EVIDENCE-BASED GI
AN ACG PUBLICATION

In Case You Missed It
2022 ACG Clinical Guideline-Gastroparesis: Limited Evidence-Based Options

Dr Elie Al Kazzi
Associate Editor

Dr Philip Schoenfeld
Editor-in-Chief

Elie Al Kazzi, MD, MPH,[1] Philip Schoenfeld, MD, MSEd, MSc (Epi)[2]

[1]*Assistant Professor of Medicine, New York University Grossman School of Medicine, New York, NY*

[2]*Chief (Emeritus), Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI.*

MOTILITY

This summary reviews Camilleri M, Kuo B, Nguyen L, et al. ACG Clinical Guideline: Gastroparesis. Am J Gastroenterol 2022;117(8):1197-1220.

Correspondence to Philip Schoenfeld, MD, MSEd, MSc. Editor-in-Chief. Email: EBGI@gi.org

Keywords: gastroparesis; metoclopramide; gastric emptying study; prucalopride

STRUCTURED ABSTRACT

Question: What are appropriate tests to diagnose gastroparesis? Which pharmacologic and non-pharmacologic therapies are superior to placebo to improve gastroparesis symptoms and improve gastric emptying?

Design: The Patient Intervention Comparison and Outcomes (PICO) format was used to develop key questions of clinical relevance to be addressed in the guideline. Two health services librarians performed literature searches of Pubmed (MEDLINE), EMBASE, and the Cochrane Library for English language publications up to 2021 in human populations using search terms consistent with key questions.

GRADE methodology was used to assess benefits and risks of therapies and diagnostic tests. When evidence was inadequate, an expert consensus was used to

make recommendations.

Patients: Adult patients, with or without diabetes, with one or more of the following cardinal symptoms of chronic nausea, vomiting, early satiety, postprandial fullness, bloating or upper abdominal discomfort in the absence of mechanical obstruction.

Interventions/Exposure:
Diagnostic testing: Scintigraphic gastric emptying (SGE), radiopaque markers, wireless motility capsule, stable isotope (^{13}C-spirulina) breath test and pyloric EndoFLIP evaluation.
Management: dietary recommendations, dopamine receptor agonists (metoclopramide, domperidone), 5-HT4 agonists (prucalopride, clebopride, revexepride, velusetrag, felcisetrag), ghrelin agonists (relamorelin), motilin agonists (erythromycin, azithromycin), dopamine D2 antagonist (haloperidol), antiemetics and central neuromodulators (aprepitant, tradipitant, nortriptyline), herbal therapies (Rikkunshito, STW5/Iberogast), acupuncture, gastric electric stimulation, intrapyloric injection of botulinum toxin and pyloromyotomy (G-POEM).

Outcomes: Diagnosis of gastroparesis (detection of delayed gastric emptying of solids), patient reported outcomes/symptoms and improvement in gastric emptying (pharmacologic and non-pharmacologic interventions).

Data analysis: The GRADE process was used to formulate the quality of evidence and the strength of recommendation for each question, based on study design, efficacy, and risks vs benefits. When the evidence was not appropriate for the GRADE process, an expert consensus approach was used to formulate key concepts statement.

The GRADE process[1,2] uses 2 types of guideline recommendations:

Strong Recommendation: Providers should recommend this intervention for most patients. A strong recommendation is usually accompanied by High or Moderate Level of Evidence from well-designed randomized controlled trials (RCTs) or RCTs with mild methodologic limitations.

Conditional Recommendation/Suggestion*:* Many providers might suggest this therapy or diagnostic test, while other providers would not suggest this intervention in similar patients. Conditional recommendations/suggestions are usually accompanied by Low quality or Very Low quality of evidence from studies without a comparator arm or placebo for comparison.

Funding: American College of Gastroenterology, through the Practice Parameters Committee.

Results: Selected guideline recommendations are listed in Table 1. Scintigraphic gastric emptying of a solid meal with a duration of at least 3 hours is recommended for diagnosis of gastroparesis (Strong Recommendation, Moderate Quality of Evidence). Shorter studies, especially gastric emptying studies which are only 90 minutes long, should not be used because they may produce false negative results.

Notably, the only strong treatment recommendations focus on therapies NOT supported for use. Neuromodulators, ghrelin agonists, and intrapyloric botox injections are not supported for use (Strong Recommendation, Moderate Quality Evidence). Small-particle diets, metoclopramide, domperidone, antiemetic agents, and 5HT4 agonists are suggested for symptom control or improvement in gastric emptying.

COMMENTARY

Why Is This Important?

In honor of Gastroparesis Awareness Month in August 2024, we're utilizing our "In Case You Missed It" (ICYMI) series to summarize a seminal guideline from 2022 that deserves further focus. This guideline demonstrates that there is a huge unmet medical need for effective treatments based on high-quality randomized controlled trials (RCTs).

Gastroparesis is commonly caused by diabetes. Idiopathic cases are also common and may occur as a post-viral syndrome. Of course, medications may also slow gastric motility. Among patients with gastroparesis, severity of delayed gastric emptying does not correlate with symptom severity. Management is further complicated by a significant overlap with functional dyspepsia. (i.e., functional dyspepsia patients report gastroparesis-type symptoms, yet have normal gastric emptying results.)

For an easily readable and concise summary of the guideline, the ACG's *Guide to the Guidelines*[3] by Brennan Spiegel and Hetal Karsan provides outstanding commentary about interpretation and application of the recommendations.

Key Study Findings

Gastroparesis is best diagnosed with a scintigraphic solid food gastric emptying study of at least 3-4 hours duration, but patients must stop pro-motility agents, antiemetics, opiods, marijuana, and neuromodulators (e.g., nortriptyline) for 48 hours before the exam and control glucose levels in order to produce accurate results.

