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Gastroparesis

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Abstract

Gastroparesis is a disorder characterized by delayed gastric emptying of solid food in the absence of a mechanical obstruction of the stomach, resulting in the cardinal symptoms of early satiety, postprandial fullness, nausea, vomiting, belching and bloating. Gastroparesis is now recognized as part of a broader spectrum of gastric neuromuscular dysfunction, which includes impaired

gastric accommodation. The overlap between upper gastrointestinal symptoms makes the distinction between gastroparesis and other disorders, such as functional dyspepsia, challenging. Thus, a confirmed diagnosis of gastroparesis requires measurement of delayed gastric emptying via an appropriate test, such as gastric scintigraphy or breath testing. Gastroparesis can have idiopathic, diabetic, iatrogenic, post-surgical, or post-viral aetiologies. The management of gastroparesis involves correcting fluid, electrolyte and nutritional deficiencies, identifying and treating the cause of delayed gastric emptying (for example, diabetes mellitus); and suppressing or eliminating symptoms with pharmacological agents as first line therapies. Several novel pharmacologic agents and interventions are currently in the pipeline and show promise to help tailor individualized therapy for patients with gastroparesis.

[H1] Introduction

A key function of the stomach is to produce acid and facilitate the peptic digestion of food. In addition to this, the main motor functions of the stomach are accommodation, which allows the delivery and storage of food, followed by trituration (grinding of food into fragments) and emptying of solid food. Gastroparesis is a chronic disorder that is characterized by delayed emptying of the stomach after eating (gastric emptying), in the absence of any mechanical obstruction, particularly pyloric stenosis[1]. Cardinal symptoms include early satiety after eating, postprandial fullness, nausea, vomiting, belching and bloating. The syndrome is caused by neuromuscular dysfunction that leads to delayed gastric emptying. To elaborate, the basic mechanisms that lead to gastroparesis involve derangements in extrinsic neural control (particularly vagal function), dysfunction of the intrinsic nerves and interstitial cells involved in local control of gastrointestinal muscle function, and the loss of function of smooth muscles.

Gastroparesis can be idiopathic, associated with diabetes mellitus, can occur after a medical intervention (iatrogenic or post-surgical), may be associated with neurological disorders or may occur after a viral or bacterial infection, such as Salmonella gastroenteritis[2] . Interestingly, Helicobacter pylori infection does not seem to influence gastric emptying or accommodation, but may be associated with heightened sensitivity in patients with functional dyspepsia (a disorder associated with accelerated or delayed gastric emptying, impaired gastric accommodation and heightened sensitivity in the upper gastrointestinal tract)[3,4]. Rarely, specific viral infections caused by herpes virus or Epstein–Barr virus may be associated with acute

dysautonomia that results in a generalized motility disorder including gastroparesis[5]. In addition, many other conditions such as Parkinson's disease, collagen vascular diseases (such as systemic sclerosis), chronic intestinal pseudo-obstruction, and other conditions can lead to gastroparesis or delayed gastric emptying (Box 1). All of these causes ultimately induce gastroparesis through induction of neuromuscular dysfunction.

In recent years, suggestions have been made to change the definition of gastroparesis to "gastroparesis and related disorders", therefore recognizing the disorder as part of a broader spectrum of gastric neuromuscular dysfunction[6]. There is symptom overlap between gastroparesis and postprandial distress syndrome, which is one of the recognized types of functional dyspepsia[7]. Functional dyspepsia may be associated with accelerated or delayed gastric emptying, impaired gastric accommodation and heightened sensitivity in the upper gut[8,9]. With the availability of measurements of gastric volume with scintigraphy, single photon emission computed tomography (SPECT), or MRI, disorders of gastric accommodation, which result typically from functional dyspepsia or prior gastric surgery (such as fundoplication or vagal injury or vagotomy) can be differentiated from gastroparesis. Thus, the term gastroparesis should be restricted to disorders in which upper gastrointestinal symptoms are associated with delayed gastric emptying.

In this Primer, we cover mechanisms of gastric innervation and emptying, before describing how these pathways are perturbed in gastroparesis. We review epidemiological data and diagnosis of gastroparesis and the effective management of this disorder. Finally, we discuss future research directions.

[H1] Epidemiology

Describing the global epidemiology of gastroparesis is challenging, as some symptoms of gastroparesis, such as upper abdominal pain or discomfort, belching, bloating, and early satiety overlap with those of functional dyspepsia[10,11]. One important aetiology of gastroparesis is diabetes mellitus; in one tertiary referral series, diabetes mellitus accounted for almost 1/3 of all cases of gastroparesis.[12] Notably, symptoms attributable to gastroparesis are reported by 5–12% of patients with diabetes mellitus[13]. In clinical practice, there are approximately equal numbers of patients with type 1 and type 2 diabetes being evaluated for upper gastrointestinal symptoms, as documented in the NIH Gastroparesis Consortium database[11]. However, community-based

studies among patients with diabetes and age-stratified and sex-stratified controls showed a similar prevalence of upper gastrointestinal (GI) symptoms in both type 1 and 2 diabetes, in studies from the United States and Australia[14,15]. Thus, documentation of delayed gastric emptying via gastric scintigraphy or breath testing is required in order to distinguish between gastroparesis and functional dyspepsia. As a result, most natural history studies of gastroparesis have been conducted in referral populations, with very few community-based studies. In addition, most epidemiological data describing the burden of gastroparesis are from the United States.

[H2] Incidence and prevalence

A population-based study in Minnesota estimated that the age-adjusted incidence of gastroparesis during a 10-year period was 2.4 cases per 100,000 person-years for men, and 9.8 cases per 100,000 person-years for women; prevalence was estimated to be 9.6 cases per 100,000 individuals for men, and 37.8 cases per 100,000 individuals for women[16]. Some individuals with typical symptoms of gastroparesis may never undergo confirmatory testing; one study estimated that as many as 1.8% of the general population may have gastroparesis, but only 0.2% are diagnosed.[17] Presumably, this relates to a lack of awareness of the disorder, and existing diagnostic confusion caused by an overlap between the symptoms of gastroparesis and functional dyspepsia. The same study reported that consultation rates were similar between those with symptoms typical for gastroparesis and those with functional dyspepsia, however, those with gastroparesis-like symptoms were unlikely to undergo a gastric emptying test[17]. Given that current estimates of prevalence are based on clinical data obtained from patients who sought medical attention, these estimates may be too low, as they could be impacted by healthcare-seeking behavior among patients with symptoms suggestive of gastroparesis.

[H2] Risk factors

The reason for the higher incidence and prevalence of gastroparesis in women is unclear. However, stomach motility is dependent on neuronal nitric oxide synthesis, and this pathway may be regulated by estrogen.[18,19] Few studies exist concerning the effect of body mass on gastroparesis. In one study of patients with type 2 diabetes, obesity was associated with an almost 10-fold increase in the odds of reporting gastroparesis symptoms[20] . Another study

demonstrated an association between higher body mass index and delayed gastric emptying on scintigraphy in a cohort of 140 Indian patients with type 2 diabetes.[6] Interestingly, it has been reported that almost 50% of patients with idiopathic gastroparesis are overweight or obese, and that symptom patterns differ according to body mass; patients who were obese or overweight had statistically significant lower scores for loss of appetite and inability to finish a meal, but statistically significantly worse scores for gastroesophageal reflux-type symptoms compared to patients of a healthy weight[11] . The role of other modifiable risk factors, such as smoking or alcohol, in gastroparesis is unproven even though sizeable proportions of patients with diabetes mellitus and control individuals used tobacco or alcohol in the same epidemiological study.[11] In one longitudinal follow-up study conducted among 262 patients with gastroparesis, treated according to the current standard of care in the USA, a history of smoking was significantly associated with no improvement in symptoms during 48 weeks of follow-up[21].

[H3] Diabetic gastroparesis.

Among a historical cohort of patients with diabetes mellitus and control individuals (269 with type 1 diabetes; 409 with type 2 diabetes; and 735 control individuals) the cumulative proportions who developed gastroparesis (based on delayed gastric emptying by standard scintigraphy or gastroparesis symptoms for >3 months plus a physician diagnosis of gastroparesis or food retention on endoscopy or upper gastrointestinal radiology) over a 10-year period were 5.2% of patients with type 1 diabetes, 1.0% of patients with type 2 diabetes, and 0.2% of control individuals.[22] By contrast, in referral populations of patients with type 1 or type 2 diabetes mellitus, the prevalence of individual symptoms suggestive of gastroparesis is between 25–53%[23], the cardinal symptoms occur in 10%,[24,25] and a clinical diagnosis of gastroparesis is made in almost 5% of patients.[13] The presence of presumed gastroparesis in patients with diabetes mellitus is associated with other end-organ damage, including retinopathy and peripheral neuropathy, higher mean levels of glycosylated haemoglobin (HbA1c, which is a measure of glycemic control over the prior three months), and lower socioeconomic status.[13,24]

The seminal studies of the long-term complications of type 1 diabetes are the Diabetes Control and Complications Trial (DCCT) and its follow-up, Epidemiology of Diabetes Interventions and Complications (EDIC). A recent report indicates that delayed gastric emptying was common (~47%) in the DCCT/EDIC cohort,[26] which is consistent with the outcomes of

cross-sectional studies.[27] Improvements in glycemic control in patients with diabetes mellitus are associated with decreases in the incidence of microvascular complications and it would not be surprising if the incidence of diabetic gastroparesis were also to decrease. In agreement with this, individuals with longstanding type 2 diabetes without evidence of autonomic impairment are usually reported to have normal gastric emptying[28].

