IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAs) PRODUCTS LIABILITY LITIGATION	)	**CIVIL ACTION**
THIS DOCUMENT RELATES TO:	)	**MDL No. 3094**
	)	**2:24-md-03094-KSM**
ALL ACTIONS / ALL CASES	)	

ELI LILLY AND COMPANY'S MOTION TO EXCLUDE OPINIONS THAT GASTROPARESIS CAN RELIABLY BE DIAGNOSED WITHOUT CONTEMPORANEOUS OBJECTIVE TESTING

For the reasons set forth in the accompanying memorandum of law, Defendant Eli Lilly and Company hereby moves the Court for an order holding that a reliable gastroparesis diagnosis requires contemporaneous objective testing, excluding Plaintiffs' experts' opinions that a reliable gastroparesis diagnosis does not require contemporaneous objective testing, and granting such other and further relief as the Court deems just and proper.

Dated: March 5, 2025

Respectfully submitted,

/s/ Samuel W. Silver

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CERTIFACATE OF SERVICE

I hereby certify that on March 5, 2025, a true and correct copy of the foregoing Motion to Exclude Opinions That Gastroparesis Can Reliably Be Diagnosed Without Contemporaneous Objective Testing was electronically filed using the Court's CM/ECF System, which will send notification of such filing to all counsel of record.

/s/ Samuel W. Silver
Samuel W. Silver

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MEMORANDUM IN SUPPORT OF ELI LILLY AND COMPANY'S MOTION TO EXCLUDE OPINIONS THAT GASTROPARESIS CAN RELIABLY BE DIAGNOSED WITHOUT CONTEMPORANEOUS OBJECTIVE TESTING

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INTRODUCTION

The overwhelming majority—more than 80 percent—of Plaintiffs in this MDL allege gastroparesis as an injury. One of the defining features of gastroparesis is delayed gastric emptying, accompanied by gastrointestinal symptoms like early fullness after meals, abdominal pain, nausea, vomiting, belching, and bloating.[1] These symptoms are non-specific; they overlap with many other, more common conditions; and they do not alone reliably indicate delayed gastric emptying or gastroparesis. Indeed, without objective testing, gastroparesis is frequently misdiagnosed—as much as 80 percent of the time.[2] Because the evidence, claims, and defenses in this case relevant to issues like warning adequacy, preemption, and causation may turn on whether a Plaintiff has gastroparesis rather than another condition with shared symptoms, the Court recognized "the importance of proving gastroparesis specifically, as opposed to gastrointestinal symptoms generally, in this litigation." CMO #18 ¶ 5.

The Court thus prioritized as "Issue 1" resolving "whether gastroparesis may be reliably diagnosed in a clinical setting absent objective testing," observing that "many of the Plaintiffs claiming to have suffered from gastroparesis have not alleged contemporaneous objective testing occurred." *Id.* ¶¶ 4, 6. Plaintiffs have not met their burden under CMO #18 and Rule 702 to proffer expert opinions providing "good grounds" to reliably diagnose gastroparesis absent such testing. *Hoefling v. U.S. Smokeless Tobacco Co., LLC*, 576 F. Supp. 3d 262, 282 (E.D. Pa. 2021).

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[1] Ex. A, American College of Gastroenterology, *Gastroparesis* (last updated June 2021), https://gi.org/topics/gastroparesis/; Ex. B, Nov. 18, 2024 Eliot Siegel Rep.; Ex. C, Nov. 18, 2024 Daniel Raines Rep.

[2] Ex. D, Cangemi, David J, et al., *Misdiagnosis of Gastroparesis is Common: A Retrospective Review of Patients Referred to a Tertiary Gastroenterology Practice*, Clinical Gastroenterology & Hepatology 21:10, at 2670-2672 (2023), https://tinyurl.com/bdf9e83b.

To start, Plaintiffs' experts affirmatively opine that objective testing ***is required*** to reliably diagnose gastroparesis in patients whose symptoms continue after medicine withdrawal. Their gastroenterologist expert, Dr. Raines, wrote that "[p]atients who experience continued symptoms following drug withdrawal require further evaluation including imaging and/or upper endoscopy followed by formal measurement of gastric emptying." Raines Rep. at 12. Their radiologist expert, Dr. Siegel, agreed: "When gastroparesis is based on a permanent (or unknown) underlying condition, it should be confirmed by GES [gastric emptying study]." Siegel Rep. at 16. There is no dispute as to Plaintiffs who allege (as most do) that their symptoms continued after medicine withdrawal; they need objective testing to reliably diagnose gastroparesis.

Plaintiffs' experts nonetheless try to carve out an exception to the need for testing for Plaintiffs who allege their symptoms stopped after medicine withdrawal. They claim they can reliably diagnose what they call "drug-induced gastroparesis" in such patients without objective testing. Siegel Rep. at 16; Raines Rep. at 12. But they offer no reliable methodology or reasoned basis for requiring testing for some types of gastroparesis, but not for others. The question on Issue 1 is not whether the medicines at issue in this MDL can cause certain gastrointestinal ***symptoms*** in some patients—all agree that they can, just as the labels clearly warn; the question is whether a physician can reliably diagnose ***gastroparesis*** without objective testing. They cannot. Those same symptoms instead may reflect one of a variety of other mechanisms, including effects on the central or peripheral nervous systems, as opposed to delayed gastric emptying. And determining whether a patient has delayed gastric emptying (an indisputable requirement for a gastroparesis diagnosis) requires contemporaneous objective testing.

Plaintiffs' experts' methodology independently suffers from numerous other problems. Their diagnostic approach is unreliable on its own terms. It is contrary to consensus diagnostic

guidelines from the American College of Gastroenterology, the American Gastroenterological Association, and other leading national and international bodies. And the experts fail to define (or provide criteria to define) the timeframe in which a reliable gastroparesis diagnosis requires objective testing. On top of that, a symptoms-based diagnostic approach has an intolerably high error rate—up to 80 percent. A methodology that is wrong most of the time is not reliable.

The Court should hold that a reliable gastroparesis diagnosis—whether symptoms subside or continue after medicine withdrawal—requires contemporaneous objective testing confirming delayed gastric emptying, and it should exclude any of Plaintiffs' experts' opinions to the contrary.

BACKGROUND

A. Issue 1 Background

Gastroparesis is the most common injury alleged in this MDL. Plaintiffs predicted that the "vast majority, over 95 percent" of all MDL claimants would allege gastroparesis. ECF No. 220, June 10, 2024 Tr. at 17; CMO #18 ¶ 4. More than 80 percent of the lawsuits filed to date allege gastroparesis.

Plaintiffs started this litigation by describing gastroparesis as a long-term condition with "no cure."[3] Unlike the transient bouts of gastrointestinal symptoms that undisputably resolve after medicine withdrawal, Plaintiffs focused on gastroparesis that is "chronic [in] nature," resulting in "persist[ent]" or "debilitating, long-lasting effects," and requiring "life-altering treatment." ECF No. 294, Master Compl. ¶¶ 43, 46; *see also* ECF No. 339, Dec. 17, 2024 Tr. at 15 (claiming that "gastroparesis problems persisted for six months or more"); ECF No. 175, July 3, 2024 Ltr. at 13 ("Plaintiffs' claims ***do not*** arise merely from nausea, vomiting, or constipation. Rather, Plaintiffs'

[3] Aug. 2, 2023, Compl., ¶ 8, ECF No. 1, *Bjorklund v. Eli Lilly and Company et al.*, Case No. 2:23-cv-01020 (W.D. La.).

claimed injuries are prolonged, life-threatening digestive dysfunction such as gastroparesis[.]") (original emphasis). Today, most Plaintiffs allege unresolved gastroparesis. For example, of the 320 Plaintiff Fact Sheets submitted to date in cases naming Lilly that also contain allegations of gastroparesis, 310 of them—96.9%—allege that they have gastroparesis that is long term or "has [not] resolved." CMO #12, Ex. A PFS § IV.B.3.b.

The Court prioritized as Issue 1 "whether gastroparesis may be reliably diagnosed in a clinical setting absent objective testing." CMO #18 ¶ 4; *see also id.* (describing the issue as whether "to reliably diagnose a patient with gastroparesis[,] the clinician would have to have performed objective testing, such as a gastric emptying study (GES), at the time symptoms presented"); *id.* (observing that "many of the Plaintiffs claiming to have suffered from gastroparesis have not alleged contemporaneous objective testing occurred"). In doing so, the Court recognized "the importance of proving gastroparesis specifically, as opposed to gastrointestinal symptoms generally, in this litigation." *Id.* ¶ 5. For example, the Court explained, "to the extent a symptom or illness was adequately warned for on the label," certain claims could "fail under the learned intermediary and similar doctrines." *Id.*; *see also* ECF No. 223, July 10, 2024 Tr. at 59-60 (questioning how the name of an injury could really be immaterial in a warning case "if the label warned about the injury").

