

GUIDELINES

AGA Clinical Practice Guideline on Management of Gastroparesis



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BACKGROUND & AIMS: Gastroparesis is a complex gastric motility disorder characterized by nausea, vomiting, and other symptoms associated with a delay in gastric emptying in the absence of mechanical obstruction. Variations in diagnostic testing and limited effective treatments make caring for this patient population challenging. The American Gastroenterological Association developed this guideline to provide recommendations for ensuring an accurate diagnosis and identifying evidence-based, effective treatments among the available pharmacologic and procedural interventions for patients with idiopathic gastroparesis or gastroparesis related to diabetes. **METHODS:** The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess evidence and develop this guideline. The Guideline Panel prioritized clinical questions and outcomes, conducted an evidence review, and used the Evidence to Decision Framework to develop recommendations. **RESULTS:** The Guideline Panel agreed on 12 recommendations. A conditional recommendation was issued against using 2-hour gastric emptying testing and in favor of 4-hour testing in patients with suspected gastroparesis. There are conditional recommendations for the use of metoclopramide and erythromycin in patients with gastroparesis. Conditional recommendations were issued against the use of domperidone, prucalopride, aprepitant, nortriptyline, buspirone, and cannabidiol as first-line therapies. In addition, conditional recommendations were issued against the routine initial use of gastric per-oral endoscopic pyloromyotomy or gastric electrical stimulation in patients with gastroparesis, reserving these treatments for select patients with symptoms refractory to medical therapies. No recommendation was given regarding the use of surgical pyloromyotomy and surgical pyloroplasty, which were identified as procedures with knowledge gaps in their use for treatment for gastroparesis. **CONCLUSIONS:** The diagnosis of gastroparesis requires the use of 4-hour gastric emptying tests. Metoclopramide or erythromycin is appropriate for initial pharmacologic treatment. Other treatment recommendations require shared patient-physician decision making. There are still considerable unmet needs in the treatment of gastroparesis.

Keywords: Prokinetic; Antiemetic; Neuromodulator; Endoscopic Myotomy; Pyloroplasty.

Executive Summary

Description of the Health Problem

Gastroparesis is a disorder of gastric motility defined by a measurable delay in gastric emptying associated with a constellation of upper gastrointestinal (GI) symptoms in the absence of mechanical obstruction. Variations in diagnostic testing strategies have made diagnosis and effective treatment challenging, and differentiating gastroparesis from other etiologies, such as functional dyspepsia associated with normal gastric emptying, as the source of upper GI symptoms on a 4-hour test can be difficult. Despite diagnostic challenges, symptoms suggestive of gastroparesis are highly prevalent, and patients with gastroparesis incur significant direct and indirect health care costs, as well as a reduction in quality of life.¹ To date, there is only 1 treatment approved by the US Food and Drug Administration (FDA) for gastroparesis (ie, metoclopramide), but newer medical and procedural approaches to this condition have been tested or are emerging. An

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Abbreviations used in this paper: AGA, American Gastroenterological Association; BTI, botulinum toxin injection; CBD, cannabidiol; CIC, chronic idiopathic constipation; CoE, certainty of evidence; ECG, electrocardiogram; EndoFLIP, endoluminal functional lumen imaging probe; FDA, US Food and Drug Administration; GCSI-DD, Gastroparesis Cardinal Symptom Index-Daily Diary; GES, gastric electrical stimulation; GI, gastrointestinal; G-POEM, gastric per oral endoscopic myotomy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IND, investigation new drug; MID, minimally important difference; PICO, population, intervention, comparator, and outcome; RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference; TCH, tetrahydrocannabinol.

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objective assessment of the available evidence of tested treatments is to be provided in this guideline.

Aims and Objectives of the Guideline

The purpose of these recommendations is to provide evidence-based guidance for patients with suspected and confirmed gastroparesis, mainly idiopathic and diabetes-related gastroparesis, including gastroparesis refractory to medical therapies based on a systematic and comprehensive synthesis of the literature. In addition, the document provides areas where further evidence is needed.

This guideline document recommendations are intended to appraise the benefits of the available therapies, including the improvement in the cardinal symptoms of nausea, vomiting, early satiety, and postprandial fullness, in addition to quality of life, while minimizing the potential adverse effects. The recommendations also account for the feasibility of the available interventions.

Target Audience

Although the Guideline Panel is aware that this Guideline and its recommendations will be read by a wide audience, including policy makers and industry, who are not its primary audience. This guideline, like all American Gastroenterological Association (AGA) guidelines, is primarily targeted toward health care providers in the field of gastroenterology and primary care who depend on such evidence-based, expert recommendations to inform their clinical practice and shared decision making with patients. We intend these recommendations to be used by clinicians to guide the management of patients and inform considerations of benefits and harms of treatments in each individual case, rather than providing a specific standard to adhere to. In this way, the guideline and its recommendations are intended to contribute to the improved delivery and management of GI health care services. We do not intend for policy makers and insurance companies to use the recommendations in this document for determining treatment coverage.

Recommendations

The list of Guideline Recommendations is provided in [Table 1](#). This guideline should be read in conjunction with the [Supplementary Material](#), which contains additional tables, figures, and other supporting material. In addition to the Clinical Decision Support Tool ([Figure 1](#)), clinicians may also find the Guideline Spotlight a helpful tool to inform their patient management and other decision making.

Guideline Development Procedures

Overview

This document represents the official recommendations of the AGA and was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.³ It adheres to best practices in guideline development as outlined by the National

Academy of Medicine (formerly Institute of Medicine), using a process outlined previously.³

Organization and Panel Composition

The Guideline Panel included 8 members ([Supplementary Table 1](#)), all selected on the basis of their specific expertise. There were 6 clinical/content experts with clinical and/or research expertise in gastroparesis and 2 methodologists with specialized GRADE guideline development skills. A librarian assisted the panel members with designing and executing the required literature searches. All panel members participated in evidence review and the senior methodologist oversaw the evidence synthesis. All members of the Guideline Committee helped review the synthesized evidence, contributed to discussion, and helped develop the recommendations and Clinical Decision Support Tool ([Figure 1](#)).

Document Review

The guideline underwent several levels of review, including an open, 30-day public comment period, external peer review by known topic experts, and patient review. Organizational-level review was carried out by the AGA Institute's Clinical Guidelines Committee and Governing Board. At each stage, the Guideline Panel considered all reviewer comments and feedback and revised the guideline to address feedback as needed.

Guideline Updates

Guidelines are living products. To remain useful, they need to be updated as new information accumulates. This document will be updated when major new research is published. The need for update will be determined by the authors and AGA Clinical Guidelines Committee.

Methods

Scope

Gastroparesis is a disorder of gastric motility defined by a measurable delay in gastric emptying in the absence of mechanical obstruction and is associated with a constellation of upper GI symptoms. Cardinal symptoms include nausea and vomiting, which may be accompanied by other symptoms, such as early satiety, postprandial fullness, abdominal pain, and bloating.⁴ Because of differences in testing methodology, in combination with the pervasiveness of upper GI symptoms among patients with other conditions, such as functional dyspepsia, making an accurate diagnosis of gastroparesis and identifying successful treatment strategies has been heretofore challenging.⁵ To date, there is only 1 FDA-approved agent for the treatment of gastroparesis (ie, metoclopramide) and many agents in the pipeline have failed to show meaningful benefit over placebo.⁶ New procedural approaches—including gastric per oral endoscopic myotomy (G-POEM)—are nonetheless emerging alongside the existing pharmacologic treatments. Despite diagnostic challenges, gastroparesis has a high prevalence, estimated to be between 21.5 and 24.2 cases per 100,000 people, with a disproportionate impact on women

Table 1. Summary of Recommendations and Implementation Considerations

Recommendation	Strength	CoE
1. In individuals with suspected gastroparesis, the AGA suggests against the use of a 2-hour (or shorter) gastric emptying study compared with a 4-hour gastric emptying study to evaluate for delayed gastric emptying. Implementation Considerations - It is important to rule out alternative and possibly coexisting causes of symptoms before considering the diagnosis of gastroparesis, especially when abdominal pain is the predominant symptom. - By performing a 4-hour study in all cases, some patients with normal emptying at 2 hours may get reclassified as delayed at 4 hours. - GES is optimally done without confounders that could affect gastric emptying, including hyperglycemia and medications that alter gastric emptying (eg, opioids, glucagon-like peptide-1 receptor agonists, and prokinetics). - The 4-hour gastric emptying should be measured directly at 4 hours to maximize accuracy and not mathematically extrapolated from earlier time points to maximize accuracy. - The 4-hour threshold applies to both scintigraphy and breath test gastric emptying studies. There are different meals used to measure gastric emptying over a 4-hour period with well-established normal values: the Eggbeaters (Post Holdings) meal consisting of liquid egg white with bread, jam, and water (250 kcal, 2% fat) used for scintigraphy; the real eggs meal consisting of 2 whole eggs, bread, and skim milk (320 kcal, 30% fat) used for scintigraphy; and the ¹³C-spirulina meal consisting of 27 g of rehydrated pasteurized scrambled egg mix with 6 saltine crackers and water (230 kcal, 30% fat) used for the stable isotope breath test. The Eggbeaters meal is the most commonly used meal for scintigraphy. The real eggs meal has been more thoroughly validated to date. General Considerations for Implementing the Treatment Recommendations in Clinical Practice - It is important to optimize glycemic control in individuals with gastroparesis in the setting of diabetes mellitus. - It is important to review the patient's current medications to eliminate medications that may alter GI tract motility; medications that can delay gastric emptying include opiate pain medications and the glucagon-like peptide-1 receptor agonists for diabetes management and weight loss. One should be cognizant of potential drug-drug interactions when considering pharmacologic interventions. - It is important to consider potential coexisting conditions that may contribute to symptoms when treating individuals with gastroparesis. - The Guideline Panel Content Experts use dietary interventions with small-particle and low-fat, low-residue diets before initiation of pharmacologic interventions or as a concomitant intervention.² - Patients with gastroparesis may need to use antiemetics as needed, including selective serotonin receptor (5HT₃) antagonists (eg, ondansetron and granisetron), histamine H1 antagonists (eg, promethazine), and/or dopamine D2 antagonists (eg, prochlorperazine). These reduce nausea and vomiting without affecting gastric emptying. - In clinical practice, the Guideline Panel Content Experts assess the efficacy and tolerance of pharmacologic interventions at 4–8 weeks to decide whether the treatment should be continued or adjusted. - The recommendations in this document are based on a comparison with no intervention.	Conditional	Low
2. In individuals with gastroparesis, the AGA suggests using metoclopramide. Comment: As part of shared decision making, patients who place a higher value on the potential risk of adverse events and lower value on the symptomatic improvement may reasonably select not to use metoclopramide. Implementation Considerations - Potential adverse effects of metoclopramide should be discussed with patients before starting treatment. The FDA issued a black box warning regarding the risk of tardive dyskinesia. - Patients on psychotropic agents and older individuals may be at higher risk for adverse events leading to discontinuation, but the absolute risk is low, including the risk of tardive dyskinesia. - Typical dosing using the oral (tablet or liquid) formulation starts with 5 mg before meals, which can be increased up to 10 mg before meals. For intranasal metoclopramide, the dose is 15 mg before meals and at bedtime. - There are different practices that aim to improve tolerability of treatment, including starting at low dose and using 1–4 weeks drug holidays every 8–12 weeks. - Medication efficacy and adverse effects, including movement disorders, are usually assessed at 4–8 weeks to decide whether the treatment should be continued. Efficacy and adverse effects are then monitored for the duration that a patient is receiving metoclopramide.	Conditional	Low

Table 1. Continued

Recommendation	Strength	CoE
3. In individuals with gastroparesis, the AGA suggests using erythromycin. Implementation Considerations - Erythromycin is thought to improve symptoms of gastroparesis due to its gastric prokinetic effects rather than by a direct antiemetic effect. - The effect of erythromycin on symptoms and gastric motility is through its motilin receptor agonist properties and is unrelated to its antibiotic properties. - Low doses (eg, 40–150 mg by mouth, 30 minutes before meals) are used to reduce potential adverse effects seen with higher doses (250–500 mg). - Because erythromycin tablets are only available in high doses, using erythromycin ethylsuccinate oral suspension allows the administration of smaller, better tolerated doses. - Tachyphylaxis often develops with prolonged, continuous use of erythromycin; in practice, efficacy is maintained using drug holidays (eg, 3 weeks on therapy, 1 week off therapy). - Safety concerns with erythromycin include development of antibiotic resistance (with long-term use), drug interactions (it is a CYP3A isoform inhibitor), and QT-prolongation. - Azithromycin has been used as a substitute for erythromycin in practice, with many of the same safety considerations, such as antibiotic resistance also applying.	Conditional	Very low
4. In individuals with gastroparesis, the AGA suggests against use of domperidone as a first-line treatment. Comment: As part of shared decision making, patients who place a higher value on the potential improvement in nausea, vomiting, and early satiety and lower value on the potential adverse events may reasonably select to use domperidone, when available. Implementation Considerations - Domperidone may be especially helpful for patients with gastroparesis who had neurologic adverse effects with metoclopramide; for patients with neurologic movement disorders, such as Parkinson's disease; and for patients declining use of metoclopramide due to concerns of its adverse effects. - Domperidone is not approved by the FDA in the United States for human use. The prescription of domperidone requires an expanded access use investigational new drug (IND) application from the FDA. The current supplier for domperidone for the FDA IND in the United States at the time of writing is exiting the business and will no longer supply the medication, based on information available from the FDA. - Before starting treatment with domperidone, patients should have blood work for serum potassium and magnesium and undergo an ECG at baseline for measurement of the QTc interval. - The Guideline Panel Content Experts usually assess the efficacy of domperidone at 4–8 weeks to decide whether the treatment should be continued. Serum potassium, magnesium, and ECG QTc interval are monitored while a patient is treated with domperidone.	Conditional	Very low
5. In individuals with gastroparesis, the AGA suggests against the use of prucalopride as a first-line treatment. Comment: As part of shared decision making, patients who place a higher value on the potential improvement in symptoms and a lower value on the potential risk of adverse effects may reasonably elect to use prucalopride, particularly if they have idiopathic gastroparesis. Implementation Considerations - Patients with gastroparesis and CIC may reasonably elect to use prucalopride for efficiency of care given prucalopride's established efficacy for CIC. - Patients with gastroparesis attributed to diabetes or connective tissue diseases may be less likely to respond to prucalopride treatment than patients with idiopathic gastroparesis. - The mechanism of action for prucalopride is purely prokinetic as a 5HT₄ receptor agonist, without any direct antiemetic effects. - Prescribers recommending prucalopride should note the warning to monitor patients for small potential risk of depression and suicidal thoughts and behavior when considering use of prucalopride.	Conditional	Very low

