

Current perspectives on the management of gastroparesis

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ABSTRACT

Gastroparesis is a condition of abnormal gastric motility characterised by delayed gastric emptying in the absence of mechanical outlet obstruction. It is seen commonly in people with diabetes but is idiopathic in a third of patients. Symptoms include nausea and vomiting, post-prandial fullness and early satiety, and abdominal bloating and discomfort. Investigations fall into three categories: gastric emptying studies, intraluminal pressure measurements and recording of gastric myoelectrical activity. Nuclear scintigraphy is considered the gold standard for diagnosing and quantifying delayed gastric emptying. Treatment options include diet and behavioural changes, prokinetic drugs and surgical interventions. New advances in drug therapy and gastric electrical stimulation techniques hold considerable promise.

KEY WORDS: Gastroparesis, (management or treatment), human

Gastroparesis is a condition of abnormal gastric motility characterised by delayed gastric emptying in the absence of mechanical outlet obstruction.^[1] It affects up to 50% of patients with longstanding diabetes mellitus. Proper gastric emptying is a pre-requisite to adequate metabolic control. Disturbance of this important function can not only cause much distress to patients but also creates a false impression of poor compliance with healthcare advice. Therefore an understanding of the condition is essential to providing an insightful service to this group of patients. Although focussing primarily on diabetic gastroparesis, the concepts discussed in this review apply equally to other causes of gastropathy. The material has been culled from recent articles in journals of international societies, Medline searches and discussions with colleagues.

Clinical features

The majority of patients with gastroparesis are females (82% in a series by Soykan *et al*).^[2] with a mean age of 34 years at the onset of symptoms. Nausea and abdominal pain are the two most common symptoms, followed by early satiety and vomiting.^[3] Abdominal pain, a frequently overlooked symptom, is described as burning or crampy in nature, and in some patients is localised to the upper abdomen. Most report nocturnal symptoms that interfere with the normal sleeping pattern, and many complain of postprandial pain. Vomiting can be in-

tractable in some patients necessitating hospitalisation during particularly severe episodes. Episodes of nausea and vomiting may last for days to months or may occur in cycles. Some patients may present with dyspeptic symptoms, including post-prandial upper abdominal discomfort, early satiety, bloating and distension, as well as nausea and vomiting.

In the series by Soykan *et al*,^[2] 62% of women with idiopathic gastroparesis reported a history of physical or sexual abuse, and physical abuse was significantly associated with abdominal pain, somatization, depression, and lifetime surgeries. However, symptoms often lack specificity for gastroparesis, and the differential diagnosis should include other causes of nausea and vomiting such as migraine, achalasia, a large pharyngeal pouch, hiatus hernia, peptic strictures, and the rumination syndrome (psychogenic vomiting).^[4] Moreover, the severity of symptoms does not always correlate with the objective evidence of the rate of gastric emptying.^[5,6]

Revicki *et al*^[7,8] have devised a questionnaire called the gastroparesis cardinal symptom index (GCSI) to measure patient-based symptom severity. It has been validated in an American multicentre population-based study of patients with confirmed gastroparesis of greater than 6 months duration. It consists of three subscales: postprandial fullness/early satiety, nausea/vomiting and bloating. Patients are asked to rate, on a

scale of 0 – 5, symptoms of nausea, retching, vomiting, stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, loss of appetite, bloating and stomach or belly appearing visibly larger. The GCSI can be used for quantifying the severity of symptoms and assessing progress with treatment.

In diabetics, frequent episodes of hypoglycaemia may occur due to delayed delivery of food to the small intestine for absorption. Diabetic gastroparesis is also frequently associated with retinopathy, nephropathy, peripheral neuropathy, and other forms of autonomic dysfunction including abnormal pupillary responses, anhidrosis, gustatory sweating, orthostatic hypotension, erectile dysfunction, retrograde ejaculation, and urinary bladder dysfunction. A *succussion splash* after overnight fast may be found clinically. Clinical features or history of other causes of gastroparesis such as prior gastric surgery, Parkinson's disease or collagen vascular disease or contributing factors such as preceding viral illness, depression or gastro-oesophageal reflux disease/ non-ulcer dyspepsia may be apparent (Figure 1).

