GASTROPARESIS

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Symptom Definitions

• **Nausea**: a subjective feeling of wanting to vomit
• **Vomiting**: forceful expulsion of gastroduodenal contents
• **Regurgitation**: effortless expulsion of esophageal or gastric contents
• **Retching**: abdominal muscle contractions with labored rhythmic respiration
• **Rumination**: effortless regurgitation of recently ingested food, may be pleasurable, re-swallowing
Gastroparesis

**Definition**
- Objectively delayed gastric emptying
- Compatible symptoms
- Mechanical obstruction excluded

**Identification**
- Suspected: symptoms, retained food at endoscopy after fast
- Quantified: gastric emptying study

FUNCTIONAL DYSPEPSIA

- epigastric pain, early satiety, nausea, vomiting
- ± disordered gastric emptying

GASTROPARESIS

- epigastric pain, early satiety, nausea, vomiting
- delayed gastric emptying

Functional Dyspepsia with/without disordered gastric emptying

- epigastric pain/pressure, early satiety, nausea, bloating, vomiting

Rapid gastric emptying

Normal gastric emptying

Mildly delayed gastric emptying

Severely delayed gastric emptying

Lacy BE, Am J Gastroenterol 2012;107:1615-20
### Delayed Gastric Emptying in FD

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Delayed emptying</th>
<th>Correlation with symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jian 1989</td>
<td>28</td>
<td>59%</td>
<td>None</td>
</tr>
<tr>
<td>Wegener 1989</td>
<td>43</td>
<td>30%</td>
<td>None</td>
</tr>
<tr>
<td>Talley 1989</td>
<td>32</td>
<td>30%</td>
<td>None</td>
</tr>
<tr>
<td>Waldron 1991</td>
<td>50</td>
<td>42%</td>
<td>None</td>
</tr>
<tr>
<td>Klauser 1993</td>
<td>69</td>
<td>35%</td>
<td>None</td>
</tr>
<tr>
<td>Scott 1993</td>
<td>75</td>
<td>28%</td>
<td>None</td>
</tr>
<tr>
<td>Stanghellini 1996</td>
<td>343</td>
<td>34%</td>
<td>female, postprandial fullness, vomiting</td>
</tr>
<tr>
<td>Maes 1997</td>
<td>344</td>
<td>30%</td>
<td>Not studied</td>
</tr>
<tr>
<td>Perri 1998</td>
<td>304</td>
<td>33%</td>
<td>postprandial fullness, nausea, vomiting</td>
</tr>
<tr>
<td>Talley 2001</td>
<td>551</td>
<td>24%</td>
<td>none</td>
</tr>
<tr>
<td>Sarnelli 2003</td>
<td>392</td>
<td>23%</td>
<td>postprandial fullness, nausea, vomiting</td>
</tr>
<tr>
<td>Talley 2006</td>
<td>864</td>
<td>34%</td>
<td>postprandial fullness</td>
</tr>
</tbody>
</table>
### Functional Dyspepsia vs. Gastroparesis

<table>
<thead>
<tr>
<th><strong>Functional dyspepsia</strong></th>
<th><strong>Gastroparesis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Making this diagnosis rests purely on symptoms or questionnaires; requires diligence and clinical expertise</td>
<td>Diagnosis is objective with a measurable entity (despite issues with the gastric emptying study)</td>
</tr>
<tr>
<td>Making this diagnosis keeps options open for future pathophysiologic evaluations and biomarkers</td>
<td>Clinical features are not necessarily associated with gastric emptying or suspected pathophysiology</td>
</tr>
<tr>
<td>Therapeutic options are broad, drugs approved for epigastric pain and postprandial distress can be used</td>
<td>Making this diagnosis risks offering advanced therapies with dangerous side effects to patients who may not need these approaches</td>
</tr>
</tbody>
</table>

Stanghellini & Tack, Gut 2014;63:1972-78
Symptoms

- Neuromuscular disorder
- Gastric motor dysfunction
- Gastric sensory dysfunction
- Delayed gastric emptying
- Abdominal pain
- Discomforts
- Nausea
- Early satiety
- Vomiting
- Weight loss
- GERD
- Functional dyspepsia
- Idiopathic gastroparesis
Gastric Emptying Scintigraphy

Scintigraphy with a standardized meal
225 kcal low-fat, egg white Tc⁹⁹m sulfur colloid radiolabelled meal
72% carb, 24% protein, 2% fat, 2% fiber
Recording at 0, 1, 2 and 4 hours

