Gastroparesis: Diagnosis and Treatment

The Stomach is an Onion

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UVA Gastroenterology
“OGRES ARE LIKE ONIONS. OGRES HAVE LAYERS, ONIONS HAVE LAYERS...

YOU GET IT? WE BOTH HAVE LAYERS.”
Learning Objectives:

• Brief review on gastric function
• Discuss similarities between functional dyspepsia and gastroparesis
• Understand how 2 specific tests are used in diagnosing gastroparesis
• Discuss issues with the process of developing treatments for gastroparesis
• Review several treatment options for gastroparesis
Diagnosis:

• “Chronic, symptomatic disorder of the stomach characterized by delayed GE without evidence of mechanical obstruction”

• Three elements central to dx:
  – Patient should be symptomatic
  – Objective evidence of gastric emptying delay
  – Absence of another organic explanation for patient’s symptoms (i.e. obstruction)

Pasricha Gastroenterol Clin N Am 2015
Fosso et al. Gastroenterology and Hepatology 2018
Functional Dyspepsia and Gastroparesis: A Spectrum of Disease

- Functional Dyspepsia
  - Bloating
  - Early satiety
  - Nausea
  - Post-prandial fullness
  - Vomiting
  - Abdominal pain

- Gastroparesis
  - Bloating
  - Early satiety
  - Vomiting
  - Abdominal pain

Pasricha Gastroenterol Clin N Am 2015
Fosso et al. Gastroenterology and Hepatology 2018
Figure 2  Role of gastric emptying testing and definition of idiopathic gastroparesis according to the Rome II definition, in which a broad upper GI symptom pattern represents functional dyspepsia.
Pathophysiology of Delayed Gastric Emptying:

<table>
<thead>
<tr>
<th>Diabetic</th>
<th>Post-surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>

- Impaired Gastric Accommodation
- Antral Hypomotility
- Pylorospasm
- Autonomic Dysfunction
- Visceral Hyperresponsivity

Problems with diagnosis of gastroparesis:

• Patient symptoms often correlate poorly with gastric function
  – Some patients with extreme sx have normal GE
  – Some patients with extreme sx have rapid GE
  – Some patients with minimal sx have severe delay in GE

• Therapies used to accelerate GE may not result in improvement in sx

• Many physicians rush to diagnose via objective testing rather than listening to patients symptoms and ruling out other etiologies (i.e. cyclic vomiting, rumination etc)

• Gold Standard GES (scintigraphy) is often not performed correctly

Be more careful which patient we label as gastroparetics
The **GOLD STANDARD:**

Gastric Emptying Scintigraphy

Consensus Recommendations for Gastric Emptying Scintigraphy: A Joint Report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine
The **GOLD STANDARD**: Gastric Emptying Scintigraphy

- **Patient Preparation**
  - Stop prokinetics and opiates 48 hours prior to test
  - Stop anticholinergic agents 48 hours prior to test
  - Fasting at least 6 hours
  - No smoking
  - BG <275 before the test
The **GOLD STANDARD:**
Gastric Emptying Scintigraphy

- **Meal Preparation and Ingestion:**
  - Standard meal (microwaved)
    - 4 ounces liquid egg white
    - 2 slices white bread
    - Strawberry jam
    - Water
    - Technetium-99m sulfur colloid (radiotracer)
  - Take 10 minutes to eat meal
  - Need to take at least 50% of meal

Abell et al. Am J Gastroenterology 2008
The **GOLD STANDARD:**

Gastric Emptying Scintigraphy

*Optimal Timing of Imaging*

Some patients with delayed emptying at 2 h normalize their emptying at the 4-h time point and some individuals with normal emptying at 2 h have delayed emptying at 4 h (43, 44). The clinical importance of delayed emptying at only certain time points is unknown. There needs to be a better understanding of the use of multiple time points in combination (e.g., 2 and 4 h). Data from Guo *et al.* suggest that the 3-h time period might be as sensitive as a 4-h study in detecting delayed GE (43). Although the original report for the Tougas *et al.* data had no 3-h measurement point, more recent studies suggest that the upper limit of normal is 28% gastric retention at 3 h after meal ingestion (51). Another study suggests that 30% is the optimal threshold for 3-h emptying data (44). A recent study using the Tougas *et al.* meal has shown that the 3-h time point is nearly comparable to the 4-h value in detecting patients with delayed GE (51).
The **GOLD STANDARD:**

**Gastric Emptying Scintigraphy**

*Assessment of Severity*

Because there is not a close correlation between the delay in GE and the symptoms, the GE test alone should probably not be used for grading the severity of the clinical disorder of gastroparesis. Grading the severity of the delay in GE has been performed in clinical research studies and might be used clinically (52). Grading for severity of delayed GE based on the 4-h value in groups related to the SD of the normal results is: grade 1 (mild): 11–20% retention at 4 h; grade 2 (moderate): 21–35% retention at 4 h; grade 3 (severe): 36–50% retention at 4 h; and grade 4 (very severe): >50% retention at 4 h.