Among patients with diabetes mellitus, once delayed gastric emptying is established, it may persist for up to 25 years of follow-up, despite evidence of improved glycemic control.[29-31] Interestingly, hospitalization rates and emergency department consultations for gastroparesis appear to be on the rise,[32-34] which is possibly owing to both an increase in awareness of gastroparesis as a potential cause of upper GI symptoms and the increased prevalence of both type 1 and type 2 diabetes.[35] Hospital admissions for exacerbation of symptoms in patients with gastroparesis are influenced by glycemic control, infection rates (most frequently urinary tract infections), and poor adherence with or intolerance of medications[36]. There are regional variations in inpatient management of patients with diabetic gastroparesis, which are likely to reflect local differences in healthcare delivery.[37] Mortality during a hospital stay has been estimated at 1.2%, mostly related to comorbidities.[38] During a 16-year period in the United States, mean hospital charges per patient for management of gastroparesis increased by 160%, and the national bill increased over 10-fold.[34]

[H2] Life expectancy

In terms of the effect of gastroparesis on life expectancy, data are conflicting. Studies conducted in referral populations demonstrate no effect of delayed gastric emptying on mortality among patients with diabetes mellitus, after 12 years of follow up in one study[39] and 25 years in a second study.[31] However, in a community-based survey in Minnesota, USA, among individuals with gastroparesis of mixed etiology (typcially documented by symptoms and delayed gastric emptying by scintigraphy or gastric food retention on imaging reports), survival was lower than expected for age- and sex-matched individuals without gastroparesis.[16]

[H1] Mechanisms/pathophysiology

Although there have been advances in understanding the mechanisms and pathophysiology of gastroparesis, there are still significant gaps in knowledge, inconsistencies across studies, potential differences between different aetiological groups (for example, diabetic versus idiopathic) and therefore individualization of therapy is currently best achieved by carefully identifying functional impairment rather than cellular mechanisms. One example is the recognition of concomitant reduction in gastric accommodation among patients presenting with symptoms suggestive of gastroparesis.

Gastroparesis and impaired gastric accommodation result from neuromuscular dysfunction of the stomach. Trituration of food in the stomach grinds food into fragments; food fragments are liquefied by a combination of gastric acid digestion and antral contractions; these contractions establish high liquid shearing forces and propel food particles against the closed pylorus before ~1–2mm sized particles are emptied into the duodenum.[40,41] Vagal innervation of the stomach by the vagus afferent nerve is essential for the gastric accommodation of consumed food. The antral contractions that are essential for triturating solid food and gastric emptying are mediated by extrinsic vagal innervation and intrinsic cholinergic neurons. In addition, intrinsic inhibitory mechanisms, such as nitrergic neurons, facilitate pyloric relaxation and intragastric peristalsis. Nitrergic neurons are pivotal for the relaxation of GI muscle ahead of a contraction, and they are responsible for descending inhibition ahead of the upstream contraction, which is induced by excitatory neurons, such as cholinergic and tachykininergic neurons.[42] These inhibitory and excitatory neural effects are transmitted through interstitial cells of Cajal (ICC) and possibly other fibroblast-like cells that have pacemaker function, and to smooth muscle cells in GI muscles, which causes the muscular layer of the stomach to behave as a multicellular electrical syncytium, so that coordinated contractions, which initiate in the proximal stomach and involve the entire circumference of the stomach, can propagate towards the antropyloric region. This electrical syncytium consists of smooth muscle cells, ICC and fibroblast-like cells, which are positive for platelet-derived growth factor receptor alpha (PDGFRα).[43] The ICCs and PDGFRα-positive cells are considered to be pacemaker cells in the GI tract and possess the ability to transmit electrical signals (**Figure 1**). In gastroparesis, delayed gastric emptying is associated with antral hypomotility and, in some patients, with pyloric sphincter dysfunction caused by neuromuscular dysfunction.

[H2] Intrinsic neuropathy

Recent studies have explored the histopathological features and expression of neurotransmitters in the intrinsic mechanisms involved in gastric motor function (**Figure 2**). Light microscopy examination of full thickness gastric biopsies from 20 patients with idiopathic gastroparesis, 20 patients with diabetic gastroparesis, and 20 controls individuals undergoing gastric bypass surgery, demonstrated no statistically significant differences between diabetic and idiopathic gastroparesis in nine morphological endpoints; these were protein gene product 9.5 (expressed in the cytoplasm of neurons and serving as a marker of nerve cells), vasoactive intestinal peptide (an inhibitory neurotransmitter), substance P (an excitatory neurotransmitter), tyrosine hydroxylase (an enzyme expressed in adrenergic neurons), protein S100β (a marker of glia), mast/stem cell growth factor receptor Kit (a cell surface marker of ICC), CD45 (cell surface marker of lymphocytic immune cells) and CD68 (a cell surface marker for monocytic immune cells), and smoothelin (a marker of smooth muscle cells). However, there were reduced numbers of inhibitory neurons expressing neuronal nitric oxide synthase (nNOS) in patients with gastroparesis, with decreased nNOS neurons in 40% of patients with idiopathic gastroparesis and in 20% of patients with diabetic gastroparesis compared to control individuals. The reduction in nNOS-positive neurons may contribute to impaired gastric emptying by reducing the coordination of gastric peristalsis that is essential to establish trituration of solid food in the gastric antrum.[44] Some, but not all reports have shown reductions in numbers of ICCs in the body of the stomach of patients with both diabetic and idiopathic gastroparesis[45,46]; such a reduction in ICCs would be expected to impair conduction of electrical activity through the electrical syncytium and, therefore, interfere with coordinated gastric electrical rhythms, peristalsis, trituration and gastric emptying. However, it is still unclear whether damage to ICCs or reductions in their number results in symptom generation. In contrast to patients with diabetic gastroparesis, biopsies from patients with idiopathic gastroparesis showed altered smooth muscle cell contractile protein expression and loss of PDGFRα^{+} cells without a significant change in the numbers of ICCs.[46]

[H3] Involvment of the immune system.

The reduction in or damage to ICCs in the stomach of some patients with gastroparesis was associated with reduction in the numbers of anti-inflammatory M2 macrophages, which normally express mannose receptor (CD206) and heme oxygenase-1 (HO1), and mediate cell repair.[45] The reduction in M2 macrophages reduces the protection of neural tissue from the effects of oxidative stress and inflammation, both of which are mechanisms involved in the pathophysiology of diabetes mellitus,[47] and may conceivably result in gastric intrinsic neural dysfunction.

Studies have provided discordant information on immune cells in biopsies; reduced numbers of M2 macrophages in one study,[45] but numbers comparable with healthy tissuein a separate study.[46] These contradictory observations on M2 macrophages are complicated by the fact that the function of the vagus nerve (which affects immune cell function) was not tested in relation to the histopathological findings, and vagal neuropathy is associated with diabetic gastroparesis. Indeed, efferent vagus signals activate and thereby release noepinephrine from splenic nerves, and the transmitter activates β2-adrenergic receptor (β2AR) expressed on T cells, which activates T cells to release acetylcholine (Ach), which acts on the α7 nicotinic acetylcholine receptor (α7 nAChR) on macrophages and other immune cells. Ultimately, the complete vagus stimulated pathway suppresses the release of pro-inflammatory cytokines.[48] Interestingly, another study found that counts of ICCs were inversely correlated with 4-hour gastric retention in patients with diabetic gastroparesis (that is slower gastric emptying was associated with higher numbers of ICC in the circular muscle per field), and myenteric immune infiltrate was associated with overall clinical severity and nausea in patients with idiopathic gastroparesis.[49] The relationship between hyperglycemia, oxidative metabolism, ICCs, and gastric emptying is the subject of ongoing research.[50]

[H3] Heme oxygenase 1.

HO1 attenuates the overall production of reactive oxygen species. In gastric tissues obtained from animal models (tested predominantly in non-obese diabetic mice), loss of HO1 leads to increased oxidative stress, loss of Kit expression (implying predominantly a loss of ICCs) and decreased expression of neuronal nitric oxide synthase, and the development of delayed gastric

emptying. Expression of HO1 is low in the muscularis propria of stomach under normal conditions, whereas HO1 is markedly upregulated in muscularis propria resident macrophages after diabetes develops in a nonobese diabetic mouse model.[51] These observations led to the hypothesis that when macrophages are not producing HO1 to reduce oxidative stress (a frequent consequence of diabetes, for example, in the causation of neuropathy), the intrinsic mechanisms that are responsible for normal motor function are damaged. Interestingly, alterations in the activity of HO1 that may result from variation in a gene controlling its synthesis supports the potential association of impaired HO1 function and development of gastroparesis. For the HMOX1 gene promoter, sequences containing longer polyGT repeats had lower transcriptional activity than sequences with fewer repeats[52,53]; therefore, shorter polyGT repeat alleles result in higher expression of HO1 protein. A recent study showed that polyGT alleles in the HO1 gene (HMOX1) are longest in patients with type 2 diabetes and gastroparesis, and the promoters were longer in patients with gastroparesis (idiopathic or diabetic) compared to control individuals.[54] However, in all the patient groups with gastroparesis studied, allele lengths were longer in African Americans compared to other ethnic groups, and the differences in the proportion of African Americans in the groups may have accounted for at least some of the differences between patients with gastroparesis and control individuals. It is still unclear whether this genetic variant is actually more prevalent in patients with gastroparesis and how it might contribute to dysfunction of the intrinsic mechanisms that impair gastric emptying.

[H3] *PDGFRα*$^{+}$ fibroblasts.

Recent insights suggest there may be abnormalities in PDGFRα^{+} fibroblasts in patients with gastroparesis. These fibroblasts were reduced in number in gastric biopsy samples from patients with idiopathic gastroparesis with increased numbers of CD68^{+} monocytes, but no change in the numbers of ICCs in one study[46]. By contrast, a second study found that PDGFRα fibroblast-like cells were not altered in distribution or overall numbers in idiopathic or diabetic gastroparesis.[55] In summary, the underlying neuromuscular and neuroimmune mechanisms of gastroparesis are currently unclear due to discordant study results, and further research is required.

[H2] Diabetic Gastroparesis

Diabetic gastroparesis is multifactorial with contributions from hyperglycemia, extrinsic (vagal) denervation, and intrinsic neural denervation (discussed above). In general, the mechanisms do not appear to differ between type 1 and type 2 diabetes, probably because gastroparesis tends to occur years after diagnosis with diabetes mellitus typically in association with other features such as neuropathy (Box 2) and oxidative stress that occur in both type 1 and 2 diabetes.

