed.

Best Practice Advice:

1. Clinicians should review symptoms and evaluate physical examination findings to exclude disorders that can mimic medically refractory gastroparesis.
2. Clinicians should verify appropriate methodology of the gastric emptying study to ensure an accurate diagnosis of delayed gastric emptying.
3. Clinicians should classify patients with gastroparesis into mild, moderate, or severe based on symptoms and the results of a properly performed gastric emptying study.
4. Clinicians should identify the predominant symptom and initiate treatment based on that symptom.
5. Clinicians should be aware of the multiple treatment options to treat nausea and vomiting.
6. Clinicians should consider the use of neuromodulators to treat gastroparesis associated abdominal pain but should not use opioids.
7. Clinicians can consider gastric electrical stimulation for gastroparesis patients with refractory/intractable nausea and vomiting who have failed standard therapy and are not on opioids.

8. Clinicians can consider G-POEM for select refractory gastroparesis patients with severe delay in gastric emptying, using a thoughtful team approach involving motility specialists and advanced endoscopists at a center of excellence.

Keywords: gastroparesis; nausea and vomiting; abdominal pain

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INTRODUCTION

Gastroparesis is a syndrome defined by symptomatic delay in gastric emptying in the absence of mechanical obstruction¹. Typical gastroparesis symptoms of nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and/or weight loss (Figure 1) overlap to a significant degree with functional dyspepsia (FD)¹⁻⁵. With an estimated prevalence per 100,000 persons of 37.8 for women and 9.6 for men⁶, approximately 5 million US adults suffer with gastroparesis-like symptoms⁷, while 7.2% of the global population report FD symptoms⁸, making gastroparesis and FD two of the most common sensorimotor disorders of the stomach^{2, 3, 9}. The etiology of gastroparesis is diverse with over 50 recognized causes. Diabetes accounts for 25%, medications (e.g., opioids, glucagon-like peptide-1 agonists), vascular disorders, connective tissue disorders and post-surgical causes are other common causes, but the largest etiologic group is idiopathic^{1, 2, 4, 7, 10, 11}. Gastroparesis negatively impacts quality of life and is a significant economic burden to the health care system^{12, 13}.

While delayed gastric emptying is the defining motor abnormality, the complex pathophysiology of gastroparesis includes impaired gastric accommodation, electrical dysrhythmias, antroduodenal dyscoordination, pyloric dysfunction, antral hypomotility, vagal nerve injury and disorders of visceral sensation^{1, 2, 4, 7, 11}. Lack of consistent reproducible relationships between global gastroparesis symptoms and gastric emptying delay complicates treatment decisions^{14, 15}, in part, because gastric emptying scans are not always performed correctly. Simply accelerating gastric emptying may not improve global gastroparesis symptoms. Further, the gastroparesis-FD overlap clouds interpretation of treatment response, since some patients with FD may be treated as if they had gastroparesis^{2, 5, 14, 16, 17}. This overlap was highlighted by the recent finding that as many as 42% of gastroparesis patients were reclassified

as having FD, while 37% of FD patients were reclassified as gastroparesis over the course of a year¹⁸. These factors explain why no single treatment has proved uniformly effective at treating global gastroparesis symptoms.

When gastroparesis symptoms persist, patients are often labeled as having medically refractory gastroparesis, despite the fact that no precise definition or dedicated treatment algorithm for this diagnosis exists in the literature. This review outlines a strategy for defining, diagnosing, and managing medically refractory gastroparesis. This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC as well as external peer review through standard procedures of Clinical Gastroenterology and Hepatology. This CPU is not intended to be a comprehensive review on gastroparesis, and will not focus on etiology, pathophysiology or diagnostic testing.

DEFINITION OF MEDICALLY REFRACTORY GASTROPARESIS

Medically refractory gastroparesis can be defined as persistent symptoms in the context of objectively confirmed gastric emptying delay, despite the use of dietary adjustment and metoclopramide as a first-line therapeutic agent. Inherent to this definition is the proviso that symptoms are not medication induced (e.g., opioids, glucagon-like peptide-1 agonists). Generally, nausea and vomiting are the predominant persistent symptoms, although all symptoms should be considered^{1-5,9}. Based on a single trial that formally studied dietary manipulation in patients with gastroparesis¹⁹, a small particle size, reduced fat diet should be employed for a minimum of 4 weeks. A reasonable trial of metoclopramide, the only Food and

Drug Administration (FDA) approved medication for gastroparesis, is a minimum of 10 mg three times daily before meals and at bedtime for at least four weeks, based on limited data and no agreed-upon standards¹. Evidence to support longer interventions from randomized, controlled trials (RCTs) is not available. Clinicians should familiarize themselves with the black box warning associated with metoclopramide use, although the risk of tardive dyskinesia from chronic metoclopramide use may be lower than previously estimated by regulatory authorities. Since there are no prospective, randomized, controlled studies comparing different management strategies (e.g., a central anti-emetic vs. a prokinetic agent), initiating treatment based on the predominant presenting symptom is a reasonable first approach.

