Gastroparesis

*Michael Camilleri[1] *, Victor Chedid[1], Alexander C. Ford[2,3], Ken Haruma[4], Michael Horowitz[5], Karen L. Jones[6], Phillip A. Low[7], Seon-Young Park[8], Henry P. Parkman[9] and Vincenzo Stanghellini[10]*

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 that 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.

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 (GI) muscle function and the loss of function of smooth muscles.

Gastroparesis can be idiopathic, associated with diabetes mellitus, may 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 of the stomach does not seem to influence gastric emptying or accommodation but may be associated with heightened sensitivity in patients with functional dyspepsia (another upper GI disorder, see below)[3,4]. Rarely, specific viral infections caused by herpesvirus 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 disease, collagen vascular diseases (such as systemic sclerosis), chronic intestinal pseudo-obstruction (CIPO) 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', thereby recognizing the disorder as part of a broader spectrum of gastric neuromuscular dysfunction[6]. Symptom overlap exists 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

*e-mail: camilleri.michael@mayo.edu

https://doi.org/10.1038/s41572-018-0038-z

Author addresses

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA.
[2]Leeds Gastroenterology Institute, Leeds Teaching Hospitals NHS Trust, Leeds, UK.
[3]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.
[4]Department of Internal Medicine 2, General Medical Center, Kawasaki Medical School, Okayama, Japan
[5]Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia.
[6]National Health and Medical Research Council of Australia Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, South Australia, Australia.
[7]Department of Neurology, Mayo Clinic, Rochester, MN, USA.
[8]Division of Gastroenterology, Chonnam National University School of Medicine, Gwangju, Republic of Korea.
[9]GI Section, Department of Medicine, Temple University School of Medicine, Philadelphia, PA, USA.
[10]Department of Digestive Diseases, Policlinico S. Orsola-Malpighi, University of Bologna, Bologna, Italy.

be restricted to disorders in which upper GI 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, the diagnosis of gastroparesis and the effective management of this disorder. Finally, we discuss future research directions.

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 one-third 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 GI 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 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.

Incidence and prevalence

A population-based study in Minnesota in the United States estimated that the age-adjusted incidence of gastroparesis during a 10-year period was 2.4 patients per 100,000 person-years for men and 9.8 patients per 100,000 person-years for women; prevalence was estimated to be 9.6 patients per 100,000 men and 37.8 patients per 100,000 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 individuals with symptoms typical for gastroparesis and individuals 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 affected by health-care-seeking behaviour among patients with symptoms suggestive of gastroparesis.

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 oestrogen[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 tenfold 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 significantly lower scores for loss of appetite and for the inability to finish a meal, but significantly worse scores for gastroesophageal reflux-type symptoms than patients of a healthy weight[11]. The role of other modifiable risk factors, such as smoking or alcohol, in gastroparesis is unproven, although 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 United States, a history of smoking was significantly associated with no improvement in symptoms during 48 weeks of follow-up[21].

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 of patients who developed gastroparesis (on the basis of 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 GI 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% and 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 complications, including retinopathy and peripheral neuropathy, higher mean levels of glycosylated haemoglobin (HbA1c; which is a measure of glycaemic control over the prior 3 months) and lower socio-economic 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 glycaemic 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 was 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 glycaemic 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 glycaemic control, infection rates (most frequently urinary tract infections) and poor adherence with or intolerance of medications[36]. Regional variations exist in the inpatient management of patients with diabetic gastroparesis that are likely to reflect local differences in health-care 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 tenfold[34].

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 after 25 years in a second study[31]. However, in a community-based survey in Minnesota in the United States, among individuals with gastroparesis of mixed aetiology (typically documented by symptoms and delayed gastric emptying measured by scintigraphy or gastric food retention on imaging reports), survival was lower than expected for age-matched and sex-matched individuals without gastroparesis[16].

Mechanisms/pathophysiology

Although there have been advances in understanding the mechanisms and pathophysiology of gastroparesis, there are still substantial gaps in knowledge, inconsistencies across studies and potential differences between different aetiological groups (for example, diabetic versus idiopathic); 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.

Gastric neuromuscular function

Gastroparesis and impaired gastric accommodation result from neuromuscular dysfunction of the stomach. Trituration of food in the stomach grinds food into fragments, and 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 ~1–2 mm sized particles are emptied into the duodenum (FIG. 1)[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 tachykinergic neurons[42]. These inhibitory and excitatory neural effects are transmitted through interstitial cells of Cajal (ICCs) and possibly other fibroblast-like cells that have pacemaker function, to the 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, ICCs and fibroblast-like cells, which are positive for

Box 1 | **Causes of gastroparesis**

- Idiopathic
- Diabetes mellitus — type 1 and type 2
- Post-surgical (fundoplication and vagotomy)
- Medications (opioids, antibiotics, antiarrhythmics and anticonvulsants)
- Neurologic disorders (Parkinson disease, amyloidosis and dysautonomia)
- Post-viral infection (norovirus, Epstein–Barr virus, cytomegalovirus and herpesvirus)
- Connective tissue disorders (scleroderma and systemic lupus erythematosus)
- Renal insufficiency

Data from REF.[119]

platelet-derived growth factor receptor-α (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 (FIG. 1). In gastroparesis, delayed gastric emptying is associated with antral hypomotility and, in some patients, with pyloric sphincter dysfunction caused by neuromuscular dysfunction.

Intrinsic neuropathy

Recent studies have explored the histopathological features and expression of neurotransmitters in gastric tissue to elucidate the intrinsic mechanisms involved in gastric motor function (FIG. 2). Light microscopy examination of full-thickness gastric biopsy samples from 20 patients with idiopathic gastroparesis, 20 patients with diabetic gastroparesis and 20 control individuals undergoing gastric bypass surgery demonstrated no statistically significant differences between diabetic and idiopathic gastroparesis in 9 morphological end points: 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 ICCs); CD45 (cell surface marker of lymphocytic immune cells); 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 with 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 one study, in contrast to patients with diabetic gastroparesis, biopsy samples 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].

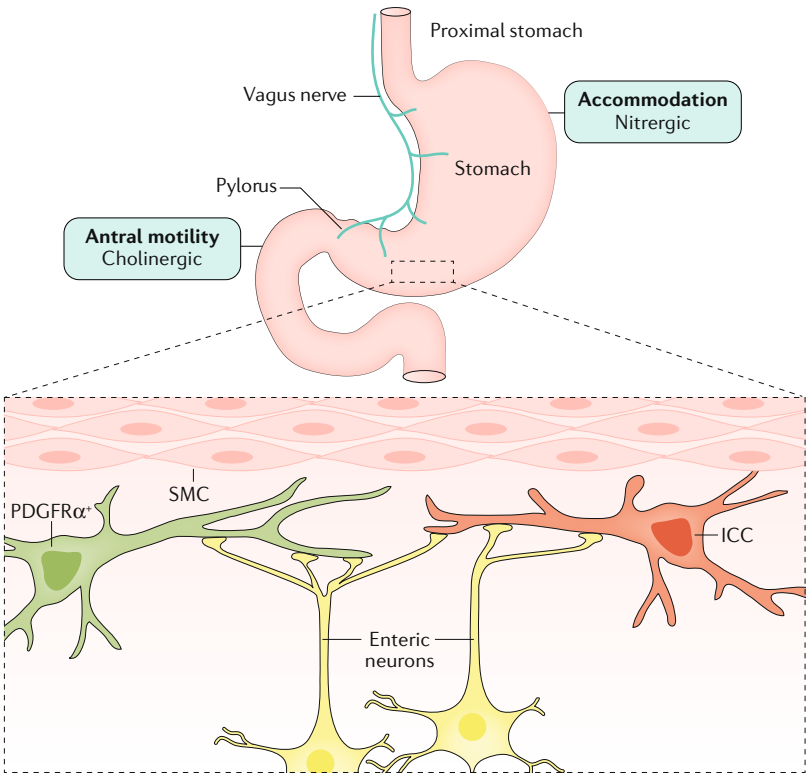

Fig. 1 | **Mechanisms of gastric accommodation and emptying.** The stomach receives extrinsic excitatory innervation from the vagus nerve, which induces antral contractility predominantly through cholinergic mechanisms; gastric accommodation is induced through inhibitory nitrergic nerves. The extrinsic nerves interact with intrinsic excitatory pathways, and electrical connectivity to smooth muscle cells (SMCs) is facilitated by interstitial cells, which causes the tunica muscularis (smooth muscle) to behave as a multicellular electrical syncytium. The interstitial cells of Cajal (ICCs) and platelet-derived growth factor receptor-α (PDGFRα)-positive cells in the smooth muscle layer are regarded as the pacemakers that convey stimulation from extrinsic vagal fibres and intrinsic enteric nerves to stimulate the SMCs. Adapted from REF.[183], Springer Nature Limited.

