Treatment of Gastroparesis in 2020

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- Professor of Medicine
- Division of Gastroenterology, Hepatology and Nutrition
- Director of Motility
- Atrium Health
Symptoms seen in gastroparetics are common reasons for outpatient visits.

Table 2
Leading Physician Diagnoses for Gastrointestinal Disorders in Outpatient Clinic Visits in the United States, 2009

<table>
<thead>
<tr>
<th>Rank</th>
<th>Diagnosis</th>
<th>Estimated visits</th>
<th>ICD-9 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GERD</td>
<td>8,863,563</td>
<td>530.11, 530.81</td>
</tr>
<tr>
<td>2</td>
<td>Abdominal pain</td>
<td>7,170,332</td>
<td>789.04, 789.06</td>
</tr>
<tr>
<td>3</td>
<td>Gastroenteritis and dyspepsia</td>
<td>4,007,198</td>
<td>535.50, 535.8</td>
</tr>
<tr>
<td>4</td>
<td>Constipation</td>
<td>3,980,439</td>
<td>564.00</td>
</tr>
<tr>
<td>5</td>
<td>Abdominal wall hernia</td>
<td>3,359,932</td>
<td>550.90, 553.10</td>
</tr>
<tr>
<td>6</td>
<td>Diverticular disease</td>
<td>2,882,166</td>
<td>550.10, 550.11</td>
</tr>
<tr>
<td>7</td>
<td>Diarrhea</td>
<td>2,402,359</td>
<td>787.91</td>
</tr>
<tr>
<td>8</td>
<td>Inflammatory bowel disease</td>
<td>1,893,759</td>
<td>555.9, 555.9</td>
</tr>
<tr>
<td>9</td>
<td>Colorectal neoplasm</td>
<td>1,744,089</td>
<td>153.0, 154.0, 154.1, 211.3</td>
</tr>
<tr>
<td>10</td>
<td>Nausea and vomiting</td>
<td>1,678,515</td>
<td>787.02, 787.03</td>
</tr>
</tbody>
</table>
Gastroparesis (GP): Costs and Hospitalizations are increasing!

Hospitalization costs for GP are increased at a rate of $3.4 million per year in children (2004 – 2013)

Symptoms seen in gastroparetics impair physical and mental health

- IFFGD gastroparesis survey questionnaire distributed to 2249 adult patients, of which N=1423 with gastroparesis (duration of disease mean 9 years with onset at least 5 years)

- Questionnaires included PAGI-SYM and SF-36 QOL

- **Most concerning symptoms reported**: Abdominal pain, nausea and vomiting

- 60% in survey were either dissatisfied or somewhat dissatisfied with treatments

- QOL was negatively correlated with most symptoms of GP and FD with physical and mental health affected

- BMI and age do not correlate with physical or mental health QOL impairments

Overlapping of Functional dyspepsia (FD) and gastroparesis (GP)

FD- Sensory and motor disorder
Prevalence 20-40%

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GP-motility disorder only?
Prev: 6.3-17.2 cases /100,000 person years

Symptoms: satiety (80-85%), bloating, nausea (90-95%), **vomiting (68%)**, loss of appetite and weight loss in absence of mechanical obstruction + delay in gastric emptying
**Abdominal pain (89-90%)**

Seen in 25-35% of FD

ROME IV: B1: Functional Dyspepsia
One or more of following: a. Bothersome postprandial fullness b. Bothersome early satiation c. **Bothersome epigastric pain** d. Bothersome epigastric burning
AND
2. **No structural disease** (including at upper endoscopy) that explains symptoms.
B1a: Postprandial distress syndrome and/or
B1b. Epigastric pain syndrome
Criteria must be fulfilled for the last 3 months with symptom onset 6 months before diagnosis

Must include one or both of the following at least 3 days a week: 1. postprandial distress severe enough to impact usual activities, 2. early satiation severe enough they can’t finish regular-sized meal

Stanghellini et al. Gastro 2016; 150: 1380-1392
Where ROME can be confusing!