Gastroparesis is heterogeneous and symptom expression – frequency, intensity, severity, and duration - varies between patients, making an accurate diagnosis essential at the outset. A careful history, thoughtful physical examination, and prudent diagnostic tests can distinguish conditions that mimic refractory gastroparesis (Figure 2). Important physical examination findings include a succussion splash (suggestive of delayed gastric emptying or gastric outlet obstruction), a bruit on auscultation of the right upper quadrant (celiac artery compression syndrome), digital ulcers and telangiectasia (scleroderma) and ascites, a mass or enlarged lymph nodes (underlying malignancy). If not recently performed a complete blood count, liver chemistries and a basic metabolic profile should be checked. Electrolyte derangements are common in patients with persistent nausea and vomiting and should be corrected. A thyroid stimulating hormone level can be checked if hypothyroidism is a concern. Hyperkalemia and a metabolic acidosis may indicate adrenal insufficiency which can be initially evaluated by measuring a fasting cortisol level. Upper endoscopy should be performed to rule out an organic cause of symptoms. Gastric emptying can be measured using several techniques (scintigraphy, ¹³C spirulina breath test,

wireless motility capsule); most US centers perform gastric scintigraphy, albeit often incorrectly with short measurement times, leading to misdiagnosis and mismanagement^{20,21}. Joint American Nuclear Medicine Society and American Neurogastroenterology and Motility Society guidelines outline key protocol requirements for performing an accurate 4-hour test²², optimally performed off opioid medication. Repeating scintigraphy may change the pathophysiological and diagnostic categorization from gastroparesis to FD and vice versa in as many as 37-42% within the course of a year, as discussed above¹⁸. Since the wireless motility capsule, an inanimate object, identifies the phase III activity front of the migrating motor complex rather than overall gastric emptying, a meal-based test provides better physiologic assessment of gastric emptying, and is thus recommended as the first-line test of gastric emptying over the wireless motility capsule⁵.

CLINICAL MANIFESTATIONS OF REFRACTORY GASTROPARESIS

Symptoms and objective data can help drive treatment choices, starting with identification of the predominant or most bothersome symptom (Figures 1, 2) using a validated symptom scoring system such as the Gastroparesis Cardinal Symptom Index (GCSI); however, overlap with FD makes this less reliable than previously thought¹⁶. Although not validated in large, prospective studies, some investigators categorize gastroparesis severity based on the extent of gastric emptying delay¹ into mild (10-15% retention at 4 hours on scintigraphy), moderate (15-35% retention at 4 hours) and severe (>35% retention at 4 hours), which may potentially guide management. Since gastric emptying scans are commonly performed incorrectly, patients should be preferentially referred to centers that adhere to guidelines on properly performing a scintigraphic study²⁰⁻²².

PATHOPHYSIOLOGY OF REFRACTORY GASTROPARESIS

The pathophysiology of refractory gastroparesis is complex (Figure 1), and it is not always possible or feasible to identify all underlying pathophysiologic abnormalities. For example, prokinetic therapy may be appropriate for predominant antral hypomotility, and pylorus-directed therapies can be considered for pyloric dysfunction. Abnormalities of visceral sensation, conditioned responses, eating disorders, alterations in CNS processing and co-existing psychological disorders are often neither considered nor addressed during diagnostic evaluation, further compounded by the fact that these can be difficult to evaluate clinically²³.

MANAGEMENT OF REFRACTORY GASTROPARESIS

Management goals consist of identifying and improving the predominant symptom, reducing the potential for complications (e.g., reflux esophagitis, malnutrition, weight loss), reducing health care utilization and improving quality of life (see Table 1 and Figure 2).

Medications for nausea and vomiting

For patients who fail metoclopramide, a variety of treatment options exist, although many of these agents have not been evaluated in large RCTs (Table 1). Whenever available, we will present data from gastroparesis studies.

Domperidone, a dopamine D₂-receptor antagonist, does not readily cross the blood brain barrier; although QT prolongation and ventricular tachycardia are risks, it has fewer central side effects than metoclopramide²⁴. Availability in the United States is only through an FDA investigational drug application. The recommended starting dose is 10 mg t.i.d.; while escalation to 20 mg q.i.d. has been reported, this should probably be avoided for cardiovascular safety

considerations¹. Published studies reveal modest efficacy, although patients studied were not defined *a priori* as having refractory gastroparesis²⁵. A single-center cohort study (n=115) of gastroparesis patients showed that 68% had an improvement in symptom scores, although 7% had cardiac side effects requiring drug cessation²⁶.

5-hydroxytryptamine₃ (5-HT₃) receptor antagonists (e.g. ondansetron, granisetron) block serotonin receptors in the chemoreceptor trigger zone and inhibit vagal afferents, thereby improving nausea and vomiting. These agents have similar efficacy; selection can be determined by price, availability, and mode of delivery. Ondansetron is available in both parenteral and enteral forms; granisetron is available as a liquid, tablets and a transdermal patch. Studies have reported efficacy of transdermal granisetron (3.1 mg/24 hr.) in decreasing symptom scores by 50% in patients with refractory gastroparesis symptoms^{6,27}.

Neurokinin (NK-1) receptor antagonists (e.g., aprepitant, tradipitant, casopitant, rolapitant) block substance P in critical areas involved in nausea and vomiting, including the nucleus tractus solitarius and the area postrema²⁸. A RCT of 126 gastroparesis patients randomized to aprepitant (125 mg/day) or placebo reported improvement of nausea and vomiting using the GCSI, but not when using visual analog score assessment of nausea intensity²⁹. Another RCT comparing tradipitant (85 mg) to placebo in diabetic or idiopathic gastroparesis over 4 weeks demonstrated improvement in nausea, especially in idiopathic gastroparesis; vomiting and overall GCSI scores also improved³⁰. While NK-1 receptor antagonists appear to improve nausea and vomiting, these symptoms improved regardless of the presence (gastroparesis) or absence (FD) of significantly delayed emptying^{16 29}, and symptoms do not necessarily correlate with gastric emptying time in many patients¹⁴. Nevertheless, up to a third of patients with troublesome nausea may benefit from these agents, provided costs are affordable.

