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Diagnosis and Management of Gastroparesis

Michael Camilleri

This review appraises the symptoms associated with gastroparesis and the optimal measurement to identify delayed gastric emptying. The diagnosis requires differentiation from functional dyspepsia, iatrogenic disease (e.g., opiates and GLP-1 agonists), and conditions associated with vomiting including rumination and cannabinoid hyperemesis. Management includes normalization of hydration and nutrition and relief of symptoms which typically requires pharmacological treatment predominantly with prokinetics and antiemetics. Metoclopramide is the only FDA-approved medication for treatment of gastroparesis, but there are restrictions for its use. Targeting the fundus and visceral sensation may also provide symptom relief. Treatment of abnormal pyloric contractility or poor distensibility may be targeted with intra-pyloric botulinum toxin injection or, increasingly in practice, gastric per-oral endoscopic myotomy. This is increasingly applied for patients not responding to dietary and pharmacological approaches. There is significant unmet need in the treatment of gastroparesis.

INTRODUCTION

The overall objectives are to review the definition, optimal measurement of gastric emptying (GE) of solids, and differential diagnosis and management of gastroparesis. It is important to distinguish between gastroparesis and functional dyspepsia which affects about 8% of people in the community in 26 countries,[1] whereas definite gastroparesis (symptoms plus delayed gastric emptying) is reported in 13.8 to 267.7 per 100,000 adults.[2,3]

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Disclosures: Michael Camilleri received a research grant regarding gastroparesis from National Institutes of Health, #R01-DK122280 (completed); and an industry research grant from Vanda Pharmaceuticals related to symptom control in patients receiving GLP-1 receptor agonists.

Definition

Gastroparesis is identified in clinical practice through recognition of the clinical symptoms and documentation of delayed GE in the absence of gastric outlet obstruction. Symptoms resulting

from gastroparesis include nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain.[4]

Diagnosis

A *sine qua non* for diagnosis of gastroparesis is an accurate, reliable assessment of emptying of solid, digestible food, appraisal for at least 3 and preferably 4 hours, robust normative data, and reproducibility. This excludes radiopaque markers and wireless motility capsule (not digestible), water or nutrient liquids as food substrates. Three available tests (2 scintigraphic and 1 stable isotope) are approved:

a. The egg-substitute 250kcal with 2% fat Eggbeaters® meal is the most widely used; the cut-off for delayed GE is >60% retention at 2 hours, and >10% retained at 4h,[5] based on 95th percentile of a study of 123 healthy volunteers.[6] This meal has an emptying profile almost identical to that of the liquid nutrient meal, Ensure.®[7] Moreover, the reproducibility on replicate testing 48 weeks apart was ~40%.[8]

b. The Mayo two scrambled real egg meal (320kcal, 30% fat) has reproducibility rate of >80%,[9] with 95%ile of GE T1/2 >174min; GE at 2h <25% emptied; GE at 4h <75% emptied, based on 319 healthy controls.[10]

c. The 13C-spirulina stable isotope breath test using reconstituted real egg 238kcal, 42% fat meal, was validated with simultaneous scintigraphy,[11] and effects of pharmacological acceleration and delay of GE.[12]

Other tests infrequently used in the diagnosis of gastroparesis are antropyloroduodenal manometry (to diagnose antral hypomotility,[13] pylorospasm,[14] differentiate neuropathy from myopathy based on amplitude of contractions[15]), or EndoFLIP of the pylorus (to identify pyloric diameter and distensibility[16,17]).

Gastrointestinal symptoms such as nausea or vomiting are significantly correlated with GE measured optimally (solid meal over ≥3h)[18] based on a systematic review and meta-analysis.[19]

Differential Diagnosis

The main considerations are functional dyspepsia (differentiation based on a reliable GE test), rumination syndrome (predominantly through classical effortless regurgitation within 20 minutes after every meal[20,21]), cyclic vomiting or cannabinoid hyperemesis syndrome (CHS) and iatrogenic disease (predominantly GLP-1 receptor agonists[22,23], opiates[24], tetrahydrocannabinol[25], and cannabidiol[26]). CHS is associated with chronic (typically years) and heavy (typically daily or near-daily) cannabis use and predominance in males.[27]

Management

Management of gastroparesis should include correction of nutritional state, relief of symptoms, improvement of GE and glycemic control in those with diabetes,[28] and identifying and treating the underlying pathophysiology.