- Functional dyspepsia
- Gastroparesis
- Cyclic vomiting syndrome & Cannabinoid Hyperemesis Syndrome
- Chronic nausea and vomiting syndrome

Stanghellini et al. Gastro 2016; 150: 1380-1392
New in pathophysiology

• Macrophage-based immune dysregulation as a role in development of gastroparesis
  • Polymorphisms in heme oxygenase-1 gene are seen in DG and IG.

• Parkinson’s Disease and gastroparesis
  • Stimulating the substantia nigra pars compacta (SNpc) increases gastric tone and motility in rats thru activation of dopamine 1 receptors in dorsal vagal complex

• Autism spectrum disorder (Phelan McDermid Syndrome)
  • Zebrafish models show decreased digestive transit time (including in upper gut) with reductions in enterochromaffin cells
Gastrointestinal problems in ASD

• Abdominal pain
• Nausea/vomiting
• Bloating
• Reflux & regurgitation of food
• Constipation
• Soiling of underwear
• Retching
• Dysphagia (choking and wet sound after meals with tilting of food to a side and arching back)
Why is gut motility important?

1. **PERIPHERAL SEROTONIN:**
   Cells in the gut produce large quantities of the neurotransmitter serotonin, which may have an effect on signalling in the brain.

2. **IMMUNE SYSTEM:**
   The intestinal microbiome can prompt immune cells to produce cytokines that can influence neurophysiology.

3. **BACTERIAL MOLECULES:**
   Microbes produce metabolites such as butyrate, which can alter the activity of cells in the blood–brain barrier.

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Smith PA. Nature 2015; 526: 312-314
We have developed an app to help caregivers track GI symptoms.

Screen shots from beta version of symptom tracker app

**Bowel Movement**
- Pain with BM
- Rush to the bathroom for BM
- Straining with BM
- Black Tarry BM
- Continue

**Reflux**
- Nausea
- Spitting up
- Regurgitated
- Experienced Retching
- Vomiting
- Choked, gagged coughed or made sound (gurgling) with throat during or after

**Pain**
- Abdominal Pain
- Severe gastrointestinal pain lasting 2 hours or longer that interrupts participation in all activities
- Tilted head to side and arched back
- Continue

**Other**
- Applied pressure to abdomen with hands or furniture
- Sleep Disturbance
- Aggressive Behavior
- Continue

Based on questionnaire
Margolis et al., 2019
J Autism Dev. Dis

The Oley Foundation
Help along the way
Animal models of GI dysmotility

PH (pharynx), IB (intestinal bulb), UI (upper intestine), LI (lower intestine), and EX (expelled)

Marijuana and Opioid Use and Abdominal pain in Gastroparesis

- NIH gastroparesis Consortium data: Marijuana is used in 11% of all patients (IG, DGP and delayed or non-delayed gastric emptying scintigraphy patients)
- Most common amongst: Young patients, current tobacco smokers.
  - Nausea and vomiting scores are higher amongst users: (2.7 vs 2.1; p= 0.002)
  - Upper abdominal pain subscores (3.5 vs 2.9; p =0.003) are higher
  - Patients on marijuana are more likely to use promethazine and dronabinol.
  - Over 50% of patients have been using it for more than 2 years

- Women have higher GCSI scores than men including upper abdominal pain (2.9 versus 2.4 score) but are hospitalized less often than men (39% versus 53%)

- Of 718 total patients, only 9% comprised of non-Hispanic blacks (most are DG), Hispanics were 12%. QOL was similar to white population.

- Opiate use is associated with increased GCSI scores and correlates with severity of abdominal pain

References:
New in diagnostics

- Rule out mechanical obstruction or Other masqueraders
- Motility testing - Test gastric emptying (transit) And motility
- Tests of gastric accommodation And gastric tone

Abdominal x ray
UGI/SBFT
Upper endoscopy
CT/MRI (abdomen or CNS)
EndoFLIP?

