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Gastroparesis: Current diagnostic challenges and management considerations

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Abstract

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Gastroparesis refers to abnormal gastric motility characterized by delayed gastric emptying in the absence of mechanical obstruction. The most common etiologies include diabetes, post-surgical and idiopathic. The most common symptoms are nausea, vomiting and epigastric pain. Gastroparesis is estimated to affect 4% of the population and symptomatology may range from little effect on daily activity to severe disability and frequent hospitalizations. The gold standard of diagnosis is solid meal gastric scintigraphy. Treatment is multimodal and includes dietary modification, prokinetic and anti-emetic medications, and surgical interventions. New advances in drug therapy, and gastric electrical stimulation techniques have been introduced and might provide new hope to patients with refractory gastroparesis. In this comprehensive review, we discuss gastroparesis with emphasis on the latest developments; from the perspective of the practicing clinician.

Keywords: Gastroparesis, Nausea; Vomiting; Prokinetic; Therapy

INTRODUCTION

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Gastroparesis is a condition of abnormal gastric motility characterized by delayed gastric emptying in the absence of mechanical outlet obstruction. The true prevalence of gastroparesis is unknown; however, it has been estimated that up to 4% of the adult population experiences symptomatic manifestations of this condition. A large study on long-term outcomes of gastroparetic adults revealed that 82% of patients were female^[1]. Gastroparesis has a higher prevalence in the patient population of tertiary medical centers than in the community hospital setting. Moreover, a widely available diagnostic test that could be applied in a standard fashion is currently lacking in the primary care setting.

PATHOPHYSIOLOGY

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Gastric motility results from the integration of tonic contractions of the fundus, phasic contractions of the antrum, and inhibitory forces of pyloric and duodenal contractions^[2]. These contractions require a complex interaction between gastric smooth muscle, the enteric nervous system and specialized pacemaker cells, the

interstitial cells of Cajal (ICC)[3]. Motor dysfunction of the stomach may result from autonomic neuropathy, enteric neuropathy, abnormalities of ICCs, fluctuations in blood glucose and psychosomatic factors[4–6].

The etiology of gastroparesis is multifactorial (Table 1). The three most common etiologies are diabetes, idiopathic, and post-surgical, especially if the vagus nerve is damaged. Other causes include medication, Parkinson's disease, collagen vascular disorders, thyroid dysfunction, liver disease, chronic renal insufficiency, intestinal pseudo-obstruction and miscellaneous[4,7].

Table 1
Causes of gastroparesis

Originating in the region of ICCs, electrical activity in the form of gastric slow waves sweeps across the stomach toward the pylorus. However, these slow waves do not directly result in contraction of the gastric smooth muscle, but instead cause a simultaneous release of neurotransmitters from the enteric nerve endings, leading to smooth muscle contraction. Although neurohumoral control of gastric emptying is incompletely understood, both motilin and ghrelin are peptides secreted by the gastrointestinal endocrine cells that have been shown to increase gastric motor function[8,9].

In general, several factors affect gastric motility. These include motor dysfunction i.e. hypomotility and pyloric spasm, sensory dysfunction (such as impaired fundic relaxation, accommodation and abnormal sensation), electrical dysfunction (such as gastric arrhythmias and abnormal propagation), CNS effects resulting in nausea and vomiting, and others such as bacterial overgrowth, visceral hyperalgesia and gastrointestinal hormones.

SYMPTOMS AND EVALUATION

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Gastroparesis is diagnosed by the presence of delayed gastric emptying in a symptomatic patient after other potential etiologies such as ulcer disease, mechanical obstruction, gastric cancer or other malignancies are excluded[10,11]. Symptoms of gastroparesis include nausea, vomiting, early satiety, bloating, post-prandial fullness, abdominal pain, weight loss and/or weight gain. These symptoms are non-specific and may mimic other disorders[10]. A simple severity grading scale has been proposed for stratification of symptoms[12] (Table 2). Also, a patient-based symptom instrument, the gastroparesis cardinal symptom index (GCSI) has been developed to assess severity of gastroparesis[13]. The GCSI total scores are based on three subscales of nausea/vomiting, post-prandial fullness/early satiety, and bloating. The GCSI scale is used to rate symptom change by either physicians or by the patient's own self-evaluations. In 146 patients with gastroparesis, nausea was present in 92%, vomiting in 84%, abdominal bloating in 75%, and early satiety in 60%. Abdominal pain or discomfort was present in 46%-89% of patients but was not the predominant symptom[4]. Abdominal pain in gastroparesis responds poorly to treatment[14]. Constipation may also be associated with gastroparesis. Treatment of constipation with an osmotic laxative has shown to improve dyspeptic symptoms as well as gastric emptying delay[15]. Complications of gastroparesis include esophagitis, Mallory-Weiss tear from chronic nausea/vomiting, malnutrition, volume depletion with acute renal failure (secondarily), electrolyte disturbances and bezoar formation[16,17].