Involvement of the immune system. The reduction in or damage to ICCs in the stomach of some patients with gastroparesis was associated with a reduction in the numbers of anti-inflammatory M2 macrophages, which normally express mannose receptor (CD206) and haem 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 biopsy samples — reduced numbers of M2 macrophages in one study[45] but numbers comparable to healthy tissue in 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 noradrenaline from splenic nerves, and the transmitter activates β_2-adrenergic receptor (β_2-AR) expressed on T cells, which activates T cells to release acetylcholine, which acts on the α_7-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 ICCs in the circular

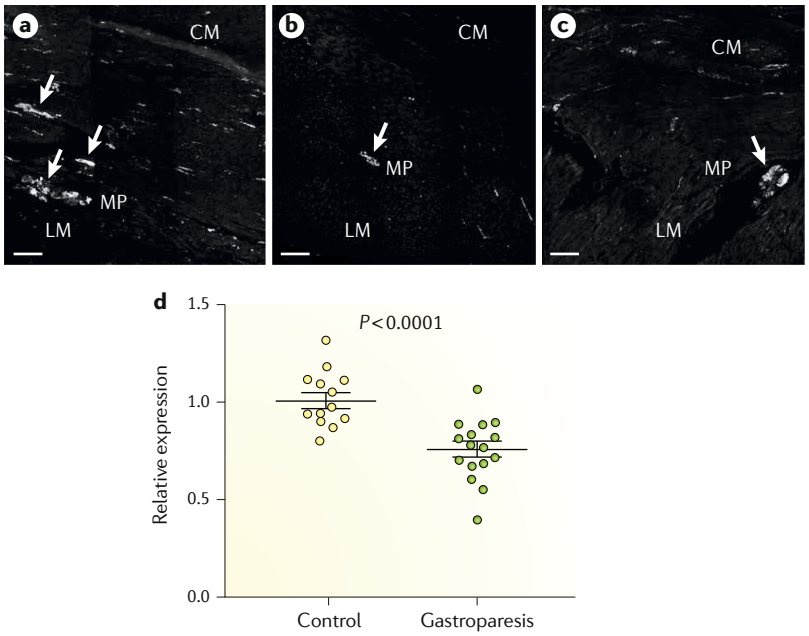

Fig. 2 | **Histological changes in gastroparesis. a–c** | Examples of histological findings from gastric biopsy samples in control individuals (part **a**) and patients with diabetic (part **b**) or idiopathic (part **c**) gastroparesis: a reduced number of neuronal nitric oxide synthase (nNOS) neurons (examples indicated by arrow) in gastric biopsy samples from patients with diabetic and idiopathic gastroparesis compared with control individuals is shown. **d** | Graph illustrates the loss of platelet-derived growth factor receptor-α (PDGFRα)-positive cells in idiopathic gastroparesis (right lower panel). CM, circular muscle; LM, longitudinal muscle; MP, myenteric plexus. Parts **a–c** are adapted with permission from REF.[44], Elsevier. Part **d** is adapted with permission from REF.[46], Wiley-VCH.

muscle per field), and myenteric immune infiltrate was associated with overall clinical severity and nausea in patients with idiopathic gastroparesis[49]. The relationship between hyperglycaemia, oxidative metabolism, inflammation, ICCs and gastric emptying is the subject of ongoing research[50].

Haem oxygenase 1. HO1 attenuates the overall production of reactive oxygen species. In gastric tissues obtained from animal models (predominantly non-obese diabetic (NOD) mice), loss of HO1 leads to increased oxidative stress, loss of Kit expression (implying predominantly a loss of ICCs) and decreased expression of nNOS as well as 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, leading to complications such as 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 *HMOX1* (encoding HO1) expression support 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 *HMOX1* are longest in patients with type 2 diabetes and gastroparesis, and the promoters were longer in patients with gastroparesis (idiopathic or diabetic) than in control individuals[54]. However, in all the patient groups with gastroparesis studied, allele lengths were longer in African Americans than in 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.

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 owing to discordant study results, and further research is required.

Diabetic gastroparesis

Diabetic gastroparesis is multifactorial, with contributions from hyperglycaemia, 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.

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

In experiments in human volunteers that imposed acute hyperglycaemia, typically 8 mmol l^{-1} (144 mg dl^{-1}) (usually 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, including an inhibition of antral

Box 2 | **Diabetic autonomic neuropathy and treatment-induced neuropathy**

Diabetic autonomic neuropathy (DAN) is a serious complication of diabetes mellitus type 1 and 2 that 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-gastrointestinal autonomic neuropathy, such as abnormal sweating, orthostatic hypotension and pupillary or bladder abnormalities[108]. In DAN, there is a gradual attrition of unmyelinated fibre function manifesting as a reduction in heart rate variation (for example, in response to deep breathing) and in sweat volume (due to peripheral nerve dysfunction)[174]. The major risk factor is severity and duration of hyperglycaemia 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 both cholinergic and adrenergic autonomic failure, sometimes associated with autoimmune antibody response[180].

Treatment-induced neuropathy of diabetes (TIND) occurs in the setting of initially high glycosylated haemoglobin (HbA1c) followed by a rapid reduction in HbA1c 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 fibres, manifesting as pain and dysautonomia, including gastroparesis[181,182]. It has been proposed that TIND results from hypoxic nerve damage, with unusual susceptibility to an abrupt reduction in endoneurial glucose. Unmyelinated fibres would be unduly susceptible, owing to a large surface area:size ratio relative to myelinated fibres[182].

contractility and delayed gastric emptying during hyperglycaemic clamp compared with euglycaemia and a dose-dependent slowing of gastric emptying with hyperglycaemia (even in the range observed postprandially) when compared with euglycaemia. Similarly, clamping blood glucose at 250 mg dl^{-1} was associated with induction of gastric dysrhythmias in healthy human volunteers[58–60]. This finding is in contrast to the effect of insulin-induced hypoglycaemia (defined as blood glucose ~2.6 mmol l^{-1}), 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 hypoglycaemia[61].

Natural history studies provide uncertain evidence of the relationship between glycaemic 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 levels had 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 glycaemic control than in diabetic patients with better glycaemic control as assessed by HbA1c[26]. It is also uncertain whether improving chronic hyperglycaemia over a fairly short time period results in a meaningful improvement in gastric emptying. Improved glycaemic 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 hyperglycaemia and gastric emptying.

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 hypoglycaemic agents such as amylin analogues (for example, pramlintide) or glucagon-like peptide 1 (GLP1) analogues or agonists (for example, liraglutide and exenatide). Dipeptidyl peptidase IV inhibitors, such as vildagliptin and sitagliptin, are not associated with gastroparesis and increase GLP1 and improve glycaemia without delaying gastric emptying[67]. Medications used in the treatment of Parkinsonism including levodopa and anticholinergic medications may also cause iatrogenic gastroparesis.

Post-surgical gastroparesis. Post-surgical gastroparesis is generally caused by 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 (LSG) 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 now rarely performed for treatment of peptic ulceration) sometimes accompanied by vagotomy as well as from partial oesophagectomy for oesophageal cancer or heart transplantation, which involve resection of the vagus nerve.

Opioids. μ-opioid agonists such as codeine, oxycodone and morphine have pharmacological effects on the GI tract. These drugs can stimulate pyloric tone, decrease gastric emptying, inhibit propulsion, increase fluid absorption in the GI tract, increase the amplitude of non-propulsive segmental contractions, increase anal sphincter tone and impair reflex relaxation of the anal sphincter in response to rectal distention[70]. At the cellular level, opioids can inhibit adenylate cyclase and Ca^{2+} channels and activate K^+ channels; this leads to a subsequent inhibition of acetylcholine release from enteric interneurons and purine and/or 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 fairly 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, including 70.9% not taking opioids, 9.9% taking opioids only as needed and 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 opioids compared with patients with gastroparesis not on opioids had higher symptom severity, lower employment rate and higher rates of hospitalizations over 1 year as well as worse outcomes with treatment for gastroparesis with prokinetic 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.

Post-viral

Post-infectious dyspepsia has been described in the literature, but the evidence is rather weak as it is based on the presence of symptoms such as myalgia during the acute onset of gastric symptoms rather than serological or tissue demonstration of viral aetiology. Gastroparesis has been rarely associated with specific viral infections — for example, Epstein–Barr virus, norovirus, herpesvirus 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 monitored 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.

Other causes of gastroparesis

Gastric neuromuscular disorders may result from extrinsic denervation, intrinsic neuropathy or 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 a more generalized motility disorder affecting other regions of the gut (for example, small bowel, lower oesophageal sphincter and oesophagus). 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.

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 affected 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.

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 and 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.

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].

Nausea and vomiting. Nausea is a highly prevalent symptom in patients with gastroparesis, irrespective of aetiology, and 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 Consortium cohort of 393 patients, a severe delay in gastric emptying was associated with more severe symptoms of vomiting[11].

Pain. In the NIH Gastroparesis Consortium 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 a gastric emptying test or with the presence of diabetic neuropathy or control of diabetes[87].

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].

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].

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 GI 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, but the stable isotope breath test[90] is also approved by regulatory agencies. These tests are well validated, and data from healthy control individuals are available (FIG. 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 radiolabelled 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.

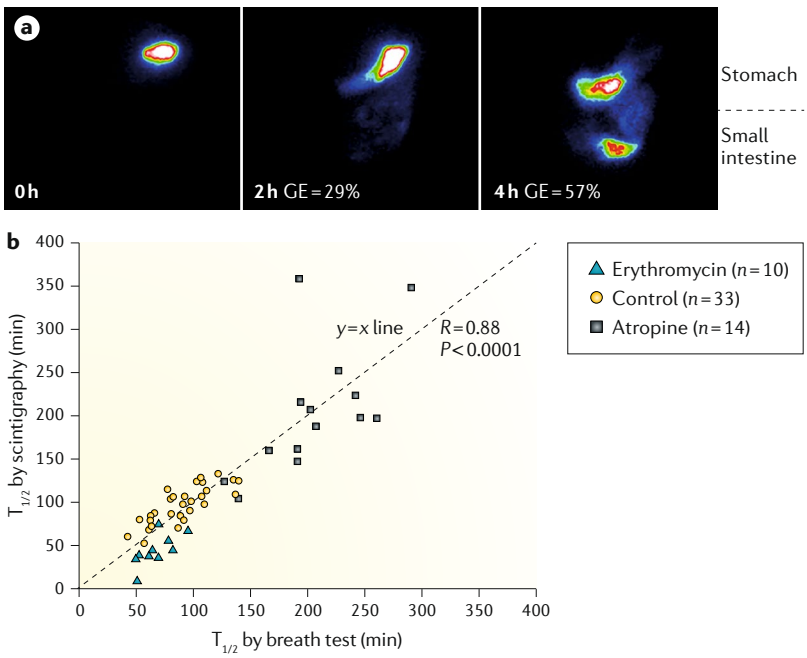

Fig. 3 | **Diagnosis of delayed gastric emptying in gastroparesis. a** | Scintigraphy: gastric emptying in a patient with type 1 diabetes, measured by scintigraphy after consumption of a solid meal containing radiolabelled food. A region of interest drawn around the isotope residing in the human stomach enables 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: after consumption of a solid meal containing stable isotope $^{13}CO_2$, end-expiratory air is collected in a glass vial and submitted to a centralized laboratory for measurement of $^{13}CO_2$ by isotope ratio mass spectrometry. Graph shows the level of accuracy that is achieved with the gastric emptying breath test (GEBT) compared with 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. GE, gastric emptying; $T_{1/2}$, gastric emptying half-time. Part **a** is adapted with permission from REF.[184], Elsevier. Part **b** is adapted with permission from REF.[185], Wiley-VCH.

