

Mistakes in gastroparesis and how to avoid them

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The term 'gastroparesis' was first coined by Kassander in 1958 to describe the fact that barium did not leave the stomach of patients with diabetes for over 24 hours — so-called 'gastroparesis diabeticorum'.¹ Nowadays it refers to a delay in gastric emptying that is associated with symptoms primarily of nausea and vomiting as well as the absence of mechanical obstruction.

In 1958, 21 cases were described, but in 2019, 5 million US individuals were diagnosed as having gastroparesis. This rapid increase in prevalence is likely to have occurred because it has become much easier to measure gastric emptying and to attribute symptoms to this without necessarily thinking through differentials. The incidence of hospital admissions for patients labelled as having gastroparesis is rapidly rising, increasing at a much faster rate than admissions for patients with nausea and vomiting, gastro-oesophageal reflux disease, gastritis or gastric ulcers, which are all remaining relatively static. Gastroparesis therefore represents a major healthcare burden.²

Gastroparesis can be idiopathic or is most frequently caused by diabetes (type 1 more than type 2) or surgical procedures that can disrupt the vagus nerve (e.g. Billroth gastrectomy, oesophagectomy, gastric bypass surgery and fundoplication).

In this article, I describe the mistakes most frequently made in patients who have a suspected diagnosis of gastroparesis. I base my discussion on the available evidence as well as clinical experience in the field.

Mistake 1 Diagnosing gastroparesis using incomplete evidence

A diagnosis of gastroparesis requires three features to be met — a delay in gastric emptying, the absence of mechanical obstruction and typical symptoms (figure 1). Typical symptoms include nausea and regurgitation/vomiting, usually of undigested food, within a few hours after a meal,

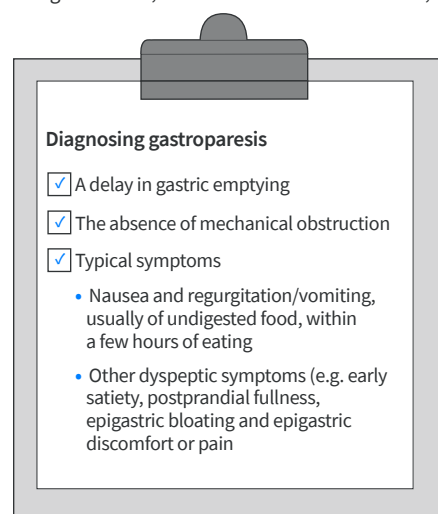
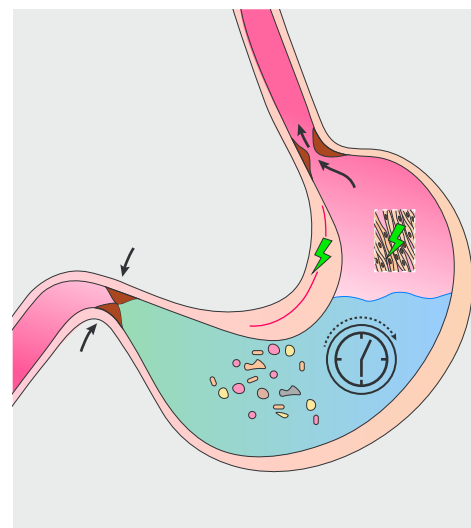


Figure 1 | Features required to make a diagnosis of gastroparesis.

but can also include other dyspeptic symptoms such as early satiety (feeling full very quickly after a few mouthfuls), postprandial fullness (feeling uncomfortably full after a meal, as if the food cannot pass through the stomach), epigastric bloating (which can be visible) and epigastric discomfort or pain. A delay in gastric emptying that is not accompanied by typical symptoms should not be classified as gastroparesis and should simply be referred to as 'delayed gastric emptying'. If the predominant symptoms are more those of dyspepsia but there is no nausea and vomiting, the diagnosis is most likely to be functional dyspepsia, which has a different treatment algorithm (see mistake 2).