Plaintiffs told the Court that Lilly was "wrong" to argue that objective tests are required to diagnose gastroparesis; according to Plaintiffs at the time, the need for testing is "not capable of assessment without the particular facts of a claim." ECF No. 185, July 3, 2024 Ltr. at 9; ECF No. 223, July 10, 2024 Tr. at 60. The Court invited Plaintiffs to produce "an expert that can say that." ECF No. 224, July 12, 2024 Tr. at 30; *see also* ECF No. 227, Aug. 8, 2024 at Tr. 16 (recognizing that Issue 1 "is going to be decided based on [the] experts"). But Plaintiffs' experts said the

opposite. They concede that objective testing is ***required*** to reliably diagnose gastroparesis in patients whose symptoms continue after medicine withdrawal—*i.e.*, objective testing is required to diagnose the type of gastroparesis that most Plaintiffs allege in this MDL. Raines Rep. at 12; Siegel Rep. at 16. And Plaintiffs' experts also fail to provide a reliable and admissible methodology for diagnosing gastroparesis without objective testing in patients whose symptoms resolve after medicine withdrawal.

B. Gastroparesis Diagnosis

Plaintiffs' experts agree that a gastroparesis diagnosis requires: (1) "gastrointestinal symptoms" like nausea; (2) "the absence of a mechanical obstruction"; and (3) "delayed gastric emptying"—*i.e.*, slowing of the movement of food out of the stomach. Siegel Rep. at 10. There is no dispute that delayed gastric emptying is critical to a gastroparesis diagnosis because it is the delayed gastric emptying that distinguishes gastroparesis, specifically, from other conditions that present with the same symptoms. *Id*. There is also no dispute that the "gastrointestinal symptoms" associated with gastroparesis "are nonspecific and overlap to a greater or lesser degree with many conditions" that have nothing to do with delayed gastric emptying. *Id.* at 10, 15. "Common potential alternative diagnoses" of those same symptoms range from "functional dyspepsia" to "neurological conditions" to a host of "[o]ther GI disorders." *Id*. at 15-16. And in patients taking GLP-1 RA medicine, symptoms of gastroparesis may not signify delayed gastric emptying at all, but instead result from the medicine's effects on the central nervous system or other mechanisms of action.[4] That is why gastrointestinal symptoms can occur even in fasting patients taking GLP-

[4] Ex. E, Bettge K, Kahle M, Abd El Aziz MS, Meier JJ and Nauck MA, *Occurrence of Nausea, Vomiting And Diarrhoea Reported as Adverse Events in Clinical Trials Studying Glucagon-Like Peptide-1 Receptor Agonists: A Systematic Analysis of Published Clinical Trials*, Diabetes Obes Metab, 2017;19(3): 336-347.

1 RAs, suggesting they are "caused by direct interactions with CNS GLP-1 receptors" and "probably ***not*** related to the effects of GLP-1 RA treatment on gastrointestinal functions (e.g., deceleration of gastric emptying)."[5]

Because of this overlap of symptoms, gastroparesis is frequently misdiagnosed. Recent research indicates that over 80% of gastroparesis diagnoses are in error.[6] The 339 "adult patients referred to Mayo Clinic Jacksonville specifically for the evaluation of [gastroparesis]" reported the following symptoms: nausea (89.1%), abdominal pain (76.4%), constipation (70.5%); vomiting (65.8%); bloating (37.5%), and early satiety (34.5%). *Id.*[7] But "[a]fter comprehensive assessment and objective testing, including [GES], the study found that 80.5% of the patients referred for evaluation and management of gastroparesis did not have gastroparesis." Ex. F, Dec. 23, 2024 Nguyen Rep. at 3-4; *see also* Ex. G, Jan. 31, 2025 Siegel Dep. at 171-74. Other research in the specific context of patients taking GLP-1 RA medicines similarly finds that gastrointestinal symptoms do not indicate delayed gastric emptying. One study showed that, of 696 patients with gastrointestinal symptoms and who "were suspected of having delayed gastric emptying such that a GES was ordered," only 241—less than 35%—"actually had delayed gastric emptying." Nguyen Rep. at 17; *see also* Ex. H, Jan. 29, 2025 Daniel Raines Dep. at 248-51; Siegel Dep. at 147-49, 153-54.[8] In other words, even when doctors had a high suspicion that delayed gastric emptying

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5 Ex. I, Michael A. Nauck, Daniel R. Quast, Jakob Wefers, Juris J. Meier, *GLP-1 Receptor Agnoists in the Treatment of Type 2 Diabetes – State-of-the-Art*, Molecular Metabolism, Vol. 46, 101102 (2021), ISSN 2212-8778 at 10 (emphasis added).

6 Ex. D, *supra* Cangemi.

7 *Id.*

8 Ex. J, Lupianez-Merly C, Dilmaghani S, Blundo R, et al., *Effects of GLP-1 Receptor or a Dual GLP-1/GIP Receptor Agonists on Gastrointestinal Symptoms and Gastric Emptying: Results From a Large Clinical Practice Database*, AGA Abstracts S-1066-S-1067 (2024).

could be present, that symptom-based prediction was wrong nearly two-thirds (65%) of the time. Plaintiffs' experts identify no contrary data.

In light of these data, it is not surprising that leading gastroenterology guidelines require objective testing to diagnose gastroparesis. The American College of Gastroenterology (ACG) identifies four types of diagnostic testing, of which GES is "the gold standard."[9] The American Gastroenterological Association (AGA) emphasizes that symptoms must be considered "in the context of objectively confirmed gastric emptying delay."[10] The Rome Foundation and International Neurogastroenterology and Motility Societies' Consensus on Idiopathic Gastroparesis (published in January 2025) recognizes that, because "symptoms of gastroparesis lack specificity, a demonstration of delayed gastric emptying is necessary for diagnosis," and "an abnormal gastric emptying test" is "***mandatory***."[11]

Plaintiffs' experts agree: "One of the necessary conditions for diagnosing gastroparesis is delayed gastric emptying[.]" Raines Dep. at 100; *see also* Siegel Rep. at 10. They also agree that GES— a "test that measures how quickly food leaves the stomach and enters the small intestine"— is "the most reliable method for objectively assessing gastric emptying and confirming the diagnosis of gastroparesis." Siegel Rep. at 18. As one of Plaintiffs' experts acknowledged, GES

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[9] Ex. K, Camilleri, Michael et al. *ACG Clinical Guideline: Gastroparesis*, 117 Am. J. of Gastroenterology 1197, 1203 (2022), doi:10.14309/ajg.0000000000001874.

[10] Ex. L, Lacy, Brian E. et al., *AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis: Expert Review*, 20 Clinical Gastroenterology and Hepatology 491, 497-98 (2022), doi:10.1016/j.cgh.2021.10.038.

[11] Ex. M, Schol, Jolien et al., *Rome Foundation and International Neurogastroenterology and Motility Societies' Consensus on Idiopathic Gastroparesis*, The Lancet, 10 Gastroenterology & Hepatology at 68, 70, 76 (2025), doi: 10.1016/S2468-1253(24)00284-X (emphasis added); *see also id.* (Gastroparesis diagnosis "requires" "delayed gastric emptying, measured by a 4 h scintigraphy or gastric emptying breath test of a mixed composition meal in the absence of mechanical obstruction.").

is "the 'gold standard' by which other tests are validated." Raines Rep. at 10-11; *see also* Siegel Rep. at 18 (explaining that the ACG and the AGA "recognize the gastric emptying study as the most reliable method for objectively assessing gastric emptying and confirming the diagnosis of gastroparesis"). GES is widely recognized as safe and is "the most common modality used in the US." Nguyen Rep. at 14; *see also* Siegel Dep. at 40-41.

Other tests that can show objective evidence of delayed gastric emptying include a Gastric Emptying Breath Test (GEBT), which "can be performed in clinicians' offices or even patients' homes," and a Wireless Motility Capsule (WMC), which involves swallowing a "Smartpill." Seigel Rep. at 12. WMC was available and frequently used until the technology owner discontinued production in 2023. Siegel Rep. at 12; Raines Rep. at 10-13; Ex. N, Feb. 13, 2025 Nguyen Dep. at 24; Nguyen Rep. at 8.

