Received: 9 September 2022 | Revised: 17 October 2022 | Accepted: 20 October 2022

DOI: 10.1111/nmo.14494

REVIEW ARTICLE

Neurogastroenterology & Motility | WILEY

Ten controversies IN gastroparesis and a look to the future

Gabriela Piovezani Ramos | Michael Camilleri

Division of Gastroenterology and Hepatology, Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Michael Camilleri, Mayo Clinic, 200 First St. S.W., Charlton Building, Room 8-110, Rochester, MN 55905, USA.
Email: camilleri.michael@mayo.edu

Funding information
National Institutes of Health, Grant/Award Number: R01-DK125680 and R01-DK122280

Abstract

Background: Gastroparesis is a complex, challenging gastrointestinal disorder presenting with upper gastrointestinal symptoms, especially nausea and vomiting, with significant impact on patients' quality of life. After ruling out mechanical obstruction, it is essential to identify delay in gastric emptying for definitive diagnosis. The most common causes are idiopathic (no identified etiology), diabetes mellitus, and postsurgical status. Management of gastroparesis focuses on dietary modifications and treatment directed to symptom relief. Unfortunately, approximately one-third of patients are refractory to pharmacological therapy, and the effectiveness of the few nonpharmacological options has been questioned.

Purpose: Extensive review of the literature identifies several uncertainties or controversies regarding the differential diagnosis based on the spectrum of symptoms, the lack of availability of reliable diagnostic test, and questions regarding effective therapeutic options. In this review, we discuss ten controversies regarding gastroparesis: clinical presentation, diagnosis, overlap syndromes, pathophysiology, etiology, as well as pharmacological and nonpharmacological therapeutic options. In addition, we briefly review studies exploring pathological, inflammatory, and molecular disturbances affecting the intrinsic neuromuscular elements that may be involved in the pathophysiology of gastroparesis and may constitute possible therapeutic targets in the future. Finally, we tabulate future research opportunities to resolve these controversies in the management of patients with gastroparesis.

KEYWORDS
diagnosis, dyspepsia, gastroparesis, molecular, nutrition, treatment

1 | INTRODUCTION: CURRENT DEFINITION, DIAGNOSIS, THERAPY, AND PITFALLS

Gastroparesis is a gastric dysmotility disorder characterized by persistent or intermittent upper gastrointestinal symptoms (UGS) including nausea, vomiting, early satiation, postprandial satiety, bloating, and/or epigastric discomfort or pain.[1,2] Diagnosis requires exclusion of mechanical obstruction and documentation of delay in gastric emptying (GE) by standardized tests.[2,3] GE scintigraphy of solids is considered the gold standard method to measure GE[4]; two other FDA-approved tests for gastroparesis diagnosis are stable

Abbreviations: ANA, antinuclear antibody; ARFID, avoidant/restrictive food intake disorder; DSM-5, diagnostic and statistical manual of mental disorders, fifth edition; D_2 antagonist, dopamine D2 receptor antagonist; ECG, esophagogastroduodenoscopy; ED, eating disorders; EGD, esophagogastroduodenoscopy; EGG, electrogastrography; FD/PDS, postprandial distress subtype; FD, functional dyspepsia; FDA, Food and Drug Administration; GAD, glutamic acid decarboxylase; GE, gastric emptying; GEBT, gastric emptying breath test; GES, gastric electric stimulation; GI, gastrointestinal; GpCRC, gastroparesis clinical research consortium; G-POEM, gastric peroral endoscopic myotomy; HMOX-1, genes encoding HO-1; HO-1, heme oxygenase-1; ICC, interstitial cells of Cajal; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; RCT, randomized controlled trial; RGF, retained gastric food; SD, standard deviation; SEM, standard error of the mean; SRMA, systematic review and network metanalysis; T ½, time to empty half the meal; UGS, upper gastrointestinal symptoms; WMC, wireless motility capsule; 5-HT4 receptor agonist, serotonin type 4 receptor agonist.

isotope gastric emptying breath test (GEBT)[5,6] using ^{13}C-Spirulina and the wireless motility capsule (WMC).[7,8] Although most patients with gastroparesis have no underlying cause identified (idiopathic), it can be associated with comorbidities such as diabetes mellitus, status postsurgery (fundoplication, bariatric procedures), and, less frequently, neuropathic and myopathic conditions (Parkinson disease, paraneoplastic syndrome, amyloidosis, and/or scleroderma).[2,3]

Management of gastroparesis involves multimodal approaches that include modified diet, nutritional support, medications targeting symptoms, and procedures aimed at reversing the putative underlying pathophysiological mechanisms such as gastric electrical stimulation, gastric peroral endoscopic myotomy (G-POEM), or laparoscopic pyloroplasty. However, the application of therapeutic strategies such as gastric electrical stimulation or G-POEM is controversial, as discussed in this article.

The pharmacological management of gastroparesis is challenging, especially because one-third of patients are refractory to medications.[9] Prokinetics are first-line therapy for gastroparesis, directed to patients' symptoms, and only metoclopramide is approved by the FDA.[10] However, other agents with prokinetic properties are used off-label, particularly 5-HT$_4$ receptor agonists and macrolide antibiotics that stimulate motilin receptors. Despite the approved and off-label medications used for gastroparesis, 20%–30% of patients are refractory to pharmacological management. Further studies should help identify a class of medication targeting the underlying pathophysiology and therefore achieve better outcomes. Table 1 summarizes the odds ratio of symptom responses in patients with gastroparesis to different drug classes.[11]

We summarize in Table 2 features and side effects of medication options for gastroparesis[12–24] including medication classes in development; this summary includes assessment of tolerability and patients' responses to therapy and how they might impact clinical management of gastroparesis. Three recent articles provide extensive information regarding the current state-of-the-art in the understanding of the presentation, mechanisms, and management including useful, practical algorithms.[1,25,26]

2 | OBJECTIVE

In clinical practice, gastroparesis is considered one of the more challenging, as there are still uncertainties regarding the spectrum of symptoms, differential diagnosis, availability of reliable diagnostic tests, and insufficient efficacy of current therapeutic options. The aim of this review is to highlight ten controversies or questions regarding gastroparesis, including clinical presentation, pathophysiology, etiology, diagnosis, overlap syndromes, and treatment. These controversies arose from the in-depth study of the current state of the art in gastroparesis, as summarized in a recent guideline document.[25] Resolving these uncertainties by prospective studies and multidisciplinary investigation should impact the diagnosis and management of patients with gastroparesis.

Key Points

- The diagnosis of gastroparesis requires use of a valid gastric emptying test.
- There is still considerable unmet need for treatment of gastroparesis.
- Innovative studies of histopathology and molecular mechanisms are indicating novel opportunities to study and treat gastroparesis.

3 | TEN CONTROVERSIES IN GASTROPARESIS

3.1 | Controversy #1. Functional dyspepsia and gastroparesis: overlapping or distinct entities?