Phenothiazine antipsychotics (e.g., prochlorperazine, chlorpromazine) reduce nausea and vomiting by inhibiting dopamine receptors in the brain³¹, but these agents have not been studied in gastroparesis or compared prospectively to other anti-emetics. A controlled trial using the substituted benzamide antipsychotic levosulpiride, which also has dopamine-2 blocking effects, in 40 diabetic gastroparesis patients, showed significant improvement of symptoms as well as gastric emptying³². Scopolamine, a muscarinic cholinergic receptor antagonist, is used off-label in gastroparesis despite lack of supporting clinical studies. Although synthetic cannabinoids (e.g. dronabinol, nabilone) are approved for chemotherapy-related nausea and vomiting, their use in gastroparesis has not been formally evaluated, with the potential to slow gastric emptying³³. Ginger improves nausea and vomiting but has not been prospectively evaluated in refractory gastroparesis³⁴.

Medications to accelerate gastric emptying

Erythromycin, a macrolide antibiotic, accelerates gastric emptying by binding to motilin receptors, thereby stimulating cholinergic activity in the antrum, and initiating phase III contractions of the migrating motor complex³⁵. Erythromycin, used intravenously in hospitalized patients (3 mg/kg every 8 hours)¹, or orally in outpatients (50-100 mg q.i.d. given 30-45 minutes prior to each of the three main meals and at bedtime), is associated with tachyphylaxis that limits effectiveness^{1, 31}. Higher oral doses may cause early satiation and pain, and may exacerbate nausea and vomiting. Although azithromycin also accelerates gastric emptying in gastroparesis, it may prolong the QT interval and increase risk of cardiac arrhythmias, similar to erythromycin³⁶.

5-HT₄ receptor agonists stimulate peristalsis through release of acetylcholine from the myenteric plexus³⁷. Cisapride appeared to be effective in some patients despite lack of RCT data, but was removed from the market due to adverse cardiac effects³⁸. Velusetrag, a highly selective 5-HT₄ receptor agonist, accelerated gastric emptying in a large phase 2 RCT, without apparent cardiac side effects³⁹, but no phase 3 RCTs have been announced to date. Prucalopride, another selective 5-HT₄ receptor agonist, accelerated gastric emptying, improved symptoms, and quality of life in both diabetic and idiopathic gastroparesis in a small RCT⁴⁰. Large, multi-center trials are needed to confirm these findings.

Relamorelin, a selective ghrelin agonist with prokinetic activity, improved core symptoms and accelerated gastric emptying in a RCT of 393 diabetics with gastroparesis diagnosed using a ¹³C-spirulina breath test⁴¹, but without improvement in vomiting compared to placebo; further prospective trials have been placed on hold. Whether the small change in gastric emptying is clinically meaningful remains unanswered.

Medications for visceral pain

Abdominal pain, common in refractory gastroparesis, markedly impairs quality of life^{12, 42}. The pathophysiology likely varies based on underlying etiology, duration of symptoms, comorbid conditions and associated psychological distress. Neuromodulators including tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) can reduce perception of pain at different levels of the brain-gut axis *via* multiple mechanisms⁴³.

High quality evidence for neuromodulator use in refractory gastroparesis is limited to a single placebo controlled RCT (NORIG trial) that studied the effects of nortriptyline, a secondary tricyclic amine⁴⁴. Using a strict primary outcome of $\geq 50\%$ reduction in two

consecutive GCSI score assessments compared to baseline, there was no difference between a tailored nortriptyline dose (adjusted at 3-week intervals up to 75 mg at 2 weeks) and placebo. Given the significant overlap between gastroparesis and FD¹⁸, more potent tertiary tricyclic amines (amitriptyline, imipramine) may potentially provide greater benefits, particularly in diabetic gastroparesis, although prospective RCT data in gastroparesis patients is lacking. However, amitriptyline improved FD patients in the functional dyspepsia treatment trial (FDTT) without slowing gastric emptying, and was more effective than the selective serotonin reuptake inhibitor (SSRI) escitalopram, especially when epigastric pain was a relevant symptom and when gastric emptying was normal⁴⁵. Other RCT data also support TCA benefit in FD with epigastric pain; although gastric emptying was not specifically evaluated in these studies, it is likely that TCA benefit would be independent of gastric emptying status. Noradrenaline reuptake inhibition, as provided by TCAs and SNRIs, is considered the main mechanism for controlling visceral pain⁴⁵.

Selective serotonin reuptake inhibitors may improve co-existing anxiety and depression in patients with refractory gastroparesis, but are unlikely to directly improve visceral pain as they do not block the reuptake of the key neurotransmitters involved in the perception of visceral pain - serotonin and norepinephrine⁴³. Mirtazapine, a tetracyclic antidepressant with noradrenergic and specific serotonergic activity, improved refractory nausea and vomiting in a cohort of 30 gastroparesis patients⁴⁶, and improved weight loss, dyspeptic symptoms, and especially early satiation in a controlled trial in FD⁴⁷.

Duloxetine, an SNRI which blocks reuptake of both serotonin and norepinephrine⁴³, improved diabetic polyneuropathic pain compared to placebo at daily doses of 60-120 mg over 12 weeks in RCTs, although nausea or constipation can develop or worsen⁴⁸. A systematic

review provided second-tier evidence that more patients treated with the anticonvulsant gabapentin (>1200 mg daily in divided doses) for neuropathic pain achieved at least >50% reduction in pain compared to placebo⁴⁹, although selective outcome reporting by industry sponsored trials for off-label use has called some of this evidence into question⁵⁰. Pregabalin is structurally related to gabapentin, but modulates calcium influx by binding to a subunit of voltage gated central nervous system calcium channels rather than GABA receptors, and inhibits release of excitatory neurotransmitter for anti-nociceptive and anticonvulsant effects. Pooled analysis from seven RCTs enrolling 1510 patients with neuropathic pain indicated a statistically significant reduction in mean pain scores over 5-13 weeks at 150 mg, 300 mg and 600 mg daily in divided doses, with dizziness, somnolence, weight gain and peripheral edema reported as side effects⁵¹.