C. Plaintiffs' Experts

Plaintiffs offer two experts to opine on gastroparesis diagnostic requirements: Dr. Raines (a gastroenterologist) and Dr. Siegel (a radiologist).[12]

Dr. Raines: Dr. Raines recognizes that many "common alternative" conditions can produce symptoms similar to gastroparesis, whereas actual gastroparesis requires a "delay in gastric emptying in the absence of mechanical obstruction." Raines Rep. at 4, 7-10. In Dr. Raines' "own practice," "30 percent of patients . . . are misdiagnosed" with gastroparesis. Raines Dep. at 285. As Dr. Raines admitted at his deposition, there are "[t]oo many things to talk about" that "would complicate a case such that you can't diagnose drug-induced gastroparesis based on history and physical alone." *Id.* at 116.

[12] Plaintiffs previously disclosed and provided an expert report from another gastroenterologist, Dr. Fass, but withdrew Dr. Fass as an expert on January 30, 2024.

Dr. Raines also admits that objective testing is required for at least some gastroparesis diagnoses. As he explains, "[p]atients who experience continued symptoms following drug withdrawal ***require*** further evaluation including imaging and/or upper endoscopy followed by formal measurement of gastric emptying by GES, GEBT, or WMC." Raines Rep. at 12 (emphasis added); *see also* Raines Dep. at 11-12 (disclaiming substantive changes to his report). He agrees that "[t]his [formal measurement] approach is consistent with various diagnostic algorithms proposed in the literature." Raines Rep. at 12-13 ("A GES, GEBT, or WMC should be ordered to document delay in gastric emptying and assess for severity.").

Dr. Raines nevertheless maintains that diagnosing so-called "[d]rug-induced" gastroparesis does not always require such testing. He describes drug-induced gastroparesis as a condition "in which symptoms of nausea, vomiting, abdominal pain, and/or early satiety develop following the initiation of a medication" that is "known to inhibit gastric motility"—and which resolve after medicine withdrawal. Raines Rep. at 10-12; *see also* Raines Dep. at 161. But he admits that his approach is out of step with medical consensus. Dr. Raines recognizes that "several guidelines" say "gastroparesis cannot be diagnosed based on symptoms alone." Raines Dep. at 149, 171. He likewise admits that his theory for symptom-based diagnosis "i[s] not spelled out" in the guidelines—even by the U.S. gastroenterology societies of which he is "an active member," all of which emphasize the need for objective testing. *Id.* at 49-54, 204.

Dr. Siegel: Dr. Siegel is not a gastroenterologist. Siegel Rep. at 3. His litigation expert report is the first time he has "put together or written an opinion on the topic" of gastroparesis diagnoses. *Id.* at 5; Siegel Dep. at 277-78. Dr. Siegel agrees "that gastroparesis is often misdiagnosed," with the evidence showing "that not all patients who experience symptoms associated with abnormal gastric emptying, in fact, have delayed gastric emptying as measured by

GES." Siegel Dep. at 165, 291; Siegel Rep. at 17 & fn.3; *see also* Siegel Dep. at 47 ("[T]he number of patients who have symptoms of . . . gastroparesis is greater than the number of patients who have gastroparesis.").

Like Dr. Raines, Dr. Siegel opines that "[w]hen gastroparesis is based on a permanent (or unknown) underlying condition, it ***should be confirmed by GES*** and upper endoscopy." Siegel Rep. at 16 (emphasis added). "[T]he symptoms of gastroparesis are nonspecific[,] overlap to a greater or lesser degree with many conditions," and can "be difficult to distinguish;" thus, "***it is important to use confirmatory diagnostic testing***." *Id.* at 15-16 (emphasis added). At his deposition, Dr. Siegel briefly reversed course on his disclosed opinion that unresolving gastroparesis should be confirmed with diagnostic testing. Siegel Dep. at 84-85, 89. But when asked how he would distinguish non-transient gastroparesis from another condition that presents similar symptoms, Dr. Siegel "d[id]n't know." *Id.* at 91. Ultimately, he chose to "stand by the report." *Id.* at 287.

Dr. Siegel, like Dr. Raines, also opines that "drug-induced gastroparesis" can be "obvious from history and physical examination" and can be diagnosed "without the need to order a GES or other imaging." Siegel Rep. at 16-17. He bases this opinion on temporal association: "If the gastric emptying effect of the drug is responsible for the patient's symptoms, they should begin to resolve as the drug clears his or her system." *Id.* However, he admits that this method "for diagnosing drug-induced gastroparesis" is not one he has "***ever actually done*** to formally diagnose a patient." Siegel Dep. at 202 (emphasis added). In fact, Dr. Siegel has never "formally diagnosed a patient with GLP-1 RA-induced gastroparesis" at all. *Id.* at 199. And each of "[t]he 100 patients or so [he] describe[s] as having diagnosed with gastroparesis in [his] report" did have an objective "gastric emptying study." *Id.* at 189, 205-06. Dr. Siegel's practice—unlike his litigation

opinions—is consistent with the guidelines from the American College of Radiology (of which Dr. Siegel is a member), which provides "that gastric emptying studies provide information that is indispensable in the management of patients presenting with upper GI symptoms." *Id.* at 113-14, 117-18.

D. Defendants' Expert

Dr. Nguyen is a Clinical Professor of Medicine and Interim Chief of Gastroenterology & Hepatology at Stanford University and current Vice Chair of the Clinical Practice Section of the AGA. Nguyen Rep. at 1-2. She is one of the leading gastroparesis researchers in the U.S. and the world. Dr. Nguyen was the Director of Neurogastroenterology and Gastrointestinal Motility in Stanford's Division of Gastroenterology, has published nearly 100 papers and book chapters on gastroparesis and similar disorders, and has frequently lectured on gastroparesis. *Id.* at 1. She was a content expert co-author of the ACG Clinical Guideline on Gastroparesis and was one of two U.S. delegates selected to work on the January 2025 Rome Consensus guidelines. *Id.* She has treated thousands of patients with gastroparesis as well as conditions that share symptoms with gastroparesis. *Id.* at 1, 15.

Dr. Nguyen agrees (like Plaintiffs' experts) that "[s]ymptoms of gastroparesis are nonspecific, meaning that they frequently overlap with the symptoms of other disorders, such as functional dyspepsia, dumping syndrome, rumination syndrome, gastritis, cyclic vomiting syndrome" and a host of "other[] conditions." *Id.* at 3, 16-17. In her own practice, Dr. Nguyen "will not make a diagnosis without a gastric emptying study (typically scintigraphy) performed consistent with the consensus methodology." *Id.* at 15. Dr. Nguyen also spends substantial "time correcting prior misdiagnoses of gastroparesis" by other physicians. *Id.* Dr. Nguyen opines that an "accept[able]… diagnosis of gastroparesis" requires an objective gastric emptying test. *Id.* at 8. This is consistent with the "guidelines by all major clinical societies involved in the evaluation

and management of gastroparesis." *Id.* For "over two decades"—and especially in recent years—organizations including the AGA, the ACG, and international bodies recognize that "the clinical standard of care for the diagnosis of gastroparesis include[s] the definitive requirement for objective gastric emptying testing." *Id.* at 8-13, 16.

LEGAL STANDARDS

Rule 702 requires this Court to "determine whether an expert's conclusions are reliable" and supported by "good grounds," with Plaintiffs bearing the burden to "demonstrate[] to the court that it is more likely than not that the proffered testimony meets the admissibility requirements." *Csaszar v. Monarch Med., LLC*, 2024 WL 1288627, at *2 (E.D. Pa. Mar. 26, 2004); Fed. R. Evid. 702. This inquiry "applies to all aspects of an expert's testimony: the methodology, the facts underlying the expert's opinion, and the link between the facts and the conclusion." *Hoefling*, 576 F. Supp. 3d at 271 (internal quotation marks omitted); *see also In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 797 (3d Cir. 2017) (explaining that "***any*** step that renders the analysis unreliable under the ***Daubert factors renders the expert's testimony inadmissible***") (original emphasis). Rule 702 was recently amended to "emphasize" that the preponderance-of-evidence admissibility showing is a threshold inquiry, rather than an eventual question of "weight for the jury." *Csaszar*, 2024 WL 1288627, at *2.