Pathophysiology

Gastric emptying reflects the integration of tonic contractions of the fundus, phasic contractions of the antrum and the inhibitory forces of pyloric and duodenal contractions. These complex phenomena require the cooperation between smooth muscle, enteric and autonomic nerves and specialized pacemaker cells, the interstitial cells of Cajal (ICC).^[9] Thus, disordered gastrointestinal motility is likely to be multifactorial in origin, including autonomic neuropathy, enteric neuropathy involving excitatory and inhibitory nerves and ICC, sudden fluctuations in blood glucose and psychosomatic factors.^[10-12]

Normal gastric myoelectrical activity is initiated by the ICC, located in the muscular wall of the gastric corpus and antrum, at a rate of 3 cycles per min.^[13] In gastroparesis, the normal electrical rhythm is replaced with bradygastrias, tachygastrias, and mixed or non-specific dysrhythmias. There are two types of ICC in humans. The first type is scattered in the circular and longitudinal muscle layers from the fundus to the antrum, loss of which is associated with low basal gastric tone and increased compliance.^[14,15] The second is associated with the

myenteric plexus between the longitudinal and circular muscle layers of the corpus and antrum, and is essential for slow wave generation.^[16] Studies have shown markedly abnormal submucous and myenteric plexuses in gastrectomy specimens from patients with severe gastroparesis, with diminished ICC both in the myenteric plexuses and within the circular and longitudinal muscle layers of the corpus, antrum and pylorus, and overall decrease in ICC density ranging from 60 to 100% depending on the area investigated.^[17,18]

A variety of neurotransmitters including noradrenaline, acetylcholine, 5-hydroxy tryptamine (5-HT) and nitric oxide (NO) are involved in initiating, maintaining and regulating gastric contractility. NO has an important function as a non-adrenergic, non-cholinergic neurotransmitter in the gut including the stomach and pylorus.^[19,20] It is synthesized by neuronal NO synthase (nNOS) in the myenteric plexus and causes relaxation of smooth muscle in the proximal stomach and appears to inhibit gastric emptying in humans.^[21,22] In diabetic mice, defects in nNOS expression, pyloric function and gastric emptying have been found to be reversed by insulin treatment.^[23] While these findings add to our understanding of the pathophysiology of gastroparesis and have implications for novel therapeutic approaches, their relevance to the human condition requires further elaboration.

Acute changes in the blood glucose concentration have a major reversible influence on gastrointestinal motor and sensory function (reviewed by Rayner *et al*).^[24] Gastric emptying is slower during hyperglycaemia and accelerated during hypoglycaemia.^[25-27] Blood glucose fluctuations even within the normal postprandial range also influence gut function and may be important in the regulation of gut motility and sensation in healthy individuals.^[24] The neuroendocrine axes, including the hypothalamic-pituitary-adrenal axis, may also influence gastrointestinal function. Corticotrophin releasing hormone, for instance, has been shown to decrease gastric motility.^[28]

Investigations

A variety of methods have been developed to assess gastric motility in humans. They can be grouped into three main categories: gastric emptying studies, intraluminal pressure measurements and recording of gastric electrical activity.

Gastric emptying studies

Nuclear scintigraphy

This is the gold standard for quantifying gastric emptying. It is the most accurate and the most physiological measure of gastric emptying currently available. The technique involves incorporation of a radioisotope tracer in a standard meal and tracking its passage through the stomach using a gamma camera.^[29] The procedure is non-invasive and requires relatively low levels of exposure to radiation, of the order of 50 MBq. The performance of the test varies considerably from centre to centre. Ideally, both solid and nutrient liquid emptying should be measured using a dual isotope technique (Figure 2).^[30] If it is only possible to use a single isotope, labelling of a

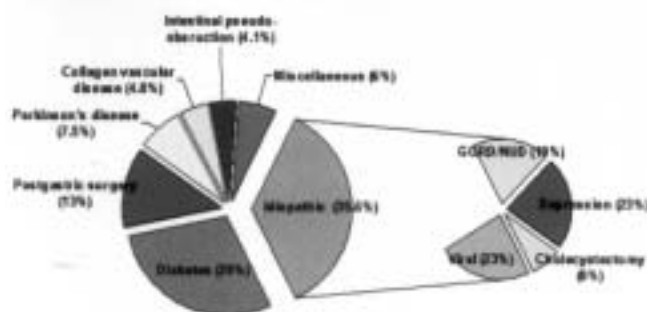


Figure 1: Common causes of gastroparesis in a series of 146 patients reported by Soykan *et al*. 2 Subgroups were identified within patients with idiopathic gastroparesis (smaller pie chart). GORD: gastro-oesophageal reflux disease. NUD: non-ulcer dyspepsia