On the other hand, a combination of the degree of GE delay and the nutritional needs or approaches necessary to support the patient’s hydration and nutrition provide a better assessment of severity and facilitate the approach to management. In a recent review, mild delay was designated as 11–15%, moderate 16–35%, and severe >35% retention at 4 h (53).
Gastric emptying scintigraphy images at 0, 30, 60, and 120 min after radioactive meal ingestion. a Healthy control with normal gastric emptying time (T 1/2 72 min). The dashed line designates the stomach. b PD patient with rapid gastric emptying time (T 1/2 26 min). c Vagotomized patient with severely increased gastric emptying time (T 1/2 > 180 min).
FIGURE 1. Compliance with 14 individual protocol variables. Results demonstrate that laboratories did not adhere to GES guidelines for most variables (9/14) ($n = 127$).
Tips on GES if you order these tests:

• Ensure 4-hour study (versus 90-minute study)
• Ensure proper meal given
• Patient OFF narcotics
• Do not order as an inpatient
• Ensure proper patient preparation (see above)
• Mislabeleing patients with gastroparesis may have implications for care
A typical tracing from a wireless motility capsule recording with time along the X-axis, pressure on the y1-axis (red line) and pH on the y2-axis (green line) and temperature (blue line). Gastric emptying time (GET), small bowel transit time (SBTT) and colonic transit time (CTT) are illustrated. Whole gut transit time is derived from the addition of GET, SBTT and CTT.
Prevalence of Delayed Gastric Emptying by GES and WMC

A

Number of subjects (%)

All patients

Diabetics

Non-diabetics

$P = .009$

$P < .001$

Lee et al. Clinical Gastroenterology and Hepatology August 2019
Diagnosis: Take Home Points

• The stomach is complicated
• Functional dyspepsia and gastroparesis exist on a continuum
• Patient symptoms do not always correlate with degree of GE delay
• Know how your hospital conducts GE studies
• Consider use of other methods to diagnosis gastroparesis (WMC, breath tests)
Treatment:

“There are persistent unmet needs in the treatment of gastroparesis, leading to both patient and physician frustration.”

- Brian Lacy, MD PhD Am J Gastro 2019
Treatment:

• Why do we find treatment so frustrating and complex?
  – We are not great at identifying what is the specific abnormality in each patient
  – We don’t have many great therapies

WE NEED BETTER DATA!
Treatment: Current Status

- One FDA-approved medication
- Many therapies have never been tested in prospective, placebo-controlled trials of patients with gastroparesis
- Some modalities used to treat sx despite supportive data
- Difficult to study -- Gastroparesis is a heterogeneous disorder
  - Prior studies grouped all gastroparesis in one category, but there are differences in mechanisms in post-surgical, diabetic, idiopathic
  - Various outcome measures
Related Studies

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRON</td>
<td>Aprepitant for the Relief of Nausea in Patients With Chronic Nausea and Vomiting of Presumed Gastric Origin Trial</td>
</tr>
<tr>
<td>GLUMIT</td>
<td>Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis</td>
</tr>
<tr>
<td>GpR</td>
<td>Gastroparesis Registry</td>
</tr>
<tr>
<td>GpR 2</td>
<td>Gastroparesis Registry 2: Continuation of the NIDDK Gastroparesis Registry for the Characterization and Clinical Course of Gastroparesis Patients</td>
</tr>
<tr>
<td>NORIG</td>
<td>Nortriptyline for Idiopathic Gastroparesis</td>
</tr>
</tbody>
</table>

Objectives

The overall objectives of the GpCRC include providing an infrastructure for the efficient design and conduct of multicenter clinical studies; performing clinical trials to investigate clinical, diagnostic, and therapeutic interventions for gastroparesis; and creating a collection of patient samples that may be used for ancillary studies of etiology and pathogenesis. Ultimately, it is hoped that this research will improve the diagnosis and treatment of patients with gastroparesis.
NIDDK Gastroparesis Clinical Research Consortium

Consortium Contributors

Clinical Sites
Johns Hopkins University (PJ Pasricha, J Clarke, S Dhalla, E Stein)
Temple University (H Parkman) University of Louisville (T Abell)
Wake Forest University (K Koch) Texas Tech University (R McCallum, I Sorastiek)
Stanford University (L Nguyen)
California Pacific Medical Center (W Snape)

