

CLINICAL REVIEWS

CME

Gastroparesis: Clinical Update

Moo-In Park, M.D., Ph.D.,¹ and Michael Camilleri, M.D.²

¹Department of Internal Medicine, College of Medicine, Kosin University, Busan, Korea; and ²Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.) Group, Mayo Clinic, Rochester, Minnesota

Gastroparesis refers to chronically abnormal gastric motility characterized by symptoms suggestive of mechanical obstruction and delayed gastric emptying in the absence of mechanical obstruction. It may be idiopathic or attributable to neuropathic or myopathic abnormalities, such as diabetes mellitus, postvagotomy, postviral infection, and scleroderma. Dietary and behavioral modification, prokinetic drugs, and surgical interventions have been used in managing patients with gastroparesis. Although mild gastroparesis is usually well managed with these treatment options, severe gastroparesis may be very difficult to control and may require referral to a specialist center if symptoms are intractable despite pharmacological therapy and dietetic support. New advances in drug therapy, botulinum toxin injection, and gastric electrical stimulation techniques have been introduced and might provide new hope to patients with refractory gastroparesis. This article critically reviews the advances in the field from the perspective of the clinician.

(Am J Gastroenterol 2006;101:1129–1139)

INTRODUCTION

Gastroparesis is a form of gastric paralysis; chronic symptoms may result from abnormal gastric motility associated with delayed gastric emptying in the absence of mechanical outlet obstruction, causing significant morbidity (1). Symptoms of gastroparesis are variable and include early satiety, nausea, vomiting, bloating, and upper abdominal discomfort. It is also relevant to note that the observed delay in gastric emptying is not always the cause of the patient's symptoms.

Gastroparesis may be attributed to a variety of underlying disorders. This review addresses the advances in epidemiology, knowledge of mechanism, diagnosis, and treatment of patients with gastroparesis from the perspective of the clinician.

EPIDEMIOLOGY

Gastroparesis is a relatively common cause of nausea, vomiting, and other upper gut symptoms in patients referred to gastroenterologists. The prevalence of gastroparesis is difficult to estimate due to incomplete correlation of symptoms with gastric emptying, the likely higher prevalence of the disorder in tertiary medical centers than in the community, and the lack of a widely available diagnostic test that can be applied in primary care. Two recent population-based studies showed that 11–18% of patients with diabetes reported symptoms consistent with upper gastrointestinal dysmotility such as nausea and vomiting (2, 3). However, 65% of patients with diabetes at an academic medical center showed

delayed gastric emptying of solids and/or liquids measured by scintigraphy (4). Delayed gastric emptying may also be present in 25–40% of adults and children with functional dyspepsia (5–9). Thus, the true prevalence of gastroparesis is still unknown.

In one large, single-center study, data from 146 gastroparesis patients seen over 6 yr were reported (10); 82% of patients were women with a mean age of 45 yr, and the mean age for onset of gastroparesis was 33.7 yr.

It is still unclear whether the higher prevalence of gastroparesis in women reflects a specific predisposition to develop delayed emptying or to manifest the symptoms of gastroparesis. Female gender has been associated with slower gastric emptying rate for solids and liquids in some studies (11, 12). In one study of seven normally menstruating women, gastric emptying of solids was significantly slower during the luteal phase of the cycle than in the follicular phase (13). It is believed that gastric muscle contractility is reduced by progesterone (14). On the other hand, a larger, recent study from Mayo Clinic showed that supplementation of estrogen, or progesterone, or combinations to postmenopausal women was not associated with any change in gastric or small bowel transit (15). There are no clear data to suggest that gastric emptying delay in gastroparesis is worse in women than in men.

ETIOLOGY

Virtually any disease or condition that can induce neuromuscular dysfunction of the gastrointestinal tract may cause gastroparesis. In one tertiary referral series, the etiologies in 146 gastroparesis patients were 36% idiopathic, 29% diabetic, 13% postgastric surgery, 7.5% Parkinson's disease,

To access a continuing medical education exam for this article, please visit www.acg.org/journalcme.

4.8% collagen vascular disorders, 4.1% intestinal pseudoobstruction, and 6% miscellaneous causes (10). The etiologies included in idiopathic gastroparesis were an acute viral gastroenteritis-like illness (23%), gastroesophageal reflux disease (GERD) and nonulcer dyspepsia (19%), and cholecystectomy. The miscellaneous group included paraneoplastic syndrome (16), rare neurological or anatomical diseases such as superior mesenteric artery syndrome, and median arcuate ligament syndrome (17). Thus, the three most common etiologies are diabetes, idiopathic, and postsurgical (18). Gastroparesis may occur as a complication of a number of different surgical procedures including vagotomy (19), fundoplication (20), the Whipple procedure (21), and lung and heart-lung transplantation (22, 23). While these data are of interest, they likely reflect tertiary referral bias and may not reflect the causes in the community.

PATHOPHYSIOLOGY

Gastric emptying results from 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 interactions between smooth muscle, enteric and autonomic nerves, and specialized pacemaker cells, the interstitial cells of Cajal (ICC) (24). There are several abnormalities that may result in motor dysfunction of the stomach including autonomic neuropathy, enteric neuropathy involving excitatory and inhibitory nerves, abnormalities of ICC, sudden fluctuations in blood glucose, and psychosomatic factors (25–27).

Patients with diabetes mellitus have reduced frequency of antral contractions, antroduodenal incoordination (28, 29), and pyloric spasm (30). The latter rarely occurs in isolation and is typically associated with antral hypomotility (10). Increased compliance of the proximal stomach (31) and abnormal postprandial proximal gastric accommodation (32) and contraction (33) may contribute to the development of delayed gastric emptying. In one study, increased phasic fundic contractions were associated with accelerated gastric emptying of liquids in diabetics (33). The main pathogenetic factors in diabetic gastroparesis are vagal autonomic neuropathy and, based on data acquired in animal models and single case reports in humans, ICC pathology (34). Hyperglycemia may play an important additional role (35, 36). Inadequate gastric accommodation in diabetes may be due to a defective nitric oxide pathway.

Delayed gastric emptying without apparent cause is probably the most common form of gastroparesis (10). A subset of these patients with idiopathic gastroparesis identifies an infectious, viral-like illness or prodrome at the onset of their illness. The pathophysiology, in general, mimics that of diabetic gastroparesis, with fundic dysaccommodation and antral hypomotility being the most frequently recorded pathophysiological mechanisms in patients with functional dyspepsia (6, 7, 37), whether or not there is acute onset (38). Abnormalities in small bowel motility may result in delayed gastric

emptying of solids (39); gastric motor dysfunction may be associated with small bowel dysmotility due to a common mechanism.

Gastric electrical dysrhythmias or reduced power of the electrical signal postprandially are associated with these conditions; however, the precise role of electrogastrography (EGG) in screening or diagnosis of gastroparesis is unclear (40, 41).

DIAGNOSIS

Gastroparesis is diagnosed by demonstrating delayed gastric emptying in a symptomatic patient after exclusion of other potential etiologies of symptoms and obstruction with endoscopy and radiological imaging.