Table 1. Continued

Recommendation	Strength	CoE
6. In individuals with gastroparesis, the AGA suggests against the use of aprepitant as a first-line treatment. Comment: As part of shared decision making, patients who place a higher value on the potential improvement in nausea and vomiting and lower value on the potential adverse effects may reasonably elect to use aprepitant. Implementation Considerations • Aprepitant, a neurokinin-1 receptor antagonist, is an antiemetic approved for chemotherapy-induced vomiting, but has no effect on gastric motor function. • Aprepitant may be helpful in patients with gastroparesis and nausea/vomiting in whom 5HT₃ receptor antagonists, such as ondansetron, and other antiemetics are not helpful.	Conditional	Low
7.1. In patients with gastroparesis, the AGA suggests against the use of nortriptyline as a first-line treatment. Comment: As part of shared decision making, patients who place a higher value on the potential improvement in early satiety, postprandial fullness, abdominal pain, and quality of life and lower value on the potential adverse effects may reasonably elect to use nortriptyline. Implementation Considerations • Patients with overlapping irritable bowel syndrome, functional dyspepsia (epigastric pain syndrome), or significant abdominal pain associated with gastroparesis may benefit from the use of tricyclic antidepressants such as nortriptyline. • When using tricyclic antidepressants in patients with gastroparesis, the Panel members use agents with fewer anticholinergic effects, such as nortriptyline, and start at low doses and increase slowly to ensure tolerance. • The Guideline Panel Content Experts inform patients being started on nortriptyline that this agent is in the class of antidepressants, however, in gastroparesis, it is being used as a peripheral neuro-modulator to reduce afferent sensory transmission to the central nervous system.	Conditional	Low
7.2. In patients with gastroparesis, the AGA suggests against the use of buspirone as a first-line treatment. Comment: As part of shared decision making, patients who place a higher value on the potential improvement in early satiety, postprandial fullness, and bloating may reasonably elect to use buspirone. Implementation Considerations • Use of buspirone may be helpful in patients with gastroparesis and predominant early satiety and bloating.	Conditional	Very low
8. In individuals with gastroparesis, the AGA suggests against the use of cannabidiol (CBD) except in the context of a clinical trial. Implementation Considerations • The single study demonstrating efficacy for CBD in gastroparesis used a pharmaceutical grade CBD (Epidiolex, Jazz Pharmaceuticals) that is approved to treat seizures due to Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years and older, and the medication is not available for clinical use in gastroparesis. • Available CBD formulations are not regulated, with varying potencies that make their impact on patients with gastroparesis unknown. • Among CBD formulations that include THC, there is concern about increased risk of CBD hyperemesis syndrome.	Conditional	Low

Table 1. Continued

Recommendation	Strength	CoE
General Considerations for Implementing the Treatment Recommendations for Refractory Gastroparesis in Clinical Practice - A patient is considered to have gastroparesis refractory to medical therapy if they have cardinal symptoms of gastroparesis (ie, nausea, vomiting, postprandial fullness, and/or early satiety) as the predominant symptoms in addition to evidence of delayed gastric emptying with no alternative explanation for the symptoms, and have failed at least 2 medical treatments including prokinetic and antiemetic agents. - In patients with gastroparesis refractory to medical therapy, it is important to ascertain the accuracy of the diagnosis and to evaluate for coexisting conditions that may be causing or contributing to the severity of the predominant symptoms. - The management of gastroparesis that is refractory to medical therapy requires a multidisciplinary approach that optimally involves the primary care provider, a gastroenterologist, and a registered dietitian, in addition to an endocrinologist in patients with diabetes. In select cases, this might also involve an interventional endoscopist and a foregut surgeon. - It is important to evaluate the nutritional status of patients with gastroparesis refractory to medical therapy and to provide nutritional support, preferably orally as tolerated by the patient, or if necessary, using enteral nutrition; parenteral nutrition is rarely used as it carries risk of serious complications like infections and blood clots.		
9. In patients with gastroparesis refractory to medical management, the AGA suggests against the routine use of pyloric botulinum toxin injection (BTI). Comment: As part of shared decision making, patients and clinicians who place a higher value on endoscopic treatment and lower value on chronic medical therapy may reasonably attempt treatment with BTI. Implementation Considerations - The Guideline Panel intended to evaluate the use of BTI in patients with refractory gastroparesis. However, the published clinical trials were not specific to refractory gastroparesis. - The need for retreatment as often as every 3 months could limit implementation from both a cost-effectiveness perspective and concern for diminishing clinical effect. - Repeat treatment may predispose to pyloric scarring, which could complicate attempts at other interventions, such as G-POEM.	Conditional	Very low
10. In patients with gastroparesis refractory to medical therapy, the AGA suggests against the routine use of gastric peroral endoscopic pyloromyotomy (G-POEM). Comment: As part of shared decision making, patients and clinicians who place a higher value on the potential improvement in symptoms and lower value on the potential risk of adverse events may reasonably select to undergo G-POEM procedure. Implementation Considerations - This procedure should be reserved for select patients with medically refractory gastroparesis. - Candidates for G-POEM should have had a diagnosis of gastroparesis with an appropriately done, 4-hour gastric emptying study, generally with at least a moderate delay in gastric emptying (20% retention at 4 hours with the Eggbeaters meal). - Candidates for G-POEM should have at least 6–12 months of moderate symptoms with the cardinal symptoms of nausea, vomiting, and/or postprandial fullness. - Before consideration of G-POEM, patients with gastroparesis should undergo a trial of other treatments for gastroparesis, including prokinetic agents and antiemetic agents.	Conditional	Low
11. In patients with gastroparesis refractory to medical therapy, the AGA makes no recommendation regarding the use of surgical pyloric interventions (pyloromyotomy or pyloroplasty).	None	Knowledge gap
12. In patients with gastroparesis refractory to medical therapy, the AGA suggests against the routine use of gastric electrical stimulation (GES). Comment: As part of shared decision making, patients and clinicians who place a higher value on the potential improvement in nausea and vomiting and lower value on the potential risk of adverse events may reasonably select to have GES placement. Implementation Considerations - This procedure should be reserved for select patients with medically refractory gastroparesis. - When used, patients should be informed that GES aims to primarily improve nausea and vomiting, not abdominal pain.	Conditional	Very low

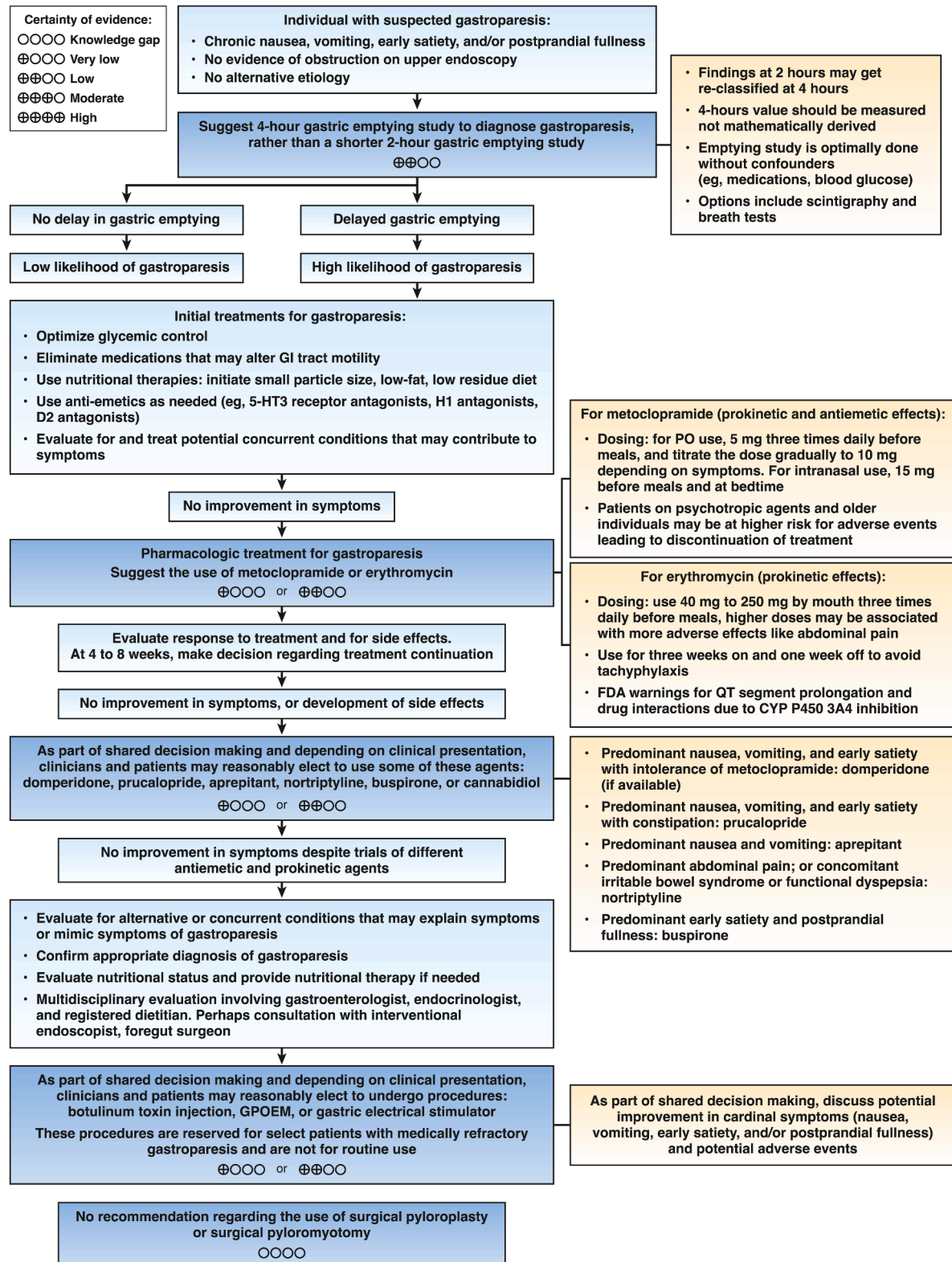


Figure 1. Clinical Decision Support Tool. Summary of the recommendations and implementation considerations for evaluating and treating patients with suspected gastroparesis.

(75% of cases).⁷ There appears to be an increased risk of mortality in gastroparesis as well, seemingly driven by the subset of patients with diabetes-associated gastroparesis and related to complications of diabetes.⁷ Patients with gastroparesis represent a considerable burden on the health care system, with more than 140,000 outpatient visits yearly in the United States and a rising number of hospitalizations.⁷⁻⁹ Furthermore, patients with gastroparesis also have decreased quality of life and higher rates of comorbid anxiety, depression, and somatization.¹⁰ People with gastroparesis are more likely to identify as disabled, to be unemployed, and to have reduced working hours.⁴ Amidst diagnostic uncertainty and substantial societal burden, the Guidelines Panel focused its review and research questions on ensuring an accurate diagnosis of gastroparesis and identifying evidence-based, effective treatments among the vast landscape of pharmacologic and procedural interventions spanning more than 40 years of research.

Formulation of Clinical Questions

The clinical questions which underpin this Guideline were developed by the Guideline Panel, with methodologists and clinical content experts working together to develop specific questions to address current knowledge gaps in this area. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcomes for each clinical question. The list of PICO questions is presented in [Supplementary Table 3](#).

There were multiple clinical questions that were considered for PICO questions but were not prioritized by the panel for inclusion in this document, and a comprehensive literature evaluation was not performed for them. For the diagnosis of gastroparesis, the panel gave priority to determining the appropriate duration of the gastric emptying test in patients with a native (unoperated) stomach. Additional questions that were considered but not prioritized include defining the thresholds used to diagnose delayed and rapid gastric emptying, differences between the meals used in gastric emptying studies, and differences between scintigraphy-based and breath test-based gastric emptying studies. In addition, the role of other diagnostic modalities, such as gastric ultrasound, endoluminal functional lumen imaging probe (Endo-FLIP), body surface gastric mapping, tests of gastric accommodation, and whole gut motility testing were considered out of the scope of this document. For the treatment of gastroparesis, the panel considered but did not investigate the following interventions: glycemic control, nutritional therapy and support, acetylcholinesterase inhibitors (eg, pyridostigmine), direct-acting cholinergic (muscarinic) agonists (eg, bethanechol), common antiemetics (5HT₃ receptor antagonists like ondansetron and granisetron, histamine H1 antagonists like promethazine, dopamine D2 antagonists like prochlorperazine), and gastric surgical procedures (eg, gastric bypass surgery and sleeve gastrectomy). When some of these questions were relevant to contextualize the recommendations, they were addressed in the implementation considerations and comments. However, they were not prioritized as PICO questions and, hence, the panel did not undertake a comprehensive literature evaluation for them.

The panel selected desirable and undesirable patient-important outcomes (ie, benefits and harms). Critical and important outcomes for decision making for all the

interventions included in this review are summarized in the evidence profiles (see Certainty of the Evidence section). The panel used the rating of the Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD) composite score and its subscales when evaluating the effect of treatment on symptoms. The scale rates the symptoms as none (0), mild (1), moderate (2), severe (3), and very severe (4) on the worst severity of the symptom over the last 24 hours.

Definition of Minimum Clinically Important Difference

The panel defined the thresholds for minimally important difference (MID) *a priori* to guide the interpretation of continuous outcomes and the certainty of evidence (CoE) assessment. The MID is the smallest difference in scores on a patient-reported outcome measure that is perceived by patients as beneficial or harmful and would lead a clinician to consider a change in treatment.¹¹ When evaluating continuous outcomes, the MID is used as an anchor to determine clinical importance of the effect estimate for the change in score. If the effect estimate exceeds the MID, the change is considered clinically important; if it falls below, the change is considered trivial. The thresholds reported by Revicki et al¹² were used after rescaling the original 0–5 scale to a 0–4 range. The MIDs used were 0.44 for nausea and vomiting, 0.62 for early satiety and postprandial fullness, 0.24 for abdominal pain, and 0.58 for the GCSI-DD total score.¹³

After the literature review was conducted and the results appraising MID in the trials evaluated were completed, a new validation study proposed a 1-point change on a 0–4 scale as a meaningful symptom change threshold when using the GCSI-DD.¹⁴ However, the latter patient response outcome had not been used in the vast majority of prior studies, and when it was used, it was not the primary end point anyway (eg, in tradipitant trials).¹⁵

Search Strategy

The systematic review process was guided by a search protocol developed *a priori* by the Guideline Panel members in collaboration with the medical librarian. The librarian conducted a comprehensive search of the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from inception to April 8, 2025, using a combination of controlled vocabulary terms supplemented with keywords. The search was limited to English language and human adults. The final strategy is available in [Supplementary Table 4](#). The bibliography of prior guidelines and the included references were searched to identify relevant studies that may have been missed. In addition, content experts helped identify any ongoing studies. To ensure that the guideline document is up to date with recent studies, the literature was searched periodically up to April 8, 2025.

Study Selection, Data Collection, and Analysis

The inclusion and exclusion criteria were based on the PICO questions developed by the Guideline Panel ([Supplementary Table 3](#)). Searches from all the databases were combined in bibliographic software, duplicates were removed,

then the references were uploaded to Covidence software for systematic reviews.¹⁶

For the diagnostic question comparing 4-hour with 2-hour gastric emptying tests, we aimed to identify randomized controlled trials (RCTs) that compared the outcomes of interventions based on those tests. As we were unable to identify any such trial, we then relied on studies reporting the diagnostic test characteristics of gastric emptying studies as measured by sensitivity, specificity, and positive and negative predictive values.