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 has been established from multicentre studies in the United States, Canada and Europe using Western-style meals, usually scrambled eggs (FIG. 3). It is important to assess the amount of food ingested when applying normal values; 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 fairly reproducible, with a 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 centres 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 contains a calorie and fat content that is intermediate that between the Eggbeaters meal (255 kcal, 2% fat) and the two-scrambled-egg meal (296 kcal, 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 glycaemia on gastric emptying, it is recommended that blood glucose should be less than 10 mmol l^{-1} or 180 mg dl^{-1} 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 with a solid meal of comparable caloric content in healthy participants. However, 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, not liquids.

The timing of scintigraphy imaging after consumption of a radiolabelled meal is also of importance. For estimating solid-phase gastric emptying, data show 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 (that is, the gastric emptying half-time ($T_{1/2}$))

Table 1 | **Tests for gastric emptying in suspected gastroparesis**

Test	Strengths	Limitations	Refs
Scintigraphy with solid meal	• Well validated • Reproducible	• Western-style meal type is not familiar to Asian patients • 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

may be calculated using a power exponential curve fitting or more simply by linear interpolation, as solid foods empty with a fairly 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 for estimation $T_{1/2}$[100].

Stable isotope breath test. The gastric emptying breath test incorporates a stable isotope, ^{13}C, in a substrate such as octanoic acid or spirulina 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 breastfeeding 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 meal is reflected by breath excretion of $^{13}CO_2$ (REFS[90,101]). The test is conducted over a 4-hour period after an 8-hour 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. Because 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 and pronounced lung or liver disease or cardiac failure[102] (FIG. 3).

Wireless motor capsule. A wireless motor capsule (WMC; SmartPill, Medtronic) has been approved by the US 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 the 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].

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 centres, can be used to assess gastric and/or small intestinal motility disturbances. In the postprandial period, a distal antral contraction pressure of <40 mmHg 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 centres 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.

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 1,287 patients with upper GI symptoms enrolled at a tertiary care centre over ~10 years measured gastric emptying by scintigraphy and gastric accommodation by SPECT and found that 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. On the basis of the current definition, gastroparesis is indistinguishable 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 elsewhere[7].

Severe gastroparesis must be clinically differentiated from CIPO. The two pathological disorders are characterized by similar clinical manifestations, GI 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 or chronic nausea and vomiting syndrome are identified as symptom subgroups of functional upper GI 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 and re-swallowing, or alternatively spitting out 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 the clinical management of rumination syndrome. Clinicians should consider a diagnosis of rumination syndrome in patients who present with consistent postprandial regurgitation. However, a diagnosis of rumination syndrome is made less likely (but not excluded) by the presence of nocturnal regurgitation, dysphagia, nausea or symptoms occurring in the absence of meals. Diaphragmatic breathing with or without biofeedback is the first-line therapy for all patients with rumination syndrome. A diagnosis can be supported by objective testing for rumination syndrome with postprandial high-resolution oesophageal impedance manometry; however, clinical 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 behaviour 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].

Prevention

There are few known preventive strategies specific to gastroparesis. The enhanced, long-term control of hyperglycaemia 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.

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, anti-emetic 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).

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].

Pharmacology

If a gastroparesis-suitable diet fails to manage symptoms, patients may be treated medically with pharmacological agents, including prokinetic and anti-emetic medications. The clinical efficacy of pharmacological agents for symptoms of nausea and vomiting is questionable on the basis of 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 (although not in all countries) include metoclopramide, domperidone and erythromycin[123].

Metoclopramide (a 5-HT_4 agonist and 5-HT_3 and dopamine D_2 antagonist) has both prokinetic and anti-emetic

Table 2 | **Treatment strategies for patients with gastroparesis**

Management strategies	Mild gastroparesis (10–15% 4 h gastric retention)	Moderate gastroparesis (15–35% 4 h gastric retention)	Severe gastroparesis (>35% 4 h gastric retention)
General measures	Review and eliminate medications inhibiting motility and optimize glycaemic 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 nutrient supplements
Nutritional support	Rarely needed	• Caloric liquids • Orally • Rarely requires nutrition by PEJ feeding tube	• Caloric liquids • Orally • May require nutrition by PEJ feeding tube
Pharmacological: prokinetic	Metoclopramide	Metoclopramide	• Metoclopramide or domperidone • Erythromycin • Prucalopride
Pharmacological: anti-emetic	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

PEJ, percutaneous endoscopic jejunal. Table based on data originally presented in REF.[119].

actions; however, it can cause both acute and chronic central nervous system 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 1,000 (REF.[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 female but not in male patients[126].

Another dopamine receptor antagonist, domperidone, exhibits gastric prokinetic as well as anti-emetic properties via action on the area postrema, which is the vomiting centre 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 (similar to 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, one-third of patients experience loss of the long-term efficacy of erythromycin (mean 11 months of 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 contraindicated as it reduces gastric accommodation, and the 5-HT_{1A} agonist buspirone is prescribed to enhance gastric accommodation and relieve symptoms, although this recommendation is based on a fairly small clinical trial[131].

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 gastroparesis, 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 side 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].

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 acotiamide is approved in Japan for the treatment of functional dyspepsia. However, there are currently no registered trials with acotiamide in gastroparesis.

Table 3 | **Pyloric interventions for gastroparesis**

Reference, institution	Intervention	Patients with gastroparesis	Complications	Symptoms	Gastric emptying
Schlomovitz et al.[148] at the Oregon Clinic, Portland, OR, USA	• POP • Laparoscopy-assisted ($n=6$) • Endoscopic ($n=1$)	• Mean age: 51 years, range 33–65 years • Sex: 7 women • Gastroparesis type: idiopathic ($n=5$); post-surgical ($n=2$)	• Intraoperative: none • Late: bleeding pyloric ulcer 2 weeks post-surgery ($n=1$)	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, postprandial fullness or epigastric pain	In 5 patients: • Mean $T_{1/2}$: pre-POP: 124 min; post-POP: 58 min ($P=0.018$) • Residual activity at 4 h: pre-POP: 21%; post-POP: 4% ($P=0.097$)
Khashab et al.[149] at international multicentres (2 in the USA, 2 in Asia and 1 in South America)	G-POEM	• 30 patients with refractory gastroparesis • Age: 47 ± 13 years • Sex: 17 women • Gastroparesis type: diabetic ($n=11$); post-surgical ($n=12$); idiopathic ($n=7$)	Immediate: capnoperitoneum (i.e. some CO_2 retained in the abdomen following laparoscopy) ($n=1$); prepyloric ulcer ($n=1$)	• Median follow-up of 6 months (IQR = 7–11) • Reduced symptoms with absence of recurrent hospitalizations: 26 of 30 • Symptoms at 6 months: nausea, 47% resolved, 50% improved and 3% not improved; vomiting, 53% resolved, 10% improved and 33% not improved; abdominal pain, 53% resolved, 20% improved, 23% unchanged and 3% worse; weight, 57% gain, 37% stable and 7% continued weight loss	• In 17 patients at 98 days (IQR = 81–105): normalized: 47%; improved: 35% • Average retention of solid meal at 4 h: 17 ± 16%
Rodriguez et al.[150] at the Cleveland Clinic, Cleveland, OH, USA	POP prior procedures: • Enteral feeding tube ($n=21$) • GES ($n=16$) • Pyloric Botox ($n=28$)	• 47 patients with gastroparesis • Age: 43.7 ± 14.8 years • Sex: 37 women • BMI: 27.2 ± 9.6 kg/m^2 • Gastroparesis type: diabetic ($n=12$); post-surgical ($n=9$); idiopathic ($n=27$)	No reported complications	• Follow-up: 30-day ($n=42$) and 90-day ($n=31$) • GCSI ($P<0.01$): total: pre-POP: 4.6 ± 0.9 and post-POP: 3.3 ± 1.4; nausea and/or vomiting: pre-POP: 4.4 ± 1.3 and post-POP: 2.9 ± 1.6; postprandial fullness: pre-POP: 4.8 ± 1.0 and post-POP: 3.8 ± 1.7; bloating: pre-POP: 4.7 ± 1.3 and post-POP: 3.1 ± 1.7	• Average retention of solid at 4 h: at baseline ($n=47$): 37.2 ± 25.1%; at 90 days ($n=16$): 20.4 ± 26.4 ± 26.1%
Malik et al.[151] at Temple and Winthrop University Hospitals, Philadelphia, PA, USA	G-POEM prior procedures: • Pyloric surgery ($n=1$) • GES ($n=3$) • Pyloric Botox ($n=11$)	• 13 patients with refractory gastroparesis • Age: 45.7 ± 10.3 years • Sex: 7 women • BMI: 27.2 ± 9.6 kg/m^2 • Gastroparesis type: idiopathic ($n=4$); diabetic ($n=1$); post-surgical ($n=8$) • 3 Nissen fundoplication • 5 oesophagectomy (4 cancer and 1 achalasia)	Intraoperative: 3 accidental mucosotomy (i.e. residual opening of the stomach mucosa) closed with clips ($n=3$)	• Average follow-up: 3 months (108 ± 69 days) • CPGAS ($n=11$): improved ($n=8$; 73%); worsened ($n=2$; 18%); unchanged ($n=1$; 9%) • Symptoms: No significant difference in GCSI scores pre-procedure 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 Université, Marseille, France	G-POEM prior procedures: • GES ($n=4$) • Pyloric Botox ($n=1$)	• 29 patients with refractory gastroparesis • Age: 52.8 ± 17.7 years • Sex: 19 women • BMI: 27.2 ± 9.6 kg/m^2 • Gastroparesis type: diabetic ($n=7$); post-surgical ($n=5$); idiopathic ($n=15$); scleroderma ($n=2$)	• Intraoperative: capnoperitoneum ($n=5$) • Early complications within 2 days of procedure: postoperative bleeding and peritoneal abscess ($n=1$); self-resolved postoperative bleeding ($n=1$)	Improvement of mean GCSI and symptoms severity: • 3 months: 23 of 38 (79%) • 6 months: 18 of 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 University, Atlanta, GA, USA	G-POEM prior procedures: GES ($n=4$)	• 16 patients with refractory gastroparesis • Age: 44.8 ± 14.8 years • Sex: 13 women • BMI: 24.7 ± 6.1 kg/m^2 • Gastroparesis type: diabetic ($n=9$); post-surgical ($n=1$); idiopathic ($n=5$); post-infectious ($n=1$)	Intraoperative: none	• Clinical efficacy (decrease in mean GCSI in at least 2 subsets of cardinal symptoms and no hospitalization for gastroparesis-related symptoms): 13 of 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 months ($n=6$): 1.46 ± 1.4	In 12 patients who underwent gastric emptying by scintigraphy after G-POEM: • Normalized retention at 4 h: 9 of 12 (75%) • Improved retention at 4 h: 3 of 12 (25%)