Persistent nausea and vomiting associated with delayed GE in the absence of outlet obstruction is classically diagnosed as gastroparesis. However, symptom-based scores (e.g., Rome IV criteria) identify most patients (87%) with these symptoms as functional dyspepsia (FD), with 95% being consistent with the postprandial distress subtype of FD (FD/PDS), rather than the epigastric pain syndrome variant of FD; in these patients, GE may be normal.[27] A Gastroparesis Clinical Research Consortium (GpCRC) study of 944 patients followed over 12 years showed that, despite generally unaltered symptom profiles over time, 37% of patients initially diagnosed with FD and 42% with gastroparesis were subsequently reclassified based on the repeat GE scintigraphy. The study documented that both groups had similar quality-of-life scores and neuropathology on gastric full-thickness biopsies. The

TABLE 1 Upper gastrointestinal symptoms outcomes with covariate analysis: Individual drug and patient category.

Variable	N	Overall outcome (95% CI)	I^2, %
All studies	23	**−0.25 (−0.37 to −0.13)**	0
Individual drugs			
D_2 antagonist *(3 metoclopramide/1 domperidone)*	4	**−0.45 (0.80 to −0.11)**	**15.4**
Ghrelin	1	−0.92 (−4.1 to 2.3)	NA
Relamorelin *Ghrelin receptor agonist*	3	**−0.3 (−0.52 to −0.07)**	**0**
Cisapride *5-HT4 receptor agonist*	8	−0.2 (−0.5 to 0.11)	0
Revexepride *5-HT4 receptor agonist*	1	0.364 (−0.21 to 0.94)	NA

Note: From Vijayvargiya et al. 2019 - adapted with permission.[11] Data in bold type are statistically significant.

TABLE 2 Confounders in pharmacological options for gastroparesis (GP) treatment.

Medication (name/class)	Confounder	What is known	Additional comments	Interpretation/resolution of confounder
Metoclopramide / peripheral cholinergic agonist and dopamine receptor antagonist	Side effect—tardive dyskinesia (TD)	FDA-approved **black box warning** Crosses blood–brain barrier Side effects: extra-pyramidal symptoms (1–10% risk of developing TD) Dose recommended: 10 mg 3–4 times daily up to 12 weeks for patients under 65 years old	2010: risk of TD <1%[21] 2013: side effects reported to FDA Adverse Event Reporting System between 2004 and 2010[14] 2010: 944 cases of TD in 40.5 million metoclopramide prescription[14] 2019: Risk estimated 0.1% per 1000 patients/year[12]	The reversal of neurological symptom after cessation of medication can underestimate the number of adverse effects reported BUT low risk of neurological side effect compared to risk of up to 10% included in the controversial FDA black-box warning.
Erythromycin; Azithromycin; Clarithromycin / motilin receptors—macrolides	Tachyphylaxis cardiovascular side effects	Accelerate gastric emptying Improve gastric symptoms in GP Short-term use (1–4 weeks) due to tachyphylaxis to the motilide Increased risk of QT interval prolongation	Tachyphylaxis seems to be higher with i.v. erythromycin[19,24] SRMA of 33 studies with 22.6 million subjects: no association of macrolide and risk of arrythmia and cardiovascular mortality[15]	1. Quest for a motilide devoid of tachyphylaxis has not been successful despite trials with mitemcinal, atilmotin (to name a few) 2. Cardiovascular side effects seem to have lower rates than expected.
Relamorelin/agonist of ghrelin receptors	Increases blood glucose levels	Potent prokinetic agent In diabetic GP: - accelerated gastric emptying of solids, by increasing antral contractions - Deterioration in glycemic control as side effect[22,23]	Is hyperglycemia the result of endocrine effect of medication? OR Is it a consequence of rapid transit without modification on antidiabetic therapy?	Constant measurement of glycemia Proactive management of hyperglycemia is advised[13]

study concluded that the diagnoses of gastroparesis and FD are essentially interchangeable[28] and led the GpCRC to propose an "umbrella" term of gastric neuromuscular disorders, regardless of the GE status.[29] On the contrary, recently, the European UEG and ESNM guideline on gastroparesis proposed distinguishing gastroparesis from FD based on their cardinal symptoms: nausea and vomiting for gastroparesis, and early satiation, postprandial fullness, and epigastric pain for FD.[1] In this respect, the recent AGA Clinical Practice Update on gastroparesis is confusing, since it recommended that clinicians should identify the predominant symptom and initiate treatment based on that symptom, including the use of central neuromodulators for the pain.[26] The confusion arises when there is objective evidence of delayed gastric emptying in the setting of predominant epigastric pain, which according to the UEG and ESNM guideline would be indicative of FD rather than gastroparesis.

Moreover, it is also conceivable that at least a component of the overlap between the two syndromes may result from the cut-off value of 10% retention at 4 h used with the low-calorie and low-fat meal in the standard GE scintigraphy test (Eggbeaters® meal).

The interpretation and "umbrella" diagnosis of gastric neuromuscular disorders are controversial and require further validation using alternative cutoffs for delayed GE other than >10% retained at 4 h. For example, in the original validation study of Tougas et al. using the GE scintigraphy method in 100 healthy controls, there were healthy volunteers with >15% retained in the stomach.[30] In addition, a recent study showed percentage of emptying at 4 h in 31 healthy controls of 95.6 ± 1.7 (SEM), from which the calculated cutoff for the 95th percentile would be 77% (i.e., the mean value 95.6 minus 18.6 [2SD]), or 86% using the more liberal 1 SD above the mean retention at 4 h.[31] Therefore, in addition to clinical symptoms, future improvements in diagnosis of delayed GE may better differentiate gastroparesis and PDS/FD with normal GE and thereby facilitate therapeutic approaches to both disorders, such as use of prokinetic agents in definitely delayed GE associated with gastroparesis, rather than using prokinetics in PDS/FD with normal GE, and applying central neuromodulators for pain disorder rather than gastroparesis.

3.2 | Controversy #2. Should scintigraphic emptying of an egg-protein meal be retained as the gold standard in screening or diagnosing delayed gastric emptying?

Gastric motility and emptying vary based on meal consistency, volume, and caloric content.[4] In 2007, a consensus statement defined the gold standard test for gastroparesis as a 4-h scintigraphy study

performed after the ingestion of a 2% fat and low-calorie (255 kcal) standard meal with radiolabeled egg whites (^{9m}Tc-sulfur colloid). Based on this test, gastroparesis was diagnosed when gastric retention was >60% after 2 h or >10% after 4 h.[4] However, with an alternative meal proposed for GE scintigraphy studies with real eggs, higher content of calories (300 kcal), and fat (30%), delayed GE was defined as gastric retention >75% at 2 h and >25% at 4 h post-meal based on normal values obtained in 319 healthy adults.[32] Recently, a study compared the performance of GE T½ of 2- and 4-h retention using the standard GE scintigraphy with the egg-protein meal. Although $T_{1/2}$ correlated strongly with retention at 2 h and to a lesser extent retention at 4 h, the GE $T_{1/2}$ had potential to misclassify patients, especially those with late-phase (4-h only) delay.[31]

Although GE of liquids or semi-solid meals alone is typically normal, even in the presence of severe gastroparesis symptoms, a subgroup of gastroparesis patients, particularly nondiabetic, have delayed GE of liquids with normal GE of solids. Therefore, measurement of liquid emptying in addition to solid GE scintigraphy test may help identify this subgroup of patients.[3,33–35]

In patients unable to tolerate eggs or egg substitutes, or with food allergies or prior upper gastrointestinal surgery, alternative methods to evaluate GE have been developed. A high caloric and fat liquid nutrient meal such as Ensure® was compared to the standard GE scintigraphy with egg whites in 20 healthy volunteers and showed similar overall GE, with a slightly longer time to empty from the distal stomach, probably due to the higher fat content of the meal. It is relevant to note that liquid nutrient meal can induce postprandial motor function, which is relevant to identify dysmotility secondary to surgery (post-vagotomy).[36] Further validation of this substrate in GE scintigraphy test in disease states is required to define its performance characteristics.