Assessment of the patient begins with a careful history aimed at understanding the patient's symptoms. Patients with gastroparesis may present with symptoms including nausea, vomiting, early satiety, bloating, discomfort or pain, and belching. However, rapid gastric emptying may result in similar dyspeptic symptoms (42), and symptoms such as fullness, bloating, and nausea may reflect dumping or gastric dysaccommodation that would not respond to a prokinetic agent. Hence, it is useful to measure gastric emptying if this is available rather than assuming symptoms reflect delayed gastric emptying.

Most patients with suspected gastroparesis require upper endoscopy or radiographic imaging to exclude mechanical obstruction or ulcer disease. The presence of retained food in the stomach after overnight fasting and absence of obstruction in the endoscopy suggests that there is ineffective antral interdigestive motility, and this is suggestive of gastroparesis. Absence of the antral component of the migrating motor complex is associated with postprandial antral hypomotility (43).

Vomiting associated with gastroparesis must be differentiated from regurgitation due to GERD or rumination syndrome, episodic vomiting in cyclic vomiting syndrome, self-induced vomiting with bulimia, and abdominal pain and vomiting in superior mesenteric artery syndrome. By history, one can usually exclude those conditions, particularly the rumination syndrome, which presents with a stereotypical, early (intraprandial or first 30 min) postprandial effortless regurgitation of food after every meal, followed by mastication and reswallowing or spitting out the food: "meal-in, meal-out, day-in, day-out" (44, 45).

The physical examination may reveal a succussion splash or foul breath, but is usually not particularly helpful in establishing the diagnosis of gastroparesis other than identifying the underlying disease that may be associated with gastroparesis. The history usually provides the lead to diagnosis (*e.g.*, autonomic symptoms suggest a neuropathic disorder; skin or joint problems may suggest a collagenosis). However, these symptoms may be nonspecific: Orthostasis may be a sign of dehydration or of an underlying autonomic neuropathy.

Thus, a gastric emptying test is required to establish a definite diagnosis of gastroparesis in patients presenting with several upper gastrointestinal symptoms. The objective evaluation of gastric emptying is also useful to differentiate patients with dyspeptic symptoms and mild impairment of gastric emptying from those who have a more significant delay in gastric emptying that results in weight loss, malnutrition, or symptoms intractable to simple dietetic and pharmacological therapy. The latter patients may require referral to a specialized center. Measuring the pressure and electrical profiles of gastric function is optional in the vast majority of patients as it does not enhance treatment options when an underlying disease is already recognized, such as diabetes. Iatrogenic causes including previous surgery (19–21), use of medications (such as opioid analgesics, tricyclic antidepressants, calcium channel blockers (14)) or psychiatric diseases (46) need to be addressed for optimal management.

TECHNIQUES TO IDENTIFY GASTROPARESIS

Gastric emptying tests that are applicable in several centers and in multicenter studies are scintigraphy with images at 1, 2, and 4 h (47), stable isotope breath test (48–50), or counting the number of radiopaque markers retained in the stomach at 6 h (51). All methods allow for centralized analysis of data. Antroduodenal motility or EGG is rarely indicated, *e.g.*, when there is no identifiable disease or mechanism causing the gastroparesis, or when the patient does not respond to medical therapy.

Gastric Emptying by Scintigraphy

Gastric emptying of a solid-phase meal by scintigraphy is considered the gold standard for the diagnosis of gastroparesis because this test quantifies the emptying of a physiologic, caloric meal that can assess the motor function of the stomach. The latter is required for trituration and emptying of solids (28). Solids provide a more relevant challenge than a liquid or homogenized meal and mimic the functions needed in daily life. Gastric emptying of digestible solids and, less commonly, liquids is delayed in gastroparesis (52). The emp-

tying of nondigestible solid particles is also delayed in many patients with gastroparesis, presumably because of the lack of the antral component of the interdigestive migrating motor complex. Measurement of gastric emptying of solids is more sensitive for detection of gastroparesis because liquid emptying may be normal even in patients with advanced disease.

A clinically useful gastric emptying test includes scintigraphic images at 3 or 4 h (Fig. 1) because this improves the accuracy and specificity in identifying gastroparesis (53, 54). Thus, retention of more than 10% at 4 h was validated in a multinational study (54). Information about the amount of food retained at 4 h also helps guide nutritional supplementation. In contrast, detailed imaging up to 90 min after meal ingestion leads to estimated, sometimes erroneous $T_{1/2}$ based on a mathematical extrapolation of the data rather than objective measurements.

Stable Isotope Breath Tests

The noninvasive ^{13}C -labeled breath test is an indirect means of measuring gastric emptying. Most commonly, ^{13}C -labeled octanoate, a medium-chain triglyceride, is incorporated into an egg or another solid meal, such as a muffin (49, 50). After ingestion and stomach emptying, ^{13}C -octanoate is rapidly absorbed in the small intestine and metabolized to $^{13}\text{CO}_2$, which is expelled from the lungs during respiration. The rate-limiting step for the signal appearing in the breath is the rate of solid gastric emptying (Fig. 2). The test assumes normal small bowel, pancreas, liver, and pulmonary functions. Several studies have demonstrated a strong correlation between the carbon-labeled breath test and scintigraphy results (48, 55). Other studies suggest a weak correlation between the two methodologies, but suggest a high degree of reproducibility within individuals (49, 56). Validation of this test in patients with emphysema, cirrhosis, celiac sprue, and pancreatic insufficiency is needed because rates of octanoate absorption and metabolism may be impaired in these disorders.

Another ^{13}C -labeled substrate that is undergoing validation studies is ^{13}C -spirulina, which is a protein-rich blue green alga grown in an environment enriched with ^{13}C , which results in more than 98% of ^{12}C being replaced by ^{13}C (57).

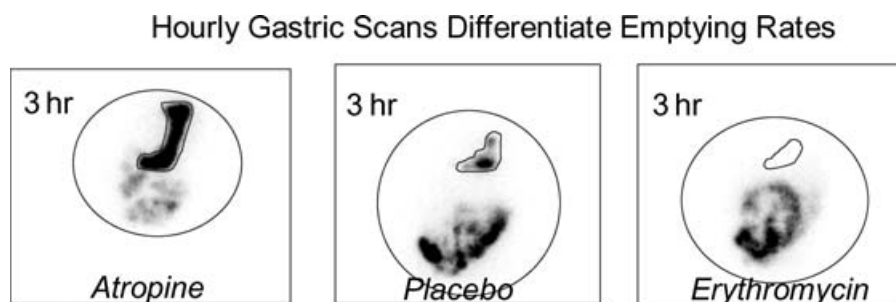


Figure 1. Effect of atropine and erythromycin, simulating the effects of delayed and accelerated gastric emptying in disease, compared with placebo on gastric emptying 3 h after ingestion of a radiolabeled meal. The region of interest is drawn around the gastric residual. Note that hourly scans taken beyond 2 h from meal ingestion document the residual proportion of the meal remaining in the stomach.

