CME

ACG Clinical Guideline: Gastroparesis

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Gastroparesis is characterized by symptoms suggesting retention of food in the stomach with objective evidence of delayed gastric emptying in the absence of mechanical obstruction in the gastric outflow. This condition is increasingly encountered in clinical practice. These guidelines summarize perspectives on the risk factors, diagnosis, and management of gastroparesis in adults (including dietary, pharmacological, device, and interventions directed at the pylorus), and they represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation process. When the evidence was not appropriate for Grading of Recommendations, Assessment, Development, and Evaluation, we used expert consensus to develop key concept statements. These guidelines should be considered as preferred but are not the only approaches to these conditions.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C598.

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INTRODUCTION

Gastroparesis (GP) is a motility disorder characterized by symptoms and objective documentation of delayed gastric emptying (GE) of solid food without mechanical obstruction, which should be excluded by imaging studies such as upper gastrointestinal (GI) endoscopy or radiology (1,2). The chronic symptoms experienced by patients with GP may be associated with acute exacerbation of symptoms after oral intake of food; the symptoms include postprandial fullness, nausea, vomiting, and upper abdominal pain.

In 2013, the American College of Gastroenterology (ACG) guideline on GP focused on the state of diagnosis and management at the time including assessment and correction of nutritional state, relief of symptoms, improvement of GE, and, in patients with diabetes, glycemic control.

Patient nutritional state should be managed by oral dietary modifications and, if oral intake is not adequate, by enteral nutrition through jejunostomy tube or rarely parenteral nutrition. Medical treatment detailed the use of prokinetic and antiemetic therapies including metoclopramide, short-term use of erythromycin, and gastric electrical stimulation (GES; approved on a humanitarian device exemption), and, in the presence of unmet clinical need, medications used off-label including domperidone, erythromycin (primarily over a short term), and centrally acting antidepressants used as symptom modulators. Second-line approaches include venting gastrostomy or feeding jejunostomy; the latter may be placed directly by percutaneous endoscopic jejunostomy (3). Modifications in percutaneous endoscopic gastrostomy jejunal feeding tubes have reduced likelihood of retrograde displacement of gastrojejunal tubes and reflux of enteral feed back into the duodenal loop and the stomach. These modifications include suture application on the connector and a balloon transgastric jejunal feeding device (4).

Intrapyloric botulinum toxin injection was not effective in 2 randomized, controlled trials (5,6). Partial gastrectomy and pyloroplasty should be used rarely, only in carefully selected patients (7). These procedures have been largely replaced by gastric per-oral endoscopic myotomy (G-POEM), which is discussed in detail in this article.

GP carries a substantial patient burden (8–10), with a negative correlation observed between symptom severity and patient quality of life. The disease also has wider impacts on healthcare burden such as increased hospitalizations and associated direct and indirect economic consequences. Several publications have demonstrated increased morbidity and mortality in patients with GP (11–14). Although GP is known to be associated with use of narcotics in pain syndromes, and opioid agents affect gastric as well as pyloric function resulting in retardation of GE, this was not an objective of the current review and is covered in a separate, recently published article (15). Nevertheless, it is important to emphasize that potent opioids were associated with worse GP (16), and pain associated with GP should not be treated with opioids (including tramadol and tapentadol, which retard orocecal transit and GE, respectively) (17,18). The treatment of pain in GP was not considered in this guideline; there are essentially no clinical trials addressing the treatment of pain in GP. However, the review addresses the use of central neuromodulators and cannabis in GP.

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In 2021, members of the European Society of Neurogastroenterology and Motility (ESNM) with expertise in GP and the United European Gastroenterology (UEG) Federation joined forces for developing comprehensive recommendations on GP (19). This involved a Delphi consensus processes, systematic literature reviews, and grading of the strengths of accepted criteria. An initial North American perspective of those recommendations has been recently published (20) with endorsement or further commentary on the recommendations by the ESNM working group, as well as commentary based on the published evidence base.

The objective of this new guideline is to document, summarize, and update the evidence and develop recommendations for the clinical management of GP, updating the 2013 ACG guideline on GP (Figure 1) (1). It is necessary to acknowledge the limitations of guideline recommendations on therapies in the absence of Food and Drug Administration (FDA)-approved therapies for GP in the United States and the limitation in duration of prescription to 3 months for the only currently approved medication, metoclopramide.

ACG guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with a particular medical problem based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose significant risks, healthcare providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and preferences to arrive at a patient-centered care approach.

METHODS

Key questions

The guideline is framed around several key questions, outlined below. The key questions were developed by the authors and vetted through the ACG leadership. We developed specific questions to address the topics of clinical relevance in the Patient Intervention Comparison and Outcomes (PICO) format (see Supplemental Materials, Supplementary Digital Content 1, http://links.lww.com/AJG/C598). Emphasis has been placed on having practical recommendations that would be helpful for practicing providers in the United States. A broad literature search was conducted to document, by means of detailed tables, information pertaining to the PICO questions, followed by a focused evaluation of the most relevant literature to develop recommendations (Table 1).

Literature search

In February and March 2019, comprehensive literature searches were conducted by 2 health sciences librarians (JP and VMV) in PubMed (MEDLINE), EMBASE, and the Cochrane Library databases. Key concepts from the PICO questions were used to develop search terms and translated to appropriate controlled vocabulary for each database; detailed strategies for each section are provided in Appendix 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/C598). Results for all searches were filtered for English language publications, and searches regarding therapeutics were further limited to human populations. Searches were updated in May 2021 using the same criteria to capture

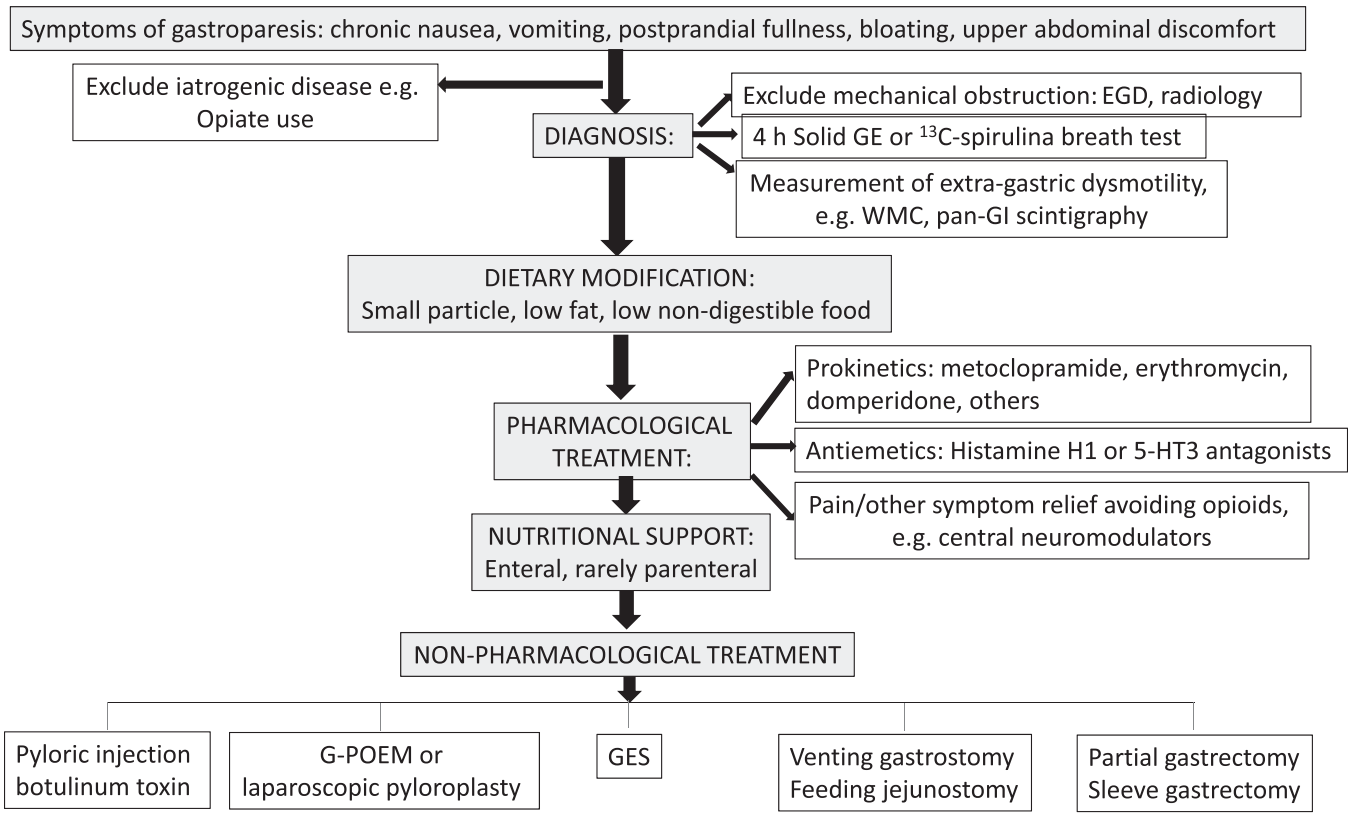

Figure 1. This algorithm updates the algorithm from the 2013 ACG guideline on gastroparesis (1). ACG, American College of Gastroenterology, EGD, esophagogastoduodenoscopy; GE, gastric emptying; GI, gastrointestinal; G-POEM, gastric per-oral endoscopic myotomy; WMC, wireless motility capsule.

Table 1. Gastroparesis recommendations

	Recommendation	GRADE level of evidence	Strength of recommendation
	Risk factors		
1.	In patients with DG, optimal glucose control is suggested to reduce the future risk of aggravation of GP.	Low	Conditional
	Diagnostic testing		
2.	SGE assessment is the standard test for the evaluation of GP in patients with upper GI symptoms. The suggested method of testing includes appraising the emptying of a solid meal over a duration of 3 h or greater.	Moderate	Strong
3.	ROM testing is not suggested for the diagnostic evaluation of GP in patients with upper GI symptoms.	Very low	Conditional
4.	WMC testing may be an alternative to the SGE assessment for the evaluation of GP in patients with upper GI symptoms.	Low	Conditional
5.	Stable isotope (^{13}C-spirulina) breath test is a reliable test for the evaluation of GP in patients with upper GI symptoms.	Low	Conditional
	Management		
6.	Dietary management of GP should include a small particle diet to increase likelihood of symptom relief and enhanced GE.	Low	Conditional
7.	In patients with idiopathic and DG, pharmacologic treatment should be considered to improve GE and GP symptoms, considering benefits and risks of treatment.	Low	Conditional
8.	In patients with GP, we suggest treatment with metoclopramide over no treatment for management of refractory symptoms.	Low	Conditional
9.	In patients with GP where domperidone is approved, we suggest use of domperidone for symptom management.	Low	Conditional
10.	In patients with GP, we suggest use of 5-HT4 agonists over no treatment to improve GE.	Low	Conditional
11.	In patients with GP, use of antiemetic agents is suggested for improved symptom control; however, these medications do not improve GE.	Low	Conditional
12.	Central neuromodulators are not recommended for management of GP.	Moderate	Strong
13.	Current data do NOT support the use of ghrelin agonists for management of GP.	Moderate	Strong
14.	Current data do NOT support the use of haloperidol for treatment of GP.	Low	Conditional
15.	GES may be considered for control of GP symptoms as a humanitarian use device.	Low	Conditional
16.	Acupuncture alone or acupuncture combined with prokinetic drugs may be beneficial for symptom control in patients with DG. Acupuncture cannot be recommended as beneficial for other etiologies of gastroparesis.	Very low	Conditional
17.	Herbal therapies such as Rikkunshito or STW5 (Iberogast) should NOT be recommended for treatment of GP.	Low	Conditional
18.	In patients with GP, EndoFLIP evaluation may have a role in characterizing pyloric function and predicting treatment outcomes after peroral pyloromyotomy.	Very low	Conditional
19.	Intrapyloric injection of botulinum toxin is not recommended for patients with GP based on randomized, controlled trials.	Moderate	Strong
20.	In patients with GP with symptoms refractory to medical therapy, we suggest pyloromyotomy over no treatment for symptom control.	Low	Conditional

DG, diabetic gastroparesis; GE, gastric emptying; GES, gastric electric stimulation; GI, gastrointestinal; GP, gastroparesis; SGE, scintigraphic gastric emptying.

literature published during the screening and review process. A hand search of references was conducted, and relevant publications identified by content experts were incorporated for analysis.