Table 3 (cont.) | **Pyloric interventions for gastroparesis**

Reference, institution	Intervention	Patients with gastroparesis	Complications	Symptoms	Gastric emptying
Shada et al.[154] at the Oregon Clinic, Portland, OR, USA	Laparoscopic pyloroplasty	• 177 patients • Mean age: 49 years, range 16–80 years • Sex: 146 women • BMI: 28 ± 7 kg/m^2 • Concurrent surgery: fundoplication (n = 103); J-tube (n = 17); G-tube (n = 10); Heller myotomy (n = 16); paraesophageal hernia repair (n = 14)	None were converted to laparotomy (open abdominal exploration)	• Median follow-up 6 months (IQR = 7–11) • Symptoms: at 1 month and 6 months postoperation, every symptom improved, with P < 0.001, except early satiety, which was unchanged	In 70 patients who underwent gastric emptying by scintigraphy after G-POEM: • Normalized: 77% • Delayed: 23%
Mancini et al.[155] at Allegheny General Hospital, Pittsburgh, PA, USA	• Laparoscopic pyloroplasty (n = 42) • Open pyloroplasty (n = 4)	• 46 patients • Mean age: 46 years, range 21–75 years • Sex: 36 women • BMI: 26.5 kg/m^2 • Gastroparesis type: diabetic (n = 15); idiopathic (n = 31)	Suture line leak after open pyloroplasty (n = 1)	GCSI improved in all symptoms and composite score on follow-up compared with baseline (P < 0.001)	In 20 patients who underwent gastric emptying by scintigraphy, there was overall improvement (70% normal), and in 13 patients with data before and after pyloroplasty, the median $T_{1/2}$ was reduced by 76 min with 39.5% normalized $T_{1/2}$
Toro et al.[156] at Emory University, Atlanta, GA, USA	Laparoscopic pyloroplasty	• 50 patients • Mean age: 49.7 years • Sex: 43 women • BMI: 25.9 kg/m2 • Gastroparesis type: 45 nondiabetic • Concurrent surgery: fundoplication (n = 14); cholecystectomy (n = 26); gastrostomy takedown (n = 24); extensive lysis of adhesions (intra-abdominal strands of tissue that may cause obstruction) (n = 4); paraesophageal hernia repair (n = 26)	No major complications	• Average follow-up: 3 months (range 1–33 months) • Re-admission rate: 14% • Symptom improvement: 82% of patients (P < 0.001)	ND

BMI, body mass index; CPGAS, Clinical Patient Grading Assessment Score; GCSI, Gastroparesis Symptom Index; GES, gastric electrical stimulation; G-POEM, gastric per-oral endoscopic pyloromyotomy; IQR, interquartile range; ND, no data available; POP, per-oral pyloromyotomy; $T_{1/2}$, gastric emptying half-time.

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 proved 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 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 GI symptoms in functional dyspepsia is buspirone, an anxiolytic medication and 5-HT_{1A} agonist, which is used to treat anxiety; buspirone 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]. Aprepitant does not alter gastric emptying but instead increases fasting and postprandial gastric volumes[143].

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 intrapyloric 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 women, in those aged <50 years and in patients without diabetes mellitus or post-surgical gastroparesis[145]. However, two double-blind studies showed an improvement in gastric emptying, but also showed a similar reduction in severity of symptoms, compared with 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 determine 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 per-oral 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 patients with 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), affect the efficacy of pyloric interventions. Reports from open-label, single-centre studies have been promising, as shown in TABLE 3 (REFS[148–156]). Clearly, controlled studies are required to assess the efficacy of pyloric interventions. Meanwhile, the algorithm in FIG. 4 has been proposed to 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 unproved whether the response to intrapyloric injection of botulinum toxin is sufficient to predict efficacy of pyloromyotomy.

Gastric electrical stimulation

Gastric contractility depends on the underlying basal electrical rhythm, which is relayed through the gastric pacemaker cells. As such, a novel method to treat gastroparesis has been considered; an artificial pacemaker might capture the electrical rhythm of the stomach and drive the contractile frequency (similar to devices used in the heart). 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; 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. On the basis of the initial studies that have shown an improvement in symptoms, particularly in patients with diabetic gastroparesis, the gastric electrical 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 centre, gastric electrical 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 the treatment of gastroparesis, particularly diabetic gastroparesis, two systematic reviews and meta-analyses exist that 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].

Diabetes and gastroparesis

The rate of gastric emptying has a major impact on the glycaemic 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 glycaemic excursions make a major contribution to 'overall' glycaemic control as assessed by HbA1c. Therefore, impaired postprandial glycaemic 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

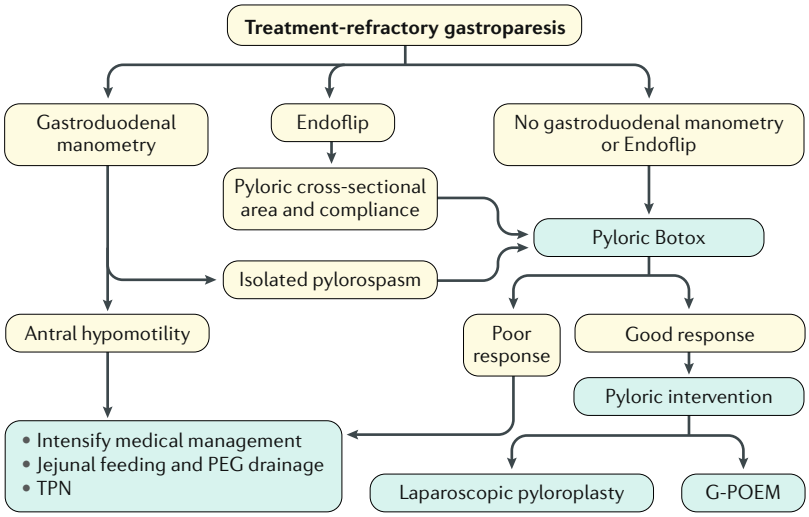

Fig. 4 | **Proposed algorithm for treatment-refractory gastroparesis.** When patients with gastroparesis have responded poorly to pharmacological and dietary interventions, they are considered for pyloric interventions. At centres that perform antroduodenal manometry, the finding of antral hypomotility would be an indication for drainage of the stomach with percutaneous endoscopic gastrostomy (PEG), jejunal feeding and, if unsuccessful in maintaining nutrition, total parenteral nutrition (TPN). If antropyloric Endoflip (endoluminal functional lumen imaging probe) 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 an open-label trial enrolling 179 patients[145]) may provide rationale for pyloric intervention, although this still requires validation. G-POEM, gastric per-oral endoscopic myotomy. Adapted from REF.[119], Springer Nature Limited.

mellitus, less insulin was required to be administered to the 5 patients with gastroparesis (compared with the 6 patients without gastroparesis) to achieve euglycaemia during the first 120 minutes after a meal, and more insulin was needed by the patients with gastroparesis between 180 and 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 hyperglycaemia and frequent hypoglycaemia, particularly postprandially. No long-term studies exist that document the benefit of maintaining optimal glycaemia in patients with diabetic gastroparesis. Therefore, the recommendation to strive for near-normal blood glucose levels in patients with diabetic gastroparesis is derived mainly from studies conducted in healthy volunteers and in patients with diabetes mellitus showing that glucose clamping at high levels of glycaemia results in delayed gastric emptying[1]. Nevertheless, optimizing glycaemic control can also be beneficial in gastroparesis, as shown in a recent multicentre pilot study in which continuous subcutaneous insulin infusion with insulin pump therapy, with continuous glucose monitoring, reduced hyperglycaemia 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.