Under this framework, medical diagnostic approaches like a "differential diagnosis" require more than "subjective belief or unsupported speculation"; they demand reasoning "grounded in 'methods or procedures of science'" and that is "sufficiently tied to the facts of the case." *Hoefling*, 576 F. Supp. 3d at 280, 285. [13] The question here is not whether a "differential

[13] The term "differential diagnosis" is sometimes used to describe a process for determining an external cause of a condition or illness, but that is not at issue now. As some courts have

diagnosis" can be a reliable methodology; the question is whether Plaintiffs' experts have met their burden to show that they can reliably diagnose gastroparesis without performing objective testing to confirm delayed gastric emptying.

A differential diagnosis approach must identify "which of two or more diseases with similar symptoms is the one from which the patient is suffering[]" using a "systematic and objective elimination of alternative causes." *U.S. v. Fleet Mgmt., Ltd.*, 332 F. App'x 753, 755 (3d Cir. 2009) (emphasis omitted). That means the "expert must 'rule in' then 'rule out' possible causes of the illness," and in doing so "offer[] a good explanation as to why his or her conclusion remains reliable" in the face of "plausible alternative cause[s]." *Hoefling*, 576 F. Supp. 3d at 281. This process-of-elimination approach requires "methodically ruling out alternative causes," to avoid "a conclusion-oriented selection process" under the guise of a "holistic" opinion. *Id.*

Ultimately, because "[f]aith in the wisdom of treating physicians is not the stuff of science," an expert must provide "evidence for why [he or she has] a 'good ground' for ruling out" other diseases—"the Court is not required to take their word for it." *Id.* at 283 (citation omitted). "'Judgment' does not substitute for scientific method; without a reliable method, result-oriented 'judgment' cannot be distinguished from scientifically or methodologically-based judgment." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 608 (D.N.J. 2002), *aff'd*, 68 F. App'x 356 (3d Cir. 2003). Moreover, when the expert's methodology relies on "nonstandard techniques," it is especially vital that any departure from normal practices "be well-explained." *Zoloft*, 858 F.3d at 797 ("[U]se of standard techniques bolster the inference of reliability; nonstandard techniques need to be well-explained.").

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observed, when determining the external cause of a condition or illness, "differential etiology is the more precise term." *Hoefling*, 576 F. Supp. 3d at 280 n.5.

ARGUMENT

I. THERE IS NO DISPUTE THAT OBJECTIVE TESTING IS REQUIRED TO RELIABLY DIAGNOSE GASTROPARESIS THAT *DOES NOT* RESOLVE AFTER MEDICINE WITHDRAWAL.

Plaintiffs' experts concede that contemporaneous objective testing is required to diagnose gastroparesis that does not resolve following medicine withdrawal. Raines Rep. at 12; Siegel Rep. at 16. Plaintiffs did not disclose any expert who opined to the contrary. The Court should thus rule that contemporaneous objective testing is required to diagnose gastroparesis that does not resolve after a patient stops using the medicine.

II. THE COURT SHOULD EXCLUDE THE OPINION THAT CONTEMPORANEOUS OBJECTIVE TESTING IS NOT NEEDED FOR GASTROPARESIS THAT *DOES* RESOLVE AFTER MEDICINE WITHDRAWAL.

Notwithstanding the consensus that contemporary objective testing is needed to reliably diagnose gastroparesis where symptoms continue after medicine withdrawal, Plaintiffs' experts opine that they can reliably diagnose gastroparesis that does resolve after medicine withdrawal without objective testing, using a "differential diagnosis" methodology. Raines Rep. at 6-8; Siegel Rep. at 11-18. This opinion should be excluded under Rule 702 because it is unreliable on its own terms, conflicts with the established medical consensus, and has a startlingly high error rate.

A. Plaintiffs' Experts Do Not Offer a Reliable Differential Diagnosis Methodology.

Plaintiffs' experts' differential diagnosis falls short of Rule 702's reliability requirements; their experts' methodology does not reliably "rule in" and "rule out" "plausible alternative cause[s]" through a "systematic and objective" process of elimination. *Hoefling*, 576 F. Supp. 3d at 281, 284; *Magistrini*, 180 F. Supp. 2d at 609-11 (similar). Their methodology cannot reliably diagnose gastroparesis—as opposed to another condition without delayed gastric emptying but that presents with the same symptoms—without contemporaneous objective testing.

An expert's methodology is "unreliable" where, as here, the "defendant points to a plausible alternative cause and the doctor offers ***no*** explanation" for ruling it out. *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 759 n.27, 760 (3d Cir. 1994) (original emphasis); *In re Zostavax (Zoster Vaccine Live) Prods. Liab. Litig.,* 579 F. Supp. 3d 675, 679 (E.D. Pa. 2021) ("expert must rule out" "obvious alternative causes").[14] Plaintiffs' experts both agree that one of the "necessary conditions for diagnosing gastroparesis" is "the presence of delayed gastric emptying." Siegel Rep. at 10; Raines Dep. at 100, 117; *accord* Siegel Dep. at 42 (agreeing that "gastroparesis requires the presence of delayed gastric emptying"). Dr. Siegel admits that though delayed gastric emptying might manifest via symptoms of gastrointestinal distress, those symptoms "are nonspecific and overlap to a greater or lesser degree with many conditions"—including "common potential alternative diagnoses." Siegel Rep. at 15.[15] He also admits that "[a]ll of the[] conditions" mimicking gastroparesis "can occur in people taking GLP-1." Siegel Dep. at 71, 247. For his part, Dr. Raines agrees that gastroparesis is only "one of many causes of nausea and vomiting," Raines Dep. at 211-12, and he could not include in his report "every possible cause of chronic nausea and vomiting [] because they're too exhaustive." *Id.* at 299; *see also id.* at 98-99 (agreeing that "[n]ot everyone who has chronic nausea and vomiting for greater than seven days has gastroparesis"). Plaintiffs' experts assert that symptom manifestation and/or the temporal connection between

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[14] *See also In re Zostavax (Zoster Vaccine Live) Prods. Liab. Litig*., 711 F. Supp. 3d 317, 318–19 (E.D. Pa. 2022) ("The law requires a plaintiff's medical expert's opinion on causation to exclude any obvious alternative cause."), *aff'd*, 2024 WL 3423709 (3d Cir. July 16, 2024); *Zoloft*, 858 F.3d at 795-96 (3d Cir. 2017) (expert must show "conclusion remained reliable in the face of alternative causes").

[15] These include "functional dyspepsia, dumping syndrome, rumination syndrome, gastritis, cyclic vomiting syndrome, cannabinoid hyperemesis, cannabis withdrawal, peptic ulcer, narcotic bowel syndrome, anorexia nervosa, bulimia nervosa, median arcuate ligament syndrome, superior mesenteric artery syndrome, postural orthostatic tachycardia syndrome, gastric outlet obstruction, biliary colic, and chronic pancreatitis, amongst others." Nguyen Rep. at 3; *see also* Siegel Rep. at 14-16; Raines Rep. at 6, 9-10.

symptom development and medicine can be used to diagnose gastroparesis, but they offer no reliable methodology to support why either metric reliably confirms delayed gastric emptying. This is especially so where the available research shows symptoms do not indicate delayed gastric emptying (including in the patients taking GLP-1 RA medicines) well over half of the time.[16]

Symptoms. Neither of Plaintiffs' experts could articulate any reliable methodology to support their opinion that the presentation of symptoms can rule out alternative causes. For example, Dr. Raines opined that the severity of symptoms could distinguish gastroparesis from one of the many other potential alternative causes, but ultimately conceded that his approach lacks any grading system and is "circular":

> Q. So you don't have a grading of the severity of symptoms that would be required to diagnose drug-induced gastroparesis in the absence of scintigraphy, true?
> A. I never created a grading system for diagnosis of drug-induced gastroparesis based on the symptoms.
> Q. You just know it when you see it?
> A. Yeah … It's more like it depends on the individual case.
> ***
> Q. The more severe the GI-related symptoms, the more likely you are to conclude that they're suffering from drug-induced gastroparesis?
> A. The more classic their presentation is for drug-induced gastroparesis, the more likely.
> **Q. *It seems circular to me, sir.***
> **A. *I know, me, too...***

Raines Dep. at 141-42 (emphasis added); *see Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 519 (W.D. Pa. 2003) (excluding opinions as "fatally circular"). Similarly, Dr. Siegel suggests that unspecified "lab values" might suffice to distinguish gastroparesis from one of the other many potential alternative causes, yet he "c[ouldn't] tell" and "d[id]n't know" "what the specific [lab values] are that would make th[e] distinction." Siegel Dep. at 90-91.

[16] Ex. J, *supra* Lupianez-Merly.