A. Hydration and nutrition

When patients with gastroparesis have significant fluid or metabolic derangements (e.g., ketoacidosis, renal insufficiency, hyperglycemia) due to nausea and vomiting or underlying metabolic diseases such as diabetes, restoration of hydration and electrolyte balance (especially K^+, Ca^{++}, Mg^{++}) is essential through per-oral or intravenous routes.[29]

Nutritional deficiencies are highly prevalent among patients with gastroparesis; up to 64% of patients with gastroparesis consume <60% of the estimated total kcal needs, and vitamin (A, B6, C,K) and mineral (iron, potassium, zinc) deficiencies are common.[30]

The first dietary modifications, that is, homogenizing solids to smaller particle size, reducing fat, and cooking of nondigestible fibers, reduced the severity of nausea, vomiting, postprandial fullness, bloating, and regurgitation/heartburn in patients with diabetic gastroparesis.[31] If these are not tolerated, stepwise nutritional interventions include liquid meals, oral nutrition supplements, enteral nutrition, and parenteral

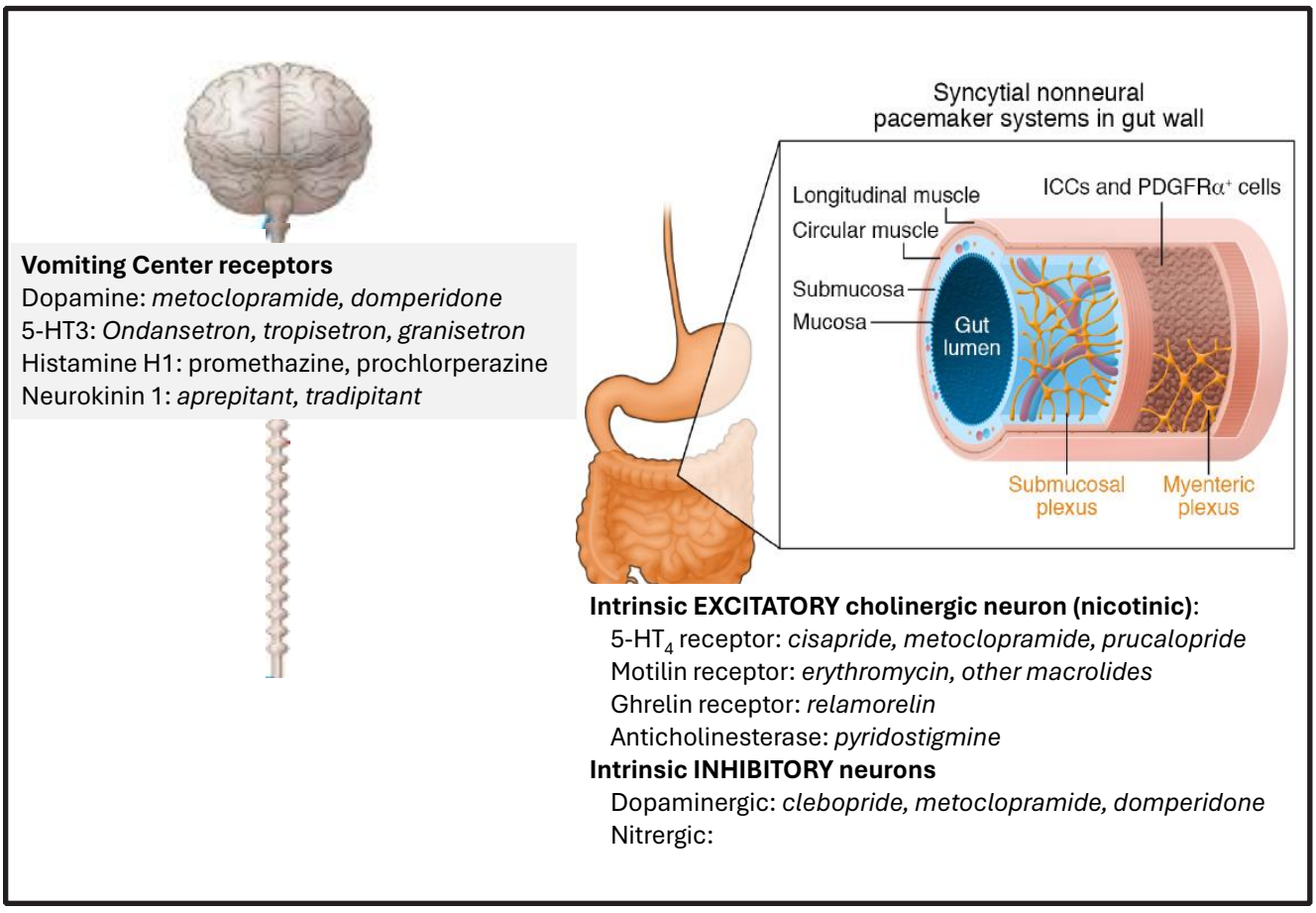

Figure 1. Conceptual summary of pharmacological approaches to treat gastroparesis directed at vomiting center receptors and neurons in the enteric nervous system