Table 2
Proposed classification of gastroparesis severity

DIAGNOSTIC TESTS

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Radiographic tests

Gastric scintigraphy: Gastric emptying scintigraphy of a radiolabeled solid meal is the gold standard for the diagnosis of gastroparesis. This test provides a physiological, non-invasive and quantitative measure of gastric emptying. Measurement of emptying of solids is more sensitive by scintigraphy. This is due to the fact that liquid emptying may remain normal despite advanced disease. A variety of foods including chicken, liver, eggs, egg whites, oatmeal, or pancakes are used as meals. The content of the meal is one of the most important variables in gastric emptying. Solids versus liquids, indigestible residue, fat content, calories and volume of the test meal, can all alter gastric emptying time. Consensus recommendations for a standardized gastric emptying procedure have recommended a universally acceptable 99-m technetium sulfur-colloid labeled low fat, egg-white meal^[18]. Medications that alter gastric emptying may be discontinued 48-72 h in advance, blood glucose in diabetics should be < 275 mg/dL on the day of the test and scinti-scanning at a minimum of 1, 2 and 4 h after test meal ingestion is performed in the upright position. This periodic measurement of radiolabeled solid meal has a specificity of 62% and a sensitivity of 93% when compared to continuous scinti-scanning^[19]. Emptying of solids exhibits a lag phase followed by a prolonged linear emptying phase. The results of this test can be reported in two ways. The simplest approach is to report percent retention at defined times (minimum 1, 2, and 4 h). Half-times ($T_{1/2}$ values) may also be calculated but may potentially be less accurate, particularly in patients with very long emptying for whom extrapolation is needed to calculate the half-time if it was not actually reached during the test. Retention of over 10% of the solid meal after 4 h is abnormal. A grading of severity based on 4 h values might be used: grade 1 (mild), 11%-20% retention at 4 h; grade 2 (moderate), 21%-35% retention at 4 h; grade 3 (severe), 36%-50% retention at 4 h; and grade 4 (very severe), > 50% retention at 4 h^[18]. Prokinetics may also be administered intravenously after the last measurement (i.e. 4 h) to evaluate if the patient is a “responder” or “non-responder” to the agent. Again, percent retained or extrapolated $T_{1/2}$ times can be calculated to assess the response. The drawbacks of the test include lack of standardization in different academic institutions, despite the current consensus recommendations, and radiation exposure, which is equivalent to about 1/3 of the average annual radiation exposure in the US from natural sources.

Radiopaque markers: After ingestion of indigestible markers, i.e. 10 small pieces of nasogastric tubing, none of the markers should remain in the stomach on an X-ray taken 6 h after ingestion with a meal^[20]. This simple test correlates with clinical gastroparesis and is readily available and inexpensive. The drawbacks of the test include lack of standardization of the meal and size of markers and difficulty of determining if the markers are located in the stomach or other regions that overlap with the stomach (e.g. proximal small bowel, transverse colon).

Ultrasonography: Transabdominal ultrasound has been used to measure emptying of a liquid meal by serially evaluating cross-sectional changes in the volume remaining in the gastric antrum over time^[21-23]. Emptying is considered complete when the antral area/volume returns to the fasting baseline. Some studies have revealed gastric emptying measurements similar to those seen with scintigraphy^[24]. Three-dimensional ultrasound is a newly-developed technique that has recently been reported to be useful in determining stomach function^[25,26] and duplex sonography can quantify transpyloric flow of liquid gastric contents. These techniques may be preferred over scintigraphy in patients such as pregnant women or children, in order to minimize radiation exposure. Drawbacks of the test include the fact that it is somewhat operator dependent, has proven reliable only for measurements of liquid emptying rates^[24], and is less reliable when the patient is obese or when excessive gastric air is present. Moreover, liquid emptying is rarely impaired in patients with severe gastroparesis.

Magnetic resonance imaging: MRI using gadolinium has been found to accurately measure semi-solid gastric emptying and accommodation using sequential transaxial abdominal scans^[27]. MRI provides excellent spatial resolution with a high sensitivity. It is also non-invasive and radiation free. Antral propagation waves can be observed and their velocity calculated. In gastroparesis, a significant reduction is seen in the velocity of these waves^[28]. MRI can also differentiate gastric meal volume and total gastric volume, allowing gastric

secretory rates to be calculated. New rapid techniques allow careful measurements of wall motion in both the proximal and distal stomach during emptying, and solid markers now permit measurement of solid meal emptying^[29,30]. The drawback of this test is the expense and lack of availability.

Single-photon emission CT: This technique uses intravenously administered 99-Tc pertechnetate that accumulates within the gastric wall rather than the lumen and provides a three-dimensional outline of the stomach^[31]. Measurement of regional gastric volumes in real-time to assess fundic accommodation and intragastric distribution can be made. The drawback of this test is the need of large radiation doses, and wide unavailability.

Stable isotope breath tests

The non-invasive 13-C-labeled octanoate breath test is an indirect means of measuring gastric emptying. It is a medium chain triglyceride which is bound to a solid meal such as a muffin. After ingestion and stomach emptying, 13-C octanoate is rapidly absorbed in the small intestine and metabolized to 13 CO₂ which is expelled from the lungs during expiration. The rate limiting step for the signal appearing in the breath is the rate of gastric emptying. Compared to detailed scintigraphy done over a period of 4 h, the breath test has a specificity of 80% and sensitivity of 86%^[32]. The test assumes normal small bowel, pancreas, liver and pulmonary functions. Some studies have demonstrated a strong correlation between the carbon-labeled breath test and gastric scintigraphy^[33,34]. The drawback of this test is the need for normal small intestinal absorption, liver metabolism, and pulmonary excretion to validate the test results.