It is tempting to infer a diagnosis of delayed gastric emptying after performing a gastroscopy that shows food in the stomach after a 6-hour fast. Although this would be a differential in a patient who has symptoms of nausea and vomiting and the right predisposing factors, such as diabetes, it is crucial to remember to consider important organic differentials, such as neoplasia, that can cause a gastric-outlet obstruction. In patients who have gastroparesis, there are usually no alarm signs, with anaemia and weight loss being rare, so finding either of these should act as a prompt to look carefully for an underlying malignancy using enteroscopy or cross-sectional imaging as



appropriate.³ In patients who have retained food and fluid in their stomach after an adequate fast, it is important to get a more complete view by repeating the gastroscopy after a longer fast and after they have stopped taking any drugs that may contribute to delayed gastric emptying (e.g. opiates). If obstructive causes have been excluded, then delayed gastric emptying would need to be confirmed using either breath testing or scintigraphy tests.

It should be noted that the degree of gastric emptying is dependent on the type of meal consumed and that the pattern and rate of emptying can vary considerably between individuals. Based on a large multicentre study, consensus guidelines have been developed to define what constitutes delayed gastric

Time after meal	Upper limit of gastric retention values for a low-fat meal
1h	90%
2h	60%
3h	30%
4h	10%

Table 1 | Diagnosing delayed gastric emptying: normal values for percentage retention of a low-fat meal.

emptying.⁴ With a typical 255 kcal (2% fat/low fat) meal, delayed gastric emptying is defined as retention $\geq 60\%$ at 2 hours and $\geq 10\%$ at 4 hours. Normal values for gastric emptying will change if the meal is high fat, nutrient drink, or mixed solid/liquid, so it is important that the correct reference ranges are used (Table 1). It is recommended that scintigraphy is performed over 4 hours to ensure accuracy of the results. With the pressures on healthcare systems, however, it is common to perform shorter studies (e.g. 90 minutes or 2 hours), but this can be misleading and can cause an overdiagnosis of gastroparesis.

Mistake 2 Not considering conditions than mimic gastroparesis

There are several conditions, including several functional gastrointestinal disorders, that can have a similar clinical presentation to gastroparesis and that are associated with delays in gastric emptying (figure 2). These conditions should therefore be considered and systematically excluded to ensure management strategies are adapted appropriately.

First is functional dyspepsia, which is the closest mimic to gastroparesis. Functional dyspepsia can be divided into epigastric pain syndrome and postprandial distress syndrome. Postprandial distress syndrome is characterised by symptoms of early satiety, postprandial fullness, epigastric bloating and epigastric discomfort or pain, symptoms that are almost identical to those of gastroparesis but with less nausea and vomiting. About a third of patients with functional dyspepsia will have mild to moderate delays in gastric emptying. The pathophysiology of functional dyspepsia is mainly due to a combination of abnormal gastric accommodation and visceral hypersensitivity. In practice, the presence of regular nausea and vomiting/regurgitation of undigested food would point towards a diagnosis of gastroparesis.

The second condition is rumination syndrome, which causes effortless regurgitation, mainly postprandially. This is a behavioural phenomenon caused by subconscious abdominal contractions that cause the regurgitation of food back into the oesophagus. It can be associated with dyspeptic symptoms and in some patients, the rumination behaviour develops as a response to the dyspepsia because it often relieves this sensation. Typical symptoms of rumination syndrome include a cycle of regurgitation followed by swallowing of the regurgitant during or after meals, with this continuing until the regurgitant becomes acidic and is then expelled orally. Rumination syndrome can be diagnosed using combined high-resolution manometry–impedance monitoring, as this can reveal a typical pattern of low-pressure gastric straining followed by regurgitation

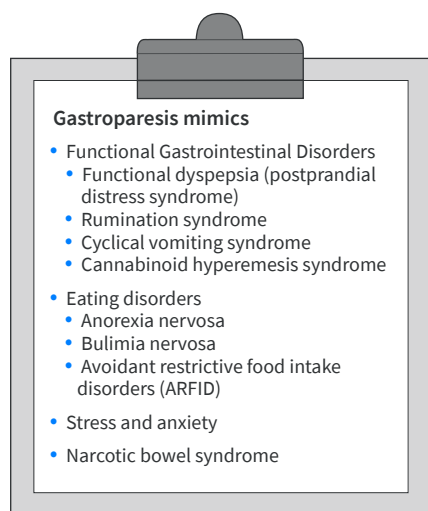


Figure 2 | Conditions than mimic gastroparesis.