In short, Plaintiffs' experts do not offer "'good grounds' for ruling out" the myriad other conditions that share common symptoms with gastroparesis. *Hoefling*, 576 F. Supp. 3d at 282; *Magistrini*, 180 F. Supp. 2d at 609-11.

Temporal connection. Plaintiffs' experts also point to the temporal connection between symptoms and medicine use. But this timing-based approach does not supply "good grounds" to reliably rule out alternative causes either. *See Zostavax*, 579 F. Supp. 3d at 675, 679-85 (rejecting even a "clear temporal link" between medicine use "and the occurrence of" symptoms). Plaintiffs' experts do not explain why a temporal relationship between symptoms and medicine use bears on the question whether a patient also has delayed gastric emptying (and thus could have gastroparesis). Nor could they. In GLP-1 RA patients, symptoms of gastroparesis like nausea, abdominal pain, and vomiting "may, rather, be caused by a direct effect on the central nervous system" that has nothing to do with delayed gastric emptying.[17] *See also* Siegel Dep. at 251 (agreeing that certain medicines can work by impacting the central nervous system, instead of or in addition to delayed gastric emptying); Nguyen Dep. at 96-97 (since studies show that most GLP-1 RA patients with gastrointestinal systems do not have delayed gastric emptying, "there has to be a different [non-delayed-gastric-emptying] mechanism that is driving these symptoms"). Where these symptoms are not accompanied by delayed gastric emptying, the underlying medical condition cannot be gastroparesis.

In re Zostavax is instructive. There, the MDL court excluded plaintiffs' expert opinions that shingles outbreaks were caused by the defendant's vaccine instead of by a naturally occurring virus identifiable by an objective "PCR test"—a test no plaintiff had undergone. *Zostavax*, 579 F. Supp. 3d at 677. Those plaintiffs asserted that the vaccine "causes shingles in 15% or more of

[17] *See* Ex. E, *supra* Bettge.

those inoculated" and that there were "temporal link[s]" as short as "seven days between [] receipt of [the vaccine] and the appearance of shingles." *Id* at 677, 683. The court held, however, that the expert failed to reliably rule out the "obvious alternative cause" of the natural virus. *Id.* at 683. In other words, even if a "temporal link" between a patient's medicine use and symptoms might allow a physician to "rule[] ***in***" certain conditions as a potential "culprit," the physician still must "rule ***out***" other "obvious alternative cause[s]" of those symptoms. *Id.* at 681-85 (emphases added). Here, Plaintiffs' experts offer no reliable basis to rule out even other conditions that could be attributable to GLP-1 RA use.

Furthermore, neither of Plaintiffs' experts provides a reliable or defined boundary for the purported temporal link he claims is sufficient to obviate the need for objective testing. According to Dr. Siegel, "drug-induced gastroparesis" does not require objective testing because "[i]f the gastric emptying effect of the drug is responsible for the patient's symptoms, they should begin to resolve as the drug clears his or her system." Siegel Rep. at 17. Dr. Siegel admitted that there are no "hard and fast rules" to guide determinations over whether symptoms "w[ere] due to [delayed] gastric emptying based on how a patient responds after the medication is withdrawn." Siegel Dep. at 80. Some patients may respond "more quickly than others" and "[s]ome may never respond" to the medicine withdrawal. *Id.* This admittedly "***indefinite***[]" temporal approach, *id.* (emphasis added), is unscientific and unreliable. *See Zostavax*, 579 F. Supp. 3d at 682-83.

Likewise, Dr. Raines reasons that "[i]mprovement in symptoms following withdrawal of an offending drug supports a diagnosis of drug-induced gastroparesis and obviates the need for additional testing." Raines Rep. at 14. And Dr. Raines claims he could diagnose gastroparesis even before withdrawal if symptoms last seven days, but he admits those seven-day symptoms overlap with many other conditions. Raines Dep. at 98-99, 163; Raines Rep. at 7-10. In any event,

he admitted that, if symptoms did not completely resolve after discontinuation, he would do more testing. Raines Dep. at 108. Plaintiffs' proposed symptom-based approach is inadmissible, as neither expert "set forth the method for weighing the evidence upon which his opinion is based." *Magistrini*, 180 F. Supp. 2d at 608; *see also Zostavax*, 579 F. Supp. 3d at 683.

Plaintiffs turn the differential diagnosis analysis "inside out and leap[] to an unreliable" conclusion: that just because a Plaintiff took a GLP-1 RA and developed symptoms that subsided after withdrawal they necessarily had gastroparesis, rather than other gastrointestinal symptoms that also happened to resolve after withdrawal. *Soldo*, 244 F. Supp. 2d at 567. Their "I know it when I see it" opinion should be excluded. *Hager v. Vertrue, Inc*., 2011 WL 4501046, at *1 (D. Mass. Sept. 28, 2011) (citing *Gen. Elec. Co. v. Joiner,* 522 U.S. 136, 146 (1997)).

The "I know it when I see it" opinion is particularly unreliable coming from Dr. Siegel. Dr. Siegel is not a gastroenterologist and has never diagnosed a patient with gastroparesis without conducting a gastric emptying study. Siegel Dep. at 189-92, 199, 202, 205-06. Dr. Seigel's opinions, for which he lacks the necessary qualifications, and which are contrary to "his own practice," should be excluded regardless. *Hoefling*, 576 F. Supp. 3d at 282.

B. Plaintiffs' Experts' Methodology Is Contrary To Settled Medical Consensus And Results In High Rates of Misdiagnosis.

Making matters worse, Plaintiffs' experts' opinions are contrary to consensus guidelines and use a methodology that frequently results in misdiagnoses. Where an expert's opinions depart from "standard techniques," the departure "need[s] to be well-explained." *Zoloft*, 858 F.3d at 797. In other words, a court should exclude a differential diagnosis where the physician "engaged in very few standard diagnostic techniques by which doctors normally rule out alternative causes" and "offered no good explanation as to why his or her conclusion remained reliable." *Feit v. Great-W. Life & Annuity Ins. Co.*, 460 F. Supp. 2d 632, 645 (D.N.J. 2006).

Here, Plaintiffs' experts' both deviate from medical consensus and fail to rule out alternative causes that share symptoms with gastroparesis. The medical consensus is unequivocal and uniform: gastroparesis cannot be diagnosed by symptoms alone; diagnosis requires objective testing.[18] The AGA recommends diagnosing refractory gastroparesis "in the context of reliably established gastric emptying delay."[19] And the Rome Foundation recognizes that, precisely because "symptoms of gastroparesis lack specificity, a demonstration of delayed gastric emptying is necessary for diagnosis," and "an abnormal gastric emptying test" is "***mandatory.***"[20] These leading authorities require an objective test because that is the only way to reliably diagnose gastroparesis as opposed to any other condition that presents with the same symptoms.

To be sure, some doctors in their clinical practices may use the term "gastroparesis" if they observe gastrointestinal symptoms in their patients who are also using a medicine (like Lilly's medicine here) where delayed gastric emptying is a well-known and labeled effect. While clinicians may forego testing if a "***treatment*** would have been the same regardless of [the] cause," that real-world practice "does not diminish the importance of [objective testing] for determining the ***cause***" of the symptoms in court. *Hoefling*, 576 F. Supp. 3d at 282-83 (original emphasis; excluding expert opinions that chewing tobacco caused oral cancer where needle biopsy of the tumor was indeterminate, a tissue biopsy was necessary to reliably rule out HPV as an alternative cause). That is so even if the testing must be contemporaneous, is no longer available, and thus would "prevent[]" a doctor "from ever being able effectively to 'rule in' or 'rule out'" an alternative cause. *See Feit v. Great W. Life & Annuity Ins. Co.*, 271 F. App'x 246, 255 (3d Cir.

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[18] Ex. K, *supra* Camilleri.

[19] Ex. L, *supra* Lacy.

[20] Ex. M, *supra* Schol (emphasis added).

2008) (affirming exclusion of opinion on cause of death); *see also Zostavax*, 579 F.Supp.3d at 677 (excluding opinions that plaintiffs' shingles outbreaks were caused by vaccine instead of by a naturally occurring virus identifiable by an objective "PCR test"—a test no plaintiff had undergone or could undergo once the rash had resolved).

Here, there is no dispute that general gastrointestinal symptoms could be caused by gastroparesis or any other number of conditions. Because of that overlap, without properly performed contemporaneous objective testing, the error rate for diagnosing symptoms as "gastroparesis" is strikingly high—as high as 80%.[21] That error rate is unacceptably high under any measure and confirms the need for contemporaneous objective testing to reliably confirm the presence of delayed gastric emptying. *See, e.g.*, *Polymer Dynamics, Inc. v. Bayer Corp.*, 2005 WL 1041197, at *3 (E.D. Pa. May 4, 2005) (margins of error between 25% and 50% were "unacceptable" and therefore "unreliable").

