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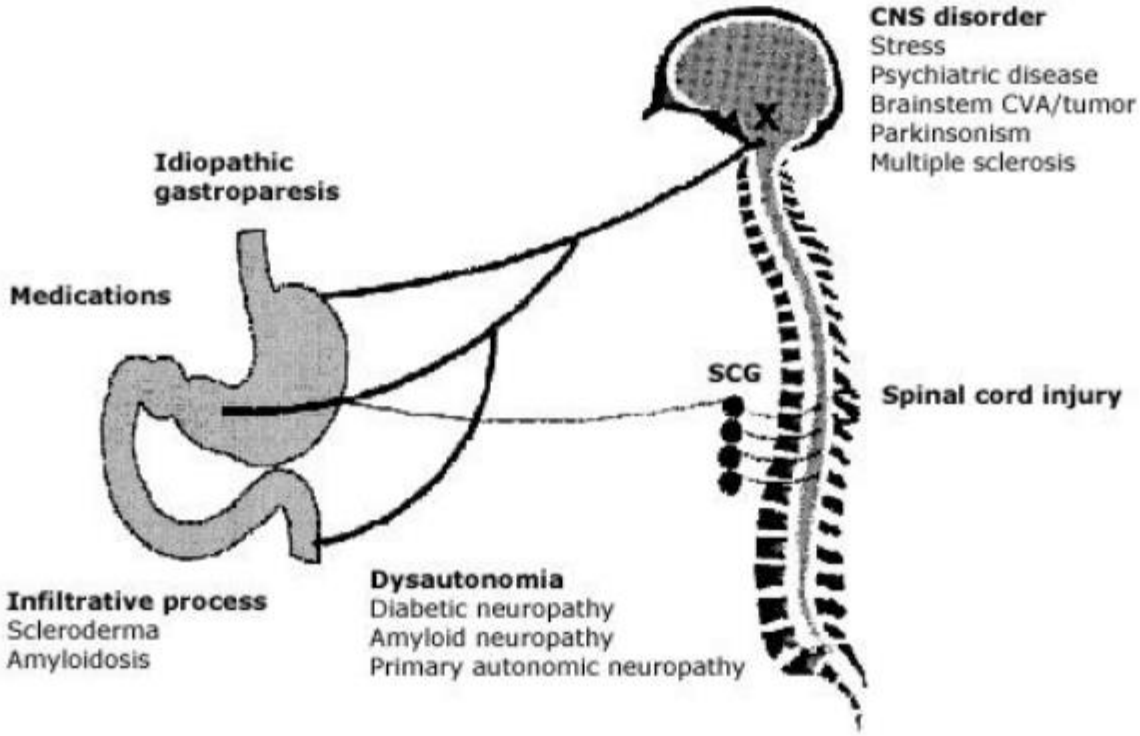
Diabetic Gastroparesis

DEFINITION — Gastroparesis is a syndrome of objectively delayed gastric emptying of solids in the absence of a mechanical obstruction and cardinal symptoms of nausea, vomiting, early satiety, belching, bloating, and/or upper abdominal pain

Overall survival was significantly lower in patients with diabetes and in those with gastroparesis than for the age- and sex-matched general population [5,6]. However, other estimates have been lower. In a United States cross-sectional population-based study using electronic medical records and results of upper gastrointestinal endoscopy and gastric emptying tests, the prevalence of gastroparesis in type 1 and type 2 diabetics was 4.6 and 1.3 percent, respectively

Neuromuscular disorders impairing gastric motor function



ETIOLOGY — Although multiple conditions have been associated with gastroparesis, the majority of cases are idiopathic, diabetic, iatrogenic (eg, medication-induced), or postsurgical

Diabetes mellitus — Diabetes mellitus (DM) is the most frequently recognized systemic disease associated with gastroparesis. Population-based studies in patients with diabetes mellitus have reported upper gastrointestinal symptoms in 11 to 18 percent of patients

The estimated 10-year cumulative incidence of gastroparesis in patients with type 1 DM and type 2 DM was estimated to be 5.2 and 1 percent, respectively [7]. In studies from referral centers and hence potentially biased to select for patients with relatively severe disease, 50 to 65 percent of patients with diabetes and upper abdominal symptoms had delayed gastric emptying [

However, in a population-based cohort study, the cumulative incidence of gastroparesis over 10 years in patients with type 1 and type 2 DM was 5 percent and 1 percent, respectively, as compared with 0.2 percent in controls [17]. Symptoms of delayed gastric emptying are more pronounced in patients with type 1 DM as compared with patients with type 2 DM