Data Coordinating Centers
Johns Hopkins Bloomberg School of Public Health (J Tonascia)
Pathology Resource Center Mayo Clinic, Rochester (G Farrugia, M Grover)

hoped that this research will improve the diagnosis and treatment of patients with
NIDDK Gastroparesis Clinical Research Consortium Goals:

• Developing gastroparesis registry
• Grouping patients into etiology of gastroparesis to determine which medications/therapies work
• Ensuring patients in studies actually have
• Focus on
  – PRO (patient reported outcomes)
    • ANMS-GCSI (Gastroparesis Cardinal Symptom Index)
    • QOL outcomes
  – Improvement in emptying
# Gastroparesis Cardinal Symptom Index

<table>
<thead>
<tr>
<th>Symptom Subscale</th>
<th>Symptom</th>
<th>None</th>
<th>Very Mild</th>
<th>Mild</th>
<th>Mod</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Retching</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Fullness/early satiety</td>
<td>Stomach fullness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Not able to finish meal</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Fullness after eating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Loss of appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Bloating/distention</td>
<td>Bloating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Belly visibly larger</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Gastroparesis Cardinal Symptom Index (From Revicki et al., Aliment Pharmacol Ther 2003)
Treatment: Therapeutic Targets

Figure 1

Pathophysiologic mechanisms serving as (potential) therapeutic targets in functional dyspepsia and gastroparesis.
# Treatment: Nausea/Vomiting

<table>
<thead>
<tr>
<th>Medications</th>
<th>Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>5–10 mg 3 to 4 times a day</td>
</tr>
<tr>
<td>Domperidone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 mg 3 to 4 times a day</td>
</tr>
<tr>
<td>Ondansetron&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 mg 3 times a day</td>
</tr>
<tr>
<td>Prochlorperazine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5–10 mg 4 times a day</td>
</tr>
<tr>
<td>Chlorpromazine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10–25 mg 4 times a day</td>
</tr>
<tr>
<td>Scopolamine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5 mg patch every 3 d</td>
</tr>
<tr>
<td>Aprepitant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80 mg every day</td>
</tr>
<tr>
<td>Dronabinol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5–10 mg 3 times a day</td>
</tr>
<tr>
<td>Tricyclic antidepressants&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25–100 mg/d</td>
</tr>
<tr>
<td>Ginger</td>
<td>1 g twice a day</td>
</tr>
</tbody>
</table>

<sup>a</sup> Off-label use.

<sup>b</sup> Only available for use in the United States via Food and Drug Administration investigational drug protocol.
# Treatment: Abdominal Pain

## Table 2
Suggested medications for management of abdominal pain

<table>
<thead>
<tr>
<th>Name</th>
<th>Class</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicyclomine</td>
<td>Anticholinergic</td>
<td>20 mg 4 times a day as needed</td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>Anticholinergic</td>
<td>0.125–0.25 mg 3 to 4 times a day as needed</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>TCA</td>
<td>25–100 mg/d</td>
</tr>
<tr>
<td>Desipramine</td>
<td>TCA</td>
<td>25–75 mg/d</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Antidepressant</td>
<td>7.5–30 mg/d</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>SNRI</td>
<td>60–120 mg/d</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Anticonvulsant</td>
<td>&gt;1200 mg/d in divided doses</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Anticonvulsant</td>
<td>100–300 mg/d in divided doses</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>μ-opioid agonist</td>
<td>Start at 50 mg twice a day</td>
</tr>
<tr>
<td>Tramadol</td>
<td>μ-opioid agonist</td>
<td>200 mg/d in divided doses</td>
</tr>
</tbody>
</table>

*Abbreviations: SNRI, serotonin and norepinephrine reuptake inhibitors; TCA, tricyclic antidepressant.*
Box 2
Suggested interventions for the management of bloating

Dietary changes (low FODMAP [fermentable oligo-, di-, mono-saccharides and polyols] diet, avoidance of fiber or gluten and minimizing carbohydrates)

Probiotics (*Bifidobacterium infantis* 35624 or VSL#3)

Poorly absorbable antibiotics such as rifaximin (550 mg 3 times a day for 2 weeks)

Pain neuromodulators, such as tricyclic antidepressants or pregabalin

Polyethylene glycol or calcium channel activators (linaclotide 145–290 μg daily) to improve slow transit

Hypnotherapy
Treatment:

• Nutrition Intervention

• Medications:
  – Metaclopramide
  – Domperidone
  – Prucalopride

• Pyloric Therapies:
  – GPOEM
  – Botox

• Other Therapies:
  – GES (gastric pacemaker)
Treatment:

**Metoclopramide**

- **What is it?**
  - Available in the US since 1979
  - Antagonist of D2 receptor and 5HT4 agonist

- **How does it work?**
  - **Gut Motility**
    - Increases LES tone
    - Increased gastric tone and intragastric pressure
    - Increased antroduodenal coordination
    - Acceleration of gastric emptying
  - **Anti Emetic**
    - Inhibits D2 and 5-HT3 receptors in the chemoreceptor trigger zone

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**Fig. 2.** Dual mechanism of action of metoclopramide. GI, gastrointestinal. (*From* Lee A, Kuo B. Metoclopramide in the treatment of diabetic gastroparesis. Expert Rev Endocrinol Metab 2010;5(5):653–62; with permission.)
Treatment: Metaclopramide

Evidence for use comes from trials from 30–40 years ago – Level of evidence is not based on currently suggested rigorous, large trials with validated patient response outcomes measured on a daily basis. Efficacy assessed in six studies (only 4 placebo-controlled trials) in diabetic gastroparesis. No trial >4 weeks. Studies showed improvement in sx and GE rates.

Camilleri Am J Gastro 2013

Table 4. Trials of metoclopramide for gastroparesis

<table>
<thead>
<tr>
<th>Reference #</th>
<th>Design</th>
<th>#, Etiology</th>
<th>Dose</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(84)</td>
<td>DB, PC, XO, RCT</td>
<td>10 DG</td>
<td>10mg q.i.d.</td>
<td>3 weeks/arm</td>
<td>Improved symptoms and vomiting; ~60% acceleration in GE liquid 150 kcal meal</td>
</tr>
<tr>
<td>(85)</td>
<td>DB, PC, PG, RCT</td>
<td>28: 5 DM, 4 PSG, 19 IG</td>
<td>10mg q.i.d.</td>
<td>3 weeks</td>
<td>Improved symptoms by 29%</td>
</tr>
<tr>
<td>(86)</td>
<td>PC, RCT</td>
<td>18 DG</td>
<td>10mg q.i.d.</td>
<td>3 weeks</td>
<td>Improved symptom score by 29%, improved GE by 25%</td>
</tr>
<tr>
<td>(87)</td>
<td>DB, PC, XO, RCT</td>
<td>13 DG with GE accelerated by metoclopramide</td>
<td>10mg q.i.d.</td>
<td>3 weeks/arm</td>
<td>Improved symptoms with mean reduction of 52.6%</td>
</tr>
<tr>
<td>(88)</td>
<td>DB, RCT, domperidone-controlled, multicenter</td>
<td>45 DG</td>
<td>10mg q.i.d.</td>
<td>4 weeks</td>
<td>Improved symptoms by 39%; similar efficacy with domperidone which had less AEs</td>
</tr>
<tr>
<td>(89)</td>
<td>DB, XO, erythromycin-controlled RCT</td>
<td>13 DG</td>
<td>10mg t.i.d.</td>
<td>3 weeks/arm</td>
<td>Both treatments accelerated GE compared with baseline and improved symptoms score</td>
</tr>
<tr>
<td>(90)</td>
<td>Open</td>
<td>1 DG</td>
<td>15mg q.i.d.</td>
<td>6 months</td>
<td>Improved symptoms, GE liquids, antral contraction frequency</td>
</tr>
<tr>
<td>(91)</td>
<td>Open</td>
<td>10 GI symptomatic (N, V) T1DM; 6 asymptomatic T1DM, 18 controls</td>
<td>10mg once</td>
<td>Acute</td>
<td>Improved GE solids</td>
</tr>
</tbody>
</table>

AEs, adverse effects; DB, double blind; DG, diabetic gastroparesis; DM, diabetic; GE, gastric emptying; GI, gastrointestinal; IG, idiopathic gastroparesis; N, nausea; PC, placebo controlled; PG, parallel group; PSG, postsurgical gastroparesis; RCT, randomized-controlled trial; T1DM, type 1 diabetics; T2DM, type 2 diabetics; V, vomiting; XO, crossover.
Treatment: Metaclopramide and Tardive Dyskinesia

An FDA Warning About Metoclopramide

William P. Kanto, Jr., MD

Metoclopramide requires a boxed warning about risk for tardive dyskinesia.

In February 2009, the FDA announced that manufacturers of metoclopramide must add a boxed warning (black box) on drug labels to warn providers and patients about the risk for tardive dyskinesia (TD) with chronic or high-dose use. Metoclopramide increases the rate of stomach emptying and is used as short-term treatment (<3 months) for gastroesophageal reflux and gastroparesis in patients who do not respond to other treatments. The director of the FDA's Center for Drug Evaluation and Research commented that although the FDA wants patients and health professionals to be able to make informed decisions regarding treatment, chronic use of metoclopramide should be avoided, except in rare circumstances in which benefit outweighs risk.

