10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

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Hyatt Regency Jersey City On The Hudson

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New Advances in Upper and Lower Motility Disorders

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Disclosures

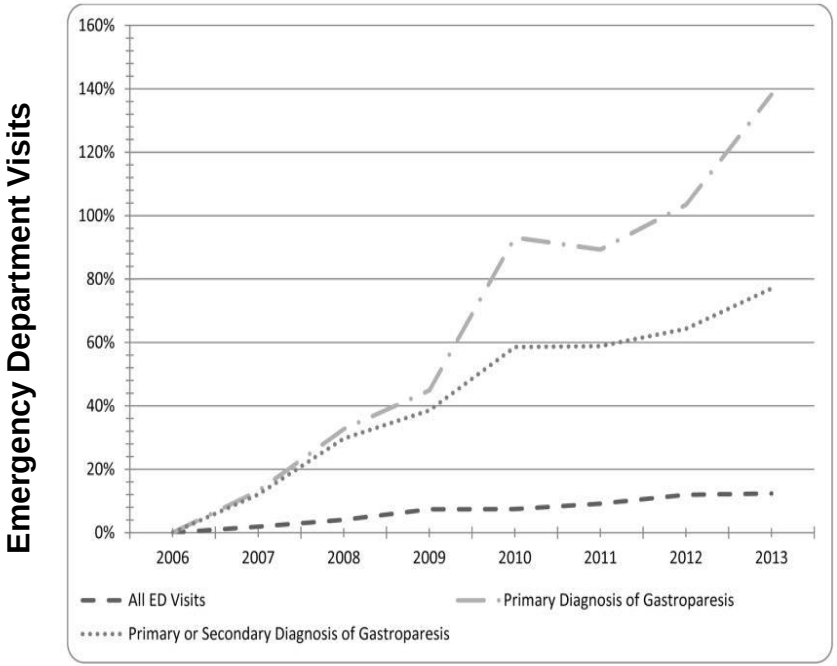
- Consultant: Ironwood, Vibrant, Ardelyx, Gimotti, Pfizer, BioAmerica
- Advisory Board: Atmo, Takeda, Aeon, Allakos, Arena, Gemelli, Evoke
- Data Monitoring Safety Board: Iqvia

Objectives

- Understand presenting symptoms and pathophysiology
- Understand recommended evaluation of patients with symptoms suggestive of gastroparesis
- Discuss therapeutic options for treating gastroparesis

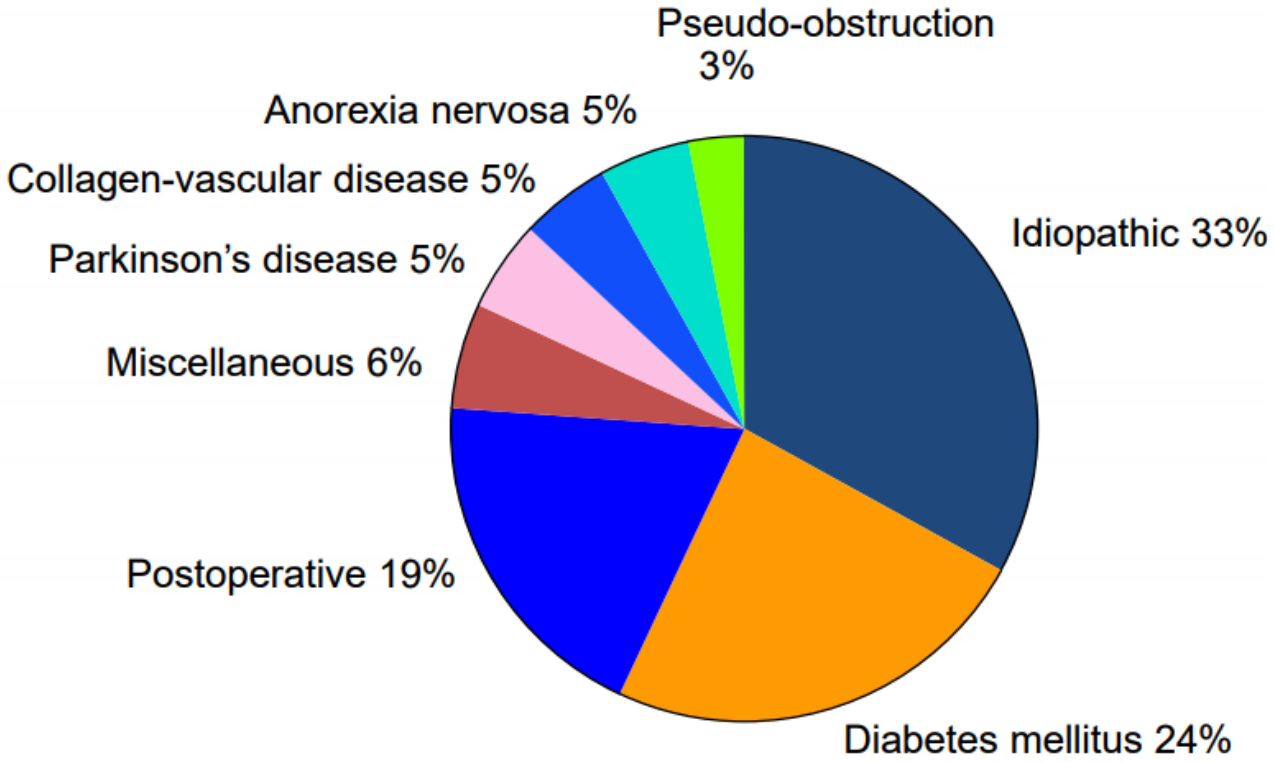
Gastroparesis

- Females >> Males (4:1)
- Median age of onset: 30’s yrs of age
- Up to 11% are disabled due to gastroparesis
- Increasing burden:



Parkman HP et al. *Gastroenterology*. 2004;127:1592–622; Soykan I et al. *Dig Dis Sci.* 1998;43:2398–404; Lacy B. *J Clinical Gastro.* 2016
Hirsch W et al. *J. of Clinical Gastroenterology.* 2017.