	Strength of Recommendation[#]	Certainty of Evidence[t]
After exclusion of mechanical obstruction, scintigraphic gastric emptying of a solid meal over a duration of 3hrs or greater remains the standard test to diagnose gastroparesis.	Strong	Moderate
Dietary management should include a small-particle diet.	Conditional	Low
Metoclopramide is suggested over no treatment for management of refractory symptoms.	Conditional	Low
Where approved for use, domperidone is suggested for symptom management.	Conditional	Low
5HT4 agonists are suggested over no treatment to improve gastric emptying.	Conditional	Low
Antiemetic agents are suggested for symptom control, but do not improve gastric emptying.	Conditional	Low
Gastric electrical stimulation may be considered for control of gastroparesis symptoms as a humanitarian use device.	Conditional	Low

Table 1. Selected guideline recommendations for management of gastroparesis.

[#]Strong Recommendation: Providers should recommend this intervention for most patients. A strong recommendation is usually accompanied by High or Moderate Level of Evidence from well-designed randomized controlled trials (RCTs), or RCTs with mild methodologic limitations.

[t]Conditional Recommendation: Many providers might suggest this therapy, while other providers would consider alternative management. This variability reflects the low quality or very low quality of evidence from studies without a comparator arm or placebo for comparison.

Initial treatment may focus on a small-particle diet[4], which essentially focuses on foods that are less than 2 mm in diameter after chewing and/or are the consistency of mashed potatoes. Metoclopramide is the only US Food and Drug Administration (FDA)-approved medication for gastroparesis and has demonstrated improvement of nausea and other symptoms as well as accelerating gastric motility in small RCTs with methodologic limitations. The risk of tardive dyskinesia with metoclopramide is frequently overestimated, and is actually about 0.1% per 1,000 person-years of use.

Caution

The major limitation is that there are so few double-blind, placebo-controlled

RCTs of potential gastroparesis treatments to identify effective treatments.

My Practice

My approach is consistent with the ACG Guideline recommendations and the commentary found in the ACG's *Guide to the Guidelines* by Spiegel and Karsan. Specifically, when I suspect gastroparesis, I get a 4-hour scintigraphic solid-food gastric emptying study with patient off opiods, marijuana, promotility agents, antiemetics and neuromodulators for 48-72 hours before the test and try to insure that glucose levels have been controlled in my diabetic patients, since hyperglycemia could impact results.

For treatment, I start with a small-particle diet and use publicly available guides from the University of Virginia.[4] If the patient has constipation, which is quite common in gastroparesis, then I'll prescribe prucalopride 2 mg twice daily, which is FDA-approved for chronic idiopathic constipation. This is the only 5-HT4 agonist that is readily available in the US. If this is inadequate and the patient is willing to try metoclopramide, then I'll discuss the risks and benefits, document that discussion, and gradually increase the dose to 10 mg 3 times daily. Officially, the FDA only approves use for up to 12 weeks, but if the patient has failed multiple interventions and is doing much better with metoclopramide, then I'll again review risks/benefits with the patient, document the discussion, and continue the medication long-term.

Domperidone 10 mg 3 times daily, which has pro-motility and anti-emetic properties, may be the most effective and safest gastroparesis treatment based on RCTs and my own clinical experience. Although it's approved for use in virtually every country in the world, it's only available in the US through an FDA-monitored extended access Investigational New Drug program[5,6], which requires a lot of paperwork. In Eastern Michigan, my patients can easily drive into Windsor, Canada, see a physician there, and fill a domperidone prescription. Your patients may want to do their own investigations about how to legally obtain domperidone.

I avoid ondansetron as an antiemetic, since it may slow intestinal motility, and frequently use cyproheptadine, which is an antihistamine, 4 mg every 8 hours as needed. Finally, if my patients are taking opiods (especially if they are using them for abdominal pain due to gastroparesis), I bluntly educate them to taper off of them or expect to live with chronic gastroparesis symptoms. Although I will see gastroparesis patients on opiods, I'm candid that their symptoms are unlikely to resolve as long as they continue opiod use. My approach is similar if the patient chronically uses cannabis. Although symptoms of cannabinoid hyperemesis syndrome may improve within 10 days of stopping marijuana use, it may take up to 2 months to see symptom improvement. So, if your patient says that they stopped marijuana for a couple of days and their nausea and abdominal discomfort did not improve, that does not eliminate cannabinoid hyperemesis syndrome as an un-

derlying cause.

For Future Research

The absence of FDA-approved therapeutics represents a huge unmet medical need for patients. This is partly due to the lack of a FDA-approved patient-reported outcome for use in RCTs.

Conflict of Interest

Drs. Al Kazzi and Schoenfeld report no relevant conflicts of interest.

REFERENCES

1. AGREE Next Steps Consortium (2017). The AGREE II Instrument [Electronic version]. https://www.agreetrust.org/resource-centre/agree-ii/. Accessed July 12, 2024.
2. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. CMAJ 2010;182:E839-842.
3. Spiegel B, Karsan H. Guide to the Guidelines, Volume 1. Bethesda, MD: American College of Gastroenterology; 2023: 67-77.
4. University of Virginia Health System Nutrition. Diet Interventions for Gastroparesis. https://med.virginia.edu>sites>2023/12>gastroparesis-long-version-2023. Accessed August 6, 2024.
5. United States Food and Drug Administration. How to Request Domperidone for Expanded Access Use. Published online February 2, 2021. https://www.fda.gov/drugs/investigational-new-drug-ind-application/how-request-domperidone-expanded-access-use. Accessed August 15, 2024.
6. United States Food and Drug Administration. Information About Domperidone. https://www.fda.gov/drugs/information-drug-class/information-about-domperidone. Accessed August 15, 2024.