(figure 3). Patients often complain that they vomit after eating; however, if a thorough history is taken, it can become clear that the vomiting is effortless (i.e. regurgitation).

The treatment for this involves education and deep-breathing exercises.

Third are cyclical vomiting and cannabinoid hyperemesis syndromes, which cause episodic attacks of vomiting that usually last for a few days and can be associated with dehydration and electrolyte imbalance. In between episodes,

patients are completely asymptomatic, which is not the case for patients with gastroparesis. Cyclical vomiting is very strongly associated with a personal or family history of migraines and cannabinoid hyperemesis syndrome is associated with heavy cannabis intake and the use of hot showers to relieve the nausea. Both of these syndromes can be associated with a delay in gastric emptying.

Eating disorders, such as anorexia nervosa and bulimia nervosa, are the fourth conditions to consider because a low body mass index is associated with delays in gastric emptying and disturbed gastric functioning. It is therefore important to look for a history of eating disorders because the treatment for such disorders involves psychological therapy and enforced nutrition, not, for example, the use of prokinetics.

Fifth are stress and anxiety, which can centrally induce nausea and vomiting. If the anxiety is directed towards food, so-called 'avoidant restrictive food intake disorder',⁵ this condition might present more like gastroparesis, with immediate postprandial nausea and vomiting. Patients may complain that they only have to see food or put it in their mouth for vomiting to occur. This very early response to food, before the food even reaches the stomach, should point more towards

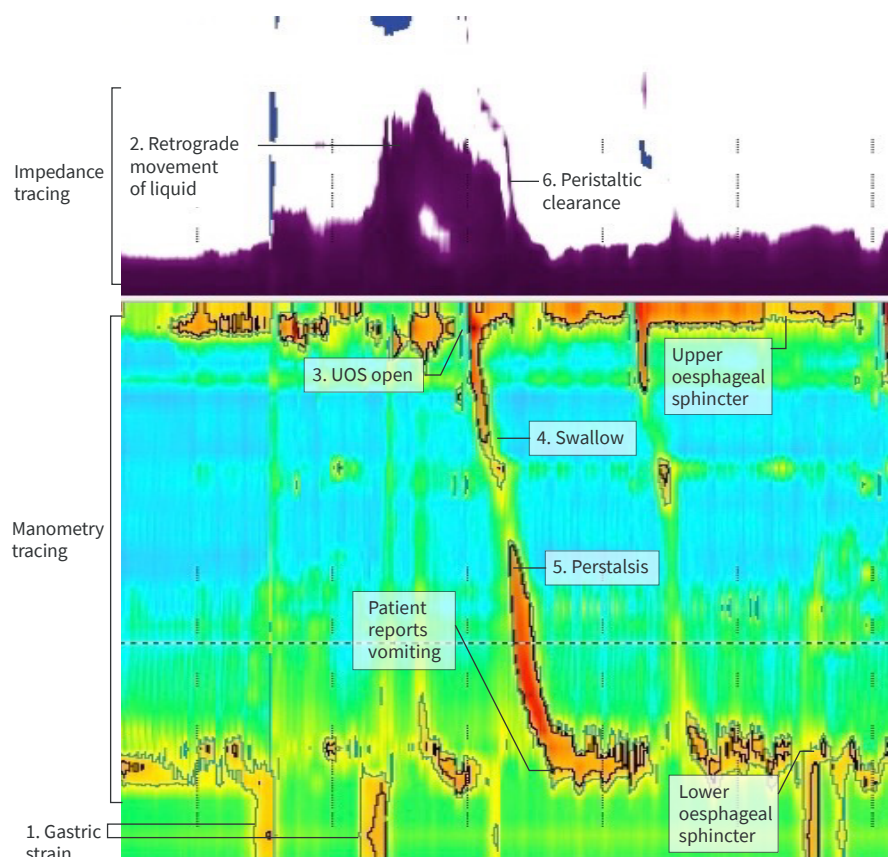


Figure 3 | Diagnosis of rumination by combined high-resolution manometry–impedance monitoring. Rumination demonstrates a typical pattern of low-pressure gastric straining followed by regurgitation.

psychological causes. In patients who have headaches or new neurological symptoms, it is important to perform a neurological examination, and cross-sectional imaging of the brain may be warranted to exclude a central lesion. Vomiting that is induced by anxiety and stress is best managed with psychotherapy (e.g. cognitive behavioural therapy or mindfulness) or pharmacological therapies (e.g. selective serotonin reuptake inhibitors).