Swallowed capsule telemetry

The ingestible “SmartPill®” (VA Boston Healthcare System, MA, USA), or telemetry capsule, offers a promising new non-radioactive method for assessing gastric emptying. This capsule measures pH, pressure and temperature using miniaturized wireless sensor technology. This has been developed for ambulatory assessment of GI transit. The time taken for the pill to be expelled from the stomach into the duodenum is measured by monitoring the time point at which the acid readings of the stomach are replaced by the dramatic increase in pH as the capsule enters the duodenum. It has been shown that gastric transit time calculated using the SmartPill correlates well with gastric scintigraphy with good sensitivity (82%) and specificity (83%)^[35]. The frequencies and amplitudes of antral contractions can be used to calculate motility indices. A current drawback is the cost of the pill and lack of widespread availability.

Antroduodenal manometry

In antroduodenal manometry, a water-perfused or solid-state manometric catheter is passed from the nares or mouth and placed fluoroscopically into the stomach and small bowel to measure actual gastroduodenal contractile activity. The frequency and amplitude of fasting, interdigestive and post-prandial contractions can be recorded, and the response to prokinetic agents can be assessed. Distinct patterns characterize the fasting and fed phases. During the fasting period, three cyclical phases known as migrating motor complex (MMC) recur approximately every 2 h: Phase I, Phase II and Phase III. Phase I is a period of motor quiescence followed by Phase II, a period of intermittent phasic contractions. Phase III, considered the “intestinal housekeeper”, consists of an integrated peristaltic wave, initiated in the antrum, that sweeps indigestible solids from the stomach into the duodenum and beyond. Feeding disrupts the MMC and replaces it with a fed motor pattern of more regular antral contractions of variable amplitude that are either segmental or propulsive in character.

Gastroparesis is characterized by loss of normal fasting MMC's and reduced postprandial antral contractions and, in some cases pylorospasm^[36]. Small intestinal motor dysfunction is detected in 17%-85% of patients with gastroparesis^[37]. Manometry can also distinguish between myopathic and neuropathic small intestinal dysmotilities. However only in approximately 20%-25% of patients diagnosed with dysmotility syndromes by antroduodenal manometry, is clinical management influenced^[38]. Antroduodenal manometry is usually

reserved for the refractory gastroparesis patient evaluated at tertiary referral centers with the benefit of provocative testing to assess manometric response to treatment^[39]. Drawbacks are that it is an invasive procedure, it needs motility expertise to perform and interpret the results, giving rise to problems with over interpretation in the unskilled hands.

Electrogastrography (EGG)

EGG measures gastric slow-wave myoelectrical activity *via* serosal, mucosal or cutaneous electrodes. It is most conveniently recorded with cutaneous electrodes positioned along the long axis of the stomach. Initially a pre-prandial recording for 45-60 min is captured. Patients are given a 500 kcal cheese or turkey sandwich and an equivalent postprandial recording is captured. The recorded signals are amplified and filtered to exclude contamination by noise from cardiorespiratory activity and patient movement. Computer analysis converts raw EGG signals to a three-dimensional plot. In healthy persons, EGG recordings exhibit uniform waveforms of 3 cycles/min, which increase in amplitude after ingestion of a meal. Abnormality of EGG is defined by rhythm disruption of more than 30% of the recording time including tachygastria (frequency of > 4 cycles/min) and bradygastria (< 2 cycles/min) and a lack of signal amplitude with eating^[40]. EGG abnormalities are present in 75% of patients with gastroparesis^[40]. EGG is considered by some authors as more of an adjunct to gastric emptying measurement for a comprehensive evaluation of patients with refractory symptoms^[40]. Drawbacks are the little documented utility of EGG in the management of patients with suspected gastric dysmotility and movement artifacts that make recordings difficult to interpret.

Other tests

The gastric barostat test consists of a high compliance balloon device placed into the stomach to measure pressure-volume relationships and visceral sensation^[41]. The drawback of this test is that it is invasive and is used therefore only as a research tool in a few tertiary centers.

The satiety test involves ingestion of water or a liquid nutrient until the patient reports maximal fullness. This test is not frequently performed and its main drawback is that results are subjective.

A common misconception is the use of barium upper gastrointestinal testing in the diagnosis of gastroparesis. Although this test can be used to evaluate anatomic abnormalities such as gastric outlet obstruction, it is not a functional study for the diagnosis of gastroparesis and other lesions such as malignancy may still be missed.

TREATMENT

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The general principles of treatment of symptomatic gastroparesis are to: (1) correct fluid, electrolyte, and nutritional deficiencies; (2) identify and rectify the underlying cause of gastroparesis if possible; and (3) reduce symptoms^[12,42].

In addition, patient education and explanation of the condition is an integral part of treatment. The disabling chronic symptoms of gastroparesis impact profoundly on the patient's sense of wellbeing, mental state, behavior and social life. Sensitive caring from the clinical team and professional counseling might be necessary to help the patient cope with the disability. Patients should be informed that a number of drugs might be tried in an attempt to discover the optimal therapeutic regimen and that the aim of treatment is to control rather than cure the disorder^[43].

The patient's drug list should be reviewed to eliminate drugs that can cause gastric dysmotility. Management can be tailored to the severity of the gastroparesis. For grade 1 (mild) gastroparesis, dietary modifications should be tried. Low doses of antiemetic or prokinetic medications can be taken on an as-needed basis. Grade 2 (compensated) gastroparesis is treated by combination of antiemetic and prokinetic medications given at scheduled regular intervals. These agents relieve the more chronic symptoms of nausea, vomiting, early satiety and bloating. They frequently have no effect on abdominal pain. In grade 3 (severe) gastroparesis or gastric

failure, more aggressive treatments including hospitalizations for i.v. hydration and medications, enteral or parenteral nutritional support and endoscopic or surgical therapy may be needed^[42].