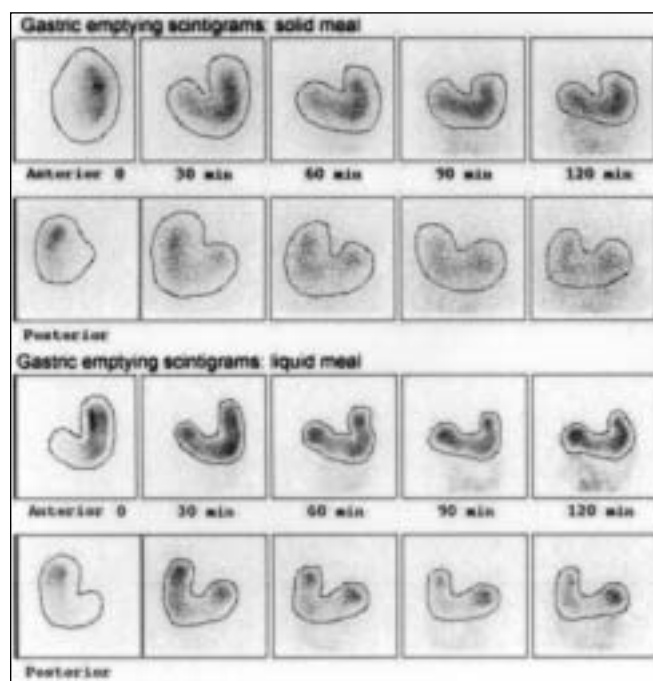


Figure 2: Sequential gastric scintigrams after radiolabeled solid (top two panels) and liquid meals (bottom two panels) in a diabetic patient with nausea, vomiting, and abdominal fullness and discomfort. Most of the radioactivity is retained in the stomach beyond 120 minutes after solid and liquid test meals, confirming delayed gastric emptying

solid meal is preferable. The most appropriate meal is a matter of local preference. It should be palatable, representative of an ordinary meal and standardised within each centre. Scrambled eggs or cooked minced beef are favoured in western societies but any culturally acceptable meal may be used. As gastric emptying may be influenced by posture and gravity, the position of the subject during the study must also be standardised. An individual test is best expressed as a curve showing the radioactivity remaining in the stomach against time, superimposed on a normal range (Figure 3). There is a wide range of normality for gastric transit times, depending on the type of meal used. In general, half the stomach contents should leave within 90 minutes. Although attempts have been made to standardise gastric emptying studies,^[31] the disadvantages of scintigraphy include the need for scrupulous standardisation of the several methodological variables, the high cost of equipment, the inability to quantify gastric secretion and exposure to radiation.

Other radiological techniques

Contrast studies using barium either in liquid form or incorporated in a solid meal are often carried out but rarely necessary. Ultrasound can be used to measure changes in the antral region after ingestion of a liquid meal, which correlates closely with gastric emptying rates.^[32] Doppler techniques may also be employed to detect intragastric flow. However, ultrasound is not reliable in the assessment of solid meal emptying. Real time magnetic resonance imaging shows considerable promise as a reliable tool for the assessment of gastric motion and to quantify increased or decreased antral motility by means of a gastric motility index.^[33] Fluoroscopy and computed tomog-