In summary, at present, the scintigraphy test with the most robust validation for GE delay involves ingestion of a solid meal (Eggbeaters® meal, or 2-egg meal). However, the availability or utilization of these meal substrates worldwide are limited, and further research including comparison with current standard solid meal emptying would help identify other semi-solid (e.g., oatmeal) or liquid nutrient (e.g., Ensure®) meals. This may conceivably reduce the time to complete the GE measurement (probably to 2 or 3 h instead of 4 h) and thereby increase the utilization of scintigraphic emptying worldwide to facilitate the clinical diagnosis of gastroparesis.

3.3 | Controversy #3. Are there valid alternatives to diagnose gastroparesis including endoscopy?

In addition to GE scintigraphy of solids, there are two other FDA-approved diagnostic tests for gastroparesis: wireless motility capsule (WMC) and gastric emptying breath test (GEBT), both reviewed elsewhere.[3] There are a few concerns regarding interpretation of these tests. WMC has been shown to empty independently of solid food. The definition of delayed GE with a cutoff of 5 h has been associated with GE scintigraphy, but it is not necessarily a precise measurement of the GE profile as obtained with solid-meal GE scintigraphy.

The use of GEBT in clinical diagnosis should ensure the application of an optimal mathematical formula for derivation of the test's parameters.[37] The numerical values of reported lag times for ^{13}C-spirulina GEBT are different from those usually reported for the lag times with GE scintigraphy, which typically are reported as the time for 10% emptying. Additionally, the clinical interpretation of the kPCD [1000 X Percent Carbon-13 Dose excreted per minute] provided at each time point of breath collection within the report is not easily interpreted clinically, except that a higher value reflects faster GE.

Given the fact that GE scintigraphy with solid meal is not available worldwide and that GE by WMC and GEBT may not achieve accuracy comparable to scintigraphy, an alternative, noninvasive approach may be measurement of conventional electrogastrography (EGG) which has been proposed in the past to identify gastric dysrhythmias as a surrogate for dysmotility. However, more recently, high-resolution mapping of gastric electrical control activity from the body surface has been studied to overcome the previous limitations of EGG. In a case–control study, including patients with gastroparesis and FD, and healthy controls, high-resolution EGG identified abnormal sustained waves in 44% of symptomatic patients, successfully discriminating a patient subgroup from controls.[36] In addition, the aberrant slow wave correlated positively with a range of gastric symptoms.[38] Further studies are needed to confirm whether and how high-resolution EGG might contribute to gastroparesis diagnosis and management.

In patients without outlet obstruction who report compliance with recommendations to fast (typically ≥8 h) before esophagogastroduodenoscopy (EGD), the identification of retained gastric food (RGF) is often attributed to gastroparesis. A retrospective study showed that 74% of patients with RGF and without obstruction had delayed GE by GE scintigraphy evaluation, and most patients with severely delayed GE were more likely to have RGF.[39] A recent study reviewed data of 85,115 EGDs performed in a single center between 2012 and 2018 and reported RGF in only 3%, with the highest frequency in those with comorbidities that are known to be risk factors for delayed GE (diabetes mellitus, gastroparesis, systemic sclerosis, amyloidosis, and gastric surgery) and, among the 2991 patients who underwent GE scintigraphy (300 kcal, 30% fat egg-meal), the positive predictive value of RGF for delayed GE was only 55%, ranging from 79% in those with type 1 diabetes mellitus to 32% in patients with no medical risk factor for impaired GE. Even though the highest prevalence of RGF was observed in patients with gastroparesis (14%), approximately one-third of patients with RGF found at EGD were without structural foregut abnormalities or medical risk factors, though use of opioids, antacids, and cardiovascular medications was associated with RGF.[40] Therefore, RGF encountered during EGD is not a pathognomonic feature of delayed GE and should not be deemed diagnostic of gastroparesis. Further evaluation with a validated GE scintigraphy test and exclusion of confounding medication(s) are recommended to ascertain the clinical significance of RGF

identified at EGD. In the future, the utilization of unsedated measurements of pyloric distensibility and diameter as well as antropyloroduodenal manometry[41,42] to identify abnormal pyloric distensibility, compliance, or motor function may also help optimize identification of the pathophysiology and guide therapy such as prokinetics for antral hypomotility and pyloromyotomy among patients with reduced pyloric distensibility, as reviewed in a recent guideline.[25]

3.4 | Controversy #4. Is there an autoimmune etiology of gastroparesis?

Several lines of evidence, listed in Table 3, have suggested that autoantibodies may drive inflammation and contribute to diverse gastrointestinal dysmotility disorders, including gastroparesis.[43–49] These small series or open-label studies are usually based on results of neural-specific autoantibodies and are rarely associated with autonomic neuropathy, in contrast to paraneoplastic gastrointestinal motility disorders with anti-Hu antibodies directed against myenteric neurons,[50] or the selective or pan-dysautonomia associated with infection with herpes family viruses.[51–55] The significance of positive antinuclear antibody (ANA), especially speckled pattern, and observations on open-label treatments with immunotherapy are preliminary. At present, there is insufficient evidence to support clinical use of immunomodulatory therapy in gastroparesis, and criteria to select which patients are candidates for immunotherapies are unclear. Further research on this topic is needed.

3.5 | Controversy #5. Does viral infection predispose to gastroparesis?

Although many patients with gastroparesis have an unidentified cause, there are a few studies suggesting a post-viral etiology.[56–59] In the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Consortium Cohort, 19% of 243 patients with gastroparesis reported a history suggestive of an infectious etiology.[60] In a single-center study, almost a quarter of patients with idiopathic gastroparesis had a history consistent with post-viral etiology; these patients presented with gradual improvement without hospitalization within 6 months of the infectious episode compared to those with non-post-viral gastroparesis who had significantly longer duration of illness and severe abdominal pain score.[61] A study evaluating the history of acute viral illness prior to the development of persistent unexplained vomiting showed that 7 of 15 patients met criteria for post-infectious gastroparesis, and symptoms improved spontaneously between 1 to 12 months after infection in 4 patients with post-infectious gastroparesis.[62] Enterovirus infections have been found by immunostaining of gastric biopsies from patients with idiopathic gastroparesis, also suggesting a potential viral etiology.[63]

It is not well established whether anti-viral therapy is effective, since most reports involve small series or single-case reports.[63,64] In summary, post-viral etiology of gastroparesis is still controversial, based on observational studies, unexplained mechanism for the delay in GE, and unclear efficacy of anti-viral treatment.