nutrition.[32] Enteral feeding should be directly into the jejunum, rather than via jejunal extension from gastrostomy tube; it is safe and leads to weight regain.[33] Parenteral nutrition is used temporarily for severe nutritional deficiency, is rarely required long term in those with intolerance of jejunal feeding, and it may be associated with complications such as infections and thromboses.[34]

B. Pharmacologic agents

Figure 1. shows a conceptual summary of pharmacological approaches to treat gastroparesis directed at vomiting center receptors and neurons in the enteric nervous system.

B. i. Prokinetics

The 2022 gastroparesis guideline[35] recommended therapies that target GE and symptoms of idiopathic and diabetic gastroparesis, while weighing the benefits and risks of the agent. Prokinetic agents enhance GE and reduce symptoms. In a systematic review of randomized, blinded, parallel, or crossover trials with optimal GE tests, meta-regression showed a positive association between accelerated GE T1/2 by at least 20.4 minutes and upper gastrointestinal symptoms.[19] This conclusion was independently confirmed.[36]

B. ii. Dopaminergic modulation

Metoclopramide approved by FDA for gastroparesis in 1979, functions through antagonism of central and peripheral dopamine receptors. Central antiemetic effects are mediated by inhibition of dopamine D2 and 5-HT3 receptors in the area postrema (vomiting center), located outside the blood–brain barrier and a target of several antiemetics.[37] Peripherally,

metoclopramide exerts prokinetic effects through agonism on 5-HT4 receptors on cholinergic neurons and antagonism of D2 receptor.[38] Metoclopramide crosses the blood-brain barrier and can cause anxiety, agitation, somnolence, and reversible extrapyramidal symptoms including tremors. In 1 in 1000-10,000 patients, irreversible tardive dyskinesia occurred.[39,40] Because of risk of neurological adverse effects, metoclopramide is only approved for a maximum of 12 weeks and carries a black box warning.

Routes of administration are oral (tablet or liquid preparation), nasal spray,[41] and parenteral (e.g., i.v. or subcutaneous) formulations.[42] As the only approved medication for gastroparesis, practitioners should prescribe lowest effective dose of liquid, nasal, or tablet formulation, 5-10 mg t.i.d. 15 minutes before meals for 12 weeks. If tolerated, there should be "drug holidays" between prescription cycles, with symptomatic remedies such as liquid or blenderized diet, antiemetic agents (e.g., ondansetron 4-8 mg b.i.d.), or short-term (to avoid tachyphylaxis) erythromycin, 40-200 mg t.i.d. as tolerated.[43]

B. iii. Other marketed agents used off-label in gastroparesis

Other marketed agents used off-label include domperidone, macrolides, and 5-HT4 receptor agonists such as cisapride and prucalopride.

B. iii. a. Domperidone

Domperidone is a peripherally acting dopamine D2 receptor antagonist that is available through the FDA's Program for Expanded Access to Investigational Drugs. The recommended dose of domperidone is 10-20 mg t.i.d. at bedtime. Its efficacy for the treatment of gastroparesis is comparable to metoclopramide.[44] A systematic review of 28 trials showed symptomatic reduction (64%), decreased hospitalization (67%), and accelerated GE (60% of the studies).[45] Domperidone does not cross the blood-brain barrier. Domperidone was associated with corrected QT interval (QTc) prolongation, and it should be avoided in patients with prolonged QTc (>470 ms in males, >450 ms in females).[46]

B. iii. b. Motilin agonists

Macrolides such as erythromycin, azithromycin, and clarithromycin are motilin receptor agonists with a prokinetic property. In a systematic review of 5 small-scaled, short-term studies, erythromycin accelerated gastric emptying and improved symptoms in 43% of patients with gastroparesis.[47] Oral erythromycin is associated with tachyphylaxis within days to weeks due to down-regulation of the motilin receptor.[48] Although erythromycin may prolong the QTc, a systematic review and network meta-analysis of 33 studies (22.6 million subjects) found no association with risk of arrhythmia or cardiovascular mortality.[49]

There are no randomized, placebo-controlled trials of azithromycin and clarithromycin to assess efficacy of symptoms in patients with gastroparesis.