Causes of Gastroparesis



Gastroparesis

Functionally delayed gastric emptying (GE)

- Cardinal Symptoms
  - Nausea (95%)
  - Postprandial vomiting (68%)
  - Early satiety (85%)
  - Abdominal bloating (90%)
  - Abdominal pain (90%)

Gastroparesis Cardinal Symptom Index (GCSI)

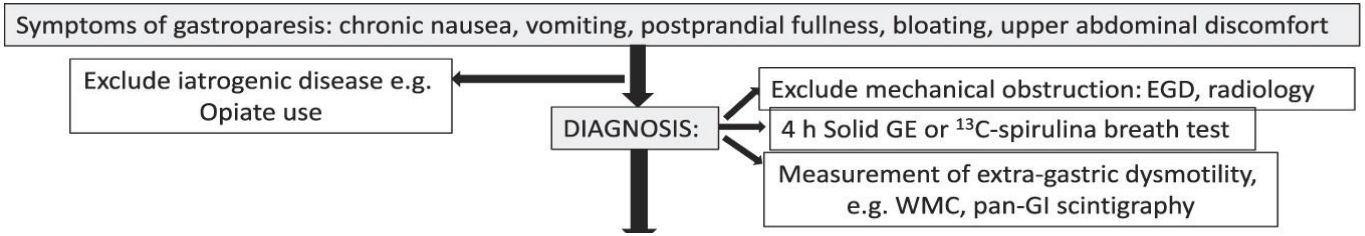
- Challenges
  - Overlap with Functional Dyspepsia (42% reclassified as FD in 1 year)
  - GE delay doesn't correlate well with symptoms
  - GE scans not always performed correctly
  - Definition of severity not well established

ACG Practice Guidelines. Camilleri et al. *Am J Gastro.* 2022; Parkman, H. *Digestive Diseases and Sciences*. 2019;**64**, 2242–2255; Pasricha PJ. *Gastroenterology*. 2021:160; 2006-2017.

Symptoms NOT Typical of Gastroparesis

- Retching – (i.e., dry heaving) reverse movement of the stomach and esophagus without vomiting
- Rumination – effortless regurgitation of recently ingested food, re-swallowed

ACG Clinical Guideline on Gastroparesis Diagnosis



- **Diagnoses Not to Miss**
  - **Rumination syndrome and/or eating disorders**
  - **Cannabinoid hyperemesis syndrome**
  - **Medications (opioids, GLP-1 antagonist, anti-cholinergics, etc)**
  - **Mechanical obstruction (EGD, cross-sectional imaging)**
  - Eating Disorders
  - Cyclic Vomiting Syndrome (CVS)
  - Adrenal insufficiency (hyperkalemia, metabolic acidosis)
  - Porphyria
  - Intestinal pseudo-obstruction

Camilleri M et al. *American College of Gastroenterology.* | ACG117(8):1197-1220, August 2022.

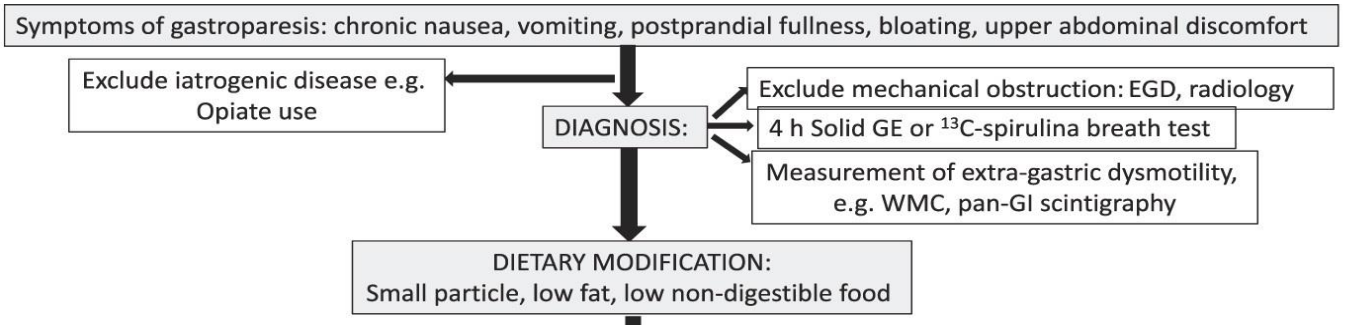
Gastric Motility Testing

Scintigraphy	**GOLD STANDARD test 4 hour test (>10% retention abnormal)**
C^{13}-Spirulina Breath Test	Office based Limited insurance coverage
Wireless Motility Capsule	Office Based Measures migrating motor complex Discontinuing production in 2023
Electrogastrography (EGG)	Measures myoelectrical activity Utility has not been established
Retained Food on Endoscopy	Not Reliable Positive predictive value: 55%

General recommendation: avoid medications that affect motility > 48 hours and blood glucose should be < 275 mg/dl

Bi D et al. *Dig Dis Sci*. 2021;66:3951-9.

