Gastroparesis: A chronic disorder

A motility disorder of the stomach characterized by delayed gastric emptying without evidence of obstruction.

Symptoms
- nausea, vomiting
- early satiety
- postprandial fullness/bloating
- loss of appetite
- upper abdominal pain
- constipation
Clinical Burden of Gastroparesis is High

Nausea and Vomiting
- Nausea is present in nearly all patients (95%)
- Nausea and vomiting decrease quality of life.
- Vomiting is more prevalent and severe in DG than IG.
- Symptoms of nausea and vomiting are important symptoms that each need to be specifically addressed.

Abdominal pain
- Pain has largely been ignored in gastroparesis
- Pain is the predominant symptom in one fifth of gastroparetics.
- Moderate-severe abdominal pain is prevalent in gastroparesis (66%), impairs quality of life, and is associated with idiopathic etiology, but not gastric emptying.
- Pain has at least as great an impact on disease severity and quality of life as nausea/vomiting.

Trends of Gastroparesis-Related Hospitalizations
United States, 1995-2004

Figure 1. Number of hospitalizations with gastroparesis as the primary diagnosis in the United States, 1995-2004.

Hospitalizations: Gastroparesis as primary diagnosis increased +158%
Gastroparesis as secondary diagnosis increased +136%
Diabetes-related increased +53%
All hospitalizations increased +13%
Etiologies of Gastroparesis

Diabetes
Postgastric surgery
Idiopathic

Other

- Metabolic Disorders: Hypothyroidism
- Medications: narcotics, anticholinergics
- Rheumatologic: Scleroderma, SLE, RSD
- Psychiatric: Eating disorders (anorexia, bulimia)
- Generalized GI Motility Disorder:
  - Intestinal pseudo-obstruction
  - GERD

Diagnosis of Gastroparesis

Symptoms

- Gastroparesis vs functional dyspepsia, ulcer, cancer

Exclusion of organic lesions

- Upper Endoscopy or Upper GI Series

Delayed Gastric emptying

- Scintigraphy (solid phase)
## Techniques to Evaluate Gastric Emptying

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Methodology</th>
<th>Imaging Standards</th>
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</thead>
<tbody>
<tr>
<td><strong>Scintigraphy</strong></td>
<td>Standard test</td>
<td>Variable methodology clinically</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standardization of Meal / Imaging</td>
</tr>
<tr>
<td><strong>Wireless Motility Capsule</strong></td>
<td>Office Test, easily standardized</td>
<td>Gastrointestinal emptying/contractility</td>
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<tr>
<td></td>
<td></td>
<td>Empties with phase III MMC</td>
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<td></td>
<td></td>
<td>Measures Whole Gut Transit</td>
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<tr>
<td><strong>GE Breath Test</strong></td>
<td>Office Based Tests, easily standardized</td>
<td>Used in US in research studies</td>
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<tr>
<td></td>
<td></td>
<td>Now approved by FDA</td>
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<td></td>
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<td>Ready to use</td>
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### Correlating Symptoms to Delayed Gastric Emptying

At TUH, 1499 patients undergoing Gastric Emptying Scintigraphy from September 2007 to January 2010.

GES was performed with ingestion of a liquid egg white meal with imaging at 0, 0.5, 1, 2, 3, and 4 hours. Patients completed the Patient Assessment of Gastrointestinal Symptoms questionnaire before GES.

629 of the 1499 patients (42%) had increased retention at 4 hours (>10%).

The symptoms correlating with gastric retention at 4 hours included:

- early satiety: $r=0.170; p<0.01$
- vomiting: $r=0.143; p<0.01$
- postprandial fullness: $r=0.123; p<0.01$
- loss of appetite: $r=0.122; p<0.01$

Pathikonda, Sachdeva Maurer AH, Parkman HP

*J Clinical Gastro* 2012
**Chronic unexplained nausea/vomiting but normal gastric emptying**

425 patients with chronic nausea & vomiting, 319 (75%) delayed, 106 normal GES.