[H3] Hyperglycemia.

The role of hyperglycemia in the pathophysiology of diabetic gastroparesis is unclear. This has been evaluated in epidemiological studies, in human studies with experimental acute hyperglycemia and in natural history studies of diabetes control. There is epidemiological evidence of associations of hyperglycemia with upper GI symptoms,[56] and studies document poor glycemic control in 36% of patients admitted to a hospital in the U.S. for exacerbations of diabetic gastroparesis.[36] Kidney and pancreas transplant probably have significant beneficial impacts on gastric emptying and associated GI symptoms, which suggests that control of hyperglycemia may be beneficial for gastroparesis.[57]

In human experiments that imposed acute hyperglycemia, typically 8mmol/L (144mg/dL) (typically associated with glucose clamp studies (in which the blood glucose is increased and maintained by infusion of glucose) there were definite effects on gastric functions; an inhibition of antral contractility and delayed gastric emptying during hyperglycemic clamp compared to euglycemia, and a dose-dependent slowing of gastric emptying with hyperglycemia (even in the range observed postprandially) when compared to euglycemia. Similarly, clamping blood glucose at 250mg/dL was associated with induction of gastric dysrhythmias in healthy human volunteers.[5859,60] This is in contrast to the effect of insulin-induced hypoglycemia (defined as blood glucose ~2.6 mmol/L) which markedly accelerates gastric emptying, possibly through stimulation of vagal function. This acceleration of gastric emptying is likely to be important in the counter-regulation of hypoglycemia.[61]

Natural history studies provide uncertain evidence of the relationship between glycemic control and gastric emptying. In a study of 129 patients, HbA1c was not a statistically significant predictor of abnormal) gastric emptying of solids using scintigraphy (discussed below).[62] In addition, long-term blood glucose levelshad no apparent association with gastric emptying in

type 2 diabetes.[63] By contrast, in the DCCT/EDIC cohort comprising exclusively patients with type 1 diabetes, gastroparesis was associated with relatively worse glycemic control compared to diabetic patients with better glycemic control as assessed by HbA1c[26] It is also uncertain whether improving chronic hyperglycemia over a relatively short term results in a meaningful improvement in gastric emptying. Improved glycemic control has, hitherto, been reported to not be associated with any change in gastric emptying in patients with delayed gastric emptying in type 1 or type 2 diabetes,[64,65] apart from one uncontrolled study.[66] Further studies are required to appraise the relationship of long-term hyperglycemia and gastric emptying.

[H2] Iatrogenic and surgical gastroparesis

The most common surgical association with gastroparesis is with fundoplication and bariatric procedures and the most common iatrogenic associations are with μ-opioid agonists and hypoglycemic agents such as amylin analogs (for example, pramlintide) or glucagon-like peptide-1 (GLP-1) analogs or agonists (for example, liraglutide and exenatide) but not dipeptidyl peptidase IV inhibitors such as vildagliptin and sitagliptin which increase GLP-1, improves glycemia without delaying gastric emptying.[67] Medications used in the treatment of Parkinsonism including levodopa and anticholinergic medications may also cause iatrogenic gastroparesis.

[H3] Post-surgical gastroparesis.

Post-surgical gastroparesis is generally caused by to damage to or entrapment of the vagus nerve, and this occurs most commonly with fundoplication or bariatric surgical interventions, as truncal vagotomy for peptic ulceration is now rarely performed. Although laparoscopic sleeve gastrectomy has been associated with aberrant distal ectopic pacemaking in the human stomach[68], there was no evidence that this caused delay in gastric emptying; in fact, the typical effect of LSG is acceleration of gastric emptying.[69]

Rarer forms of post-surgical gastroparesis result from Billroth I and II gastrectomy (which are rarely performed nowadays for treatment of peptic ulceration) sometimes accompanied by vagotomy, as well as partial esophagectomy for esophageal cancer or heart transplantation which involve resection of the vagus nerve.

[H3] Opioids.

Mu- Opioids such as codeine, oxycodone and morphine, have pharmacological effects throughout the GI tract. They decrease gastric emptying and stimulate pyloric tone, inhibit propulsion, increase the amplitude of non-propulsive segmental contractions, increase fluid absorption in the small and large intestine, increase anal sphincter tone, and impair reflex relaxation of the anal sphincter in response to rectal distention.[70] At the cellular level, opioids inhibit adenylate cylase and nerve terminal Ca^{2+} channels and activate K^{+} channels, leading to an inhibition of Ach release from enteric interneurons and purine/nitric oxide release from inhibitory motor neurons.[71] In the stomach, opioids stimulate pyloric sphincter tone and phasic pressure, and inhibit gastric motility such as antral contractility,[72,73] resulting in impaired gastric emptying, postprandial nausea and early satiety.[70] Many recent series of patients with gastroparesis show relatively high prevalence of concomitant treatment with opioids and central neuromodulator drugs, such as antidepressants (74-77).

The effects of opioids on gastroparesis are illustrated by the report from Temple University in 223 patients with gastroparesis: 70.9% not taking opioids, 9.9% taking opioids only as needed, 19.3% on chronic scheduled opioids for at least 1 month; of the latter group, 8.1% were on opioids for gastroparesis and/or stomach pain. The patients on chronic scheduled opioidscompared to non-opioid controls with gastroparesis had higher symptom severity, lower employment rate, and higher rates of hospitalizations over 1 year, and worse outcomes with treatment for gastroparesis with prokinetics agents and gastric electrical stimulation.[78,79] These data have to be assessed in the context that higher hospitalization rates and resource utilization are common to chronic opioid users in general and are not unique to those with gastroparesis.

[H2] Post-viral

Post-infectious dyspepsia has been described in the literature, but the evidence is rather weak as it is based on presence of symptoms such as myalgia during the acute onset of symptoms rather than serological or tissue demonstration of viral etiology. Gastroparesis has been rarely associated with specific viral infections, for example, Epstein-Barr virus, norovirus, herpes virus and cytomegalovirus usually in association with the development of autonomic dysfunction such as postural hypotension or abnormal sweating; this form of post-viral gastroparesis in the setting of dysautonomia has a poor prognosis.[5] A viral illness preceding the onset of gastroparesis is

generally associated with a good prognosis when patients are followed for ~1 year.[80,81] The few available literature reports do not provide data on the typical time lag from virus infection to development of gastroparesis, or whether there are any genetic or acquired factors that predispose to the development of post-viral gastroparesis.

[H2] Other causes of gastroparesis

Gastric neuromuscular disorders may result from extrinsic denervation, intrinsic neuropathy, disorders of pacemaker cells or of smooth muscle. Smooth muscle disorders (myopathic disorders) may be infiltrative (for example, scleroderma) or degenerative (for example, hollow visceral myopathy, amyloidosis, and rarely, mitochondrial cytopathy). Myopathic disorders are invariably associated with a component of more generalized motility disorder affecting other regions of the gut, for example, small bowel, lower esophageal sphincter (LES) and esophagus. Moreover, scleroderma is associated with systemic features such as CREST (calcinosis, Raynaud's, esophageal, sclerodactyly and telangiectasia) syndrome, and there may be external ophthalmoplegia or skeletal muscle involvement in mitochondrial cytopathy. The degeneration of smooth muscle cells and/or surrounding fibrosis is considered to be the mechanism underlying the impairment of gastric emptying in these disorders.

[H1] Diagnosis, screening and prevention

In general, the severity of gastroparesis is assessed by the degree of nutritional impairment or weight loss, or the degree of delay to gastric emptying (for example, the proportion of food retained in the stomach at 4 hours), which will be impacted by the method and meal used to assess the overall function of the stomach. Several symptom severity scales also exist to assess clinical signs and symptoms.

[H2] Clinical Signs and Symptoms

The clinical symptoms of gastroparesis include nausea, vomiting, early satiety, postprandial fullness, bloating, belching and upper abdominal discomfort which may overlap with symptoms observed in functional dyspepsia and accelerated gastric emptying.[82,83] Several symptom severity scales exist, which are used as patient-reported symptom assessments in gastroparesis, including

the Gastroparesis Symptom Index (GCSI), which is based on the comprehensive Patients Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYMP)[84], and the revised GCSI-Daily Diary (GCSI-DD).[85] These scales have been used in clinical trials to assess the effects of treatment in clinical studies of gastroparesis. However, the scales have not been utilized for assessment of symptoms in clinical practices, such as deciding whether patients should undergo diagnostic studies of diverse gastric functions.

[H3] Clustered symptoms.

The cardinal symptoms of gastroparesis typically occur in combination, not as individual symptoms. In a cohort of 483 patients with type 1 and 2 diabetes mellitus, upper GI symptoms occurred in clusters, for example, pain with early satiety and heartburn; heartburn with bloating, early satiety, nausea and vomiting; and regurgitation with bloating, nausea and vomiting.[86] The symptoms of idiopathic and diabetic gastroparesis are similar, although vomiting and early satiety are more frequent in diabetic gastroparesis and pain is more frequent in idiopathic gastroparesis.[74]

[H3] Nausea and vomiting.

Nausea is a highly prevalent symptom in patients with gastroparesis, irrespective of aetiology, and it is frequently associated with vomiting.[74,75] As mentioned above, vomiting occurs more often in diabetic gastroparesis than in idiopathic gastroparesis. However, in patients with idiopathic gastroparesis from the NIH Gastroparesis Cohort of 393 patients a severe delay in gastric emptying was associated with more severe symptoms of vomiting.[11]

[H3] Pain.

In the NIH Consortium Gastroparesis Cohort, the predominant symptoms were pain and/or discomfort in 21% of patients (in two-thirds of these patients, this pain was graded at moderate or severe) and nausea and/or vomiting in 44% of patients. The presence of pain was not associated with the results of gastric emptying test, or with presence of diabetic neuropathy or control of diabetes.[87]

[H3] Early satiety.

Severe early satiety and postprandial fullness are common in both diabetic and idiopathic gastroparesis, and severity is associated with the severity of other gastroparesis symptoms, that is, body weight, gastric emptying, and the volume of water that a patient is able to consume at a constant rate in a water load test.[76]

[H3] Bloating.