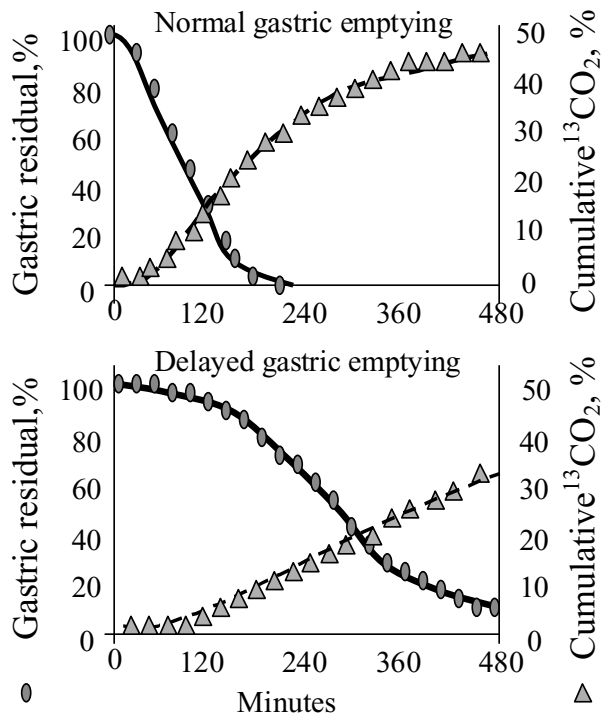


Figure 2. Gastric emptying by scintigraphy with simultaneous cumulative $^{13}\text{CO}_2$ excretion in breath showing normal (above) or delayed (below) gastric emptying. Note that, in the presence of delayed emptying, the cumulative excretion of $^{13}\text{CO}_2$ does not reach a steady state. (Reproduced with permission from Lee J-S *et al.* *Am J Gastroenterol* 2000;95:2751–61.)

^{13}C breath tests do not involve ionizing radiation and can be used to test children and pregnant mothers, patients in the community, or even at the bedside where gamma camera facilities are not readily available.

Radiopaque Markers

Feldman *et al.*, developed a radiological method for assessing gastric emptying of an indigestible solid in humans (51). None of the 10 solid radiopaque markers (small pieces of nasogastric tubing) should remain in the stomach on an X-ray taken 6 h after ingestion together with a meal (donuts and 7-Up in the initial study!). Standardization of the meal is essential and further validation of normal *versus* abnormal would be required, given the potential variation in donut nutrient (*i.e.*, fat) content and the impact of fat on emptying rate. The size of the markers and the viscosity of the meal may also affect gastric emptying measurements (58). However, this simple test correlates with clinical gastroparesis and it has been claimed that it may be more sensitive than scintigraphy (59). Further validation and testing of performance characteristics are needed. Moreover, it may be difficult to determine if markers are located in the stomach or other regions that overlap with stomach (*e.g.*, proximal small bowel, transverse colon).

Ultrasonography

Several authors have applied ultrasonography to measure gastric emptying and duodenogastric reflux; this is generally more applicable for emptying of liquids. The primary measurement of antral cross-sectional area is an indirect measure of gastric emptying (60–62). There is some operator dependence of this technique.

TECHNIQUES TO ASCERTAIN THE MECHANISM LEADING TO GASTROPARESIS

Antroduodenal Manometry

Antroduodenal manometry measures phasic pressure changes due to actual contractions and provides information about coordination of gastric, pyloric, and duodenal motor function in the fasting and postprandial periods. In gastroparesis, antroduodenal manometry may exhibit a decreased frequency and amplitude of antral contractions, and phase III complexes typically originate in the duodenum rather than the distal stomach (43). In patients with diabetic gastroparesis, increased tonic and phasic activity of pylorus (pylorospasm) or irregular bursts of small intestinal contractions were observed (28, 43). Furthermore, the prevalence of concomitant small intestinal motor dysfunction in patients with gastroparesis ranges from 17% to 85% in the studies in the literature (43, 63). Antroduodenal manometry may differentiate antral or small intestinal neuropathic and myopathic disease and may suggest unsuspected small bowel obstruction or rumination syndrome (40, 64). Myopathic disorders are characterized by average amplitudes of <40 mmHg in the antrum and <10 mmHg in the small bowel (65). Antroduodenal manometry is usually reserved for the refractory patient evaluated at tertiary referral centers.

Electrogastrography

EKG records gastric myoelectrical activity, or the gastric electrical slow wave (66), which is responsible for controlling the maximal frequency and the aboral propagation of distal gastric contractions. An abnormal cutaneous EKG is defined when the percent time in dysrhythmia exceeds 30% of the recording time and/or when meal ingestion fails to elicit an increase in signal amplitude (41). Gastric dysrhythmias, including tachygastria and bradygastria, and decreased amplitude (“power”) responses to meal ingestion have been characterized in patients with idiopathic and diabetic gastroparesis (67). EKG is considered by some authors as an adjunct to gastric emptying measurement for a comprehensive evaluation of patients with refractory symptoms suggestive of an upper gastrointestinal motility disorder (41, 64). However, to date, there has been little documented utility of EKG in the management of patients with suspected gastric dysmotility.

MANAGEMENT: WHICH TREATMENT WORKS?

The principles for management of gastroparesis involve correction of hydration and nutrition and selection from a

variety of medical, endoscopic, or surgical options. To restore hydration and nutrition, the enteral route is preferable. Correction of electrolyte and glycemic control, use of antiemetics with caution (given the theoretical potential for interactions with other drugs sharing cytochrome P450 metabolism, although such interaction appears to be encountered very seldomly in clinical practice), prokinetics, pain relief without narcotics (*e.g.*, tramadol 50–75 mg), and venting gastrostomy/jejunostomy have been applied for several years. New approaches include endoscopic botox injection, gastric electrical stimulation, and surgery.

Dietary Recommendations

Maintaining an adequate oral intake of fluids and nutrients is the goal of therapy for gastroparesis. Dietary recommendations rely on measures that promote or, at least theoretically, do not retard gastric emptying, although few studies have been performed to validate this concept. Liquids are emptied more rapidly than solids, and both lipids and indigestible fibers tend to delay gastric emptying. Therefore, small, frequent low-fat meals consisting of complex carbohydrates (starch-based foods) are consumed to avoid gastric distention and attendant symptoms of bloating, satiety, and nausea. Enteral alimentation delivered into the small intestine may be helpful in patients with dysmotility restricted to the stomach. In some severe cases, total parenteral nutrition may be needed, if there is involvement of the small bowel and after a failed trial of enteral nutrition at infusion rates required to maintain weight.

Correction of Glycemic Control

Correction of glycemic control is often regarded as an important part of the management of gastroparesis in diabetes. There are data suggesting that hyperglycemia *per se* may impair gastric emptying; however, the magnitude of delay due to hyperglycemia may not be clinically significant (68, 69). On the other hand, hyperglycemia may reduce the response of the stomach to prokinetic agents such as erythromycin (70). Therefore, glycemic control is desirable in every patient.