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 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 QOL 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 than with idiopathic gastroparesis. An increasing severity of vomiting, irrespective of gastroparesis aetiology, correlated negatively with both disease-specific QOL, according to the PAGI-QOL, and generic QOL, using the 36-item Short Form Health Survey (SF-36).

Bloating and upper abdominal pain or discomfort also affect QOL. Greater severity of bloating was associated with progressive impairments in disease-specific QOL on the PAGI-QOL and on physical and mental components of the SF-36 (REF.[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 (REF.[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 significantly more common in non-white patients in this study. Many patients with gastroparesis have coexistent mood disorders[11,163] or may take drugs for pain relief that have deleterious physiological and psychological effects, such as opioides[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].

Outlook

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

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 additional study includes clarifying the diagnostic roles of the WMC and of the measurement of pyloric sphincter 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 or sites of biopsy of the 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 on the basis of the histopathological findings.

Management of hyperglycaemia

In patients with diabetic gastroparesis, hyperglycaemia 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 affects glycaemic 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].

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; 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 characterization should be a goal for research in the future.

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 American Neurogastroenterology and Motility Society daily diary as a patient response outcome should lead to greater opportunities for novel pharmacological and device treatments to be developed for gastroparesis. The substantial unmet clinical need of patients with gastroparesis should galvanize the efforts of all investigators to relieve their suffering.

Published online: 01 November 2018

1. Camilleri, M., Parkman, H. P., Shafi, M. A., Abell, T. L. & Gerson, L. American College of Gastroenterology clinical guideline: management of gastroparesis. *Am. J. Gastroenterol.* **108**, 18–37 (2013). **This paper presents the most recent clinical guideline for the management of gastroparesis**.
2. Mearin, F. et al. Dyspepsia and irritable bowel syndrome after a *Salmonella* gastro-enteritis outbreak: one-year follow-up cohort study. *Gastroenterology* **129**, 98–104 (2005).
3. Thumshirn, M. et al. Gastric accommodation in non-ulcer dyspepsia and the roles of *Helicobacter pylori* infection and vagal function. *Gut* **44**, 55–64 (1999).
4. Tack, J. et al. Clinical and pathophysiological characteristics of acute-onset functional dyspepsia. *Gastroenterology* **122**, 1738–1747 (2002).
5. Vassallo, M., Camilleri, M., Caron, B. L. & Low, P. A. Gastrointestinal motor dysfunction in acquired selective cholinergic dysautonomia associated with infectious mononucleosis. *Gastroenterology* **100**, 252–258 (1991).
6. Pasricha, P. J. & Parkman, H. P. Gastroparesis: definitions and diagnosis. *Gastroenterol. Clin. N. Am.* **44**, 1–7 (2015).
7. Enck, P. et al. Functional dyspepsia. *Nat. Rev. Dis. Primers* **3**, 17081 (2017). **This Review presents an excellent synthesis of the state of the art and science in functional dyspepsia**.
8. Park, S. Y. et al. Gastric motor dysfunction in patients with functional gastroduodenal symptoms. *Am. J. Gastroenterol.* **112**, 1689–1699 (2017). **This paper presents data on different pathophysiological subgroups in almost 1,300 patients with upper GI symptoms**.
9. Stanghellini, V. et al. Gastroduodenal disorders. *Gastroenterology* **150**, 1380–1392 (2016). **This paper presents the most recent Rome IV document on upper GI dysfunctions and related symptom complexes**.
10. Stanghellini, V. & Tack, J. Gastroparesis: separate entity or just a part of dyspepsia? *Gut* **63**, 1972–1978 (2014).
11. Parkman, H. P. et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. *Gastroenterology* **140**, 101–115 (2011).
12. Soykan, I., Sivri, B., Sarosiek, I., Kiernan, B. & McCallum, R. W. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig. Dis. Sci.* **43**, 2398–2404 (1998).