Bloating is prevalent in patients with gastroparesis, with 41% of patients reporting mild symptoms and 14% of patients reporting severe symptoms. Bloating severity relates to female sex and heavier body mass.[11] However, gastric emptying did not correlate with bloating severity.[77]

[H2] Diagnosis

Patients with postprandial upper abdominal symptoms such as nausea, vomiting, postprandial fullness, bloating and epigastric pain are candidates for gastric motility tests. Patients must first undergo an upper gastrointestinal endoscopy; if this test does not reveal a cause for the symptoms, patients can begin motility and functional investigations. The most relevant functional test is a measurement of gastric emptying. Gastric emptying is best assessed with scintigraphy[88,89] conducted over at least 3 hours; stable isotope breath test[90] is also approved by regulatory agencies; these tests are well validated, and data from healthy control individuals are available (Figure 3). When results from tests of gastric emptying are inconclusive particularly in patients with prominent postprandial fullness or early satiety, measurements of gastric accommodation are also indicated. Impaired gastric accommodation is diagnosed with validated methods where available such as SPECT[91] and MRI,[92] or with screening tests such as the proximal stomach size on the gastric scintiscan (taken immediately after radiolabeled meal ingestion),[93] or by a water load or nutrient drink test.[94]

Table 1 shows some of the more widely used tests to measure gastric motility in suspected gastroparesis.

[H3] Gastric emptying scintigraphy.

Gastric emptying scintigraphy is a functional test involving the ingestion of a solid meal containing a radioisotope with short half-life, typically ^{99m}Tc, and have been established from

multicenter studies in the United States, Canada, and Europe, using Western style meals, usually scrambled eggs (**Figure 3**); it is important to assess the amount of food ingested when applying normal values, and therefore the meals need to be of sufficient calorie and fat content to serve as a minor "stress test" for the stomach, but not so large as to be impossible to be consumed by symptomatic patients.[88,95] Gastric emptying scintigraphy is relatively reproducible with good concordance correlation coefficient (0.54~0.83) between two repeated studies.[96] Although this Western style meal has the advantage of good tolerability by the majority of symptomatic patients, it has some limitations. First, Western style meals are not familiar to most Asian patients. Therefore, some Asian centers have modified the components of the test meal, instead using rice-based meals composed of steamed rice, a microwaved egg and water (267 kcal: 57% carbohydrate; 23% fat and 19% protein), which contain a calorie and fat content that is intermediate between the Eggbeaters meal (255kcal, 2% fat) and the 2 scrambled egg meal 296kcal, 30% fat) typical of the Western style meals,[88,89] to measure gastric emptying by scintigraphy. Using this modified meal, the upper limits of gastric retention at 2 hours and 4 hours post consumption (95th percentile) were 49.8% and 8.8%, respectively[97], which is similar to values (60% at 2 hours; 10% at 4 hours) obtained using the Eggbeaters meal in consensus guidelines.[88] Given the possible effects of glycemia on gastric emptying, it is recommended that blood glucose should be less than 10mmol/L or 180mg/dL in the fasting period before starting the gastric emptying test.

Second, a few patients may not be able to tolerate any solid food. Moreover, the low fat and calorie content of the test meal may not adequately test gastric motility, and may fail to identify impaired gastric motor function in some patients. Therefore, alternative test meals have been proposed, such as a liquid nutrient meal (Ensure Plus® meal) which has a very similar gastric emptying profile when compared to a solid meal of comparable caloric content in healthy participants, but these alternative test meals have yet to be clinically validated in male or female patients with gastroparesis[98]. Moreover, the operational definition of gastroparesis relies on a delay in emptying solid foods, and not liquids.

The timing of scintigraphy imaging after consumption of a radiolabelled meal is also of importance. For estimating solid phase gastric emptying, data shows that imaging up to 4 hours after meal consumption detects more patients with delayed gastric emptying than imaging over 90 or 120 minutes.[99] The time for 50% of the meal to empty ($T_{1/2}$) may be calculated using a

power exponential curve fitting, or more simply by linear interpolation, as solid foods empty with a relatively linear pattern in the postlag phase, that is the phase after trituration of solids has been completed, and the solid phase of the meal starts to empty linearly from the stomach. This simplification with scans obtained hourly for up to 4 hours reduces costs and provides a relevant parameter that appraises overall gastric emptying, such as the percentage of the meal emptied at 2, 3, and 4 hours after consumption; in addition, linear interpolation between the percentages emptied at 1-4 hours allows estimation of gastric emptying half-time ($T_{1/2}$).[100]

[H3] Stable isotope breath test.

The gastric emptying breath test incorporates a stable isotope, ^{13}C, in a substrate such as octanoic acid or spiruluna platensis (blue-green algae) This noninvasive method is easy to perform, with similar cost to scintigraphy, and does not involve exposing patients to ionizing radiation; therefore, these tests are possible to use in pregnant or breast-feeding women, and in children. The principle underlying this test, which has been clinically validated as an alternative to gastric emptying scintigraphy, is that the rate of gastric emptying of the ^{13}C substrate incorporated in the solid mealis reflected by breath excretion of $^{13}CO_2$.[90,101] The test is conducted over a 4 hour period after an 8h fast. Pre-meal breath samples are collected, patients eat a special test meal, and after consuming the meal, additional breath samples (typically every 30 minutes) are collected at specified times. Thus, as the meal empties from the stomach, the medium chain triglyceride (octanoic acid) or the amino acids in spirulina (which contains 50%– 60% protein, 30% starch, and 10% lipid) rapidly undergo digestion, absorption, and metabolism to produce $^{13}CO_2$ which is exhaled in the breath. Since the rate limiting step of all of these processes is the rate of gastric emptying, the cumulation of $^{13}CO_2$ in breath reflects the rate of gastric emptying. Confounders that may influence the test results are changes in endogenous CO_2 excretion caused by physical activity such as walking and malabsorption, pancreatic exocrine insufficiency, significant lung or liver disease, or cardiac failure (**Figure 3**).[102]

[H3] Wireless motor capsule.

A wireless motor capsule (WMC) (SmartPill^{TM}) has been approved by the U.S. FDA for the evaluation of gastric emptying and colonic transit in patients with suspected slow transit constipation. Once ingested, the WMC measures pH, temperature, and pressure throughout the

GI tract.[103] The completion of gastric emptying is demonstrated by an abrupt change in pH into alkaline range due to WMC passage into the duodenum. Gastric emptying by WMC correlated moderately with simultaneous gastric emptying of a low-fat meal measured by concurrent scintigraphy.[104] However, there was only 52.5% agreement with scintigraphy,[105] and further validation in patients with gastroparesis is required.[105]

[H3] Gastroduodenal manometry.

Antroduodenal manometry is the intraluminal measurement of the pressure activity in the distal stomach and duodenal loop during fasting and postprandially. The technique, which is conducted at very few centers, can be used to assess gastric and/or small intestinal motility disturbances. In the postprandial period, a distal antral contraction pressure of <40mmHg is suggestive of a myopathic disorder, and reduced frequency of normal amplitude distal antral contractions is suggestive of myopathic or neuropathic dysfunction[106]. Interestingly, manometry studies of 102 patients with gastroparesis showed abnormalities suggestive of neurogenic derangement in the proximal small bowel, especially in patients with documented delayed gastric emptying[107]. These data confirm earlier observations of small intestinal involvement in the neuropathic process in some patients who present with upper GI symptoms suggestive of gastroparesis.[108]

At centers that perform antroduodenal manometry, the finding of antral hypomotility and failure to respond to prokinetics and anti-emetics would be an indication for drainage of the stomach with percutaneous endoscopic gastrostomy, support of nutrition with jejunal feeding and, if unsuccessful in maintaining nutrition, institution of long-term total parenteral nutrition

[H2] Differential Diagnosis

The symptoms of gastroparesis are nonspecific and may result from other sensory or motor disorders of the upper GI tract, including impaired gastric accommodation. A study of 1287 patients with upper GI symptoms enrolled at a tertiary care center over ~10 years measured gastric emptying by scintigraphy and gastric accommodation by SPECT, and found there were approximately equal numbers of patients with either delayed gastric emptying, or impaired gastric accommodation, or a combination of both, or the absence of both.[8] Thus, getting the right diagnosis for the patient's upper GI symptoms is an essential first step. Based on the current

definition, gastroparesis is undistinguishable from functional dyspepsia with delayed gastric emptying. Approximately 25–35% of patients with dyspeptic symptoms are estimated to have delayed gastric emptying.[9,10] Functional dyspepsia is reviewed in another primer article.[7]

Severe gastroparesis must be clinically differentiated from chronic intestinal pseudo-obstruction (CIPO). The two pathological disorders are characterized by similar clinical manifestations, gastrointestinal motor abnormalities and some form of underlying neuromuscular disorder.[44,107,109] The main difference between patients with gastroparesis and patients with CIPO is that patients with CIPO have episodes resembling mechanical intestinal obstruction. Correct diagnosis is essential, as patients with CIPO are more frequently exposed to useless and potentially dangerous surgical procedures.

Other conditions to differentiate from gastroparesis are rumination syndrome,[110,111] cannabinoid hyperemesis syndrome (CHS),[112] and cyclic vomiting syndrome (CVS)[113]. Chronic unexplained nausea and vomiting CUNV) or chronic nausea and vomiting syndrome (CNVS) are identified as symptom subgroups of functional upper gastrointestinal disorders with unknown prevalence and overlap of symptoms with gastroparesis and functional dyspepsia[9].

Patients with rumination syndrome may present with effortless, repetitive regurgitation, chewing or sucking and re-swallowing or spitting of previously ingested food. The disorder is not associated with nausea, but weight loss can occur and rumination can be mistaken for vomiting. The diagnosis is primarily based on careful history and clinical observation, and the manifestations are similar in adults and adolescents.[110,111] A recent review made a series of recommendations regarding clinical management of rumination syndrome: Clinicians strongly should consider rumination syndrome in patients who report consistent postprandial regurgitation.: The presence of nocturnal regurgitation, dysphagia, nausea, or symptoms occurring in the absence of meals does not exclude rumination syndrome, but makes it less likely. Diaphragmatic breathing with or without biofeedback (given by speech therapists, psychologists, gastroenterologists, and other health practitioners) is the first-line therapy in all cases of rumination syndrome. Objective testing for rumination syndrome with postprandial high-resolution esophageal impedance manometry can be used to support the diagnosis, but expertise and lack of standardized protocols are current limitations[114].