Similar symptom severity for nausea, retching, vomiting, stomach fullness, early satiety, postprandial fullness, loss of appetite, bloating, visibly larger stomach. Total GCSI scores were not correlated with gastric retention in either group.

Those with delayed gastric emptying were more likely to be diabetic.
State anxiety scores were slightly higher among patients with delayed GE.

**CONCLUSIONS:**
Patients with nausea and vomiting with normal gastric emptying represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis. This syndrome is not categorized in the medical literature--it might be a separate clinical entity.

**Assessment of Gastric Accommodation during Gastric Emptying**

Impaired GA can be evaluated using current standardized solid-meal GES.

Impaired GA is associated with early satiety.

Impaired GA may explain early satiety in patients with normal GES.

Routine visual assessment of GA as a part of a GES study may allow for better correlation of symptoms to abnormalities of gastric motility.

**Assessment of Gastric Accommodation during Gastric Emptying**

**Normal Fundic Accommodation**

**Impaired Fundic Accommodation**

Arau, Parkman, Maurer. DDW 2014
General Principles for Treatment of Patients With Gastroparesis

Correct fluid, electrolyte, nutritional deficiencies

Identify and treat the underlying cause

Suppress or eliminate symptoms; primarily nausea, vomiting

Quigley, Hasler, Parkman. Gastroenterology 2000; 120:263

Treatment of Gastroparesis

**General Items**

Avoid medications that can delay stomach emptying
Glucose control for diabetic patients

**Diet**

low fiber and roughage
low in fat (fat increases CCK and delays GE)
Liquid nutrients are better tolerated over solid food
small meals, usually multiple 4-6/day
Nutrition Consultation

**Antiemetic Agents**

Compazine, Tigan (affect CNS vomiting center)
Ondansetron, a 5-HT-3 receptor antagonist

**Prokinetic Agents**

Metoclopramide, a dopamine receptor antagonist
Erythromycin, a motilin receptor agonist
Domperidone, a dopamine receptor antagonist
Commonly Used Prokinetic Agents

<table>
<thead>
<tr>
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<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td><strong>Metoclopramide</strong></td>
<td>Approved for gastroparesis</td>
<td>Side Effects</td>
</tr>
<tr>
<td></td>
<td>Acts as prokinetic and antiemetic</td>
<td>Acute/Chronic</td>
</tr>
<tr>
<td></td>
<td>both may act for efficacy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Available po, IV, SQ</td>
<td></td>
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<tr>
<td><strong>Erythromycin</strong></td>
<td>Potent gastrokinetic agent</td>
<td>Side Effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute/Chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachyphylaxis (loss of effect)</td>
</tr>
<tr>
<td><strong>Domperidone</strong></td>
<td>Acts as prokinetic and antiemetic</td>
<td>Not approved in the USA</td>
</tr>
<tr>
<td></td>
<td>Less side effects than metoclopramide</td>
<td>Available with FDA IND</td>
</tr>
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</table>

Metoclopramide to Treat Gastroparesis due to Diabetes Mellitus

Randomized, double-blind, controlled trial of metoclopramide in 10 patients with diabetic gastroparesis

Metoclopramide increased gastric emptying

Overall symptoms and symptoms of vomiting were reduced during metoclopramide treatment.

Poor correlation between improved gastric emptying and decreased symptoms.

Metoclopramide improves symptoms of diabetic gastroparesis:

- Peripheral effect of gastric smooth muscle to increase gastric emptying
- Central effect on chemoreceptor vomiting zone to decrease nausea.

Snape, Battle, et al.
Ann Intern Med 1982;96:444
Domperidone in the Management of Symptoms of Diabetic Gastroparesis

Single-Masked Study: 208/269 (77%) patients with diabetic gastroparesis improved on Domperidone 20 mg po QID
Randomized Placebo-Controlled, Double-Masked Withdrawal Phase: Placebo group had greater deterioration in total symptom scores compared to domperidone

Erythromycin in the Short-Term and Long-Term Control of Dyspepsia Symptoms in Gastroparesis

25 patients with gastroparesis
Treated with low dose erythromycin suspension (50-100 mg TID)
**Randomized, Placebo-Controlled Trial of Botulinum Toxin A for the Treatment of Gastroparesis**

Botulinum toxin type A (Botox) binds to presynaptic acetylcholine terminals producing blockade at the level of the neuromuscular junction preventing cholinergic transmission and promoting muscle relaxation.