Screening

Between February 2019 and July 2021, a team of 5 content experts (DA, TA, MC, BK, and LN) screened a total of 1,908 distinct references retrieved by the original and updated searches.

Each reference was screened independently by no fewer than 2 reviewers, with a third reviewer resolving any conflicts. The inclusion criteria were original research studies on the incidence, diagnosis, and treatment of GP in adult populations, predominantly based on observational studies and randomized, controlled trials. Open-label and observational studies of treatment modalities were included in the tables. Exclusion criteria were inclusion in the previous ACG guideline (although, where relevant, these were included in tables for completeness of the literature surveyed), theoretical studies using computational models, animal trials, pediatric populations, and publications without original data analysis.

Although no restriction was placed on publication dates during the retrieval process, emphasis was placed during screening by content experts on studies published after the searches included in the previous guideline, and tables from the 2013 guideline were updated with more recent evidence from the literature. Similarly, searches were not limited by age

Table 2. GRADE quality criteria (21)

Study design	Quality of evidence	Reduced factors	Increased factors
Randomized trials	High	Risk of bias	Large effect
		−1 serious	+1 large
		−2 very serious	+2 very large
	Moderate	Inconsistency	Dose response
		−1 serious	+1 if gradient
		−2 very serious	
		Indirectness	Confounding
		−1 serious	+1
		−2 very serious	
Observational studies	Low	Imprecision	
		−1 serious	
		−2 very serious	
	Very low	Publication bias	
		−1 likely	
		−2 very likely	

range within the databases, but any retrieved studies on an exclusively pediatric population were manually excluded during screening. Review articles, correspondence, and other publications without original data were excluded from analysis, although relevant reviews were retained for hand search of their included references.

After screening, a total of 121 references were identified for inclusion and progressed for evidence appraisal in July 2021.

Assessment

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process (Table 2) (21) was used to assess the quality of evidence for each question, by 2 formally trained GRADE methodologists (RHY and KG) to evaluate the quality of the evidence and strength of the recommendations. The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect. A strength of recommendation is given as either strong (noted as "recommendations," and meaning that most patients should receive the recommended course of action) or conditional (noted as "suggestions," and meaning that many patients should have this recommended course of action, but different choices may be appropriate for some patients) based on the quality of evidence, risks vs benefits, feasibility, and costs, taking into account perceived patient and population-based factors. Furthermore, a narrative evidence summary for each section provides important details for the data supporting the statements. The panel have additionally highlighted "key concepts" that were not included in the GRADE assessment. Key concepts are statements to which the GRADE process has not been applied and often include definitions and epidemiological statements rather than diagnostic or management recommendations.

NARRATIVE REVIEW OF EVIDENCE

Risk factors

Recommendation

1. In patients with diabetic gastroparesis (DG), optimal glucose control is suggested to reduce the future risk of aggravation of GP (conditional recommendation, low level of evidence).

Optimal glucose control reduces the future risk of aggravation of the GP. Acute hyperglycemia delays GE in patients with diabetes, and, in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study, delayed GE was associated with GI symptoms and with measures of early and long-term hyperglycemia (22). However, it was unknown whether better glycemic control increases the risk of hypoglycemia or improves hemoglobin A1c levels and GI symptoms in DG.

Continuous subcutaneous insulin infusion and continuous glucose monitoring were assessed in 45 poorly controlled type 1 or 2 patients with diabetes and GP (20). Symptom scores decreased with lower nausea/vomiting, fullness/early satiety, and bloating/distention scores as well as quality-of-life scores, and volumes of liquid nutrient meals tolerated increased at 24 weeks. In conclusion, continuous subcutaneous insulin infusion plus continuous glucose monitoring seems to be safe with minimal risk of hypoglycemic events and associated improvements in glycemic control, GP symptoms, quality of life, and meal tolerance in patients with poorly controlled diabetes and GP. This study supports the safety, feasibility, and potential benefits of improving glycemic control in DG (23). On the other hand, after 6 months of intensive therapy, which led to decreased levels of glycosylated hemoglobin (from mean 10.6% $\pm$ 0.3% to 9% $\pm$ 0.4%), GE $T_{1/2}$ did not change (24). Nevertheless, Izzy et al. (25) documented that HbA1C level is significantly associated with the 4-hour retention value on nuclear GE scan.

Diagnostic testing

After exclusion of mechanical obstruction, diverse tests are available to objectively document the presence of delayed GE. The gold standard is scintigraphic GE (SGE); this section addresses the diverse methods available for diagnosis of GP.

Recommendation

2. SGE is the standard test for the evaluation of GP in patients with upper GI symptoms. The suggested method of testing includes appraising the emptying of a solid meal over a duration of 3 hours or greater (strong recommendation, moderate level of evidence).

Optimal duration of GE tests. It is customary to recommend cessation for 48 hours before the test of medications

including opioids, cannabinoids, prokinetics, antiemetics, and neuromodulators with potential impact on the results of the GE test.

Based on a systematic review and meta-analysis (26) of the literature from 2007 to 2017 that included studies evaluating the association between GE (in 92 studies: 26 breath test, 62 scintigraphy, 1 ultrasound, and 3 wireless motility capsule [WMC]) and nausea, vomiting, early satiety/postprandial fullness, abdominal pain, and bloating, 25 studies provided quantitative data for meta-analysis (15 scintigraphy studies enrolling 4,056 participants and 10 breath test studies enrolling 2,231 participants). Meta-regression demonstrated a significant difference between optimal and suboptimal GE test methods when comparing delayed GE with nausea and vomiting. Studies using optimal GE test methodology (that is solid meal and at least 3 hours of data collection) showed significant associations between GE and nausea (odds ratio [OR]: 1.6; 95% confidence interval [CI]: 1.4–1.8), vomiting (OR: 2.0; 95% CI: 1.6–2.7), abdominal pain (OR: 1.5; 95% CI: 1.0–2.2), and early satiety/fullness (OR: 1.8; 95% CI: 1.2–2.6) for patients with upper GI symptoms. Among patients with diabetes, the most significant association with delayed GE was with the symptom of early satiety and fullness but not with nausea and vomiting (26). Therefore, systematic review and meta-analysis supports an association between optimally measured delayed GE and upper GI symptoms. It is worth noting that scintigraphic assessment should be ideally performed up to 4 hours unless it is documented that more than 90% of the solid meal has emptied at 3 hours (27).

Potential confounding between GP and functional dyspepsia

There is increasing attention (28) to the possibility that GP and functional dyspepsia (FD) may be on a spectrum of gastric dysfunction. Despite generally unaltered symptoms over time, 42% of patients initially diagnosed with GP, and 37% of those diagnosed with FD were reclassified based on presence or absence of GE delay on repeat SGE (28). Degree of impairment of GE may vary over time in patients whose symptoms are generally unaltered over the same time. However, it is also conceivable that part of the overlap of the syndromes reflects the cutoff value of 10% retention at 4 hours that is applied to identify patients with delayed GE based on the ingestion of a 255-kcal, 2% fat Egg Beaters meal. Further studies are required to appraise the optimal meal composition and cutoff to define normality to address the reported significant overlap between GP and FD, which may be confounded by the low calorie and fat content of the meal and the use of >10% retention at 4 hours to define delayed GE. It has been emphasized that the distinction between the 2 diagnoses is relevant because of the better prognosis of FD in contrast to the persistence of GP (28).

Diagnosis of GP using scintigraphy

Recommendation

3. Radiopaque markers (ROM) testing is not suggested for the diagnostic evaluation of GP in patients with upper GI symptoms (conditional recommendation, very low level of evidence).

Compared with ROM. There is evidence that GE is accelerated similarly by rectal or oral cisapride when measured by scintigraphy and by ROM (29,30). Several lines of evidence (31,32) suggest that scintigraphy, when compared with ROM, is more accurate in assessing the emptying of the digestible solid food from the stomach. For example, Olausson et al. (32) documented sensitivity and specificity of the ROM test were 34% and 97%, respectively, and in contrast to results from scintigraphy, which correlate with GI symptom severity, results from the ROM test did not. Given that scintigraphy is the gold standard, it is not possible to assess sensitivity and specificity of ROM; however, it is important to acknowledge that the intersubject coefficients of variation (COVinter) for SGE $T_{1/2}$ were similar in males and females (total 319 healthy controls), overall 24.5% (M 26.0%, F 22.5%), and COVinter for GE at 4 hours was 9.6%. The intra-individual coefficient of variation (COVintra) in 47 healthy controls for $T_{1/2}$ and GE at 4 hours were 23.8% and 12.6% (33). Similarly, the mean absolute differences in 60 patients with upper GI symptoms undergoing repeat GE studies by scintigraphy an average of 15 days apart were 25 min for GE $T_{1/2}$ and 7% at 1 hours, 9% at 2 hours, and 7% at 4 hours (34).

Recommendation

4. WMC testing may be an alternative to the SGE assessment for the evaluation of GP in patients with upper GI symptoms (conditional recommendation, low quality of evidence).

Compared with wireless motility capsule (WMC). The results from measurements by SGE and WMC differ. Overall agreement in results between the 2 methods was 75.7% (kappa = 0.42). In subjects without diabetes, the WMC detected a higher proportion of subjects with delayed GE (33.3%) than SGE (17.1%) ($P < 0.001$); by contrast, a higher proportion of subjects with diabetes had delayed GE detected by SGE (41.7%) than by WMC (17.1%) ($P = 0.002$). Severe delays in GE were observed in a higher proportion of subjects by WMC (13.8%) than by SGE (6.9%) ($P = 0.02$). Rapid GE was detected in a higher proportion of subjects by SGE (13.8%) than by WMC (3.3%) ($P < 0.001$) (35,36). Research supports WMC testing as an alternative test to SGE for the evaluation of GP in patients with upper GI symptoms, and one advantage is that it provides a measure of gastric contractile amplitude, and this can correspond to the timing of capsule emptying documented by the change in pH measured as the capsule traverses the pylorus.