Both CHS and CVS are characterized by recurrent episodes of severe nausea and vomiting, often associated with abdominal pain, in the absence of any underlying recognizable cause other than the use of cannabis in CHS. The main clinical feature that distinguishes CHS and CVS from gastroparesis is that both disorders are characterized by a substantial absence of symptoms between episodes. Delayed gastric emptying is strongly associated with vomiting,[115] and has been reported in patients with CHS[116]. By contrast, normal or even accelerated gastric emptying is considered to represent a supportive criterion for the diagnosis of CVS.[117] Notably, compulsive hot bathing or showering behavior is a clinical feature that has been traditionally considered of diagnostic value for CHS,[112] but this behaviour may also be present in patients with CVS[118] and helps to distinguish both conditions from gastroparesis. CHS can be distinguished from CVS if there is resolution of nausea and vomiting episodes following cessation of cannabis use. Common and uncommon causes of nausea and vomiting are discussed in detail elsewhere.[9,119]

[H2]Prevention

There are few known preventive strategies specific to gastroparesis. The enhanced, long term control of hyperglycemia in patients with diabetes mellitus can prevent the occurrence of diabetic neuropathy. In addition, the risk of post-surgical gastroparesis can be improved by pyloroplasty, which is an incision of the pyloric region that increases the diameter of the gastroduodenal junction and removes any impediment to flow, to enhance gastric emptying in patients undergoing gastric surgery. Finally, choice of medication may help to prevent iatrogenic gastroparesis (for example, opioid associated gastroparesis) by the use of alternative drugs that achieve the same effect.

[H1] Management

Management of gastroparesis involves correcting fluid, electrolyte, and nutritional deficiencies; identifying and treating the cause of delayed gastric emptying (for example, diabetes mellitus); and suppressing or eliminating symptoms.[1] Therapeutic strategies rely on dietary modification,

medications that stimulate gastric motor activity, antiemetic drug therapy and non-pharmacological measures such as endoscopic or surgical intervention or gastric electrical stimulation. Here we focus on a general treatment strategy that is based on the severity of the objective gastric retention at 4 hours (management is reviewed in detail in ref. 119) (**Table 2**).

[H2] Dietary Modifications

Dietary modifications represent the first line of treatment for gastroparesis and are generally used for all patients, regardless of disease severity. Oral intake is preferable for nutrition and hydration in patients with gastroparesis. As patients often have early satiety, they are recommended to eat small meals and to avoid foods high in fat and indigestible fibres, because these delay gastric emptying.[1,77] When small meals are eaten as part of the gastroparesis diet, more frequent meals, such as three meals per day plus two snacks, are often needed to maintain caloric intake. Patients are advised to consume liquids such as soups, as the gastric emptying of caloric liquids or homogenized solids is often preserved in patients with gastroparesis, who can tolerate smaller sizes of such meals ingested more frequently rather than large meals three times per day[1]. Importantly, a high-fat diet, with solid meals increases the severity and frequency of symptoms among patients with gastroparesis;[120] by contrast, a small particle size diet reduces upper GI symptoms (nausea, vomiting, bloating, postprandial fullness, regurgitation and heartburn) in patients with diabetic gastroparesis.[121]

[H2] Pharmacology

If a gastroparesis-suitable diet fails to manage symptoms, patients may be treated medically with pharmacological agents including prokinetic and antiemetic medications. The clinical efficacy of pharmacological agents for symptoms of nausea and vomiting is questionable, based on analysis of data of 425 patients.[122] Gastric prokinetic medications increase the rate or amplitude of stomach contractions and, thus, increase the rate of gastric emptying. Medications currently approved (though not in all countries) include metoclopramide, domperidone, and erythromycin.[123]

Metoclopramide (a 5-HT_4 agonist,5-HT_3 and dopamine D_2 antagonist), has both prokinetic and antiemetic actions; however, it can cause both acute and chronic CNS side effects in some patients, including depression, anxiety, tremors and tardive dyskinesia (which may be

reversible or irreversible, and may be less prevalent than 1 in 1000,[124], in contrast to the estimated 1–10% risk previously suggested in a guideline.[125] In the United States, metoclopramide is approved for diabetic gastroparesis for up to 12 weeks duration. A nasal spray formulation of metoclopramide in gastroparesis has demonstrated efficacy in females, not in male patients.[126]

Another dopamine receptor antagonist, domperidone, exhibits gastric prokinetic as well as antiemetic properties via action on the area postrema, which is the vomiting center present in the brainstem. Domperidone does not readily cross the blood–brain barrier; therefore, this drug is much less likely to cause extrapyramidal side effects than metoclopramide. However, domperidone (like the macrolide erythromycin, which is also used as a prokinetic) is associated with prolongation of the cardiac QTc interval. Domperidone is not currently approved in the United States, but is available in many other countries in Europe and Asia. Oral erythromycin, a pure prokinetic agent that acts on motilin receptors, produced an improvement in symptoms in 43% of patients;[127] however, a third of patients experience loss of the long term efficacy of erythromycin (mean 11 months' follow up)[128] due to tachyphylaxis.[129] Erythromycin is not approved for the treatment of gastroparesis in any country and is used off-label, typically for a short period of less than a month.

Some patients with post-surgical gastroparesis or diabetic gastroparesis may have impaired gastric accommodation in addition to impaired gastric emptying[130]. In such patients, erythromycin is contra-indicated as it reduces gastric accommodation, and the 5-HT_{1A} agonist, Buspirone, is prescribed to enhance gastric accommodation and relieve symptoms, though this recommendation is based on relatively small clinical trial.[131]

[H3] New prokinetic drugs.

Several promising new prokinetic agents are in the pipeline for the treatment of gastroparesis. Relamorelin is a ghrelin receptor agonist that stimulates gastric body and antral contractions, accelerates gastric emptying, and has been shown in phase IIA and IIB clinical studies to increase gastric emptying of solids and reduce the symptoms of gatroparesis, particularly nausea, fullness, bloating and pain.[132,133] Relamorelin is currently being tested in phase III trials which should also provide information on the optimal subcutaneous dose of this treatment. In addition, prucalopride a 5-HT_4 receptor agonist without cardiac adverse effects, is approved in most

countries, other than the United States, for the treatment of chronic constipation. The drug accelerates gastric emptying and was shown in a preliminary report to relieve symptoms in 28 patients with idiopathic gastroparesis.[134]

[H3] New drugs for impaired gastric accommodation.

Acotiamide has fundus-relaxing and prokinetic properties owing to the ability of this drug to antagonize the inhibitory muscarinic type 1 and type 2 autoreceptors on cholinergic nerve endings and to inhibit acetylcholinesterase. The drug enhances gastric accommodation and emptying[135] and relieves dyspeptic symptoms,[136] and it is approved in Japan for treatment of functional dyspepsia. However, there are currently no registered trials with acotiamide in gastroparesis.

[H3] Approved Drugs Used Off Label.

Several drugs that are approved for other conditions are used by clinicians 'off-label' to treat the symptoms of gastroparesis. Although not proven efficacious in a randomized, controlled trial in patients with gastroparesis,[137] nortriptyline (a tricyclic antidepressant) is used for relief of pain. In a study conducted in patients with functional dyspepsia, amitriptyline (a tricyclic antidepressant as well as a muscarinic receptor antagonist) improved symptoms in patients with dyspeptic symptoms who did not have delayed gastric emptying[138] and it modestly improved sleep quality.[139]

Mirtazapine, an antidepressant with central adrenergic and serotonergic activity with direct anti-emetic activity possibly related to 5-HT_3 antagonist activity,[140] provides symptom relief for patients with functional dyspepsia and weight loss, a condition with substantial overlap with gastroparesis. However, mirtazapine is not actually approved for treatment of functional dyspepsia. Encouragingly, an open-label study of mirtazapine in patients with gastroparesis was associated with improvements in nausea, vomiting, retching and loss of appetite.[141] Another drug that is used off-label to treat upper gastrointestinal symptoms in functional dyspepsia is buspirone, an anxiolytic medication and 5-HT_{1A} agonist, which is used to treat anxiety; it enhances gastric accommodation and reduces postprandial symptoms in patients with functional dyspepsia.[131] Last, aprepitant, a neurokinin antagonist approved for use for the treatment of chemotherapy-induced emesis, was efficacious in the treatment of nausea in some patients with

gastroparesis and related disorders.[142] It does not alter gastric emptying, but increases fasting and postprandial gastric volumes.[143]

[H2] Pyloric Intervention

As mentioned above, delayed gastric emptying in gastroparesis is associated with antral hypomotility and, in some patients, with pyloric sphincter dysfunction in the form of pylorospasm; it is important to note that this intervention is not performed for pyloric stenosis.[144] Botulinum toxin blocks the exocytosis of acetylcholine in cholinergic nerve endings, thereby blocking the increased tone or spasm of the pyloric sphincter. An open-label study using intra-pyloric botulinum type A (Botox) injection in 179 patients with gastroparesis was associated with a decrease in gastroparesis symptoms at 1–4 months in 92 patients (51.4%). An improved response was observed in those who received a higher dose, in females, in those aged <50 years, and in patients without diabetes mellitus or post-surgical gastroparesis.[145] Two double-blind studies showed an improvement in gastric emptying, but a similar reduction in severity of symptoms compared to placebo.[146,147] Botulinum toxin injections do not result in sustained improvement in the symptoms of gastroparesis, but may provide temporary relief, lasting on average 3 months. Further studies are necessary to work out the specific patients who may most benefit from the use of this treatment; it is also still unclear whether a positive clinical response to botulinum toxin injection is valid for selecting patients for more permanent interventions of the pylorus, which are discussed next.