32 patients randomized to receive either Botox 200 units (n=16) or Saline 5 ml (n=16)

Friedenberg, Palit, Parkman, Nelson. Am J Gastroenterology 2008

**Outcomes in Gastroparesis using NIH GpR1**

Patients with gastroparesis (diabetic or idiopathic) in GpR1.

Only 28% of 262 patients symptomatically improved at 48 weeks with decrease GCSI ≥1.

Chronic nature of gastroparesis. The disease burden remains high.

<table>
<thead>
<tr>
<th>Positive predictors for improvement</th>
<th>OR</th>
<th>p</th>
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<tbody>
<tr>
<td>age ≥50 years</td>
<td>3.35</td>
<td>0.001</td>
</tr>
<tr>
<td>GCSI score</td>
<td>2.87</td>
<td>0.001</td>
</tr>
<tr>
<td>antidepressant use</td>
<td>2.27</td>
<td>0.02</td>
</tr>
<tr>
<td>gastric retention &gt;20% at 4 hours</td>
<td>2.22</td>
<td>0.02</td>
</tr>
<tr>
<td>initial infectious prodrome</td>
<td>2.22</td>
<td>0.05</td>
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</table>

<table>
<thead>
<tr>
<th>Negative predictors for improvement</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>anxiolytics</td>
<td>0.28</td>
<td>0.02</td>
</tr>
<tr>
<td>pain modulator use</td>
<td>0.34</td>
<td>0.01</td>
</tr>
<tr>
<td>abdominal pain (moderate/severe)</td>
<td>0.40</td>
<td>0.04</td>
</tr>
<tr>
<td>overweight/obese</td>
<td>0.43</td>
<td>0.01</td>
</tr>
<tr>
<td>depression</td>
<td>0.45</td>
<td>0.03</td>
</tr>
<tr>
<td>smoking history</td>
<td>0.46</td>
<td>0.04</td>
</tr>
<tr>
<td>gastroesophageal reflux severity</td>
<td>0.66</td>
<td>0.01</td>
</tr>
</tbody>
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Pasricha et al. Gastroenterology 2015
Tricyclic Antidepressants for Chronic Vomiting in Diabetic Patients

24 diabetic patients treated with tricyclic antidepressants for nausea and vomiting after an unsatisfactory response to prokinetic therapy.

TCAs: Amitriptyline, nortriptyline, desipramine.

Starting doses 10-25 mg/day; final maintenance dose: 10-75 mg/day.

NORIG Trial: Main Outcomes

Nortriptyline did not improve overall symptoms, as defined by our primary outcome measure, in idiopathic gastroparesis over a 15 week period.

At 3 weeks: Improvement in nausea and abdominal pain at nortriptyline (10 mg), but not sustained over time as dosing was increased.

At 15 weeks: Higher doses of nortriptyline were associated with improvements in appetite, satiety, and body weight.
Continuous Glucose Monitoring (CGM) Plus Continuous Subcutaneous Insulin Infusion (CSII) Reduces Hypoglycemia in Diabetes (DM) with Gastroparesis (GP): A Multicenter Pilot Study (GLUMIT)

GLUMIT tested safety and efficacy of CSII and CGM in 45 individuals with uncontrolled DM (A1c >8%) and GP (>10% 4 hr retention) (20% T1DM). CSII+CGM for 24-week study. Patients recommended to use dual wave boluses for meal boluses, adjust insulin dose based on sensor glucose trends and predictive alerts.

Diabetic Outcomes:
Baseline A1c levels (9.4±1.4 %) decreased by 1.1% at 24 weeks (P=0.0002 vs. baseline).