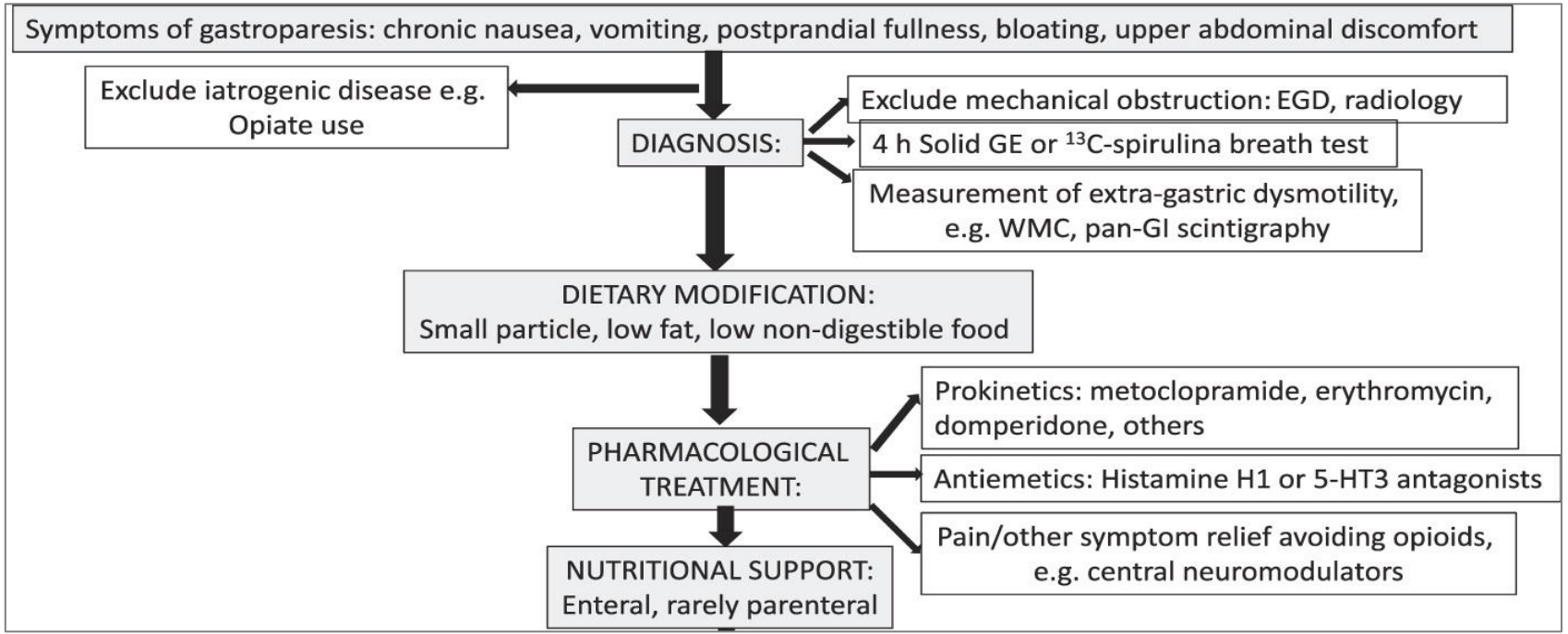
ACG Clinical Guideline on Gastroparesis Dietary Recommendations



- Small particle, low-fat diet better tolerated than jejunal nutrition or TPN
- G-J tube better tolerated than NJT, j-tube, TPN
- Exclusive long-term TPN is associated with significant morbidity and mortality
  - (68% 15 year survival rate)
- Remember vitamin supplementation (iron, B1, folate, vit B12, etc.)
- <u>Refer to a dietitian!</u>

Camilleri M et al. *American College of Gastroenterology.* | ACG117(8):1197-1220, August 2022.

ACG Clinical Guideline on Gastroparesis Pharmacological Treatments



Prokinetics

Medication	Mechanism of Action (Dosage)	Side Effects
Metoclopramide	- Dopamine D_2 receptor antagonist - 5-HT_4 agonist/ 5-HT_3 antagonist **5-10 mg qid for < 12 weeks** **5 mg QID: > 65 yrs, CC <60 mL/min, Child's B or C** **Available: po, IV, SQ, and intranasal**	Most common (> 10%): restlessness, drowsiness, fatigue, and lassitude **Box warning 2009 for** Tardive Dyskinesia: discontinue for signs or symptoms of TD
Domperidone (IND required in the USA)	Peripheral dopamine D_2 receptor antagonist **10 mg po qid**	Cardiac arrhythmias (QT prolongation): avoid if QTc >450 ms males; >470 ms females Increased prolactin levels Extrapyramidal Avoid with concomitant CYP3A4 inhibitors
Erythromycin Azithromycin Clarithryomycin	Motilin receptor agonist **50-250 po/IV mg qid**	QT prolongation Tachyphylaxis (short term use 1-4 weeks)
Prucalopride	5-HT_4 receptor agonist **1-2 mg po qd**	Diarrhea

Anti-Emetics

Medication (examples)	Mechanism of Action	Side Effects
Diphenhydramine Promethazine Meclizine Scopalamine	**Anti-histamine/Anti-muscrarinic**	CNS depression (elderly)
Apretitant, Tradipitant, Casopitant, rolapitant	**NK 1 antagonist**	Approved for chemotherapy-related N/VX
Granisetron Ondansetron	**5-HT3 antagonist**	QT prolongation Tachyphylaxis
Dronabinol, Nabilone	**Synthetic Cannabinoids**	Approved for chemotherapy-related N/V
Prochlorperazine Promethazine, Chlorpromazine	**Phenothiazines (D2, muscarinic and histamine (H1) antagonists)**	Orthostatic hypotension, TD, dystonia, NMS
Mertazapine	**Anti-depressant (alpha-2 adrenergic receptors, 5-HT subtype, H1 receptor)**	Drowsiness and lethargy/fatigue