CONCLUSION

For these reasons, Lilly respectfully requests the Court hold that a reliable gastroparesis diagnosis—whether symptoms continue after medicine withdrawal or not—requires contemporaneous objective testing, and it should exclude any of Plaintiffs' experts' opinions to the contrary.

[21] Plaintiffs' experts could quantify an error rate for their own approach, to the extent they claim it differs from the highly error-prone symptom-based approach. *See* Siegel Dep. at 261-62; Raines Dep. at 210-12. That failure alone weighs heavily toward exclusion under Rule 702. *See Soldo*, 244 F. Supp. 2d at 527; *id.* at 516 (excluding opinion where expert "cannot articulate a known error rate for his application of the differential diagnosis, except to state that erroneous conclusions based on the differential diagnosis are 'constantly sobering'").

Dated: March 5, 2025

Respectfully submitted,

/s/ Samuel W. Silver

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Attorneys for Defendant Eli Lilly and Company

CERTIFICATE OF SERVICE

I hereby certify that on March 5, 2025, a true and correct copy of the foregoing Memorandum In Support Of Eli Lilly And Company's Motion To Exclude Opinions That Gastroparesis Can Reliably Be Diagnosed Without Contemporaneous Objective Testing was electronically filed using the Court's CM/ECF System, which will send notification of such filing to all counsel of record.

/s/ Samuel W. Silver
Samuel W. Silver

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAs) PRODUCTS LIABILITY LITIGATION	)	**CIVIL ACTION**
THIS DOCUMENT RELATES TO:	)	**MDL No. 3094**
	)	**2:24-md-03094-KSM**
ALL ACTIONS / ALL CASES	)	

[PROPOSED] ORDER

AND NOW, this _____ day of _____, 2025, upon consideration of Eli Lilly and Company's Motion to Exclude Opinions That Gastroparesis Can Reliably Be Diagnosed Without Contemporaneous Objective Testing, briefing in support thereof, and any response in opposition and reply brief, it is hereby **ORDERED** that Eli Lilly and Company's Motion is **GRANTED.** A reliable gastroparesis diagnosis requires contemporaneous objective testing, and Plaintiffs' experts' opinions to the contrary shall be excluded.

IT IS SO ORDERED.

KAREN SPENCER MARSTON, J.

Exhibit A

AMERICAN COLLEGE OF GASTROENTEROLOGY
Advancing Digestive Health, Improving Patient Outcomes

Gastroparesis

Gastroparesis Overview

Gastroparesis is a chronic disorder which means delayed stomach emptying without a blockage. In healthy people, when the stomach is functioning normally, contractions of the stomach help to crush ingested food and then propel the pulverized food into the small intestine where further digestion and absorption of nutrients occurs.

Symptoms

Symptoms include fullness after meals, pain, nausea vomiting, weight loss, belching and bloating. Certain foods like fatty foods, or carbonation may cause symptoms. The feeling of fullness after starting a meal is very common. Weight loss may also occur.

Causes

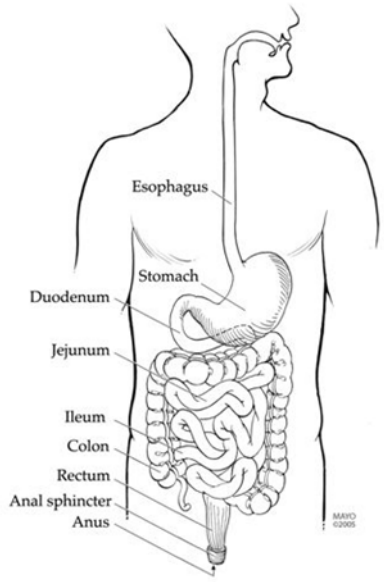
Diabetes is one of the more common causes. Gastroparesis may also occur after stomach surgery. Other causes include bacterial and viral infections. Narcotics, antidepressants and other medications which delay stomach emptying may also cause gastroparesis. There are a group of patients with gastroparesis where there is no obvious cause.

Table 1

Medications associated with impaired gastric emptying

Narcotic
Tricyclic antidepressants
Calcium channel blockers
Clonidine
Dopamine agonists
Lithium
Nicotine
Progesterone
Marijuana (THC) significantly delays gastric emptying and should be avoided

Diagnosis



Gastric emptying study is the most commonly used test. It is a test using a tiny amount of radioactive material mixed with food. With imaging equipment, it measures the rate of emptying of the stomach after taking a meal. A delay in gastric emptying indicates gastroparesis.

13 C spirulina Gastric Emptying Breath Test is a non radioactive test to evaluate for gastroparesis. It is a test also using labeled food where the patient provides breath samples for analysis.

Wireless capsule system called (SmartPill®) is a capsule that contains a small electronic device. This device records information as it travels to your stomach and intestine. The information is transmitted to a receiver worn on the waist. The capsule is passed in your stool.

Treatment

Importance of Nutrition as Treatment in Gastroparesis

The initial treatment in patients with gastroparesis is to create a diet that will improve the symptoms. Your physician may recommend eating frequent small meals and to avoid fatty, spicy, acidy and high fiber foods. Your physician may also recommend soups or more liquid containing meals..

In addition, we always want to make sure our patients are well hydrated.

Those patients with diabetes should have good control of their sugars.

Medicines that delay stomach emptying should be avoided if possible.

Metoclopramide

Is an important medicine to treat gastroparesis. There are risks in using this medication that you need to discuss with your physician. She will help you weigh the pros and cons and help you make the best decision for your situation.

Erythromycin - You may know erythromycin as an antibiotic. Erythromycin also causes stomach contractions. Your physician may consider this option if you fail to respond to metoclopramide or you wish to try something else. Erythromycin also has side effects. It does not work after 4 weeks. Your doctor will also help you weigh the pros and cons of using this medication.

Anti Emetics (Medications to control nausea and vomiting) - Your physician may also consider the use of medications like prochlorperazine (Compro), diphenhydramine (Several brand names including Benadryl), ondansetron (Zofran). There are risks and benefits to these medications as well.

Special Treatments

G -POEM (gastric peroral endoscopic myotomy) is a specialized procedure done in those patients who have not responded to other therapies. It involves minimally invasive surgery of the stomach performed by endoscopy.

An **endoscopy** is a test that is performed after giving intravenous sedation. A small tube is inserted in the stomach where the surgery occurs.

There are additional experimental options that your doctor may discuss with you including surgically placing an electric stimulation device on your stomach. The electrical stimulation helps control symptoms.

There are several newer pharmacological agents on the horizon that offer promise in treating gastroparesis .

Figure 1: Gastrostomy and jejunostomy anatomy

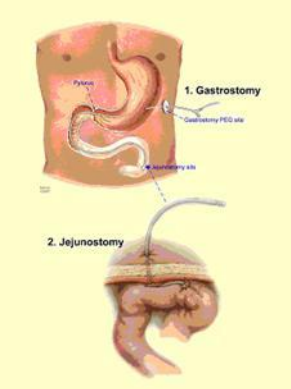


Figure 2: Oro-jejunal feeding tube

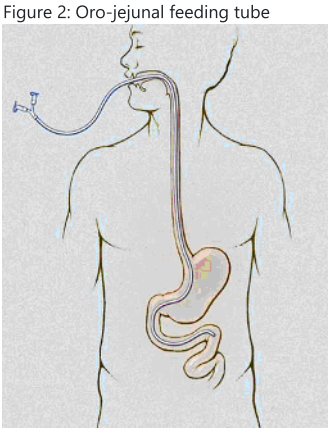


Figure 3: Wireless Capsule Monitoring System

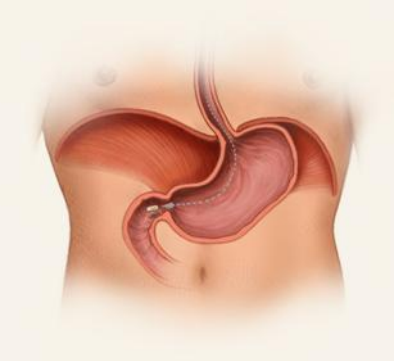
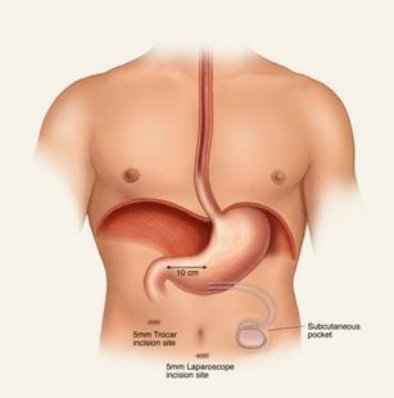


Figure 4: Electrical Gastric Stimulation



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Peter S. Buch,, MD, FACG, Frank H Netter, MD School of Medicine, North Haven, CT – Updated June 2021.