<table>
<thead>
<tr>
<th></th>
<th>Hypoglycemia (&lt;70 mg/dL)</th>
<th>Euglycemia (71-180 mg/dL)</th>
<th>Hyperglycemia (&gt;180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.9%</td>
<td>44.0%</td>
<td>52.1%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1.7% (P&lt;0.0001)</td>
<td>51.8% (p=0.004)</td>
<td>46.5% (p=0.04)</td>
</tr>
</tbody>
</table>

9 severe hypoglycemic events (third party assistance) occurred (2 during 2-8 week screening phase and 7 during 24 week treatment phase); 6 related to mismatches of insulin boluses/meal ingestion, 2 to insulin over-dosing, 1 no explanation.

Patients who had episodes of severe hypoglycemia had more severe GP at baseline, with nausea/vomiting scores 63.0% greater (p=0.002) and early satiety scores 18.2% greater (p=0.04) vs. those who did not have these episodes.

Summary: in DM patients with GP the CSII + CGM protocol for 6 months improved glycemic control with less time in hypoglycemia, more time in euglycemia and with an acceptable safety profile. Patients with more severe GP warrant more careful surveillance.

Pilot Study of the Safety, Feasibility, and Efficacy of Continuous Glucose Monitoring (CGM) and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG)

Diabetics with gastroparesis are advised to lower blood sugars to reduce symptoms. The potential of continuous glucose monitoring (CGM) coupled with intensive insulin regimens to safely reduce hyperglycemia and improve gastroparesis manifestations is unproved.

45 diabetics with gastroparesis, poorly controlled (A1c >8%) with gastroparesis (>10% 4 h retention); 29% type 1, 21±11 yr diabetes duration.

Gastroparesis Outcomes: Baseline Change at wk 12 Change at wk 24

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change at wk 12</th>
<th>Change at wk 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GCSI score</td>
<td>29.3±7.1</td>
<td>-7.2±8.2 (p&lt;0.001)</td>
<td>-6.6±8.8 (p&lt;0.001)</td>
</tr>
<tr>
<td>Nausea/Vomiting subscore</td>
<td>8.1±4.2</td>
<td>-2.9±4.0 (p&lt;0.001)</td>
<td>-2.8±4.1 (p&lt;0.001)</td>
</tr>
<tr>
<td>Fullness/Early satiety</td>
<td>14.1±3.6</td>
<td>-3.1±4.5 (p&lt;0.001)</td>
<td>-2.4±4.5 (p=0.002)</td>
</tr>
<tr>
<td>Bloating/Distention</td>
<td>7.1±2.3</td>
<td>-1.3±2.9 (p=0.001)</td>
<td>-1.5±2.5 (p=0.001)</td>
</tr>
<tr>
<td>Water load tolerance</td>
<td>430±207</td>
<td>0±243 (p=0.99)</td>
<td>-33±190 (p=0.31)</td>
</tr>
<tr>
<td>Liquid nutrient tolerance</td>
<td>420±258</td>
<td>15±117 (p=0.47)</td>
<td>59±176 (p=0.05)</td>
</tr>
</tbody>
</table>

Conclusions:
Symptom and nutrient tolerance benefits were maintained for the 24 week phase of intensive monitoring and therapy.
This uncontrolled pilot study shows the feasibility and potential for dual benefits improving both diabetes control and lowering gastroparesis symptom burdens.
**Refractory Gastroparesis**

Jejunostomy tube for feeding into small intestine  
bypassing gastroparetic stomach  
Gastrostomy tube for venting of stomach

Gastric electric stimulation  
Gastric pacing vs high frequency stimulation  
suppressing symptoms, particularly nausea, vomiting

Pyloromyotomy/pyloroplasty

Central line for Total Parenteral Nutrition (PICC)  
If long term, problems with infection, thrombosis

Gastrectomy (last resort)  
near-total  
completion, for post surgical gastroparesis

**Granisetron (5-HT3 Receptor Antagonist) Transdermal System**  
Improves Refractory Nausea and Vomiting in Gastroparesis
Initiation of Enteral Nutrition
Surgical Jejunostomy

Severe weight loss
(weight loss >10% of usual body weight over 6 months)

Repeated hospitalizations for refractory gastroparesis intravenous hydration and/or intravenous medication.