Pharmacological Agents

Metoclopramide has both prokinetic and central antiemetic actions. The antiemetic effect occurs as a result of dopamine (D₂) and serotonin (5-HT₃) receptor antagonism on vagal and brainstem pathways (71). Prokinetic effects are related to the facilitation of acetylcholine release from enteric cholinergic neurons (5-HT₄ receptors), to dopamine D₂ receptor antagonism in the myenteric plexus, and to direct smooth muscle contraction via muscarinic receptor sensitization (72, 73). The prokinetic effects of metoclopramide are limited to the proximal gut. Metoclopramide is effective for the short-term treatment of gastroparesis for up to several weeks (74, 75). Dopamine D₂ receptor antagonism in the vomiting center enhances its antiemetic activity, but it may also result in high prolactin levels and gynecomastia. The long-term utility of metoclopramide has not been proven (76). Metoclopramide

can be administered parenterally when symptoms are severe, but its use is limited by central nervous system side effects in up to 40% of patients (76). Restricting the total daily dose to 40 mg per day and using the liquid formula to improve the pharmacokinetics of the drug tend to reduce the central side effects and provide some clinical efficacy. Efficacy of cisapride and metoclopramide was demonstrated in small, often single-center studies rather than in large, phase III trials. Domperidone is another dopamine D₂ receptor antagonist with evidence of efficacy in the published literature (77, 78); it is available in the United States through an FDA-approved IND process.

The evidence still points to cisapride, a 5-HT₄ agonist that facilitates release of acetylcholine from myenteric cholinergic nerves throughout the gut, as one of the more effective prokinetics (79). Cisapride stimulates antral and duodenal contractions, improves antroduodenal coordination, and accelerates gastric emptying (80, 81) and small bowel transit in chronic intestinal dysmotility (39, 82, 83). Cisapride accelerates gastric emptying and decreases symptoms in patients with gastroparesis for 1 yr (81, 84). However, it has been withdrawn from use as it prolongs the QT interval in a dose-dependent manner and was associated with potentially fatal cardiac arrhythmias (85, 86). Preliminary data suggest that a newly synthesized compound derived from cisapride (ATI-7505), that appears devoid of cardiac toxicity and is not metabolized by cytochrome P450 enzymes, has been shown to stimulate gastric emptying (87).

Erythromycin is most effective when used intravenously (*e.g.*, erythromycin lactobionate 3 mg/kg (88)); it stimulates motilin and cholinergic receptors (89) and induces dumping of food and nondigestible material from the stomach. There is some evidence of efficacy in long-term use of the oral preparation (90) and even in a 4-wk trial of patients with scleroderma (91).

Novel prokinetic therapies include the 5-HT₄ agonist tegaserod (92). Novel motilides are ABT 229 (93) and mitemincin (94, 95), which is also called GM-611. The latter is an acid-resistant macrolide with minimal antibiotic activity, has a direct action on muscle motilin receptors, and has shown great promise by increasing gastric emptying, but the clinical improvement of symptoms did not reach the same level of efficacy.

Recently, ghrelin was shown to accelerate gastric emptying in studies in patients with diabetic gastroparesis (96, 97) or idiopathic gastroparesis (98). To date, efficacy in symptom relief appears low.

Phosphodiesterase 5 inhibition with sildenafil restores gastric emptying of liquids in an animal model of diabetes (99), suggesting sildenafil has potential as a new promising therapeutic agent for diabetic gastroparesis. Sildenafil also reduced the dysrhythmia of the stomach induced experimentally by hyperglycemia in humans (100). On the other hand, a thorough study of the effects of sildenafil on human gastric sensorimotor functions showed that the drug significantly increases postprandial gastric volume and slows liquid (though

not solid) emptying rate (101). Sildenafil also inhibits interdigestive motor activity of the antrum and duodenum (102). Clinical trials are clearly needed before this medication can be considered for the treatment of gastroparesis.

Restoring postprandial normoglycemia with analogs of amylin, an enterogastrone produced by pancreatic acinar cells, is clinically desirable; however, such compounds as amylin and GLP-1 retard gastric emptying by inhibition of vagal function, and these agents should be used with caution in gastroparetics (103, 104). Exenatide or Exendin-4 mimics glucagon-like peptide-1 and restores euglycemia postprandially but there is a significant delay in gastric emptying and 55% patients develop nausea, 17% vomiting (105).

Intrapyloric Injection of Botulinum Toxin

Manometric studies of patients with diabetic gastroparesis show prolonged periods of increased pyloric tone and phasic contractions, known as pylorospasm (27). Botulinum toxin is a potent inhibitor of neuromuscular transmission and has been used to treat spastic somatic muscle disorders as well as achalasia (106). Intrapyloric injection of botulinum toxin has been reported to be efficacious in several open-label studies (107–109). In a preliminary report, saline or Botox[®] 4 × 25 U was injected into the pylorus of 12 patients with gastroparesis, 2 diabetic and 10 idiopathic, in a double-blind, placebo-controlled, cross-over study. Gastric emptying of solids improved with Botox treatment, but the symptoms were not different at the end of each arm of the study (110).

In a large, open-label, observational study, 43% had a response to botulinum toxin treatment that lasted a mean of approximately 5 months. Male gender was associated with a response to this therapy; however, durability of response was unrelated to gender. Vomiting as a major symptom predicted no response (111). In summary, the available information does not yet support the widespread application of this treatment modality in gastroparesis.

Gastrostomy or Jejunostomy Placement

Medical treatment is effective in most people with gastroparesis. However, 2–5% of patients are refractory to drug therapy and require multiple hospitalizations (112). In refractory patients with severe nausea and vomiting, placement of a gastrostomy tube for intermittent decompression by venting or suctioning may provide symptom relief, especially of interdigestive fullness and bloating secondary to retained intragastric gas and liquids. Venting gastrostomy may be needed to relieve severe gastric stasis. Venting jejunostomy in patients with chronic intestinal pseudoobstruction needing total parenteral nutrition was shown to reduce the need for repeat hospitalizations by a factor of 5 compared with a historical control period (113, 114). Venting gastrostomies or jejunostomies may be placed endoscopically, surgically, or by interventional radiology. The results of endoscopically placed venting (percutaneous endoscopic gastrostomy [PEG] or jejunostomy [PEJ]) for gastroparesis are still unclear.

For patients with gastroparesis who are unable to maintain nutrition with oral intake, placement of a feeding jejunostomy may decrease symptoms and reduce hospitalizations (115). The therapeutic response to jejunostomy infusion may be predicted by a trial of nasojejunal feedings (116). Jejunostomy tubes are effective for providing nutrition, fluids, and medications if there is normal small intestinal motor function (115). Except in cases of profound malnutrition or electrolyte disturbance, enteral feedings are preferable to chronic parenteral nutrition because of the significant risks of infection and liver disease with the latter treatment, especially in diabetic patients.

Surgical Treatment of Gastroparesis

There are limited controlled data concerning surgical treatment of diabetic or idiopathic gastroparesis (116). Surgery is performed only as a last resort in carefully evaluated patients with profound gastric stasis (116).

Forstner-Barthell *et al.* (117) reviewed early and long-term results of near-total gastrectomy for severe postvagotomy gastric stasis in 62 patients with prior vagotomy and a median of four previous gastric operations. These authors suggested that clinical benefit occurs in 43% of patients. Hospital mortality was zero. Complications were noted in 25 patients (40%) and included narcotic withdrawal (18%), ileus (10%), wound infection (5%), intestinal obstruction (2%), and anastomotic leak (5%). Preoperatively, modified Visick scores were grade III (37%) or IV (63%). All or most symptoms were relieved in 43% of the patients (Visick grade I or II), but 57% of patients remained in Visick grade III or IV. Nausea, vomiting, and postprandial pain decreased from 93% to 50%, 79% to 30%, and 58% to 30%, respectively ($p < 0.05$). Chronic pain, diarrhea, and dumping syndrome remained unchanged. Nausea, need for total parenteral nutrition, and retained food in stomach predict poor outcome following surgery.