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Gastroparesis Patient Facing Podcast

Controversies in Gastroparesis: Discussing the Sticky Points featuring Dr. Brennan Spiegel and Dr. Brian Lacy

AJG Guidelines Update: Gastroparesis featuring Dr. Millie Long and Dr. Michael Camilleri

Podcasts - Brian E. Lacy, MD, PhD, FACG

- Dyspepsia: Full podcast
- Gastroparesis, Nausea & Vomiting and Dyspepsia - Full Podcast
- Gastroparesis: Full podcast
- Nausea & Vomiting - Full podcast

Handout on Gastroparesis

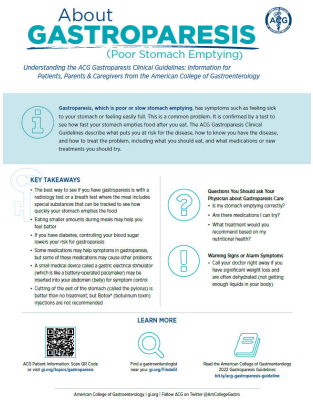

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Exhibit B

IN RE: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAS) PRODUCTS LIABILITY LITIGATION (MDL 3094)

EXPERT REPORT

By:

Eliot L. Siegel, M.D.

Date: November 18, 2024

Eliot L. Siegel, M.D.

TABLE OF CONTENTS

I. SCOPE OF REPORT

I have been asked to render opinions on the methods that may be used to diagnosis gastroparesis with an emphasis on diagnostic imaging studies, particularly Gastric Emptying Scintigraphy. I have been compensated for my efforts consistent with my Fee Schedule. *See Exhibit D: Fee Schedule.*

My opinions offered in this report are stated to a reasonable degree of medical and scientific certainty. I reserve the right to supplement or amend the opinions that I have offered in this report upon the availability of new or additional information.

II. CREDENTIALS, EXPERTISE AND EXPERIENCE

I am a physician who is board-certified by the American Board of Radiology with an additional certification of "special competence" in Nuclear Medicine with over 37 years of experience in diagnostic imaging. I am recognized as a fellow of the American College of Radiology as well as the Society of Imaging Informatics in Medicine, where I was recently awarded the Society Gold Medal Award.

Since 1987, I served as the Chief of Diagnostic Radiology and Nuclear Medicine at the VA Maryland Healthcare System and subsequently became the Regional Lead of Diagnostic Imaging for the VA's Veterans Integrated Services Network 5, which includes West Virginia, Washington D.C. and Maryland. Additionally, I am currently an adjunct Professor at the University of Maryland, where I previously served as Vice Chair for many years. I have additional adjunct appointments as well, as a Professor of Bioengineering at the University of Maryland College Park and as a Professor of Computer Science at the University of Maryland Baltimore County. Previously, I was a Lecturer and Instructor at Johns Hopkins University where I taught Radiology residents. I recently stepped down from my full-time faculty position at the University of Maryland and my position as Chief of Diagnostic Radiology and Nuclear Medicine at the VA Maryland Healthcare System in order to create an entity that will provide outpatient nuclear medicine services throughout the United States with an emphasis on radiopharmaceutical therapy for cancer patients.

As a faculty member at the University of Maryland, I have given over 500 lectures on a wide variety of different topics in nuclear medicine to medical students, radiology residents, nuclear medicine residents and referring clinical services. I have also given more than two dozen grand round talks around the country, and those visits have typically included nuclear medicine lectures to the residents and faculty members. I provided routine clinical coverage and leadership of the nuclear medicine department at the VA for over 37 years and have also provided clinical and on-call coverage at the University of Maryland in nuclear medicine. I have given lectures at national scientific meetings on nuclear medicine with an emphasis on informatics applications in nuclear medicine and PET/CT scanning and dose reduction. I recently edited a two-volume book on PET/CT and AI and have been asked to edit/write a book on PET/CT for the Radiologic Clinics of North America PET Imaging.

During my 37 plus year career as a nuclear medicine physician and radiologist, I have interpreted tens of thousands of nuclear medicine examinations, including over 1,000 gastric emptying studies, in addition to CT scans, MRIs and other imaging studies of patients with suspected gastroparesis.

I am considered a leading expert in the field of informatics and nuclear medicine. Additionally, I have written over 300 articles and book chapters on the topics of nuclear medicine and informatics and have edited numerous books as well. I have also delivered more than 1,000 presentations around the world. During my career, I have received numerous recognitions for excellence in my field. These include, but are not limited to, a 1993 Department of Veterans Affairs Commendation for Excellence, The Smithsonian Award: Laureate Improving Health Care Operations through High-Speed Network in 1998 and Diagnostic Imaging Magazine's International Editor's and Readers Award for Innovation in Radiology in 2000. In 2002, I was named runner up for the Aunt Minnie educator of the year award as well as Aunt Minnie Top 5 researcher of the year. Also in 2002, I was named one of Diagnostic Imaging Magazine's top twenty most influential people in radiology. In 2003, I won Aunt Minnie most influential researcher of the year award. I was elected as a Fellow of the Society of Computer Applications in Radiology in 2003 and named one of the top ten radiologists in the world by Medical Imaging magazine in 2006 and again in 2007. In 2006, I was recognized at the University of Maryland for outstanding teaching and was named the University of Maryland School of Medicine Mentor of the Year. I was elected as a Fellow of the American College of Radiology in 2009[1] and was given the RSNA Honored Educator Award in 2020. In 2023, I was awarded the Society for Imaging Informatics highest honor, the Gold Medical Award. As of November 16, 2024, 157 of my publications have been cited for a total of 3,949 times which puts me in the top 5% of physicians in this category.

In addition to my clinical and research work, I am a dedicated teacher and mentor to dozens of faculty members, residents, fellows and medical and undergraduate students. I am frequently asked to give presentations at venues throughout the United States and world in topics related to medical informatics, artificial intelligence, and nuclear medicine. I enjoy teaching and have given hundreds of lectures on general topics in nuclear medicine including topics related to gastric emptying. As a radiologist, in addition to nuclear medicine, I have worked as an interventional radiologist as well as a cross-sectional imaging radiologist, specializing in the interpretation of CT, MRI, and ultrasound studies. I am excited to currently serve in the newly emerging, pioneering field of theranostics, which represents a fusion between therapeutic oncology using cutting edge radiopharmaceuticals and diagnostic imaging.

Radiologists typically undergo five years of training including an internship and four years of training in all aspects of diagnostic and interventional radiology and nuclear medicine. Many radiologists such as myself have an additional year (as in my case in nuclear medicine) or two in fellowship training in subspecialties in radiology such as nuclear medicine, interventional radiology, musculoskeletal or neuroradiology. Radiologists receive extensive training in

[1] The American College of Radiology ("ACR") was founded in 1923 and is at the forefront of radiology. A Fellow of the American College of Radiology is one of the highest honors the ACR can bestow on a member. ACR Fellows demonstrate a history of service to the College, organized radiology, teaching and/or research. This honor is conferred on members who have been approved and elected by the ACR Board of Chancellors.

gastrointestinal radiology and are taught to perform fluoroscopic evaluations of the entire GI tract including imaging of the esophagus, stomach, small bowel and stomach, I have taught dozens of radiology residents how to perform and interpret these GI examinations. In my role as nuclear medicine physician, I have lectured on and taught about nuclear medicine studies such as gastrointestinal emptying studies, GI bleeding studies, hepatobiliary studies and PET/CT evaluation of the gastrointestinal tract. I have worked closely with colleagues who specialize in GI medicine as a diagnostic imaging consultant on their patients during my entire career.

I have diagnosed gastroparesis, particularly in patients with diabetes, on at least 100 occasions. I have also interpreted the presence or absence of mechanical obstruction via CT and upper GI imaging on thousands of occasions and reported the presence of retained food and gastric distension, gastric wall thickening, gastric masses on CT in thousands of cases. I have been frequently asked to evaluate patients presenting with acute and chronic abdominal pain on CT and MRI and ultrasound and for nuclear medicine evaluation.