For the therapeutic interventions, we aimed to identify RCTs that compared the interventions of interest with placebo, sham intervention, or no intervention. For the pharmacologic interventions with no identified RCT, we did not address the agent of interest (eg, mirtazapine, desipramine, and amitriptyline). For the procedural and surgical interventions, we anticipated absence of RCTs for some of the PICO questions and aimed to identify comparative observational studies for those interventions.

One clinical content expert and 1 methodologist screened each reference and conducted a full-text review of the eligible studies (Supplementary Figure 1). Any conflicts were resolved with adjudication by consensus.

Data were extracted from each study, including study characteristics, such as year of publication, study site, study population, intervention, comparison group, outcomes, and methods for risk-of-bias assessment. Data from the included studies was extracted by 2 panel members independently. If an RCT had multiple arms, the panel combined groups so that the only difference between the intervention and control group was the intervention of interest. For cross-over trials, we used data that combined both periods and considered the impact of the washout period in the risk-of-bias assessment. When the numeric values were not reported in the text, we extracted the data presented in plots (eg, box and whisker plots) using a plot digitizer.¹⁷ If an abstract of an unpublished clinical trial was identified, we tried to contact the authors for additional data. We also tried to contact the corresponding authors of published studies as needed to request additional data (eg, data on individual symptoms).

Risk of bias was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials, including for parallel and crossover trials; the Risk of Bias in Non-Randomized Studies of Interventions tool for nonrandomized studies; and QUADAS-2 tool for diagnostic accuracy studies.^{18–20} The risk-of-bias assessment for each study was performed by both the senior and junior methodologists separately and in a blinded manner, and disagreements were resolved by discussion. The *robvis* visualization tool was used to produce the traffic light plots.²¹

Meta-analyses were conducted when more than 1 study contributed data for the same intervention and outcome. Dichotomous outcomes were pooled to obtain a relative risk (RR) and continuous outcomes were pooled to obtain a mean difference with 95% CI. If different scales were used by the different studies, we scaled them to be consistent with GCSI-DD (0–4 scale). When the studies used scales other than or different from the GCSI-DD and GCSI, we conducted sensitivity analyses using standardized mean difference (SMD) to assess the robustness of the findings. To contextualize the SMDs, we standardized the MID reported by Revicki et al¹² using the SDs from their study.¹³ For the meta-analyses, the generic inverse-variance method of weighting was used and the random-

effects model applied using the restricted maximum-likelihood estimator to estimate between study variance. However, if the number of studies was too small (fewer than 4) to estimate the between-study variance, a fixed-effect model was used. The Guideline Panel assessed the statistical heterogeneity using the I^2 statistic. When a sufficient number of studies was presented with no substantial heterogeneity ($I^2 < 50\%$), we planned to assess for publication bias using funnel plot asymmetry tests.²² When we did not identify trials comparing an intervention with placebo or no intervention, but we did identify trials that compared an intervention with another intervention, we conducted a network meta-analysis using a random-effects model to estimate the effect of the intervention relative to placebo via the indirect comparison. For the diagnostic accuracy studies, the accuracy estimates from the studies were pooled using the logit transformation and the bivariate random-effects model.

The panel used the packages *meta* (version 7.0-0), *net-meta* (version 2.9-0), and *mada* (version 0.5.11) in R, version 4.4.1 to conduct the statistical analyses.^{23–26}

Certainty of the Evidence

The Guideline Panel used the GRADE approach to assess the CoE for the effect of the intervention on each outcome using the GradePro Guideline Development Tool software (Evidence Prime; <https://gradepro.org>). The GRADE approach considers factors such as study design, population studied, risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias to rate the CoE as high, moderate, low, or very low (Supplementary Table 5). The results of certainty assessment are reported with each recommendation.

Development of Recommendations

The process of translation of evidence into guideline recommendations followed the GRADE Evidence to Decision framework and was achieved by means of discussion during virtual meetings of the Guideline Committee. The Evidence to Decision framework considers the CoE, balance of benefits and harms, patient values and preferences, feasibility, acceptability, and equity. Evidence-to-Decision tables are presented for each recommendation. The panel did not explicitly incorporate cost or cost-effectiveness. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications.

The interpretation of strength of recommendations is summarized in Table 2. The CoE and the strength of recommendation are provided for each clinical question. As per GRADE methodology, recommendations are labeled as “strong” or “conditional.” The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. A conditional recommendation against an intervention should be interpreted as indicating that although most individuals in the described situation would not benefit from the intervention, many might still benefit. Therefore, shared decision making is essential to ensure that the chosen approach reflects each patient’s values, preferences, and individual risk profile.

A systematic search for studies on health equity and disparities was performed using the MEDLINE/PubMed Health Disparities and Minority Health Search Strategy filter (Supplementary Table 4), and the identified references were reviewed and summarized when identified.

Recommendations

Question 1: Should 2-hour vs 4-hour gastric emptying studies be used to diagnose gastroparesis?

Recommendation 1: In individuals with suspected gastroparesis, the AGA suggests against the use of a 2-hour (or shorter) gastric emptying study compared with a 4-hour gastric emptying study to evaluate for delayed gastric emptying. (*Conditional recommendation, low certainty of evidence*)

Implementation Considerations

- It is important to rule out alternative and possibly coexisting causes of symptoms before considering the diagnosis of gastroparesis, especially when abdominal pain is the predominant symptom.
- By performing a 4-hour study in all cases, some patients with normal emptying at 2 hours may get reclassified as delayed at 4 hours.
- Gastric electrical stimulation (GES) is optimally done without confounders that could affect gastric emptying, including hyperglycemia and medications that alter gastric emptying (eg, opioids, glucagon-like peptide-1 receptor agonists, and prokinetics).
- The 4-hour gastric emptying should be measured directly at 4 hours to maximize accuracy and not mathematically extrapolated from earlier time points to maximize accuracy.
- The 4-hour threshold applies to both scintigraphy and breath test gastric emptying studies.

There are different meals used to measure gastric emptying over a 4-hour period with well-established normal values: the Eggbeaters (Post Holdings) meal consisting of liquid egg white with bread, jam, and water (250 kcal, 2% fat) used for scintigraphy; the real eggs meal consisting of 2 whole eggs, bread, and skim milk (320 kcal, 30% fat) used for scintigraphy; and the ¹³C-spirulina meal consisting of 27 g of rehydrated pasteurized scrambled egg mix with 6 saltine crackers and water (230 kcal, 30% fat) used for the stable isotope breath test. The Eggbeaters meal is the most commonly used meal for scintigraphy. The real eggs meal has been more thoroughly validated to date.

Summary of the Evidence

We did not identify any RCT or comparative study that compared the impact of testing protocol on outcomes. Evidence informing the recommendation for the diagnosis of delayed gastric emptying was derived from cohort studies that reported the diagnostic test performance of a 2-hour gastric emptying study compared with a 4-hour gastric emptying study. We identified 8 studies that reported the results of gastric emptying studies evaluated at 2 hours and 4 hours ([Supplementary Table 6](#)).^{27–34} The studies included 4309 patients who underwent gastric emptying studies using solid meals radiolabeled with technetium-99m. We

did not identify studies that compared results of breath testing at 2 hours vs 4 hours. The indications for the gastric emptying studies varied and were not limited to patients with cardinal gastroparesis symptoms. The pooled sensitivity and specificity of 2-hour gastric emptying studies were 0.57 (95% CI, 0.51–0.62) and 0.94 (95% CI, 0.91–0.96), compared with 4-hour gastric emptying studies as reference standard. The studies were at high risk for bias, mainly due to patient selection ([Supplementary Table 7](#)). We also identified 2 prior systematic reviews that evaluated the association between gastric emptying with symptoms, and response to therapy supporting the 4-hour gastric emptying test over shorter test durations.^{35,36}

Benefits and Harms

Although a 2-hour test may be more convenient and could potentially decrease the cost of testing, it is associated with high rate of false-negative and false-positive results. The mean prevalence of gastroparesis in the included studies was approximately 30% and the pooled sensitivity of a 2-hour test was 0.57 (95% CI, 0.51–0.58) ([Supplementary Figure 2](#)); thus a 2-hour test may be associated with a 12% false-negative rate. Those patients will be assumed not to have gastroparesis and may continue to be symptomatic without appropriate treatment. They may also receive additional testing in an attempt to identify the cause of their symptoms. A 2-hour test had a pooled specificity of 0.94 (95% CI, 0.93–0.95) ([Supplementary Figure 3](#)), which correlates with 4% false-positive rate based on prevalence of 30% using the 4-hour result as the standard. Those patients will be assumed to have gastroparesis and may receive inappropriate medical therapy with potential for adverse events and ultimately may be considered refractory to treatment and receive surgical intervention in an attempt to alleviate symptoms. A systematic review that evaluated the association between upper GI symptoms and gastric emptying showed that using optimal gastric emptying test methods, defined as a study that appraises emptying of a solid meal for at least 3 hours, showed an association between gastric emptying and symptoms, compared with using suboptimal testing methods (eg, predominantly liquid meals or assessment of gastric emptying over more than 3 hours).³⁶ Another systematic review found that when gastric emptying is measured optimally with a solid meal over 3 or more hours, pharmacologic treatments that improved gastric emptying half-life by 26.8 minutes were associated with a clinical improvement in symptoms.³⁵

Certainty in Evidence of Effects

The overall certainty in the evidence across the critical outcomes and considering both benefits and harms was low. This certainty applies mainly to the diagnostic test accuracy, as we could not identify any study to compare the impact of different diagnostic approaches on patient important outcomes. The CoE was rated down due to

Table 2. Interpretation of Strong and Conditional Recommendations Using the GRADE Framework^a

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

^aStrong recommendations are indicated by statements that lead with “we recommend,” and conditional recommendations are indicated by statements that lead with “we suggest.”

concerns regarding serious risk of bias, as outlined above, and indirectness, as not all the included patients had suspected gastroparesis. The evidence profile and Evidence to Decision framework are presented in [Supplementary Tables 8 and 9](#).

Discussion

The gastric emptying test is usually performed with images obtained at 0, 1, 2, and 4 hours after meal ingestion to determine the amount remaining in the stomach at each time period. A 4-hour diagnostic test is time-consuming for patients and facilities and has increased costs related to the longer study requiring more personnel and facility time. Shortening the length of testing without sacrificing test accuracy would be beneficial to patients and health systems alike. A shortened test could improve access to testing for symptomatic patients, especially with scintigraphy. However, based on pooled results, the shortened test length would decrease the sensitivity of the study and may compromise specificity. Extending the time to 4 hours is important to detect cases with normal emptying at 2 hours, but delay at 4 hours. Testing for 4 hours increased the number of cases classified as gastroparesis by 25%.³⁰ In clinical practice, delayed gastric emptying at 2 hours with normal or borderline delay at 4 hours leads to a therapeutic trial for gastroparesis.

Presently, there are 2 types of meals that have well-defined normal values in scintigraphy. One is the Eggbeaters meal, which is a low-fat meal consisting of liquid egg white, 2 slices of toasted bread, jelly, and a cup of water.³⁷ A second meal is the real eggs meal, which is a higher caloric, higher-fat meal consisting of 2 eggs, toast, and a glass of skim milk.³⁸ Regardless of the test meal chosen for evaluation, all panel members agreed on the importance of a 4-hour study to ensure diagnostic accuracy.

The Eggbeaters meal with imaging at 0, 1, 2, and 4 hours is currently the most commonly used assessment of gastric

emptying nationwide. This low-fat, egg white meal was chosen to measure gastric emptying without confounding by hormonal release from fatty meals and uses store-bought ingredients for standardization across centers. The initial, multi-institutional study that developed the Eggbeaters meal protocol investigated 123 healthy subjects from 11 medical institutions in the United States, Canada, and Europe. Based on that study, using this method, delayed gastric emptying (increased gastric retention) was determined to be >90% at 1 hour, >60% at 2 hours, and >10% gastric retention at 4 hours.³⁷ In an observational study of 75 patients seen at 5 tertiary centers, moderate gastric retention of >20% at 4 hours using the Eggbeaters meal predicted which patients would respond to G-POEM in the treatment of medically refractory gastroparesis.³⁹ Reproducibility of the Eggbeaters meal in symptomatic patients has not been assessed. In a multicenter cohort assessing the disease course of patients with chronic upper GI symptoms receiving clinically indicated treatment, 42% of patients with an initial diagnosis of gastroparesis (defined as gastric retention >10% at 4 hours) using the Eggbeaters protocol were reclassified at 48 weeks as having functional dyspepsia with normal gastric emptying (defined as <10% retention at 4 hours) and 37% of patients with functional dyspepsia were reclassified as having gastroparesis in the same timeframe.⁴⁰

The real eggs meal with imaging at 0, 1, 2, and 4 hours has normative data based on 319 healthy controls from a single center.⁴¹ The normal values are <75% retained at 2 hours, <25% retained at 4 hours, and gastric emptying half-life <175 minutes. Data supporting its use emanate from 214 symptomatic patients, including those with functional dyspepsia, postfundoplication, rumination, and diabetes-associated dyspepsia, as well as 1287 patients with upper GI symptoms evaluated in clinical practice.^{42,43} In single-center cohorts of patients with dyspeptic symptoms and either baseline functional dyspepsia (normal

gastric emptying <25% retention at 4 hours) or gastroparesis (>25% retention at 4 hours), approximately 85% of the patients randomized to placebo retained their diagnosis on repeat testing performed between 3 days and 4 weeks later.⁴⁴ Results using the real eggs meal protocol also appear to be responsive to prokinetic medications in placebo-controlled clinical trials. Using the 5HT₄ receptor agonists feclisetrag in patients with gastroparesis and velusetrag in healthy controls, the investigators found significant changes in gastric emptying using the real eggs meal.^{45,46} The magnitude of these changes in gastric emptying in response to those prokinetics conforms with the threshold (reduction in gastric emptying half-life by 26 minutes) for clinically significant improvement in symptoms of gastroparesis in a meta-analysis that included patients assessed using multiple methods of gastric emptying measurement.³⁵ Therefore, this shows that the real eggs meal has been used to document responsiveness to pharmacologic agents.

The ¹³C-spirulina gastric emptying breath test uses a protein-rich, blue-green algae labeled with a stable (nonradioactive) isotope (¹³C) incorporated into a freeze-dried egg mix with 6 saltine crackers and 180 mL of water. ¹³C is only released from the algal cells after the egg mix is emptied from the stomach, releasing ¹³C-enriched CO₂ into the body's bicarbonate pool to be excreted by the lungs and measured over a 4-hour period.⁴⁷ In a study of 30 healthy controls and 15 patients with dyspepsia, the ¹³C-spirulina gastric emptying breath test demonstrated high reproducibility and excellent performance characteristics relative to 4-hour scintigraphy using the real eggs meal (3%–4% different).⁴⁸ The test appears to be responsive to pharmacologic agents and does not involve radiation exposure, in contrast to scintigraphic assessments of gastric emptying. Potential pitfalls include inaccuracy due to malabsorptive processes (eg, celiac disease) that would impair digestion of the radiolabeled algae, liver disease that might impact on the metabolism of the substrate, and lung disease that may impact on pulmonary excretion of the labeled ¹³C.^{48–51} The gastric emptying breath test is widely used in pharmacologic treatment studies for gastroparesis, as it can be easily standardized and performed by clinical research personnel. It is also approved for evaluation of patients in clinical practice, where it is being used increasingly.