13. Aleppo, G. et al. Reported gastroparesis in adults with type 1 diabetes (T1D) from the T1D Exchange clinic registry. *J. Diabetes Compl.* **31**, 1669–1673 (2017).
14. Bytzer, P. et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus. *Arch. Intern. Med.* **161**, 1989–1996 (2001).
15. Maleki, D. et al. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch. Intern. Med.* **160**, 2808–2816 (2000).
16. Jung, H. K. et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology* **136**, 1225–1233 (2009).
This paper presents a strong epidemiological study on gastroparesis.
17. Rey, E. et al. Prevalence of hidden gastroparesis in the community: the gastroparesis "iceberg". *J. Neurogastroenterol. Motil.* **18**, 34–42 (2012).
18. Ravella, K. et al. Chronic estrogen deficiency causes gastroparesis by altering neuronal nitric oxide synthase function. *Dig. Dis. Sci.* **58**, 1507–1515 (2013).
19. Showkat Ali, M. et al. Gender and estradiol as major factors in the expression and dimerization of nNOSalpha in rats with experimental diabetic gastroparesis. *Dig. Dis. Sci.* **57**, 2814–2825 (2012).
20. Boaz, M., Kislov, J., Dickman, R. & Wainstein, J. Obesity and symptoms suggestive of gastroparesis in patients with type 2 diabetes and neuropathy. *J. Diabetes Compl.* **25**, 325–328 (2011).
21. Pasricha, P. J. et al. Outcomes and factors associated with reduced symptoms in patients with gastroparesis. *Gastroenterology* **149**, 1762–1774 (2015).
22. Choung, R. S. et al. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. *Am. J. Gastroenterol.* **107**, 82–88 (2012).
23. Dickman, R. et al. Prevalence of symptoms suggestive of gastroparesis in a cohort of patients with diabetes mellitus. *J. Diabetes Compl.* **27**, 376–379 (2013).
24. Kofod-Andersen, K. & Tarnow, L. Prevalence of gastroparesis-related symptoms in an unselected cohort of patients with type 1 diabetes. *J. Diabetes Compl.* **26**, 89–93 (2012).
25. Almogbel, R. A., Alhussan, F. A., Alnasser, S. A. & Algeffari, M. A. Prevalence and risk factors of gastroparesis-related symptoms among patients with type 2 diabetes. *Intl. J. Health Sci.* **10**, 397–404 (2016).
26. Bharucha, A. E. et al. Delayed gastric emptying is associated with early and long-term hyperglycemia in type 1 diabetes mellitus. *Gastroenterology* **149**, 330–339 (2015).
This article presents an important longitudinal study of diabetes complications including gastroparesis.
27. Phillips, L. K., Deane, A. M., Jones, K. L., Rayner, C. K. & Horowitz, M. Gastric emptying and glycaemia in health and diabetes mellitus. *Nat. Rev. Endocrinol.* **11**, 112–128 (2015).
28. Boronikolos, G. C. et al. Upper gastrointestinal motility and symptoms in individuals with diabetes, prediabetes and normal glucose tolerance. *Diabetologia* **58**, 1175–1182 (2015).
29. Jones, K. L. et al. A longitudinal study of gastric emptying and upper gastrointestinal symptoms in patients with diabetes mellitus. *Am. J. Med.* **113**, 449–455 (2002).
30. Kong, M. F., Horowitz, M., Jones, K. L., Wishart, J. M. & Harding, P. E. Natural history of diabetic gastroparesis. *Diabetes Care* **22**, 503–507 (1999).
31. Chang, J., Rayner, C. K., Jones, K. L. & Horowitz, M. Prognosis of diabetic gastroparesis—a 25-year evaluation. *Diabetes Med.* **30**, e185–e188 (2013).
This important article describes the natural history of diabetic gastroparesis.
32. Wang, Y. R., Fisher, R. S. & Parkman, H. P. Gastroparesis-related hospitalizations in the United States: Trends, characteristics, and outcomes, 1995–2004. *Am. J. Gastroenterol.* **103**, 313–322 (2008).
33. Hirsch, W. et al. Emergency department burden of gastroparesis in the United States, 2006 to 2013. *J. Clin. Gastroenterol.* https://doi.org/10.1097/MCG.0000000000000972 (2017).
34. Wadhwa, V. et al. Healthcare utilization and costs associated with gastroparesis. *World J. Gastroenterol.* **23**, 4428–4436 (2017).
35. Nusrat, S. & Bielefeldt, K. Gastroparesis on the rise: Incidence versus awareness? *Neurogastroenterol. Motil.* **25**, 16–22 (2013).
36. Uppalapati, S. S., Ramzan, Z., Fisher, R. S. & Parkman, H. P. Factors contributing to hospitalization for gastroparesis exacerbations. *Dig. Dis. Sci.* **54**, 2404–2409 (2009).
37. Bielefeldt, K. Regional differences in healthcare delivery for gastroparesis. *Dig. Dis. Sci.* **58**, 2789–2798 (2013).
38. Bielefeldt, K. Factors influencing admission and outcomes in gastroparesis. *Neurogastroenterol. Motil.* **25**, 389–398 (2013).
39. Hyett, B. et al. Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis. *Gastroenterology* **137**, 445–452 (2009).
This paper provides the details of the morbidity and complications of diabetic gastroparesis.
40. Meyer, J. H., Thomson, J. B., Cohen, M. B., Shadchehr, A. & Mandiola, S. A. Sieving of solid food by the canine stomach and sieving after gastric surgery. *Gastroenterology* **76**, 804–813 (1979).
41. Meyer, J. H., Elashoff, J., Porter-Fink, V., Dressman, J. & Amidon, G. L. Human postprandial gastric emptying of 1-3-millimeter spheres. *Gastroenterology* **94**, 1315–1325 (1988).
42. Grider, J. R. & Makhlouf, G. M. Regulation of the peristaltic reflex by peptides of the myenteric plexus. *Arch. Int. Pharmacodyn. Ther.* **303**, 232–251 (1990).
43. Sanders, K. M., Ward, S. M. & Koh, S. D. Interstitial cells: regulators of smooth muscle function. *Physiol. Rev.* **94**, 859–907 (2014).
This important review discusses the pacemaker cells in the GI tract.
44. Grover, M. et al. Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology* **140**, 1575–1585 (2011).
45. Bernard, C. E. 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.* **26**, 1275–1284 (2014).
46. Herring, B. P. et al. Idiopathic gastroparesis is associated with specific transcriptional changes in the gastric muscularis externa. *Neurogastroenterol. Motil.* **30**, e13230 (2018).
47. Stadler, K. Oxidative stress in diabetes. *Adv. Exp. Med. Biol.* **771**, 272–287 (2012).
48. Han, B., Li, X. & Hao, J. The cholinergic anti-inflammatory pathway: an innovative treatment strategy for neurological diseases. *Neurosci. Biobehav. Rev.* **77**, 358–368 (2017).
49. Grover, M. et al. Clinical-histological associations in gastroparesis: results from the Gastroparesis Clinical Research Consortium. *Neurogastroenterol. Motil.* **24**, 531–539 (2012).
50. Hayashi, Y. et al. Hyperglycemia increases interstitial cells of Cajal via MAPK1 and MAPK3 signaling to ETV1 and KIT, leading to rapid gastric emptying. *Gastroenterology* **153**, 521–535 (2017).
51. Choi, K. M. et al. Heme oxygenase-1 protects interstitial cells of Cajal from oxidative stress and reverses diabetic gastroparesis. *Gastroenterology* **135**, 2055–2064 (2008).
52. Yamada, N. et al. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to emphysema. *Am. J. Hum. Genet.* **66**, 187–195 (2000).
53. Chen, Y. H. et al. Microsatellite polymorphism in promoter of heme oxygenase-1 gene is associated with susceptibility to coronary artery disease in type 2 diabetic patients. *Hum. Genet.* **111**, 1–8 (2002).
54. Gibbons, S. J. et al. Repeat polymorphisms in the *Homo sapiens* heme oxygenase-1 gene in diabetic and idiopathic gastroparesis. *PLOS ONE* **12**, e0187772 (2017).
55. Grover, M. et al. Platelet-derived growth factor receptor alpha (PDGFRalpha)-expressing "fibroblast-like cells" in diabetic and idiopathic gastroparesis of humans. *Neurogastroenterol. Motil.* **24**, 844–852 (2012).
56. Bytzer, P. et al. GI symptoms in diabetes mellitus are associated with both poor glycemic control and diabetic complications. *Am. J. Gastroenterol.* **97**, 604–611 (2002).
57. Gaber, A. O. et al. Changes in gastric emptying in recipients of successful combined pancreas-kidney transplants. *Dig. Dis.* **9**, 437–443 (1991).
58. Coleski, R. & Hasler, W. L. Coupling and propagation of normal and dysrhythmic gastric slow waves during acute hyperglycaemia in healthy humans. *Neurogastroenterol. Motil.* **21**, 492–499 (2009).
59. Fraser, R. J. et al. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* **33**, 675–680 (1990).
60. Schvarcz, E. et al. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology* **113**, 60–66 (1997).
61. Russo, A. et al. Insulin-induced hypoglycaemia accelerates gastric emptying of solids and liquids in long-standing type 1 diabetes. *J. Clin. Endocrinol. Metab.* **90**, 4489–4495 (2005).
62. Bharucha, A. E., Camilleri, M., Forstrom, L. A. & Zinsmeister, A. R. Relationship between clinical features and gastric emptying disturbances in diabetes mellitus. *Clin. Endocrinol. (Oxf.)* **70**, 415–420 (2009).
63. Holzapfel, A. et al. Gastric emptying in Type II (non-insulin-dependent) diabetes mellitus before and after therapy readjustment: no influence of actual blood glucose concentration. *Diabetologia* **42**, 1410–1412 (1999).
64. Chang, J. et al. A 25-year longitudinal evaluation of gastric emptying in diabetes. *Diabetes Care* **35**, 2594–2596 (2012).
65. Halland, M. & Bharucha, A. E. Relationship between control of glycemia and gastric emptying disturbances in diabetes mellitus. *Clin. Gastroenterol. Hepatol.* **14**, 929–936 (2016).
66. Laway, B. A., Malik, T. S., Khan, S. H. & Rather, T. A. Prevalence of abnormal gastric emptying in asymptomatic women with newly detected diabetes and its reversibility after glycemic control - a prospective case control study. *J. Diabetes Compl.* **27**, 78–81 (2013).
67. Vella, A. et al. Effects of dipeptidyl peptidase-4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. *Diabetes* **56**, 1475–1480 (2007).
68. Berry, R. et al. Patterns of abnormal gastric pacemaking after sleeve gastrectomy defined by laparoscopic high-resolution electrical mapping. *Obes. Surg.* **27**, 1929–1937 (2017).
69. Vigneshwaran, B. et al. Impact of sleeve gastrectomy on type 2 diabetes mellitus, gastric emptying time, glucagon-like peptide 1 (GLP-1), ghrelin and leptin in non-morbidly obese subjects with BMI 30–35.0 kg/m^2: a prospective study. *Obes. Surg.* **26**, 2817–2823 (2016).
70. Camilleri, M., Lembo, A. & Katzka, D. A. Opioids in gastroenterology: treating adverse effects and creating therapeutic benefits. *Clin. Gastroenterol. Hepatol.* **15**, 1338–1349 (2017).
71. Galligan, J. J. & Akbarali, H. I. Molecular physiology of enteric opioid receptors. *Am. J. Gastroenterol. Suppl.* **2**, 17–21 (2014).
72. Camilleri, M. et al. Dose-related effects of synthetic human beta-endorphin and naloxone on fed gastrointestinal motility. *Am. J. Physiol.* **251**, G147–G154 (1986).
73. Reynolds, J. C., Ouyang, A. & Cohen, S. Evidence for an opiate-mediated pyloric sphincter reflex. *Am. J. Physiol.* **246**, G130–G136 (1984).
74. Parkman, H. P. et al. Similarities and differences between diabetic and idiopathic gastroparesis. *Clin. Gastroenterol. Hepatol.* **9**, 1056–1064 (2011).
75. Parkman, H. P. et al. Nausea and vomiting in gastroparesis: similarities and differences in idiopathic and diabetic gastroparesis. *Neurogastroenterol. Motil.* **28**, 1902–1914 (2016).
This paper provides an important summary of the features of idiopathic and diabetic gastroparesis observed in the NIH Gastroparesis Consortium study in United States.
76. Parkman, H. P. et al. Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. *Neurogastroenterol. Motil.* **29**, e12981 (2017).
77. Hasler, W. L. et al. Bloating in gastroparesis: severity, impact, and associated factors. *Am. J. Gastroenterol.* **106**, 1492–1502 (2011).
78. Jehangir, A. & Parkman, H. P. Chronic opioids in gastroparesis: relationship with gastrointestinal symptoms, healthcare utilization and employment. *World J. Gastroenterol.* **23**, 7310–7320 (2017).
79. Maranki, J. L. et al. Predictive factors for clinical improvement with Enterra gastric electric stimulation treatment for refractory gastroparesis. *Dig. Dis. Sci.* **53**, 2072–2078 (2008).
80. Oh, J. J. & Kim, C. H. Gastroparesis after a presumed viral illness: clinical and laboratory features and natural history. *Mayo. Clin. Proc.* **65**, 636–642 (1990).
81. Naftali, T., Yishai, R., Zangen, T. & Levine, A. Post-infectious gastroparesis: clinical and electrogastrographic aspects. *J. Gastroenterol. Hepatol.* **22**, 1423–1428 (2007).
82. Tack, J., Bisschops, R. & Sarnelli, G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* **127**, 1239–1255 (2004).
This classic paper describes different pathophysiological subgroups in a large number of