3.6 | Controversy #6. The role of eating disorders in patients presenting with gastroparesis

There is the chicken and the egg question: Does gastroparesis cause eating disorder (ED) or does the ED result in gastroparesis? Among psychiatric disorders, feeding and eating disorders are defined by abnormal eating habits that frequently begin in late childhood or early adulthood.[65] Food avoidance and dietary restriction are frequently recommended as part of the treatment for gastroparesis, or they are initiated by gastroparesis patients themselves for symptom management. Typically, dietary recommendations include eating smaller meal portions, a small particle diet, and avoiding high fat and non-digestible fiber content.[10,66–69] Several studies with and without standardized diagnostic methods for gastroparesis have shown that some ED, notably anorexia nervosa, were associated with delayed GE.[70–75]

A systematic review evaluating the association between ED and disorders of gut-brain interaction showed that anorexia nervosa and bulimia nervosa were the most frequent ED associated with

TABLE 3 Possible evidence of autoimmune etiology of gastroparesis.

Evidence	Literature review
Immune dysfunction in gastroparesis	Full-thickness gastric biopsies from refractory GP patients: increased CD38 infiltration in muscle layers; increased immune cells and macrophages[45]
Autoantibodies present in patients with gastroparesis symptoms	1. Several autoantibodies associated with autoimmune disorders presenting with GP symptoms,[44,46] for example, antibody to glutamic acid decarboxylase (GAD) in diabetes mellitus 2. Antinuclear antibody (ANA) titer used to screen autoimmune disorders was elevated in 17% of patients with GP, independently of GP etiology[47]
Immunomodulatory treatment improved gastroparesis symptoms	1. Retrospective study: 6 of 11 patients with refractory GP and positive GAD antibodies improved symptoms after immunotherapy, in special IVIG[49] 2. Open-label study: IVIG for 12 weeks improved GP symptoms in 9 of 14 patients with GP and identified serological and/or tissue evidence of immunological abnormality after therapy[43]

Abbreviations: ANA, antinuclear antibody; GAD, antibody to glutamic acid decarboxylase; GP, gastroparesis; IVIG, injection immunoglobulin.

gastroparesis. Whether the gastric dysmotility is secondary to food restriction, emesis, or is also influenced by patient nutritional state, and is not a primary disorder, is unclear.[76] In 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) included a new condition called avoidant/restrictive food intake disorder (ARFID), in which patients want to prevent feared negative consequences (e.g., vomiting), have low interest in eating, low appetite, or aversion to sensory characteristics of food, resulting in nutritional deficiencies.[77,78] Recently, it was shown that more than 50% of patients with gastroparesis/dyspepsia symptoms have significant symptoms of feeding and eating disorders, and almost 40% met the criteria for ARFID. In addition, although the severity of symptoms of ARFID was not associated with degree of gastric retention, it was significantly associated with gastroparesis symptom severity.[79]

Given these insights, it is extremely important, especially in younger patients with suspected gastroparesis and weight loss, to obtain a good psychiatric history to rule out ED because it can be masqueraded by delayed GE and symptoms suggestive of gastroparesis.

3.7 | Controversy #7. Do upper GI symptoms result from dysmotility beyond the stomach?

There is overlap between several disorders of gut–brain interaction and GI motility disorders.[80] In a multicenter study of patients with prior diagnosis of gastroparesis, less than 50% had delayed GE as measured by WMC, but, among patients with symptoms of gastroparesis, there was evidence of prolongation of colonic transit, suggesting that non-gastric dysmotility may also be present in gastroparesis and it could contribute to patients' symptoms.[81] In addition, a GpCRC study of 209 patients with symptoms of gastroparesis showed that more than 40% of those with suspected gastroparesis had delayed small bowel or colonic transit (each about 25%) as measured by WMC, regardless of presence or absence of delayed GE.[82] These observations are consistent with studies conducted a decade earlier by our group showing that 52% of patients presenting with chronic and/or recurrent nausea and/or vomiting had a rectal evacuation disorder and almost 16% had delayed colonic transit. These symptoms did not result from generalized motility disorders since they were not associated with delayed GE.[83]

The lower gastrointestinal disorders can manifest upper GI symptoms by induction of viscerovisceral reflexes that alter gastric functions and lead to symptoms, as has been demonstrated by effect of painless rectal distention on gastric functions in healthy volunteers.[83,84] In summary, although apparently controversial, published evidence suggests that non-gastric dysmotility is relatively common in patients with gastroparesis symptoms. Therefore, presentation with persistent upper GI symptoms may require clinical and physiological evaluation of extragastric dysmotility, particularly colonic dysmotility and rectal evacuation disorders, starting with careful history and digital rectal evaluation similar to appraisal of chronic constipation, as well as quantitative studies such as WMC or pan-gastrointestinal scintigraphy.[85]

3.8 | Controversy #8. Should gastric electrical stimulation be abandoned as nonpharmacological treatment of gastroparesis?

Whether neuromodulation via implanted electric stimulators is effective for treatment of refractory gastroparesis is still controversial in the literature. Open-label and observational studies have generally suggested substantial benefit of gastric electric stimulation, but randomized, controlled trials and systematic reviews have questioned its efficacy and led to marked reduction in the number of patients undergoing this treatment.[86,87] Furthermore, the risks associated with device implantation, such as site infection or lead migration, may occur in around 10% of patients.[88] However, three recently published articles provide reasons for pause before abandoning GES therapy, and these are summarized in Table 4.[89–91]

TABLE 4 Literature review providing rationale to perform gastric electric stimulation.

Study design/features	Results
Open-label follow-up Multicenter study[91] 142 GP +	24 months after GES implantation: • Improve quality-of-life score—GIQLI (in special nondiabetic GP) • Increased 25.5% the proportion of patients vomiting less than once per month • Decreased healthcare cost
Prospective cohort study Multicenter study[89] 238 GP+/GES− 81 GP +/GES +	48 weeks after GES implantation: • Improve: Nausea in GP+/GES + GCSI in GP+/GES +
Randomized, controlled trial[90] 172 chronic/refractory vomiting (133 GP +)	16 weeks after GES implantation: • Improved symptoms • Not improved gastric emptying • Not improved quality-of-life score

Abbreviations: GES, gastric electric stimulation; GCSI, gastroparesis cardinal symptoms index; GIQLI, gastrointestinal quality of life score; GP +, diagnosis of gastroparesis; GP +/GES -, gastroparesis without gastric electric stimulation; GP +/GES +, gastroparesis with gastric electric stimulation; GP, gastroparesis; SRMA, systematic review and meta-analysis; TD, tardive dyskinesia.

Although the overall benefit of gastric electric stimulation for refractory gastroparesis remains controversial, there is documented clinical utility in idiopathic and diabetic gastroparesis, consistent with its humanitarian approval by the FDA. In addition, a recent large multicenter study documented better outcomes with gastric electric stimulation in gastroparesis patients with refractory vomiting,[89] as shown in Table 5. Further studies should elucidate which subgroup of patients with gastroparesis or those with abnormalities on high-resolution mapping of gastric electrical control activity from the body surface would most benefit from treatment with gastric electrical stimulation.

3.9 | Controversy #9: Should endoscopic pyloromyotomy be performed in patients with gastroparesis?

After many open-label trials and systematic reviews and meta-analyses published over a decade (reviewed in Ref. [25]) had documented the efficacy in relief of symptoms of gastroparesis and enhancement of gastric emptying, typically over 3 to 6 months' follow-up, the first pilot sham-controlled trial of endoscopic pyloromyotomy (or G-POEM) was published[92] and documented a 50% reduction in total GCSI score as well as acceleration of gastric emptying of a 200 kcal, 2% fat egg-substitute meal. The trial was stopped after data on 41 patients were available, based on the data safety monitoring board recommendation when a prespecified interim analysis after 40% randomization identified greater efficacy with G-POEM compared with sham treatment. The recommendation was justified by perceived risks of general anesthesia in patients undergoing the sham procedure. The sample of the 6-month treatment trial was too small to provide conclusive evidence of efficacy in idiopathic and postsurgical.