The final condition to consider is narcotic bowel syndrome (also known as opiate-induced central sensitisation syndrome), which is caused by the side effects of opiates on the gut. Typically, patients have worsening abdominal pain, but they can also have nausea, vomiting and epigastric bloating, which are symptoms similar to that of gastroparesis. As gastric emptying is delayed by opiates, it is useful to reassess symptoms and gastric emptying in patients once they have been weaned off them (see mistake 6).

Mistake 3 Failing to investigate biopsychosocial factors in patients with gastroparesis

It is important to remember that in patients who have gastroparesis, there is no correlation between the severity of symptoms and the severity of disease.⁶ In fact, the symptoms are not necessarily related to the delayed gastric emptying alone but arise due to a complex interplay between abnormal physiology (e.g. delayed gastric emptying or possible visceral hypersensitivity) and psychosocial factors such as poor sleep, low mood, stress, and poor diet.

It is therefore important for the successful management of gastroparesis to use a biopsychosocial approach and ask about these factors and manage them rather than simply targeting the delayed gastric emptying with prokinetics, pyloric Botox or more invasive therapies such as gastric peroral endoscopic myotomy and gastric pacing. It is also important to consider the role that visceral hypersensitivity has to play, as it will cause nutrient intolerance and pain even with post-pyloric feeding (e.g. nasojejunal feeding) and will need to be treated with neuromodulators.

Mistake 4 Ineffectively addressing nutritional issues in patients with gastroparesis

Foods that are high in fibre and fat are emptied from the stomach more slowly, so patients with gastroparesis should be advised to stick to a low-fibre, low-fat diet and to eat little and often. Liquids are easier to tolerate, so patients who continue to have difficulty consuming solids can

be moved onto a liquid diet or a small-particle diet (i.e. foods that can be mashed with a fork). One randomised controlled trial found that a 20-week dietary intervention with a small-particle diet was associated with an improvement in the symptoms of nausea, vomiting, early satiety, postprandial fullness, heartburn and regurgitation compared with a low glycaemic index diet.⁷ However, neither the small-particle diet nor the low glycaemic index diet had any effect on upper abdominal pain.⁷

The complications of gastroparesis include dehydration as well as electrolyte and nutritional deficiencies, which are secondary to the vomiting. Weight loss is rare but is present in about 8% of patients, usually those with a severe delay in gastric emptying. Enteral nutrition may be needed in patients who have nutritional deficiencies and weight loss, and it is important that such patients are assessed by a dietician. Nutritional treatment can start with oral liquid supplements, but if patients continue to vomit and have associated weight loss, despite optimising the use of prokinetics, they may need post-pyloric feeding. If patients do not tolerate post-pyloric feeding (i.e. they have ongoing vomiting), this would suggest that it is not the delay in gastric emptying that is the problem but, instead, that they may have a problem with visceral hypersensitivity and that this should be the target of treatment. Pain is not a clear indication of a requirement for jejunal feeding and if patients are overweight and do not have significant weight loss or nutritional deficiencies, then jejunal feeding may not be needed.⁸ As weight loss is rare and usually associated with severe delays in gastric emptying, it is important to consider other factors that may be contributing to vomiting in patients with weight loss and only mild to moderate delays in gastric emptying (e.g. eating disorders).

Mistake 5 Not optimising the medications for gastroparesis

It is important to optimise the medications used to treat patients with gastroparesis, whilst avoiding the following mistakes.

Firstly, for prokinetics to work most effectively, they need to be taken half an hour before meals to induce gastric motility. Patients therefore need to be educated about this.