Gastric Electrical Stimulation

Three principal methods of gastric electrical stimulation have been described: gastric electrical pacing, high-frequency gastric electrical stimulation, and sequential neural electrical stimulation. The first method aims to reset a regular slow-wave rhythm, but is unable to reestablish efficient contractions and a normal gastric emptying. High-frequency gastric electrical stimulation, although inadequate to restore normal gastric emptying, appears to improve nausea and vomiting, quality of life, and nutritional status. The last method, neural electrical gastric stimulation, consists of a microprocessor-controlled sequential activation of a series of annular electrodes that encircle the distal two-thirds of the stomach and induce propagated contractions causing a forceful emptying of the gastric content (118).

A device that provides high-frequency electrical stimulation of the stomach has been approved by the FDA through a humanitarian device exemption (119).

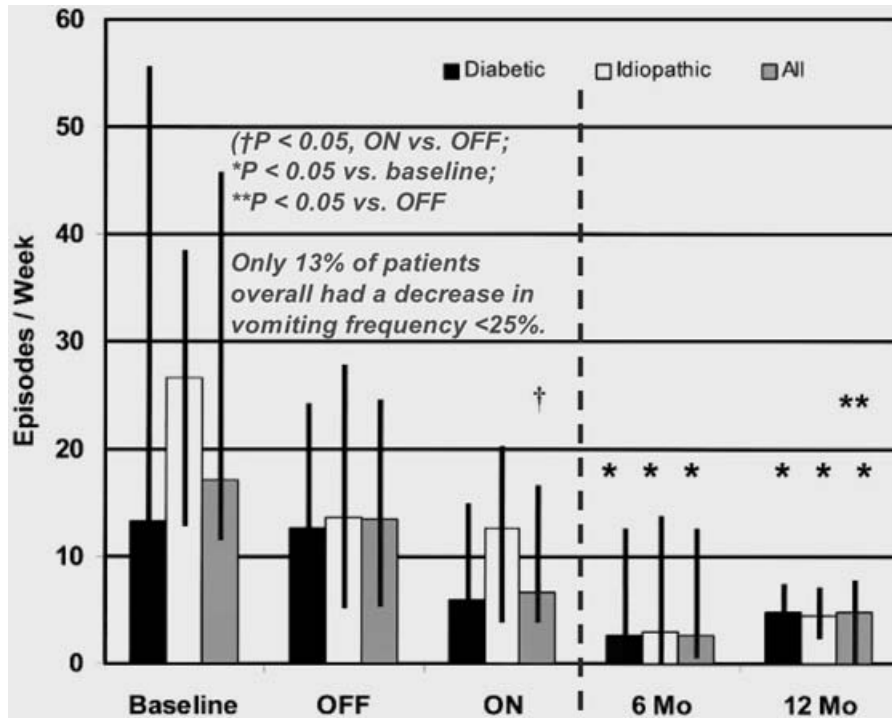


Figure 3. Effect of gastric electrical stimulation on number of vomiting episodes per week. Off and on refer to the cross-over, randomized, controlled study. The data for 6 and 12 months refer to open-label treatment. Note that, with the off-on study, there is a significant reduction of vomiting episodes per week for the entire group, but the frequency was essentially unchanged for the idiopathic group. (Reprinted from *Gastroenterology*, Vol. 125, Abell T., et al, Gastric electrical stimulation for medically refractory gastroparesis, 421-428, 2003, with permission from American Gastroenterological Association.)

Improvement in symptoms and reduced need for nutritional support were documented in open-label studies (120–123) and in subgroups (specifically, diabetics responded better than idiopathic gastroparetics (Fig. 3)) in a double-blind, cross-over study (124). The main clinical effects are reduced vomiting frequency and reduced hospitalizations. The mechanism of symptom relief is unclear. Interpretation of effectiveness is hampered by the continued administration of treatments including medications and nutritional support. In a preliminary report of diabetic gastroparesis (125), high-frequency gastric electrical stimulation was provided to ~60 patients over ~5 yr and results were generally confirmed, although the overall assessment of efficacy was complicated by the fact that a sizeable number of patients did not experience benefit, others required removal of the device for infection, and death from complications of the diabetes occurred during follow-up (125). New studies continue to show promise including increasing BMI and even acceleration of gastric emptying (126); however, further investigation is needed to confirm the effectiveness of gastric stimulation in a long-term, blinded fashion.

CONCLUSION

Clinical features and underlying diseases may suggest the presence of gastroparesis. Gastric dysaccommodation or accelerated gastric emptying may result in dyspeptic symptoms such as early satiety, nausea, and bloating, which may sug-

gest gastroparesis, and, hence, formal measurement of gastric emptying is key before starting therapy whenever this form of test is available. Several tests including gastric emptying scintigraphy and stable isotope breath tests are available for the evaluation of patients with suspected gastroparesis. Management of patients with gastroparesis is focused on nutritional support and prokinetics in the majority of patients and treating any associated depression (127). New prokinetic agents that appear to be safer and to maintain efficacy may be available in the next few years. Endoscopic venting and feeding tubes placed in accordance with symptoms and nutritional requirements result in reduced need for hospitalization in patients with refractory gastroparesis. Surgery is rarely indicated, and completion gastrectomy for those with prior surgery may help only 43% of patients. Novel approaches including new prokinetics, botulinum toxin injection to pylorus, and gastric electrical stimulation have been tested in patients with gastroparesis. Further well-controlled studies are still needed to better define appropriate approaches to this challenging condition.

ACKNOWLEDGMENTS

Dr. Camilleri is supported by grants RO1-DK54681, RO1-DK67071, and K24-DK02638 from the National Institutes of Health. The excellent secretarial support of Mrs. Cindy Stanislav is gratefully acknowledged.

Reprint requests and correspondence: Michael Camilleri, M.D., Mayo Clinic, Charlton 8-110, 200 First St. S.W., Rochester, MN 55905.

Received September 14, 2005; accepted December 16, 2005.