**Gastric emptying scintigraphy- GES
**Wireless motility capsule- WMC
**Breath testing (spirulina)-GEBT-FDA approved
**Antroduodenal Manometry
SMURFCAKE

*Nutrient Drink Test
***Electrogastrography- Slow waves
*Balloon Barostat

Not-validated but done:
***SPECT?
***MRI?
***US

- * for FD
- ** for GP
- *** for both

Courtesy of Braden Kuo’s lab
<table>
<thead>
<tr>
<th>LAB PROCEDURE</th>
<th>PPE RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wireless motility capsule</td>
<td>N95 mask, or surgical mask with a face shield, gloves, face shield (and/or alternate protective eye wear), and gown, gloves, and gown</td>
</tr>
<tr>
<td>Gastric emptying Breath test</td>
<td>N95 mask, double gloves, face shield (and/or alternate protective eye wear), and gown</td>
</tr>
<tr>
<td>Antroduodenal Manometry</td>
<td>N95 mask, double gloves, face shield, (and/or alternate protective eye wear), and gown</td>
</tr>
<tr>
<td>Colonic manometry</td>
<td>N95 mask, double gloves, face shield (and/or alternate protective eye wear), and gown</td>
</tr>
</tbody>
</table>

Pure Prokinetics only help delayed gastric emptying

- N= 151 who had both GES and WMC
- Responses to pure or mixed prokinetics may depend on presence of delayed gastric emptying on GES or WMC.
- Pure prokinetics were Azi/Ery, bethanechol, prucalopride and botulinum toxin
- No diff between diabetics versus nondiabetics
- Symptoms respond better to DRAs like domperidone with normal emptying, but DRAs may not be as effective in improving symptoms with emptying delays.

GSCI scores similarly improved
Gastric emptying scintigraphy

Radiation exposure is required for this scan – done over 4 hours
Meal must be consumed within 10 minutes!!!

Only FDA-approved (2015) Breath test used to diagnosis delayed gastric emptying in adult patients 18 years and older without radiation exposure.

Validated in dual-labeled studies against the 4 hour Gastric scintigraphy (GES) with high diagnostic concordance with GES.
## Smurfcake transit study

Meal components we made had to be similar to gastric scintigraphy

<table>
<thead>
<tr>
<th>Component</th>
<th>Egg white</th>
<th>Sugar</th>
<th>Jam</th>
<th>Flour</th>
<th>Protein powder</th>
<th>Butter/oil</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbs</td>
<td>45</td>
<td>100</td>
<td>38.7</td>
<td></td>
<td></td>
<td></td>
<td>183.7</td>
</tr>
<tr>
<td>Protein</td>
<td>51</td>
<td></td>
<td>1.6</td>
<td>10</td>
<td></td>
<td></td>
<td>62.6</td>
</tr>
<tr>
<td>Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.1</td>
<td></td>
<td>5.1</td>
</tr>
<tr>
<td>Fiber</td>
<td></td>
<td></td>
<td>3.2</td>
<td></td>
<td></td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>254.6</td>
</tr>
</tbody>
</table>

**Meal for ingestion**

![Graph showing time from ingestion to stooling with two categories: No GI Distress and GI Distress.](graph.png)
MRI ‘manometry’

Slide and video Courtesy of Luca Marciani and the Nottingham group- Dr. Alex Menys and Dr. Caroline Hoad
Dynamic changes of pylorus via EndoFLIP in gastroparesis

- EndoFLIP pre and post-G-POEM (N=20) with balloon inflations (30-40, 50 ml) for ≥1 minute at each volume
- Prevalence of each phasic contraction profile was compared before and after G-POEM
- All patients were refractory to medical treatment and had undergone botulinum toxin injection (1-3 sessions)

Watts L S Baker JR et al.
NGM June 2020
G-POEM outcomes in gastroparesis – No sham trials... yet

GCSI and QOL improvements up to 6 months (n=28), 18 months (N=7)

USE OF HEALTHCARE RESOURCES BEFORE AND AFTER G POEM

N=30, One tertiary center (Emory)
1 patient had pneumothorax
Mean hospitalization time- 2.4 +/- 1 day

Mekaroonkamol, P & Cai Q et al. CGH. 2019;17:82–89
New and old therapies explored
“Older” Therapeutic options

- Diet - small frequent meals, low fiber/low residue

- Medications:
  - Antiemetics
  - Prokinetics
  - PPIs
  - Neuromodulators

- PEG-J or PEJ/TPN

- Pylorus-directed therapies (new)