Pyloroplasty (to widen the pylorus and prevent spasm) or pyloromyotomy (an incision in the wall of the pylorus by endoscopic intervention, referred to as peroral pyloroplasty or gastric POEM [per-oral endoscopic myotomy]) performed surgically or endoscopically (Table 3), are procedures being offered to patients who are refractory to other treatments, including pharmacological approaches. The literature currently does not provide insight on the proportion of patients who are refractory to other treatments and undergo pyloric interventions. The basic rationale for this approach is the observation of pylorospasm in an unknown proportion of patientswith gastroparesis, particularly diabetic gastroparesis.[144] However, it is unclear whether factors such as the presence of concomitant antral hypomotility, or differences in compliance or "elasticity" of the pyloric area (for example as a result of scarring) impact the efficacy of pyloric interventions. Reports from open-label, single-center studies have been promising, as shown in

Table 3.[148-156] Clearly, controlled studies are required to assess the efficacy of pyloric interventions. Meanwhile, the algorithm in **Figure 4**, has been proposedto help guide the selection of patients for pyloric interventions, using measurement of pyloric sphincter abnormalities (Endoflip®; Endoluminal Functional Lumen Imaging Probe) or the symptomatic response to pyloric botox injections.[119] However, it is important to note that Endoflip measures stiffness or compliance at the pylorus rather than active contractions or sphincter tone, and it is as yet unproven whether the response to intra-pyloric injection of botulinum toxin is sufficient to predict efficacy of pyloromyotomy.

[H2] Gastric Electrical Stimulation

Gastric contractility depends on the underlying basal electrical rhythm, which is relayed through the gastric pacemaker cells. Therefore, a novel method for gastroparesis has been considered; that as in the heart, an artificial pacemaker might capture the electrical rhythm of the stomach and drive the contractile frequency. Unfortunately, there is as yet no clinical device that has been able to entrain the basal electrical rhythm of the human stomach, although this has been achieved in experimental animal models, and therefore it has not yet been possible to test a pacemaker system in the stomach with the same objective as that achieved in the heart.

Gastric electrical stimulation was originally developed to enhance gastric emptying, however, the technique has evolved to become a high frequency stimulation that appears to interfere with sensory transduction to the brain and thus provides a treatment for refractory symptoms in gastroparesis. Based on the initial studies that have shown an improvement in symptoms, particularly in patients with diabetic gastroparesis, the gastric electric neurostimulator was granted approval from the FDA under the Humanitarian Device Exemption, for the treatment of chronic intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic aetiology in patients aged 18–70 years. In 151 patients with refractory gastroparesis treated at a single center, gastric electric stimulation at least moderately improved symptoms in 43%.[157] The response in patients with diabetes mellitus was better than in patients with gastroparesis from other aetiologies. Patients with symptoms of nausea, loss of appetite, and early satiety were the best responders. Although there are a number of open-label studies suggesting the efficacy of gastric electrical stimulation in treatment of gastroparesis, particularly diabetic gastroparesis, two systematic reviews and meta-analyses exist, which recommend

caution in recommending gastric electrical stimulation outside of research studies. This recommendation is made on the basis of insufficient efficacy of gastric electrical stimulation in the few controlled trials comparing "stimulation switched off" versus "stimulation on" gastric electrical stimulation treatment as well as symptom regression to the mean, that is the natural tendency for symptoms to improve from the high level at the time of initiation of treatment to a later time, while the patient was receiving stimulator treatment.[96,97]

[H2] Diabetes and gastroparesis

The rate of gastric emptying has a major impact on the glycemic response to carbohydrate-containing meals in healthy individuals and in patients with diabetes mellitus, particularly in the initial postprandial increment.[27] Notably, the delayed gastric emptying that characterizes gastroparesis in patients with diabetes mellitus can affect the postprandial blood glucose response. Furthermore, postprandial glycemic excursions make a major contribution to 'overall' glycemic control as assessed by HbA1c. Therefore, impaired postprandial glycemic control represents an important target for management in patients with diabetic gastroparesis. In patients treated with insulin, delayed gastric emptying may result in a mismatch of the timing of exogenous, preprandial insulin and the actual delivery of nutrients, including carbohydrates, from the stomach to the small intestine. In a study involving 11 patients with type 1 diabetes mellitus, less insulin was required to be administered to the five patients with gastroparesis (compared to the 6 patients without gastroparesis) to achieve euglycemia during the first 120 minutes after a meal, and more insulin was needed by the patients with gastroparesis between 180–240 minutes.[158] Furthermore, delayed gastric emptying in patients with type 1 diabetes mellitus has recently been reported to be associated with an overall increase in blood glucose during the day, which may reflect the discordance between the timing of the preprandial insulin and the later absorption of food due to delayed gastric emptying.[159]

Patients with diabetic gastroparesis frequently exhibit labile blood glucose with periods of marked hyperglycemia and frequent hypoglycemia, particularly postprandially. No long-term studies exist that document the benefit of maintaining optimal glycemia in patients with diabetic gastroparesis. Therefore, the recommendation to strive for near normal blood glucose levels in patients with diabetic gastroparesis derives mainly from studies conducted in healthy volunteers and in patients with diabetes mellitus showing that glucose clamping at high levels of glycemia

results in delayed gastric emptying.[1] Nevertheless, optimizing glycemic control can also be beneficial in gastroparesis, as shown in a recent multicenter pilot study, in which continuous subcutaneous insulin infusion with insulin pump therapy, with continuous glucose monitoring, reduced hyperglycemia and HbA1c levels in patients with diabetic gastroparesis.[160] Patients also showed associated improvements in gastroparesis symptoms and in tolerance of nutrients, which were maintained for the 24-week phase of intensive monitoring and therapy.

[H1] Quality of Life

Quality of life (QOL) in patients with gastroparesis is impaired compared with the general population,[161] and to a level that is similar to patients with other chronic medical and psychological disorders.[162] In one large study of 335 patients with gastroparesis conducted in the United States, the average impairment of disease-specific QOL, measured using the Patient Assessment of Upper Gastrointestinal Disorders Quality of Life (PAGI-QOL) questionnaire, was moderate.[77]

The degree of impairment in QOL relates to the duration and severity of symptoms.[163] The cardinal symptoms of gastroparesis are nausea and vomiting. In one study, nausea appeared to be of a similar severity in patients with either idiopathic or diabetic gastroparesis, and increasing severity of nausea was associated with impaired quality of life on the PAGI-QOL.[164] These results have been replicated in another study,[75] but in this patient cohort vomiting was more severe among those with diabetic gastroparesis as compared to idiopathic gastroparesis. An increasing severity of vomiting, irrespective of gastroparesis etiology, correlated negatively with both disease-specific quality of life, according to the PAGI-QOL, and generic quality of life, using the short-form 36 (SF-36).

Bloating and upper abdominal pain or discomfort also impact QOL. Greater severity of bloating was associated with progressive impairments in disease-specific quality of life on the PAGI-QOL, and physical and mental components of the SF-36.[77] Moreover, greater severity of upper abdominal pain and discomfort was also associated with statistically significantly higher levels of impairment on the PAGI-QOL and the SF-36.[87] In another study, there was a negative correlation between abdominal pain severity and QOL, but there was no correlation between pain severity and gastric emptying.[165]

A greater degree of impairment of QOL has been reported in non-white patients in the United States,[166] although diabetic gastroparesis was statistically significantlymore common in non-white patients in this study. Many patients with gastroparesis have co-existent mood disorders[11,163] or may take drugs for pain reliefthat have deleterious physiological and psychological effects, such as opiates,[78] but the impact of these factors on QOL is unclear. The presence of a chronic long-term health condition and illness perceptions in patients with gastroparesis appear to negatively influence both psychological health and QOL.[167]

Evidence for any beneficial effects of the available treatments for gastroparesis on QOL is limited. In a randomized, controlled trial of a small particle size diet in patients with diabetic gastroparesis, although symptoms improved, there was no improvement in QOL.[121] Moreover, there is very little evidence for a positive impact of most pharmacological therapies, including nortriptyline,[137] aprepitant,[142] relamorelin,[132,133] or revexepride.[168] In one randomized controlled trial, domperidone appeared to improve QOL, but only among those who responded to the drug.[161] Gastric electrical stimulation and per-oral endoscopic pyloromyotomy have demonstrated beneficial effects, but only in uncontrolled studies.[169,170]

[H1] Outlook

This section looks into the foreseeable future with optimism, as there are important advances in gastroparesis on the horizon.

[H2] Improved diagnosis

New techniques are becoming available that can be applied to investigate or diagnose motor dysfunctions in gastroparesis, however these techniques require further study and validation. This includes clarifying the diagnostic roles of the WMC and of the measurement of pyloric sphinter abnormalities using Endoflip in the identification of gastric hypomotility and abnormal pyloric compliance respectively. Moreover, the role of pathological diagnosis needs to be defined. Several studies have demonstrated the feasibility of obtaining adequate biopsy samples of the neuromuscular layers of the stomach to interrogate the cause of gastroparesis. For example, recent studies suggested that a novel endoscopic muscle biopsy technique of stomach[171] and duodenum[172] appeared to be technically feasible, reproducible and safe to obtain

enough proper muscle tissue to evaluate the pathological status of the enteric nervous system. Technical details that are missing before these biopsies can be recommended for clinical diagnosis include clear definitions of normal values, optimizing the site(s) of biopsy of gastric muscle layer for optimal diagnostic information, and correlation between histological findings and treatment outcomes to inform clinicians on the optimal treatment to be prescribed based on the histopathological findings.