REFERENCES

- Agrawal S, Stollman NH, Rogers AI. University of Miami Division of Clinical Pharmacology therapeutic rounds: Update on diagnosis and treatment of gastroparesis. *Am J Ther* 1999;6:97–109.
- Bytzer P, Talley NJ, Leemon M, et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: A population-based survey of 15000 adults. *Arch Intern Med* 2001;10:1989–96.
- Maleki D, Locke GR 3rd, Camilleri M, et al. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med* 2000;9:2808–16.
- Jones KL, Russo A, Stevens JE, et al. Predictors of delayed gastric emptying in diabetes. *Diabetes Care* 2001;24:1264–9.
- Stanghellini V, Tosetti C, Paternico A, et al. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996;110:1036–42.
- Tack J, Bisschops R. Mechanisms underlying meal-induced symptoms in functional dyspepsia. *Gastroenterology* 2004;127:1844–7.
- Bredenoord AJ, Chial HJ, Camilleri M, et al. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2003;1:264–72.
- Chitkara DK, Delgado-Aros S, Bredenoord AJ, et al. Functional dyspepsia, upper gastrointestinal symptoms, and transit in children. *J Pediatr* 2003;143:609–13.
- Chitkara DK, Camilleri M, Zinsmeister AR, et al. Gastric sensory and motor dysfunction in adolescents with functional dyspepsia. *J Pediatr* 2005;146:500–5.
- Soykan I, Sivri B, Sarosiek I, et al. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci* 1998;43:2398–404.
- Datz FL, Christian PE, Moore J. Gender-related differences in gastric emptying. *J Nucl Med* 1987;28:1204–7.
- Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. *Gut* 1996;39:299–305.
- Gill RC, Murphy PD, Hooper HR, et al. Effect of the menstrual cycle on gastric emptying. *Digestion* 1987;36:168–74.
- Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology* 2004;127:1592–622.
- Esfandyari T, Gonenne J, Stephens D, et al. Do female sex hormones alone or in combination alter gastrointestinal and colonic transit in healthy postmenopausal females? A randomized, controlled study. *Gastroenterology* 2005;128:A272.
- Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* 1984;86:1592–610.
- Malagelada JR, Stanghellini V. Manometric evaluation of functional upper gut symptoms. *Gastroenterology* 1985;88:1223–31.
- Kendall BJ, McCallum RW. Gastroparesis and the current use of prokinetic drugs. *Gastroenterology* 1993;1:107–14.
- Eagon JC, Miedema BW, Kelly KA. Postgastrectomy syndromes. *Surg Clin North Am* 1992;72:445–65.
- Hunter RJ, Metz DC, Morris JB, et al. Gastroparesis: A potential pitfall of laparoscopic Nissen fundoplication. *Am J Gastroenterol* 1996;91:2617–8.
- Muller MW, Friess H, Beger HG, et al. Gastric emptying following pylorus-preserving Whipple and duodenum-preserving pancreatic head resection in patients with chronic pancreatitis. *Am J Surg* 1997;173:257–63.
- Berkowitz N, Schulman LL, McGregor C, et al. Gastroparesis after lung transplantation. Potential role in postoperative respiratory complications. *Chest* 1995;108:1602–7.
- Sodhi SS, Guo JP, Maurer AH, et al. Gastroparesis after combined heart and lung transplantation. *J Clin Gastroenterol* 2002;34:34–9.
- Huizinga JD. Neural injury, repair, and adaptation in the GI tract. IV. Pathophysiology of GI motility related to interstitial cells of Cajal. *Am J Physiol* 1998;275:G381–6.
- Vinik AI, Maser RE, Mitchell BD, et al. Diabetic autonomic neuropathy. *Diabetes Care* 2003;26:1553–79.
- Ziegler D, Schadeewaldt P, Pour Mirza A, et al. [¹³C]octanoic acid breath test for non-invasive assessment of gastric emptying in diabetic patients: Validation and relationship to gastric symptoms and cardiovascular autonomic function. *Diabetologia* 1996;39:823–30.
- Ordog T, Takayama I, Cheung WK, et al. Remodeling of networks of interstitial cells of Cajal in a murine model of diabetic gastroparesis. *Diabetes* 2000;49:1731–9.
- Camilleri M, Brown ML, Malagelada JR. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. *Gastroenterology* 1986;91:94–9.
- Houghton LA, Read NW, Heddl R, et al. Relationship of the motor activity of the antrum, pylorus, and duodenum to gastric emptying of a solid-liquid mixed meal. *Gastroenterology* 1988;94:1285–91.
- Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 1986;90:1919–25.
- Samsom M, Salet GA, Roelofs JM, et al. Compliance of the proximal stomach and dyspeptic symptoms in patients with type I diabetes mellitus. *Dig Dis Sci* 1995;40:2037–42.
- Samsom M, Roelofs JM, Akkermans LM, et al. Proximal gastric motor activity in response to a liquid meal in type I diabetes mellitus with autonomic neuropathy. *Dig Dis Sci* 1998;43:491–6.
- Frank JW, Saslow SB, Camilleri M, et al. Mechanism of accelerated gastric emptying of liquids and hyperglycemia in patients with type II diabetes mellitus. *Gastroenterology* 1995;109:755–65.
- Zarate N, Mearin F, Wang XY, et al. Severe idiopathic gastroparesis due to neuronal and interstitial cells of Cajal degeneration: Pathological findings and management. *Gut* 2003;52:966–70.
- Fraser RJ, Horowitz M, Maddox AF, et al. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1990;33:675–80.
- Horowitz M, Maddox AF, Wishart JM, et al. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 1991;18:229–34.
- Greydanus MP, Vassallo M, Camilleri M, et al. Neurohormonal factors in functional dyspepsia: Insights on pathophysiological mechanisms. *Gastroenterology* 1991;100:1311–8.
- Tack J, Demedts I, Dehondt G, et al. Clinical and