TD is characterized by involuntary, repetitive movements of the limbs; lip smacking; tongue protrusion; eye movements and blinking; puckering of the lips; and impaired movement of the hands. No treatment exists, and symptoms are rarely reversible, although they might lessen or resolve after the drug is stopped. Development of TD is related to duration of treatment and number of doses taken. Older women and patients who have received the drug for more than 3 months seem to have the highest risk.

COMMENT

Metoclopramide is a commonly used drug, and this warning will reduce its use. If a clinician chooses to treat a patient with metoclopramide, duration of treatment should not exceed 3 months, patients should be informed about the risk for TD, and the drug should be stopped at the first sign of symptoms. Use of metoclopramide in infants must be monitored closely because early signs of TD might be difficult to identify.
Treatment: Metaclopramide and Tardive Dyskinesia

• What is the true risk of TD reported in the literature? (lower than we think; 0.1% per 1,000 patient years; one in 34,000 prescriptions)

• What clinical factors should be considered before prescribing metaclopramide? (elderly, female, cirrhosis, renal insufficiency, taking neuroleptic meds, pre-diagnosed movement d/o)

• How should metaclopramide be prescribed? (liquid, lowest dose possible, drug holidays)

Rao A, Camilleri M. Aliment Pharmacol Ther 31, 11–19
### TABLE 1  Review of studies on the presence of tardive dyskinesia in patients treated with metoclopramide

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>Background population</th>
<th>Number of cases with TD</th>
<th>Estimate of TD per patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilholm et al(^{39})</td>
<td>1984</td>
<td>11 M prescriptions</td>
<td>11</td>
<td>1 per 2760</td>
</tr>
<tr>
<td>Bateman et al(^{33})</td>
<td>1985</td>
<td>15.9 M prescriptions</td>
<td>4</td>
<td>1 per 2000</td>
</tr>
<tr>
<td>Kenney et al(^{40})</td>
<td>2008</td>
<td>23 653 movement disorder patients</td>
<td>171</td>
<td>7 per 1000</td>
</tr>
<tr>
<td>Shaffer et al(^{41})</td>
<td>2002</td>
<td>Unknown</td>
<td>87</td>
<td>---</td>
</tr>
<tr>
<td>Sewell &amp; Jeste(^{42})</td>
<td>1992</td>
<td>Unknown</td>
<td>67</td>
<td>---</td>
</tr>
<tr>
<td>Ganzini et al(^{43})</td>
<td>1993</td>
<td>51 Veteran's Affairs patients</td>
<td>15</td>
<td>1 per 3</td>
</tr>
<tr>
<td>Sewell et al(^{44})</td>
<td>1994</td>
<td>51 Veteran's Affairs patients</td>
<td>14</td>
<td>1 per 3</td>
</tr>
<tr>
<td>Merrill et al(^{13})</td>
<td>2013</td>
<td>80 000 patients</td>
<td>34</td>
<td>1 per 23 000</td>
</tr>
<tr>
<td>Bateman et al(^{46})</td>
<td>1989</td>
<td>2557 patients</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rao &amp; Camilleri(^{47})</td>
<td>2010</td>
<td>Review</td>
<td>---</td>
<td>&lt;10 per 1000</td>
</tr>
<tr>
<td>Swedish Medical Products Agency(^{48})</td>
<td>2018</td>
<td>60 255 patients</td>
<td>1</td>
<td>1 per 1 000 000</td>
</tr>
</tbody>
</table>

Abbreviation: TD, tardive dyskinesia.
Key Points

- Metoclopramide is a gastroprokinetic and antiemetic that works through blockade of dopamine receptors. As the drug crosses the blood-brain barrier, it can cause movement disorders.

- Investigations through authority statistics show few neuromuscular side effects and the risk for tardive dyskinesia as an irreversible movement disorder of ~0.1% per 1000 patient years.

- In a broad sense, the use of metoclopramide should not be hampered by few instances of reported dyskinesia where old age, renal and liver insufficiency, diabetes and antipsychotic drug therapy are apparent risk factors.
Treatment: Domperidone

Mechanism of action

Domperidone increases the amplitude of esophageal motor function and antroduodenal contractions, coordinates peristalsis across the pylorus, and accelerates gastric emptying. The effect of domperidone on gastric emptying has been shown in short-term studies (Table 2).