These features underscore the differences in emptying of a solid meal that could be homogenized in the stomach from the emptying of a solid nondigestible capsule, which is greater than 1.5 cm in length and which typically empties from the stomach with the re-establishment of the interdigestive migrating motor complex after the emptying of a meal (37); the capsule is able to provide information about the amplitude of pressure activity in the stomach and small bowel, which may be relevant, e.g., to identify myopathic diseases of the gut or severe antral hypomotility or disorders of motility affecting other regions of the gut such as the small bowel or colon (38). However, overall GP symptoms and nausea/vomiting, early satiety/fullness, bloating/distention, and upper abdominal pain subscores showed no relation to WMC transit (38).

Transit delays beyond the stomach were found in 45.6% of patients with suspected GP who underwent WMC testing: 22.8% small bowel, 31.5% colonic, and 5.4% global (35). Such extragastric dysmotility may be considered in patients with symptoms of GP; indeed, up to 64.7% of patients with symptoms of GP have been found to have slow transit constipation by ROM study (39), and, among 149 patients evaluated at a single tertiary referral center, 77 (52%) had rectal evacuation disorders, and 21 patients (15%) with delayed colonic transit associated with slow ascending colon emptying halftime in 9 and delayed colonic transit because of evacuation disorder in 12 patients (40). The WMC, as with pan-GI scintigraphy, provides opportunity to appraise motor function through the entire GI tract (38,41), which may be indicated in patients with GI symptoms.

Compared with intragastric food identified on upper GI endoscopy. Retained gastric food (RGF) is frequently identified during esophagogastroduodenoscopy; however, this should not be deemed to be diagnostic of GP. In a retrospective study of 85,116 esophagogastroduodenoscopies, 2991 patients without structural abnormalities had undergone SGE using a standard 320-kcal 30% fat egg meal. Overall, the positive predictive value of RGF for delayed GE was 55%. However, the positive predictive value varied from 32% in patients without risk factors to 79% in patients with type 1 diabetes. Opioids, cardiovascular medications, and acid suppressants were associated with RGF (42). Therefore, the presence of RGF should not be assumed to be diagnostic of GP, and confounding by medications should be excluded in such patients.

Diagnosis of GP using a stable isotope breath test and comparison with scintigraphy

Recommendation

5. Stable isotope (^{13}C-spirulina) breath test is a reliable test for the evaluation of GP in patients with upper GI symptoms (conditional recommendation, low quality of evidence).

The stable isotope GE breath test using 13-carbon spirulina has been validated in simultaneous measurements performed with the gold standard scintigraphy and a solid test meal. This has been validated both in patients with upper GI symptoms and healthy controls as well as in pharmacologically induced slowing or acceleration of GE (43,44). Although the kappa statistic is not provided, a validation study of 38 healthy volunteers and 129 patients with clinically suspected delayed GE showed that, at 80% specificity, the 45- and 180-minute samples combined were 93% sensitive to identify accelerated GE, and 150- and 180-minute combined were 89% sensitive for delayed GE (43). The test is also approved for use in children.

Additional value of gastric function tests that do not measure emptying, including electrogastrography

There are the 3 types of cutaneous electrogastrography (EGG): (1) single channel, (2) low resolution, and (3) high resolution. They all measure different aspects of gastric electrical activity. In addition, both mucosal and serosal electrical measurements of EGG are also performed. Single-channel cutaneous EGG measures only frequency; low-resolution EGG measures frequency and amplitude and some measures of propagation; high-resolution EGG measures frequency, amplitude, and more precise measures of propagation such as initiation and conduction of gastric electrical signals. The prevalence of 3 cycles per minute (cpm) electrical control activity measured by single-channel EEG was more prevalent in patients with gastric outlet obstruction compared with patients with idiopathic gastroparesis (IG) or healthy controls (45). High-amplitude and excessively regular 3 cpm EGG patterns were identified in gastric outlet obstruction, whereas high-amplitude and excessively regular 3 cpm EGG patterns differentiated IG and healthy controls and were more likely in those with delayed GE (45,46) and in patients with cyclical vomiting and diabetic gastropathy (47) including uremic diabetics and children with diabetes (48,49). In another study, patients with depleted interstitial cells of Cajal (50) had significantly more tachygastria and significantly greater total symptom scores compared with those patients whose gastric full-thickness biopsies showed less interstitial cells of Cajal depletion.

Using high-resolution electrical mapping (256 electrodes; 36 cm^2) (51), it was shown that 9 patients with chronic unexplained nausea and vomiting had slow-wave dysrhythmias, with only 1 of 9 controls showing these dysrhythmias. Dysrhythmias included abnormalities of initiation (stable ectopic pacemakers and unstable focal activities) and conduction (retrograde propagation, wavefront collisions, conduction blocks, and re-entry) across slow, normal, or fast frequencies; dysrhythmias also showed velocity anisotropy (mean, 3.3 mm/s longitudinal vs 7.6 mm/s circumferential; $P < 0.01$). Such high-resolution, spatial mapping is recommended, especially because of the evidence that abnormalities of slow-wave initiation aberrant conduction and low-amplitude activity in GP often occur at normal frequency, which could be missed by tests that lack spatial resolution (52).

In summary, studies suggest a complimentary role of spatial mapping EGG for identification of the pathophysiologic mechanism of gastric function (53). However, at this time, it is unclear that the information is clinically meaningful. Ongoing research of high-resolution EGG should help clarify its clinical role, including its role in patients with FD.

Other tests for GP based on full-thickness biopsies

The evidence regarding changes at the level of the stomach as identified in histological and molecular studies performed on biopsies taken from patients with GP is detailed in the Supplement. Similar to the ESNM Consensus Statement (19), we do not recommend the routine use of full-thickness biopsies. Full-thickness biopsies should be reserved for research purposes to help better understand the causes of GP, identify biomarkers, guide therapy, and predict outcomes.

MANAGEMENT OF GP

Small particle diet and nutrition interventions

Recommendation

6. Dietary management of GP should include a small particle diet to increase likelihood of symptom relief and enhance GE (conditional recommendation, low quality of evidence).

Avoidant/restrictive food intake disorder symptoms are frequent in patients with GP (54), and the ESNM guidelines recommend that eating disorders must be considered in patients with GP (19).

After the pioneering randomized, controlled trial by Olausson et al. (55) demonstrated efficacy of small particle diet compared with normal diet for relief of symptoms, improving GE and enhancing glycemic control (56) in patients with diabetes, a systematic review (57) of all study types evaluated current evidence-based nutrition interventions involving a total of 15 studies and of 524 subjects, using a stepwise process, progressing from oral nutrition to jejunal nutrition and lastly to parenteral nutrition. Small particle, low-fat diets were significantly better tolerated than the converse, with jejunal nutrition before consuming oral food significantly improving oral intake and motility. In more progressive cases, percutaneous endoscopic gastrostomy with jejunal extension nutrition had lower reported symptoms than other enteral routes. Exclusive long-term parenteral nutrition is a feasible option for advanced cases, with a 68% survival rate at 15-year duration, although oral intake plus parenteral nutrition is associated with higher survival rates. The primary role of maintaining or reinstating oral intake was recommended to reduce morbidity and mortality risk.

Pharmacologic agent use in GP

Recommendations

7. In patients with idiopathic and DG, pharmacologic treatment should be considered to improve GE and GP symptoms, considering benefits and risks of treatment (conditional recommendation, low quality of evidence).
8. In patients with GP, we suggest treatment with metoclopramide over no treatment for management of refractory symptoms (conditional recommendation, low quality of evidence).
9. In patients with GP where domperidone is approved, we suggest use of domperidone for symptom management (conditional recommendation, low quality of evidence).
10. In patients with GP, we suggest use of 5-HT4 agonists over no treatment to improve GE (conditional recommendation, low quality of evidence).

The 2 medications with the largest number of individual clinical trials for GP are metoclopramide and domperidone.

Metoclopramide is the only US FDA-approved medication for the treatment of GP. The FDA placed a Black Box warning on metoclopramide because of the risk of side effects, including tardive dyskinesia. The efficacy of metoclopramide in the treatment of DG has been assessed in studies that are summarized in Table 3 (58–68), which include newer trials involving the intranasal formulation of metoclopramide. The most common adverse effects of metoclopramide nasal spray were dysgeusia (bad, metallic, or bitter taste), headache, and fatigue.

Regulatory authorities issued restrictions and recommendations regarding long-term use of metoclopramide at oral doses exceeding 10 mg 3–4 times daily because of the risk of development of tardive dyskinesia; the restrictions include use for $<$12 weeks and age $<$65 years. Studies in the past decade have addressed the risk of tardive dyskinesia in contrast to reversible involuntary movements on treatment with metoclopramide. First, the relative risk (69) of tardive dyskinesia in metoclopramide users in a VA medical center was not significantly greater than in nonuser controls (relative risk (RR): 1.67; 95% CI: 0.93–2.97). Second, it was estimated that the risk of tardive dyskinesia from metoclopramide use is likely to be $<$1% (70). The most comprehensive assessment (71) showed that the risk of tardive dyskinesia from metoclopramide is in the range of 0.1% per 1,000 patient years, below a previously estimated 1%–10% risk suggested in treatment guidelines by regulatory authorities. High-risk groups are elderly women, diabetics, patients with liver or kidney failure, and patients with concomitant antipsychotic drug therapy, which reduces the threshold for neurological complications.

The FDA package insert on metoclopramide specifies that restlessness, drowsiness, fatigue, and lassitude occurred in approximately 10% of patients who received 10 mg 4 times daily. No other quantitative data are provided in the FDA-approved insert on the prevalence of other, reversible central nervous system disorders with metoclopramide. One study (72) that documented the epidemiology of extrapyramidal reactions to metoclopramide was studied by examining reports in the Adverse Reactions Register of the Committee on the Safety of Medicines in the United Kingdom in the period 1967–1982. Of an estimated 15.9 million prescriptions, there were 479 reports of extrapyramidal reactions (455 of dystonia-dyskinesia, 20 of parkinsonism, and 4 of tardive dyskinesia). A more recent study of metoclopramide adverse events in the FDA Adverse Event Reporting System for the period 2004–2010 yielded reports of 4,784 neurological reactions and 944 reports were for tardive dyskinesia; the total number of prescriptions was almost 40.5 million (73). These data suggest that 0.1% of prescriptions are associated with nontardive dyskinesia neurological symptoms, which seem to be low estimates and may reflect the fact that medication cessation with reversal of the neurological symptoms may not be reported to regulatory agencies.

Domperidone is available for treatment of GP under a special program administered by the FDA. Table 4 provides a summary of clinical trials with domperidone (63,74–85). Domperidone has been tested in studies that involved patients with IG, DG, or postsurgical GP (PSG), and it has been associated with symptom improvement manifested as lower overall scores or reduction in frequency and intensity of symptoms of GP. Four studies have also documented acceleration of GE compared with control or baseline.

Table 5 summarizes efficacy of other prokinetic agents (5-HT_4 and ghrelin receptor agonists) on symptoms or GE (64,86–99). As a group of medications, prokinetics have the most substantive clinical trials, and overall evidence suggests that they provide symptomatic benefit. For all the medications, the recommendation is conditional for use of treatment over no treatment to improve GE. The methodological assessment for the 5-HT4 agonists concluded that there were inconsistent data for symptom improvement.

Another class of agents is the motilin agonists, which are used in the treatment of GP in adults and children. These medications include erythromycin, clarithromycin, and azithromycin. These medications are generally used in the short term (1–4 weeks) because of development of tachyphylaxis to motilides (100). Based on a systematic review and network meta-analysis of 33 studies and data on 22.6 million subjects, macrolide use was not associated with the risk of arrhythmia or cardiovascular mortality (101).