B. iii. c. 5-HT4 agonists used off-label

Prucalopride is highly selective for 5-HT4 receptors. Two available randomized, placebo-controlled, cross-over trials of prucalopride in gastroparesis[50,51] showed greater benefit in patients with idiopathic gastroparesis than in gastroparesis secondary to underlying diseases (diabetes or connective tissue diseases).

Cisapride accelerated GE and improved symptoms in placebo-controlled trials conducted in short-term or medium-term trials (e.g., 6- or 8-week duration) in gastroparesis.[35] Cisapride is a potent inhibitor of the human ether-à-go-go-related gene (hERG) potassium channel and with reports, extremely rarely, of cardiac arrhythmias. It is also only available for compassionate use in selected cases in the USA.

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B. III. d. Cholinesterase inhibitors used off-label for gastroparesis

Neostigmine is a short-acting (15-30min) parenteral acetylcholinesterase (ACE) inhibitor that induces fasting gastroduodenal motor activity,[52] accelerates GE of liquids in critically ill patients with delayed GE,[53] and should only be used in hospital, as it induces vagotonia and bradycardia; EKG monitoring and atropine 0.6-1.2mg should be available while neostigmine is administered.

Pyridostigmine has longer duration of action (4h), is available as liquid or tablet, and is prescribed at a dose of 60mg t.i.d. In an open-label series in children with gastrointestinal dysmotilities, pyridostigmine was beneficial in relief of symptoms.[54]

B. III. e. Ghrelin receptor agonist

Ghrelin is a 28-amino acid orexigenic hormone found primarily in the stomach. A pharmacological dose of ghrelin increased proximal gastric tone through central and peripheral effects.[55] Relamorelin, a pentapeptide ghrelin receptor agonist, increased the frequency of distal antral contractions without inhibiting gastric accommodation or inducing satiation.[56]

Relamorelin had proven clinical efficacy and safety in phase 2A and 2B, randomized, controlled trials in patients with diabetic gastroparesis but not in subsequent phase III trials.[57]

C. Antiemetics

C. i. 5-HT3 antagonists

Ondansetron targets stomach distention, alleviating nausea without affecting gastric compliance, volume, or accommodation.[58] Ondansetron is available as oral tablet, oral dissolution, and intravenous formulations, and is dosed at 4-8mg every 8 hours as needed. Ondansetron can cause QTc prolongation and rarely cardiac arrhythmia. Baseline EKG is recommended. Granisetron is also available orally and i.v., and the sustained release transdermal patch of granisetron significantly improved nausea and vomiting in an open-label study of 51 patients with gastroparesis.[59] Tropisetron, effective for cancer or chemotherapy-induced nausea and vomiting, has potential in gastroparesis based on a dog study.[60]

Constipation is a known adverse effect of this class of medications.

C. ii. Agents targeting multiple receptors

Prochlorperazine is primarily a D2 receptor antagonist, with ability to block histaminergic, cholinergic, and noradrenergic receptors. Promethazine primarily acts as an antagonist for histamine receptors (H1), with additional antagonism at dopamine, adrenergic, N-methyl-D-aspartate, and muscarinic cholinergic receptors.

Scopolamine competes for binding at muscarinic (M1) receptors, inhibiting cholinergic nerve stimulation.

All these antiemetics are available in orally disintegrating tablets, dermal, or rectal formulations for patients with gastroparesis. Cholinergic side effects like sedation, dry mouth, and constipation are frequent. Promethazine may be habit forming and is reserved as a "rescue" agent.

Mirtazapine acts on several receptors: presynaptic α2 adrenergic receptors, several 5-HT receptor subtypes, and H1 receptor. Agonist effects on central and peripheral 5-HT1A receptors influence gastric receptive fundic relaxation. In a 4-week trial in gastroparesis, mirtazapine improved nausea, vomiting, retching, loss of appetite, and patient grading assessment compared with pretreatment.[61]

C. iii. Neurokinin-1 antagonists

Aprepitant (approved for chemotherapy-induced emesis) affects the vomiting center in the brainstem and enhances gastric accommodation without slowing GE.[62] In a randomized, double-blind, placebo-controlled trial of 126 patients with chronic nausea and vomiting of presumed gastric origin, aprepitant, 125mg daily, significantly reduced severity of nausea, vomiting, and overall

symptoms.[63]