Dietary manipulation

Dietary recommendations rely on measures that promote gastric emptying or, at least theoretically, do not retard gastric emptying. At the outset, it is advisable to introduce an experienced dietician who can discuss and explore the patient's tolerance of solids, semi-solids and liquids, as well as dietary balance, meal size and timing of meals. Fats and fiber tend to retard emptying, thus their intake should be minimized. This should be stressed as many of these patients who often concomitantly also have constipation, have been told to take fiber supplementation for treatment of their constipation. Multiple small low fat meals about four or five times each day should be recommended. Carbonated liquids should be avoided to limit gastric distention. Patients are instructed to take fluids throughout the course of the meal and to sit or walk for 1-2 h after meals. If the above measures are ineffective, the patient may be advised to consume the bulk of their calories as liquid since liquid emptying is often preserved in patients with gastroparesis. Poor tolerance of a liquid diet is predictive of a future poor success^[42].

Correction of glycemic control

Patients with diabetes should be counseled to achieve optimal glycemic control. Hyperglycemia itself delays gastric emptying, even in the absence of neuropathy or myopathy, which is likely to be mediated by reduced phasic antral contractility and induction of pyloric pressure waves. Hyperglycemia can inhibit the accelerating effects of prokinetic agents^[44]. Measures more likely to be effective include more aggressive glucose monitoring, with frequent dosing of short acting insulin preparations to prevent post-prandial hyperglycemia. Prevention of wide fluctuations of hyperglycemia may be more important than maintenance of a given steady-state blood glucose level^[45]. Improvement of glucose control increases antral contractility, corrects gastric dysrhythmias and accelerates emptying.

Pharmacological therapy

The pharmacotherapy of gastroparesis is stepwise, incremental and long term. The most commonly used drug classes include pro-motility and anti-emetic agents. There has been little in the way of randomized controlled investigations directly comparing the different agents. Consequently, a selection of drugs is used by trial and error.

Prokinetic agents: Prokinetic medications enhance the contractility of the GI tract, correct gastric dysrhythmias, and promote the movement of luminal contents in the antegrade direction. Prokinetics may improve predominantly symptoms of nausea, vomiting and bloating. They do not seem to relieve abdominal pain and early satiety associated with gastroparesis. They should be administered 30 min before meals to elicit maximal clinical effects. Bedtime doses are often added to facilitate nocturnal gastric emptying of indigestible solids. The response to treatment is usually judged clinically rather than with serial gastric emptying tests because symptom improvements correlate poorly with the acceleration of gastric emptying^[46]. A meta-analysis assessing benefits of four different drugs in 514 patients in 36 clinical trials reported that the macrolide antibiotic erythromycin is the most potent stimulant of gastric emptying, while erythromycin and the dopamine receptor antagonist, domperidone, are best at reducing symptoms of gastroparesis^[47]. Several factors must be considered when choosing a prokinetic drug for patients with gastroparesis, including efficacy, toxicity, regional availability and cost.

(I) Erythromycin. Erythromycin is a macrolide antibiotic that is also a motilin receptor agonist^[48]. The intravenous form is the most potent stimulant of solid and liquid gastric emptying^[49-50]. Motilin is a polypeptide hormone present in the distal stomach and duodenum that increases lower esophageal sphincter pressure and is responsible for initiating the MMC in the antrum of the stomach^[51-52]. Erythromycin binds to motilin receptors and hence increases the amplitude of antral peristalsis, triggers premature MMC phase III

activity, and stimulates gastric emptying^[53]. Interestingly, erythromycin has also been shown to accelerate emptying in post-vagotomy and antrectomy patients^[54]. This may be due to its stimulatory effects on the fundus.

Erythromycin should be started at a low dose (200 mg per 5 mL) and is most rapidly absorbed when administered as a suspension^[55]. However, tachyphylaxis develops in patients on chronic erythromycin therapy, due to down-regulation of motilin receptors which can develop as early as a few days of initiating therapy^[53]. If tachyphylaxis develops, erythromycin can be discontinued for 2 wk and then restarted again. Intravenous erythromycin is used occasionally for inpatients with severe refractory gastroparesis^[55]. Common side effects include skin rashes, nausea, cramping and abdominal pain. A large cohort reported that erythromycin increases the risk of sudden cardiac arrest by 2.01 times when compared to control population^[56]. The risk for death was further increased in those patients who also were on CYP3A (cytochrome P-450 3A) inhibitors such as selected antipsychotics, cardiac antiarrhythmics, antifungals, calcium antagonists, antidepressants, and anti-emetics. Therefore, prior to initiating EES therapy for treatment of gastroparesis, all these factors need to be considered. Although this has not undergone formal testing, in our institution, a QTc of 450 ms in men and 460 ms in women has been used as the cut-off value over which EES is not administered due to risk of QT prolongation.