Table 3. Trials of metoclopramide for gastroparesis

Design	N, etiology	Dose (p.o.)	Duration	Results	Reference
DB, PC, PG RCT	28 patients: 5 DG, 4 vagotomy and pyloroplasty, and 19 IG	10 mg qid	3 wk	Symptomatic benefit vs placebo: mean TSS for metoclopramide:18.4 prestudy to 7.2 poststudy; for placebo, 19.1 prestudy to 12.9 poststudy	Perkel 1979, ref. 58
DB, PC, PG RCT	55 patients: 21 vagotomy and drainage, 5 DM, and 29 IG delayed GE	10 mg qid	3 wk	Metoclopramide significantly decreased symptom scores of surgical and idiopathic patients	Perkel 1980, ref. 59
DB, PC, XO, RCT	10 DM	10 mg qid	3 wk/arm	Improved symptoms and vomiting; ~60% acceleration in GE liquid 150-kcal meal	Snape 1982, ref. 60
DB, PC, PG, RCT	28: 5 DG, 4 PS, and 19 IG	10 mg qid	3 wk	Improved symptoms by 29%	Perkel 1979, ref. 58
PC, RCT	18 DG	10 mg qid	3 wk	Improved symptom score by 29% and GE by 25%	McCallum 1983, ref. 61
DB, PC, XO, RCT	13 DM with GE accelerated by i.m. metoclopramide	10 mg qid	3 wk/arm	Improved symptoms with mean reduction of 52.6%	Ricci 1985, ref. 62
DB, RCT	45 diabetic, domperidone-controlled multicenter trial	10 mg qid	4 wk	Improved symptoms by 39%; similar efficacy with domperidone, which had less AEs	Patterson 1999, ref. 63
DB, XO, RCT	13 DG; erythromycin-controlled	10 mg tid	3 wk/arm	Both treatments accelerated GE compared with baseline and improved symptoms score	Erbas 1993, ref. 64
Open	1 diabetic	15 mg qid	6 mo	Improved symptoms, GE liquids, and antral contraction frequency	Longstreth 1977, ref. 65
Open	10 GI symptomatic T1DM, 6 asymptomatic T1DM, and 18 HC	10 mg i.v.	Single dose	Improved GE solids	Loo 1984, ref. 66
Open, PG, RCT	89 T1DM or T2DM GP	10-, 20-mg spray or 10-mg tab qid	6 wk	Nasal 10- and 20-mg group had lower TSS compared with the oral 10-mg group; more side effects, especially nausea with oral	Parkman 2014, ref. 67
DB, PC, PG, RCT	285 T1DM 1 or T2DM with delayed GE or nausea and vomiting.	10- or 14-mg nasal spray qid	4 wk	GP symptom scores were reduced significantly in female subjects, not in male subjects. Adverse effects: dysgeusia, headache, and fatigue.	Parkman 2015, ref. 68

(Updated from Ref. 1, Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical Guideline: Management of Gastroparesis. Am J Gastroenterol 2013; 108:18-37).
DB, double-blind; DG, diabetic gastroparesis; DM, diabetic; GE, gastric emptying; GE, gastric emptying; GI, gastrointestinal; GI, gastroparesis; HC, healthy controls; IG, idiopathic gastroparesis; NA, not available; PC, placebo-controlled; PG, parallel-group; PS, postsurgical gastroparesis; RCT, randomized, controlled trial; T1DM, type 1 diabetes mellitus; AE, adverse event; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TSS, total symptom score; XO, crossover; bid, twice daily; tid, 3 times daily; qid, 4 times daily; i.v., intravenous; i.m., intramuscular.

Antiemetics and central neuromodulators in GP

Recommendations

11. In patients with GP, use of antiemetic agents is suggested for improved symptom control; however, these medications do not improve GE (conditional recommendation, low quality of evidence).
12. Central neuromodulators are not recommended for management of GP (strong recommendation, moderate quality of evidence).
13. Current data do NOT support the use of ghrelin agonists for management of GP (strong recommendation, moderate quality of evidence).
14. Current data do NOT support the use of haloperidol for treatment of GP (conditional recommendation, low quality of evidence).

Table 6 summarizes efficacy of antiemetics and central neuromodulators in GP (102–108). These are therapies commonly used for symptom relief in GP. The central neuromodulator studied with the highest level of evidence was the tricyclic antidepressant, nortriptyline, in IG (104). In this randomized, placebo-controlled trial, nortriptyline was no better than placebo in relieving global symptoms of GP, but some improvement in abdominal pain was noted. In a study of amitriptyline, 50 mg/d, there was no retardation of GE in patients with FD (109). Further randomized controlled trials (RCTs) are needed to determine the efficacy of other central neuromodulators. Although there are no formal randomized trials, experience with use of haloperidol in emergency department treatment of patients presenting with GP has led to reduced need for morphine treatment and admission to hospitals (110), rather than documenting effect on GP symptoms

Other drug therapies for GP

A recent study has targeted previously described impaired nitric oxide metabolism and an abnormal tetrahydrobiopterin (BH-4)

Table 4. Summary of clinical trials with domperidone

Type of study	N, etiology	Dose	Duration	Symptom improvement vs baseline (open) or vs placebo (RCT)	Δ Gastric emptying	Adverse effects	Reference
Open, po	3 DM	10 mg qid	1 wk	Yes, not quantified	Improved, not quantified	NA	Watts 1985, Ref. 74
Open, po	12 IG, 3 DM, and 2 PS	20 mg qid	48 mo	68.3% ($P < 0.05$)	34.5% ($P < 0.05$)	↑ Prolactin (100%), symptoms (17.6%)	Soykan 1997, Ref. 75
Retrospective, po	57 DM	Max. dose 80 mg/d	377 d	70% patients improved	NA	16%	Kozarek 1990, Ref. 76
Open	6 DM	20 mg qid	6 mo	79.2% ($P < 0.01$)	26.9% (NS)	NA	Koch 1989, Ref. 77
Open	12 DM	20 mg tid	Single oral dose 40 mg	Chronic oral administration 20 mg tid (35–51 d) reduced symptoms	↑ Solid and liquid emptying	NA	Horowitz 1985, Ref. 78
RCT, PG, PC, withdrawal study	208 DM	20 mg qid	4 wk	53.8% lower overall score with domperidone ($P = 0.025$)	NA	2%–3% ↑ prolactin, similar to placebo	Silvers 1998 Ref. 79
RCT, PC, XO + open label 1 yr	13 DM	NA	8 wk	↓ in symptom frequency and intensity ($P < 0.03$); symptomatic improvement averaging >1y	NA	NA	Braun 1989, Ref. 80
RCT, PC, XO	6 DM	10 mg i.v.	Single	NA	↑ homogenized solid emptying	NA	Heer 1983, Ref. 81
RCT, PC, XO cisapride (C) or DOM (D)	8 IG; 3 DM	0.8 mg/kg (C) tid or 0.9 mg/kg (D) tid	4 wk	No overall benefit over placebo; 2 of 3 DM improved	NA	Gas pains, skin rash	Franzese 2002, Ref. 82
RCT, PC, XO	11 upper GI distress: 3 DM + severe gastric retention	10 mg qid	4 wk each Rx	2/3 diabetics improved with DOM Rx; among total 11 patients, no superiority of DOM over placebo	NA	Abdominal gas pains, skin rash, itching, sweating, dizziness, and constipation	Nagler 1981, Ref. 83
RCT, PG, DOM vs metoclopramide	93 DM	DOM 20 mg qid; metoclopramide 10 mg qid	4 wk	41.19% improved vs baseline (NA); NS vs metoclopramide	NA	Somnolence 49% metoclopramide, 29% DOM	Patterson 1999, Ref. 84
RCT, PG, PC in the second phase among initial responders over 4 wks	208 DM responders to initial single-blind treatment with same dose	20-mg domperidone qid	4 wk	Symptom severity increased in both groups, worse with placebo. For HR-QOL (SF-36), improvement in physical component score, borderline in physical functioning, but no difference in 7/8 other HR-QOL subscales	NA	Not reported in study	Farup 1998, Ref. 85
Cohorts in the NIH GP consortium (63% IG)	181 in the DOM group; 567 in the non-DOM group	Not standardized	Up to 96 wk	DOM patients: moderate but significantly more improvement in GP outcomes: GCSI, nausea, fullness, upper abdominal pain, GERD scores, and PAGI-QOL	NA	No significant cardiovascular or other DOM-related complications	Sarosiek 2021, Ref. 86

(Updated from Ref. 1, Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical Guideline: Management of Gastroparesis. Am J Gastroenterol 2013; 108:18-37).
DM, diabetic; DOM, domperidone; GCSI, Gastroparesis Cardinal Symptom Index; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GP, gastroparesis; HR-QOL, health-related quality of life; IG, idiopathic gastroparesis; NA, not available; NS, not significant; PAGI-QOL, patient assessment of upper gastrointestinal disorders–quality of life; PC, placebo-controlled; PG, parallel-group; po, oral; PS, postsurgical gastroparesis; RCT, randomized, controlled trial; Rx, treatment; XO, crossover; bid, twice daily; tid, 3 times daily; qid, 4 times daily; i.v., intravenous.

Table 5. Summary of efficacy of other prokinetic agents (5-HT_4 and ghrelin receptor agonists) on symptoms or GE

Medication/trial design	N, etiology	Dose (p.o.)	Duration	Efficacy	Reference
				5-HT4 agonists	
Clebopride PC, DB, RCT	76 with dyspeptic syndromes and x-ray proven delayed GE	0.5 mg tid	3 mo	Clebopride was more effective than placebo in reducing or relieving symptoms	Bavestrello 1985, Ref. 87
Prucalopride PC, DB, XO, RCT	13 DM and 2 connective tissue disease	4 mg/d	Two 4-wk treatments with 2 wks washout	GE faster on prucalopride; GCSI scores were lower than baseline but not different between treatment arms. Meal-related symptom scores over time or cumulative score were not significantly different between groups. GE was more rapid in the prucalopride treatment period	Andrews 2021, Ref. 88
Prucalopride PC, DB, XO, RCT	28 IG and 6 DG	2 mg/d	Two 4-wk treatments with 2-wk washout	Prucalopride significantly improved the total GCSI, subscales of fullness/satiety, nausea/vomiting, and bloating/distention, overall PAC-QOL score, and GE $T_{1/2}$; also, all efficacies were shown only in the idiopathic group	Carbone 2019, Ref. 89
Revexepride: PG, DB, PC, stratified, repeated dose RCT	62 non-DM; 30 DM (55 female and 37 male); gastroparesis symptoms, and slower baseline GEBT $T_{1/2}$ in the placebo group	0.02, 0.1, or 0.5 mg tid	4 wk	Large interindividual differences in GEBT with no significant treatment effect; GCSI and PAGI-SYM scores decreased at week 2 and decreased further at week 4 in all groups including placebo. Quality of life improved in all treatment groups after 4 wk of treatment	Tack et al. 2016, Ref. 90
Velusetrag: DB, PC, RCT; 3-period XO	18 DG and 16 IG	5, 15, or 30 mg po daily	7 d each period	GE $T_{1/2}$ numerically reduced with all 3 doses of velusetrag vs placebo. Efficacy was similar between subjects with diabetic and IG	Kuo 2021, Ref. 91
Felcisetrag: DB, PC, RCT	36: 22 IG, 14 DG	0.1, 0.3, or 1.0 mg i.v., daily	3 d	Felcisetrag significantly accelerated GE, small bowel transit, ascending colon emptying ($T_{1/2}$), and colonic transit at 48 h	Chedid 2021, Ref. 92
Ghrelin agonist					
Relamorelin RCT, PC, XO	10 T1DM with previous delayed GE	100 μg SQ	Single dose	Decreased gastric retention of solids at 1h and 2h and decreased GCSI-DD scores and nausea/vomiting/fullness/pain scores	Shin 2013, Ref. 93
Relamorelin RCT, PC, PG	204 DG + moderate to severe symptoms and delayed GE	10 μg SQ daily or 10 μg SQ bid	12 wk	Relamorelin (10 μg bid) significantly accelerated GE and significantly reduced vomiting vs placebo. Among patients with baseline vomiting, relamorelin accelerated GE, reduced vomiting, and improved other symptoms	Lembo 2016, Ref. 94
Relamorelin RCT, PC, PG	393 DM with moderate to severe gastroparesis symptoms	10 μg or 30 μg or 100 μg or placebo SQ bid	12 wk	75% reduction in vomiting frequency vs baseline (NS compared with placebo). All 4 symptoms of DG (composite or individual symptoms) significantly reduced over 12 wk in all 3 relamorelin doses and accelerated GE vs placebo. Adverse effect: impaired glycemic control with relamorelin	Camilleri 2017, Ref. 95