Finally, opioid analgesics (e.g., morphine, oxycodone, hydromorphone, etc.) should not be used to manage chronic visceral abdominal pain, as they further delay gastric emptying, increase the risk of narcotic bowel syndrome, and create the potential for addiction, tolerance, and overdose.

Gastric electrical stimulation (GES)

The FDA approved gastric electrical stimulation (GES; Enterra Therapy) using high frequency (12 cycles per minute), low energy stimuli for the treatment of drug refractory nausea and vomiting due to gastroparesis in 2000. Although GES use continues to stimulate debate, some consistent themes have emerged from available literature. The precise mechanism of action remains unknown, but GES does not accelerate gastric emptying; its beneficial effects may occur *via* modulation of the gastric pacemaker, interstitial cells of Cajal, sensory afferents, other

myoneural pathways, or the release of peptides⁵²⁻⁵⁷. However, GES does improve refractory nausea and vomiting in some patients with gastroparesis, and may improve glycemic control, nutritional status and quality of life, while reducing hospitalizations and medication use⁵²⁻⁵⁷. Even though one study reported a reduction in self-reported “severe” pain⁵⁸, persistent abdominal pain is not an indication for GES, and opioid use is a contraindication. Refractory symptoms of shorter duration are more likely to respond than prolonged intractable symptoms⁵³. Whether patients with refractory diabetic gastroparesis respond better than those with idiopathic gastroparesis remains controversial^{54, 57, 59}. Temporary electrical stimulation may predict response to GES, and should be offered, if available⁶⁰. Thus, GES could be an option for gastroparesis patients with refractory/intractable nausea and vomiting who have failed standard therapy, are not on opioids, and do not have abdominal pain as the predominant symptom (Figure 2).

Pylorus directed therapies

The pylorus plays a critical role in the control of gastric emptying. Abnormalities of pyloric tone and pressure (e.g. “pylorospasm”), and dyscoordination between antral contractions and pyloric relaxation, may impair gastric emptying and contribute to symptoms in some patients^{7, 61}. Deep pyloric biopsies have demonstrated that pyloric stenosis and reduced numbers of interstitial cells of Cajal may contribute to pyloric dysfunction⁶². Accurately measuring pyloric basal tone, phasic pressures, and relaxation is difficult, and endoscopy, fluoroscopy, and antroduodenal manometry all have significant limitations. The functional lumen imaging probe (FLIP) uses impedance planimetry to record cross sectional area and minimum diameter of any hollow viscus, from which estimates of sphincter distensibility and compliance can be

generated⁶³. While FLIP has primarily been used to study the esophagus, limited pyloric data are available^{63, 64}, with some studies showing diminished pyloric distensibility in select patients with gastroparesis⁶³. However, FLIP has not been validated to segregate physiologic from pathologic changes in pyloric distensibility across all causes of gastroparesis; it is also expensive, invasive, and not widely available.

Intrapyloric botulinum toxin injection

Although early studies of intrapyloric botulinum toxin injection improved gastroparesis symptoms in diabetic patients^{65, 66}, two larger placebo-controlled studies showed no benefit over placebo^{67, 68}. No studies have focused on gastroparesis patients with severe emptying delay, which may be the population most likely to benefit. One study suggested benefit in gastroparesis with decreased pyloric distensibility on FLIP⁶⁹, but this requires further confirmation before recommendation as a means to select patients. At present, although generally safe, available data argues against use of botulinum toxin in refractory gastroparesis, except in clinical trials⁷⁰.

Transpyloric stent placement

Transpyloric stent placement should be considered investigational in refractory gastroparesis for the lack of data from prospective, sham-controlled trials and concerns over stent migration, despite limited case reports describing symptom improvement.

Gastric per oral myotomy

The success of per oral endoscopic myotomy (POEM) in achalasia spurred study of a similar endoscopic technique in refractory gastroparesis, termed gastric POEM (G-POEM) or

gastric per oral pyloroplasty (G-POP). Two separate multi-center trials noted improvement in symptoms and reduction in gastric emptying times^{71, 72}. Pooled analysis including 8 other open label and retrospective studies suggest a reduction in post-procedure GCSI scores and improved gastric emptying, with 6.8% overall adverse events⁷³. Although technically feasible, randomized, sham-controlled studies do not exist, and long-term follow up data are not available. Thus, although intriguing, G-POEM should not be considered first-line therapy, and should only be performed at tertiary care centers using a team approach of experts (motility specialists, advanced endoscopists) with extensive experience in treating refractory gastroparesis patients. Finally, G-POEM has the theoretical potential to induce dumping syndrome, which has a deleterious effect on food tolerance and quality of life⁷⁴.

Other Endoscopic and Surgical Interventions

Enteral nutrition may be required when nausea, vomiting, early satiety, and weight loss persist despite adequate trials of medications and endoscopic therapies. An endoscopic/surgical trans-jejunal tube or a combined G-J tube should be placed beyond the pylorus, and case series demonstrate weight recovery with acceptable morbidity and mortality, allowing removal after an average 20 months⁷⁵. In the occasional patient with nutritional compromise, parenteral nutrition may improve symptoms and provide a bridge to other therapies. The role of laparoscopic pyloroplasty or sleeve gastrectomy is unclear given the absence of large, well-designed, sham-controlled trials. Partial or total gastrectomy is rarely required, carries a risk of dumping syndrome, and should be considered only after all available therapies have been exhausted, preferably at a tertiary care center.