Peripherally-selective dopamine D2 receptor antagonist
Treatment: Domperidone

• How is it given?
  – 10mg tid; can increase to 20mg tid

• Why do we worry about it?
  – Only available in the US as compassionate use IND
  – Concern for QT prolongation
Treatment: Domperidone

- QT Prolongation
  - Seen in IV use
  - “No studies have been performed in the US to investigate the correlation of oral domperidone and development of CV adverse events”
  - Retrospective chart review from Texas Tech with IND
  - 64 patients included
  - 10 pts (15%) with prolonged QT
  - No adverse CV events

Attachment D - Domperidone Protocol
Please use track-changes if you deviate in any way from this protocol

Domperidone is a dopamine antagonist with gastropokinetic properties; domperidone does not readily cross the blood-brain barrier.

Purpose:
To provide oral domperidone to patients ≥12 years of age where, according to the investigator’s judgment, a prokinetic effect is needed for the relief of refractory gastroesophageal reflux disease with upper gastrointestinal (GI) symptoms, gastroparesis, and chronic constipation in patients whom the potential benefit may outweigh the risk of cardiovascular adverse reactions including QT prolongation, Torsades de Pointes, and death.

Objective:
To allow the use of domperidone by patients with gastrointestinal disorders who have failed standard therapy.

Inclusion Criteria:
1. Male or female
2. Age 12 and older
3. Symptoms or manifestations secondary to GERD (e.g., persistent esophagitis, heartburn, upper airway signs or symptoms or respiratory symptoms), gastrointestinal motility disorders such as nausea, vomiting, severe dyspepsia or severe chronic constipation that are refractory to standard therapy.
4. Patients must have a comprehensive evaluation to eliminate other causes of their symptoms.
5. Patient has signed informed consent for the administration of domperidone that informs the patient of potential adverse events including:
   • cardiac arrhythmias including QT prolongation and death
   • increased prolactin levels
   • extrapyramidal side effects
   • breast changes
   • There is a potential for increased risk of adverse events with the drugs listed on page 14.

Exclusion Criteria:
History of, or current, arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes. Patients with minor forms of ectopy (PACs) are not necessarily excluded.

1. Clinically significant bradycardia, sinus node dysfunction, or heart block. Prolonged QTc (QTc > 450 milliseconds for males, QTc > 470 milliseconds for females).
2. Hepatic dysfunction
3. Renal insufficiency
4. Clinically significant electrolyte disorders.
5. Gastrointestinal hemorrhage or obstruction
7. Pregnant or breast feeding female
8. Known allergy to domperidone
Treatment Plan:
10-30 mg of oral domperidone administered QID. Patients should be started at the lowest dose and maintained at the lowest effective dose given the increased risk of serious cardiovascular reactions with increasing exposures of domperidone. Patients should be evaluated before doses are increased (see the Assessment and Monitoring Requirements for Domperidone INDs table below).

Withdrawal Criteria:
1. Patients may withdraw from the trial at any time.
2. Patients must be withdrawn for the following:
   - The patient withdraws consent.
   - While on treatment, EKGs demonstrate QTc> 450 milliseconds for males, QTc>470 milliseconds for females, or there is a change in QTc greater than or equal to 60 milliseconds from baseline.
   - Development of serious electrolyte abnormalities.
   - The patient is not receiving therapeutic benefit from domperidone.
(Please note that the reason for withdrawal must be reported)

Assessment and Monitoring Requirements for Domperidone INDs:

<table>
<thead>
<tr>
<th>Informed Consent</th>
<th>Screening Visit</th>
<th>Every 2-Month Visit (the first year)</th>
<th>Every 6-Month Visit Thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>12-Lead EKG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of labs (CBC, liver panel, renal panel)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(Re)Assessment of domperidone use (Benefit/Risk)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Review concomitant medication</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1. Required Additional Visits:
   - **If an increase in domperidone dose is being considered**, schedule an additional patient visit to perform each of the evaluations shown prior to increasing the domperidone dose. In all patients whose domperidone dose was increased, perform each of the evaluations shown at an every 2-month visit for the first year after the domperidone dose was increased, and then at an every 6-month visit thereafter.
   - **If considering starting any concomitant medication that may interact with domperidone**, schedule an additional patient visit to perform each of the evaluations shown prior to starting the
concomitant medication (see list below in the section “Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone”). In all patients who have started any concomitant medication that may interact with domperidone, perform each of the evaluations shown at an every 2-month visit for the first year after the concomitant medication was started, and then at an every 6-month visit thereafter.