Gastrointestinal complications of diabetes typically occur in patients who have had the disorder for more than five years. Patients with diabetes mellitus have abnormalities at several levels in the process of gastric emptying, including abnormal postprandial proximal gastric accommodation and contraction, and reduced frequency of antral contractions. These abnormalities are primarily due to autonomic dysfunction or abnormal intrinsic nervous system (eg, nitrergic neurons, or interstitial cells of Cajal, the pacemaker system of the gut)

Hyperglycemia (blood glucose >200 mg/dL) may also contribute to delayed gastric emptying. Although acute hyperglycemia, associated with poorly controlled diabetes, typically has a reversible effect on gastric emptying, chronic hyperglycemia is associated with an increased risk of neuropathy. The pathogenesis of delayed gastric emptying in diabetes is discussed in detail, separately.

Clinical features — Patients with gastroparesis can present with nausea (93 percent), vomiting (68 to 84 percent), abdominal pain (46 to 90 percent), early satiety (60 to 86 percent), postprandial fullness, bloating, and, in severe cases, weight loss [9,56]. The vomitus may contain food ingested several hours previously.
The predominant symptom may vary based on the underlying etiology. In a retrospective study that included 416 patients with gastroparesis, patients with idiopathic gastroparesis reported more early satiety, postprandial fullness, and abdominal pain as compared with patients with diabetic gastroparesis. In contrast, patients with diabetic gastroparesis had more severe retching and vomitin

Bloating is common in gastroparesis and is severe in many individuals. In one study of 335 individuals with gastroparesis, bloating was at least mild in 76 percent and severe in 41 percent of individuals [57].

While abdominal pain is a frequent symptom in patients with gastroparesis, it is rarely the predominant symptom (18 percent). In patients whose predominant symptom is abdominal pain, other causes should be sought [58]. The pain is usually localized to the upper abdomen and is often described as burning, vague, or crampy. Approximately 60 percent report exacerbation of pain after eating. In one case series, pain interfered with sleep in 80 percent of patients. However, the severity of abdominal pain did not correlate with a delay in gastric emptying, suggesting that the cause of pain in this tertiary referral cohort may not have been gastroparesi

Physical examination — Abdominal examination may reveal epigastric distention or tenderness, but not guarding or rigidity. There may be a succussion splash

Patients may have signs of the underlying disorder resulting in gastroparesis. As an example, patients with systemic sclerosis and Raynaud phenomenon may have taut skin in the hands and chest, telangiectasia, small joint arthropathy, and crackles over the lower lung fields from interstitial lung disease. In diabetic patients, gastrointestinal complications are often associated with other signs of autonomic dysfunction [64,65]. These may include orthostatic hypotension and absence of the pupillary reaction to light with persistence of the accommodation response (the pseudo-Argyll-Robertson pupil or tonic pupil

Exclude mechanical obstruction — All patients with suspected delayed gastric emptying and, in particular, patients with colicky abdominal pain should undergo a careful upper gastrointestinal endoscopy. We also perform computed tomographic (CT) enterography or magnetic resonance (MR) enterography to exclude mechanical obstruction (eg, from a small bowel mass or superior mesenteric artery syndrome).
A barium follow-through examination is performed if CT/MR enterography are unavailable. The presence of retained food after an overnight period of fasting, although supportive of a diagnosis of gastroparesis, is not diagnostic

Scintigraphic gastric emptying — The most cost-effective, simple, and widely available technique to confirm the presence of delayed gastric emptying of solids is scintigraphy (figure 2). Documenting the presence of delayed gastric emptying and assessing the severity is best achieved by evaluating the gastric emptying of solids. Since liquids often empty from the stomach normally even when solids are abnormally retained, assessment of liquid emptying is generally unnecessary unless dumping syndrome is suspected

f patients are too sick to tolerate a solid meal, a liquid nutrient meal containing radioisotope may be used to permit scintigraphic measurement of gastric emptying [68]. However, it is important to establish normal values for comparison as the physical characteristics and fat content of the meal impact the rate of emptying and hence the normal values for gastric emptying [69]. Other centers [70] utilize real eggs or omelettes with higher fat content (~300 kcal with 30 percent fat) to test for gastroparesis arguing that the higher fat content provides an improved test for gastric motor function; the emptying profiles of different meal substrates are reviewed elsewhere [71]. Importantly, when an optimal gastric emptying test is conducted (solid meal, sufficient calories, assessed over at least three hours), there is a good correlation between the delayed gastric emptying and symptoms [72].