[H2] Management of hyperglycemia

In patients with diabetic gastroparesis, hyperglycemia that is associated with a mismatch between the emptying of nutrients and preprandial insulin administration should be proactively managed. Increasingly, it is recommended that management of both type 1 and type 2 diabetes mellitus should be 'personalized', that is, targeted towards individual patient characteristics. One of the phenotypic variants that impacts glycemic control is gastric emptying. It is conceivable that, in the future, gastric emptying will be measured more 'routinely' to optimize preprandial insulin dosing. The availability of a validated gastric emptying breath test that is standardized and allows measurement at the point of care suggests that such measurements are feasible. An additional benefit of such a management strategy is the early identification of gastroparesis, thus providing an earlier opportunity for treatment.[173]

[H2] Personalized therapy

In patients with gastroparesis, individualized treatment may be indicated for patients with specific pathophysiological features, for example, the severity of gastric emptying delay, antral hypomotility, pylorospasm, reduced accommodation and extrinsic vagal denervation. For all of these features (other than antropyloric motility), there are noninvasive tests to assess gastric emptying, gastric electrical rhythm and gastric accommodation and, therefore, such a strategy could be implemented. However, clinical trials conducted to date have not sufficiently characterized the pathophysiology to inform practitioners on the individualization of treatment. This should be a goal for research in the future.

[H2] New pharmacological agents and interventions

A requirement exists for new pharmacological agents that are validated for the treatment of gastroparesis. New pharmacologic agents such as relamorelin, prucalopride and aprepitant are promising and require further validation in robust phase III clinical trials. Meanwhile, off-label use of approved medications anchors current management in addition to dietary interventions. These approved medications also require validation in clinical trials to establish that they are indeed effective for the treatment of gastroparesis.
Similarly, pyloric interventions, including endoscopic pyloroplasty, require further validation, hopefully with sham controlled trials.

We believe that the psychometric validation, reliability and responsiveness to treatment demonstrated by the ANMS-daily diary as a patient response outcome should lead to greater opportunities for novel pharmacological and device treatments to be developed for gastroparesis. The significant unmet clinical need of patients with gastroparesis should galvanize the efforts of all to relieve their suffering.

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Conflicts of interest

Dr. Camilleri carries out consulting with Allergan on relamorelin (consulting fee to his employer, Mayo Clinic), consulting with Shire on prucalopride (consulting fee to his employer, Mayo Clinic) and has received a research grant from Takeda for study on TAK-954. All the other authors declare no significant conflicts of interest.

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Display items

Box 1: Causes of gastroparesis[a]

Idiopathic

Diabetes mellitus – type 1 and type 2

Post-surgical (fundoplication, vagotomy)

Medications (opioids, antibiotics, antiarrhythmics, anticonvulsants

Neurologic disorders (Parkinsons disease, amyloidosis, dysautonomia)

Post-Viral infection (norovirus, Epstein Barr virus, cytomegalovirus, herpes virus

Connective tissue disorders (scleroderma, systemic lupus erythematosus)

Renal insufficiency

[a]Data are from ref. 119, Lacy B, Parkman H, Camilleri M. Am. J. Gastroenterol. **113**, 647-659 (2018).

Box 2: Diabetic autonomic neuropathy and Treatment-induced Neuropathy of Diabetes

Diabetic autonomic neuropathy (DAN) is a serious complication of diabetes mellitus type 1 and 2, which usually occurs as symmetric peripheral polyneuropathy. The vast majority of DAN is chronic and develops after >10 years of diabetes mellitus, especially in patients with poorly controlled disease. At the time of presentation with gastroparesis, patients may have symptoms consistent with non-GI autonomic neuropathy, such as abnormal sweating, orthostatic hypotension, pupillary or bladder abnormalities.[108] In DAN, there is a gradual attrition of unmyelinated fibre function manifesting as a reduction in heart rate variation (e.g. in response to deep breathing) and in sweat volume (due to peripheral nerve dysfunction).[174] The major risk factor is severity and duration of hyperglycemia in patients with type 1 and 2 diabetes.[174] Other risk factors are hypertension, smoking, age and dyslipidemia.[175-177] The pathogenesis of DAN involves the complex interplay of metabolic, vascular (both macrovascular and microvascular) and hormonal factors.

Screening for DAN starts with clinical evaluation (symptoms and signs of postural dizziness, abnormal sweating, and associated numbness and paraesthesiae in the hands and feet), documentation of the lack of sinus arrhythmia on a 12-lead electrocardiogram[178] or Holter (prolonged ambulatory) monitoring, and ultimately conducting a more comprehensive autonomic reflex screen and computing a composite autonomic score, as described elsewhere.[179] DAN can develop acutely or subacutely and have features of bothcholinergic and adrenergic autonomic failure, sometimes associated with autoimmune antibody response.[180]

Treatment-induced neuropathy of diabetes (TIND) occurs in the setting of initially high HbA1c followed by a rapid reduction in HbA1c (glycosylated hemoglobin) by at least 2% within 3 months[181] in either type 1 or 2 diabetes . It is characterized by painful sensorimotor neuropathy with disproportionate involvement of small fibers, manifesting as pain and dysautonomia, including gastroparesis.[181,182] It has been proposed that of TIND results from hypoxic nerve damage, with unusual susceptibility to an abrupt reduction in endoneurial glucose. Unmyelinated fibers would be unduly susceptible, owing to a large surface area to size ratio relative to myelinated fibers.[182]

Figure 1: Mechanisms of gastric accommodation and emptying

The stomach receives extrinsic excitatory innervation from the vagus nerve, which induces antral contractility predominantly through cholinergic mechanisms; gastric accommodation is induced through inhibitory nitrergicnerves. The extrinsic nerves interact with intrinsic excitatory pathways, and electrical connectivity to smooth muscle cells is facilitated by interstitial cells, which causes the tunica muscularis (smooth muscle) to behave as a multicellular electrical syncytium.. The interstitial cells of Cajal (ICC) and PDGFRα-positive cells in the smooth muscle layer are regarded as the pacemakers that convey stimulation from extrinsic vagal fibers and intrinsic enteric nerves to stimulate the smooth muscle cells.

Figure 2: Histological changes in gastroparesis

(CM=circular muscle, LM = longitudinal muscle, MP= myenteric plexus). Examples of abnormal histological findings in patients with gastroparesis: a reduced number of neuronal nitric oxide synthase (nNOS) neurons (examples indicated by arrow) **[**in gastric biopsy samples from patients with idiopathic and diabetic gastroparesis compared to control individuals (upper panel). The appearance of PDGFRα^{+} cells and ICCs in human stomach (ICCs stained for KIT (green) and PDGFRα+-fibroblast-like cells (red) in gastric tissue from a patient with idiopathic gastroparesis (left lower panel **[**Graph illustrates the loss of PDGFRα^{+} cells in idiopathic gastroparesis (right lower panel) Reproduced from ref. 44 Grover M et al, Gastroenterology 2011;140: 1575-85;; and ref. 46 Herring et al. Neurogastroenterol Motil. 2018 Apr;30(4):e13230.)

Figure 3: Diagnosis of delayed gastric emptying in gastroparesis

A. SCINTIGRAPHY: Gastric emptying in a patient with type 1 diabetes, measured by scintigraphy after consumption of a solid meal containing radiolabelled food. A region of interest drawn around the isotope residing in the human stomach provides for accurate measurement of gastric emptying. Radiolabelled food is still visible in the stomach by scintigraphy after 4 hours, which demonstrates delayed gastric emptying

B. BREATH TEST Upper panel shows the method of collecting end-expiratory air in a glass vial and submitting to a centralized laboratory for measurement of $^{13}CO_2$ by isotope ratio mass spectrometry. Lower panel shows the level of accuracy that is achieved with gastric emptying

breath test [GEBT] compared to simultaneous scintigraphy measurements of gastric emptying of the same meal under control conditions, or pharmacological stimulation or inhibition of gastric emptying. Thus, there is good correlation between scintigraphy and breath test methods of assessing gastric emptying, and GEBT provides an accurate measurement of gastric emptying in humans using validated mathematical analyses. Reproduced from ref. 183 Shin et al CGH 201311:1453-1459 and ref. 184 Viramontes et al Neurogastro & Motility 13:567-574, 2001.

Figure 4. Proposed algorithm for treatment refractory gastroparesis (reproduced from ref. 119, Lacy BE, Parkman HP, Camilleri M. Chronic nausea and vomiting: evaluation and treatment. Am J Gastroenterol 2018;113:647-659)**.** When patients with gastroparesis have responded poorly to pharmacological and dietary interventions, they are considered for pyloric interventions. At centers that perform antroduodenal manometry, the finding of antral hypomotility would be an indication for drainage of the stomach with percutaneous endoscopic gastrostomy, jejunal feeding and if unsuccessful in maintaining nutrition, total parenteral nutrition. If antropyloric EndoFLIP demonstrates narrow pyloric diameter or poor compliance, the patient may be a candidate for pyloric intervention. If such tests are not performed, a successful therapeutic trial of pyloric botulinum toxin injection (as observed in a 179 patient open label trial [see reference 145]) may provide rationale for pyloric intervention though this still requires validation.

Table 1. Tests for gastric emptying in suspected gastroparesis

Test	Strengths	Limitations	References
Scintigraphy with solid meal	• Well-validated • Reproducible	• Western style meal type is not familiar to Asian. • Solid meal is not tolerable in some patients	76,96-98
Stable isotope breath test	• Easy to perform • No risk of radiation exposure	• Easily influenced by physical activity	101,102
Wireless motor capsules	• Provides information on transit through small bowel and colon	• Test is not yet validated for use in patients with suspected gastroparesis	104,105

Table 2: Treatment strategies for patients with gastroparesis

Management strategies	**Mild gastroparesis (10–15% 4h gastric retention)**	**Moderate gastroparesis (15–35% 4h gastric retention)**	**Severe gastroparesis (>35% 4h gastric retention)**
General measures	Review and eliminate medications inhibiting motility, optimize glycemic control in patients with diabetes.		
Diet	• Small, frequent meals • Low fat, low fibre diet • Small particle diet when symptomatic	• Small, frequent meals • Low fat, low fibre diet • Small particle diet when symptomatic	• Blenderized diet • Routine use of liquid nutriend supplements
Nutritional support	• Rarely needed	• Caloric liquids • Orally (PO) • Rarely requires nutrition by PEJ [percutaneous	• Caloric liquids • PO • May require nutrition by PEJ tube

		endoscopic jejunal feeding] tube	
Pharmacological: prokinetic	• Metoclopramide	• Metoclopramide	• Metoclopramide OR • Domperidone • Erythromycin • Prucalopride
Pharmacological: antiemetic	• Promethazine OR • Prochlorperazine	• Promethazine OR • Prochlorperazine • Ondansetron	• Ondansetron • Aprepitant OR • Mirtazapine
Pharmacological: symptom modulators	• Not needed	• Not needed	• Nortriptyline
Non-pharmacological	• Not needed	• Not needed	• Gastrostomy tube decompression • Laparoscopic and endoscopic interventions

Table 2 is based on data originally presented in ref. 119, Lacy BE, Parkman HP, Camilleri M. Chronic nausea and vomiting: evaluation and treatment. Am J Gastroenterol 2018;113:647-659 .