Additional ACG Guideline Recommendations

<u>Treatments NOT recommended based on current evidence</u>

Central neuromodulators (though commonly used)

Opioids

Haloperidol

Herbal therapies (e.g. Rikkunshito, STW5 (Iberogast))

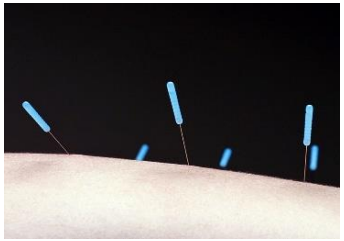
<u>Insufficient Evidence</u>

IVIG

Ginger

<u>May be beneficial</u>

Acupuncture (+/- prokinetic drugs) in diabetic gastroparesis

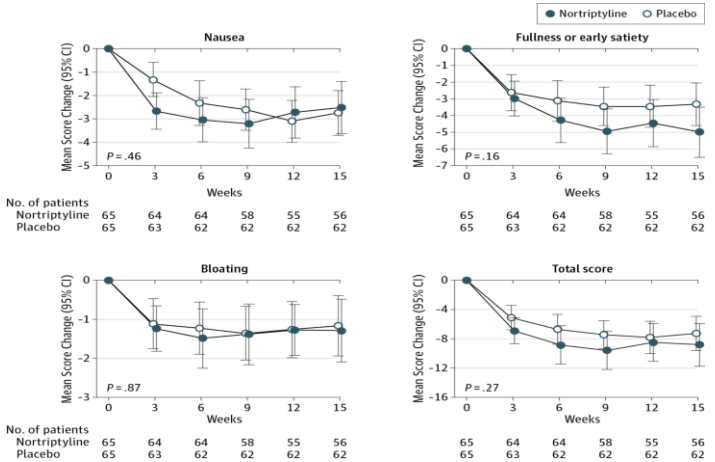


Camilleri et al. *ACG Guidelines Gastroparesis.* 2022; Lacy B et al. *Clinical Gastroenterology and Hepatology.* 2022.

Nortriptyline vs. Placebo for Idiopathic Gastroparesis
The NORIG Trial

- 130 patients with idiopathic gastroparesis
- Nortriptyline increased at 3-week intervals (10, 25, 50, 75 mg) up to 75 mg
- No difference in symptoms
- Treatment stopped: nortriptyline [29%] > placebo [9%]

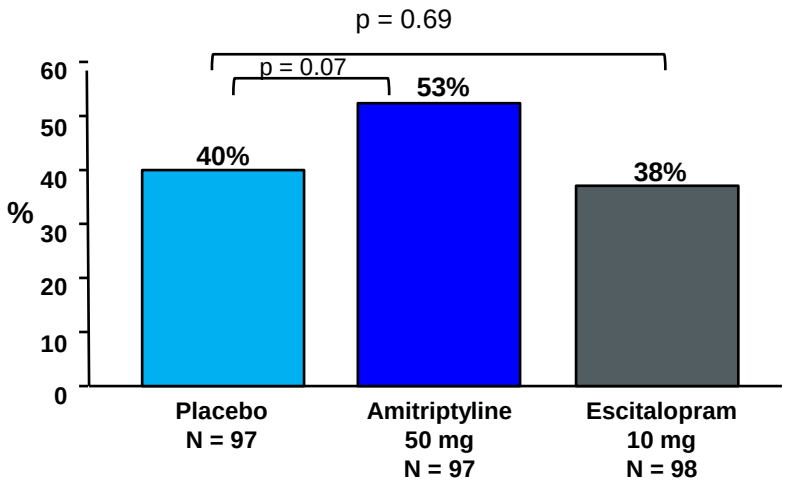
Central neuromodulators are not recommended for management of GP (strong recommendation, moderate quality of evidence).



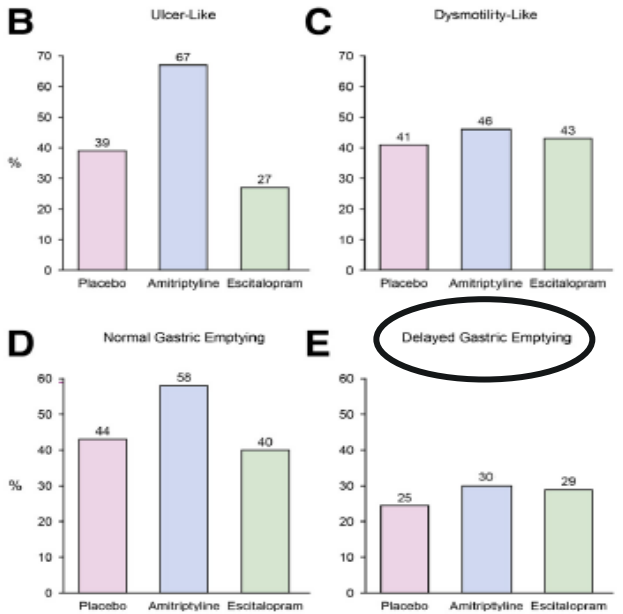
Camilleri et al. *ACG Guidelines Gastroparesis.* 2022; Parkman et al. *JAMA*. 2013;310(24):2640-2649.