Pretest instructions – Medications that affect gastric emptying should be stopped at least 48 hours before diagnostic testing [4]. Based on the pharmacokinetics of the medication, the medication may need to be stopped more than 48 hours before testing. Patients with diabetes should have blood glucose measured before starting the gastric emptying test, and hyperglycemia should be treated. The test should be performed only once blood glucose levels are <180 mg/dL.

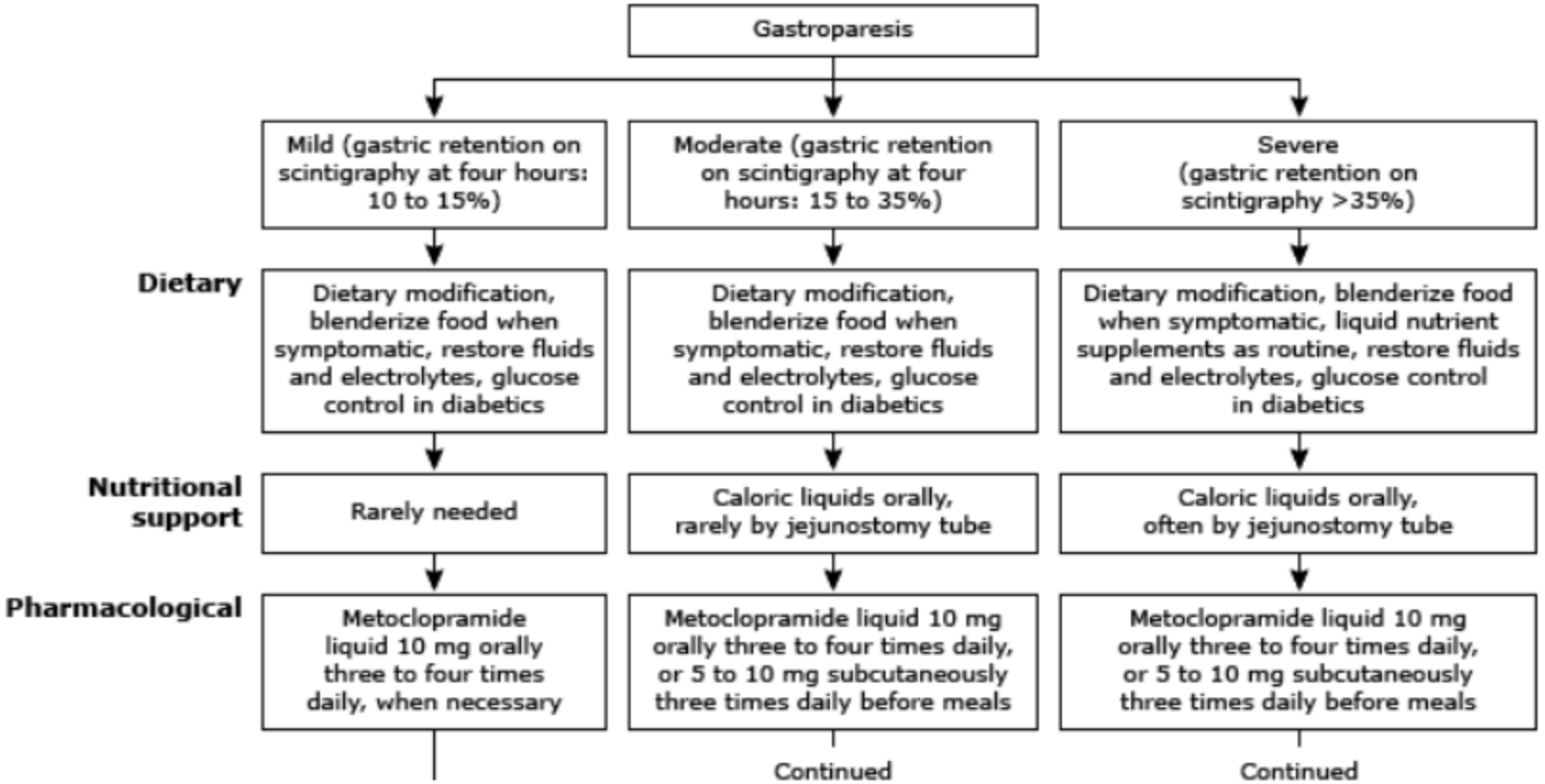
Interpretation of test results – Delayed gastric emptying is defined as gastric retention of >10 percent at four hours and/**or** >60 percent at two hours when using the standard low fat, scrambled egg protein meal described above [73]. Although the severity of symptoms do not always correlate with the rate of gastric emptying, delayed gastric emptying has been classified based on the extent of gastric retention on scintigraphy at four hours into the following:

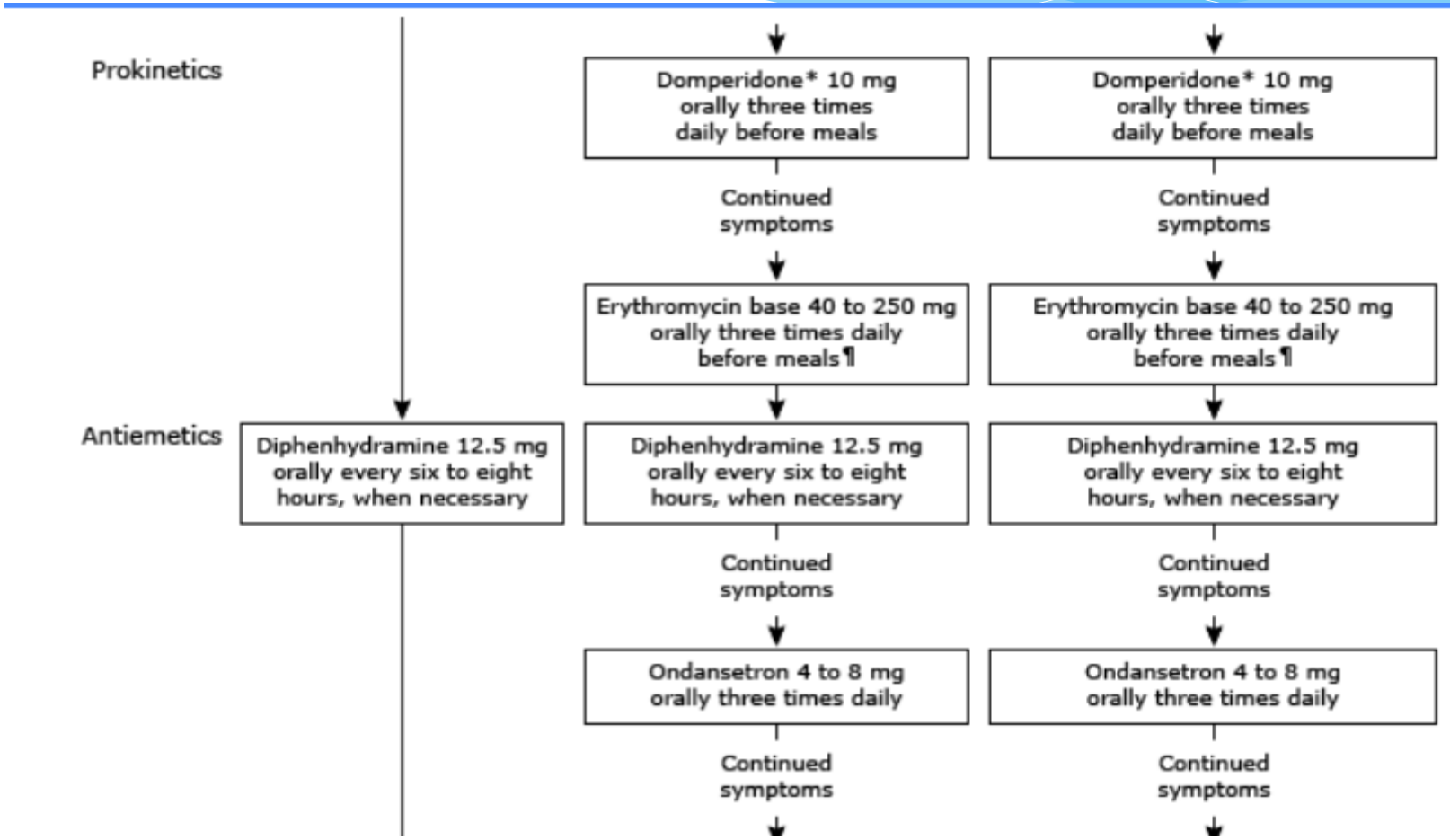
- Mild – 10 to 15 percent
- Moderate – 15 to 35 percent
- Severe – >35 percent