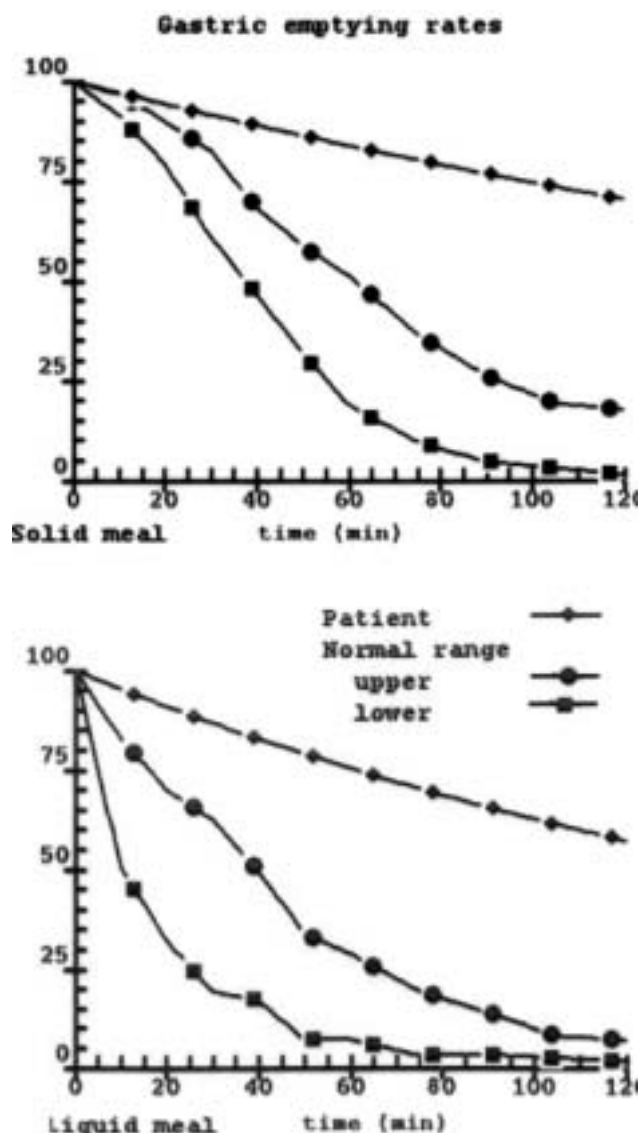


Figure 3: Gastric emptying rates in the same patient as in figure 1. There is a significant retention of radioactivity in the stomach compared to the normal range. $T_{1/2}$ for emptying of solid meal was 235 minutes (top) and for liquid meal 147 minutes (bottom)

raphy (CT) are insensitive and entail high levels of exposure to radiation.

Breath tests

The time course of breath hydrogen excretion after ingestion of lactulose correlates with upper gastrointestinal transit time; breath hydrogen measurement 12 hours after the ingestion of a test meal containing potato starch and lactulose has, therefore, been suggested as a useful, inexpensive outpatient screening test for identifying those symptomatic patients who should undergo more definitive studies and those in whom gastroparesis can be excluded.^[34] Other breath tests including radio-labelled CO_2 are also in use. However, these tests require sampling over several hours. Quicker and more accurate methods involving ^{13}C -octanoic acid breath tests have been developed and found to exhibit highly significant positive correla-

tion to scintigraphy.^[35,36]

Endoscopy

Upper gastrointestinal endoscopy is usually normal but is important in excluding other pathologies such as peptic ulcers and outlet obstruction.

Intraluminal pressure measurements

Manometry

Manometry has been used to characterise the temporal and spatial distribution of pressures in the antrum, pylorus and duodenum.^[37] It is a highly specialised technique and is generally limited to the research setting at present.

Gastric myoelectrical activity

External electrogastrography

External electrogastrography (EGG) using cutaneous electrodes is well established as a method of demonstrating myoelectrical activity. Diagnosis of gastric dysrhythmias identifies an objective neuromuscular abnormality in patients with upper gastrointestinal symptoms. The EGG diagnosis of gastric dysrhythmias provides new insights into gastric neuromuscular abnormalities and guides therapies to improve symptoms. It is, however, not widely available and cannot monitor gastric contractile activity accurately.^[38]

Other tests

Tests of autonomic function are often carried out but rarely required to make the diagnosis.

Treatment

The main goal of treatment is to improve the patient's comfort by accelerating gastric emptying. This may be achieved by dietary changes, drug therapy, or rarely surgical interventions.

Diet and behavioural therapy

It is essential to maintain an adequate intake of fluids and nutrients while attempting to minimise symptoms. A stepwise approach to diet and nutrition may be adopted depending on the severity of symptoms. When symptoms are mild, dietetic modifications may not be required. At the other extreme when symptoms are severe, only liquids may be tolerated. Sugared beverages and soft drinks (not 'diet' colas) sipped slowly throughout the day and fat-free soups eaten in small portions at frequent intervals may provide sufficient calories and nutrients for up to three days. Rarely, parenteral nutrition support may be required temporarily to tide over particularly severe episodes. When symptoms are less pronounced, milk and milk products, fruit juices, bread and cereals, eggs, poultry, fish, ground lean meats, well-cooked vegetables and low-fat desserts may be reintroduced. In general, fats including vegetable oils and high-fibre foods such as cabbage and cauliflower usually delay gastric emptying and intake should be reduced or avoided. Small meals at frequent intervals, 4-6 times daily, are usually better tolerated than less frequent but larger meals.