Evidence Gaps and Future Research

Additional studies are needed to compare the impact of the utilization of different meals and thresholds on relevant patient outcomes. Studies could compare the diagnostic accuracy of the different meals performed in the same patients with symptoms of gastroparesis in diagnosing

gastroparesis by gastric emptying scintigraphy. Further studies might compare outcomes among patients treated for suspected gastroparesis based on the results of one test protocol vs the other. The duration of the test could be optimized; we advocate for a 4-hour test over a 2-hour test; would a 3-hour test suffice? The panel also acknowledges that current gastric emptying testing does not necessarily correlate well with symptom severity and additional strategies are needed to bridge this gap. Finally, more longitudinal data are needed to understand the stability of gastric emptying results over time, because current data using the Eggbeaters meal suggest that some patients may switch between normal and delayed emptying over time with retesting; whether this is from the disease process or from the characteristics of the gastric emptying test is unclear.⁴⁰

General Considerations for Implementing the Treatment Recommendations in Clinical Practice

- It is important to optimize glycemic control in individuals with gastroparesis in the setting of diabetes mellitus.
- It is important to review the patient's current medications to eliminate medications that may alter GI tract motility; medications that can delay gastric emptying include opiate pain medications and the glucagon-like peptide-1 receptor agonists for diabetes management and weight loss. One should be cognizant of potential drug-drug interactions when considering pharmacologic interventions.
- It is important to consider potential coexisting conditions that may contribute to symptoms when treating individuals with gastroparesis.
- The Guideline Panel Content Experts use dietary interventions with small-particle and low-fat, low-residue diets before initiation of pharmacologic interventions or as a concomitant intervention.²
- Patients with gastroparesis may need to use antiemetics as needed, including selective serotonin receptor (5HT₃) antagonists (eg, ondansetron and granisetron), histamine H1 antagonists (eg, promethazine), and/or dopamine D2 antagonists (eg, prochlorperazine). These reduce nausea and vomiting without affecting gastric emptying.
- In clinical practice, the Guideline Panel Content Experts assess the efficacy and tolerance of pharmacologic interventions at 4–8 weeks to decide whether the treatment should be continued or adjusted.
- The recommendations in this document are based on a comparison with no intervention.

Question 2: Should metoclopramide be used for the treatment of individuals with gastroparesis?

Recommendation 2: In individuals with gastroparesis, the AGA suggests using metoclopramide. (*Conditional recommendation, low certainty of evidence*)

Comment: As part of shared decision making, patients who place a higher value on the potential risk of adverse events and lower value on the symptomatic improvement may reasonably select not to use metoclopramide.

Implementation Considerations

- Potential adverse effects of metoclopramide should be discussed with patients before starting treatment. The FDA issued a black box warning regarding the risk of tardive dyskinesia.
- Patients on psychotropic agents and older individuals may be at higher risk for adverse events leading to discontinuation, but the absolute risk is low, including the risk of tardive dyskinesia.
- Typical dosing using the oral (tablet or liquid) formulation starts with 5 mg before meals, which can be increased up to 10 mg before meals. For intranasal metoclopramide, the dose is 15 mg before meals and at bedtime.
- There are different practices that aim to improve tolerability of treatment, including starting at low dose and using 1–4 weeks drug holidays every 8–12 weeks.
- Medication efficacy and adverse effects, including movement disorders, are usually assessed at 4–8 weeks to decide whether the treatment should be continued. Efficacy and adverse effects are then monitored for the duration that a patient is receiving metoclopramide.

Summary of the Evidence

Evidence informing the recommendation to use metoclopramide was derived from 7 clinical trials that compared the use of metoclopramide with placebo in individuals with gastroparesis. Five of the trials used oral metoclopramide and 2 trials used intranasal metoclopramide. The oral metoclopramide trials were published between 1979 and 1985, and 2 of them were crossover trials.^{52–56} They included a total of 150 patients with gastroparesis. The diagnosis of gastroparesis was based on a barium burger study or scintigraphy. The oral metoclopramide trials informed the evidence on the effect of metoclopramide on individual gastroparesis symptoms. The studies used scoring systems other than the GCSI for measurement of the outcomes, thus, sensitivity analyses were conducted using SMD. The 2 intranasal metoclopramide trials were published in 2015 and 2024, and only 1 of them required scintigraphy to confirm the diagnosis of gastroparesis.^{57,58} They included 492 patients. They only reported the

changes in composite symptom severity score. Overall, the metoclopramide trials were limited by lack of information regarding randomization and deviations from the intended interventions for the older trials, and by selection of the reported outcome for the newer trials, which reported the composite symptoms score rather than individual symptom scores. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 10 and 11](#).

Benefits and Harms

Metoclopramide led to a reduction in nausea by 0.24 points (95% CI, -0.96 to 0.45 points; number of studies/number of participants [N/n] = 2/41; I^2 = 63%) and vomiting by 0.92 points (95% CI, -1.46 to -0.38 points; N/n = 3/51; I^2 = 86%), which was considered a clinically important reduction based on the MID of -0.44, which was a threshold that we defined *a priori*. It also led to a reduction in early satiety by 0.12 points (95% CI, -0.95 to 0.71 points; N/n = 2/41; I^2 = 50%), postprandial fullness by 0.2 points (95% CI, -1.01 to 0.61 points; N/n = 1/28), and the symptom severity score by 0.54 points (95% CI, -0.98 to -0.11 points; N/n = 6/593; I^2 = 79%). Results of sensitivity analyses using SMD showed consistent findings, except for attenuation of the effect on the vomiting outcome. None of the studies reported the change in quality of life in individuals receiving metoclopramide compared with placebo. The risk of serious adverse events was lower in individuals who received metoclopramide compared with placebo (RR, 0.64; 95% CI, 0.17 to 2.41; N/n = 3/439; I^2 = 45%), and the risk of adverse events leading to discontinuation of treatment was higher in patients who received metoclopramide compared with placebo (RR, 2.15; 95% CI, 0.89 to 5.19; N/n = 5/501; I^2 = 3%), mostly GI (eg, diarrhea and nausea) and neurologic (eg, restlessness and confusion) symptoms. The forest plots are presented in [Supplementary Figures 4–8](#).

Certainty in Evidence of Effects

The overall CoE was low. The CoE was rated down due to concerns for serious risk of bias (arising from randomization process, deviation from intended intervention, and in measurement of the outcome), serious inconsistency (studies varied in their conclusion based on MID with $I^2 \geq 50\%$), and serious to very serious imprecision (wide CIs crossing 1 or more effect size thresholds). Publication bias was not suspected. The evidence profile and Evidence to Decision framework are presented in [Tables 3 and 4](#).

Discussion

The panel noted the significant reduction in the major symptoms after treatment with metoclopramide experienced by patients with gastroparesis, including nausea, vomiting, early satiety, and postprandial fullness, as well as the reduction in symptom severity score. The forest plots showed overall trends in favor of metoclopramide, and the 95% CI in reduction in vomiting almost exceeded

Table 3. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile: Should Metoclopramide Compared With No Metoclopramide Be Used for Patients With Gastroparesis?

No. of studies (design)	Certainty assessment					No. of patients		Effect		Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metoclopramide	No metoclopramide	Relative (95% CI)	Absolute (95% CI)	
Nausea (follow-up: 3 wk; assessed with: scaled to GCSI-DD; MID 0.44; scale from: 0–4) 2 (RCTs)	Serious ^a	Serious ^b	Not serious	Serious ^c	None	27	27	—	MD 0.24 lower (0.93 lower to 0.45 higher)	⊕○○○ Very low ^{a,b,c}
Vomiting (follow-up: 3 wk; assessed with: scaled to GCSI-DD; MID 0.44; scale from: 0–4) 3 (RCTs)	Serious ^a	Serious ^d	Not serious	Not serious ^e	None	37	37	—	MD 0.92 lower (1.46 lower to 0.38 lower)	⊕⊕○○ Low ^{a,d,e}
Early satiety (follow-up: 2 wk; assessed with: scaled to GCSI-DD; MID 0.62; scale from: 0–4) 2 (RCTs)	Serious ^a	Serious ^b	Not serious	Serious ^c	None	27	27	—	MD 0.12 lower (0.95 lower to 0.71 higher)	⊕○○○ Very low ^{a,b,c}
Postprandial fullness (follow-up: 3 wk; assessed with: scaled to GCSI-DD; MID 0.62; scale from: 0–4) 1 (RCT)	Serious ^a	Not serious	Not serious	Serious ^f	None	14	14	—	MD 0.2 lower (1.01 lower to 0.61 higher)	⊕⊕○○ Low ^{a,f}
Symptoms severity score (follow-up: range 3 to 4 wk; assessed with: scaled to GCSI-DD; MID 0.58; scale from: 0–4) 6 (RCTs)	Serious ^g	Not serious ^h	Not serious	Serious ⁱ	None	357	262	—	MD 0.54 lower (0.98 lower to 0.11 lower)	⊕⊕○○ Low ^{a,h,i}
Abdominal pain (follow-up: 3 wk; assessed with: scaled to GCSI-DD; MID 0.24) 1 (RCT)	Serious ^a	Not serious	Not serious	Serious ^j	None	14	14	—	MD 1.2 lower (2.01 lower to 0.39 lower)	⊕⊕○○ Low ^{a,j}

Table 3. Continued

No. of studies (design)	Certainty assessment					No. of patients		Effect		Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metoclopramide	No metoclopramide	Relative (95% CI)	Absolute (95% CI)	
Quality of life, not reported	—	—	—	—	—	—	—	—	—	—
Serious adverse events (follow-up: range 3–4 wk) 3 (RCTs)	Not serious	Serious ^k	Not serious	Serious ^l	None	3/217 (1.4%)	5/222 (2.3%)	RR 0.64 (0.17–2.41)	8 fewer per 1000 (from 19 fewer to 32 more)	⊕⊕○○ Low ^{k,l}
Adverse events leading to discontinuation of treatment (follow-up: range 3–4 wk) 5 (RCTs)	Not serious ^m	Not serious	Not serious	Serious ^l	None	14/250 (5.6%)	6/251 (2.4%)	RR 2.15 (0.89–5.19)	27 more per 1000 (from 3 fewer to 100 more)	⊕⊕⊕○ Moderate ^{l,m}

MD, mean difference.

^aPossible bias arising from randomization process, deviation from intended intervention, and measurement of outcome.

^bOne of the studies showed small improvement and the other study showed no-to-trivial harm. $I^2 = 50\%$ – 63% .

^cConcern for very serious imprecision because CI included small benefit, no-to-trivial benefits and harms, and small harm. Although the CI included numerous thresholds, we rated down once only because the wide CI probably resulted from the inconsistency.

^dTwo studies showed small improvement and 1 study showed small harm. $I^2 = 86\%$. There was also inconsistency in results when assessed using the SMD and using the rescaled scores.

^eAlthough the CI included small benefit and no-to-trivial benefit, we did not rate down for serious imprecision because the wide CI was probably because of the inconsistency.

^fConcern for serious imprecision because CI included small benefit, no-to-trivial benefit, and no-to-trivial harm.

^gPossible bias arising from randomization process, deviation from intended intervention, and measurement of outcome in 4 studies (Perkel et al,⁵³ Perkel et al,⁵⁴ Snape et al,⁵⁵ and Ricci et al⁵⁶), which contributed approximately 60% of pooled estimate.

^hOnly study, Snape et al,⁵⁵ which contributed 13% of the pooled estimate, showed extreme results. The remaining studies showed consistent findings thus we did not rate down for inconsistency.

ⁱConcern for serious imprecision as the CI included small benefit and no-to-trivial benefit.

^jVery small sample size, $n = 28$.

^kOne study showed increased risk of adverse events and the other showed decreased risk.

^lCI included both increased and decreased risk of adverse events.

^mPossible bias arising from randomization process, deviation from intended intervention, and measurement of outcome in 3 studies (Perkel et al,⁵³ Perkel et al,⁵⁴ and Ricci et al⁵⁶), which contributed <15% of pooled estimate. Thus, we did not rate down.

Table 4. Evidence-to-Decision Framework: Should Metoclopramide Compared With No Metoclopramide Be Used for Patients With Gastroparesis?

	Judgment					
	Desirable effects	Trivial	Small	Moderate	Large	Do not know
Undesirable effects		Large	Moderate	Small	Trivial	Do not know
CoE	Very low		Low	Moderate	High	No included studies
Values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	—
Balance of effects	Favors the comparison	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Do not know
Equity	Reduced		Probably reduced	Probably no impact	Probably increased	Do not know
Acceptability	No		Probably no	Probably yes	Yes	Do not know
Feasibility	No		Probably no	Probably yes	Yes	Do not know

the threshold for MID. However, the panel appreciated the heterogeneity in the results between studies, and the fact that the clinical trials were performed on relatively small numbers more than 4 decades ago using diagnostic tests that are not recommended in the current Guideline. Nevertheless, including the larger, more recent studies using the intranasal formulation of metoclopramide showed a statistically significant benefit over placebo, leading to the conclusion that treatment with metoclopramide is indicated over no metoclopramide. Because of the FDA black box warning regarding tardive dyskinesia and recommendation to prescribe for only up to 12 weeks, however, the panel expressed concern regarding implementation, as well as concern about the acceptability of the recommendation, given perceived risks. Increased risk of adverse events leading to discontinuation may be seen more often in older individuals or those on psychotropic agents.⁵⁹ However, the absolute risk of tardive dyskinesia with metoclopramide use is low; prescription database studies from Scandinavia and the United Kingdom estimated prevalences of 1 in 17,800 or 1 in approximately 35,000 prescriptions, respectively.^{60,61} A 2019 article that reviewed the literature estimated the risk of tardive dyskinesia from metoclopramide to be in the range of only 0.1% per 1000 patient-years.⁶² A recent study based on large health care database reported similar findings, with tardive dyskinesia occurring in <1% of patients, including patients who used metoclopramide continuously for a median duration of 490 days.⁶³ The Guideline Panel Content Experts usually assess the efficacy of the intervention at 4–8 weeks to decide whether the treatment should be continued. Efficacy and adverse effects are monitored for the duration of the time that a patient is receiving metoclopramide. Since the FDA suggested treatment duration of 3 months, many clinicians give a drug holiday of 1 week to 1 month to decide whether further treatment with metoclopramide is needed.⁶³

Evidence Gaps and Future Research

Better understanding of the types of patients who might respond to metoclopramide are needed, including the type and severity of symptoms, the type of gastroparesis, and the severity of the delay in gastric emptying. There is an opportunity to further appraise efficacy of metoclopramide, particularly in relation to the effects on individual symptoms in the large clinical trials that were performed in the past decade with the intranasal formulation. In addition, the safety of prolonged use of metoclopramide in a chronic condition like gastroparesis needs further evaluation, particularly in relation to the risk of developing irreversible, chronic tardive dyskinesia (in contrast to reversible involuntary movements that cease when metoclopramide is discontinued). Additional research is also needed to determine whether the risk of tardive dyskinesia is modified by intermittent use or “drug holidays,” such as temporarily stopping the medication after 3 months of treatment. Finally, research should examine the specific role of concomitant treatment with psychotropic

agents on the reported occurrence of tardive dyskinesia in patients treated with metoclopramide.