SUMMARY

In patients with foregut symptoms attributed to gastroparesis, a diagnosis of refractory gastroparesis requires persistent symptoms, particularly nausea and vomiting, in the context of reliably established gastric emptying delay. Identification of the dominant refractory symptom directs management efforts, particularly escalation of medical management. Pursuing invasive therapeutic options based on a single GES without clinical context may close the door on potentially effective management options targeting FD and other mimics of gastroparesis. Our knowledge gap remains vast, and areas for future research include study of pathophysiology and etiology, as well as identification of clinical and investigation-based (e.g. FLIP) predictors of response to each management approach. Studies targeting gastroparesis phenotypes that benefit most from management options discussed in this review will help refractory gastroparesis patients.

FIGURE LEGENDS

Figure 1. Putative factors involved in the generation of refractory gastroparesis symptoms. Both central processes and local gastroduodenal mechanisms may participate in symptom generation. Exaggerated visceral perception, altered central processing, learned behaviors including food aversion, and ongoing psychological distress may all potentially contribute to clinical presentation and symptom intensity.

Figure 2. Proposed algorithm for management of refractory gastroparesis symptoms. Patients can be phenotyped into two categories based on presenting symptoms: nausea/vomiting predominant, and abdominal pain/discomfort predominant symptoms. This pathway assumes that anatomic/organic causes for symptoms have been ruled out with upper endoscopy and selective imaging, if clinically indicated. In the appropriate patients, celiac artery compression syndrome can be initially evaluated with a mesenteric duplex, and superior mesenteric artery syndrome can be evaluated with radiologic imaging (e.g., small bowel follow through or CT enterography). Intestinal pseudoobstruction can be diagnosed by symptoms, laboratory tests, and imaging studies. In particular, cyclic vomiting syndrome and cannabinoid hyperemesis syndrome need to be differentiated from nausea/vomiting predominant gastroparesis. Management options depend on the degree of patient reported symptoms and/or the degree of gastric emptying delay (mild, moderate and severe) on a 4-hour gastric emptying scan.

Table 1. Treatment Options for Refractory Gastroparesis Symptoms

<u>Treatment</u>	<u>Dose</u>
Medications for nausea and vomiting	
Ondansetron	4-8 mg bid or tid
Granisetron	1 mg bid
Granisetron patch	34.3 mg patch weekly
Prochlorperazine	5-10 mg qid
Chlorpromazine	10-25 mg tid or qid
Meclizine	12.5-25 mg tid
Scopolamine	1.5 mg patch every 3 days
Dimenhydrinate	25-50 mg tid
Diphenhydramine	12.5-25 mg tid
Trimethobenzamide	300 mg tid
Aprepitant	80 mg qd
Ginger	1 g bid
Medications to accelerate gastric emptying	
Metoclopramide	5-20 mg tid-qid
Domperidone	10-20 mg tid-qid*
Medications for visceral pain	
Tricyclic agents**	
Amitriptyline	25-100 mg/day
Imipramine	25-100 mg/day
Desipramine	25-75 mg/day
Nortriptyline	25-100 mg/day
Serotonin and norepinephrine reuptake inhibitors	
Duloxetine	60-120 mg/day
Anticonvulsants	
Gabapentin	>1200 mg/day in divided doses
Pregabalin	100-300 mg/day in divided doses
Other antidepressants	
Mirtazapine	7.5-30 mg/day
Other interventions	
Endoscopic injection of botulinum toxin A	
Gastric per-oral endoscopic myotomy (G-POEM)	
Gastric electrical stimulation	
Enteral feeding	
Cognitive and behavioral therapy, hypnotherapy	

Note that metoclopramide is the only FDA approved medication for gastroparesis; all other agents are considered off-label use. Gastric electrical stimulation is approved under a Humanitarian Device Exemption (HDE).

*Only available for use in the U.S. via FDA investigational drug protocol. Doses above 10 mg tid not recommended for risk of QT prolongation.

**Amitriptyline and imipramine are tertiary amines and are more likely to have side effects (e.g., sedation) than secondary amines (desipramine and nortriptyline). Nortriptyline was not found to be effective in idiopathic gastroparesis, although it has not been tested prospectively in patients with diabetic gastroparesis. Tricyclic antidepressants also suppress nausea and vomiting.