patients with functional dyspepsia, including delayed emptying and reduced gastric accommodation.
83. Talley, N. J. et al. Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. *Am. J. Gastroenterol.* **96**, 71–76 (2001).
84. Revicki, D. A. et al. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment. Pharmacol. Ther.* **18**, 141–150 (2003).
85. Revicki, D. A. et al. Evaluating symptom outcomes in gastroparesis clinical trials: validity and responsiveness of the Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD). *Neurogastroenterol. Motil.* **24**, 456–463 (2012).
86. Ricci, J. A. et al. Upper gastrointestinal symptoms in a U. S. national sample of adults with diabetes. *Scand. J. Gastroenterol.* **35**, 152–159 (2000).
87. Hasler, W. L. et al. Factors related to abdominal pain in gastroparesis: contrast to patients with predominant nausea and vomiting. *Neurogastroenterol. Motil.* **25**, 427–438 (2013).
88. Tougas, G. et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am. J. Gastroenterol.* **95**, 1456–1462 (2000).
89. Camilleri, M. et al. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. *Neurogastroenterol. Motil.* **24**, 1076–e562 (2012).
90. Szarka, L. 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.* **6**, 635–643 (2008).
91. Bouras, E. P. et al. SPECT imaging of the stomach: comparison with barostat, and effects of sex, age, body mass index, and fundoplication. Single photon emission computed tomography. *Gut* **51**, 781–786 (2002).
92. Fidler, J. et al. Application of magnetic resonance imaging to measure fasting and postprandial volumes in humans. *Neurogastroenterol. Motil.* **21**, 42–51 (2009).
93. Orthey, P. et al. Intragastric meal distribution during gastric emptying scintigraphy for assessment of fundic accommodation: correlation with symptoms of gastroparesis. *J. Nucl. Med.* **59**, 691–697 (2018).
94. Tack, J., Caenepeel, P., Piessevaux, H., Cuomo, R. & Janssens, J. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. *Gut* **52**, 1271–1277 (2003).
95. Grybäck, P. et al. Nationwide standardisation and evaluation of scintigraphic gastric emptying: reference values and comparisons between subgroups in a multicentre trial. *Eur. J. Nucl. Med.* **27**, 647–655 (2000).
96. Desai, A. et al. Reproducibility of gastric emptying assessed with scintigraphy in patients with upper G. I. symptoms. *Neurogastroenterol. Motil.* **30**, e13365 (2018).
97. Vasavid, P. et al. Normal solid gastric emptying values measured by scintigraphy using Asian-style meal: a multicenter study in healthy volunteers. *Neurogastroenterol. Motil.* **20**, 371–378 (2014).
98. Sachdeva, P. et al. Use of a high caloric liquid meal as an alternative to a solid meal for gastric emptying scintigraphy. *Dig. Dis. Sci.* **58**, 2001–2006 (2013).
99. Abell, T. L. 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.* **103**, 753–763 (2008).
100. Zinsmeister, A. R., Bharucha, A. E. & Camilleri, M. Comparison of calculations to estimate gastric emptying half-time of solids in humans. *Neurogastroenterol. Motil.* **24**, 1142–1145 (2012).
101. Ghoos, Y. F. et al. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. *Gastroenterology* **104**, 1640–1647 (1993).
102. van de Casteele, M. et al. Oxidative breakdown of octanoic acid is maintained in patients with cirrhosis despite advanced disease. *Neurogastroenterol. Motil.* **15**, 113–120 (2003).
103. Maqbool, S., Parkman, H. P. & Friedenberg, F. K. Wireless capsule motility: comparison of the SmartPill GI monitoring system with scintigraphy for measuring whole gut transit. *Dig. Dis. Sci.* **54**, 2167–2174 (2009).
104. Kuo, B. et al. Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. *Aliment. Pharmacol. Ther.* **27**, 186–196 (2008).
105. Hasler, W. L. et al. Relating gastric scintigraphy and symptoms to motility capsule transit and pressure findings in suspected gastroparesis. *Neurogastroenterol. Motil.* **30**, e13196 (2018).
106. Camilleri, M. et al. American Neurogastroenterology and Motility Society consensus statement on intraluminal measurement of gastrointestinal and colonic motility in clinical practice. *Neurogastroenterol. Motil.* **20**, 1269–1282 (2008). **This consensus document discusses methods to measure gastric motor functions**.
107. Cogliandro, R. et al. Gastroparesis is more an intestinal than a gastric disease [abstract Sa1567]. *Gastroenterology* **154** (Suppl. 1), S-313 (2018).
108. Camilleri, M. & Malagelada, J. R. Abnormal intestinal motility in diabetics with the gastroparesis syndrome. *Eur. J. Clin. Invest.* **14**, 420–427 (1984).
109. Stanghellini, V. et al. Chronic intestinal pseudo-obstruction: manifestations, natural history and management. *Neurogastroenterol. Motil.* **19**, 440–452 (2007).
110. Chial, H. J., Camilleri, M., Williams, D. E., Litzinger, K. & Perrault, J. Rumination syndrome in children and adolescents: diagnosis, treatment, and prognosis. *Pediatrics* **111**, 158–162 (2003).
111. O'Brien, M. D., Bruce, B. K. & Camilleri, M. The rumination syndrome: clinical features rather than manometric diagnosis. *Gastroenterology* **108**, 1024–1029 (1995). **This classical paper describes the symptoms and clinical features of rumination syndrome**.
112. Allen, J. H., de Moore, G. M., Heddle, R. & Twartz, J. C. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut* **53**, 1566–1570 (2004).
113. Sagar, R. C. et al. Cyclic vomiting syndrome is a prevalent and under-recognized condition in the gastroenterology outpatient clinic. *Neurogastroenterol. Motil.* **30**, e13174 (2018).
114. Halland, M., Pandolfino, J. & Barba, E. Diagnosis and treatment of rumination syndrome. *Clin. Gastroenterol. Hepatol.* **16**, 1549–1555 (2018).
115. Stanghellini, V. et al. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* **110**, 1036–1042 (1996).
116. Galli, J. A., Sawaya, R. A. & Friedenberg, F. K. Cannabinoid hyperemesis syndrome. *Curr. Drug Abuse Rev.* **4**, 241–249 (2011).
117. Cooper, C. J. et al. Rapid or normal gastric emptying as new supportive criteria for diagnosing cyclic vomiting syndrome in adults. *Med. Sci. Monit.* **20**, 1491–1495 (2014).
118. Venkatesan, T. et al. An Internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome (CVS). *Exp. Brain Res.* **232**, 2563–2570 (2014).
119. Lacy, B. E., Parkman, H. P. & Camilleri, M. Chronic nausea and vomiting: evaluation and treatment. *Am. J. Gastroenterol.* **113**, 647–659 (2018).
120. Homko, C. J., Duffy, F., Friedenberg, F. K., Boden, G. & Parkman, H. P. Effect of dietary fat and food consistency on gastroparesis symptoms in patients with gastroparesis. *Neurogastroenterol. Motil.* **27**, 501–508 (2015).
121. Olausson, E. A. et al. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am. J. Gastroenterol.* **109**, 375–385 (2014). **This important clinical trial demonstrates the importance of attention to particle size in the diet in patients with gastroparesis**.
122. Pasricha, P. J. et al. Characteristics of patients with chronic unexplained nausea and vomiting and normal gastric emptying. *Clin. Gastroenterol. Hepatol.* **9**, 567–576 (2011).
123. McCallum, R. W. & George, S. J. Gastric dysmotility and gastroparesis. *Curr. Treat. Opt. Gastroenterol.* **4**, 179–191 (2001).
124. Rao, A. S. & Camilleri, M. Review article: metoclopramide and tardive dyskinesia. *Aliment. Pharmacol. Ther.* **31**, 11–19 (2010).
125. Parkman, H. P., Hasler, W. L. & Fisher, R. S. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology* **127**, 1592–1622 (2004).
126. Parkman, H. P., Carlson, M. R. & Gonyer, D. Metoclopramide nasal spray reduces symptoms of gastroparesis in women, but not men, with diabetes: results of a phase 2B randomized study. *Clin. Gastroenterol. Hepatol.* **13**, 1256–1263 (2015).
127. Maganti, K., Onyemere, K. & Jones, M. P. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am. J. Gastroenterol.* **98**, 259–263 (2003).
128. Dhir, R. & Richter, J. E. Erythromycin in the short- and long-term control of dyspepsia symptoms in patients with gastroparesis. *J. Clin. Gastroenterol.* **38**, 237–242 (2004).
129. Thielemans, L. et al. Desensitization of the human motilin receptor by motilides. *J. Pharmacol. Exp. Ther.* **313**, 1397–1405 (2005).
130. Chedid, V. et al. Characterization of upper gastrointestinal symptoms, gastric motor functions and associations in patients with diabetes at a referral center. *Am. J. Gastroenterol.* https://doi.org/10.1038/s41395-018-0234-1 (2018).
131. Tack, J., Janssen, P., Masaoka, T., Farre, R. & Van Oudenhove, L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. *Clin. Gastroenterol. Hepatol.* **10**, 1239–1245 (2012).
132. Camilleri, M. et al. Efficacy and safety of relamorelin in diabetics with symptoms of gastroparesis: a randomized, placebo-controlled study. *Gastroenterology* **153**, 1240–1250 (2017).
133. Lembo, A. et al. Relamorelin reduces vomiting frequency and severity and accelerates gastric emptying in adults with diabetic gastroparesis. *Gastroenterology* **151**, 87–96 (2016).
134. Carbone, F. et al. A controlled, cross-over trial shows benefit of prucalopride for symptom control and gastric emptying enhancement in idiopathic gastroparesis. *Gastroenterology* **150**, S213–S214 (2016).
135. Matsueda, K., Hongo, M., Tack, J., Saito, Y. & Kato, H. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. *Gut* **61**, 821–828 (2012).
136. Tack, J. et al. Long-term safety and efficacy of acotiamide in functional dyspepsia (postprandial distress syndrome)-results from the European phase 3 open-label safety trial. *Neurogastroenterol. Motil.* **30**, e13284 (2018).
137. Parkman, H. P. et al. Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. *JAMA* **310**, 2640–2649 (2013).
138. Talley, N. J. et al. Effect of amitriptyline and escitalopram on functional dyspepsia: a multicenter, randomized controlled study. *Gastroenterology* **149**, 340–349 (2015). **This randomized controlled trial of central neuromodulators in functional dyspepsia demonstrates a better outcome in patients with normal gastric emptying treated with tricyclic antidepressants and no benefit with selective serotonin reuptake inhibitors**.
139. Herrick, L. M. et al. Effects of amitriptyline and escitalopram on sleep and mood in patients with functional dyspepsia. *Clin. Gastroenterol. Hepatol.* **16**, 401–406 (2018).
140. Anttila, S. A. & Leinonen, E. V. A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev.* **7**, 249–264 (2001).
141. Malamood, M., Roberts, A., Kataria, R., Parkman, H. P. & Schey, R. Mirtazapine for symptom control in refractory gastroparesis. *Drug Des. Devel. Ther.* **11**, 1035–1041 (2017).
142. Pasricha, P. J. et al. Aprepitant has mixed effects on nausea and reduces other symptoms in patients with gastroparesis and related disorders. *Gastroenterology* **154**, 65–76 (2018).
143. Jacob, D. et al. Effects of NK1 receptors on gastric motor functions and satiation in healthy humans: results from a controlled trial with the NK1 antagonist aprepitant. *Am. J. Physiol. Gastrointest. Liver Physiol.* **313**, G505–G510 (2017).
144. Mearin, F., Camilleri, M. & Malagelada, J. R. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* **90**, 1919–1925 (1986). **This classic original article demonstrates pyloro-spasm in patients with diabetic gastroparesis**.
145. Coleski, R., Anderson, M. A. & Hasler, W. L. Factors associated with symptom response to pyloric injection of botulinum toxin in a large series of gastroparesis patients. *Dig. Dis. Sci.* **54**, 2634–2642 (2009).
146. Arts, J. et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment. Pharmacol. Ther.* **26**, 1251–1258 (2007).
147. Friedenberg, F. K., Palit, A., Parkman, H. P., Hanlon, A. & Nelson, D. B. Botulinum toxin A for the treatment of