Table 5. (*continued*)

Medication/trial design	N, etiology	Dose (p.o.)	Duration	Efficacy	Reference
Relamorelin and TZP-101 or TZP 102: 6 RCTs in SRMA	DG (N = 557)	Diverse doses		Significantly improved overall gastroparesis symptoms (standardized mean difference, −0.34; 95% CI, −0.56 to −0.13) and significantly improved symptoms, including nausea, vomiting, early satiety, and abdominal pain	Hong 2020, Ref. 96
Motilin agonists					
Erythromycin RCT, PC, XO	10 T1DM	200 mg i.v.; 250 mg p.o. tid	4 wk	Solid meal retention at 2h: 63 ± 9% with placebo; 4 ± 1% with erythromycin; no effects on the symptoms	Janssens 1990, Ref. 97
Erythromycin open trials of i.v. and p.o.	10 IG and 4 DG; 4 patients dropped out	6 mg/kg i.v. 500 mg tid-ac and qhs	Single dose; 4 wk and open 8.4 mo	Solid meal retention at 2h: 85 ± 11% (SD) at baseline; 20 ± 29% on i.v. erythromycin ($P < 0.001$); 48 ± 21% after 4 wk of oral therapy ($P < 0.01$). Reduction in total symptom scores and a significant reduction in global assessment scores	Richards 1993, Ref. 98
Erythromycin vs metoclopramide RCT, XO	13 DG	p.o. 250 mg tid erythromycin; p.o.10 mg tid metoclopramide	3 wk each period	Compared with baseline, improved GE parameters after both erythromycin and metoclopramide, with improved total GI symptom scores, more pronounced with erythromycin	Erbas 1993, Ref. 64
Erythromycin RCT, PC, XO	20 IG (FD + delayed GE)	200 mg i.v.	Single dose	Erythromycin accelerated (breath test) solid GE T½ = 146 (27) vs 72 (7) min and liquid GE T½ = 87 (6) vs 63 (5) min; no overall symptom improvement except for bloating	Arts 2005, Ref. 99
Erythromyin vs azithromycin retrospective case-control analysis	120 patients (27 DM) underwent SGE with provocative testing	250 mg i.v. of each drug	Single dose	Both treatments accelerated GE with no difference between the 2 treatments: Erythromyin GE T½ = 166 ± 68 min baseline to 11.9 ± 8.4 min; Azithromycin GE T½ = 178 ± 77 min baseline to 10.4 ± 7.2 min	Larson 2010, Ref. 100

CI, confidence interval; DB, double-blind; DG, diabetic gastroparesis; DM, diabetic; GCSI, Gastroparesis Cardinal Symptom Index; GE, gastric emptying; GEBT, gastric emptying breath test; i.v., intravenous; IG, idiopathic gastroparesis; N, number; NA, not available; p.o., oral; PAC-QOL, patient assessment of constipation–quality of life; PAGI-SYM, patient assessment of upper gastrointestinal disorders–symptoms; PC, placebo-controlled; PG, parallel-group; po, oral; PSG, postsurgical gastroparesis; RCT, randomized, controlled trial; SGE, GE by scintigraphy; SQ, subcutaneous; SRMA, systematic review and meta-analysis; XO, crossover; bid, twice daily; tid, three times daily; ac, before meal.

pathway in GP patients with diabetes mellitus. This phase II study needs confirmation in other larger controlled studies (111).

A number of other medications are being developed for treatment of GP. These include 5-HT4 receptor agonists (prucalopride, felcisetrag, and velusetrag) and dopamine D2/D3 receptor antagonists, and the therapeutic trials of these medications are included in Table 5.

Use of pharmacotherapy to reduce the future aggravation of GP

Based on a referral center experience, predictors of responsiveness to pharmacotherapy (112) were identified. A good response to pharmacological agents can be expected in the viral and dyspeptic subgroups of idiopathics, Parkinson disease, and the majority of diabetics; whereas a poorer outcome to prokinetics can be expected in postvagotomy patients, those with connective tissue disease, a subgroup of diabetics (e.g., with evidence of vagal neuropathy), and the subset of IG dominated by abdominal pain and history of physical and sexual abuse (112). The comprehensive NIH GP Consortium database of 748 patients (85) showed 181 (24%) on domperidone and 567 not receiving domperidone; 63% had IG. Compared with patients not receiving domperidone, those patients who were receiving domperidone (median time on domperidone after initiation of 32 weeks, 95% CI: 25–35 weeks) experienced moderate but significantly more improvement in GP outcome

Table 6. Efficacy of antiemetics and central neuromodulators in GP

Medication/trial design	N, etiology	Dose	Duration	Efficacy	Reference
Aprepitant PC, PG, DB, RCT	126 patients with at least moderate chronic nausea and vomiting	p.o. 125 mg/d	4-wk	Aprepitant did not reduce symptoms of nausea (primary outcome measure) but significantly reduced secondary outcomes: in symptom severity for nausea, vomiting, and overall symptoms. Adverse events (mild or moderate severity) commoner in aprepitant (35%) vs placebo (17%).	Pasricha 2018, Ref. 103
Tradipitant PC, PG, DB, RCT	152 adults with IG (90) or DG (61)	p.o. 85 mg bid	4 wk	Significant decrease in nausea score (reduction of 1.2) at week 4; significant increase in nausea-free days at week 4 with even greater effects in patients with nausea and vomiting at baseline (n = 101). A >1-point improvement in GCSI score in 46.6% on tradipitant compared with 23.5% on placebo.	Carlin 2021, Ref. 104
Nortriptyline PG, PC, DB RCT	130 IG	Dose escalation at 3-wk intervals (10, 25, 50, and 75 mg) to 75 mg at 12 wk	15 wk	No difference in primary outcome measure (decrease from the patient's baseline GCSI score of at least 50% on 2 consecutive 3-wk GCSI assessments during 15 wk of treatment); more treatment cessation in the nortriptyline group (29%) than the placebo group (9%); numbers of adverse events not different.	Parkman 2013, Ref. 105
Haloperidol PC, RCT	33 emergency department patients with acute exacerbation of diagnosed GP	5 mg vs placebo both + conventional therapy (selected by treating physician)	Single dose	One hour after therapy, the mean pain and nausea scores in the haloperidol group were 3.13 and 1.83 compared with 7.17 and 3.39 in the placebo group (symptoms on a 10-point scale). No adverse events were reported.	Roldan 2017, Ref. 106
STW5 or STW5-11 vs cisapride DB, double dummy, RCT	186 dysmotility type of FD	NA	NA	The lower limit of the confidence interval for both herbal preparations was above the predefined lower limit of the equivalence border and hypothesis of noninferiority was proven for STW 5 and STW 5-II.	Rosch 2002, Ref. 107
STW 5, PC, PG, DB, RCT	103 patients with FD and GP	20 drops tid	4 wk	Improvement of the GIS ($P = 0.08$) and the proportion of patients with a treatment response ($P = 0.03$) were more pronounced in the STW 5 group compared with placebo. No effect on GEBT.	Braden 2009, Ref. 108
Survey questionnaire of treatment of nausea in clinical practice	102 patients: GP 43.1%, FD 27.5%, PSG 8.8%, other 2.0%, and undetermined multiple 10.8%.			Patient-reported best treatments were marijuana, ondansetron, and promethazine. Least effective treatments were erythromycin, diphenhydramine, buspirone, gabapentin, pregabalin, acupuncture, and Iberogast. Promethazine was more effective in patients with a higher GCSI.	Zikos 2018, Ref. 109

DB, double-blind; DG, diabetic gastroparesis; DM, diabetic; FD, functional dyspepsia; GCSI, Gastroparesis Cardinal Symptom Index; GE, gastric emptying; GEBT, gastric emptying breath test; GIS, gastrointestinal symptom; GP, gastroparesis; IG, idiopathic gastroparesis; NA, not available; p.o., oral; PC, placebo-controlled; PG, parallel-group; PSG, postsurgical gastroparesis; RCT, randomized, controlled trial; XO, crossover.

measures of the Gastroparesis Cardinal Symptom Index (GCSI) total score, nausea and fullness subscales, upper abdominal pain score, gastroesophageal reflux disease score, and the patient assessment of upper GI disorders—quality-of-life score.

In a systematic review (113) of 14 studies that evaluated GE and upper GI symptoms, including IG or DG, and including only studies with optimal GE test methods being evaluated, there was a significant positive association between improvements in GE and upper GI symptoms in response to prokinetic agents.

Immunological therapies

There is insufficient evidence to support routine clinical use of autoimmune therapies in management of GP. A retrospective analysis of 11 female patients (114) with drug- and device-resistant GP with coexisting positive autoimmune profiles who were treated for 8–12 weeks with diverse immunomodulatory treatment showed that total symptom score improved in 6 of 11 patients, with maximum GI symptom improvement with intravenous immunoglobulin (IVIg) (2 of the 3 patients treated). In a subsequent open-label study, 14 patients (3 DG, 1 PSG, and 10 IG) with serological and/or tissue evidence of immunological abnormality, IVIg therapy (400 mg/kg infusion weekly for 12 weeks) was associated with significant improvement in symptoms scores for nausea, vomiting, early satiety, and abdominal pain, and 9/14 patients were responders to this open-label treatment (115). This study built on the retrospective medical record review, suggesting a positive experience among 11 patients treated with IVIg or combined mycophenolate mofetil with methylprednisolone or only mycophenolate mofetil therapy (114).

Nonpharmacological therapy for GP: GES, acupuncture, and herbal medicines

Recommendation

15. Gastric electric stimulation (GES) may be considered for control of GP symptoms as a humanitarian use device (HUD) (conditional recommendation, low quality of evidence).

GES is approved as an HUD, as defined by the FDA for medically refractory DG or IG. The recommendation includes the use of GES in humanitarian use.