Better absorption of medications to gain therapeutic levels when vomiting prevents this.

Gastric decompression: Gastrostomy/jejunostomy tube(s).

Clinical Improvement with Enterra Gastric Electric Stimulation
Treatment for Refractory Gastroparesis
The Temple Experience (2004-2006)

Overall, 14 of 28 (50%) patients felt improved.
Nausea/vomiting subscore improved
Abdominal pain did not change.

GCSI Scores: Subgroup Analysis

<table>
<thead>
<tr>
<th>GCSI Score</th>
<th>N=10</th>
<th>N=2</th>
<th>N=12</th>
<th>N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/V</td>
<td>2.3</td>
<td>2.7</td>
<td>2.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Abd Pain</td>
<td>3.0</td>
<td>3.3</td>
<td>3.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Three Predictive Factors:
Diabetic patients better than idiopathic
Chief complaint of nausea/vomiting
Not taking narcotic analgesics.
Gastric Electric Stimulation for Refractory Gastroparesis: A Prospective Analysis of 151 Patients at a Single Center

Heckert, et al. DDS 2015

Laparoscopic pyloroplasty for gastroparesis results in sustained symptom improvement


Laparoscopic Heineke-Mikulicz pyloroplasty performed in 26 patients. Laparoscopic assisted, flexible trans-oral endoscopic circular stapled pyloroplasty used 2 patients.

GES T1/2 decreased from 320 to 112 min and normalized in 71%.

Improvements were seen at 1 month for nausea, vomiting, bloating, abdominal pain, and GER symptoms.

Improvement persisted at 3 months for nausea, vomiting, bloating, abdominal pain and GERD symptoms.

Prokinetic use was significantly reduced from 89% to 14%.

Minimally invasive pyloroplasty provides excellent outcomes for patients with gastroparesis. With technological advancements, a totally endoscopic pyloroplasty may be a less invasive option.

Endoscopic Pyloromyotomy for Gastroparesis

Submucosal Tunnel  Pyloromyotomy

Assessing Pyloric Sphincter Pathophysiology using Impedance Planimetry in Patients with Gastroparesis

Impedance planimetry is a novel technique that can be used to assess pyloric physiologic characteristics: pressure, diameter, length, cross sectional area, distensibility.

Early satiety and postprandial fullness were inversely correlated with diameter and cross-sectional area (CSA) of the pyloric sphincter.

No significant differences were seen comparing diabetic and idiopathic gastroparetics.

This technology may be of benefit to help select patients with pyloric sphincter abnormalities.

Malik, Sankinini et al. NGM 2015
## On the Horizon for Gastroparesis

**FDA Guidance on Gastroparesis (7/2015)**

### Diagnostic testing
- Assessment of fundic accommodation
- Breath test for gastric emptying
- Assessing histopathology in patients with Gp Symptoms

### New treatments

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatments</th>
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<tbody>
<tr>
<td>Prokinetic agents</td>
<td>Motilin receptor agonists</td>
</tr>
<tr>
<td></td>
<td>Ghrelin receptor agonists</td>
</tr>
<tr>
<td></td>
<td>5-HT4 receptor agonists</td>
</tr>
<tr>
<td></td>
<td>Dopamine type 2 receptor antagonists</td>
</tr>
<tr>
<td>Antiemetic agents</td>
<td>5HT3 receptor antagonists</td>
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<tr>
<td></td>
<td>NK1 receptor antagonists</td>
</tr>
<tr>
<td>Surgical treatments</td>
<td>Re-evaluation of gastric stimulation parameters</td>
</tr>
<tr>
<td>Endoscopic treatments</td>
<td>Endoscopic pyloromyotomy</td>
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<tr>
<td></td>
<td>Endoscopically placed gastric electric stimulation</td>
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