Erythromycin is a motilin-receptor agonist and an effective prokinetic, but it should not be used for too long. In a randomised control study of metoclopramide 10 mg three times a day versus erythromycin 250 mg three times a day in patients with delayed gastric emptying, there was a reduction in symptoms and in the gastric emptying time for both groups, but there was better symptomatic improvement in the erythromycin group.⁹ However, erythromycin is associated with tachyphylaxis, which means that its use should be limited to a few weeks. For acute

flares, it can be used as an add-on to existing treatments, after which time it should be stopped.

Serotonergic agents (e.g. prucalopride) should also be considered for the treatment of gastroparesis. Prucalopride is an agonist of the 5-HT₄ (5-hydroxytryptamine 4) receptor and it works to improve gastrointestinal transit. It is typically used to treat slow-transit constipation in females but also helps to speed up gastric emptying. In a randomised placebo-controlled trial of prucalopride versus placebo in patients with idiopathic gastroparesis, 4 weeks of prucalopride led to improved gastric emptying, reduced symptoms and better quality of life.¹⁰ The usual dose is 2 mg once a day and it can be increased to 4 mg once a day, although higher doses are associated with more side effects (e.g. headaches and diarrhoea). It can be helpful to trial prucalopride in patients who do not respond to first-line treatment, particularly if they also suffer with constipation (e.g. in patients with scleroderma or other connective tissue disorders who have upper and lower gastrointestinal hypomotility with slow-transit constipation and delayed gastric emptying).

It is also important to consider the potential serious side effects of prokinetic medications. Metoclopramide is associated with extrapyramidal side effects, such as dystonia and akathisia after a single dose or tardive dyskinesia and Parkinsonism after prolonged doses. Therefore, metoclopramide should not be prescribed in the long term. If patients respond symptomatically to metoclopramide, it is helpful to convert them to another prokinetic to be used more long term. Domperidone is an option that is not associated with extrapyramidal side effects. However, domperidone is associated with a prolonged QT interval, so it is imperative that patients have an ECG to check for a normal QT interval before initiation of treatment — the ECG should be repeated once patients have been started on domperidone to ensure that the QT interval remains in the normal range.

Mistake 6 Ignoring the role of drugs such as opiates in generating symptoms

Opiates cause delayed gastric emptying and symptoms of gastroparesis, so it is hard to interpret the clinical picture in patients on opiates. In a study of 223 patients with a diagnosis of gastroparesis, 20% were on regular opiates and 10% were on opiates on an as-required basis.¹¹ The median morphine equivalent was 60 mg per day. Patients on opiates had more intense and longer lasting nausea, more frequent and severe vomiting, more retching, more heartburn, increased chest discomfort, more upper abdominal pain and increased hospitalizations than patients who were not taking opiates.¹¹ Therefore, in patients with suspected gastroparesis and opiate

use, it is important to wean them off the opiates and to repeat the gastric emptying testing to get a more accurate assessment of their symptoms and physiology in the absence of the confounding effects of the opiates.

Other medications that are associated with delayed gastric emptying include anticholinergics (e.g. hyoscine), antipsychotics and incretins (e.g. liraglutide). It is therefore imperative to take a thorough medication history in the assessment of gastroparesis and to consider the withdrawal of certain drugs in the management plan, especially opiates.

Mistake 7 Overlooking the treatment of gastro-oesophageal reflux disease

In patients with gastroparesis, failure to empty the stomach results in the regurgitation of acids and non-acids, and it is not uncommon for patients with gastroparesis to have coexistent gastro-oesophageal reflux disease.¹² Over time, pathological acid reflux can lead to oesophagitis, peptic stricturing and, rarely, Barrett's oesophagus.

It is important that these patients take high-dose proton-pump inhibitors (PPIs) twice a day to prevent the progression of acid-induced damage to the oesophagus. In the presence of uncertainty about medication absorption (because of the recurrent vomiting of tablets), it can be helpful to use orodispersible tablets of PPIs (e.g. orodispersible lansoprazole or omeprazole).