Tradipitant is an investigational agent which was demonstrated to decrease nausea score, increase nausea-free days, and improve the GCSI score in patients with gastroparesis compared to placebo.[64] Benefit was documented when controlling for drug exposure, rescue medications, and baseline severity inflation.[65]

C. iv. Cannabinoid agents

The primary ingredient in marijuana is tetrahydrocannabinol (THC), a nonselective cannabinoid receptor agonist. Although THC delays gastric emptying of solids,[66] a database of 506 patients with gastroparesis, showed 12% used medical or recreational marijuana for symptomatic relief.[67]

Cannabidiol (CBD), a low-THC extract from Cannabis sativa approved for seizure disorders, blocks CBR1 and CBR2 receptors. CBD twice daily (Epidiolex® escalated to 20mg/kg/d) in 44 patients[68] was efficacious in gastroparesis, with reduction in total GCSI score, ability to finish a normal-sized meal, vomiting, and overall symptom severity, despite slower GE of solids. CBD's effectiveness was attributed to anxiolytic and visceral analgesic properties.[69]

D. Neuromodulators for pain relief

Patients frequently experience abdominal pain with gastroparesis; however, those primarily presenting with abdominal pain should be evaluated for alternative diagnoses. In a randomized trial involving 130 patients diagnosed with idiopathic gastroparesis, nortriptyline did not demonstrate superiority over placebo in alleviating symptoms, as measured by the GCSI score.[70]

E. Targeting the fundus

About 20% of 284 patients with proven gastroparesis have increased gastric accommodation.[71] Erythromycin (motilin and cholinergic receptor agonism) stimulates both fundic contraction and antral motor function and accelerates GE.[72,73] Erythromycin was tested in an open-labeled study: at 4 weeks, there was acceleration of GE and reduced symptoms, but efficacy was lost over time,[74] reflecting tachyphylaxis.[48]

For dyspeptic symptoms with both reduced GE and reduced accommodation,[75] buspirone, a 5-HT1A agonist with anxiolytic properties, improved aggregate symptoms and nausea in response to a nutrient challenge meal in healthy controls.[76] On the other hand, patients with moderate-to-severe early satiety or postprandial fullness and other symptoms of gastroparesis did not benefit from treatment with buspirone.[77]

Although mirtazapine has 5-HT1A effects, the improvements in nausea, vomiting, retching, and loss of appetite[61] appear unrelated to alteration in gastric accommodation.[78]

F. Targeting the pylorus

In a subset of patients with gastroparesis, pyloric dysfunction, characterized by abnormally prolonged and intense tonic contractions of the pylorus, was noted.[14] After excluding iatrogenic dysfunction (e.g. opiates),[24] open-label studies showed intrapyloric injection of botulinum toxin had short-term (<6 months) efficacy in accelerating GE and improving symptoms.[79] However, two randomized, placebo-controlled trials did not confirm efficacy in achieving symptom improvement.[80,81] Measurements of pyloric diameter and distensibility index may predict response to therapy, particularly post–G-POEM (discussed below)[82] or after botulinum toxin injection for relief of vomiting.[83]

G. Electrical approaches

Gastric electric stimulation (GES) may be considered for control of gastroparesis symptoms as a humanitarian use device. Randomized, crossover trials of gastric electric stimulation have shown mixed results, sometimes with improvement in symptoms but no differences in gastrointestinal quality of life, nutritional parameters, or GE, suggesting possible effects on visceral afferents rather than the motor function of stomach (trials reviewed elsewhere[35]).

H. Endoscopic or surgical approaches

In patients with gastroparesis with symptoms refractory to medical therapy, pyloromyotomy (nowadays almost exclusively through G-POEM) is recommended over no treatment for symptom control,[35] based predominantly on open-label studies. One sham-controlled study of 6 months' duration documented relief of symptoms and

improved GE with G-POEM procedure.[84]

In 177 patients with gastroparesis, laparoscopic pyloroplasty improved GE in 90% of patients and induced short-term improvement of nausea, vomiting, bloating, and abdominal pain. However, morbidity rate was 6.8%, including leaks requiring further surgery.[85]

CONCLUSION

A careful appraisal of symptoms is necessary in suspected gastroparesis: "If patient has predominant pain, think again". A solid GE test is essential. Normalization of hydration and nutrition, and relief of symptoms typically requires pharmacological treatment. G-POEM is increasingly applied for patients not responding to dietary and pharmacological approaches. ■

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