Gastroparesis and GCSI subscores suggest that the main differences in outcome were for postprandial fullness and bloating rather than nausea/vomiting. As discussed elsewhere, the observations on the pylorus suggest that the pyloromyotomy increased the dimensions of the pylorus without significant effect on distensibility index.[93] Since detailed understanding of motor pathophysiology in the patients with gastroparesis included in the trial were not provided, it is unclear whether responders had

TABLE 5 Pathological and molecular changes in gastric tissue samples of patients with gastroparesis.

Pacemaker cells—gastric motor function		
Ref.	**Gastric sample/population**	**Results/discussion**
45	Gastric body *20 DG/20 IG* *20 controls*	Substantial loss (>50%) of ICC was found in half of patients with both IG and DG Loss of ICC correlated with the degree of delay in gastric emptying in DG
97	Gastric antrum *17 GP patients* *5 controls*	Substantial loss (more than 50%) of ICC was found in 62% of DG and 58% of IG patients.
96	Gastric tissue examined with TEM *40 GP/24 controls*	• Injury to ICC in almost all GP subjects • Loss of contact between ICCs, and between the pacemakers and nerves and muscle • Differences in severity of ultrastructural changes between DG and IG
Macrophage-driven inflammation in gastroparesis		
45	Gastric body *20 DG/20 IG* *20 controls*	Increased CD68 cells in GP (marker for macrophages and other phagocytic cells)
95	Gastric body *20 GP/20 controls*	*Imbalance in macrophage population* • Loss of CD206+ (M2 anti-inflammatory macrophages) • Loss of M2 macrophages correlated to ICC loss • M2 macrophages cell count did not differ from control
97	Gastric antrum *17 GP/5 controls*	Loss of 40–45% M2 macrophages in circular muscle Loss of >50% M2 macrophages in myenteric plexus Positive correlation between CD206+ and number of ICC
Transcriptomic and proteomic analysis of stomach		
1. Highest level of expression of Macrophages along with fibroblast and endothelial cells[98–100] 2. DG and IG ➔ unique and overlapping transcriptomic signatures[99] −65 differentially expressed genes were common in both etiologies of GP -Immune profile analysis: Genes associated with M1 macrophages (pro-inflammatory) were enriched in IG patients compared to control 3. Decreased mRNAs associated with PDGF BB signaling (fibroblast-like pacemaker cells)[100] 4. Inflammatory molecules (prostaglandins; complement proteins) →correlate with delay in GE[98,99] 5. CD206+ macrophages express HO-1 (which reverses delay GE in animal models) → polymorphism in genes encoding HO-1 have been identified in GP patients (longer alleles genes).[101,102]		

Abbreviations: DG, diabetic gastroparesis; GE, gastric emptying; GP, gastroparesis; HO-1, heme oxygenase-1; ICC, interstitial cells of Cajal; IG, idiopathic gastroparesis; TEM, transmission electron microscopy.

TABLE 6 Summary of areas for ongoing controversy and future research.

	Clinical controversies		Needing further research	
Diagnosis	WMC—capsule does not empty with the digestible solid-meal ^{13}C-GEBT—application of optimal mathematical formula is required		Validation of semi-solid/liquid nutrient meal as substrate to scintigraphy	Gastric electric dysmotility measured by high-resolution body surface mapping
Differential diagnosis	Retained gastric food during upper endoscopy is not diagnostic of gastroparesis	With suspected gastroparesis and weight loss—Rule out eating disorders even if GE is delayed	Gastroparesis and functional dyspepsia: Overlap or distinct entities?	
Etiology	Rule out non-gastric dysmotility that might be contributing to gastrointestinal symptoms.		Autoimmune gastroparesis—When to use immunomodulatory therapy	Post-viral etiology—observational data; unexplained mechanism
Treatment	Only one approved prokinetic medication (metoclopramide) Pharmacological treatment fails in 20–30% of patients Off-label medications might be an option		Gastric electrical stimulation: only one RCT in gastroparesis with refractory vomiting	G-POEM: One sham-controlled trial with benefits for diabetic gastroparesis
Pathobiological mechanisms	—		Underlying physiopathology involving pacemaker cells and macrophages	Transcriptomic and proteomic analysis of the stomach biopsies

Abbreviations: ^{13}C-GEBT, stable isotope gastric emptying breath test using ^{13}C-Spirulina; WMC, wireless motility capsule.

pylorospasm, or antral hypomotility, both or neither. Thus, further sham-controlled trials are necessary to establish the place of G-POEM in management of gastroparesis and should include detailed assessment of antropyloroduodenal function as well as pyloric distensibility.[41,42]

3.10 | Controversy #10. Is there conclusive evidence regarding the pathobiological mechanisms of gastroparesis based on histopathological or molecular studies?

The intrinsic or enteric pathological basis of gastroparesis reflects neuromuscular pathophysiology involving two populations of pacemaker cells: interstitial cells of Cajal (ICC) and platelet-derived growth factor receptor alpha (PDGFRα+) fibroblast-like cells. These cells, in addition to smooth muscle cells, are responsible for gastric motor function.[48,94] Disturbances in these structures have been demonstrated in recent studies, which examined full-thickness gastric tissues from patients with gastroparesis, and some of the results are described in Table 5.[29,45,95–102]

The molecular changes observed in pathology analysis of stomach from gastroparesis subjects may usher in new understanding about the underlying pathobiology of gastroparesis. However, there are still unresolved questions regarding sampling bias, need for robust correlation with symptoms and motor function, and need for development of appropriate treatments to reverse the pathobiology to prove the importance of these mechanisms. Unfortunately, to date, the one study with Hemin to reverse the defect in heme oxygenase-1 failed due to inadequate pharmacokinetics of the available medication that could be tested in patients with gastroparesis.[103] Therefore, further research is required to better elucidate how molecular changes could improve the management of refractory gastroparesis, and, at present, the significance of the molecular studies is unclear or controversial.

4 | CONCLUSION

Although gastroparesis is rarely considered a life-threatening condition, patients with gastroparesis carry a substantial burden with significative impact to their quality of life, as well as increased morbidity.[104] In addition, gastroparesis contributes to healthcare burden with direct and indirect economic consequences.[105] Although a recent guideline has detailed several important recommendations for management of gastroparesis,[25] the in-depth analysis shows that further studies are needed to resolve the identified controversies regarding gastroparesis, specifically related to diagnosis, differential diagnosis, etiology, treatment, and pathobiological mechanisms as summarized in Table 6, and to identify therapeutic targets to improve the management and quality of life of the patients with gastroparesis.

AUTHOR CONTRIBUTION

Both authors designed the research questions; conducted extensive literature review; wrote and revised the manuscript; and approved the final version. All authors approved the final version of the article, including the authorship list.

ACKNOWLEDGMENT

The authors thank Mrs. Cindy Stanislav for secretarial assistance.

FUNDING INFORMATION

Michael Camilleri receives funding for research on gastroparesis from National Institutes of Health (R01-DK122280 and R01-DK125680).