Question 3: Should erythromycin be used for the treatment of individuals with gastroparesis?

Recommendation 3: In individuals with gastroparesis, the AGA suggests using erythromycin. (*Conditional recommendation, very low certainty of evidence*)

Implementation Considerations

- Erythromycin is thought to improve symptoms of gastroparesis due to its gastric prokinetic effects rather than by a direct antiemetic effect.
- The effect of erythromycin on symptoms and gastric motility is through its motilin receptor agonist properties and is unrelated to its antibiotic properties.
- Low doses (eg, 40–150 mg by mouth, 30 minutes before meals) are used to reduce potential adverse effects seen with higher doses (250–500 mg).
- Because erythromycin tablets are only available in high doses, using erythromycin ethylsuccinate oral suspension allows the administration of smaller, better tolerated doses.
- Tachyphylaxis often develops with prolonged, continuous use of erythromycin; in practice, efficacy is maintained using drug holidays (eg, 3 weeks on therapy, 1 week off therapy).
- Safety concerns with erythromycin include development of antibiotic resistance (with long-term use), drug interactions (it is a CYP3A isoform inhibitor), and QT prolongation.
- Azithromycin has been used as a substitute for erythromycin in practice, with many of the same safety considerations, such as antibiotic resistance also applying.

Summary of the Evidence

There were no well-designed placebo-controlled RCTs studying the effect of erythromycin on symptoms of gastroparesis. Evidence informing the recommendation to use erythromycin was derived from a trial that compared the use of erythromycin with metoclopramide and 7 trials that compared the use of metoclopramide with placebo in individuals with gastroparesis.^{52–58,64} The results of the trials were included in a network meta-analysis to provide an estimate for the effect of erythromycin compared with placebo. The trial comparing erythromycin with metoclopramide was a crossover trial, which assessed the efficacy of the medications using a composite symptom severity score composed of the combined severity scores for nausea, vomiting, abdominal pain, abdominal bloating, early satiety, diarrhea, constipation, and anorexia, rated

from 0 to 3 with a maximum score of 24 for the composite score. The trial was limited to patients with severe symptoms of gastroparesis in the settings of diabetes and evidence of delayed gastric emptying on a semisolid gastric emptying study. The trial was overall at high risk of bias due to limited reporting of the randomization process, missing outcomes data, and potential bias in the measurement of the outcome and selection of the reported outcomes. In this study, erythromycin was more efficacious than metoclopramide. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 12 and 13](#).

Benefits and Harms

Based on the network meta-analysis, erythromycin reduced GCSI-DD by 0.81 points (95% CI, –1.64 to 0.01 points) compared with placebo ([Supplementary Figures 9 and 10](#)), and this exceeds the MID total score for clinical relevance GCSI-DD total score of 0.58. There were no adverse effects reported in either erythromycin or metoclopramide groups of the clinical trial. However, the FDA package for erythromycin has warnings regarding hepatotoxicity, QT segment prolongation, and drug interactions due to inhibition of Cytochrome P450 3A4 (involved in the metabolism of colchicine, some 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, calcium channel blockers, and other medications). The FDA package insert also reports nausea, vomiting, abdominal pain, and diarrhea as potential adverse effects.⁶⁵

Certainty in Evidence of Effects

The overall CoE was very low. The CoE was rated down due to concerns for serious risk of bias (bias in measurement of the outcome), serious indirectness (indirect comparison from network meta-analysis), and very serious imprecision (very wide CI crossing more than 1 effect size threshold). Publication bias was not suspected. The evidence profile and Evidence to Decision framework are presented in [Supplementary Tables 14 and 15](#).

Discussion

The motilin receptor agonists, classically erythromycin, are a class of drugs that are used to treat gastroparesis on an off-label basis. Motilin receptors mediate the gastric portion of the phase III migrating motor complex of the GI tract, increasing antral contractility and improving gastric emptying. Although erythromycin may improve symptoms of gastroparesis due to its gastric prokinetic effects, it has no direct effect on nausea and vomiting, unlike dopamine receptor antagonists (eg, metoclopramide and domperidone). Erythromycin is a strong prokinetic agent; intravenous erythromycin (3 mg/kg intravenous infusion over 45 minutes) is occasionally used to clear the stomach in patients hospitalized because of acute gastroparesis symptoms with evidence of food retention or in those undergoing upper endoscopy for upper GI bleeding.^{66,67} The gastric prokinetic effects of erythromycin result from stimulation of the motilin receptor, and are unrelated to its

antibiotic properties. Low doses (eg, 40–150 mg by mouth, 30 minutes before meals) are used to reduce the potential adverse effects, such as nausea, vomiting, abdominal pain, and diarrhea, which are seen with higher doses (250–500 mg). However, erythromycin tablets are only available in 250 and 500-mg tablets, which are difficult to divide due to tablet coating. Erythromycin ethylsuccinate oral suspension (EryPed; Abbott) allows the administration of smaller, better-tolerated doses. Motilin receptors are known to undergo internalization leading to tachyphylaxis with prolonged exposure, reducing efficacy over time.⁶⁸ Because of this tachyphylaxis, these drugs are often administered for a limited period of time with drug holidays, such as using a 3 weeks on therapy, 1 week off therapy approach. Safety concerns with erythromycin include development of antibiotic resistance (with long-term use), drug interactions (it is a CYP3A isoform inhibitor), and QT prolongation. Anecdotal evidence suggests these adverse effects are fewer with oral, compared with intravenous, administration of erythromycin. Azithromycin has been used as a substitute to erythromycin and is effective in accelerating gastric emptying with a similarly favorable clinical response, but also similar adverse effect profile.⁶⁹

Evidence Gaps and Future Research

The evidence for the efficacy of erythromycin in gastroparesis was rated as a conditional recommendation due to the very low certainty of evidence. The main study from which this recommendation was derived compared erythromycin with metoclopramide for 3 weeks in patients with diabetes-associated gastroparesis. A significant improvement in GI symptoms was observed with both drugs, but was more pronounced with erythromycin. To better understand the efficacy of erythromycin in gastroparesis, placebo-controlled trials would be valuable. Additional data are also needed on which specific symptoms of gastroparesis improve with erythromycin treatment. The panel suggests using this primarily for symptoms attributed to gastric stasis, particularly early satiety and postprandial fullness. In addition to patients with diabetes-associated gastroparesis, other subgroups should be studied as well, such as patients with idiopathic and postsurgical gastroparesis. Because of the risk of tachyphylaxis with continued use, studies that identify the optimal duration of treatment and the ideal length of treatment interruption to restore efficacy would be particularly helpful. Finally, the development of motilin receptor agonists without antibiotic properties would be helpful in mitigating the risk of antibiotic resistance; several have been studied in the past, but have not been found to be efficacious in RCTs, possibly due to tachyphylaxis of the motilin receptor.

Question 4: Should domperidone be used for the treatment of individuals with gastroparesis?

Recommendation 4: In individuals with gastroparesis, the AGA suggests against use of domperidone as a first-line treatment. (*Conditional recommendation, very low certainty of evidence*)

Comment: As part of shared decision making, patients who place a higher value on the potential improvement in nausea, vomiting, and early satiety and lower value on the potential adverse events may reasonably select to use domperidone, when available.

Implementation Considerations

- Domperidone may be especially helpful for patients with gastroparesis who had neurologic adverse effects with metoclopramide; for patients with neurologic movement disorders, such as Parkinson's disease; and for patients declining use of metoclopramide due to concerns of its adverse effects.
- Domperidone is not approved by the FDA in the United States for human use. The prescription of domperidone requires an expanded access use investigational new drug (IND) application from the FDA. The current supplier for domperidone for the FDA IND in the United States at the time of writing is exiting the business and will no longer supply the medication, based on information available from the FDA.
- Before starting treatment with domperidone, patients should have blood work for serum potassium and magnesium and undergo an electrocardiogram (ECG) at baseline for measurement of the QTc interval.
- The Guideline Panel Content Experts usually assess the efficacy of domperidone at 4–8 weeks to decide whether the treatment should be continued. Serum potassium, magnesium, and ECG QTc interval are monitored while a patient is treated with domperidone.

Summary of the Evidence

Evidence informing the recommendation to use domperidone was derived from 2 RCTs that compared the use of domperidone with placebo in individuals with gastroparesis.^{70–72} One of the trials was an enriched enrollment randomized withdrawal trial. The trials included 224 patients with gastroparesis diagnosed based on scintigraphy, and 1 of them was limited to patients with diabetes, and the other was limited to patients with idiopathic gastroparesis. Only 1 of the trials reported the effect of domperidone on individual symptoms. The studies used scoring systems different than GCSI, thus sensitivity analyses were conducted using SMD. Overall, the trials were limited by lack of

information regarding the randomization process and any bias arising from the measurement of outcomes. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 16 and 17](#).

Benefits and Harms

Domperidone led to a reduction in nausea score by 0.28 points (95% CI, -0.61 to 0.05 points; N/n = 1/208), vomiting by 0.19 points (95% CI, -0.41 to 0.04 points; N/n = 1/208), early satiety by 0.41 points (95% CI, -0.73 to -0.10 points; N/n = 1/208), and the symptoms severity score by 0.37 points (95% CI, -0.58 to -0.16 points; N/n = 2/228; $I^2 = 84\%$). Although the improvement in symptoms was statistically significant, the reduction in these scores was not clinically significant based on the predefined MID thresholds. Clinically important changes in the abdominal pain score and the quality of life scores were not observed. Sensitivity analyses using SMD showed consistent findings. No serious adverse events or adverse events were reported in the trials. Forest plots are presented in [Supplementary Figures 11–16](#).

Based on observational studies, the use of domperidone, compared with nonuse, is associated with increased risk of sudden cardiac death and ventricular arrhythmia (adjusted odds ratio, 1.69; 95% CI, 1.46–1.95; $I^2 = 0\%$).⁷³

Certainty in Evidence of Effects

The overall CoE was very low. The CoE was rated down due to concerns for serious risk of bias (arising from the randomization process and in measurement of the outcome), serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold), and suspected publication bias. The evidence profile and Evidence to Decision framework are included in [Supplementary Tables 18 and 19](#).

Discussion

The panel acknowledged significant reductions in early satiety and symptom severity scores with a trend toward improvement in nausea and vomiting within the data. Clinical experience of those on the panel suggests that domperidone confers meaningful benefits to a subset of patients with gastroparesis, but there are no data to help identify the subset of patients likely to improve before initiating treatment. Initial studies looked at domperidone primarily in diabetic gastroparesis.^{74,75} Panel members noted that the benefit of domperidone may be related to its unique mechanism of action as both a prokinetic and antiemetic—a class shared with metoclopramide only—with the antiemetic effect in particular providing benefits to the responders. In contrast to metoclopramide, domperidone does not cross the blood–brain barrier and has fewer neurologic adverse effects than metoclopramide. The panel acknowledged a small but serious risk of cardiac arrhythmias and sudden death with domperidone use, particularly among those older than 60 years old, those taking higher doses, and those using other QT-prolonging medications or CYP3A4 inhibitors concurrently.⁷⁶ In clinical use, panel members check baseline blood work for serum potassium and magnesium and an ECG, followed by monitoring of safety and

efficacy at 4 and 8 weeks after treatment initiation, and at each follow-up visit. This includes clinical assessment, as well as repeat blood work and ECG, at each visit. Panel members expressed concerns about implementation, as domperidone is not approved for sale in the United States and requires an IND application from the FDA. Although several gastroenterology practices maintain this program for their patients, there were concerns that the current supplier for the FDA IND program is exiting the business, therefore, jeopardizing the current pathway for legitimate domperidone access in the United States.

Evidence Gaps and Future Research

The panel suggested the need to identify new agents that are mechanistically similar to domperidone (providing both prokinetic and antiemetic effects with minimal blood–brain barrier penetration) with a better efficacy and cardiac risk profile. Initial studies with domperidone were performed primarily in diabetes-associated gastroparesis; studies in different etiologies of gastroparesis would be of benefit to assess the type of patient in whom domperidone might be best suited. Further research should also continue to reassess the real-world risk of domperidone use with any eye toward potentially expanding access in the future.

Question 5: Should prucalopride be used for the treatment of individuals with gastroparesis?

Recommendation 5: In individuals with gastroparesis, the AGA suggests against the use of prucalopride as a first-line treatment. (*Conditional recommendation, very low certainty of evidence*)

Comment: As part of shared decision making, patients who place a higher value on the potential improvement in symptoms and a lower value on the potential risk of adverse effects may reasonably elect to use prucalopride, particularly if they have idiopathic gastroparesis.

Implementation Considerations

- Patients with gastroparesis and chronic idiopathic constipation (CIC) may reasonably elect to use prucalopride for efficiency of care given prucalopride's established efficacy for CIC.
- Patients with gastroparesis attributed to diabetes or connective tissue diseases may be less likely to respond to prucalopride treatment than patients with idiopathic gastroparesis.
- The mechanism of action for prucalopride is purely prokinetic as a 5HT₄ receptor agonist, without any direct antiemetic effects.
- Prescribers recommending prucalopride should note the warning to monitor patients for small potential risk of depression and suicidal thoughts and behavior when considering use of prucalopride.

Summary of the Evidence

Evidence informing the recommendation to use prucalopride was derived from 2 crossover RCTs that compared the use of prucalopride with placebo in individuals with gastroparesis.^{77,78} The studies included 49 patients with gastroparesis diagnosed based on scintigraphy. One study was limited to individuals with idiopathic gastroparesis, and the other was limited to patients with gastroparesis attributed to diabetes mellitus or mixed connective tissue disease. Overall, the trials were at low risk for bias. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 20 and 21](#).

Benefits and Harms

Prucalopride led to a reduction in the composite nausea and vomiting score by 0.18 points (95% CI, -0.53 to 0.17 points; N/n = 2/42; $I^2 = 31\%$), composite early satiety and postprandial fullness score by 0.2 points (95% CI, -0.58 to 0.18 points; N/n = 2/42; $I^2 = 75\%$), and the symptom severity score by 0.22 points (95% CI, -0.50 to 0.07 points; N/n = 2/42; $I^2 = 82\%$). However, the reduction in the scores did not meet the threshold for clinical importance. There was an increased risk of serious adverse effects observed (RR, 2.8; 95% CI, 0.12 to 66.05; N/n = 2/42) and adverse events leading to discontinuation of treatment (RR, 1.87; 95% CI, 0.18 to 19.47; N/n = 2/42) in patients who received prucalopride compared with placebo. Prucalopride led to a reduction in abdominal pain and improvement in quality of life, but these changes did not meet the threshold for clinical importance. Of the 2 studies, the one focused on idiopathic gastroparesis showed favorable results, whereas the study involving primarily diabetes-related gastroparesis did not. Forest plots are presented in [Supplementary Figures 17–22](#).