Drug Therapy

Several prokinetic agents have been used successfully in controlling symptoms of gastroparesis.^[39]

Metoclopramide

This is one of the oldest and most commonly used antiemetic-prokinetic drugs. It is a central and peripheral dopamine-2 (D_2) receptor antagonist and is effective in improving gastric emptying by increasing antral contractions, coordinating antral-duodenal motility, and reducing fundic relaxation.^[40] It can be administered parenterally when symptoms are severe, but its use is limited by central nervous system (CNS) side effects in as many as 40% of patients.^[41]

Domperidone

Like metoclopramide, domperidone is a very effective D_2 antagonist. However, it does not cross the blood-brain barrier, and is therefore associated with fewer CNS side effects.^[42] At doses of 10-30 mg orally half an hour before meals and bedtime, it can reduce gastrointestinal symptoms and hospitalisations from gastroparesis, enhance quality of life, and accelerate gastric emptying.^[43] It can, however, cause increased serum prolactin levels, and the most commonly reported side effects (approximately 5% of treated patients) are gynecomastia in men and breast enlargement and lactation in women.

Erythromycin

This macrolide antibiotic also has motilin receptor agonist properties, and has been shown to improve gastric emptying rates.^[44] It gives better improvement of total score for GI symptoms than metoclopramide^[45] but therapy is often complicated by cramping and abdominal pain.^[44] Low doses may prevent tachyphylaxis and downregulation of motilin receptors, and liquid preparations are better absorbed. In a recent study,^[46] 50-100 mg erythromycin as oral suspension three times a day plus at bedtime showed improvements in gastroparetic symptoms in the majority of subjects during both short-term (83%) and long-term (11 ± 7 months) follow-up (67%), with short-term response predicting long-term response. It is used as an add-on drug with other prokinetic agents, but unlike metoclopramide and domperidone, it can also improve bowel motility. However, it is less effective orally than as an intravenous preparation, and response may vary, particularly in diabetics with fluctuating blood glucose concentrations.^[47,48] It may also slow small intestinal transit.^[49] Moreover, non-existence of trials looking at the long term complications and drug interactions resulting in potentially dangerous complications, particularly *torsades de pointes* is a major cause for concern.

Tegaserod

This is a recently introduced 5-HT₄-receptor agonist that possesses stimulatory motor effects throughout the digestive tract. It is indicated for short-term treatment of irritable bowel syndrome in women with constipation as the main complaint.^[50] Although the evidence is scanty, it has found an off-license use as a promotility agent in patients with gastroparesis. It does not have anti-emetic properties.

Cisapride

This prokinetic agent stimulates the stomach via 5-HT₄ receptors and is relatively free of CNS side effects, and results in faster gastric emptying than metoclopramide.^[51] However, it has been withdrawn from use as it prolongs the QT interval in a dose-dependent manner and is associated with an unacceptably high rate of potentially fatal cardiac arrhythmias.^[52,53]

Other pharmacotherapeutic agents

In most patients with gastroparesis there may also be a role for anti-reflux and acid suppression treatment with histamine-2 receptor antagonists such as ranitidine and proton pump inhibitors such as omeprazole. Various other prokinetic agents including other macrolides and macrolide-derivatives, the muscarinic cholinergic agent bethanecol, levosulpiride and clonidine have been tried with varying degrees of success. Unlike erythromycin, specific motilin receptor agonists without antibiotic properties have not been found efficacious in preliminary studies.^[54,55] Other drugs such as sildenafil citrate (ViagraTM),^[56] 5-HT₃ antagonists (e.g. ondansetron),^[57] and kappa opiate agonists are currently undergoing evaluation and/or drug development. There are also anecdotal reports of the usefulness of marijuana. One drug that deserves special mention is botulinum toxin. Early reports suggest that pyloric injection of botulinum toxin is effective in relieving symptoms in idiopathic and diabetic gastroparesis.^[58-60]

Surgery

Medical treatment is effective in most people with gastroparesis; however, severe gastroparesis refractory to drug therapy is encountered in 2 to 5% of patients and is associated with multiple hospitalisations. The main role of surgery is in palliating symptoms, decompressing the stomach, providing access for enteral nutrition and enhancing gastric emptying. Surgical techniques such as the gastrostomy and jejunostomy procedures provide a stoma for drainage and nutrition and have a role as a temporary measure. These may be carried out either by open, laparoscopic^[61] or percutaneous endoscopic methods.^[62] However, they are associated with significant complications.^[63] Transpyloric insertion of a feeding tube has also been described for those patients too sick to undergo a major procedure,^[64] and pyloroplasty may have a role in enhancing gastric emptying in some patients. Major gastric resections, such as partial or total gastrectomies with Roux-en-Y reconstructions, have been shown to palliate symptoms such as vomiting in those patients who have intractable diabetic gastroparesis with poor life expectancy.^[65] Completion gastrectomy appears effective in postsurgical gastroparesis.^[63] However, a recent advance in the surgical management of gastroparesis involving implantation of an electrical device to stimulate gastric myoelectrical activity may reduce the need for these drastic procedures.