Amitryptyline, Not Escitalopram, Improves Symptoms in Functional Dyspepsia

Primary Endpoint: Adequate Relief (%)
≥ 5/12 weeks of adequate relief

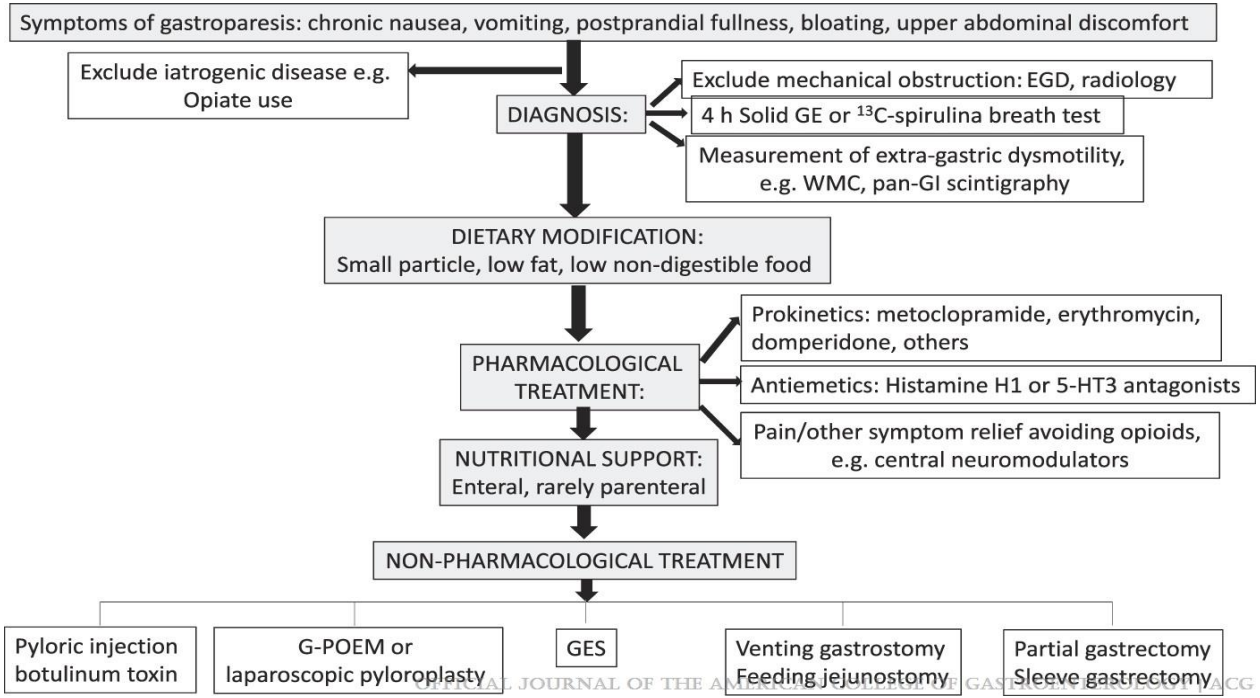


Patients with ulcer-like but not dysmotility-like FD improved with amitriptyline



Talley et al. *Gastroenterol.* 2015;149:340.

ACG Clinical Guideline on Gastroparesis Non-Pharmacological Management



Camilleri M et al. *American College of Gastroenterology.* | ACG117(8):1197-1220, August 2022.

Intrapyloric Botulinum Toxin Injection

- BTX- 100-200 U: relaxation of the pyloric sphincter
- Short duration of action (< 6 months)
- Two small RDBPCs – BTX not superior to placebo
- Decreased distensibility on FLIP may improve pt selection
- Guidelines do not recommended based on RDBPC trials
- Frequently used!!

Camilleri M et al. *Am Journal of Gastroenterology.* 2022; Despre C. *GI Endoscopy.* 2019;90:754-760.

Jejunostomy Tube for Enteral Feeding

- Placement
  - Endoscopic J-tube placement
  - Endoscopic/radiology placed G-J systems
  - Laparotomy/ laparoscopy
- Issues with tubes
  - Bridge therapy
  - Leaking
  - Smell
  - Migration with G-J tubes
  - Body image issues
  - Lack of symptom control

Fontana RJ. *Am J Gastroenterol.* 1996;91:2174.

Gastric Electric Stimulation (GES)

- FDA) Humanitarian Use Device (HUD) exemption
- High frequency, low energy electrical stimulation
- Surgically placed bipolar electrode leads
- External hand-held programming unit FDA-approved
- May help nausea/vomiting; not pain or gastric emptying
- Diabetics > Idiopathic/post-surgical
- High-quality sham/blinded studies are lacking

Gastric Peroral Endoscopic Myotomy (G-POEM)

Chung H et al. *Clin Endosc.* 2018 51:28.

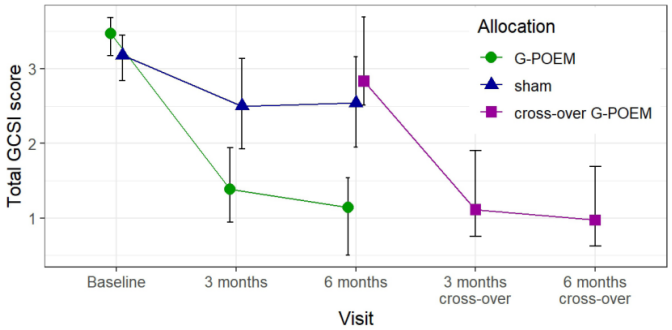
G-POEM for Gastroparesis: Sham-Controlled Trial

Pooled analyses: improvement in symptoms and reduction in GE times

Randomized sham controlled trial (n = 41; 17 DM, 13 postsurgical, 11 idiopathic)

Primary outcome (>50% reduction in GCSI) for G-POEM vs sham (71% vs. 22% p=0.005)