Mistake 8 Failing to address poorly controlled blood glucose levels in patients with diabetic gastroparesis

Delayed gastric emptying is present in 27–65% of patients with type 1 diabetes and 30% of patients with type 2 diabetes, and hyperglycaemia is independently associated with delayed gastric emptying. The presence of gastroparesis in the setting of diabetes is a consequence of autonomic neuropathy that results from a longstanding poor control of blood glucose levels as well as from daily fluctuations caused by episodic hyperglycaemia. This means that gastroparesis is less likely to develop with good management of diabetes, the maintenance of normal blood glucose levels and the absence of microvascular complications.

Unfortunately, gastroparesis makes it very difficult to control postprandial blood glucose levels and it is not uncommon for patients who have diabetes to struggle to accurately predict how much insulin they need. This can result in a vicious cycle in which gastroparesis leads to vomiting, diabetic ketoacidosis and high blood glucose levels, which further worsen the gastroparesis. In such patients, using a closed-loop system with a continuous glucose sensor

and a 24-hour insulin pump can dramatically improve the stability of blood glucose levels, as well as reduce gastroparesis-type symptoms. In one study, 24 weeks of treatment with a closed-loop system led to more time in euglycaemia, significantly less nausea, vomiting, early satiety, postprandial fullness and bloating, as well as to an improved tolerance of liquid-nutrient meals.¹³

Mistake 9 Treating pain by speeding up gastric emptying

Upper abdominal pain is common in gastroparesis. It is present in almost 90% of patients and is most commonly present in the epigastrium.¹⁴ A third of patients will describe the pain as severe, with this being more likely if they are female and if they have any of the following — anxiety, depression, somatisation and opiate use.

There is no correlation between the severity of the pain and the severity of the gastric emptying delay. Therefore, medication or treatment that aims to reverse the gastroparesis by speeding up gastric emptying (e.g. prokinetics, pyloric Botox or gastric pacing) will not treat the pain. Pain is usually a marker of underlying visceral hypersensitivity, so it should be managed using a biopsychosocial approach (e.g. by addressing anxiety and depression or by managing and reducing opiate use) and using medications such as PPIs or neuromodulators (e.g. mirtazapine or pregabalin), as for functional dyspepsia.

Mistake 10 Not selecting patients appropriately for gastric pacing

Gastric pacing involves the delivery of electrical stimulation to the stomach via an implanted pacemaker system that consists of a neurostimulator and two leads. Implantation is done under general anaesthetic via an open or laparoscopic approach. The rate and amplitude of stimulation can be adjusted wirelessly with a handheld external programmer. Patients may need to return to hospital for adjustment or reprogramming of the device to optimise the effect on gastric emptying. Gastric pacing is thought to work by interfering with sensory transmission to the brain, thereby improving certain symptoms.

Results from open-label studies of gastric pacing are mixed. In studies that involve 'blinding' the patients as to whether the pacemaker is on or off, there was no evidence for an improvement in symptoms.¹⁵ The best results seem to be in patients with nausea and vomiting, who have diabetes and who are not on opiates, so patient selection is crucial.

The gastric pacing device can be associated with multiple complications, including device

migration, lead displacement, pain at the implantation site, bowel obstruction and, in rare cases, erosion through the skin. In patients who have noninflammatory connective tissue disorders with skin involvement, there seems to be a high prevalence of complications so, although no studies have formally assessed this yet, in our practice, we do not recommend gastric pacing for these patients.