Wireless motility capsule – A wireless motility capsule (WMC) can simultaneously measure phasic pressure amplitudes, temperature, and pH as it traverses different segments of the gastrointestinal trac

^{13}C breath testing – C^{13}-labeled acetate, octanoic acid breath tests, or spirulina (a plant-based protein source) have been used to assess gastric emptying [84-86]. After ingestion of the stable isotope labeled test meal, the expiratory 13-CO_2 concentration is measured (eg, by mass spectrometry or infrared spectroscopy). The test is noninvasive and, unlike scintigraphy, avoids radiation exposure. Most studies suggest that the accuracy of these breath tests in normal and pathologic conditions is less than that of scintigraphic measurements of gastric emptying [85,87,88]. The spirulina ^{13}C breath test was approved by the US Food and Drug Administration to diagnose gastroparesis in April 2015 [89]. Approval was based on the observation in a study of 115 patients who underwent simultaneous scintigraphy and spirulina ^{13}C breath test. At 80 percent specificity, the ^{13}C-spirulina breath test samples at 150 and 180 minutes had a combined sensitivity of 89 percent for delayed gastric emptying

Management of adult patients with gastroparesis




Prokinetics
Domperidone* 10 mg orally three times daily before meals
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Continued symptoms
Continued symptoms
Erythromycin base 40 to 250 mg orally three times daily before meals¶
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Antiemetics
Diphenhydramine 12.5 mg orally every six to eight hours, when necessary
Diphenhydramine 12.5 mg orally every six to eight hours, when necessary
Diphenhydramine 12.5 mg orally every six to eight hours, when necessary
Continued symptoms
Continued symptoms
Ondansetron 4 to 8 mg orally three times daily
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Continued symptoms
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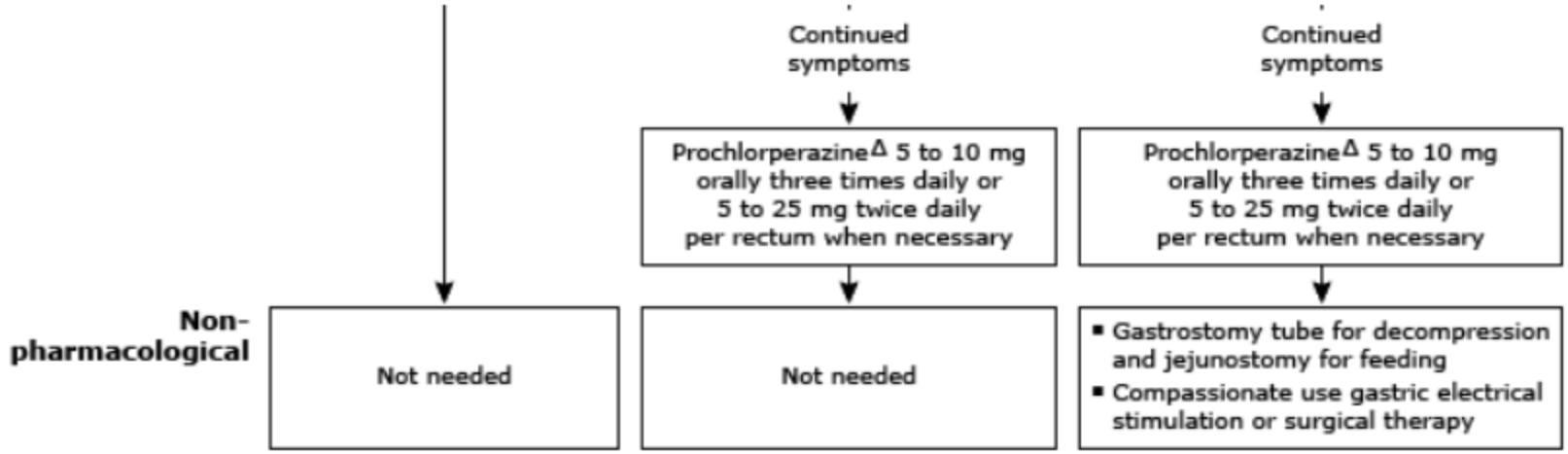

PEJ: percutaneous endoscopic jejunostomy; PEG: percutaneous endoscopic gastrostomy.