(II) Metoclopramide. Metoclopramide is a substituted benzamide with several prokinetic actions, which include combined serotonin 5-hydroxytryptamine (HT) 4 receptor agonism, dopamine D2 receptor antagonism, and direct stimulation of gut smooth muscle contraction. The drug also has anti-emetic effects *via* brainstem D2 receptor antagonism, vagal and brainstem 5-HT₃ receptor antagonism. The prokinetic properties of metoclopramide are limited to the proximal gut. Metoclopramide increases esophageal, fundic and antral contractile amplitudes, elevates lower esophageal sphincter pressure, and improves antropyloroduodenal coordination. Metoclopramide is administered orally in pill or liquid suspension form. Intravenous forms commonly are reserved for inpatients that cannot retain oral medications. Subcutaneous administration has also been reported to provide symptom control^[57]. At least five controlled trials and four open label series have studied the efficacy of metoclopramide in gastroparesis^[10]. In these nine trials, symptoms improved in seven studies, but improvement in gastric emptying was noted in only five. Patients may develop tolerance to the prokinetic action of metoclopramide over time; however, its antiemetic effects are sustained^[58]. Metoclopramide is effective for the short-term treatment of gastroparesis for up to several weeks^[59,60]. The long-term utility of metoclopramide has not been proven^[61]. Side effects of metoclopramide occur in up to 30% of patients and result from antidopaminergic effects on the CNS. Acute dystonic reactions such as facial spasm, oculogyric crisis, trismus, and torticollis occur in 0.2%-6% of patients and are often observed in patients less than 30 years of age and within 48 h of initiating therapy^[62]. Drowsiness, fatigue, and lassitude are reported by 10% of patients. Metoclopramide can worsen depression. Other side effects include restlessness, agitation, irritability, akathisia and hyperprolactinemic effects. Prolonged treatment with metoclopramide can produce extrapyramidal symptoms. These symptoms usually subside with 2-3 mo of discontinuation of the drug. Irreversible tardive dyskinesia is a catastrophic consequence that occurs in 1% to 10% of cases when metoclopramide is taken for more than 3 mo^[62]. This condition is disabling and can develop without warning, therefore, it should be discussed in detail with the patients or their families with documentation of the discussion in their medical record. The current standard has been to sign an informed consent to document communicating the risks of metoclopramide.

(III) Domperidone. Domperidone, a benzimidazole derivative, is a peripheral dopamine D2 receptor antagonist with benefits similar to those of metoclopramide. Domperidone does not cross the blood-brain barrier and consequently it has fewer central side effects. Brainstem structures regulating vomiting are outside the blood-brain barrier, therefore, domperidone has potent central anti-emetic action. At least five controlled trials and four open case series have assessed domperidone in patients with gastroparesis and diabetic gastropathy^[63]. Symptoms improved in all studies, but accelerated gastric emptying was not uniformly observed. Domperidone may show tachyphylaxis on repeated administration^[64]. Adverse reactions to

domperidone are commonly related to hyperprolactinemia due to the porous blood-brain barrier in the anterior pituitary^[65]. These include menstrual irregularities, breast engorgement, and galactorrhea. An intravenous formulation of domperidone was removed in 1980 due to generation of cardiac arrhythmias^[66]. Domperidone is not approved by the FDA for prescription in the United States, although it can be obtained in Canada, Mexico, New Zealand, Europe, and Japan. It is available in the US with approval of local institutional review boards, through an FDA investigational new drug application (IND) to patients with gastroparesis refractory to other therapies.

(IV) Tegaserod. This is a 5-HT₄ receptor partial agonist used in the treatment of constipation predominant irritable bowel syndrome. In healthy volunteers, the drug stimulates small-intestinal motility and post-prandial antral and intestinal motility. Tegaserod has been shown to accelerate gastric emptying in some^[67] but not all studies of healthy volunteers^[68]. Tegaserod was completely withdrawn from the US market in April 2008 due to a reported increase in the risk of cardiovascular adverse effects.

(V) Cisapride. Cisapride is a 5-HT₄ receptor agonist with weak 5-HT₃ antagonist properties that once was widely used for gastroparesis. This drug was withdrawn from the market in the United States in 2000 because of numerous reports of sudden death from cardiac arrhythmias^[69]. Although the drug is still available overseas in numerous countries and obtainable from overseas websites, a recent consensus document did not recommend its use in gastroparesis^[12].

(VI) Bethanechol. Bethanechol is an approved smooth muscle muscarinic agonist that increases lower esophageal sphincter pressure and evokes fundoantral contractions but does not induce propulsive contractions or accelerate gastric emptying^[70]. Rarely, the drug may be used as an adjunct with other prokinetic medications in patients refractory to standard treatment with prokinetics and anti-emetic drugs. Prominent adverse effects include abdominal cramps, skin flushing, diaphoresis, lacrimation, salivation, nausea, vomiting, bronchoconstriction, urinary urgency, and miosis. Dangerous cardiovascular effects include abrupt decreases in blood pressure in hypertensive patients and atrial fibrillation in patients with hyperthyroidism.

(VII) Drugs in research. (1) Motilin receptor agonists. (a) Azithromycin is a macrolide antibiotic similar to erythromycin. It has been postulated that azithromycin is also a motilin receptor agonist. In preliminary studies, intravenous administration of azithromycin improves antroduodenal contractions as measured by manometry^[71]. However, there are no data available revealing an improvement in gastric emptying rates or patient symptoms after the administration of i.v. or oral azithromycin. The potential benefit of azithromycin is the longer half-life (68 h) as compared to erythromycin (1.5-2 h) and thus the less frequent dosing may help improve compliance with the medication (once a day *versus* four times a day). Furthermore, azithromycin is not metabolized, and elimination is largely in the feces, following excretion into the bile, with less than 10% excreted in the urine. Thus, it does not utilize the P-450 pathway in the liver and has less adverse effects due to drug interactions. It also appears that azithromycin has lower pro-arrhythmic potential compare with erythromycin but nevertheless cardiac adverse events have been reported^[72-74]. From that prospective, it seems prudent to check the length of the QTc interval prior to initiating azithromycin therapy as well. (b) Mitomecinal is also a macrolide derived motilin receptor agonist with prokinetic properties. It does not have any antimicrobial actions. It produced symptom benefit in patients with diabetic gastropathy who had a body mass index of

