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), postsurgical, 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
<table>
<thead>
<tr>
<th>Drug and or Class</th>
<th>Mechanism / Efficacy</th>
<th>Dosing</th>
<th>Adverse effects / Cons</th>
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| **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 antiemetics |
| **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.)

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