* Domperidone is not commercially available in the United States. It may be obtained by investigational new drug application to the U Food and Drug Administration and is widely available in other countries. Refer to topic.

¶ Intravenous erythromycin lactobionate 3 mg/kg every eight hours is available for treatment of acute gastroparesis in hospitalized patients.

Δ The use of prochlorperazine with metoclopramide is expected to increase the risk of extrapyramidal symptoms; consider avoiding combined use.

Adapted from: Camilleri M. Clinical practice. Diabetic gastroparesis. N Engl J Med 2007; 356:820.

Graphic 79991 Version 7.0

Metoclopramide — Metoclopramide is first-line therapy for gastroparesis [1]. Metoclopramide, a dopamine 2 receptor antagonist, a 5-HT4 agonist, and a weak 5-HT3 receptor antagonist, improves gastric emptying by enhancing gastric antral contractions and decreasing postprandial fundus relaxation. Metoclopramide is approved by the US Food and Drug Administration (FDA) for treatment of gastroparesis for no longer than 12 weeks unless patients have a therapeutic benefit that outweighs the risks. The side effects associated with metoclopramide include central side effects of anxiety, restlessness, and depression, hyperprolactinemia, and QT interval prolongation

Domperidone — Domperidone is an alternative to metoclopramide in patients with gastroparesis [1]. However, domperidone, a dopamine 2 antagonist, is not readily available in the United States but is available in Canada and in other countries. In the United States, domperidone can be prescribed to patients only through an FDA Investigational New Drug application. Use of domperidone is, therefore, reserved to patients whose symptoms fail to respond to metoclopramide or with side effects to metoclopramide

Macrolide antibiotics

Erythromycin — Erythromycin, a motilin agonist, induces high-amplitude gastric propulsive contractions that increase gastric emptying [36,37]. Erythromycin also stimulates fundic contractility, or at least inhibits the accommodation response of the proximal stomach after food ingestion [38]. Patients who fail to respond to a trial of metoclopramide and domperidone should be treated with oral erythromycin (liquid formulation, 40 to 250 mg three times daily before meals

Antiemetics — We treat patients with persistent nausea and vomiting despite prokinetics with antihistamines (eg, diphenhydramine 12.5 mg orally or intravenously every six to eight hours as needed) and in patients with persistent symptoms, 5HT3 antagonists (eg, ondansetron 4 to 8 mg orally three times daily). Antiemetics have not been studied in the management of patients with gastroparesis, and their use in gastroparesis is based on their efficacy in controlling nonspecific nausea and vomiting and in chemotherapy-induced emesis. Prolongation of the QT interval and central side effects have limited the use of phenothiazines (eg, prochlorperazine 5 to 10 mg orally three times daily, 5 to 25 mg twice daily per rectum as needed) to patients who remain symptomatic despite antihistamines and 5HT3 antagonist

ricyclic antidepressants — The use of tricyclic antidepressants (TCAs) is limited to treat symptoms of abdominal pain and vomiting despite a venting gastrostomy tube for decompression. In open-label trials, low-dose nortriptyline, a TCA with low anticholinergic effects, has been demonstrated to decrease symptoms of nausea, vomiting, and abdominal pain in patients with diabetic and idiopathic gastroparesis [56,57]. However, TCAs can potentially decrease the rate of gastric emptying. In addition, results from a randomized trial failed to demonstrate a benefit of nortriptyline in improving global symptoms of gastroparesis [58].

An alternative central neuromodulator that can be considered is mirtazapine, which is an antidepressant with central adrenergic and serotonergic activity with direct anti-emetic activity possibly related to 5-HT_3 antagonist activity and demonstrated benefit in patients with gastroparesis

Gastric electrical stimulation — Gastric electrical stimulation is reserved for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting (eg, with persistence of symptoms despite antiemetic and prokinetic drug therapy for at least one year), who are not on opioids and who do not have pain as a predominant symptom [3]. G-POEM should be reserved for patients with refractory gastroparesis. There is evidence from a pilot sham-controlled study that G-POEM is efficacious in gastroparesis, particularly in patients with diabetic gastroparesis [80]. In the United States, the gastric electrical neurostimulator (Enterra Therapy system) has been approved as a humanitarian exemption device for diabetic and idiopathic gastroparesis. In a randomized cross-over trial of the same device in 172 patients with chronic (>12 months) refractory vomiting, the device reduced vomiting frequency when it was on compared to when the device was off

Reference up to date

THANKS FOR ATTENTION