Certainty in Evidence of Effects

The overall CoE was very low. The CoE was rated down due to concerns for serious risk of bias (arising due to missing outcome data), and serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold). Publication bias was not suspected. The evidence profile and Evidence to Decision frameworks are included in [Supplementary Tables 22 and 23](#).

Discussion

There are a number of serotonergic receptor agonists that have been evaluated for use in gastroparesis, including prucalopride, a selective 5HT₄ agonist, which has no appreciable cardiac adverse effects, as were seen with cisapride and perhaps tegaserod. Prucalopride is currently approved for use in CIC and works exclusively as a pro-motility agent. As such, the rationale for use in gastroparesis is related to improvement in gastric emptying, which may result in a reduction of symptoms due to gastric retention, such as nausea, vomiting, and postprandial fullness. In fact, the 2 RCTs of prucalopride vs placebo that were included in the current assessment revealed significant improvements in these areas. However, when judged on the basis of

meaningful improvement, they did not reach a predefined threshold of clinical significance. Other 5HT₄ agonists, such as velusetrag and naronapride, have been found to accelerate gastric emptying as well.^{46,79} The current recommendation comes with an acknowledgement that many of the patients who had symptom improvement had idiopathic gastroparesis. Together with the existing approval for patients with CIC, it is possible that some patients—especially those with coexisting constipation—who would be candidates for prucalopride therapy, would reasonably elect to treat both conditions with 1 medication. Prucalopride has been associated with reports of new-onset or worsening depression, as well as suicidal thoughts and behavior, particularly in the initial weeks of treatment. Whether specific counseling is needed to patients regarding the potential risk for mood disturbances and suicidal ideation and/or behavior is unknown, as there has been no evidence of a causal association between prucalopride treatment and these outcomes.^{80–82}

Evidence Gaps and Future Research

Given the small number of patients on which the current recommendations are based, future research should focus on generating larger RCTs with longer durations of treatment from which to better assess the potential benefits and harms of prucalopride. These studies should also focus on assessing the effects of prucalopride on different etiologies of gastroparesis, to better identify whether specific subgroups may more likely benefit from therapy. Finally, these studies should specifically include an analysis of the potential psychological implications of prucalopride to better inform patients and clinicians about any true risks.

Question 6: Should neurokinin-1 receptor antagonists be used for the treatment of individuals with gastroparesis?

Recommendation 6: In individuals with gastroparesis, the AGA suggests against the use of aprepitant as a first-line treatment. (Conditional recommendation, low certainty of evidence)

Comment: As part of shared decision making, patients who place a higher value on the potential improvement in nausea and vomiting and lower value on the potential adverse effects may reasonably elect to use aprepitant.

Implementation Considerations

- Aprepitant, a neurokinin-1 receptor antagonist, is an antiemetic approved for chemotherapy-induced vomiting, but has no effect on gastric motor function.
- Aprepitant may be helpful in patients with gastroparesis and nausea/vomiting in whom 5HT₃ receptor antagonists, such as ondansetron, and other antiemetics are not helpful.

Summary of the Evidence

Evidence informing the recommendation to use aprepitant was derived from 1 clinical trial that compared the use of aprepitant with placebo in individuals with nausea and

symptoms suggestive of gastric origin.⁸³ The trial included 126 patients, but only 57% of patients had delayed gastric emptying. The trial was at low risk of bias. In addition, there were 2 clinical trials that evaluated the use of another neurokinin-1 receptor antagonist, tradipitant, in patients with gastroparesis.^{15,84} However, they were not used in developing the recommendation, as tradipitant has not yet been approved by the FDA and is not presently available. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 24 and 25](#).

Benefits and Harms

Compared with placebo, aprepitant led to a reduction in nausea by 0.30 points (95% CI, -0.61 to 0.01 points; N/n = 1/122), vomiting by 0.20 points (95% CI, -0.44 to 0.04 points; N/n = 1/122), early satiety and postprandial fullness by 0.20 points (95% CI, -0.49 to 0.09 points; N/n = 1/117), and the symptom severity score by 0.10 points (95% CI, -0.36 to 0.16 points; N/n = 1/122), which did not represent clinically important reductions based on the predefined MID thresholds. Abdominal pain had a clinically important reduction by 0.40 points (95% CI, -0.69 to -0.11 points; N/n = 1/122). There was no clinically important change in quality of life. The risk of serious adverse events (RR, 3.00; 95% CI, 0.12 to 72.26; N/n = 1/126) and adverse events leading to discontinuation of treatment (RR, 2.00; 95% CI, 0.52 to 7.65; N/n = 1/126) were possibly higher in patients who received aprepitant compared with placebo. It is important to note that the lack of benefit was based on the outcome predefined by the panel, as we relied on GCSI-DD when reported. The trial also reported results based on the 2-week Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM), that showed more improvement in nausea and vomiting. Forest plots are presented in [Supplementary Figures 23–27](#).

Certainty in Evidence of Effects

The overall CoE was low. The CoE was rated down due to concerns for serious indirectness (trial included patients with chronic unexplained nausea and vomiting without requiring evidence of delayed gastric emptying), and serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold). Publication bias was not suspected. The evidence profile and Evidence to Decision framework are included in [Supplementary Tables 26 and 27](#).

Discussion

The AGA Panel suggested against the use of aprepitant for first-line management of gastroparesis due to its small benefit in producing clinically meaningful reductions in nausea and vomiting. Aprepitant is currently approved for management of chemotherapy-induced nausea and vomiting, as well as for postoperative nausea and vomiting or chemotherapy-induced emesis. In chemotherapy-induced nausea and vomiting, aprepitant is often used as an additive agent to 5HT₃ antagonists, such as ondansetron. In patients with gastroparesis, aprepitant may be helpful in patients in whom 5HT₃ antagonists are not helpful.

Aprepitant is available in both oral and intravenous forms. Access to its use for management of gastroparesis can be difficult due to limited insurance coverage and its high cost.

Evidence Gaps and Future Research

Larger studies focusing on use of neurokinin-1 receptor antagonists in patients with gastroparesis are needed to justify regular clinical use. The evaluated trial of aprepitant included patients with chronic unexplained nausea and vomiting and the results are extrapolated from the 57% of patients with delayed gastric emptying. In addition, it appeared that the clinical effect of aprepitant differed based on the choice of outcome measure. Aprepitant did not produce a meaningful reduction in nausea based on visual analog scale, however, it did seem to decrease symptom severity for nausea, vomiting, and overall symptoms using the GCSI based on a 2-week recall. Given limited effective treatments for gastroparesis, future trials using neurokinin-1 receptor antagonists will need the correct choice of outcome to ensure success and clinical relevance.

In addition to nortriptyline and buspirone, the panel aimed to identify trials that evaluated the use of mirtazapine in patients with gastroparesis, but could not identify any RCTs. A single-arm cohort study, without a control group, involving 30 patients with refractory gastroparesis found that mirtazapine may improve nausea and vomiting; the medication was discontinued by one-fifth of the patients due to adverse events, mainly altered mood and slurred speech.⁸⁵

Question 7.1: Should nortriptyline, as a neuromodulator, be used for the treatment of individuals with gastroparesis?

Recommendation 7.1: In patients with gastroparesis, the AGA suggests against the use of nortriptyline as a first-line treatment. (*Conditional recommendation, low certainty of evidence*)

Comment: As part of shared decision making, patients who place a higher value on the potential improvement in early satiety, postprandial fullness, abdominal pain, and quality of life and lower value on the potential adverse effects may reasonably elect to use nortriptyline.

Implementation Considerations

- Patients with overlapping irritable bowel syndrome, functional dyspepsia (epigastric pain syndrome), or significant abdominal pain associated with gastroparesis may benefit from the use of tricyclic antidepressants, such as nortriptyline.
- When using tricyclic antidepressants in patients with gastroparesis, the panel members use agents with fewer anticholinergic effects, such as nortriptyline, and start at low doses and increase slowly to ensure tolerance.
- The Guideline Panel Content Experts inform patients being started on nortriptyline that this agent is in the class of antidepressants, however, in gastroparesis, it is being used as a peripheral neuromodulator to reduce afferent sensory transmission to the central nervous system.

Summary of the Evidence

Evidence informing the recommendation to use nortriptyline was derived from 1 clinical trial that compared the use of nortriptyline with placebo in individuals with idiopathic gastroparesis and moderate symptoms severity.⁸⁶ The trial included 130 patients with moderate to severe idiopathic gastroparesis and evidence of delayed gastric emptying. The trial was at low risk for bias overall. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 28 and 29](#).

Benefits and Harms

Nortriptyline led to worsening of the nausea score by 0.05 points (95% CI, -0.33 to 0.43 points; N/n = 1/118) compared with placebo, which was not a clinically important change. It led to a reduction in early satiety and postprandial fullness by 0.34 points (95% CI, -0.72 to 0.04 points; N/n = 1/118) and symptom severity score by 0.14 points (95% CI, -0.47 to 0.18 points; N/n = 1/118), which were not considered as clinically important changes compared with placebo. There was no change in abdominal pain (mean difference, 0; 95% CI, -0.47 to 0.47; N/n = 1/118). Nortriptyline led to a possible clinically important improvement in quality of life based on Short Form 36 Physical Component Score (mean difference, 2.1; 95% CI, -1.01 to 5.21; N/n = 1/118), but not the Mental Component Score. The risk of serious adverse events (RR, 5.00; 95% CI, 0.6 to 41.63; N/n = 1/130) and adverse events leading to discontinuation of treatment (RR, 3.17; 95% CI, 1.35 to 7.42; N/n = 1/130) were higher in patients who received nortriptyline compared with placebo. Forest plots are presented in [Supplementary Figures 28–33](#).

Certainty in Evidence of Effects

The overall CoE was low. The CoE was rated down serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold). Publication bias was not suspected. The evidence profile and Evidence to Decision framework are included in [Supplementary Tables 30 and 31](#).

Discussion

Tricyclic antidepressants, such as nortriptyline, have central and peripheral neuromodulatory mechanisms. Peripherally, nortriptyline functions as a neuromodulator, reducing sensory afferent transmission to the central nervous system. Although the cardinal symptoms of gastroparesis, including nausea and or vomiting, were not significantly improved with nortriptyline, there was a numeric reduction in early satiety and postprandial fullness, as well as improvement in overall symptom severity and quality of life. Nevertheless, the observed trends toward symptom improvement, together with the clinical experience of the experts on the panel, led the group to comment that some patients may derive a benefit from nortriptyline treatment. Concurrently, the panel acknowledged a trend toward increased risk of serious adverse effects with a

significantly increased risk of adverse events causing discontinuation. The panel felt that nortriptyline and other tricyclic antidepressants could be useful in patients with gastroparesis who also had irritable bowel syndrome (primarily the diarrhea-predominant subtype) given stronger evidence supporting its use in irritable bowel syndrome.⁸⁷ Clinical experience of the content experts on the panel suggests that tricyclic antidepressants should be started at low doses (10–25 mg), given at night to help avoid adverse effects, and increased slowly to maximize effect while minimizing risk of adverse effects. Use of secondary imines (eg, nortriptyline and desipramine) over tertiary amines (eg, amitriptyline and imipramine) is also thought to minimize anticholinergic adverse effects. Other types of antidepressants are also used in gastroparesis; mirtazapine is often used for nausea and vomiting. Panel members highlighted the common misconception that tricyclic antidepressants would further prolong gastric emptying in patients with gastroparesis; slowing of gastric emptying was not observed in healthy controls treated with up to 50 mg daily of nortriptyline or in patients with functional dyspepsia treated with up to 50 mg of amitriptyline.^{88,89}

Evidence Gaps and Future Research

Patients with overlapping disorders of gut-brain interaction—including gastroparesis, functional dyspepsia, and irritable bowel syndrome—are commonly encountered in clinical practice. Further RCTs of nortriptyline should focus on patients with pain-predominant manifestations of gastroparesis or overlapping irritable bowel syndrome to determine whether there is a differential response in these patient populations with known high symptom burden and health care resource utilization.

Question 7.2: Should buspirone, as a neuromodulator, be used for the treatment of individuals with gastroparesis?

Recommendation 7.2: In patients with gastroparesis, the AGA suggests against the use of buspirone as a first-line treatment. (Conditional recommendation, very low certainty of evidence)

Comment: As part of shared decision making, patients who place a higher value on the potential improvement in early satiety, postprandial fullness, and bloating may reasonably elect to use buspirone

Implementation Considerations

- Use of buspirone may be helpful in patients with gastroparesis and predominant early satiety and bloating.

Summary of the Evidence

Evidence informing the recommendation to use buspirone was derived from 1 clinical trial that compared the use of buspirone to placebo in individuals with early satiety and postprandial fullness with other symptoms suggestive of gastric origin.⁹⁰ The trial included 96 patients with

moderate to severe symptoms. Delayed gastric emptying was not required for inclusion in the trial, and only approximately 50% of the included patients had delayed gastric emptying. The trial was at low risk for bias overall. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 32 and 33](#).

Benefits and Harms

Compared with placebo, buspirone led to a reduction in the nausea and vomiting score by 0.04 points (95% CI, -0.51 to 0.43 points; N/n = 1/78), early satiety and postprandial fullness score by 0.32 points (95% CI, -0.68 to 0.04 points; N/n = 1/96), and total symptom severity score by 0.45 points (95% CI, -0.79 to -0.11 points; N/n = 1/78), which were not clinically important changes based on the predefined MIDs. There was possible worsening in the abdominal pain score by 0.14 points (95% CI, -0.43 to 0.70 points; N/n = 1/78), as well as quality of life as measured by the Short Form 36 Physical (mean difference, -2.07; 95% CI, -5.0 to 0.86; N/n = 1/78) and Mental Components. Subgroup analysis reported in the study suggested that buspirone may provide more benefit in patients with severe bloating at baseline.⁹⁰ There was no clinically important difference in the risk of serious adverse events between patients who received buspirone and placebo (RR, 1.04; 95% CI, 0.07 to 16.19; N/n = 1/96). Forest plots are presented in [Supplementary Figures 34–39](#).

Certainty in Evidence of Effects

The overall CoE was very low. The CoE was rated down due to concerns for serious indirectness (delayed gastric emptying was not required for inclusion), and serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold). Publication bias was not suspected. The evidence profile and Evidence to Decision framework are included in [Supplementary Tables 34 and 35](#).

Discussion

Buspirone is a 5HT₁ receptor agonist approved for treatment of anxiety due to its effects on the central nervous system. Several studies have been performed with buspirone in functional dyspepsia, where it has peripheral actions enhancing gastric accommodation and improving the symptom of early satiety. The single clinical trial of buspirone in patients with symptoms of gastroparesis comparing buspirone with placebo did not show significant improvements in nausea, vomiting, early satiety, postprandial fullness, or overall symptoms severity score. Despite these findings, Panel Content Experts felt that buspirone could be useful in patients with gastroparesis whose predominant symptoms are early satiety and bloating, especially in the absence of any signal suggesting increased risk of serious adverse events among those treated with buspirone.