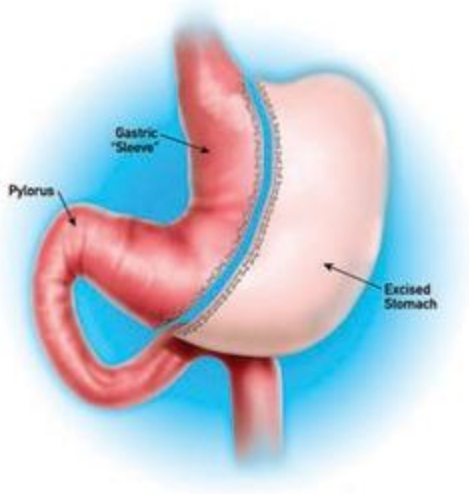
Diabetics (89% vs. 17%) > idiopathic (67% vs. 20%) > post-surgical (50% vs. 29%)



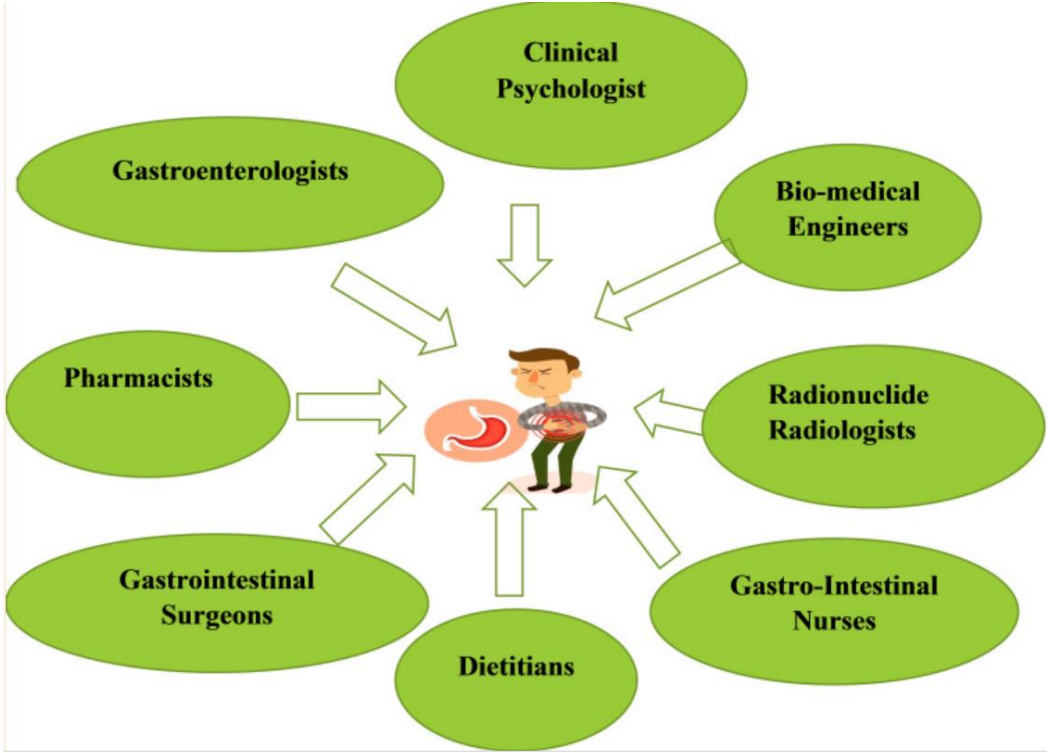
Spadaccini M et al. *Gastrointest Endosc.* 2020; Martinek J et al. *Gut.* 2022.

Sleeve-Gastrectomy for Gastroparesis

- No randomized sham trials
- Potentially beneficial in patients with impaired fundic relaxation may be better candidates
- Further studies are needed



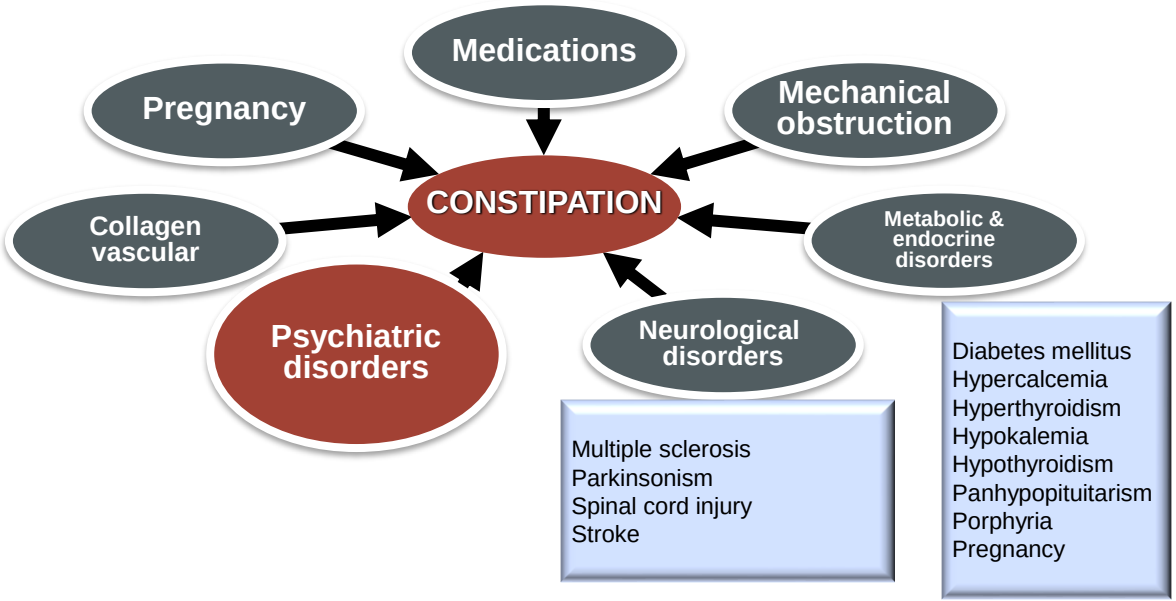
Multidisciplinary Approach to Gastroparesis Management