- Gastric stimulation

- Surgery (G-POEM)

- Behavioral therapies
  - (Cognitive behavioral therapy, Accupuncture, hypnotherapy and others)
Current Treatments available for symptoms of nausea and vomiting

Metochlopramide
Gastroparesis diet: Improves symptoms in normal but does NOT worsen symptoms in delayed colonic transit

N=15

Figure 3: Individual symptoms and symptom scores at baseline versus at 6 month follow-up in patients with delayed colonic transit (DCT)
Prucalopride and gastroparesis

- Randomized controlled trial
- N=34 with GP (28 idiopathic, 7 men, mean age 42 +/- 13 years,
  Prucalopride 2 mg qd versus placebo x 4 weeks
- SAES:
  - N=1 pt had small bowel volvulus
- AE: N=3 nausea and HA
- CIC approval only by FDA

EFFICACY AND SAFETY OF RELAMORELIN IN DIABETICS WITH SYMPTOMS OF GASTROPARESIS: A RANDOMIZED, PLACEBO-CONTROLLED STUDY

Change from baseline through week 12 in DGSSD (4-symptom [nausea, postprandial fullness, abdominal pain, bloating] composite score in total numeric points).

New Gastric electrical stimulation in GP findings: results from the national gastroparesis registry

- Severity of GP is higher in GES patients (P < 0.001)
- Higher use of narcotics and other meds (P<0.05)
- GCSI scores are higher (P <0.001)
- 4 hr Gastric scintigraphy was more delayed in GES group
- Study included all causes of GP (including IGP)
- More drastic response in those with more severe delays
Vagal Stimulation in idiopathic gastroparesis

• Self administered gammaCore vagal nerve stimulator (nVNS) x 4 weeks in 15 participants

• A bilateral transcutaneous cervical non-invasive nVNS used BID for prophylaxis and not during flares- total 4 stimulations (2 on each side over vagus nerve)

• Primary endpoint: reduction of GCSI-dd of 0.75 after nVNS
  • 40% met primary endpoint
  • Reduction in gastric emptying was seen (t ½ 155 versus 129 mins) P=0.53
  • Those who responded had more severe BL symptoms
  • Improvements were mainly in fullness/early satiety and appetite subscales

Gottfried-Blackmore, A et al. & Nguyen, L NGM 2019
Neuromodulators Do Not Delay Gastric Emptying

Impact of gastroparesis diet on those with delayed GET by WMC

Figure 2: Baseline (BL) and long-term (6 months) symptom scores for patients with delayed GET after diet recommendations.

All p-values are significant.
## Differentiating FD from GP

<table>
<thead>
<tr>
<th>Findings</th>
<th>Gastroparesis</th>
<th>Functional dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>Motility disorder with ICC loss ? Sensory disturbance too?</td>
<td>Sensory and motor dysfunction with Impaired accommodation</td>
</tr>
<tr>
<td>Predominant symptoms</td>
<td>Nausea, vomiting and postprandial pain predominate *Weight loss often occurs</td>
<td>Early satiation, postprandial distress, epigastric burning, postprandial fullness</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Gastric scintigraphy, wireless motility capsule, C^{13} Spirulina Breath testing</td>
<td>Rome IV criteria</td>
</tr>
<tr>
<td>Gastric Scintigraphy findings</td>
<td>Delay</td>
<td>1/3 Delay, &lt; 5% Rapid, 1/3 Normal GES</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>Acute or &gt; 3 months Waxing and waning</td>
<td>Symptom onset 6 months, duration 3 months with symptoms occur 3 days/week</td>
</tr>
<tr>
<td>PPI use</td>
<td>May delay gastric emptying</td>
<td>Helps symptoms</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>+/- benefit</td>
<td>Benefit symptoms</td>
</tr>
</tbody>
</table>

The bad part of 2020!
The UGLY

MISSING THIS

The Oley Foundation

Help along the way

invites you to join us

for a FREE ONE DAY regional conference

Saturday, April 25, 2020

Omni Hotel Charlotte

132 E Trade Street, Charlotte, North Carolina 28202

9:30 a.m.- 5:00 p.m.
The good!