- pathophysiological characteristics of acute-onset functional dyspepsia. *Gastroenterology* 2002;122:1738–47.
39. Camilleri M, Brown ML, Malagelada JR. Impaired transit of chyme in chronic intestinal pseudoobstruction. Correction by cisapride. *Gastroenterology* 1986;91:619–26.
 40. Camilleri M, Hasler WL, Parkman HP, et al. Measurement of gastrointestinal motility in the GI laboratory. *Gastroenterology* 1998;115:747–62.
 41. Parkman HP, Hasler WL, Barnett JL, et al; American Motility Society Clinical GI Motility Testing Task Force. Electrogastrography: A document prepared by the gastric section of the American Motility Society Clinical GI Motility Testing Task Force. *Neurogastroenterol Motil* 2003;15:89–102.
 42. Delgado-Aros S, Camilleri M, Cremonini F, et al. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. *Gastroenterology* 2004;127:1685–94.
 43. Camilleri M, Malagelada JR. Abnormal intestinal motility in diabetics with the gastroparesis syndrome. *Eur J Clin Invest* 1984;14:420–7.
 44. O'Brien MD, Bruce BK, Camilleri M. The rumination syndrome: Clinical features rather than manometric diagnosis. *Gastroenterology* 1995;108:1024–9.
 45. Chial HJ, Camilleri M, Williams DE, et al. Rumination syndrome in children and adolescents: Diagnosis, treatment, and prognosis. *Pediatrics* 2003;111:158–62.
 46. Chaudhuri TK, Fink S. Gastric emptying in human disease states. *Am J Gastroenterol* 1991;86:533–8.
 47. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: Establishment of international control values. *Am J Gastroenterol* 2000;95:1456–62.
 48. Ghoo YF, Maes BD, Geypens BJ, et al. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. *Gastroenterology* 1993;104:1640–7.
 49. Choi MG, Camilleri M, Burton DD, et al. Reproducibility and simplification of ¹³C-octanoic acid breath test for gastric emptying of solids. *Am J Gastroenterol* 1998;93:92–8.
 50. Bromer MQ, Kantor SB, Wagner DA, et al. Simultaneous measurement of gastric emptying with a simple muffin meal using [¹³C]octanoate breath test and scintigraphy in normal subjects and patients with dyspeptic symptoms. *Dig Dis Sci* 2002;47:1657–63.
 51. Feldman M, Smith HJ, Simon TR. Gastric emptying of solid radiopaque markers: Studies in healthy subjects and diabetic patients. *Gastroenterology* 1984;87:895–902.
 52. Couturier O, Bodet-Milin C, Querellou S, et al. Gastric scintigraphy with a liquid-solid radiolabeled meal: Performances of solid and liquid parameters. *Nucl Med Commun* 2004;25:1143–50.
 53. Thomforde GM, Camilleri M, Phillips SF, et al. Evaluation of an inexpensive screening scintigraphic test of gastric emptying. *J Nucl Med* 1995;36:93–6.
 54. Guo JP, Maurer AH, Fisher RS, et al. Extending gastric emptying scintigraphy from two to four hours detects more patients with gastroparesis. *Dig Dis Sci* 2001;46:24–9.
 55. Braden B, Adams S, Duan LP, et al. The [¹³C]acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. *Gastroenterology* 1995;108:1048–55.
 56. Choi MG, Camilleri M, Burton DD, et al. [¹³C]octanoic acid breath test for gastric emptying of solids: Accuracy, reproducibility, and comparison with scintigraphy. *Gastroenterology* 1997;112:1155–62.
 57. Viramontes BE, Kim DY, Camilleri M, et al. Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. *Neurogastroenterol Motil* 2001;13:567–74.
 58. Rhie JK, Hayashi Y, Welage LS, et al. Drug marker absorption in relation to pellet size, gastric motility and viscous meals in humans. *Pharm Res* 1998;15:233–8.
 59. Poitras P, Picard M, Dery R, et al. Evaluation of gastric emptying function in clinical practice. *Dig Dis Sci* 1997;42:2183–9.
 60. Marzio L, Giacobbe A, Conoscitore P, et al. Evaluation of the use of ultrasonography in the study of liquid gastric emptying. *Am J Gastroenterol* 1989;84:496–500.
 61. Darwiche G, Almer LO, Bjorgell O, et al. Measurement of gastric emptying by standardized real-time ultrasonography in healthy subjects and diabetic patients. *J Ultrasound Med* 1999;18:673–82.
 62. Hausken T, Li XN, Goldman B, et al. Quantification of gastric emptying and duodenogastric reflux stroke volumes using three-dimensional guided digital color Doppler imaging. *Eur J Ultrasound* 2001;13:205–13.
 63. Dooley CP, el Newihi HM, Zeidler A, et al. Abnormalities of the migrating motor complex in diabetics with autonomic neuropathy and diarrhea. *Scand J Gastroenterol* 1988;23:217–23.
 64. Camilleri M. Study of human gastroduodenojejunal motility. *Applied physiology in clinical practice. Dig Dis Sci* 1993;38:785–94.
 65. Thumshirn M, Bruninga K, Camilleri M. Simplifying the evaluation of postprandial antral motor function in patients with suspected gastroparesis. *Am J Gastroenterol* 1997;92:1496–500.
 66. Chen JD, McCallum RW. Clinical applications of electro-gastrography. *Am J Gastroenterol* 1993;88:1324–36.
 67. Chen JD, Lin Z, Pan J, et al. Abnormal gastric myoelectrical activity and delayed gastric emptying in patients with symptoms suggestive of gastroparesis. *Dig Dis Sci* 1996;41:1538–45.
 68. Fraser RJ, Horowitz M, Maddox AF, et al. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1990;33:675–80.
 69. Frank JW, Saslow SB, Camilleri M, et al. Mechanism of accelerated gastric emptying of liquids and hyperglycemia in patients with type II diabetes mellitus. *Gastroenterology* 1995;109:755–65.
 70. Jones KL, Kong MF, Berry MK, et al. The effect of erythromycin on gastric emptying is modified by physiological changes in the blood glucose concentration. *Am J Gastroenterol* 1999;94:2074–9.
 71. Ramsbottom N, Hunt JN. Studies of the effect of metoclopramide and apomorphine on gastric emptying and secretion in man. *Gut* 1970;11:989–93.
 72. Eisner M. Gastrointestinal effects of metoclopramide in man. In vitro experiments with human smooth muscle preparations. *BMJ* 1968;4:679–80.
 73. Monkovic I, Willner D, Adam MA, et al. Substituted benzamides. 1. Potential nondopaminergic antagonists of chemotherapy-induced nausea and emesis. *J Med Chem* 1988;31:1548–58.
 74. Perkel MS, Moore C, Hersh T, et al. Metoclopramide therapy in patients with delayed gastric emptying: A randomized, double-blind study. *Dig Dis Sci* 1979;24:662–6.
 75. Snape WJ Jr, Battle WM, Schwartz SS, et al. Metoclopramide to treat gastroparesis due to diabetes mellitus: A double-blind, controlled trial. *Ann Intern Med* 1982;96:444–6.
 76. Lata PF, Pigarelli DL. Chronic metoclopramide therapy for diabetic gastroparesis. *Ann Pharmacother* 2003;37:122–6.