Evidence Gaps and Future Research

Although the study that evaluated the use of CBD for gastroparesis comes from a single clinical trial that assessed patients with symptoms of gastroparesis and moderate to severe symptoms of postprandial fullness and early satiety. Of note, the subgroup of patients with severe bloating at baseline seemed to derive a benefit in the early satiety/postprandial fullness symptoms from buspirone compared with those with lesser degrees of bloating. As bloating is a particularly difficult symptom to treat across GI conditions, a larger trial adequately powered to examine this subgroup could be of great clinical utility. Studies could be performed in gastroparesis patients with impaired fundic accommodation to help augment patients with defined pathophysiologic abnormalities that might respond to buspirone.

Question 8: Should cannabidiol be used for the treatment of individuals with gastroparesis?

Recommendation 8: In individuals with gastroparesis, the AGA suggests against the use of cannabidiol (CBD) except in the context of a clinical trial. (Conditional recommendation, low certainty of evidence)

Implementation Considerations

- The single study demonstrating efficacy for CBD in gastroparesis used a pharmaceutical grade CBD (Epidiolex) that is approved to treat seizures due to Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years and older, and the medication is not available for clinical use in gastroparesis.
- Available CBD formulations are not regulated, with varying potencies that make their impact on patients with gastroparesis unknown.
- Among CBD formulations that include tetrahydrocannabinol (THC), there is concern about increased risk of cannabinoid hyperemesis syndrome.

Summary of the Evidence

Evidence informing the recommendation to use CBD was derived from 1 clinical trial that compared the use of CBD with placebo in individuals with idiopathic or diabetes-associated gastroparesis.⁹¹ The trial included 44 patients. The trial was at low risk for bias overall. The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 36 and 37](#).

Benefits and Harms

CBD led to a clinically important reduction in the vomiting score by 0.70 points (95% CI, -1.13 to -0.27 points; N/n = 1/44), early satiety by 0.77 points (95% CI, -1.45 to -0.09 points; N/n = 1/44), symptom severity score by 0.61 points (95% CI, -0.97 to -0.25 points; N/n = 1/44), and abdominal pain score by 0.64 points (95% CI, -1.4 to 0.12 points; N/n = 1/44).

compared with placebo. There was also a trivial reduction in the nausea and postprandial fullness scores. There was no clinically important difference in the risk of serious adverse events (RR, 1.10; 95% CI, 0.07 to 16.43; N/n = 1/44) and no adverse events leading to discontinuation of treatment were reported. Forest plots are presented in [Supplementary Figures 40–44](#).

Certainty in Evidence of Effects

The overall CoE was low. The CoE was rated down due to serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold; and the optimal information size was not met). Publication bias was not suspected. The evidence profile and Evidence to Decision frameworks are included in [Supplementary Tables 38 and 39](#).

Discussion

Some patients with refractory nausea and vomiting use marijuana to treat their symptoms, particularly nausea, vomiting, and lack of appetite. The orexigenic, antiemetic, and pain-relieving properties may explain marijuana's frequent use for the treatment of GI symptoms. The main pharmacologically active chemicals in cannabis are THC and CBD. Our current understanding is that the actions of cannabis are mediated through the endocannabinoid system, which includes the cannabinoid receptors CB1 and CB2—receptors activated by cannabis. THC works by binding to and activating CB1 and CB2. Cannabinoids are thought to mediate their antiemetic effects via CB1 receptors in the dorsal vagal complex of the brainstem. The single study demonstrating efficacy for CBD in gastroparesis was performed in patients with idiopathic and diabetes-associated gastroparesis, and used the pharmaceutical-grade CBD (Epidiolex), which is approved to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis. The clinically important reduction in vomiting, early satiety, and abdominal pain seen with CBD in this study was tempered by the fact that it is unlikely that the form of CBD used in the study would be available for gastroparesis. The panel felt additional studies, particularly larger multicenter studies, were needed to document the efficacy of CBD for symptoms of gastroparesis. Finally, there are numerous formulations of CBD with varying potency with unknown effects in gastroparesis. A stronger endorsement of CBD for use in gastroparesis (despite evidence in its favor) was deferred due to concerns that patients and their clinicians may use such a recommendation to justify use of CBD outside of the studied formulation. There is the concern that frequent CBD use in the absence of FDA-approved non-THC-contaminated formulations could lead to worsening nausea and vomiting as part of cannabinoid hyperemesis syndrome.^{92,93}

Evidence Gaps and Future Research

Although the study that evaluated the use of CBD for gastroparesis was well-designed with positive results, the panel felt that larger studies are needed, specifically looking at different formulations more likely to be available to patients. The study found that CBD improves some symptoms of gastroparesis, however, marijuana and CBD can slow gastric emptying, which might aggravate symptoms in some patients, particularly those with severely delayed gastric emptying. Because gastroparesis is a chronic condition, prolonged treatment with CBD might be needed. Long-term daily administration of cannabis, or marijuana, is associated with cannabinoid hyperemesis syndrome, a variant of cyclic vomiting syndrome, which would be deleterious for patients with gastroparesis with nausea and vomiting. Long-term marijuana use has also been associated with depression, anxiety, and respiratory issues. Although there are fewer adverse effects with CBD, long-term use of CBD may be linked to liver damage and thyroid issues. Further research is needed to understand any potential adverse effects from chronic CBD use specifically.

Management of Gastroparesis Refractory to Medical Therapy

General Considerations for Implementing the Treatment Recommendations for Refractory Gastroparesis in Clinical Practice

- A patient is considered to have gastroparesis refractory to medical therapy if they have cardinal symptoms of gastroparesis (ie, nausea, vomiting, postprandial fullness, and/or early satiety) as the predominant symptoms, in addition to evidence of delayed gastric emptying with no alternative explanation for the symptoms, and have failed at least 2 medical treatments, including prokinetic and antiemetic agents.
- In patients with gastroparesis refractory to medical therapy, it is important to ascertain the accuracy of the diagnosis and to evaluate for coexisting conditions that may be causing or contributing to the severity of the predominant symptoms.
- The management of gastroparesis that is refractory to medical therapy requires a multidisciplinary approach that optimally involves the primary care provider, a gastroenterologist, and a registered dietitian, in addition to an endocrinologist in patients with diabetes. In select cases, this might also involve an interventional endoscopist and a foregut surgeon.
- It is important to evaluate the nutritional status of patients with gastroparesis refractory to medical therapy and to provide nutritional support, preferably orally as tolerated

by the patient, or if necessary, using enteral nutrition; parenteral nutrition is rarely used as it carries risk of serious complications like infections and blood clots.

The search for studies on health equity and disparities identified an observational study using the National Inpatient Sample, which reported potential economic and racial disparities in the surgical management of gastroparesis, which is usually reserved for medically refractory gastroparesis. The study found that patients who were Black, uninsured, and/or hospitalized in rural setting were less likely to receive surgical treatments for gastroparesis.⁹⁴

Question 9: Should pyloric botulinum toxin injection (BTI) be used for the treatment of individuals with gastroparesis refractory to medical therapy?

Recommendation 9: In patients with gastroparesis refractory to medical management, the AGA suggests against the routine use of botulinum toxin injection (BTI). (Conditional recommendation, very low certainty of evidence)

Comment: As part of shared decision making, patients and clinicians who place a higher value on endoscopic treatment and lower value on chronic medical therapy may reasonably attempt treatment with BTI.

Implementation Considerations

- The Guideline Panel intended to evaluate the use of BTI in patients with refractory gastroparesis. However, the published clinical trials were not specific to refractory gastroparesis.
- The need for retreatment as often as every 3 months could limit implementation from both a cost-effectiveness perspective and concern for diminishing clinical effect.
- Repeat treatment may predispose to pyloric scarring, which could complicate attempts at other interventions, such as G-POEM.

Summary of the Evidence

Evidence informing the recommendation to use BTI was derived from 2 clinical trials that compared the use of BTI with sham intervention (saline injection).^{95,96} Arts et al⁹⁵ conducted a crossover randomized clinical trial that included 23 patients with gastroparesis. The patients were followed for 1 month only after treatment and crossover occurred at 1 month, which raised concerns regarding carryover effect. Friedenberg et al⁹⁶ conducted a parallel RCT, which included 32 patients with moderate to severe symptoms who were also followed for 1 month after treatment only. In both trials, it was not clear whether the patients were required to be refractory to treatment to be included. The evidence was also informed by another trial conducted by Gonzalez et al.⁹⁷ The trial compared the use of G-POEM with pyloric BTI in patients with

gastroparesis refractory to medical therapy for more than 1 year. The trial included 40 patients with idiopathic, diabetes-associated, and/or postoperative gastroparesis.⁹⁷ The details of the trial characteristics and risk-of-bias assessment are reported in [Supplementary Tables 40 and 41](#).

Benefits and Harms

After 1 month, compared with saline injection, BTI was associated with a worsening in the symptom severity score, which was not clinically important (pooled mean difference, 0.17; 95% CI, -0.34 to 0.67; N/n = 2/44; I^2 = 0%). There was a possible decrease in the risk of serious adverse events in patients who received saline injection compared with BTI (RR, 0.67; 95% CI, 0.13 to 3.47; N/n = 2/44), and the risk of periprocedural adverse events was higher in patients who received BTI compared with saline injection (RR, 2.0; 95% CI, 0.6 to 6.64; N/n = 2/44). The trials did not report the impact of BTI on individual symptoms. As outlined in the section on G-POEM, BTI injection had comparable efficacy with G-POEM based on the trial by Gonzalez et al.⁹⁷ Forest plots are presented in [Supplementary Figures 45 and 46](#).

When G-POEM was compared with pyloric BTI, there was no clinically important difference between the 2 interventions in the nausea and vomiting score (mean change, 0.0; 95% CI, -0.75 to 0.75; N/n = 1/37), early satiety and postprandial fullness score (mean change, -0.08; 95% CI, -0.78 to 0.51; N/n = 1/37), or symptom severity score (mean change, -0.24; 95% CI, -0.86 to 0.38; N/n = 1/37) at 3 months. The findings were similar when assessed again at 12 months.⁹⁷

Certainty in Evidence of Effects

The overall CoE was very low. The CoE was rated down due to concerns for very serious risk of bias (arising from randomization process, period and carry-over effect, and selection of reported results), and serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold, and small sample size). Publication bias was not suspected. The evidence profile and Evidence to Decision framework are included in [Supplementary Tables 42 and 43](#).

Discussion

BTI is used for treatment in patients with gastroparesis, a practice based primarily on noncontrolled open-label studies showing improvement in symptoms. However, there are 2 randomized double-blind studies that did not show efficacy that led to our statement. The panel noted that the 2 included studies had significant limitations, including small sample sizes and limited follow-up periods. Notably, although the current recommendation evaluates the use of BTI for refractory gastroparesis, the included clinical trials did not impose this restriction on participants. However, the suggestion against the use of BTI for routine use in gastroparesis acknowledges that current clinical practice

sees BTI largely used for refractory disease—in patients not responding to medical therapies. Panel members acknowledged the results of the Gonzalez et al⁹⁷ clinical trial showing a similar benefit to G-POEM and BTI at 3 and 12 months in medically refractory gastroparesis. These findings suggest that BTI may be as beneficial as G-POEM in selected patients, especially when considered alongside the sham-controlled trial by Martinek et al,⁹⁸ which demonstrated the relative benefit of G-POEM. A recent study suggested that patients with decreased pyloric compliance as assessed by EndoFLIP impacted a favorable response to BTI.⁹⁹ The panel noted the common use of BTI in clinical practice as a predictive strategy for the prediction of G-POEM responders, but this practice, although logical, lacks robust supporting evidence. A recent systematic review of studies evaluating predictors of outcomes after G-POEM included 3 studies suggesting that a positive response to BTI may be associated with a positive response to G-POEM. However, these studies were mostly small, observational, and limited by potential confounding.^{100–103} Although feasibility is high and risk of adverse events relatively low, reliance on BTI may necessitate repeat treatments as often as every 3–6 months with risk for diminishing efficacy. Moreover, repeat treatments have the potential to cause pyloric scarring, which could complicate attempts at other interventions, such as G-POEM. A retrospective analysis of different botulinum toxin doses, suggested the 200-unit dose produced a more favorable response compared with 100 units.¹⁰⁴ Improved patient selection for use of BTI may produce a more favorable response. Reduced pyloric compliance as measured by functional lumen imaging probe has been suggested to yield a more favorable response.¹⁰⁵ In patients with postfundoplication gastroparesis, there may be a beneficial response to BTI.^{106,107}

Evidence Gaps and Future Research

Future high-quality, sham-controlled trials with adequate follow-up time performed specifically in medically refractory gastroparesis patients would be beneficial to provide further evidence for or against the use of BTI in refractory gastroparesis. In addition, prospective comparative data on the use of BTI in predicting response to other interventions like G-POEM and surgical pyloromyotomy would help to further inform its current use in this setting. Sham-controlled trials of BTI in specific gastroparesis etiologies that may be hypothesized to benefit from BTI, including postvaginal injury or postfundoplication, may also aid in identifying subpopulations in whom BTI may be more effective. Other knowledge gaps in the utilization of BTI include the role of EndoFLIP in predicting response to BTI, which has been reported previously but needs further validation. Lastly, the optimal effective dose of BT has not been clearly established and warrants further investigation. Prior studies have used doses of both 100 units and 200 units, both of which are supported by the experts on the panel.

Question 10: Should gastric peroral endoscopic pyloromyotomy (G-POEM) be used for the treatment of individuals with gastroparesis refractory to medical therapy?

Recommendation 10: In patients with gastroparesis refractory to medical therapy, the AGA suggests against the routine use of G-POEM. (*Conditional recommendation, low certainty of evidence*)

Comment: As part of shared decision making, patients and clinicians who place a higher value on the potential improvement in symptoms and lower value on the potential risk of adverse events may reasonably select to undergo G-POEM procedure.

Implementation Considerations

- This procedure should be reserved for select patients with medically refractory gastroparesis.
- Candidates for G-POEM should have had a diagnosis of gastroparesis with an appropriately done, 4-hour gastric emptying study, generally with at least a moderate delay in gastric emptying (20% retention at 4 hours with the Eggbeaters meal).
- Candidates for G-POEM should have at least 6–12 months of moderate symptoms with the cardinal symptoms of nausea, vomiting, and/or postprandial fullness.
- Before consideration of G-POEM, patients with gastroparesis should undergo a trial of other treatments for gastroparesis, including prokinetic agents and antiemetic agents.

Summary of the Evidence

Evidence informing the recommendation to use G-POEM was derived from 1 clinical trial that compared the use of G-POEM with a sham intervention in individuals with gastroparesis refractory to medical therapy.⁹⁸ The trial included 41 patients with either idiopathic, diabetes-associated, or postoperative gastroparesis. The patients had to have severe and refractory symptoms for more than 6 months, despite treatment with antiemetics and prokinetic agents. The evidence was also partially informed by the Gonzales et al⁹⁷ trial, summarized in Recommendation 9, which compared the use of G-POEM with pyloric BTI in patients with gastroparesis refractory to medical therapy for more than 1 year. Both trials were at low risk for bias overall. We also identified multiple observational studies that compared the use of G-POEM with surgical pyloric interventions, gastric electric stimulators, and in combination with other interventions.^{108–112} The observational studies were at high risk for bias overall and were not used to inform the recommendation. The details of the studies characteristics and risk-of-bias assessment are reported in [Supplementary Tables 44 and 45](#).