2. EKG Monitoring:
   • Screening Visit:
     – A new 12-Lead EKG will be obtained at the Screening Visit.
   • Assessment immediately After Initiation of Domperidone:
     – In all patients, a 12-Lead EKG will be obtained 3 to 7 days after domperidone is started.
     – Timing of the EKG will be 1 hour after the first domperidone dose of the day in which the EKG is done.
     – Patients with clinically significant changes in EKG’s from baseline will be followed up with a repeat EKG.
   • Routine EKG Monitoring on a Stable Dose of Domperidone:
     – In all patients, obtain an EKG at an every 2-month visit for the first year, and then at an every 6-month visit thereafter.
     – Timing of the EKG will be 1 hour after the first domperidone dose of the day in which the EKG is done.
     – Patients with clinically significant changes in EKG’s from baseline will be followed up with a repeat EKG.
   • Additional EKG Requirements if a Domperidone Dose Increase is Being Considered:
     – In all patients, a 12-Lead EKG will be obtained at the additional visit prior to increasing the domperidone dose, and 3 to 7 days after the domperidone dose is increased.
     – Timing of the EKG will be 1 hour after the first domperidone dose of the day in which the EKG is done.
     – Patients with clinically significant changes in EKG’s from baseline will be followed up with a repeat EKG.
     – In all patients whose domperidone dose was increased, obtain an EKG at an every 2-month visit for the first year after the domperidone dose was increased, and then at an every 6-month visit thereafter.
   • Additional EKG Requirements if Starting Any Concomitant Medication that May Interact With Domperidone:
     – In all patients, a 12-Lead EKG will be obtained prior to starting the concomitant medication, and 3 to 7 days after the concomitant medication is started (see list below in the section “Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone”).
     – Timing of the EKG will be 1 hour after the first domperidone or domperidone/concomitant medication dose of the day in which the EKG is done.
     – Patients with clinically significant changes in EKG’s from baseline will be followed up with a repeat EKG.
     – In all patients who have started concomitant medications (see list below in the section “Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone”), obtain an EKG at an every 2-month visit for the first year after the concomitant medication was started, and then at an every 6-month visit thereafter.
Treatment: Domperidone

• 2015 study at Temple University (followed for 16 months)
• 125 patients with refractory gastroparesis
• Measured changes in PRO (patient reported outcomes)
  – Patient Assessment of UGI sx (includes GCSI)
  – Clinical Patient Grading Assessment Scale
• 101 completed study
• 43% reported side effects; 14% stopped drug
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Total</th>
<th>Stopping treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Palpitations</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Heartburn</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lactation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged QT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hand tremor</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Disorientation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anxiousness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44</strong></td>
<td><strong>14</strong></td>
</tr>
</tbody>
</table>
Table 2  Symptom scores at baseline and at follow-up in 101 patients treated with domperidone

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3.5 ± 1.3</td>
<td>2.5 ± 1.5</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retching</td>
<td>2.1 ± 1.7</td>
<td>1.2 ± 1.5</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.2 ± 1.9</td>
<td>1.2 ± 1.6</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early satiety</td>
<td>3.7 ± 1.3</td>
<td>2.8 ± 1.6</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postprandial fullness</td>
<td>3.9 ± 1.2</td>
<td>2.8 ± 1.6</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stomach fullness</td>
<td>3.6 ± 1.2</td>
<td>2.6 ± 1.4</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>3.2 ± 1.4</td>
<td>2.3 ± 1.6</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bloating</td>
<td>2.9 ± 1.6</td>
<td>2.3 ± 1.6</td>
<td>0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Stomach visibly larger</td>
<td>2.6 ± 1.8</td>
<td>1.9 ± 1.7</td>
<td>0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>2.8 ± 1.6</td>
<td>1.9 ± 1.6</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper abdominal discomfort</td>
<td>2.9 ± 1.6</td>
<td>2.1 ± 1.5</td>
<td>0.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.4 ± 1.9</td>
<td>1.7 ± 1.8</td>
<td>0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.6 ± 1.7</td>
<td>1.1 ± 1.4</td>
<td>0.5</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD
Treatment: Prucalopride

• Prucalopride
  – Highly selective 5HT$_4$ receptor agonist
  – Approved in US for chronic idiopathic constipation
  – May have efficacy in gastroparesis
    • Recent Double-blind, randomized placebo crossover study from Belgium in patients with idiopathic gastroparesis showed improvement in:
      – Fullness/satiety
      – Nausea/vomiting
      – Bloating/distension
      – Decreased GE time