Table 3. Pyloric interventions for gastroparesis

Reference, Institution	Intervention	Gastroparesis Patients	Complications	Symptoms	Gastric emptying
Schlomovitz et al.[148] at The Oregon Clinic, Portland, OR, USA	POP • 6 laparoscopy-assisted • 1 endoscopic	▪ 7 females ▪ Mean Age: 51 y, range 33 65y ▪ Gastroparesis Type: ○ 5 Idiopathic ○ 2 Post-surgical	▪ Intra-operative :none ▪ Late: 1 bleeding pyloric ulcer 2 weeks post surgery	▪ Mean follow-up of 6.5 months: ○ Improved or resolved in: 6 patients ○ Significant improvement in Nausea (p=0.01) ○ Significant improvement in Epigastric burning (p=0.029) ○ No significant improvement in Vomiting, Early Satiety, Post-prandial fullness, Epigastric pain	▪ In 5 patients: - mean GE t1/2: pre: 124 min, post: 58 min (p = 0.018) - residual activity at 4 hr: pre:21%, post:4%, (p = 0.097)
Khashab et al.[149] International multicenter (2 in the U.S., 2 in Asia, 1 in South America)	G-POEM	▪ 30 patients with refractory gastroparesis ▪ Age: 47± 13 y ▪ Sex: 17 females ▪ Gastroparesis Type: ○ 11 Diabetic ○ 12 Post-surgical ○ 7 Idiopathic	▪ Immediate: 1 capnoperitoneum (that is some CO2 retained in the abdomen following laparoscopy) and 1 prepyloric ulcer	▪ Median follow-up of 6 months (IQR, 7–11) ▪ Reduced symptoms with absence of recurrent hospitalizations: 26/30 ▪ Symptoms at 6 months: nausea, 47% resolved, 50% improved, 3% not improved; vomiting: 53% resolved, 10 % improved, 33% not improved; abdominal Pain: 53% resolved, 20% improved, 23% unchanged, 3% worse; weight: 57% gain, 37% stable, 7% continued weight loss	▪ In n=17 at 98 days (IQR, 81-105): ▪ Normalized:47% ▪ Improved: 35% ○ Average retention of solid meal at 4h: 17 ± 16%
Rodriguez et al.[150] at Cleveland Clinic, Clevaland, OH, USA	POP • (Prior Procedures: ○ Enteral feeding tube: 21	▪ 47 with gastroparesis ▪ Age: 43.7± 14.8 y ▪ Sex: 37 Females ▪ BMI: 27.2 ± 9.6 kg/m^2 ▪ Gastroparesis Type:	▪ No reported complications	▪ Follow-Up: ○ 30-day (n=42) ○ 90-day (n=31) ▪ GCSI (p value<0.01) ○ Total: Pre: 4.6±0.9; Post:3.3±1.4	▪ Average retention of solid at 4 h: ▪ At baseline (n=47): 37.2 ± 25.1%

	○ GES:16 ○ Pyloric Botox: 28)	○ 12 Diabetic ○ 9 Post-surgical ○ 27 Idiopathic		○ Nausea/vomiting: Pre: 4.4±1.3; Post: 2.9±1.6 ○ Post-prandial fullness: Pre: 4.8±1.0; Post: 3.8±1.7 ○ Bloating: Pre: 4.7±1.3; Post: 3.1±1.7	▪ At 90-days (n=16): 20.4 ± 26.1%
Malik et al.[151] at Temple and Winthrop University Hospitals, Philadelphia, PA, USA	G-POEM Prior Procedures: • Pyloric surgery: 1 • GES: 3 • Pyloric botox: 11	▪ 13 patients with refractory gastroparesis ▪ Age: 45.7± 10.3 y ▪ Sex: 7 Females ▪ BMI: 27.2 ± 9.6 kg/m^2 ▪ Gastroparesis Type: ○ 4 Idiopathic ○ 1 Diabetic ○ 8 Post-surgical - 3 Nissen fundoplication - 5 esophagectomy (4 cancer, 1 achalasia)	○ Intraoperative: 3 accidental mucosotomy (residual opening of the stomach mucosa)) closed with clips	▪ Average follow up: 3 months (108 ± 69 days) ▪ Clinical Patient Grading Assessment Score (CPGAS) (n=11): ○ Improved: 8 (73%) ○ Worsened: 2 ○ Unchanged: 1 ▪ Symptoms: No significant difference in GCSI scores pre- and post-procedure	▪ Average retention of solid at 4 h: (p= 0.10): ▪ baseline (n=13): 49 ± 24% ▪ follow-up (n=6): 33 ± 28%
Gonzalez et al.[152] at Aix Marseille Universite, Marseille, France	G-POEM Prior Procedures: ○ GES: 4 ○ Pyloric botox: 1	▪ 29 patients with refractory gastroparesis ▪ Age: 52.8± 17.7 y ▪ Sex: 19 Females ▪ BMI: 27.2 ± 9.6 kg/m^2 ▪ Gastroparesis Type: ○ 7 Diabetic ○ 5 Post-surgical ○ 15 Idiopathic ○ 2 Scleroderma	▪ Intraoperative: 5 capnoperitoneum ○ Early complications within 2 days of procedure : 1 post-op bleeding and peritoneal abscess; 1 self-resolved post-operative bleeding	▪ Improvement of mean GCSI and symptoms severity: ▪ 3 month: 23/38 (79%) ▪ 6 month: 18/26 (69%)	▪ Average retention of solid at 4 h (p=0.07) ▪ baseline (n=28): 40 ± 34% 2 months (n=23): 28 ± 45%

Dacha et al.[153] at Emory Univsersity, Atlanta, GA, USA	G-POEM Prior Procedures: ○ gastric electrical stmulation: 4	▪ 16 patients with refractory gastroparesis ▪ Age: 44.8 ±14.8 y ▪ Sex: 13 Females ▪ BMI: 24.7 ± 6.1 kg/m^2 ▪ Gastroparesis Type: ○ 9 Diabetic ○ 1 Post-surgical ○ 5 Idiopathic ○ 1 Post-infectious	▪ Intraoperative: None	▪ Clinical efficacy (decrease in mean GCSI in at least 2 subsets of cardinal symptoms, and no hospitalization for gastroparesis-related symptoms): 13/16 (81%) ▪ Average GCSI ○ Baseline: 3.40±0.5 ○ 1 month (n=16): 1.49±0.96 ○ 6 months (n=13): 1.36±0.91 ○ 12 monhts (n=6): 1.46±1.4	▪ In n=12 who underwent GE by scintigraphy post-G-POEM: ○ Normalized retention at 4 h: 9/12 (75%) ○ Improved retention at 4 h: 3/12 (25%)
Shada et al.[154] at The Oregon Clinic, Portland, OR, USA	Laparoscopic pyloroplasty	▪ 177 patients ▪ Age: 49 (range 16-80) years ▪ Sex: 146 Females ▪ BMI: 28 ± 7 kg/m^2 ▪ Concurrent surgery: ○ Fundoplication:103 ○ J-tube: 17 ○ G-tube: 10 ○ Heller myotomy 16 ○ Paraesophageal hernia repair: 14	▪ None were converted to laparotomy (open abdominal explorastion)[	▪ Median follow-up 6 months (IQR, 7–11) ▪ Symptoms: ○ At 1 month and 6 months post-op every symptom improved with p <0.001 except early satiety which was unchanged	▪ In n=70 who underwent GE by scintigraphy post-G-POEM: ▪ Normalized in 77% ▪ Delayed: 23%
Mancini et al.[155] at Allegheny General Hospital, Pittsburgh, PA, USA	Laparoscopic pyloroplasty (n=42) Open pyloroplasty (n=4)	▪ 46 patients ▪ Age (range): 46 (21-75) years ▪ Sex: 36 Females ▪ BMI: 26.5 kg/m^2 ▪ Gastroparesis Type: ○ 15 Diabetic ○ 31 Idiopathic	▪ Suture line leak after open pyloroplasty, n=1	▪ GCSI improved in all symptoms and composite score on follow up compared to baseline (p<0.001)	▪ In=20 who underwent GE by scintigraphy, overall improvement (70% normal) and in 13 with data pre- and post-pyloroplasty, median T1/2 was reduced by 76 minutes with 39.5% normalized GE $T_{1/2}$
Toro et al.[156] at Emory University, Atlanta, GA, USA	Laparoscopic pyloroplasty	▪ 50 patients ▪ Age: 49.7 years ▪ Sex: 43 Females ▪ BMI: 25.9 kg/m2 ▪ Gastroparesis Type:	▪ No major complications	▪ Average follow up: 3 months (range 1-33 months) ▪ Readmission rate: 14%	ND

		○ 45 nondiabetic ▪ Concurrent surgery: ○ Fundoplication: 14 ○ Cholecystectomy: 26 ○ Gastrostomy takedown: 24 ○ Extensive lysis of adhesions (intra-abdominal strands of tissue that may cause obstruction) : 4 ▪ Paraesophageal hernia repair: 26		▪ Symptoms improvement: 82% of patients ($p<0.001$)	

POP, per-oral pyloromyotomy; G-POEM, gastric Per-Oral Endoscopic PyloroMyotomy; GE, gastricemptying**;** GCSI, gastroparesis Symptom Index.; ND, No data available