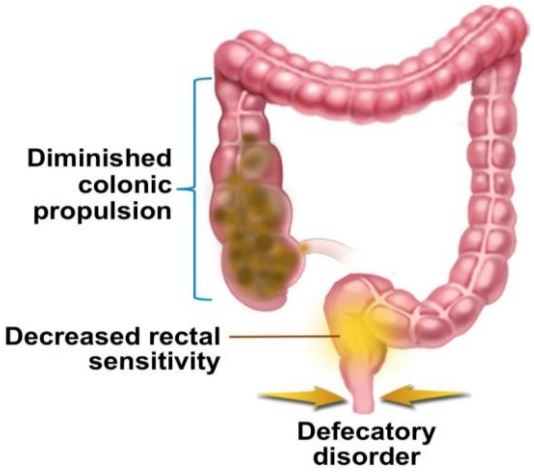
SC Egboh, S Abere. *Cureus*. 2022 Jan; 14(1).

Causes of Constipation

- Functional (most common)
- Secondary (important to rule out!)

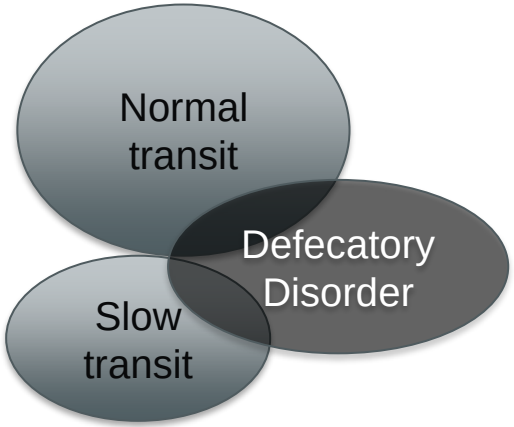


Pathophysiology of Functional Constipation

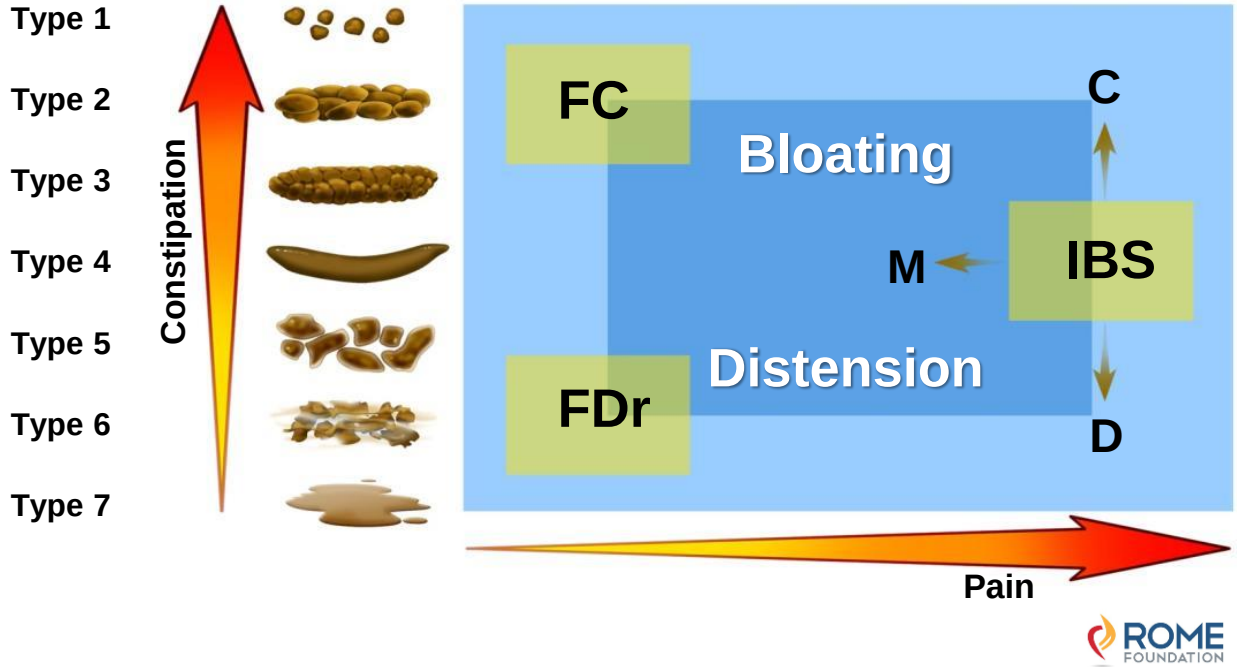


Schiller LR. Aliment Pharmacol Ther. 2001; 15:749
Mertz H et al. Am J Gastroenterol. 1999; 94:609