< 35 kg/m² and with hemoglobin A1C values < 10%^[75]. In addition, tachyphylaxis was not observed during the study period. (c) Atilmotin is another motilin receptor agonist, which, when given i.v., has been shown to accelerate gastric emptying of liquids and solids in healthy subjects^[76]. It is not known whether atilmotin has significant effects on symptoms in patients with gastroparesis. (d) Ghrelin is a neurohumoral transmitter secreted by the stomach and is believed to play a physiological role as a stimulant of food intake and is also structurally related to motilin. Ghrelin has prokinetic properties, and has been shown to accelerate gastric emptying of a test meal in diabetic patients with slow gastric emptying^[77], as well as improve gastric emptying

and decreased meal-related symptoms in patients with idiopathic gastroparesis^[78]. (2) Dopamine antagonists and serotonin agonists. (a) Itopride is a new D2 antagonist with anti-acetylcholinesterase effects. This drug showed prokinetic properties in animal models as well as promising effects in functional dyspepsia^[79]. However, in healthy subjects, itopride had no effect on gastric emptying^[80]. (b) Sulpiride is a dopamine blocker used for psychiatric disorders. Initial studies have shown that oral levosulpiride is superior to placebo^[81], and may be as effective as cisapride in relieving nausea and vomiting in patients with gastroparesis^[82,83]. Although this drug is not new, further studies are of interest to see whether it deserves a more established position for these gastrointestinal indications. (c) Mosapride is a 5-HT₄ receptor agonist that accelerates gastric emptying in healthy volunteers and patients with diabetic gastroparesis^[84]. In contrast to cisapride, mosapride has little effect on potassium-channel activity and seems to exhibit a significantly lower cardiac dysrhythmogenic potential^[85]. (d) Renzapride is a combined 5-HT₄ receptor agonist and 5-HT₃-receptor antagonist. Future studies are needed to determine if renzapride exhibits efficacy in gastroparesis^[42]. (3) Miscellaneous. (a) Physostigmine and neostigmine are muscarinic receptor activators that stimulate gut motor activity by increasing acetylcholine levels. These drugs increase gastric contractions but have limited action in accelerate gastric emptying. However, pyridostigmine has been recently noted to reduce symptoms in a patient with gastroparesis secondary to underlying autoimmune disease^[86]. (b) Nizatidine is a H₂-receptor antagonist which exhibits anticholinesterase activity and stimulates gastric emptying but its efficacy in long-term treatment of gastroparesis is unknown^[87]. (c) Cholecystokinin receptor antagonists such as loxiglumide and dexloxiglumide accelerate gastric emptying in some studies. The utility of such agents in gastroparesis remains to be determined^[88]. (d) Sildenafil is a phosphodiesterase 5 inhibitor which has been shown to restore gastric emptying of liquids in an animal model of diabetes^[89]. Sildenafil also reduced the dysrhythmias of the stomach induced experimentally by hyperglycemia in humans^[90]. On the other hand, a thorough study of the effects of sildenafil on human gastric sensimotor functions showed that the drug significantly increases postprandial gastric volume and slows liquid (though not solid) emptying rate^[91]. Sildenafil has also been found to inhibit interdigestive motor activity of the antrum and duodenum^[92]. Clinical trials are clearly needed before this medication can be considered for the treatment of gastroparesis.

Anti-emetic medications: It is likely that a component of the clinical benefits observed with some of the available prokinetic drugs, such as metoclopramide and domperidone, stem from their anti-emetic actions on brain-stem nuclei. Nausea and vomiting are the most disabling symptom of gastroparesis and anti-emetic agents without stimulatory activity are often used alone or in concert with prokinetic drugs to treat gastroparesis. Antiemetic medications act on a broad range of distinct receptors subtypes in the peripheral and central nervous systems. Like prokinetics, the choice of antiemetic is empirical and it is reasonable to try the less expensive therapies initially.

(I) Phenothiazines. These are the most commonly prescribed traditional antiemetics which include prochlorperazine and tiethyperazine. These drugs are both dopamine and cholinergic receptor antagonists acting on the area postrema (chemoreceptor trigger zone) in the brainstem. Prochlorperazine can be administered in the tablet form, liquid suspension, suppository and by injection. Side effects include sedation and extra-pyramidal effects such as drowsiness, dry mouth, constipation, skin rashes and Parkinsonian-like tardive dyskinesia.

(II) Serotonin 5-HT₃ receptor antagonist. These medications include ondansetron, granisetron, and dolasetron and are useful for prophylaxis of chemotherapy induced nausea and vomiting, as well as symptoms occurring post operatively or during radiation therapy. These drugs may act on the chemoreceptor trigger zone as well as on peripheral afferent nerve fibers within the vagus nerve^[42]. Ondansetron has no effect on gastric emptying in healthy volunteers and patients with gastroparesis and moreover can cause constipation^[93,94]. This class of drugs maybe helpful when all other drugs have failed to provide symptom relief and are best given on an as-needed basis.

(III) Anti-histamines. Antihistamines acting on H1 receptors exhibit central antiemetic effects[42].