CONFLICT OF INTEREST

Michael Camilleri has consulted for AEON Pharma, Zealand Biopharma, Aditum Bio, Takeda, and Aclipse Therapeutics regarding the topic of gastroparesis. Gabriela Piovezani Ramos has no conflicts of interest.

ORCID

Michael Camilleri https://orcid.org/0000-0001-6472-7514

REFERENCES

1. Schol J, Wauters L, Dickman R, et al. United European gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis. *United European Gastroenterol J*. 2021;9(3):287-306.
2. Zheng T, Camilleri M. Management of gastroparesis. *Gastroenterol Hepatol (N Y)*. 2021;17(11):515-525.
3. Camilleri M, Sanders KM. Gastroparesis. *Gastroenterology*. 2022;162(1):68-87 e61.
4. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and motility society and the Society of Nuclear Medicine. *Am J Gastroenterol*. 2008;103(3):753-763.
5. Viramontes BE, Kim DY, Camilleri M, et al. Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. *Neurogastroenterol Motil*. 2001;13(6):567-574.
6. Szarka LA, Camilleri M, Vella A, et al. A stable isotope breath test with a standard meal for abnormal gastric emptying of solids in the clinic and in research. *Clin Gastroenterol Hepatol*. 2008;6(6):635-643. e631.
7. Bharucha AE, Camilleri M, Veil E, Burton D, Zinsmeister AR. Comprehensive assessment of gastric emptying with a stable isotope breath test. *Neurogastroenterol Motil*. 2013;25(1):e60-e69.
8. Cassilly D, Kantor S, Knight LC, et al. Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. *Neurogastroenterol Motil*. 2008;20(4):311-319.
9. Heckert J, Thomas RM, Parkman HP. Gastric neuromuscular histology in patients with refractory gastroparesis: relationships to etiology, gastric emptying, and response to gastric electric stimulation. *Neurogastroenterol Motil*. 2017;29(8):e13068.
10. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. American College of G. clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013;108(1):18-37. quiz 38.
11. Vijayvargiya P, Camilleri M, Chedid V, Mandawat A, Erwin PJ, Murad MH. Effects of promotility agents on gastric emptying and symptoms: a systematic review and meta-analysis. *Gastroenterology*. 2019;156(6):1650-1660.
12. Al-Saffar A, Lennernas H, Hellstrom PM. Gastroparesis, metoclopramide, and tardive dyskinesia: risk revisited. *Neurogastroenterol Motil*. 2019;31(11):e13617.
13. Camilleri M, Lembo A, McCallum R, et al. Overall safety of relamorelin in adults with diabetic gastroparesis: analysis of phase 2a and 2b trial data. *Aliment Pharmacol Ther*. 2020;51(11):1139-1148.
14. Ehrenpreis ED, Deepak P, Sifuentes H, Devi R, Du H, Leikin JB. The metoclopramide black box warning for tardive dyskinesia: effect on clinical practice, adverse event reporting, and prescription drug lawsuits. *Am J Gastroenterol*. 2013;108(6):866-872.
15. Gorelik E, Masarwa R, Perlman A, Rotshild V, Muszkat M, Matok I. Systematic review, meta-analysis, and network meta-analysis of the cardiovascular safety of macrolides. *Antimicrob Agents Chemother*. 2018;62(6):e00438-18.
16. Larson JM, Tavakkoli A, Drane WE, Toskes PP, Moshiree B. Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. *J Neurogastroenterol Motil*. 2010;16(4):407-413.
17. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol*. 2003;98(2):259-263.
18. Nelson AD, Camilleri M, Acosta A, et al. Effects of ghrelin receptor agonist, relamorelin, on gastric motor functions and satiation in healthy volunteers. *Neurogastroenterol Motil*. 2016;28(11):1705-1713.
19. Ng PC, So KW, Fung KS, et al. Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child Fetal Neonatal ed*. 2001;84(3):F177-F182.
20. Potter TG, Snider KR. Azithromycin for the treatment of gastroparesis. *Ann Pharmacother*. 2013;47(3):411-415.
21. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. *Aliment Pharmacol Ther*. 2010;31(1):11-19.
22. Shin A, Camilleri M, Busciglio I, et al. The ghrelin agonist RM-131 accelerates gastric emptying of solids and reduces symptoms in patients with type 1 diabetes mellitus. *Clin Gastroenterol Hepatol*. 2013;11(11):1453-1459 e1454.
23. Shin A, Camilleri M, Busciglio I, et al. Randomized controlled phase Ib study of ghrelin agonist, RM-131, in type 2 diabetic women with delayed gastric emptying: pharmacokinetics and pharmacodynamics. *Diabetes Care*. 2013;36(1):41-48.
24. Thielemans L, Depoortere I, Perret J, et al. Desensitization of the human motilin receptor by motilides. *J Pharmacol Exp Ther*. 2005;313(3):1397-1405.
25. Camilleri M, Kuo B, Nguyen L, et al. ACG clinical guideline: gastroparesis. *Am J Gastroenterol*. 2022;117(8):1197-1220.
26. Lacy BE, Tack J, Gyawali CP. AGA clinical practice update on management of medically refractory gastroparesis: expert review. *Clin Gastroenterol Hepatol*. 2022;20:491-500.
27. Pasricha PJ, Colvin R, Yates K, et al. Characteristics of patients with chronic unexplained nausea and vomiting and normal gastric emptying. *Clin Gastroenterol Hepatol*. 2011;9(7):567-576. e561-564, 576.e4.
28. Pasricha PJ, Grover M, Yates KP, et al. Functional dyspepsia and gastroparesis in tertiary care are interchangeable syndromes with common clinical and pathologic features. *Gastroenterology*. 2021;160(6):2006-2017.
29. Pasricha PJ, Grover M, Yates KP, et al. Progress in gastroparesis - a narrative review of the work of the gastroparesis clinical research consortium. *Clin Gastroenterol Hepatol*. 2022. doi: 10.1016/j.cgh.2022.05.022

30. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol*. 2000;95(6):1456-1462.
31. Gardella R, Silver PJ, Shahsavari D, Maurer AH, Parkman HP. Gastric half emptying time (T[1/2]) for 4-h gastric emptying scintigraphy simplifies reporting but reduces detection of gastroparesis. *Neurogastroenterol Motil*. 2022;34(5):e14261.
32. Camilleri M, Iturrino J, Bharucha AE, et al. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. *Neurogastroenterol Motil*. 2012;24(12):1076-e1562.
33. Chaudhuri TK, Fink S. Gastric emptying in human disease states. *Am J Gastroenterol*. 1991;86(5):533-538.
34. Sachdeva P, Malhotra N, Pathikonda M, et al. Gastric emptying of solids and liquids for evaluation for gastroparesis. *Dig Dis Sci*. 2011;56(4):1138-1146.
35. Ziessman HA, Chander A, Clarke JO, Ramos A, Wahl RL. The added diagnostic value of liquid gastric emptying compared with solid emptying alone. *J Nucl Med*. 2009;50(5):726-731.
36. Sachdeva P, Kantor S, Knight LC, Maurer AH, Fisher RS, Parkman HP. Use of a high caloric liquid meal as an alternative to a solid meal for gastric emptying scintigraphy. *Dig Dis Sci*. 2013;58(7):2001-2006.
37. Odunsi ST, Camilleri M, Szarka LA, Zinsmeister AR. Optimizing analysis of stable isotope breath tests to estimate gastric emptying of solids. *Neurogastroenterol Motil*. 2009;21(7):706-e738.
38. Gharibans AA, Coleman TP, Mousa H, Kunkel DC. Spatial patterns from high-resolution Electrogastrography correlate with severity of symptoms in patients with functional dyspepsia and gastroparesis. *Clin Gastroenterol Hepatol*. 2019;17(13):2668-2677.
39. Coleski R, Baker JR, Hasler WL. Endoscopic gastric food retention in relation to Scintigraphic gastric emptying delays and clinical factors. *Dig Dis Sci*. 2016;61(9):2593-2601.
40. Bi D, Choi C, League J, Camilleri M, Prichard DO. Food residue during esophagogastroduodenoscopy is commonly encountered and is not pathognomonic of delayed gastric emptying. *Dig Dis Sci*. 2021;66(11):3951-3959.
41. Zheng T, Vosoughi K, Busciglio I, Tebay L, Burton D, Camilleri M. Fasting pyloric diameter and distensibility by functional endoluminal imaging probe in unsedated healthy volunteers. *Neurogastroenterol Motil*. 2022;34:e14386.
42. Zheng T, BouSaba J, Sannaa W, Eckert DJ, Burton DD, Camilleri M. Comprehensive characterization of antral and pyloric contractions by high resolution manometry: applied physiology in suspected gastroparesis. *Am J Physiol Gastrointest Liver Physiol*. 2022;323(3):G255-G264.
43. Ashat M, Lewis A, Liaquat H, et al. Intravenous immunoglobulin in drug and device refractory patients with the symptoms of gastroparesis-an open-label study. *Neurogastroenterol Motil*. 2018;30(3):e13256.
44. Dhamija R, Tan KM, Pittock SJ, Foxx-Orenstein A, Benarroch E, Lennon VA. Serologic profiles aiding the diagnosis of autoimmune gastrointestinal dysmotility. *Clin Gastroenterol Hepatol*. 2008;6(9):988-992.
45. Grover M, Farrugia G, Lurken MS, et al. Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology*. 2011;140(5):1575-1585 e1578.
46. Jun HS, Khil LY, Yoon JW. Role of glutamic acid decarboxylase in the pathogenesis of type 1 diabetes. *Cell Mol Life Sci*. 2002;59(11):1892-1901.
47. Parkman HP, Van Natta ML, Makol A, et al. Prevalence and clinical correlates of antinuclear antibody in patients with gastroparesis. *Neurogastroenterol Motil*. 2022;34(5):e14270.
48. Sharma A, Coles M, Parkman HP. Gastroparesis in the 2020s: new treatments, new paradigms. *Curr Gastroenterol Rep*. 2020;22(5):23.
49. Soota K, Kedar A, Nikitina Y, Arendale E, Vedanarayanan V, Abell TL. Immunomodulation for treatment of drug and device refractory gastroparesis. *Results Immunol*. 2016;6:11-14.
50. Lennon VA, Sas DF, Busk MF, et al. Enteric neuronal autoantibodies in pseudoobstruction with small-cell lung carcinoma. *Gastroenterology*. 1991;100(1):137-142.
51. Besnard M, Faure C, Fromont-Hankard G, et al. Intestinal pseudoobstruction and acute pandysautonomia associated with Epstein-Barr virus infection. *Am J Gastroenterol*. 2000;95(1):280-284.
52. Debinski HS, Kamm MA, Talbot IC, Khan G, Kangro HO, Jeffries DJ. DNA viruses in the pathogenesis of sporadic chronic idiopathic intestinal pseudo-obstruction. *Gut*. 1997;41(1):100-106.
53. Vassallo M, Camilleri M, Caron BL, Low PA. Gastrointestinal motor dysfunction in acquired selective cholinergic dysautonomia associated with infectious mononucleosis. *Gastroenterology*. 1991;100(1):252-258.
54. Venkataraman S, Alexander M, Gnanamuthu C. Postinfectious pandysautonomia with complete recovery after intravenous immunoglobulin therapy. *Neurology*. 1998;51(6):1764-1765.
55. Yahr MD, Frontera AT. Acute autonomic neuropathy. Its occurrence in infectious mononucleosis. *Arch Neurol*. 1975;32(2):132-133.
56. Lobrano A, Blanchard K, Abell TL, et al. Postinfectious gastroparesis related to autonomic failure: a case report. *Neurogastroenterol Motil*. 2006;18(2):162-167.
57. Oh JJ, Kim CH. Gastroparesis after a presumed viral illness: clinical and laboratory features and natural history. *Mayo Clin Proc*. 1990;65(5):636-642.
58. Thongpooswan S, Chyn E, Alfishawy M, et al. Polyradiculopathy and gastroparesis due to cytomegalovirus infection in AIDS: a case report and review of literature. *Am J Case Rep*. 2015;16:801-804.
59. Yeh J, Wozniak LJ, Vargas JH, Ament ME. Postinfectious gastroparesis: a case series of three adolescent females. *Clin Pediatr (Phila)*. 2012;51(2):140-145.
60. Jaffe JK, Paladugu S, Gaughan JP, Parkman HP. Characteristics of nausea and its effects on quality of life in diabetic and idiopathic gastroparesis. *J Clin Gastroenterol*. 2011;45(4):317-321.
61. Bityutskiy LP, Soykan I, McCallum RW. Viral gastroparesis: a subgroup of idiopathic gastroparesis--clinical characteristics and long-term outcomes. *Am J Gastroenterol*. 1997;92(9):1501-1504.
62. Naftali T, Yishai R, Zangen T, Levine A. Post-infectious gastroparesis: clinical and electerogastrographic aspects. *J Gastroenterol Hepatol*. 2007;22(9):1423-1428.
63. Barkin JA, Czul F, Barkin JS, Klimas NG, Rey IR, Moshiree B. Gastric enterovirus infection: a possible causative etiology of gastroparesis. *Dig Dis Sci*. 2016;61(8):2344-2350.
64. Sawin-Johnson KN, Packer CD. Norovirus-induced gastroparesis. *Cureus*. 2019;11(12):e6283.
65. Hay P. Current approach to eating disorders: a clinical update. *Intern Med J*. 2020;50(1):24-29.
66. Grover M, Farrugia G, Stanghellini V. Gastroparesis: a turning point in understanding and treatment. *Gut*. 2019;68(12):2238-2250.
67. Kim BJ, Kuo B. Gastroparesis and functional dyspepsia: a blurring distinction of pathophysiology and treatment. *J Neurogastroenterol Motil*. 2019;25(1):27-35.
68. Olausson EA, Storsrud S, Grundin H, Isaksson M, Attvall S, Simren M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am J Gastroenterol*. 2014;109(3):375-385.
69. Parkman HP, Camilleri M, Farrugia G, et al. Gastroparesis and functional dyspepsia: excerpts from the AGA/ANMS meeting. *Neurogastroenterol Motil*. 2010;22(2):113-133.
70. Abell TL, Malagelada JR, Lucas AR, et al. Gastric electromechanical and neurohormonal function in anorexia nervosa. *Gastroenterology*. 1987;93(5):958-965.
71. Holt S, Ford MJ, Grant S, Heading RC. Abnormal gastric emptying in primary anorexia nervosa. *Br J Psychiatry*. 1981;139:550-552.