Table 7 shows efficacy of several bioelectric treatments including vagal nerve stimulation, spinal cord stimulation, and GES (116–141). A recent randomized, crossover trial of ON vs OFF GES in patients with medically refractory vomiting with or without delayed GE, GES decreased the vomiting frequency. Severity of nausea and appetite improved while ON compared with OFF. However, there were no differences in GI quality of life, nutritional parameters, or GE (120). Randomized, crossover trials of GES for medically refractory DG or IG have shown mixed results, which may reflect the variation in trial designs with differing timing of the ON vs OFF randomization and crossover (119–123). Other modalities of electrostimulation (vagal and spinal cord) seem promising; however, larger randomized, sham-controlled trials are needed to determine the efficacy. However, documented clinical usefulness in both IG and DG (documented in Table 7) suggests there is a role for GES in accordance with its HUD approval.

Recommendations

16. Acupuncture alone or acupuncture combined with prokinetic drugs may be beneficial for symptom control in patients with DG. Acupuncture cannot be recommended as beneficial for other etiologies of GP (conditional recommendation, very low quality of evidence).
17. Herbal therapies such as Rikkunshito or STW5 (Iberogast) should NOT be recommended for treatment of GP (conditional recommendation, low quality of evidence).

Table 8 summarizes information on effects of electroacupuncture, acupuncture, and herbal medicines in GP (142–153). The evidence available does not support their use in clinical practice.

Pyloric interventions: diagnostic and therapeutic

Recommendations

18. In patients with GP, EndoFLIP evaluation may have a role in characterizing pyloric function and predicting treatment outcomes after peroral pyloromyotomy (conditional recommendation, very low quality of evidence).
19. Intrapyloric injection of botulinum toxin is not recommended for patients with GP based on randomized, controlled trials (strong recommendation, moderate quality of evidence).
20. In patients with GP with symptoms refractory to medical therapy, we suggest pyloromyotomy over no treatment for symptom control (conditional recommendation, low quality of evidence).

Table 9 shows results of EndoFLIP for selection of patients for pyloromyotomy or pyloric botulinum toxin injection (154–160). Current evidence suggests that such measurements of pyloric diameter and distensibility index or compliance are associated with greater gastric retention, and that the measurements may predict response to therapy, particularly, significant enlargement of the post–G-POEM pyloric diameter (158). It is reasonable to consider such pyloric interventions in a clinical trial and to include assessments of pyloric physiology to appraise the impact of pyloric dysfunctions on outcomes. Thus, although intrapyloric injection of botulinum toxin is not recommended for patients with GP based on randomized, controlled trials (161), a recent large multicenter study from France documents the efficacy of botulinum toxin injection, particularly for the relief of vomiting, when patients are selected based on measurements of pyloric distensibility (160).

Efficacy of G-POEM for GP based on open-label studies

Table 10 shows efficacy of G-POEM for GP based on open-label studies (162–180). Overall, these open-label studies suggest there is benefit in terms of symptom improvement and improved GE, although most studies were of only 3–6 months' duration. A 12-month study showed 56% patients improved at 1 year (172). Symptom control after endoscopic pyloromyotomy is comparable

Table 7. Efficacy of several bioelectric therapies in GP

Device/trial design	Patients	Efficacy	Reference
Vagal stimulation			
Open-label pilot study: Short-term noninvasive cervical vagal nerve stimulation in patients with drug-refractory GP	23 patients with GP for 3 wk and 7 of these for 6 wk.	Response rates were 35% at 3 wk and 43% for 3–6 wk. Improvements in mean total GCSI and subscales were noted.	Paulon 2017, Ref. 117
Open-label pilot study: Noninvasive vagal nerve stimulation for 4 wks improves symptoms and GE in patients with IG	15 patients with mild to moderate IG	Improvement in total GCSI symptom scores and 3 subscales, with 40% participants meeting primary endpoint; therapy also associated with a reduction in GE T1/2.	Gottfried-Blackmore 2020, Ref. 118
Spinal cord stimulation			
Open-label study of spinal stimulation in patients with abdominal pain, with the majority having GP	23 patients, 96% white and 79% women, with GP in 63%	After 12 mo of 10-KHZ spinal cord stimulation, 78% of patients had >50% reduction in pain, and 64% remitted in pain. Other outcomes improved in most patients.	Kapural 2020, Ref. 119
Controlled trials in gastric electric stimulation (GES)			
Temporary GES			
RCT, PC, XO trial of 2 consecutive, 4-d sessions of temporary GES	58 patients (47 females) with GP symptoms: 38 IG; 13 DG, 7 PSG	Overall slight, NS daily decrease in average vomiting scores First session was significant, but not significant after XO. Temporary GES may improve symptoms such as vomiting.	Abell T 2011, Ref. 120
Permanent GES			
GES reduces refractory vomiting in a randomized, XO trial	218 patients in 19 centers, 97 with DG and 121 with IG were included and 46 were excluded; thus, 172 patients were implanted and analyzed	A randomized, XO trial for 4 mo of GES decreased vomiting in DG and IG, irrespective of baseline GE.	Ducrotte 2020, Ref. 121
Multicenter, DB, XO, RCT of GES	17 DG and 16 IG	Self-reported vomiting frequency significantly reduced in the on vs off period and consistent with the significant patient preference for the on vs off period; vomiting frequency decreased, and symptom severity and quality of life improved at 6 and 12 mo. Once unblinded, the symptom improvement continued at 1 year.	Abell T 2003, Ref. 122
Randomized XO study of GES with all patients turned on for 6 wk and then with consecutive 3-mo XO periods with device on or off	55 patients with DG	6 wk of GES therapy significantly reduced vomiting and gastroparetic symptoms in patients with DG.	McCallum R 2010, Ref. 123
Prospective, DB, randomized, XO study of GES with all patients initially having device on for 6 wk followed by DB consecutive 3-mo XO periods with device either on or off.	32 patients with IG	GES implanted with on stimulation was shown to decrease vomiting symptoms in the initial 6 wk on period. NS reduction in vomiting symptoms in on vs off period. Sustained decrease in vomiting and days of hospitalization at 12 mo in the on group.	McCallum R 2013, Ref. 124
2 separate but related studies of the effect of GES on pancreatic function in GP patients: Single-blinded, RCT compared with normal controls	9 patients with GP and GES and 9 healthy controls	Pancreatic elastase was significantly different for GES on vs off: 508 on vs 378 off. Total GI symptoms were significantly lower on vs off. Pancreatic polypeptide and heart rate were borderline improved with on vs off.	Luo 2004, Ref. 125
DB, prospective, single-arm, RCT Study of GES in DG	7 DG patients	No evidence was found for GES-induced modulation of the visceral sensory system and central excitability. Some changes in symptoms noted with GES.	Frokjaer 2009, Ref. 126
Propensity score matching. Effect of GES in GP with prospective data	319 patients with GP symptoms, of which 81 had GES and 231 without GES	Patients treated with GES had clinically significant improvement in GP symptoms. When adjusted by propensity scoring, only nausea remained significant.	Abell T 2019, Ref. 127

Table 7. (*continued*)

Device/trial design	Patients	Efficacy	Reference
Controlled with medical arm but not randomized study with 1 yr of baseline and 3 yr of treatment with 2 groups: GES vs intensive medical therapy	9 GES patients and 9 similar patients in an outpatient medical program	GES was found to be more effective in improving long-term GI symptoms, decreased costs, and less use of healthcare resources than intensive medical therapy.	Cutts 2005, Ref. 128
Meta-analyses assessing effectiveness of gastric electrical stimulation			
NICE guidance on GES for GP	Several studies reviewed, 2 metanalysis, and 2 RCT, XO	Diabetics with severe symptoms may benefit from therapy.	Kong 2015, Ref. 129
SRMA 13 studies, 12 lacked controls and 1 blinded and randomized	13 studies, 12 lacked controls and 1 blinded and randomized	After GES, improvements in TSS score (3/13 studies), vomiting severity (4/13), nausea severity (4/13), SF-36 physical composite score (4/13), SF-36 mental composite score (4/13), requirement for enteral or parenteral nutrition (8/13), and 4-hr GE (5/13). Weight gain (in 3/13) did not reach overall significance, 3 device removal or reimplantation rate was 8.3%. Beneficial in improving symptoms in patients with GP.	O'Grady 2009, Ref. 130
SRMA 5 studies randomly allocated patients to periods with or without GES	5 randomized trials 16 open-label studies	TSS scores did not differ between these periods with or without GES in randomized trials. Open-label studies showed a significant decrease in TSS scores, which was also shown with medical therapy or placebo arms, or botulinum toxin. Meta-regression analysis showed that significant differences in baseline TSS ratings impacted TSS ratings during treatment. Argues against the use of GES outside of strict clinical trials as viable treatment option.	Levinthal 2017, Ref. 131
SRMA	21 studies	GES seems to offer significant improvement in symptom control in a subset of patients.	Lal 2015, Ref. 132
SRMA	10 studies	GES is an effective modality for treating GP refractory to less invasive treatment.	Chu 2012, Ref. 133
Selected open-label trials of gastric electrical stimulation			
Multicenter, open-label GES experience in France	142 patients (60 diabetic and 82 nondiabetic) and medicoeconomic data were available for 96 patients (36 diabetic and 60 nondiabetic)	24 mo after implantation. GIQLI score increased, with a more significant improvement in nondiabetic than in diabetic patients. Proportion of patients vomiting less than once per month increased by 25.5%. GES decreased mean overall healthcare costs (saving of average $3348/patient/year), with. Savings greater for diabetic patients (4096 US$/patient/year).	Gourcerol 2020, Ref. 134
Open-label GES study	16 patients with PSG refractory to medical therapy	Severity and frequency of all 6 upper GI symptoms, TSS, physical composite score, and mental composite score significantly improved after 6 mo and sustained at 12 mo; 4/7 stopped jejunal feeding; mean number of hospitalization days significantly reduced by a mean 25 d compared with previous year. No effect on GE.	McCallum 2005, Ref. 135
Open-label GES study	37 GP patients preop and 1-y post-GES implant	8/27 off prokinetics; 9/26 off antiemetics at 1y; mean TSS significantly reduced, overall SF-36 scores (HR-QOL) significantly improved, and hospitalizations decreased from 50 $\pm$ 10 d for the year before GES therapy to 14 $\pm$ 3 d. GE was not significantly improved.	Lin 2005, Ref. 136
Open-label GES study	55 patients with GP with follow-up information for over 3y	Of the 55 patients, 10 died of unrelated complications, 6 had devices removed, and 2 could not be reached. 37 patients had activated GES for mean 45 mo: TSS, hospitalization days, and the use of medications all significantly reduced at 1 and 3 years. Among 15/37 patients requiring nutritional support, only 5 continued beyond 3y. Mean HbA1c in diabetics reduced from 9.5% to 7.9% at 3y.	Lin 2006, Ref. 137

Table 7. (*continued*)