Carbone et al  Am J Gastroenterol 2019
## Treatment: Pylorospasm and Botox

**Table 1**
Important trials in the study of botulinum toxin for gastroparesis

<table>
<thead>
<tr>
<th>Source Study</th>
<th>Number of Patients</th>
<th>Study Design</th>
<th>Cause of Gastroparesis</th>
<th>BoNT Dose (IU)</th>
<th>Assessment of Pyloric Function?</th>
<th>Subjective Outcomes</th>
<th>Objective Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezzeddine et al, 2002</td>
<td>6</td>
<td>Prospective, open-label</td>
<td>DM</td>
<td>100</td>
<td>No</td>
<td>Significant improvement in symptoms at 6 wk</td>
<td>Significant improvement in gastric emptying at 6 wk</td>
</tr>
<tr>
<td>Miller, 2002</td>
<td>10</td>
<td>Prospective, open-label</td>
<td>Idiopathic</td>
<td>80–100</td>
<td>No</td>
<td>90% patients with significant improvement in symptoms at 4 wk</td>
<td>70% patients demonstrated improvement in solid emptying at 4 wk, no improvement in liquids</td>
</tr>
<tr>
<td>Bromer et al, 2005</td>
<td>63</td>
<td>Retrospective, open-label</td>
<td>Idiopathic (35), DM (26), postoperative (2)</td>
<td>100 or 200</td>
<td>No</td>
<td>~43% patients with improved symptoms lasting ~5 mo</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Arts et al, 2007</td>
<td>23</td>
<td>Randomized controlled, double-blind, crossover</td>
<td>Idiopathic (19), DM (2), postoperative (2)</td>
<td>100</td>
<td>No</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Friedenberg et al, 2008</td>
<td>32</td>
<td>Randomized controlled, double-blind</td>
<td>DM (18), idiopathic (13), postoperative (1)</td>
<td>200</td>
<td>No</td>
<td>No difference</td>
<td>Improved gastric emptying at 4 wk</td>
</tr>
<tr>
<td>Coleski et al, 2009</td>
<td>179</td>
<td>Retrospective, open-label</td>
<td>DM (81), idiopathic (79)</td>
<td>100, 150, or 200</td>
<td>No</td>
<td>~51% patients with improved symptoms at 1–4 wk</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Hooft et al, 2014</td>
<td>13</td>
<td>Retrospective, open-label</td>
<td>Postoperative</td>
<td>100</td>
<td>No</td>
<td>Not evaluated</td>
<td>Improved gastric emptying in 76% patients at 4 wk</td>
</tr>
</tbody>
</table>
Treatment: Botox

• Not currently recommended for therapy
  – Unless you specifically ask experts

• Ongoing questions:
  – Were studies too small?
  – How were patients selected – did they have pylorospasm?
  – Where do you inject? 4 quadrants? How much? EUS guided?
  – Maybe patients have more than one factor contributing to gastroparesis – not just pylorospasm

Pasricha et al Gastrointestinal Endoscopy Clinics N America 2019
Treatment: G-POEM

- Pylorospasm – “abnormally prolonged high amplitude contractions”
- How do we determine which patients have gastroparesis related to pylorospasm?
  - EndoFLIP (measures distensibility of the sphincter)
- Most data from endoscopists rather than functional/motility

Hasler et al Dig Dis Sci 2018
Treatment: G-POEM

- **Most recent study:**
  - 37 patients with gastroparesis underwent EndoFLIP and G-POEM
  - 70% patients had improvement in GCSI
  - 46% improvement in GES
  - 30% normalization

Hasler et al Dig Dis Sci 2018
Vosoughi GIE 2020
Treatment: Gastric Electrical Stimulation “Gastric Pacemaker”

- Approved as HUD (Humanitarian Use Device) in 2000 for treatment of diabetic or idiopathic gastroparesis
- CONTROVERSIAL
- Data has been source of much debate as difficult to perform placebo-controlled trials

Abell et al. Neurogastro and Motility 2019
How would this work?

Fig. 1. Proposed mechanisms of action of the gastric electrical neurostimulator. a Demonstrated effects. (From Reddymasu SC, Sarosiek I, Mccallum RW. Severe gastroparesis: medical therapy or gastric electrical stimulation. Clin Gastroenterol Hepatol 2010;8(2):121; with permission.)
Treatment: “Gastric Pacemaker”

- Gastroparesis Clinical Research Consortium
  - 319 patients enrolled
  - 25% (81) had GES implanted over 48 week time period
  - Patients who received GES were:
    - Clinically worse (based on GCSI)
    - More delayed GE

- **When corrected for severity of illness, patients receiving pacemaker were not significantly improved compared to those without the pacemaker**
  - Other than mild improvement in nausea

- Maybe we just haven’t found the right patients for this therapy?

Abell et al. Neurogastro and Motility 2019
“Refractory gastroparesis is among the most difficult therapeutic challenges in gastroenterology.”