Commonly prescribed antiemetics include diphenhydramine, dimenhydrinate and meclizine. These agents are most useful to treat symptoms related to motion sickness. The mechanism of action is poorly understood but is likely to involve both labyrinthine and chemoreceptor trigger zones. Side effects include drowsiness, dry mouth, blurred vision, difficulty urinating, constipation, palpitations, dizziness, insomnia and tremor.

(IV) Low-dose tricyclic antidepressants. Tricyclic antidepressants (TCAs) impair gastrointestinal motility through their anticholinergic activity but have been shown to relieve nausea, vomiting and pain in functional dyspepsia[95,96]. In a recent publication, 88% of diabetic patients with nausea and vomiting reported benefits with TCAs[97], of which one third had delayed gastric emptying, suggesting that these agents may have utility in gastroparesis. However, formal prospective trials of these antidepressants for the treatment of gastroparesis have not been performed, thus their use is still considered off-label. Side effects of low-dose TCAs are uncommon, excessive sedation and dry mouth occasionally limits use.

(V) Other antiemetics. (1) Cannabinoids. Cannabinoid drugs such as dronabinol have been studied for improvement of gastrointestinal symptoms from chemotherapy and appear to have potency similar to standard antidopaminergics. Their benefit for gastroparesis has not been evaluated and they may also delay gastric emptying. (2) Benzodiazepines. These are useful for anticipatory nausea and vomiting before chemotherapy, but their efficacy in gastroparesis is unknown. These drugs maybe useful for their sedating effects in those patients with associated anxiety. (3) Neurokinin NK1-receptor antagonists. These are new antiemetics which treat both acute and delayed chemotherapy-induced nausea and vomiting[98,99], but their actions on gastric motor activity and symptoms in gastroparesis are uninvestigated. (4) Corticosteroids. Corticosteroids are employed as antiemetics in the postoperative setting or in the prevention of chemotherapy-induced emesis. One individual with idiopathic myenteric ganglionitis exhibited improvement with corticosteroid therapy, confirming the inflammatory basis of some cases of upper gut dysmotility[100].

Complementary and alternative therapies: Ginger, a traditional Chinese antiemetic agent, has weak 5-HT₃ receptor antagonist properties and has gastric slow wave antidysrhythmic effects in humans[101,102]. These therapies are often given for treatment of nausea and vomiting of diverse etiologies. Acupressure and electrical acustimulation on the P6 acupuncture point reduce nausea postoperatively, after chemotherapy, and during nausea of pregnancy. One group observed benefits with acupuncture in 35 diabetic gastroparesis patients[103].

Medications for control of symptoms other than nausea and vomiting: (1) Early satiety. Early satiety has been related to defects in fundic accommodation in patients with functional dyspepsia[104]. Nitrates, buspirone, sumatriptan, and selective serotonin reuptake inhibitors promote fundic relaxation in this condition[105,106]. The use of fundic relaxants in managing early satiety in gastroparesis has not been investigated; (2) Abdominal pain. Epigastric pain is disabling in some individuals with gastroparesis and can result in excessive utilization of healthcare resources. The pathogenesis of pain is poorly understood and treatments for this symptom are largely unsatisfactory. Pain in gastroparesis has been postulated to be due to sensory rather than motor dysfunction, and therapies to reduce afferent dysfunction may be more effective for this symptom[107]. However, this hypothesis has not been tested. Although, non-steroidal anti-inflammatory drugs (NSAID's) have been shown to ameliorate gastric slow wave dysrhythmias in several healthy subjects [108], their adverse effects including renal dysfunction and ulcerogenic properties, limit their usage on a chronic basis. Antidepressant medications may help with gastroparesis associated neuropathic pain[109]. These include low dose tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs) and combined serotonin/noradrenaline reuptake inhibitors. Paroxetine, an SSRI, may selectively accelerate small intestinal transit[110,111]. Opiates, including milder agents such as tramadol, should be avoided because of their inhibitory effects on motility as well as risk of addiction. (3) Nutritional support, enteral and parenteral. Some patients with refractory gastroparesis benefit from enteral or parenteral nutrition intermittently for symptom flares or for permanent support. Patients with chronic symptoms of gastroparesis may develop dehydration, electrolyte abnormalities and/or extreme

malnutrition. The choice of nutritional support and its administration route depends on the severity of disease. The indications for supplementation of enteral nutrition include unintentional loss of 10% or more of the usual body weight during a period of 3 to 6 mo, inability to achieve the recommended weight by the oral route, repeated hospitalizations for refractory symptoms, interference with delivery of nutrients and medications, need for nasogastric intubation to relieve symptoms, and nausea and vomiting resulting in poor quality of life [42]. Except in cases of profound malnutrition or electrolyte disturbance, enteral feeding are preferable to chronic parenteral nutrition because of the significant risks of infection and liver disease in the latter treatment. On the other hand, short-term total parenteral nutrition (TPN) can reverse rapid weight decline and ensure adequate fluid delivery. Home intravenous TPN may be needed for individuals who cannot tolerate enteral feeding. Several options for enteral access and feeding are available and no data exists favoring one approach over the other. However, nasogastric tubes and gastrostomy tubes are not encouraged due to the possibility of worsening gastroparesis and risk of pulmonary aspiration. Jejunostomy tubes are preferred in order to bypass the gastroparetic stomach except if the patient has small bowel dysmotility. Short-term nasojejunal feeding is often used to help determine if the patient will tolerate chronic small bowel feeding through a permanent enteral access. Formulas that are low in osmolarity (e.g. Peptamen, Isocal) and with a caloric density of 1.0-1.5 cal/mL are recommended. A dietician should be consulted early on. Initially, infusion rates should be low and then advanced every 4-12 h as tolerated to meet caloric needs. Eventually, infusions can be converted to nocturnal feedings to free up daytime h for optional oral intake and to participate in normal daily activities.