Device/trial design	Patients	Efficacy	Reference
Open-label GES study	15 patients with GP	Four patients (4 idiopathic) failed to improve more than 20% on multiple assessments after a year of therapy. All diabetic patients experienced a durable symptomatic improvement with GES. GES nonresponders had less severe vomiting preoperatively.	Musunuru 2010, Ref. 138
Open-label GES clinical experience	221 patients with GP: 142 (64%) DG, 48 (21%) IG, 31 (14%) PSG	At follow-up of at least 1 yr, there was association of symptom improvement with improved GE in DG, not in IG. Patient age, sex, baseline TSS score, and baseline gastric retention had no significant effect on clinical improvement in response to GES.	Hou 2012, Ref. 139
Open-label experience	4 patients with GP	Mean length of hospital stay in the year pre-GES was 81.75 d and 62.25 d in the year post-GES; also no improvement in glycemic control after GES.	Hannon 2011, Ref. 140
Open-label follow-up study of GES after successful initial temporary GES	IG 9, DG 3 with long-duration symptoms (7.3 yr)	Short-term data: improved TSS, body weight, BMI, and serum albumin by 3–6 mo. Intermediate (1–2 yr) and long-term (5 years) data: continued improvement in TSS, weekly vomiting frequency score, QOL measures, and maintained weight gain.	Abell T 2003, Ref. 141
Open-label GES study	Refractory GP: DG 39, PSG 9, and IG 7	TSS and the physical and mental composite scores of QOL improved significantly; GE did not change; BMI and body weight increased; days spent in hospital admissions significantly decreased.	Forster 2003, Ref. 142

DG, diabetic gastroparesis; DM, diabetic; GCSI, Gastroparesis Cardinal Symptom Index; GE, gastric emptying; GES, gastric electrical stimulation; GIQLI, gastrointestinal quality of life; GP, Gastroparesis; HR-QOL, health-related quality of life; IG, idiopathic gastroparesis; NA, not available; NS, not significant; PC, placebo-controlled; PG, parallel-group; po, oral; PSG, postsurgical gastroparesis; RCT, randomized, controlled trial; TSS, total symptom severity; XO, crossover.

with surgical myotomy; however, endoscopic myotomy has been associated with fewer postprocedural complications and shorter length of hospital stay. A recent study has identified benefit in relief of symptoms as well as improved GE with G-POEM procedure followed for 6 months in a sham-controlled study (173). Other pylorus-directed procedures are also available such as surgical pyloroplasty, although there is more evidence on G-POEM. Heineke-Mikulicz pyloroplasty involves longitudinal incision across the pylorus, which is then closed transversely, and this results in division of both longitudinal and circular muscle layers. In 177 patients with GP, laparoscopic pyloroplasty achieved improved GE in 90% of patients and induced short-term improvement of nausea, vomiting, bloating, and abdominal pain. However, morbidity rate was 6.8%, with problems such as confirmed leaks or further surgical interventions including jejunostomy and subtotal gastrectomy (181).

CONCLUSION AND A LOOK TO THE FUTURE

This guideline has focused on the diagnosis and treatment of GP in adults (including dietary, pharmacological, device, and interventions directed at the pylorus). The recommendations made are guided by assessment using GRADE methodology. Nevertheless, this is an area with considerable ongoing innovation, validation, and research that is likely to impact future iterations of these guidelines. In particular, the following have potential future impact on the management of GP: The diagnostic value of WMC for GP and for measurements of pan-GI transit and pressure profiles and autonomic nervous system dysfunction are under investigation. Similarly, studies are exploring the optimal approaches to select and individualize patients for treatments including documentation of circulating antibodies, measurements of the pylorus and high-resolution antropyloroduodenal manometry, extensive surface EGG (high-resolution electrical mapping), and full-thickness antral and pyloric biopsies. Such advances should clarify the role of immunotherapies, novel pharmacological agents, pyloric interventions, bioelectric therapy, and surgical approaches for GP.

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CONFLICTS OF INTEREST

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Table 8. Effect of electroacupuncture, acupuncture, and herbal medicines in GP

Electroacupuncture			
Device/trial design	**Patients**	**Efficacy**	**Reference**
Multicenter sham-controlled, XO, 4-wk RCT of transcutaneous electroacupuncture (TEA) through surface ECG electrodes at acupoints PC6 and ST36.	26 DG patients, 18 completed study; TEA performed using pulse trains self-applied for 2 h. Postlunch/dinner	4-wk TEA, not sham-TEA, significantly improved 5 of 9 GP symptoms: Nausea by 29.7%, vomiting by 39.3%, abdominal fullness by 21.4%, bloating by 20.6%, and retching by 31.1%. A significant change in pain was also noted with TEA.	Xu 2015, Ref. 143
Acupuncture			
Device/trial design	Patients	Efficacy	Reference
Single-blind, RCT, XO trial of acupuncture for 1 wk vs sham acupuncture with 1-mo washout period	25 DG patients	Real acupuncture was associated with significantly greater reductions in gastric retention at 2 h and 4 h and in the GCSI score with no differences in fasting blood glucose or HbA1c	Li 2015, Ref. 144
Single-center, DG comparison of acupuncture to control	Acupuncture treatment group (n = 16 (5M/11F), 5 times per week 40 min each for 10 d, and a control group (n = 16 (7M/9F).	Compared with the control group, acupuncture resulted in the clinically significant improvement of the severity of symptoms and the GCSI nausea by 68.4%, retching by 76.8%, vomiting by 86.7%, stomach fullness by 62.5%, not able to finish a normal-sized meal by 21.2%, stomach visibly larger by 13.4%, loss of appetite by 12.8%, feeling excessively full after meals by 64.7%, and bloating by 22.5%	Kostitska 2016, Ref. 145
Single-center, RCT of acupuncture applied to Zusanii once per day and other acupoints compared with metoclopramide 20 mg tid i.m.	Acute PSG in 63 patients	Significant differences in gastric drainage volume, cure rate, and number of treatments with cure rate were 90.6% with acupuncture and 32.3% with metoclopramide	Sun 2010, Ref. 146
Single-center comparison of 6-d Rx with acupoint stimulation (bilateral TEA) at Neiguan, PC-6 or prokinetic (metoclopramide, cisapride, and erythromycin)	30 mechanically ventilated neurosurgical ICU patients with delayed GE [gastric residual volume (GRV) > 500 mL for ≥2 d]	After 5 d of treatment, 80% of patients in the acupoint group successfully developed feeding tolerance (GRV <200 mL/24 h) vs 60% in the prokinetic group; benefit was documented from day 1 of treatment. Similarly, feeding balance improved significantly on all days of treatment with acupoint vs prokinetic therapy.	Pfab 2011, Ref. 147
Single-center, open-label treatment with needleless TEA	11 patients with DG evaluated with visual stimulation (vs to evoke nausea and EEG	TEA improves gastric dysrhythmia and ameliorates nausea. TEA treatment of nausea provoked by vs resulted in a change of dominance from right to left inferior frontal lobe activity on EEG.	Sarosiek 2017, Ref. 148
RCT of acupuncture points:group A Zhongwan (CV 12) and Zusanli (ST 36); group B, Neiguan (PC 6) and Zusanli (ST 36); group C, nonacupoint and Zusanli (ST 36).	99 patients with GP at 3 clinical centers	Treatment was performed for 30 min every day, 5 d as a course of treatment. GCSI scores of each group after treatment and at follow-up were significantly lower than those before treatment ($P < 0.01$), and the reduction in group A [Zhongwan (CV 12) and Zusanli (ST 36)] was greater than that of groups B and C ($P < 0.01$). SF36 scores were similar in the 3 groups.	Xuefen 2020, Ref. 149
SRMA of acupuncture either manually stimulated (24 studies) or electrically stimulated (8 studies).	32 studies with a total of 2601 participants: DG (31 studies) or PSG (1 study)	There was low-certainty evidence that symptom scores of participants receiving acupuncture did not differ from those receiving sham acupuncture at 3 mo when measured by a validated scale. There was very low-certainty evidence that acupuncture had "improved" symptoms compared with gastrokinetic medication (4–12 wk) (12 studies; 963 participants).	Kim 2018, Ref. 150
SRMA of 14 RCTs of acupuncture	14 RCTs of DG	Acupuncture treatment had a higher response rate than controls (RR, 1.20 [95% confidence interval (CI), 1.12 to 1.29], $P < 0.00001$) and significantly improved dyspeptic symptoms compared with the control group.	Yang 2013, Ref. 151
Open-label treatment with behavioral technique, autonomic training with directed imagery (verbal instructions)	26 patients with chronic nausea and vomiting	Gastrointestinal symptoms decreased by >30% in 58% of the treated patients; responders manifested mild to moderate delay in baseline GE; the sympathetic adrenergic measure (change in the foot cutaneous blood flow in response to cold stress) predicted improvement in autonomic training outcome.	Rashed 2002, Ref. 152

Table 8. (*continued*)

Electroacupuncture			
Device/trial design	**Patients**	**Efficacy**	**Reference**
Chinese herbal medicine			
SRMABanxiaxiexin decoction for DG	16 RCTs involving 1302 patients	Effect of banxiaxiexin decoction (BXXD) for DG was superior to the control group (n = 1302, RR 1.23, 95% CI 1.17 to 1.29). Methodological quality of included studies was low, and long-term efficacy and safety are still uncertain.	Tian 2013, Ref. 153
SRMA in comparison with conventional treatment (Western medicine treatment [metoclopramide, mosapride, cisapride, and domperidone]), placebo, and no treatment (blank) for DG	Ten RCTs involving 867 patients (441 in the experimental groups [herbs alone], and 426 in the control groups [all prokinetic])	Effects of Xiangshaliujunzi Decoction (XSLJZD) for the treatment of DG were superior to the control group (n = 867, RR = 1.33, 95% CI: 1.24–1.42) based on symptoms and GE. Evidence remains weak because of the poor methodological quality of the included studies.	Tian 2014, Ref. 154

DG, diabetic gastroparesis; GCSI, Gastroparesis Cardinal Symptom Index; GE, gastric emptying; GP, gastroparesis; PSG, postsurgical gastroparesis; RCT, randomized, controlled trial; SRMA, systematic review and meta-analysis; TEA, transcutaneous electroacupuncture; XO, crossover.