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Bibliography

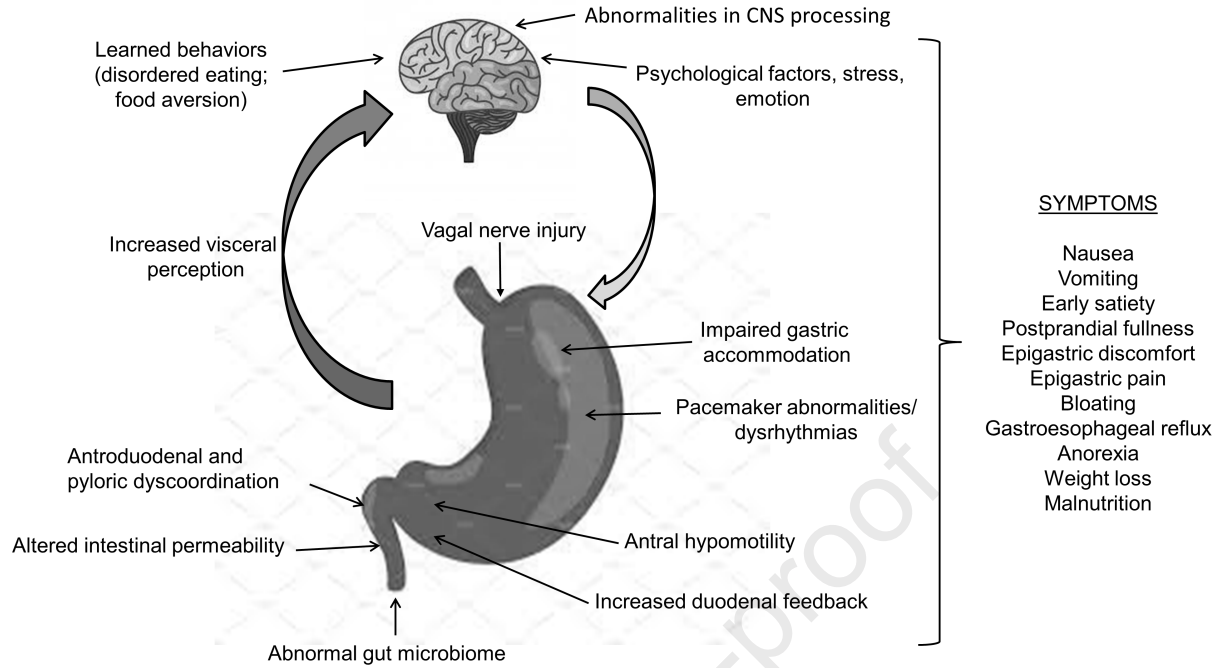
1. Camilleri M, Parkman HP, Shafi MA, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18-37; quiz 38.
2. Cangemi DJ, Lacy BE. Gastroparesis and functional dyspepsia: different diseases or different ends of the spectrum? *Curr Opin Gastroenterol* 2020;36:509-517.
3. Ford AC, Mahadeva S, Carbone MF, et al. Functional dyspepsia. *Lancet* 2020;396:1689-1702.
4. Aziz I, Palsson OS, Whitehead WE, et al. Epidemiology, Clinical Characteristics, and Associations for Rome IV Functional Nausea and Vomiting Disorders in Adults. *Clin Gastroenterol Hepatol* 2019;17:878-886.
5. Schol J, Wauters L, Dickman R, et al. United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis. *United European Gastroenterol J* 2021;9:287-306.
6. Jung HK, Choung RS, Locke GR, 3rd, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology* 2009;136:1225-33.
7. Moshiree B, Potter M, Talley NJ. Epidemiology and Pathophysiology of Gastroparesis. *Gastrointest Endosc Clin N Am* 2019;29:1-14.
8. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology* 2021;160:99-114 e3.
9. Lacy BE. Functional dyspepsia and gastroparesis: one disease or two? *Am J Gastroenterol* 2012;107:1615-20.
10. Navas CM, Wadas ED, Zbib NH, et al. Gastroparesis and Severity of Delayed Gastric Emptying: Comparison of Patient Characteristics, Treatments and Medication Adverse Events. *Dig Dis Sci* 2021;66:526-534.
11. Park SY, Acosta A, Camilleri M, et al. Gastric Motor Dysfunction in Patients With Functional Gastrointestinal Symptoms. *Am J Gastroenterol* 2017;112:1689-1699.
12. Lacy BE, Crowell MD, Mathis C, et al. Gastroparesis: Quality of Life and Health Care Utilization. *J Clin Gastroenterol* 2018;52:20-24.
13. Wang YR, Fisher RS, Parkman HP. Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995-2004. *Am J Gastroenterol* 2008;103:313-22.
14. Janssen P, Harris MS, Jones M, et al. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am J Gastroenterol* 2013;108:1382-91.
15. Vijayvargiya P, Jameie-Oskoei S, Camilleri M, et al. Association between delayed gastric emptying and upper gastrointestinal symptoms: a systematic review and meta-analysis. *Gut* 2019;68:804-813.
16. Lacy BE, Everhart K, Crowell MD. Functional Dyspepsia: Clinical Symptoms, Psychological Findings, and GCSI Scores. *Dig Dis Sci* 2019;64:1281-1287.
17. Wauters L, Dickman R, Drug V, et al. United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia. *United European Gastroenterol J* 2021;9:307-331.