Gastric electrical stimulation (GES)

The development of implantable gastric stimulators has revolutionized the operative management of drug-refractory gastroparesis. There are three main methods of GES: (a) high

energy, low frequency entraining, (b) low energy, high frequency stimulation and (c) sequential gastric neural stimulation.^[66] Gastric pacing by high energy, low frequency GES attempts to entrain a regular gastric slow wave rhythm of 3 cycles per minute, and has been found to improve symptoms and gastric emptying in patients with gastroparesis.^[67] However, it appears unsatisfactory at re-establishing efficient gastric contractions. Continuous low energy, high frequency stimulation via electrodes in the muscle wall of the antrum connected to a neurostimulator in an abdominal wall pocket has been found to significantly decrease vomiting frequency and gastrointestinal symptoms and improve quality of life in patients with severe gastroparesis for up to a year of follow-up.^[68-71] The device (Enterra, Medtronic, Minneapolis, USA) is approximately the size of a cardiac pacemaker and is implanted subcutaneously in the abdominal wall at the time of laparoscopy or laparotomy. Two electrodes are placed one centimetre apart in the smooth muscle about 10 cm from the pylorus along the greater curvature of the antrum.^[72] Intraoperative endoscopy is performed at the time of implantation to ensure that the leads are not accidentally pushed into the lumen of the stomach and are positioned appropriately in the muscularis propria. Further refinements to the technique, such as the use of endoscopic ultrasound to guide placement,^[73] are likely to make the procedure safer and more popular in the near future. Although both these methods of GES can improve symptom scores and quality of life, they fail to achieve normal gastric emptying. The most promising GES technique involves microprocessor-controlled electrical activation of a series of annular electrodes that encircle the distal two thirds of the stomach.^[74,75] This sequential gastric neural stimulation induces propagated antral contractions, resulting in forceful gastric emptying. However, it has so far been studied only in the dog and human studies are awaited.

Summary

Gastroparesis is a difficult condition to diagnose, and recognition is aided by awareness of the clinical features and common scenarios in which it is encountered. The diagnosis is usually suspected on clinical grounds but symptoms are often non-specific and other causes should be excluded; a gastric emptying study $t_{1/2}$ greater than 120 minutes is usually regarded as confirmatory. All patients with gastroparesis should receive simple education on dietary and behavioural changes, and improving glycaemic control in those with diabetes.^[76] Pharmacotherapeutic options are limited but effective in the majority of patients, and newer approaches such as artificial gastric electrical stimulation hold considerable promise. When symptoms are mild but inadequately controlled by these measures, antiemetic-prokinetic therapy may be offered on an as-required basis, for instance, before a large, rich meal or at bedtime when the stomach is bloated. Patients with persistent symptoms or intermittent but severe symptoms may require regular antiemetic-prokinetic therapy. Domperidone or metoclopramide are good first line agents, with the addition of low-dose erythromycin in those with persistent symptoms. At the present time, other prokinetic agents are best reserved

for specialist use in selected patients. Implantable gastric stimulators should be considered at the time of laparotomy or laparoscopy in patients with severe symptoms requiring stomach decompression procedures; however, they are not yet widely available. Of 146 patients with gastroparesis seen over 6 years in the series by Soykan *et al.*,^[2] 74% required continuous prokinetic therapy, 22% were able to discontinue prokinetics, 5% underwent gastric surgery, 6.2% went onto gastric electrical stimulation, and 7% died. Enteral or parenteral nutrition support was required in 21% at some point.

A good response to pharmacotherapy can be expected in the majority of patients with gastroparesis due to diabetes, Parkinson's disease, and viral and dyspeptic subgroups of idiopathic gastroparesis.^[2] Gastroparesis due to connective tissue disease or prior gastric surgery responds less favourably to prokinetic agents. Thus, recognition of the cause of gastroparesis may guide the treatment approach and predict response.

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