Benefits and Harms

After 3 months, compared with sham intervention, G-POEM led to a clinically important reduction in the nausea and vomiting score by 0.80 points (95% CI, -1.35 to -0.25 points; N/n = 1/41), early satiety and postprandial fullness score by 1.28 points (95% CI, -1.78 to -0.78 points; N/n = 1/41), and symptom severity score by 1.20 points (95% CI, -1.84 to -0.56 points; N/n = 1/41). Improvements were similar at 6-month follow-up. There was no clinically important change in quality of life as measured by Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life at 3 months, but there was possible improvement at 6 months (mean change, -0.7; 95% CI, -1.53 to 0.13; N/n = 1/41). The risk of serious adverse events was possibly increased (RR, 1.51; 95% CI, 0.42 to 5.48; N/n = 1/41), as well as an increased risk of procedural and periprocedural adverse events in patients who had G-POEM compared with the sham intervention. Forest plots are presented in [Supplementary Figures 47–51](#).

As detailed in Recommendation 9, when G-POEM was compared with pyloric BTI, GCSI decreased in both groups, with G-POEM having a numerically higher clinically relevant success rate, although there were no clinically important differences between the 2 interventions in the nausea and vomiting score, early satiety and postprandial fullness score, or symptom severity score at 3 months and 12 months.⁹⁷

Certainty in Evidence of Effects

The overall CoE was low. The CoE was rated down due to concerns for serious to very serious imprecision (wide CIs crossing 1 or more effect size threshold; and small sample size). Publication bias was not suspected. The evidence profile and Evidence to Decision framework are included in [Supplementary Tables 46 and 47](#).

Discussion

The panel acknowledges that numerous recent studies have demonstrated the efficacy of G-POEM, but these studies rely on retrospective cohort data reporting a center's experience comparing G-POEM with surgical techniques, such as robotic pyloroplasty or gastric electric stimulator placement. Furthermore, there may be important and unmeasured differences in expected outcomes between surgical techniques of pyloromyotomy and pyloroplasty that are not addressed when compared with G-POEM. Importantly, the panel's recommendation seemingly contrasts with the results of numerous observational studies, which suggest a benefit of G-POEM. However, the guidelines panel excluded these studies due to the high risk of bias.

The panel acknowledges that select patient populations may benefit from G-POEM, which led to the conditional recommendation for selective use of G-POEM instead of using it routinely. Compared with sham and

pyloric BTI, G-POEM did provide at least modest duration (12 months) benefit among patients with refractory disease. Two predictive factors for success for G-POEM that are often used include EndoFLIP of the pylorus to assess pyloric compliance and diameter and use of BTI of the pylorus; these are promising, but more studies are needed supporting these practices.¹⁰¹ The panel's clinical experts defined refractory disease—and, therefore, those patients appropriate for consideration of G-POEM—as chronic symptoms of nausea, vomiting, and/or postprandial fullness of at least 6 months duration having failed at least 3 months of a prokinetic agent like metoclopramide and at least 1 antiemetic treatment. The panel's more cautious approach to G-POEM recognizes the increased risk of serious adverse events with an invasive, irreversible procedure for which the evidence of benefit was derived from a single clinical trial. Importantly, the panel felt that a blanket positive recommendation could lead to hasty, inappropriate referrals for G-POEM without a more concerted trial of medical therapy.

Evidence Gaps and Future Research

Because the apparent benefit of G-POEM was derived from a single clinical trial, the most important research priority is replicating these positive findings in other RCTs. Furthermore, longevity of the efficacy to G-POEM needs to be delineated. Acknowledging the heterogeneous patient population diagnosed with gastroparesis, additional research is also needed to determine the patients most likely to benefit from the procedure, especially subgroups defined by gastroparesis etiology (eg, diabetes-associated, idiopathic, and postsurgical) and predominant symptom type. Similarly, additional studies providing best practices and normative data for pyloric functional lumen imaging probe would be helpful to determine whether any measurements from this technology or others could clarify those most likely to benefit from G-POEM. Similarly, the response to botulinum toxin or endoscopic balloon dilation of the pylorus before G-POEM as a potential predictor of treatment response needs further study and validation.

Question 11: Should surgical pyloric interventions (pyloromyotomy or pyloroplasty) be used for the treatment of individuals with gastroparesis refractory to medical therapy?

Recommendation 11: In patients with gastroparesis refractory to medical therapy, the AGA makes no recommendation regarding the use of surgical pyloric interventions (pyloromyotomy or pyloroplasty). (No recommendation, knowledge gap)

Summary of the Evidence

Evidence informing the recommendation to use surgical pyloric interventions was derived from observational clinical studies. The studies compared the use of surgical pyloromyotomy with G-POEM, surgical pyloroplasty with G-POEM, any surgical pyloric interventions with gastric electric stimulators, and surgical pyloroplasty combined with GES compared with surgical pyloroplasty alone.^{110,111,113,114} The studies were at high risk for bias overall mainly due to confounding, selection of participants, and measurement of outcomes. Due to the lack of evidence comparing the surgical interventions to sham interventions and the lack of clinical trials comparing them to other interventions, we were unable to estimate their efficacy. Thus, this area was considered to be a knowledge gap. The details of the studies characteristics and risk-of-bias assessment are reported in [Supplementary Tables 48 and 49](#).

Discussion

Current evidence on surgical pyloric interventions for gastroparesis consisted of observational clinical studies with high risk of bias rather than RCTs. Therefore, the panel determined that there is insufficient high-quality evidence to support a recommendation for or against the routine use of surgical pyloric interventions in clinical practice. As a result, the panel emphasizes the need for further clinical trials on the use of surgical pyloromyotomy and pyloroplasty. The guidelines for G-POEM suggesting its use for medically refractory patients who have tried treatment with prokinetic agents like metoclopramide and antiemetic agents would apply to this therapy as well. Surgical pyloromyotomy and pyloroplasty involve incision of both the circular and longitudinal muscles of the pylorus, whereas endoscopic pyloromyotomy cuts only the circular muscle. Thus, there may be a benefit to performing surgical pyloromyotomy or pyloroplasty in patients who do not respond to G-POEM. Surgical pyloromyotomy and pyloroplasty can also be used for pyloric therapies when intra-abdominal surgery is being performed, such as placement of a gastric electric stimulator or performing fundoplication. Preliminary studies suggest an added clinical benefit of performing pyloroplasty at the time of placement of a gastric electric stimulator.^{115,116}

Evidence Gaps and Future Research

There is a need for sham-controlled RCTs evaluating surgical pyloric interventions in patients with gastroparesis. Head-to-head clinical trials comparing surgical pyloric interventions with endoscopic pyloric interventions in patients with refractory gastroparesis are also needed. The role of GES in combination with surgical pyloric interventions also needs to be addressed in prospective studies. Further research is also needed to identify subgroups of patients who will benefit from surgical pyloric interventions, for example those with postoperative gastroparesis or gastric retention.

Question 12: Should gastric electrical stimulation (GES) be used for the treatment of individuals with gastroparesis refractory to medical therapy?

Recommendation 12: In patients with gastroparesis refractory to medical therapy, the AGA suggests against the routine use of GES. (*Conditional recommendation, very low certainty of evidence*)

Comment: As part of shared decision making, patients and clinicians who place a higher value on the potential improvement in nausea and vomiting and lower value on the potential risk of adverse events may reasonably select to have GES placement.

Implementation Considerations

- This procedure should be reserved for select patients with medically refractory gastroparesis.
- When used, patients should be informed that GES aims to primarily improve nausea and vomiting, not abdominal pain.

Summary of the Evidence

Evidence informing the recommendation to use GES was derived from 4 crossover randomized clinical trials that compared having GES turned on with GES turned off after placement of the stimulator.^{117–120} The trials included 277 with gastroparesis refractory to medical therapy, including antiemetics and prokinetics. The patients had idiopathic, diabetes-associated, or postoperative gastroparesis. It is relevant to note that for the largest trial of 172 patients, delayed gastric emptying was not a requirement for inclusion.¹²⁰ None of the trials included a washout period between having the stimulator turned on and off, which raised concerns for possible carryover effect that could bias the results toward a null effect, that is, underestimating the efficacy of GES. The trials used scoring systems different than GCSI, thus sensitivity analyses were conducted using the SMD. Some of trials were at risk for bias due to missing outcome data, measurement of the outcome, and selection of the reported results. We also identified multiple observational studies that compared the use of GES with G-POEM, surgical pyloric interventions, and combined with other interventions.^{108,109,112–114} The observational studies were at high risk for bias overall and were not used to inform the recommendation. The details of the studies characteristics and risk-of-bias assessment are reported in [Supplementary Tables 50 and 51](#).

Benefits and Harms

Compared with having GES off, having GES on led to minimal improvements in the vomiting frequency score by 0.26 points (95% CI, -0.50 to -0.02 points; N/n = 3/229; I^2 = 55%), nausea score by 0.28 points (95% CI, -0.47 to 0.08 points; N/n = 3/229; I^2 = 76.1%), early satiety score by 0.11 points (95% CI, -0.28 to 0.07 points; N/n = 3/229; I^2 = 48.9%), postprandial fullness score by 0.15 points

(95% CI, -0.54 to 0.24 points; $N/n = 2/57$; $I^2 = 34.1\%$), symptom severity score by 0.09 points (95% CI, -0.35 to 0.17 points; $N/n = 3/90$; $I^2 = 20.5\%$), and abdominal pain score by 0.02 points (95% CI, -0.20 to 0.16 points; $N/n = 3/229$; $I^2 = 0\%$). Sensitivity analyses using SMDs showed consistent findings. In the trial that reported change in quality of life during the randomized phase, GES had no clinically important effect on quality of life over the 4-month period. Approximately 7% of patients who had the GES placement developed serious adverse events. Forest plots are presented in [Supplementary Figures 52–57](#).

Certainty in Evidence of Effects

The overall CoE was very low. The CoE was rated down due to concerns for risk of bias (arising from carryover effects, missing outcome data, and selection of reported outcomes), inconsistency (studies varied in their conclusion based on MID), and imprecision (wide CIs crossing 1 or more effect size threshold). Publication bias was suspected for some of the outcomes. The evidence profile and Evidence to Decision frameworks are included in [Supplementary Tables 52 and 53](#).

Discussion

GES presently involves high frequency stimulation of the stomach using parameters that were chosen to improve gastric emptying in preclinical studies. Patients may see improvement in symptoms of nausea and vomiting with GES without an improvement in gastric emptying; some studies suggest it has an effect on vagal sensory afferent nerves.¹²¹ Earlier studies suggested patients with diabetes had a better response to GES than idiopathic gastroparesis. Despite not meeting the minimal clinically important difference for outcomes, the panel felt that the numeric reduction in nausea and weekly vomiting frequency suggests that GES may provide a benefit to certain patients. After placement of a GES, patients responding well can have the gastric stimulation parameters increased by changing the current, frequency, and/or duration of stimulation. When to increase or how to increase has not been well studied, although there are empiric suggestions available. The panel felt that use of GES in gastroparesis should be balanced by an acknowledgment of the risk of serious adverse events (7%) often needing surgical treatment; these include infection and intestinal obstruction from the wires. In addition, additional surgery is needed for a battery change or even device removal. Data from observational studies suggest similar rates of needing additional surgery after placement. For example, a recent large cohort study that included 157 patients who had GES placement showed that 15.3% required additional procedures.¹²² GES has been evaluated in combination with other therapies. A recent study suggests added efficacy when a pyloroplasty is performed with placement of the GES—this combination of 2 complementary treatments increases gastric emptying and may further reduce symptoms.¹¹³ Temporary gastric stimulation with temporary endoscopically placed stimulating wires into the stomach is being used by some centers

to help predict patients who might respond to surgical placement of the gastric stimulator.¹²³ Note should be made of the data being derived from 4 RCTs, several comparative observational studies, and 1 retrospective cohort study. In the latter 2 study designs, GES was compared with G-POEM, pyloric surgical interventions, or was used as salvage therapy after failure of pyloric surgical intervention or G-POEM was performed after failure of GES. As for the clinical trials, they demonstrated an improvement in symptoms that fell below the MID threshold in the primary analyses. Although the trials used different scales to measure symptom severity, and the trial by Ducrotte et al¹²⁰ used a nonlinear scale for vomiting, sensitivity analyses using SMDs showed consistent findings: improvements in vomiting and other symptoms remained below the MID thresholds. Therefore, the panel issued a conditional recommendation for the selective use of gastric electrical stimulators, rather than routine use, in patients with medically refractory disease. GES treatment for gastroparesis should be reserved for select patients with medically refractory gastroparesis, particularly those with nausea and vomiting.

Evidence Gaps and Future Research

The panel suggested the need for future studies using a parallel group design to generate better quality data. Different subgroups of patients (diabetes-associated, idiopathic, and postsurgical) should be studied. Use of temporary gastric stimulation with endoscopically placed stimulating wires might help determine which patients might benefit from surgically placed gastric stimulators. Stimulator settings and location of the stimulating wires in the stomach were derived empirically and have not been well studied. The presently available device uses high-frequency stimulation that does not entrain gastric slow waves. Clinically, the panel felt that additional studies combining GES with other treatment modalities, such as pyloroplasty, might offer more complementary mechanisms of action. Finally, the panel hoped to see studies elucidating the physiologic effects of GES on gastric sensorimotor function beyond just the ideal device parameters to better understand which patient subgroups may respond to therapy and build a plausible physiologic rationale for use.

Conclusions

This AGA Guideline critically assessed the studies available for diagnosing gastroparesis and the treatments used for gastroparesis. Patient evaluation for diagnosis of gastroparesis should involve a 4-hour gastric emptying scintigraphy test, rather than shorter studies of 2 hours or less, as a number of patients will not be diagnosed properly with shorter studies. Metoclopramide or erythromycin are appropriate for initial pharmacologic treatment for patients with gastroparesis. Other treatment recommendations require shared physician-patient decision-making based on patient preferences and supportive evidence. For a number of treatments, this guideline provides helpful suggestions on the types of patients to consider for other treatments and

suggestions for implementation of other treatments. A Clinical Decision Support Tool is depicted in Figure 1. Overall, there is still considerable unmet need in the treatment of gastroparesis, and carefully performed randomized trials to evaluate efficacy of treatments are necessary.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at 10.1053/j.gastro.2025.08.004.

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Conflicts of interest

Each Guideline Panel nominee underwent a vetting process that required disclosure of all conflicts of interest. Reported conflicts were reviewed by the Chair of the AGA Clinical Guidelines Committee and adjudicated against rules and criteria in the Clinical Guidelines Committee Conflict of Interest Policy. Only nominees whose conflict of interest status ([Supplementary Table 2](#)) complied with this policy were appointed.

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