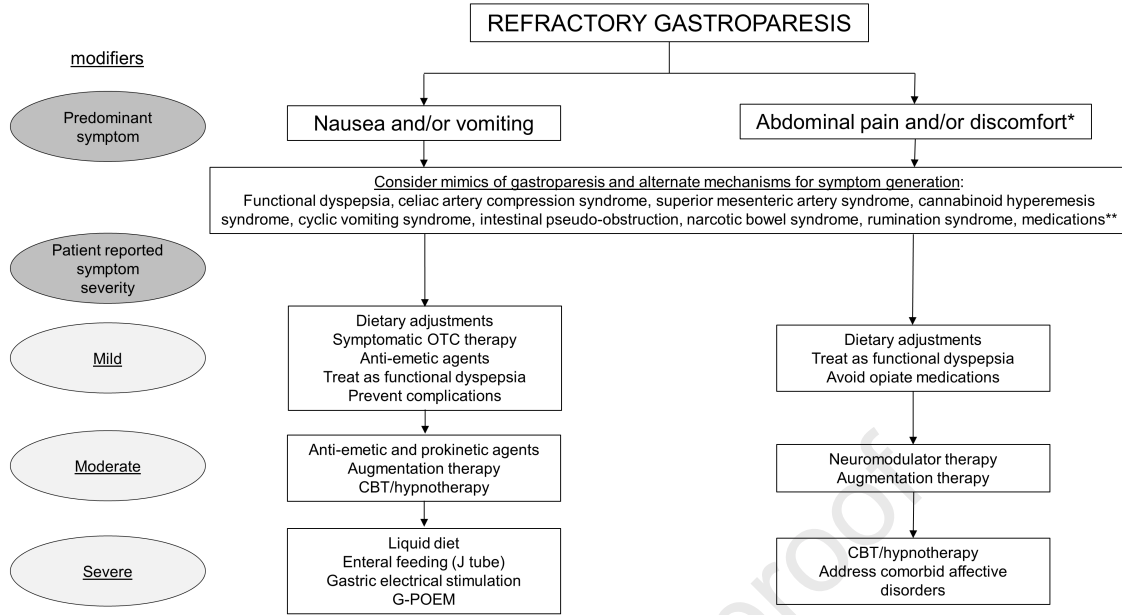
18. Pasricha PJ, Grover M, Yates KP, et al. Functional Dyspepsia and Gastroparesis in Tertiary Care are Interchangeable Syndromes With Common Clinical and Pathologic Features. *Gastroenterology* 2021;160:2006-2017.
19. Olausson EA, Storsrud S, Grundin H, et al. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am J Gastroenterol* 2014;109:375-85.
20. Wise JL, Vazquez-Roque MI, McKinney CJ, et al. Gastric Emptying Scans: Poor Adherence to National Guidelines. *Dig Dis Sci* 2020.
21. Farrell MB, Costello M, McKee JD, et al. Compliance with Gastric-Emptying Scintigraphy Guidelines: An Analysis of the Intersocietal Accreditation Commission Database. *J Nucl Med Technol* 2017;45:6-13.
22. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol* 2008;103:753-63.
23. Snodgrass P, Sandoval H, Calhoun VD, et al. Central Nervous System Mechanisms of Nausea in Gastroparesis: An fMRI-Based Case-Control Study. *Dig Dis Sci* 2020;65:551-556.
24. Drolet B, Rousseau G, Daleau P, et al. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. *Circulation* 2000;102:1883-5.
25. Acosta A, Camilleri M. Prokinetics in gastroparesis. *Gastroenterol Clin North Am* 2015;44:97-111.
26. Schey R, Saadi M, Midani D, et al. Domperidone to Treat Symptoms of Gastroparesis: Benefits and Side Effects from a Large Single-Center Cohort. *Dig Dis Sci* 2016;61:3545-3551.
27. Midani D, Parkman HP. Granisetron Transdermal System for Treatment of Symptoms of Gastroparesis: A Prescription Registry Study. *J Neurogastroenterol Motil* 2016;22:650-655.
28. Navari RM, Schwartzberg LS. Evolving role of neurokinin 1-receptor antagonists for chemotherapy-induced nausea and vomiting. *Onco Targets Ther* 2018;11:6459-6478.
29. Pasricha PJ, Yates KP, Sarosiek I, et al. Aprepitant Has Mixed Effects on Nausea and Reduces Other Symptoms in Patients With Gastroparesis and Related Disorders. *Gastroenterology* 2018;154:65-76 e11.
30. Carlin JL, Lieberman VR, Dahal A, et al. Efficacy and Safety of Tradipitant in Patients with Diabetic and Idiopathic Gastroparesis in a Randomized, Placebo-Controlled Trial. *Gastroenterology* 2020.
31. Lacy BE, Parkman HP, Camilleri M. Chronic nausea and vomiting: evaluation and treatment. *Am J Gastroenterol* 2018;113:647-659.
32. Mansi C, Savarino V, Vigneri S, et al. Gastrokinetic effects of levosulpiride in dyspeptic patients with diabetic gastroparesis. *Am J Gastroenterol* 1995;90:1989-93.
33. Camilleri M. Cannabinoids and gastrointestinal motility: Pharmacology, clinical effects, and potential therapeutics in humans. *Neurogastroenterol Motil* 2018;30:e13370.
34. Chaiyakunapruk N, Kitikannakorn N, Nathisuwan S, et al. The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis. *Am J Obstet Gynecol* 2006;194:95-9.

35. Broad J, Mukherjee S, Samadi M, et al. Regional- and agonist-dependent facilitation of human neurogastrointestinal functions by motilin receptor agonists. *Br J Pharmacol* 2012;167:763-74.
36. Larson JM, Tavakkoli A, Drane WE, et al. Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. *J Neurogastroenterol Motil* 2010;16:407-13.
37. Briejer MR, Akkermans LM, Schuurkes JA. Gastrointestinal prokinetic benzamides: the pharmacology underlying stimulation of motility. *Pharmacol Rev* 1995;47:631-51.
38. Feldman M, Smith HJ. Effect of cisapride on gastric emptying of indigestible solids in patients with gastroparesis diabeticorum. A comparison with metoclopramide and placebo. *Gastroenterology* 1987;92:171-4.
39. Manini ML, Camilleri M, Goldberg M, et al. Effects of Velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation. *Neurogastroenterol Motil* 2010;22:42-9, e7-8.
40. Carbone F, Van den Houte K, Clevers E, et al. Prucalopride in Gastroparesis: A Randomized Placebo-Controlled Crossover Study. *Am J Gastroenterol* 2019.
41. Camilleri M, McCallum RW, Tack J, et al. Efficacy and Safety of Relamorelin in Diabetics With Symptoms of Gastroparesis: A Randomized, Placebo-Controlled Study. *Gastroenterology* 2017;153:1240-1250 e2.
42. Cherian D, Sachdeva P, Fisher RS, et al. Abdominal pain is a frequent symptom of gastroparesis. *Clin Gastroenterol Hepatol* 2010;8:676-81.
43. Drossman DA, Tack J, Ford AC, et al. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut-Brain Interaction): A Rome Foundation Working Team Report. *Gastroenterology* 2018;154:1140-1171 e1.
44. Parkman HP, Van Natta ML, Abell TL, et al. Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. *JAMA* 2013;310:2640-9.
45. Talley NJ, Locke GR, Saito YA, et al. Effect of Amitriptyline and Escitalopram on Functional Dyspepsia: A Multicenter, Randomized Controlled Study. *Gastroenterology* 2015;149:340-9 e2.
46. Malamood M, Roberts A, Kataria R, Parkman HP, Schey R Mirtazapine for symptom control in refractory gastroparesis. *Drug Des Devel Ther.* 2017 Mar 30;11:1035-1041.
47. Tack J, Ly HG, Carbone F, et al. Efficacy of Mirtazapine in Patients With Functional Dyspepsia and Weight Loss. *Clin Gastroenterol Hepatol* 2016;14:385-392 e4.
48. Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med* 2005;6:346-56.
49. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 2008;31:1448-54.
50. Vedula SS, Bero L, Scherer RW, et al. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med* 2009;361:1963-71.
51. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2011:CD007938.
52. FAMILONI BO, ABELL TL, GAN Z, et al. Driving gastric electrical activity with electrical stimulation. *Ann Biomed Eng* 2005;33:356-64.