References

1. Kassander P. Asymptomatic gastric retention in diabetics (gastroparesis diabetorum). *Ann Intern Med* 1958; 48: 797–812.
2. Wang YR, Fisher RS and Parkman HP. Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995–2004. *Am J Gastroenterol* 2008; 103: 313–322.
3. Parkman HP, Yates K, Hasler WL, et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. *Gastroenterology* 2011; 140: 101–115.
4. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *J Nucl Med Technol* 2008; 36: 44–54.
5. Murray HB, Jehangir A, Silvernale CJ, et al. Avoidant/restrictive food intake disorder symptoms are frequent in patients presenting for symptoms of gastroparesis. *Neurogastroenterol Motil* 2020; 32: e13931.
6. Wuestenberghs F, Juge M, Melchior C, et al. Association between symptoms, quality of life, and gastric emptying in dyspeptic patients. *J Neurogastroenterol Motil* 2019; 25: 534–543.
7. Olsson EA, Störsrud S, Grundin H, et al. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am J Gastroenterol* 2014; 109: 375–385.
8. Paine P, McMahon M, Farrer K, et al. Jejunal feeding: when is it the right thing to do? *Frontline Gastroenterol* 2019; 11: 397–403.
9. Erbas T, Varoglu E, Erbas B, et al. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. *Diabetes Care* 1993; 16: 1511–1514.
10. Carbone F, Van den Houte K, Clevers E, et al. Prucalopride in gastroparesis: a randomized placebo-controlled crossover study. *Am J Gastroenterol* 2019; 114: 1265–1274.
11. Jehangir A and Parkman HP. Chronic opioids in gastroparesis: relationship with gastrointestinal symptoms, healthcare utilization and employment. *World J Gastroenterol* 2017; 23: 7310–7320.
12. Fass R, McCallum RW and Parkman HP. Clinical Roundtable Monograph: Treatment challenges in the management of gastroparesis-related GERD. *Gastroenterol Hepatol* 2009; 5 (Suppl 18): 4–11.
13. Calles-Escandón J, Koch KL, Hasler WL, et al. Glucose sensor-augmented continuous subcutaneous insulin infusion in patients with diabetic gastroparesis: an open-label pilot prospective study. *PLoS One* 2018; 13: e0194759.
14. Parkman HP, Wilson LA, Hasler WL, et al. Abdominal pain in patients with gastroparesis: associations with gastroparesis symptoms, etiology of gastroparesis, gastric emptying, somatization, and quality of life. *Dig Dis Sci* 2019; 64: 2242–2255.
15. Zoll B, Jehangir A, Malik Z, et al. Gastric electric stimulation for refractory gastroparesis. *J Clin Outcomes Manag* 2019; 26: 27–38.

Your gastroparesis briefing

UEG Week

- 'Comprehensive motility analysis in patients with decompensated gastroparesis undergoing gastric per-oral endoscopic pyloromyotomy: relation to treatment outcomes' presentation in the 'Third-space endoscopy' session at UEG Week Virtual 2020 [<https://ueg.eu/library/comprehensive-motility-analysis-in-patients-with-decompensated-gastroparesis-undergoing-gastric-per-oral-endoscopic-pyloromyotomy-relation-to-treatment-outcomes/234626>].
- 'EsoFLIP pyloric dilation in gastroparesis improves gastric emptying, pyloric distensibility and symptoms' presentation in the 'Update in gastro-intestinal disorders' session at UEG Week Virtual 2020 [<https://ueg.eu/library/esoflip-pyloric-dilation-in-gastroparesis-improves-gastric-emptying-pyloric-distensibility-and-symptoms/234871>].
- 'European guideline on functional dyspepsia and gastroparesis – UEG and ESNM clinical management guideline' presentation in the 'Nausea and vomiting' session at UEG Week Virtual 2020 [<https://ueg.eu/library/european-guideline-on-functional-dyspepsia-and-gastroparesis-ueg-and-esnm-clinical-management-guideline/234957>].
- 'New impulses in management of gastroparesis' session at UEG Week 2019 [<https://ueg.eu/library/session/new-impulses-in-management-of-gastroparesis/156/2587>].
- 'Dyspepsia and gastroparesis: How to diagnose and treat?' session at 25th UEG Week 2017 [<https://ueg.eu/library/dyspepsia-nausea-and-vomiting-gi-physiology-tests-are-useful-in-clinical-practice-con/153999>].

Standards and Guidelines

- Weusten BLAM, Barret M, Bredenoord AJ, et al. Endoscopic management of gastrointestinal motility disorders – part 1: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2020; 52: 498–515 [<https://ueg.eu/library/endoscopic-management-of-gastrointestinal-motility-disorders-part-1-european-society-of-gastrointestinal-endoscopy-esge-guideline/234067>].
- Keller J, Bassotti G, Clarke J, et al. Expert consensus document: advances in the diagnosis and classification of gastric and intestinal motility disorders. *Nat Rev Gastroenterol Hepatol* 2018; 15: 291–308 [<https://ueg.eu/library/expert-consensus-document-advances-in-the-diagnosis-and-classification-of-gastric-and-intestinal-motility-disorders/175925>].