delayed gastric emptying. *Am. J. Gastroenterol.* **103**, 416–423 (2008).
148. Shlomovitz, E. et al. Early human experience with per-oral endoscopic pyloromyotomy (POP). *Surg. Endosc.* **29**, 543–551 (2015).
149. Khashab, M. A. et al. Gastric per-oral endoscopic myotomy for refractory gastroparesis: results from the first multicenter study on endoscopic pyloromyotomy (with video). *Gastrointest. Endosc.* **85**, 123–128 (2017).
150. Rodriguez, J. H. et al. Per oral endoscopic pyloromyotomy for refractory gastroparesis: initial results from a single institution. *Surg. Endosc.* **31**, 5381–5388 (2017).
151. Malik, Z. et al. Gastric per oral endoscopic myotomy (G-POEM) for the treatment of refractory gastroparesis: early experience. *Dig. Dis. Sci.* **63**, 2405–2412 (2018).
152. Gonzalez, J. M., Benezech, A., Vitton, V. & Barthet, M. G-POEM with antro-pyloromyotomy for the treatment of refractory gastroparesis: mid-term follow-up and factors predicting outcome. *Aliment. Pharmacol. Ther.* **46**, 364–370 (2017).
153. Dacha, S. et al. Outcomes and quality-of-life assessment after gastric per-oral endoscopic pyloromyotomy (with video). *Gastrointest. Endosc.* **86**, 282–289 (2017).
154. Shada, A. L. et al. Laparoscopic pyloroplasty is a safe and effective first-line surgical therapy for refractory gastroparesis. *Surg. Endosc.* **30**, 1326–1332 (2016).
155. Mancini, S. A., Angelo, J. L., Peckler, Z., Philp, F. H. & Farah, K. F. Pyloroplasty for refractory gastroparesis. *Am. Surgeon* **81**, 738–746 (2015).
156. Toro, J. P. et al. Efficacy of laparoscopic pyloroplasty for the treatment of gastroparesis. *J. Am. Coll. Surgeons* **218**, 652–660 (2014).
157. Heckert, J., Sankineni, A., Hughes, W. B., Harbison, S. & Parkman, H. Gastric electric stimulation for refractory gastroparesis: a prospective analysis of 151 patients at a single center. *Dig. Dis. Sci.* **61**, 168–175 (2016).
158. Ishii, M. et al. Altered postprandial insulin requirement in IDDM patients with gastroparesis. *Diabetes Care* **17**, 901–903 (1994).
159. Parthasarathy, G. et al. Relationship between gastric emptying and diurnal glycemic control in type 1 diabetes mellitus: a randomized trial. *J. Clin. Endocrinol. Metab.* **102**, 398–406 (2017).
160. Calles-Escandón, J. et al. Glucose sensor-augmented continuous subcutaneous insulin infusion in patients with diabetic gastroparesis: an open-label pilot prospective study. *PLOS ONE* **13**, e0194759 (2018).
161. Farup, C. E. et al. Effect of domperidone on the health-related quality of life of patients with symptoms of diabetic gastroparesis. *Diabetes Care* **21**, 1699–1706 (1998).
162. Lacy, B. E., Crowell, M. D., Mathis, C., Bauer, D. & Heinberg, L. J. Gastroparesis: quality of life and health care utilization. *J. Clin. Gastroenterol.* **52**, 20–24 (2018).
163. Yu, D. et al. The burdens, concerns, and quality of life of patients with gastroparesis. *Dig. Dis. Sci.* **62**, 879–893 (2017).
164. Jaffe, J. K., Paladugu, S., Gaughan, J. P. & Parkman, H. P. Characteristics of nausea and its effects on quality of life in diabetic and idiopathic gastroparesis. *J. Clin. Gastroenterol.* **45**, 317–321 (2011).
165. Cherian, D., Sachdeva, P., Fisher, R. S. & Parkman, H. P. Abdominal pain is a frequent symptom of gastroparesis. *Clin. Gastroenterol. Hepatol.* **8**, 676–681 (2010).
166. Friedenberg, F. K., Kowalczyk, M. & Parkman, H. P. The influence of race on symptom severity and quality of life in gastroparesis. *J. Clin. Gastroenterol.* **47**, 757–761 (2013).
167. Woodhouse, S., Hebbard, G. & Knowles, S. R. Exploring symptom severity, illness perceptions, coping styles, and well-being in gastroparesis patients using the common sense model. *Dig. Dis. Sci.* **63**, 958–965 (2018).
168. Tack, J., Rotondo, A., Meulemans, A., Thielemans, L. & Cools, M. Randomized clinical trial: a controlled pilot trial of the 5-HT4 receptor agonist revexepride in patients with symptoms suggestive of gastroparesis. *Neurogastroenterol. Motil.* **28**, 487–497 (2016).
169. McCallum, R. W. et al. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin. Gastroenterol. Hepatol.* **8**, 947–954 (2010).
170. Mekaroonkamol, P. et al. Gastric peroral endoscopic pyloromyotomy reduces symptoms, increases quality of life, and reduces healthcare usage for patients with gastroparesis. *Clin. Gastroenterol. Hepatol.* https://doi.org/10.1016/j.cgh.2018.04.016 (2018).
171. Rajan, E. et al. Innovative gastric endoscopic muscle biopsy to identify all cell types, including myenteric neurons and interstitial cells of Cajal in patients with idiopathic gastroparesis: a feasibility study (with video). *Gastrointest. Endosc.* **84**, 512–517 (2016).
172. Rajan, E. et al. Endoscopic muscle biopsy sampling of the duodenum and rectum: a pilot survival study in a porcine model to detect myenteric neurons. *Gastrointest. Endosc.* **87**, 600–606 (2018).
173. Marathe, C. S., Rayner, C. K., Wu, T., Jones, K. L. & Horowitz, M. Gastric emptying and the personalized management of type 1 diabetes. *J. Clin. Endocrinol. Metab.* **103**, 3503–3506 (2018).
174. Dyck, P. J. et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* **43**, 817–824 (1993).
175. Dyck, P. J. et al. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. *Diabetes Care* **22**, 1479–1486 (1999).
176. Papanas, N. & Ziegler, D. Risk factors and comorbidities in diabetic neuropathy: an update 2015. *Rev. Diabet. Stud.* **12**, 48–62 (2015).
177. Wiggin, T. D. et al. Elevated triglycerides correlate with progression of diabetic neuropathy. *Diabetes* **58**, 1634–1640 (2009).
178. Park, S.-Y., Camilleri, M., Packer, D. & Monahan, K. Upper gastrointestinal complications following ablation therapy for atrial fibrillation. *Neurogastroenterol. Motil.* **29**, e13109 (2017).
179. Suarez, G. A. et al. The autonomic symptom profile: a new instrument to assess autonomic symptoms. *Neurology* **52**, 523–528 (1999).
180. Vernino, S. et al. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N. Engl. J. Med.* **343**, 847–855 (2000).
181. Gibbons, C. H. & Freeman, R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. *Brain* **138**, 43–52 (2015).
182. Low, P. A. & Singer, W. Treatment-induced neuropathy of diabetes: an energy crisis? *Brain* **138**, 2–3 (2015).
183. Sanders, K. M., Koh, S. D., Ro, S. & Ward, S. M. Regulation of gastrointestinal motility—insights from smooth muscle biology. *Nat. Rev. Gastro. Hep.* **9**, 633–645 (2012).
184. Shin, A. et al. Ghrelin agonist RM-131 accelerates gastric emptying of solids and reduces symptoms in patients with type 1 diabetes mellitus. *Clin. Gastroenterol. Hepatol.* **11**, 1453–1459 (2013).
185. Viramontes, B. E. et al. Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. *Neurogastroenterol. Motil.* **13**, 567–574 (2001).

Acknowledgements
The authors thank and acknowledge the excellent secretarial assistance of C. Stanislav, Mayo Clinic.

Author contributions
Introduction (M.C.); Epidemiology (M.C. and A.C.F.); Mechanisms/pathophysiology (M.C., V.C., K.H., M.H., K.L.J. and P.A.L.); Diagnosis, screening and prevention (M.C., K.H., K.L.J., S.-Y.P. and V.S.); Management (M.C., V.C. and H.P.P.); Quality of life (M.C. and A.C.F.); Outlook (M.C.); Overview of the Primer (M.C.).

Competing interests
M.C. consults with Allergan on relamorelin (consulting fee to his employer, Mayo Clinic) and consults 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 other authors declare no noteworthy conflicts of interest.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Reviewer information
Nature Reviews Disease Primers thanks M. Bashashati, K. Bielefeldt, P. Hellström, G. Sanger and the other anonymous referee(s) for their contribution to the peer review of this work.