- Albibi R, McCallum RW. Metoclopramide: Pharmacology and clinical application. *Ann Intern Med* 1983;98:86–95.
77. Silvers D, Kipnes M, Broadstone V, et al. Domperidone in the management of symptoms of diabetic gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. DOM-USA-5 Study Group. *Clin Ther* 1998;20:438–53.
78. Patterson D, Abell T, Rothstein R, et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. *Am J Gastroenterol* 1999;94:1230–4.
79. Quigley EM, Hasler WL, Parkman HP. AGA technical review on nausea and vomiting. *Gastroenterology* 2001;120:263–86.
80. Fraser RJ, Horowitz M, Maddox AF, et al. Postprandial antropyloroduodenal motility and gastric emptying in gastroparesis—effects of cisapride. *Gut* 1994;35:172–8.
81. Braden B, Enghofer M, Schaub M, et al. Long-term cisapride treatment improves diabetic gastroparesis but not glycaemic control. *Aliment Pharmacol Ther* 2002;16:1341–6.
82. Camilleri M, Malagelada J-R, Abell TL, et al. Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. *Gastroenterology* 1989;96:704–12.
83. Camilleri M, Balm RK, Zinsmeister AR. Symptomatic improvement with one-year cisapride treatment in neuropathic chronic intestinal dysmotility. *Aliment Pharmacol Ther* 1996;10:403–9.
84. Abell TL, Camilleri M, DiMugno EP, et al. Long-term efficacy of oral cisapride in symptomatic upper gut dysmotility. *Dig Dis Sci* 1991;36:616–20.
85. Evans AJ, Krentz AJ. Should cisapride be avoided in patients with diabetic gastroparesis? *J Diabetes Complications* 1999;13:314–5.
86. Wang SH, Lin CY, Huang TY, et al. QT interval effects of cisapride in the clinical setting. *Int J Cardiol* 2001;80:179–83.
87. Camilleri M, ATI abstract for DDW 2006 (in press)
88. Dibaise JK, Quigley EM. Efficacy of prolonged administration of intravenous erythromycin in an ambulatory setting as treatment of severe gastroparesis: One center's experience. *J Clin Gastroenterol* 1999;28:131–4.
89. Coulie B, Tack J, Peeters T, et al. Involvement of two different pathways in the motor effects of erythromycin on the gastric antrum in humans. *Gut* 1998;43:395–400.
90. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. *Am J Gastroenterol* 1993;88:203–7.
91. Fiorucci S, Distrutti E, Gerli R, et al. Effect of erythromycin on gastric and gallbladder emptying and gastrointestinal symptoms in scleroderma patients is maintained medium term. *Am J Gastroenterol* 1994;89:550–5.
92. Tougas G, Chen Y, Luo D, et al. Tegaserod improves gastric emptying in patients with gastroparesis and dyspeptic symptoms. *Gastroenterology* 2003;124:A54.
93. Talley NJ, Verlinden M, Geenen DJ, et al. Effects of a motilin receptor agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitus: A randomised, double blind, placebo controlled trial. *Gut* 2001;49:395–401.
94. Fang J, McCallum R, DiBase J, et al. Effect of mitemincinal fumarate (GM-611) on gastric emptying in patients with idiopathic or diabetic gastroparesis. *Gastroenterology* 2004;126:A483.
95. McCallum RW, Fogel R, Fang JC, et al. Mitemincinal fumarate (GM-611) provided symptomatic relief of diabetic gastroparesis, especially in type I diabetes: Results of a 12-week, multi-center, double-blind, placebo-controlled, randomized phase 2b study (gm-611-05). *Gastroenterology* 2005;128:A467.
96. Binn M, Albert C, Gougeon A, et al. Effect of ghrelin on gastric emptying in patients with neurogenic gastroparesis. *Gastroenterology* 2005;128:A59.
97. Murray CD, Martin NM, Patterson M, et al. Ghrelin enhances gastric emptying in diabetic gastroparesis: A double blind, placebo controlled, crossover study. *Gut* 2005;54:1693.
98. Tack J, Depoortere I, Bisschops R, et al. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. *Aliment Pharmacol Ther* 2005;22:847–53.
99. Watkins CC, Sawa A, Jaffrey S, et al. Insulin restores neuronal nitric oxide synthase expression and function that is lost in diabetic gastropathy. *J Clin Invest* 2000;106:373–84.
100. Coleski R, Gonlachanvit S, Owyang C, et al. Selective reversal of hyperglycemia-evoked gastric myoelectric dysrhythmias by nitrenergic stimulation in healthy humans. *J Pharmacol Exp Ther* 2005;312:103–11.
101. Sarnelli G, Sifrim D, Janssens J, et al. Influence of sildenafil on gastric sensorimotor function in humans. *Am J Physiol Gastrointest Liver Physiol* 2004;287:G988–92.
102. Bortolotti M, Mari C, Lopilato C, et al. Sildenafil inhibits gastroduodenal motility. *Aliment Pharmacol Ther* 2001;15:157–61.
103. Vella A, Lee JS, Camilleri M, et al. Effects of pramlintide, an amylin analogue, on gastric emptying in type 1 and 2 diabetes mellitus. *Neurogastroenterol Motil* 2002;14:123–31.
104. Schirra J, Nicolaus M, Roggel R, et al. Endogenous GLP-1 controls endocrine pancreatic secretion and antro-pyloroduodenal motility in humans. *Gut* 2006;55:243–51.
105. Heine RJ, Van Gaal LF, Johns D, et al; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial. *Ann Intern Med* 2005;143:559–69.
106. Pasricha PJ, Ravich WJ, Hendrix TR, et al. Intraspincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995;332:774–8.
107. Ezzeddine D, Jit R, Katz N, et al. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002;55:920–3.
108. Lacy BE, Zayat EN, Crowell MD, et al. Botulinum toxin for the treatment of gastroparesis: A preliminary report. *Am J Gastroenterol* 2002;97:1548–52.
109. Miller LS, Szych GA, Kantor SB, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *Am J Gastroenterol* 2002;97:1653–60.
110. Arts J, Caenepeel P, Degreef T, et al. Randomized double-blind cross-over study evaluating the effect of intrapyloric injection of botulinum toxin on gastric emptying and symptoms in patients with gastroparesis. *Gastroenterology* 2005;128:A81.
111. Bromer MQ, Friedenberg F, Miller LS, et al. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. *Gastrointest Endosc* 2005;61:833–9.
112. Syed AA, Rattansingh A, Furtado SD. Current perspectives on the management of gastroparesis. *J Postgrad Med* 2005;51:54–60.
113. Pitt HA, Mann LL, Berquist WE, et al. Chronic

- intestinal pseudo-obstruction. Management with total parenteral nutrition and a venting enterostomy. *Arch Surg* 1985;120:614–8.
114. Murr MM, Sarr MG, Camilleri M. The surgeon's role in the treatment of chronic intestinal pseudoobstruction. *Am J Gastroenterol* 1995;90:2147–51.
 115. Fontana RJ, Barnett JL. Jejunostomy tube placement in refractory diabetic gastroparesis: A retrospective review. *Am J Gastroenterol* 1996;91:2174–8.
 116. Jones MP, Maganti K. A systematic review of surgical therapy for gastroparesis. *Am J Gastroenterol* 2003;98:2122–9.
 117. Forstner-Barthell AW, Murr MM, Nitecki S, et al. Near-total completion gastrectomy for severe postvagotomy gastric stasis: Analysis of early and long-term results in 62 patients. *J Gastrointest Surg* 1999;3:15–21.
 118. Bortolotti M. The “electrical way” to cure gastroparesis. *Am J Gastroenterol* 2002;97:1874–83.
 119. US Food and Drug Administration. H990014 Enterra™ Therapy System (formerly named Gastric Electrical Stimulation (GES) system). Issued March 31, 2000. Available at: <http://www.fda.gov/cdrh/ode/H990014sum.html>. Accessed June 12, 2003.
 120. Familoni BO, Abell TL, Voeller G, et al. Electrical stimulation at a frequency higher than basal rate in human stomach. *Dig Dis Sci* 1997;42:885–91.
 121. McCallum RW, Chen JD, Lin Z, et al. Gastric pacing improves emptying and symptoms in patients with gastroparesis. *Gastroenterology* 1998;114:456–61.
 122. Forster J, Sarosiek I, Delcore R, et al. Gastric pacing is a new surgical treatment for gastroparesis. *Am J Surg* 2001;182:676–81.
 123. Abell TL, Van Cutsem E, Abrahamsson H, et al. Gastric electrical stimulation in intractable symptomatic gastroparesis. *Digestion* 2002;66:204–12.
 124. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003;125:421–8.
 125. McCallum RW, Lin Z, Sarosiek I, et al. Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. *Gastroenterology* 2005;128:A485.
 126. Mason RJ, Lipham J, Eckerling G, et al. Gastric electrical stimulation: An alternative surgical therapy for patients with gastroparesis. *Arch Surg* 2005;140:841–6.
 127. Lustman PJ, Freedland KE, Griffith LS, et al. Fluoxetine for depression in diabetes: A randomized double-blind placebo-controlled trial. *Diabetes Care* 2000;23:618–23.

CONFLICT OF INTEREST

Guarantor of the article: M. Camilleri

Specific author contributions: Dr. M. Park, literature review, Dr. M. Camilleri, concepts, general content, literature review

Financial support: None

Potential competing interests: None