53. Musunuru S, Beverstein G, Gould J. Preoperative predictors of significant symptomatic response after 1 year of gastric electrical stimulation for gastroparesis. *World J Surg* 2010;34:1853-8.
54. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003;125:421-8.
55. Lin Z, Forster J, Sarosiek I, et al. Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. *Diabetes Care* 2004;27:1071-6.
56. Lin Z, McElhinney C, Sarosiek I, et al. Chronic gastric electrical stimulation for gastroparesis reduces the use of prokinetic and/or antiemetic medications and the need for hospitalizations. *Dig Dis Sci* 2005;50:1328-34.
57. Ducrotte P, Coffin B, Bonaz B, et al. Gastric Electrical Stimulation Reduces Refractory Vomiting in a Randomized Crossover Trial. *Gastroenterology* 2020;158:506-514 e2.
58. Lahr CJ, Griffith J, Subramony C, et al. Gastric electrical stimulation for abdominal pain in patients with symptoms of gastroparesis. *Am Surg* 2013;79:457-64.
59. McCallum RW, Lin Z, Forster J, et al. Gastric electrical stimulation improves outcomes of patients with gastroparesis for up to 10 years. *Clin Gastroenterol Hepatol* 2011;9:314-319 e1.
60. Abell TL, Johnson WD, Kedar A, et al. A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis. *Gastrointest Endosc* 2011;74:496-503 e3.
61. Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 1986;90:1919-25.
62. Moraveji S, Bashashati M, Elhanafi S, et al. Depleted interstitial cells of Cajal and fibrosis in the pylorus: Novel features of gastroparesis. *Neurogastroenterol Motil* 2016;28:1048-54.
63. Desprez C, Roman S, Leroi AM, et al. The use of impedance planimetry (Endoscopic Functional Lumen Imaging Probe, EndoFLIP((R))) in the gastrointestinal tract: A systematic review. *Neurogastroenterol Motil* 2020;32:e13980.
64. Jehangir A, Malik Z, Petrov RV, et al. EndoFLIP and Pyloric Dilation for Gastroparesis Symptoms Refractory to Pyloromyotomy/Pyloroplasty. *Dig Dis Sci* 2020.
65. Ezzeddine D, Jit R, Katz N, et al. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002;55:920-3.
66. Lacy BE, Crowell MD, Schettler-Duncan A, et al. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. *Diabetes Care* 2004;27:2341-7.
67. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther* 2007;26:1251-8.
68. Friedenberg FK, Palit A, Parkman HP, et al. Botulinum toxin A for the treatment of delayed gastric emptying. *Am J Gastroenterol* 2008;103:416-23.
69. Desprez C, Melchior C, Wuestenberghs F, et al. Pyloric distensibility measurement predicts symptomatic response to intrapyloric botulinum toxin injection. *Gastrointest Endosc* 2019;90:754-760 e1.
70. Pasricha TS, Pasricha PJ. Botulinum Toxin Injection for Treatment of Gastroparesis. *Gastrointest Endosc Clin N Am* 2019;29:97-106.

71. Khashab MA, Ngamruengphong S, Carr-Locke D, et al. Gastric per-oral endoscopic myotomy for refractory gastroparesis: results from the first multicenter study on endoscopic pyloromyotomy (with video). *Gastrointest Endosc* 2017;85:123-128.
72. Kahaleh M, Gonzalez JM, Xu MM, et al. Gastric peroral endoscopic myotomy for the treatment of refractory gastroparesis: a multicenter international experience. *Endoscopy* 2018;50:1053-1058.
73. Spadaccini M, Maselli R, Chandrasekar VT, et al. Gastric peroral endoscopic pyloromyotomy for refractory gastroparesis: a systematic review of early outcomes with pooled analysis. *Gastrointest Endosc* 2020;91:746-752 e5.
74. Tack J, Arts J, Caenepeel P, et al. Pathophysiology, diagnosis and management of postoperative dumping syndrome. *Nat Rev Gastroenterol Hepatol* 2009;6:583-90.
75. Fontana RJ, Barnett JL. Jejunostomy tube placement in refractory diabetic gastroparesis: a retrospective review. *Am J Gastroenterol* 1996;91:2174-8.





GES: gastric emptying study; OTC: over the counter; CBT: cognitive and behavioral therapy; G-POEM: gastric per oral endoscopic myotomy

*Abdominal pain is present in many, but not all patients with gastroparesis. Data from tertiary care centers reveal a higher prevalence of pain compared to the general community.

**see references 1,5,31 for a comprehensive list of gastroparesis mimics and a differential diagnosis