Endoscopic treatment

Therapeutic endoscopy with pyloric injection of botulinum toxin A may provide benefit in some patient with gastroparesis. Botulinum toxin A is a bacterial toxin that inhibits acetylcholine release, causing muscle paralysis. Manometric studies in patients with diabetic gastroparesis have shown evidence of prolonged pylorospasm producing a functional outlet obstruction[36]. Several uncontrolled case series have reported reduced symptoms and acceleration of gastric emptying after botulinum toxin treatment[112-114]. The largest series reported 63 highly selected patients with primary idiopathic gastroparesis, 43% of whom responded symptomatically with mean response duration of 5 mo[115]. A double-blind controlled trial found no efficacy of botulinum toxin over placebo[116]. However, this report was underpowered to detect the effect of the drug. Another recent double-blind placebo-controlled trial revealed that intrapyloric injection of botulinum toxin improved gastric emptying in patients with gastroparesis, although this benefit was not superior to placebo at one month. Also, in comparison to placebo, symptoms did not improve significantly after 1 mo of injection[117]. The use of botulinum toxin for gastroparesis is considered off-label and should be considered when other accepted therapies have failed or produced unacceptable side effects. To date, few adverse effects have been reported with botulinum toxin therapy.

Surgical treatment

Surgical intervention is increasingly used to treat medically refractory/severe gastroparesis. Limited data are available concerning surgical treatment of gastroparesis[118]. The most common procedure is gastric electrical stimulation (GES). Other procedures offered include venting/feeding gastrostomy and jejunostomy tubes, surgical pyloroplasty, gastrectomy and surgical drainage procedures and pancreatic transplantation in diabetic patients. Apart from GES and feeding tubes, other surgical procedures are performed as a last resort in carefully evaluated patients with profound gastric stasis.

GES: Over the past decade, GES has been used for treatment of medically refractory gastroparesis[10,12,119]. Paced GES using an implantable stimulator (Enterra therapy, by Medtronic Inc.) has been approved by the FDA through a humanitarian device exemption. Electrical stimulation is delivered by two electrodes usually placed laproscopically on to the serosal surface of the stomach overlying the pacemaker area in the body of the stomach. Leads from the electrodes connect to a pulse generator that resembles a cardiac pacemaker that is implanted in a subcutaneous pocket of the anterior abdominal wall. The pulse generator delivers low energy

0.1-s trains of pulses at a frequency of 12 cycles/min. Within each pulse train, individual pulses oscillate at a frequency of 14 cycles/s^[119]. Although the exact mechanism of action of the GES is unknown, the clinical effect is believed to be mediated by local neurostimulation. The stimulation impulses used are able to excite nerves but are too weak to excite gastric smooth muscles. Furthermore, poor correlation is observed between patients' symptoms and gastric emptying rates^[119,120]. It has been hypothesized that the mechanism may stem from a vagal and cerebral pathway^[121]; however, GES has been shown to work well even in patients with vagotomy^[122]. Multiple uncontrolled studies in diabetic, idiopathic and post-surgical gastroparesis have shown efficacy of GES. In one uncontrolled multicenter trial, 35 of 38 patients experienced > 80% reductions in nausea and vomiting which persisted for 2.9-15.6 mo, with an associated 5.5% increase in weight and reduced requirement of supplemental nutrition^[123]. Other studies reported similar long-term symptom benefits, which may persist for at least 10 years with improvements in body mass index, serum albumin and glycemic control^[124,125]. In the only controlled trial of GES, 33 patients with idiopathic or diabetic gastroparesis completed a 2-mo double-blind, crossover, sham stimulation-controlled phase followed by 12 mo uncontrolled observation, with the device activated^[119]. During the blinded phase, frequency of weekly vomiting in all patients was 6.8 times when the device was ON as opposed to 13.5 times when it was OFF. Although there was not a significant reduction in the total symptom score (TSS) in the ON vs OFF state, 21 patients preferred the stimulation ON, whereas seven preferred OFF and five had no preference. Symptom reductions were more impressive during the unblinded phase where median vomiting frequency decreased by > 80% for 50% of all patients. TSS was also significantly improved in all patients from a score of 16.8 at baseline to 11.1 and 11.4 at 6 and 12 mo, respectively. The major adverse effect of GES is infection resulting in removal of the device in approximately 10% of patients^[119,123]. The frequency of such infections seems to be decreasing during recent years. This may be explained by more careful surgical technique and the increasing use of laparoscopy instead of open surgery. The second concern is of the non-responder issue. In the earlier mentioned randomized trial^[119] 13% of the patients were non-responders with < 25% symptom reduction. There seems to be a higher non-responder rate in idiopathic gastroparesis^[125,126]. Abell and colleagues have applied temporary mucosal GES with endoscopically placed electrodes and used the effects on symptoms after ≥ 3 d as a measure of response^[127].

Other surgical options: 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. Pyloroplasty may be considered as another option but limited data are available on the efficacy of this procedure. There are limited controlled data concerning gastrectomy in gastroparesis^[118]. A study of patients with near-total gastrectomy revealed long-term symptom relief in 43% patients with postsurgical gastroparesis^[128]. The literature is sparse concerning correction of diabetic gastroparesis status post-pancreas and pancreas-kidney transplant in patients with type 1 diabetes^[129,130].

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