Subtypes of Constipation



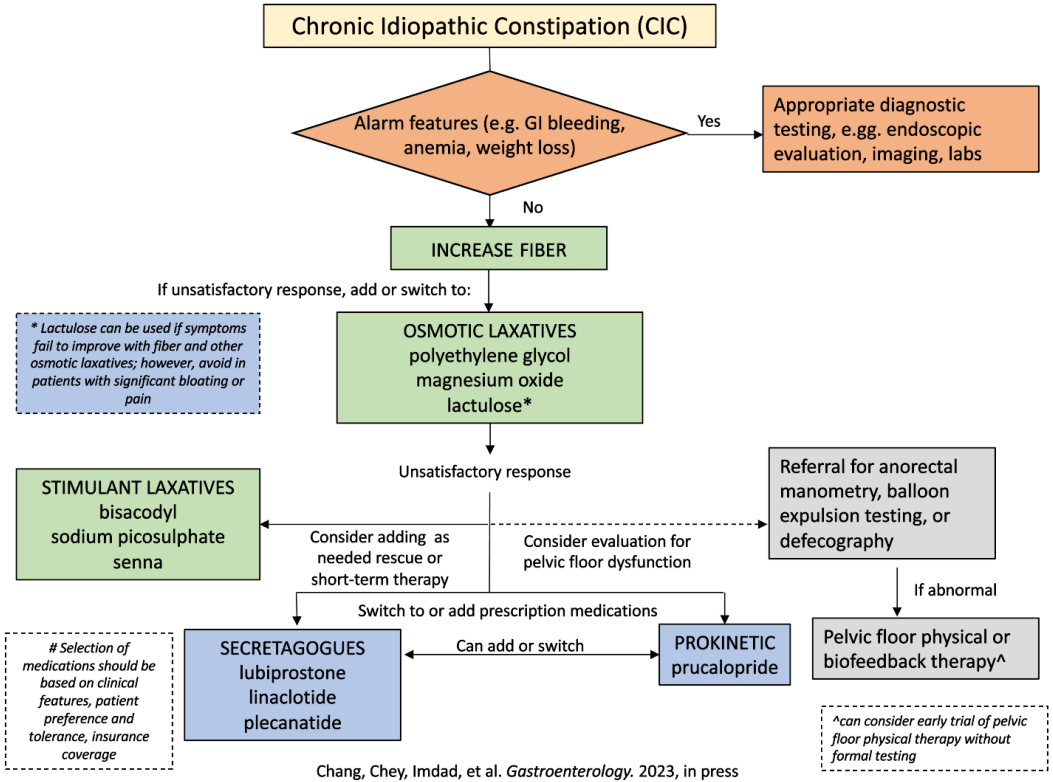
Differentiating Functional Constipation From IBS-C



FC = functional constipation; FDr = functional diarrhea; IBS = irritable bowel syndrome; IBS-C = IBS with predominant constipation; IBS-D = IBS with predominant diarrhea; IBS-M = IBS with mixed bowel habits (C and D)

Lacy BE et al. *Gastroenterology*. 2016;150(6):1393-1407.

AGA/ACG Joint Guidelines



Chang, Chey, Imdad, et al. *Gastroenterology.* 2023, in press

Vibrating Capsule for Chronic Idiopathic Constipatin

Vibration Capsule Program
Two Stimulation Cycles, each ~ 2 hours:
Each Vibration cycle: 3 seconds on and 16s rest

FDA cleared (2022)
Class II Medical Device

Activation POD:
- Used for activating the capsule

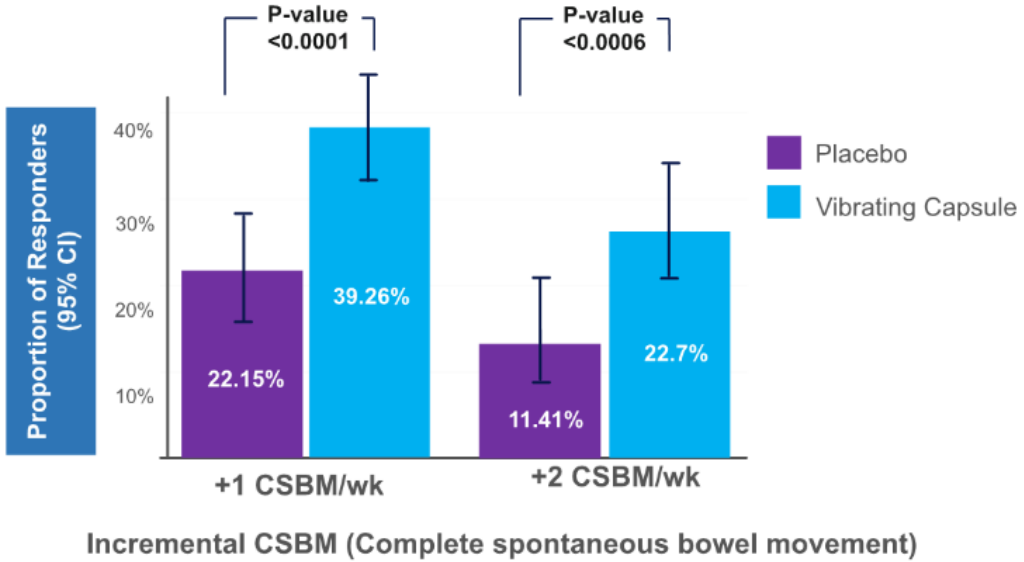
E-Diary: Patient Reporting APP
- Daily stool data
- Symptoms
- Capsule ingestion information
- Compliance
- Rescue
- Adverse Events

Vibrating Capsule: Phase III Results

N=312 (SBM 1.5- 3.0 per week)
5 capsule/wk x 8 wks

Secondary endpoints: improved straining, consistency and QOL

Mild vibrating sensation was reported by 11% of patients in the vibrating capsule group, none withdrew from the trial



Rao et al. *Gastroenterology.* 2023.

Take Home Messages

- Gastroparesis
  - Initial management includes diet, anti-nausea and prokinetic agents
  - Pyloric Botox, G-POEM, Neuroenteric stimulator can be considered in refractory patients in specialized centers
- Constipation
  - Joint AGA/ACG guideline recommendations for pharmacological treatment were recent published
  - Vibrating capsule may be effective in patients with CIC