Confounders:
stress, medications, smoking
blood glucose level
gender

Friedenberg FK, CGH 2005; Stanghellini & Tack, Gut 2014;63:1972-78
Quantification of Gastric Emptying

• **Standard**: scintigraphy of solid phase meal
  – discontinue medications affecting gastric emptying for 48-72 hours
  – Narcotics, anticholinergics delay emptying
  – Metoclopramide, domperidone, erythromycin accelerate emptying
  – Euglycemia is best for a reliable study

• Wireless motility capsule
  – Correlates 85% with T-90% emptying

• $^{13}$C octanoate breath tests

*Camilleri M et al, Am J Gastroenterol 2013;108:18-37*
Causes of Delayed Gastric Emptying

- Idiopathic 33%
- Diabetes mellitus 24%
- Postoperative 19%
- Miscellaneous 6%
- Parkinson’s disease 5%
- Collagen-vascular disease 5%
- Anorexia nervosa 5%
- Pseudo-obstruction 3%

Diabetes mellitus 24%
Idiopathic 33%
Postoperative 19%
Mechanisms

- Fundal hypomotility
- Antral hypomotility
- Gastric arrhythmia
- Lack of antro-pyloro-duodenal coordination
Evaluation

Screen for:
• Diabetes mellitus (especially uncontrolled glucose levels)
• Thyroid dysfunction
• Neurological disease
• Prior gastric or bariatric surgery
• Autoimmune disorders

Viral prodrome (post viral gastroparesis):
• Symptoms may improve over time

Medication induced delay in gastric emptying:
• Narcotics, GLP-1 and amylin analogs, cyclosporin

Confounding diagnoses:
• Cyclic vomiting syndrome, cannabinoid hyperemesis
• Rumination syndrome
• Eating disorders

Management of Gastroparesis

- Treatment of the underlying condition
- Nutritional and dietary treatment
- Prokinetic/antiemetic drugs
- Neuromodulators
- Feeding tube
- Gastric stimulation
Effect of Type of Food on Symptoms

High fat solid meals are least tolerated, low fat liquid meals are best tolerated.
## Dietary Recommendations

<table>
<thead>
<tr>
<th>Provoking foods</th>
<th>Alleviating and tolerable foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange juice</td>
<td>Saltines</td>
</tr>
<tr>
<td>Fried chicken</td>
<td>Jello</td>
</tr>
<tr>
<td>Cabbage</td>
<td>Graham crackers</td>
</tr>
<tr>
<td>Oranges</td>
<td>Applesauce</td>
</tr>
<tr>
<td>Sausage</td>
<td>Popsicles</td>
</tr>
<tr>
<td>Pizza</td>
<td>White rice</td>
</tr>
<tr>
<td>Peppers</td>
<td>Potato</td>
</tr>
<tr>
<td>Onions</td>
<td>Salmon</td>
</tr>
<tr>
<td>Tomato juice</td>
<td>Clear soup</td>
</tr>
<tr>
<td>Lettuce</td>
<td>White fish</td>
</tr>
<tr>
<td>Coffee</td>
<td>Pretzels</td>
</tr>
<tr>
<td>Salsa</td>
<td>Sweet potato</td>
</tr>
<tr>
<td>Broccoli</td>
<td>Tea</td>
</tr>
<tr>
<td>Bacon</td>
<td>Ginger ale</td>
</tr>
<tr>
<td>Roast beef</td>
<td>White bread</td>
</tr>
</tbody>
</table>

- Acidic, fatty, spicy and fiber rich foods provoke symptoms
- Bland, sweet, salty and starchy foods alleviate symptoms
Nutritional Management

More frequent, small meals
Avoid fatty meals
Small particle diet
Liquids better tolerated than solids
Glycemic control

Metoclopramide

Phase 3 MMC-like activity
# Prokinetic/Antiemetic Treatments

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Prokinetic</th>
<th>Antiemetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cisapride</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Tegaserod (Zelnorm)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Domperidone (Motilium)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Meclizine (Antivert)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Trimethobenzamide (Tigan)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Granisetron (Kytril)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dolasetron (Anzemet)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Palonosetron (Aloxi)</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Effects of Prokinetics on Symptoms and Gastric Emptying

**Functional dyspepsia**

<table>
<thead>
<tr>
<th></th>
<th>Cumulative symptom score</th>
<th>Solid gastric emptying t1/2 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Idiopathic gastroparesis**

<table>
<thead>
<tr>
<th></th>
<th>Cumulative symptom score</th>
<th>Solid gastric emptying t1/2 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tack et al 2000 and Arts et al 2004
Prokinetics in Gastroparesis

• Dopamine-2 receptor antagonists
  – metoclopramide, domperidone
• Serotonin-4 receptor agonists
  – cisapride, tegaserod, prucalopride
• Motilin receptor agonists
  – erythromycin
• Ghrelin receptor agonists
  – ulimorelin
Meta-regression analysis: Effect of Medications used in Gastroparesis

No relationship between symptom improvement and change in gastric emptying

p=0.4

Neuromodulators in Delayed Gastric Emptying

Mirtazapine accelerated gastric emptying in both normal dogs and delayed gastric emptying induced by rectal distension.

