AGA Clinical Guideline: Update on Management of Medically Refractory Gastroparesis

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Definition and Symptoms

- **Gastroparesis** - syndrome defined by symptomatic delay in gastric emptying in the absence of mechanical obstruction
- Typical symptoms - nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and/or weight loss
- Significant overlap in symptoms with functional dyspepsia
- Etiology – diabetes, medications (opioids, GLP-1 agonists), post-surgical, idiopathic
- **Medically refractory gastroparesis** – persistent symptoms, with objectively confirmed delayed gastric emptying, despite dietary adjustment and metoclopramide (first line therapeutic agent)

Pathophysiology of Gastroparesis

- Complex pathophysiology including:
  - Impaired gastric accommodation, electrical dysrhythmias, antroduodenal dyscoordination, pyloric dysfunction, antral hypomotility, vagal nerve injury and disorders of visceral sensation
- **Simply accelerating gastric emptying may not improve global symptoms**
  - Not validated to categorize gastroparesis severity based on the extent of gastric emptying delay
- Prokinetic therapy may benefit predominant antral hypomotility, and pylorus-directed therapies can be considered for pyloric dysfunction

Medically Refractory Gastroparesis – Initial Eval

- Generally, nausea and vomiting are the predominant persistent symptoms
- Should have failed initial treatment to classify as refractory, including:
  - Small particle size, reduced fat diet for a minimum of 4 weeks
  - Reglan (minimum of 10 mg TID AC and qhs) for at least four weeks
- Basic workup should have been performed to confirm diagnosis of gastroparesis and exclude other etiologies: TSH, fasting AM cortisol, upper endoscopy, gastric emptying study
- Ensure accurate gastric scintigraphy performed – **4-hour test off opiates**
- Repeating scintigraphy may change the diagnosis from gastroparesis to functional dyspepsia and vice versa in as many as 37-42% within the course of a year
- Meal based gastric scintigraphy recommended as the first-line test of gastric emptying over the wireless motility capsule

Medically Refractory Gastroparesis - Management

- Management goals – **identifying and improving the predominant symptom**, and reducing potential complications (malnutrition, weight loss, esophagitis)
- A variety of medical treatment options exist for refractory gastroparesis, though few have been evaluated in large RCTs

Lacy BE, Tack J, Gyawali CP, AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis: Expert Review, Clinical Gastroenterology and Hepatology (2021), doi: https://doi.org/10.1016/j.cgh.2021.10.038.

Medications for Medically Refractory Gastroparesis

	Drug and or Class	Mechanism / Efficacy	Dosing	Adverse effects / Cons
Medications for Nausea and Vomiting	**Domperidone**	- Dopamine D2-receptor antagonist - Does not readily cross the blood brain barrier, fewer central side effects than Metoclopramide - 68% had an improvement in symptom scores	- Recommended starting dose 10mg TID ; escalation to 20mg QID has been reported, but should be avoided for CV safety	- QT prolongation and ventricular tachycardia are risks - Availability in the US is only through an FDA investigational drug application
	5-HT3 antagonists (Ondansetron & Granisetron)	- Block serotonin receptors in the chemoreceptor trigger zone and inhibit vagal afferents - Similar efficacy between Ondansetron & Granisetron - Transdermal Granisetron decreases symptom scores by 50% in patients with refractory gastroparesis symptoms	- Ondansetron – 4-8mg BID – TID - Granisetron – 1mg BID - Granisteron patch - 34.3 mg patch weekly	- Selection can be determined by price, availability, and mode of delivery
	Neurokinin (NK-1) receptor antagonists (aprepitant, tradipitant, casopitant, rolapitant)	- Block substance P in critical areas involved in nausea and vomiting - Appear to improve nausea/vomiting in up to 1/3 of patients	- Aprepitant 80mg qd	- Symptoms improved regardless of presence or absence of gastroparesis
	Phenothiazine antipsychotics (e.g., prochlorperazine, chlorpromazine)	- Reduce nausea and vomiting by inhibiting dopamine receptors in the brain	- Prochlorperazine 5-10mg BID - Chlorpromazine 10-25 mg TID or QID	- Have not been studied in gastroparesis or compared prospectively to other anti-emetics
Medications to Accelerate Gastric Emptying	**Erythromycin**	- Macrolide antibiotic, accelerates gastric emptying by binding to motilin receptors	- Intravenously in hospitalized patients (3 mg/kg every 8 hours), or PO in outpatients (50-100 mg QID (AC and qhs))	- Tachyphylaxis limits effectiveness - Higher oral doses may cause early satiation and pain, and may exacerbate nausea and vomiting - QT prolongation, risk of cardiac arrhythmia
	5-HT4 receptor agonists (Cisapride, Velusetrag, Prucalopride)	- Cisapride – appeared effective - Velusetrag – accelerated gastric emptying in phase 2 RCT - Prucalopride – accelerated gastric emptying and improved symptoms	- Velusetrag experimental - dosing not yet approved - Prucalopride 2mg qd	- Cisapride off market due to adverse cardiac effects - Other agents not yet approved for gastroparesis

Medications for Medically Refractory Gastroparesis (cont.)

	Drug and/or Class	Mechanism / Efficacy	Dosing	Adverse effects / Cons
Medications for Visceral Pain	**TCA (Nortriptyline, Amitriptyline, Imipramine)**	- Noradrenaline reuptake inhibition is considered the main mechanism for controlling visceral pain - Per NORIG trial, no improvement in GCSI score on Nortriptyline over placebo - Greatest benefit in patients with functional dyspepsia overlap	- Amitriptyline 25-100 mg/qd - Imipramine 25-100 mg/qd - Desipramine 25-75 mg/qd - Nortriptyline 25-100 mg/qd	- Does not improve gastric emptying - Evidence in functional dyspepsia but not gastroparesis
	SNRI (Duloxetine)	- Improved diabetic polyneuropathic pain	- 60-120 mg/day	- Can worsen nausea or constipation in higher doses
	Pregabalin	- Inhibits release of excitatory neurotransmitter for anti-nociceptive and anticonvulsant effects - Pooled data from seven RCTs indicates reduction in pain	- 100-300 mg/day in divided doses	- Adverse effects - dizziness, somnolence, weight gain and peripheral edema

Gastric Electrical Stimulation

- Precise mechanism unknown; does not increase gastric emptying, rather modulates the gastric pacemaker and interstitial cells of Cajal
- Does improve refractory nausea & vomiting
- 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

Pylorus directed therapies

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

Pylorus directed therapies include:

- **Intrapyloric botulinum injection** - available data argues against use of botulinum toxin in refractory gastroparesis, except in clinical trials
- **Transpyloric stent placement** – should be considered investigational, lack of data
- **Gastric per oral myotomy** (GPOEM) - Two separate multi-center trials noted improvement in symptoms and reduction in gastric emptying times.
- Studies suggest a reduction in post-procedure GCSI scores and improved gastric emptying
- Should only be performed at tertiary care centers using a team approach of experts