Table 9. EndoFLIP for selection of patients for pyloromyotomy or pyloric botulinum toxin injection

Patients	Measurement	Results	Reference
21 HC, 27 patients with GP and 5 patients with esophagectomy	Fasting pyloric pressure and compliance	Fasting pyloric compliance 25.2 ± 2.4 mm/mm Hg in HV, 16.9 ± 2.1 mm/mm Hg in GP ($P < 0.05$) and 10.9 ± 2.9 mm/mm Hg in patients with esophagectomy (; $P < 0.05$). Pyloric dilation in 10 GP patients with low fasting pyloric compliance increased compliance from 7.4 ± 0.4 to 20.1 ± 4.9 mm/mm Hg ($P < 0.01$) and improved the GIQLI score.	Gourcerol 2015, Ref. 155
54 patients (39 IG, 15 DG)	Fasting pyloric diameter, CSA, pressure, length, DI	Wide range seen in diameter (5.6–22.1 mm) and distensibility (1–55 mm^2/mm Hg) of the pylorus. Symptoms of early satiety and postprandial fullness were inversely correlated with pyloric sphincter diameter and CSA.	Malik 2015, Ref. 156
47 DG patients and 67 IG patients with nausea and vomiting	Sleeve manometry and EndoFLIP performed sequentially during the same endoscopy	Basal pyloric pressure was elevated (>10 mm Hg) in 34 patients (42% of patients with delayed emptying); significant decrease in distensibility in patients with gastric retention (>20% at 4 h) compared with patients with normal gastric retention (<10%).	Snape 2016, Ref. 157
30 IG patients and 14 DG patients	Fasting pyloric diameter, CSA, and DI	Greater gastric retention tended to correlate with decreased CSA and pyloric DI. Greater pyloric compliance at baseline correlated with greater improvement in early satiety and nausea at 8 wk and greater pyloric DI correlated with improvement in upper abdominal pain.	Saadi 2018, Ref. 158
37 patients with refractory GP	Fasting CSA, balloon pressure, and DI	Post–G-POEM CSA and DI were significantly higher in the clinical success group and improvement in GE.	Vosoughi 2020, Ref. 159
20 patients with refractory GP	Fasting pyloric diameter and DI before and after G-POEM	G-POEM increased mean and maximum pyloric diameters and mean and maximum pyloric DI on 50-mL EndoFLIP inflation; therapy enhances pyloric opening but may not impair pyloric closure. The clinical success of G-POEM using EndoFLIP inflated to 50 mL had specificity of 100% and sensitivity of 72.2% (area under the curve 0.72) at a distensibility threshold of 9.2 mm^2/mm Hg.	Watts 2020, Ref. 160
35 patients with GP: 11 DG, 6 PSG, and 17 IG	Fasting pyloric diameter and distensibility before BOTOX	19/35 patients with reduced (<10 mm^2/mm Hg) pyloric distensibility) had benefits: TSS decreased at 3 mo and gastric fullness, bloating and GIQLI score, and GE $T_{1/2}$ all improved; no such benefit in those with normal distensibility.	Desprez 2019, Ref. 161

CSA, cross-sectional area; DG, diabetic gastroparesis; DI, distensibility index; GIQLI, Gastrointestinal Quality of Life Index; GP, gastroparesis; HC, healthy controls; IG, idiopathic gastroparesis; NA, not available; PSG, postsurgical gastroparesis; TSS, total symptom score.

Table 10. Efficacy of G-POEM for gastroparesis based on open-label studies

No. of patients	Types of GP patients	Changes in GE	Changes in symptoms	Duration follow-up	Adverse events	Ref. No.
29	DG = 7 IG = 15 PSG = 5 scleroderma = 2	70% normalized	79% at 3 mo; 69% at 6 mo. GCSI improved from 3.5 to 0.9 at 3 mo	3 and 6 mo	17% (2/12) pneumoperitoneum requiring decompression	Gonzalez 2017, Ref. 163
16	DG = 9 IG = 5 PSG = 1 Postinfectious = 1	75% normalized, 25% improved	81% improvement. GCSI improved from baseline of 3.4 to 1.46 12 mo later	12 mo	None	Dacha 2017, Ref. 164
47	DG = 12 IG = 27 PSG = 8	4-h retention improved: from 37.2% to 20.4%	GCSI improved from 4.6 to 3.3	3 mo (follow-up in 31/47 patients)	1 death (unrelated)	Rodriguez 2017, Ref. 165
30	DG = 11 IG = 7 PSG = 12	47% normalized	No validated outcome measure available	6 mo	2/30 (6%): 1 prepyloric ulcer and 1 capnoperitoneum	Khashab 2017, Ref. 166
13	DG = 1 IG = 4 PSG = 8	4/6 improved; % retention at 4 h improved from 49% to 33%	In 11: 4 considerably better, 4 somewhat better, 1 no Δ, 2 worse	3 mo	3 accidental mucosotomy closed with clips; 1 pulmonary embolism	Malik 2018, Ref. 167
16	DG = 3 PSG = 13	Mean % retention (radiolabeled bread) at 2h from 69.3% to 33.4%	Mean total symptom score from 24.25 to 6.37; 13/16 substantial improvement	3 mo	1 pyloric stenosis at day 45	Xu 2018, Ref. 168
20	DG = 10 Nondiabetic = 10	% Retention at 4 h improved from 57.5% to 15%; and 30% normalized	GCSI improved from 3.5 to 1.3; QOL improved	3 mo	3 mild hemorrhage, 3 gastric perforation, 1 moderate dyspepsia	Jacques 2019, Ref. 169
40	DG = 15 Nondiabetic = 25 (of which 18 were IG)	% Retention at 4 h reduced by 41.7%	Improved GCSI, nausea/vomiting, not bloating	Median 15 mo	1 tension capnoperitoneum, 1 exacerbation of COPD; 1 (Ehlers-Danlos syndrome) Disrupted mucosotomy + ulcer	Mekaroonkamol 2019, Ref. 170
22	DG = 8, IG = 14, all with GES and most with diverse other procedures	In 7/11 with post–G-POEM, GE was normal	GCSI improved (reduction 1.63 points); improved all subscores	1 and 3 mo	1 laparoscopy for pain because of capnoperitoneum and adhesions	Strong 2019, Ref. 171
38	PSG (76% for fundoplication or hiatal hernia repair)	% Retention at 4 h improved from 46.4% to 17.9%; 50% normalized	GCSI improved (mean reduction 1.29 points); improved all subscores	1 mo	2 readmissions: 1 melena; 1 dehydration	Strong 2019, Ref. 172
80	IG (41.3%), PSG (35%) and DG (23.8%).	GE scintigraphy improvement in 64.2% and normalized in 47.2% (of 53 cases with test) at 3 mo	Decrease in total GCSI >1 + >25% decrease in at least 2 of the subscales In 66.6% at 12 mo	3 mo GES, 12 mo clinical	3 symptomatic capnoperitoneum, 1 mucosotomy; 1 thermal mucosal injury	Vosoughi 2021, Ref. 173
9	5 PSG, 2 DG, 1 IG, and 1 PSG and diabetic		Mean GSCI decreased from 3.16 to 0.86 (3 mo), 0.74 (6 mo), 1.07 (12 mo) and 1.31 (24 mo [ns]) after the procedure. GIQLI improved from baseline at 12 mo; not significant at 24 mo	Median follow-up was 23 (range 12–31) mo	1 delayed bleeding from gastric ulcer	Hustak 2020, Ref. 174

Table 10. (*continued*)

No. of patients	Types of GP patients	Changes in GE	Changes in symptoms	Duration follow-up	Adverse events	Ref. No.
76	GP with median duration 48 mo; median gastric retention at 4 h 45% and median GCSI 3.6	High rate of gastric retention at 4 h was significantly associated with clinical failure	Clinical success in 65.8% of patients at 1 yr, with median of reduction in GCSI score of 41%; high preop GCSI satiety score predicted clinical success	At least 1 y		Ragi 2021, Ref. 175
SRMA	14 studies with total 276 patients	Pooled GE scintigraphy normalization rate was 61.3% (95% CI, 51.5%–70.8%)	Clinical symptom improvement rate was 88.2% (95% CI, 83.6%–93.1%). Mean GCSI score improvement rate: 90.2% at 1 mo, 83.3% at 3 mo, 70.3% at 6 mo, 52.4% at 12 mo, and 57.1% at 18 mo.	Up to 18 mo	Intraoperative complications were found in about 3.2% and postoperative adverse events in 2.1%	Zhang 2019, Ref. 176
SRMA	6 studies	GE scintigraphy not improved	Improvement in GCSI score after 3 mo of G-POEM as compared with pre–G-POEM GCSI scores.	3 mo	Pooled rate of total adverse events was 9% (95% C.I. 2.7–25.9).	Garg 2020, Ref. 177
SRMA	272 patients in 8 studies	The pooled results of 4-h GE scintigraphy were 41.89% (95% CI, 32.75%–51.03%) pre–G-POEM and 16.48% (95% CI, 9.83%–23.14%) post–G-POEM	Pooled rates of GCSI were 3.25 (95% CI, 2.75–3.75) preprocedure, 1.80 (95% CI, 1.10–2.49) at 1–3 mo, 1.56 (95% CI, 0.45–2.68) at 6 mo, and 1.10 (95% CI, 0.75–1.45) at 12 mo	1, 3, 6, and 12 mo	Pooled adverse events rate was 12% 95% CI, 6%–19%	Li 2021, Ref. 178
SRMA	10 studies, 292 patients	GE scintigraphy, significant decrease of the residual percentage at 2 and 4 h	Significant symptomatic improvement was achieved after 83.9% of procedures	Mean follow-up, 7.8 ± 5.5 mo).	The overall adverse event rate was 6.8%.	Spadaccini 2020, Ref. 179
Laparoscopic pyloroplasty compared with G-POEM procedure						
60	Retrospective comparison lap pyloroplasty (LP) vs G-POEM, single-center, 30 per group (19 IG, 6 PSG, 5 DG), matched by propensity scoring	LP and G-POEM both resulted in similar, significant improvements in GCSI scores (overall and each of 3 subscales) with no differences between treatment groups	LP and G-POEM both resulted in similar, significant improvements in objective GE with no differences between treatment groups	1-mo outcome (28 G-POEM, 22 LP) 3-mo outcome (25 G-POEM, 21 LP)	Longer length of stay, operative time, more estimated blood loss, and complications in the LP group (surgical site infection, pneumonia, and unplanned ICU admission	Landreneau 2019, Ref. 180
SRMA	G-POEM (332 in 11 studies) vs surgical pyloroplasty (375 in 7 studies	4-h GE scintigraphy success results: G-POEM 85.1% (95% CI 68.9–93.7) and surgical pyloroplasty 84% (95% CI 64.4–93.8) with no significant difference	Clinical success, based on the GCSI score: G-POEM 75.8% (95% CI 68.1–82.1) and surgical pyloroplasty 77.3% (95% CI 66.4–85.4), with no significant difference		Overall adverse events were comparable	Mohan 2020, Ref. 181

DG, diabetic gastroparesis; GCSI, Gastroparesis Cardinal Symptom Index; GE, gastric emptying; GIQLI, Gastrointestinal Quality of Life Index; GP, gastroparesis; IG, idiopathic gastroparesis; LP, laparoscopic pyloroplasty; PSG, postsurgical gastroparesis; QOL, quality of life; SRMA, systematic review and meta-analysis; TSS, total symptom score; XO, crossover.

Potential competing interest: MC: single-center research studies: Allergan, Takeda, and Vanda; consulting with compensation to his employer: Takeda and Alpha Sigma Wasserman. TA: investigator: Censa, Cindome, Vanda, Allergan, and Neurogastrix; consultant: Censa, Nuvaira, Takeda, and Medtronic; speaker: Takeda and Medtronic; reviewer: UpToDate; writer: Med Study; editorial:

Neuromodulation, Wikistim; ADEPT-GI: IP for autonomic/enteric diagnosis and therapies. BK: clinical trials with Takeda, Vanda, and Alpha Sigma Wasserman, GSK; consulting with Takeda, Cindome, and Neurogastrix; speaking for Medtronic. LN: investigator: Allergan and Vanda; consultant: AbbVie, Ironwood, Alnylam, Eli Lilly, Evoke, Gemelli, Neurogastrx, Pendulum, Phathom, RosVivo, Salix, and Takeda. Scientific advisory board: Gemelli and RosVivo. VMV: nothing to disclose. JP: nothing to disclose. KG: nothing to disclose. RY: consultant through institutional agreement: Medtronic, Ironwood Pharmaceuticals, Diversatek, and StatLinkMD; research support: Ironwood Pharmaceuticals; advisory board: Phathom Pharmaceuticals; RJS Mediagnostix.

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