Mirtazapine is a norepinephrine and serotonin reuptake inhibitor.

Several case reports exist of use in patients.

Nortriptyline for Gastroparesis Symptoms

130 patients with idiopathic gastroparesis from 7 centers
Abnormal gastric emptying study, and GCSI score >21 required for enrollment
Equally randomized to nortriptyline and placebo

Parkman H et al, JAMA 2013;310:2640-9
Neuromodulators Improve Symptoms in Functional Nausea and Vomiting

Agents used:
- Tricyclic antidepressants
- SSRI
- SNRI
- Zonisamide
- Levetiracetam

## Major Pros and Cons of Antidepressants for Functional Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Low dosage effect, anticholinergic, rapid onset</td>
<td>Sedation, anticholinergic, weight gain, metabolic syndrome</td>
</tr>
<tr>
<td>SSRI</td>
<td>Better tolerated, weight neutral</td>
<td>Insomnia; GI upset</td>
</tr>
<tr>
<td>SNRI</td>
<td>Pain relief</td>
<td>Sedation</td>
</tr>
<tr>
<td>NDRI</td>
<td>Weight loss, less sexual side effects</td>
<td>Anxiety/agitation</td>
</tr>
</tbody>
</table>

*All have sexual side effects, seizure potential, and other potential adverse effects*
Management has shifted away from prokinetics and has moved towards symptomatic management with antiemetics, and neuromodulators.
Invasive Therapies

- Botulinum toxin injection
- Percutaneous feeding jejunostomy
- Gastric electrical stimulation
- Partial gastrectomy
Gastric Electrical Stimulation

Option for:
- Chronic idiopathic intractable vomiting
- Symptomatic disorders with abnormal gastric emptying
- Failure of medical therapy
- Not narcotic based symptoms
- Candidate for abdominal surgery

Caveats
- Does not necessarily improve gastric emptying
- Not of value in cyclic vomiting
Symptom Response to Gastric Electrical Stimulation

Gastric Emptying Response to Electrical Stimulation

T1/2 (min)

- Solid emptying
- Liquid emptying

Baseline (n = 8)
Temporary implant (n = 7)
3 months (n = 5)
6 Months (n = 5)
12 Months (n = 3)

Definitive implant

Tack J, institutional experience
## Mechanism of Effect of Gastric Electrical Stimulation on Symptoms

<table>
<thead>
<tr>
<th>Effect</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced gastric emptying</td>
<td>-</td>
</tr>
<tr>
<td>Gastric electrical pacing</td>
<td>-</td>
</tr>
<tr>
<td>Inhibition of gastric arrhythmia's</td>
<td>-</td>
</tr>
<tr>
<td>Placebo effect</td>
<td>-</td>
</tr>
<tr>
<td>Decreased visceral sensitivity</td>
<td>+</td>
</tr>
<tr>
<td>Enhanced accommodation to a meal</td>
<td>+</td>
</tr>
</tbody>
</table>
Impact of Gastric Stimulation Therapy on Vomiting

No difference between ‘on’ and ‘off’ periods
This may suggest a significant placebo effect
Management of Symptoms in the Patient with Gastroparesis

1. Exclude remediable causes

2. Stabilize nutrition & glycemic control

- Pain dominant symptoms
- Nausea, vomiting, other non-pain symptoms

3. Antiemetic-prokinetics, antiemetics

4. Neuromodulators (TCAs, other antidepressants, newer antiepileptics)

5. Gastric electrical stimulation

6. Psychological/behavioral therapies
Prognosis

Summary

- Gastroparesis and functional dyspepsia can be indistinguishable by clinical presentation
- Delayed gastric emptying is the basis of diagnosis of gastroparesis, but can be also be encountered in functional dyspepsia
- Interest has shifted towards symptom based management approaches over prokinetic therapy
- Neuromodulators and gastric electrical stimulation are options in refractory states