72. Hutson WR, Wald A. Gastric emptying in patients with bulimia nervosa and anorexia nervosa. *Am J Gastroenterol*. 1990;85(1):41-46.
73. Inui A, Okano H, Miyamoto M, et al. Delayed gastric emptying in bulimic patients. *Lancet*. 1995;346(8984):1240.
74. Robinson PH, Clarke M, Barrett J. Determinants of delayed gastric emptying in anorexia nervosa and bulimia nervosa. *Gut*. 1988;29(4):458-464.
75. Szmukler GI, Young GP, Lichtenstein M, Andrews JT. A serial study of gastric emptying in anorexia nervosa and bulimia. *Aust N Z J Med*. 1990;20(3):220-225.
76. Stanculete MF, Chiarioni G, Dumitrascu DL, Dumitrascu DI, Popa SL. Disorders of the brain-gut interaction and eating disorders. *World J Gastroenterol*. 2021;27(24):3668-3681.
77. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (DSM)*. 5th ed. American Psychiatric Association; 2013.
78. Thomas JJ, Lawson EA, Micali N, Misra M, Deckersbach T, Eddy KT. Avoidant/restrictive food intake disorder: a three-dimensional model of neurobiology with implications for etiology and treatment. *Curr Psychiatry Rep*. 2017;19(8):54.
79. Burton Murray H, Jehangir A, Silvernale CJ, Kuo B, Parkman HP. Avoidant/restrictive food intake disorder symptoms are frequent in patients presenting for symptoms of gastroparesis. *Neurogastroenterol Motil*. 2020;32(12):e13931.
80. Locke GR 3rd, Zinsmeister AR, Fett SL, Melton LJ 3rd, Talley NJ. Overlap of gastrointestinal symptom complexes in a US community. *Neurogastroenterol Motil*. 2005;17(1):29-34.
81. Sarosiek I, Selover KH, Katz LA, et al. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. *Aliment Pharmacol Ther*. 2010;31(2):313-322.
82. Hasler WL, May KP, Wilson LA, et al. Relating gastric scintigraphy and symptoms to motility capsule transit and pressure findings in suspected gastroparesis. *Neurogastroenterol Motil*. 2018;30(2). doi: 10.1111/nmo.13196
83. Kolar GJ, Camilleri M, Burton D, Nadeau A, Zinsmeister AR. Prevalence of colonic motor or evacuation disorders in patients presenting with chronic nausea and vomiting evaluated by a single gastroenterologist in a tertiary referral practice. *Neurogastroenterol Motil*. 2014;26(1):131-138.
84. Youle MS, Read NW. Effect of painless rectal distension on gastrointestinal transit of solid meal. *Dig Dis Sci*. 1984;29(10):902-906.
85. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med*. 2003;349(14):1360-1368.
86. Levinthal DJ, Bielefeldt K. Systematic review and meta-analysis: gastric electrical stimulation for gastroparesis. *Auton Neurosci*. 2017;202:45-55.
87. O'Grady G, Egbuji JU, Du P, Cheng LK, Pullan AJ, Windsor JA. High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis. *World J Surg*. 2009;33(8):1693-1701.
88. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology*. 2003;125(2):421-428.
89. Abell TL, Yamada G, McCallum RW, et al. Effectiveness of gastric electrical stimulation in gastroparesis: results from a large prospectively collected database of national gastroparesis registries. *Neurogastroenterol Motil*. 2019;31(12):e13714.
90. Ducrotte P, Coffin B, Bonaz B, et al. Gastric electrical stimulation reduces refractory vomiting in a randomized crossover trial. *Gastroenterology*. 2020;158(3):506-514 e502.
91. Gourcerol G, Coffin B, Bonaz B, et al. Impact of gastric electrical stimulation on economic burden of refractory vomiting: a French Nationwide multicentre study. *Clin Gastroenterol Hepatol*. 2020;20(8):1857-1866.e1.
92. Martinek J, Hustak R, Mares J, et al. Endoscopic pyloromyotomy for the treatment of severe and refractory gastroparesis: a pilot, randomised, sham-controlled trial. *Gut*. 2022;71:2170-2178.
93. Camilleri M. Choosing G-POEM or other treatments for gastroparesis. *Gut*. 2022;71:2145-2146.
94. Sanders KM, Kito Y, Hwang SJ, Ward SM. Regulation of gastrointestinal smooth muscle function by interstitial cells. *Physiology (Bethesda)*. 2016;31(5):316-326.
95. Bernard CE, Gibbons SJ, Mann IS, et al. Association of low numbers of CD206-positive cells with loss of ICC in the gastric body of patients with diabetic gastroparesis. *Neurogastroenterol Motil*. 2014;26(9):1275-1284.
96. Faussone-Pellegrini MS, Grover M, Pasricha PJ, et al. Ultrastructural differences between diabetic and idiopathic gastroparesis. *J Cell Mol Med*. 2012;16(7):1573-1581.
97. Grover M, Bernard CE, Pasricha PJ, et al. Diabetic and idiopathic gastroparesis is associated with loss of CD206-positive macrophages in the gastric antrum. *Neurogastroenterol Motil*. 2017;29(6):e13018.
98. Grover M, Dasari S, Bernard CE, et al. Proteomics in gastroparesis: unique and overlapping protein signatures in diabetic and idiopathic gastroparesis. *Am J Physiol Gastrointest Liver Physiol*. 2019;317(5):G716-G726.
99. Grover M, Gibbons SJ, Nair AA, et al. Transcriptomic signatures reveal immune dysregulation in human diabetic and idiopathic gastroparesis. *BMC Med Genomics*. 2018;11(1):62.
100. Herring BP, Chen M, Mihaylov P, et al. Transcriptome profiling reveals significant changes in the gastric muscularis externa with obesity that partially overlap those that occur with idiopathic gastroparesis. *BMC Med Genomics*. 2019;12(1):89.
101. Choi KM, Gibbons SJ, Nguyen TV, et al. Heme oxygenase-1 protects interstitial cells of Cajal from oxidative stress and reverses diabetic gastroparesis. *Gastroenterology*. 2008;135(6):2055, e2051-2052-2064.
102. Gibbons SJ, Grover M, Choi KM, et al. Repeat polymorphisms in the Homo sapiens heme oxygenase-1 gene in diabetic and idiopathic gastroparesis. *PLoS One*. 2017;12(11):e0187772.
103. Bharucha AE, Daley SL, Low PA, et al. Effects of hemin on heme oxygenase-1, gastric emptying, and symptoms in diabetic gastroparesis. *Neurogastroenterol Motil*. 2016;28(11):1731-1740.
104. Jung HK, Choung RS, Locke GR 3rd, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology*. 2009;136(4):1225-1233.
105. Chen YJ, Tang W, Ionescu-Ittu R, et al. Health-care resource use and costs associated with diabetic and idiopathic gastroparesis: a claims analysis of the first 3 years following the diagnosis of gastroparesis. *Neurogastroenterol Motil*. 2022;34(9):e14366.

How to cite this article: Ramos GP, Camilleri M. Ten controversies IN gastroparesis and a look to the future. *Neurogastroenterology & Motility*. 2022;00:e14494. doi: 10.1111/nmo.14494