Radiologists and nuclear medicine physicians are considered the "physician's physician" because they become consultants to physicians in not only the detection of disease but in diagnosis as well. Diagnosis involves the greater context of the history and presenting signs and symptoms of patients. The specialized knowledge of radiologists helps to not only interpret the findings but also guide referring clinicians in the most appropriate test to perform on patients. Many physicians consult directly with radiologists prior to requesting a study and also consult with radiologists and discuss the findings in a radiology report. Because of the comprehensive variety of different specialties that radiologists work with in medicine, surgery and psychiatry, radiologists develop a broad and often deep perspective on not only diagnosis but also appropriate clinical care. This is true for sub-specialist clinicians and especially true for primary care, non-subspecialist providers. Often, for example, incidental findings are made on imaging studies such as when an emergency CT scan to evaluate for pulmonary clots demonstrates an incidental finding such as an early lung cancer. It is the radiologists' responsibility to educate the referring physician about these incidental findings and advise them about appropriate follow up steps. As such radiologists serve as "bridges" of information across different types of specialists and levels of practitioners including physician assistants and nurse practitioners. This central role in support of other physicians and health care providers in detection, diagnosis, and recommendations for care has earned radiologists the reputation as the physician's physician.

III. METHODOLOGY

This report and my opinions are based upon my education, training, research, expertise and experience as a physician practicing radiology and nuclear medicine for more than 37 years. In generating this report, I applied the same rigorous standards that I routinely utilize in my work as editor, author, and peer-reviewer.

At the outset of generating this report and forming my opinions, I developed a comprehensive list of search terms relevant to the question that I was given. I started with a basic search of gastric emptying, gastroparesis and the GLP-1 agonists, and then, using Google Scholar, PubMed and general Google searches, located articles, publications and medical literature on-topic. Using the citations and references within, I performed backward and forward searches

resulting in additional relevant articles, publications, medical literature and other source material. From there, I continually expanded my search terms to include keywords explicitly listed in the material as well as derived from my own further consideration. *See Exhibit B: Search Terms*. I then ran my completed list of search terms through a broad group of credible and reliable online sources to generate a library of literature, including reviewed publications, meta-analyses, guidelines and other materials relevant to the mandate that I was given. *See Exhibit A: Materials Considered List*.

I considered material both supportive and unsupportive of the opinions that I have offered in this report. Lastly, I reviewed GLP-1 RA prescribing information and specific GLP-1 RA drug labels.

IV. GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAS)

Glucagon-like peptide receptor agonists (GLP-1 RAs) are a class of medications that are indicated for the treatment of type two diabetes mellitus, as an adjunct to diet and exercise, and for weight loss in overweight and obese adults with other comorbidities, and as an adjunct to lifestyle modification. GLP-1 RA medications are modified versions of the natural GLP-1 hormone and mimic the GLP-1 hormone by binding to and activating GLP-1 receptors (a G protein-coupled receptor) found in the pancreas, brain, heart and gastrointestinal tract. The GLP-1 hormone has a relatively short half-life of around 1-2 minutes. However, GLP-1 RA medications have been designed to be much more resistant to degradation and can have a half-life of a few hours up to as many as seven days. Although I am not offering a general causation opinion in this report, consistent with the scope of my report, I have reviewed the literature on GLP-1RA medications that shows they slow gastric emptying of solids. (Halawi 2017) (Masselli 2022). I also noted in my review of the relevant labeling that delayed gastric emptying is associated with all of the relevant drugs.[2]

V. ANATOMY OF THE STOMACH AND GASTRIC EMPTYING

The organs of the upper GI tract are the oropharynx, esophagus, stomach, and duodenum (*see figure 1*).

[2] I was informed by Plaintiffs' counsel that the relevant drug compounds are liraglutide, dulaglutide, semaglutide, and tirzepatide. Labels for all of these dugs disclose the fact that they can delay gastric emptying. (Package Insert, Saxenda, 11/1/2024) (Package Insert, Victoza, 11/1/2024) (Package Insert, Wegovy, 11/1/2024) (Package Insert, Ozempic, 11/1/2024) (Package Insert, Dulaglutide, 11/2/2024) (Package Insert, Mounjaro, 11/1/2024) (Package Insert, Zepbound, 11/1/2024).

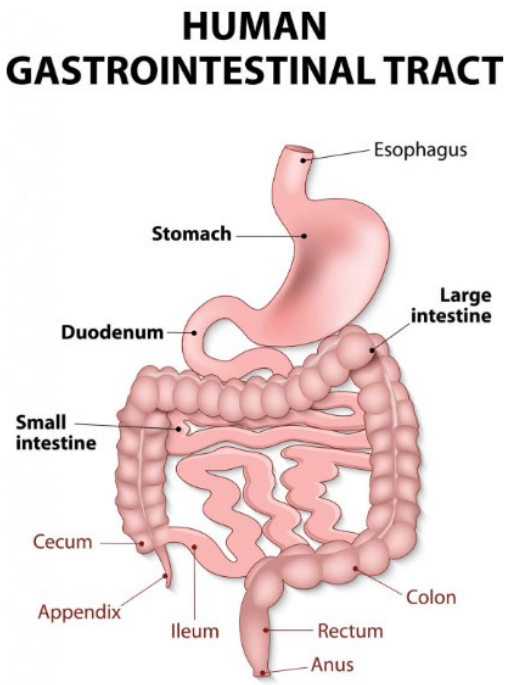

Figure 1 – Human Gastrointestinal Tract (Gastroenterology, 2024)

Gastric emptying is the process by which food intake contained in the stomach is moved into the duodenum. Following ingestion, mechanical breakdown begins in the stomach via a series of churning and grinding motions designed to physically break down food into small, 1-2 millimeter particles. Chemical digestion then occurs as the stomach secretes enzymes and gastric acid to promote further breakdown.

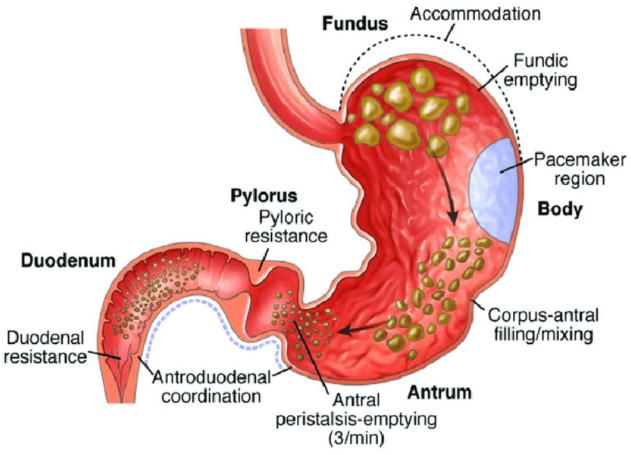

Figure 2 – Illustration of Peristalsis (Parkman, 2009)

Movement from the stomach into the duodenum then occurs through a series of muscle contraction processes referred to as peristalsis (*see Figure 2*), a coordinated "systolic" contraction of the antrum and the pylorus. The coordinated muscle contractions of the stomach are generated

by the interstitial cells of Cajal (ICC), which functions as the "pacemaker" of the stomach. The pylorus and the terminal end of the antrum contract almost simultaneously, analogous to the systolic phase of the heart where chambers contract together. The timing of this contraction is crucial. The pylorus begins to close near the onset of the terminal antral contraction, ensuring that only a small amount of antral contents enters the duodenum before the opening is sealed. After this contraction, the antrum relaxes, and the process repeats in cycles, typically occurring about three times per minute in sync with the gastric slow wave frequency. At the same time, contents in the terminal antrum collide with the closed pylorus and are forced back into the proximal antrum, creating a retropulsive flow.

These coordinated contractions cause mixing and grinding of gastric contents, known as trituration which contributes significantly to the mechanical breakdown of food particles. This process is essential for reducing food into smaller, more manageable pieces that can be effectively digested and absorbed in the small intestine. The jet-like retropulsion (*see figure 3*) creates turbulence in the gastric contents, promoting thorough mixing of food particles with gastric secretions**.** The forceful backward flow helps in further breaking down food particles by causing them to collide with each other and the stomach walls**.** Retropulsion helps ensure that only adequately small particles pass through the pylorus into the duodenum**.** The pylorus acts as a gatekeeper, closing to prevent premature emptying and allowing retropulsion to occur**.** When the pylorus opens, it allows small, well-ground particles to pass into the duodenum.

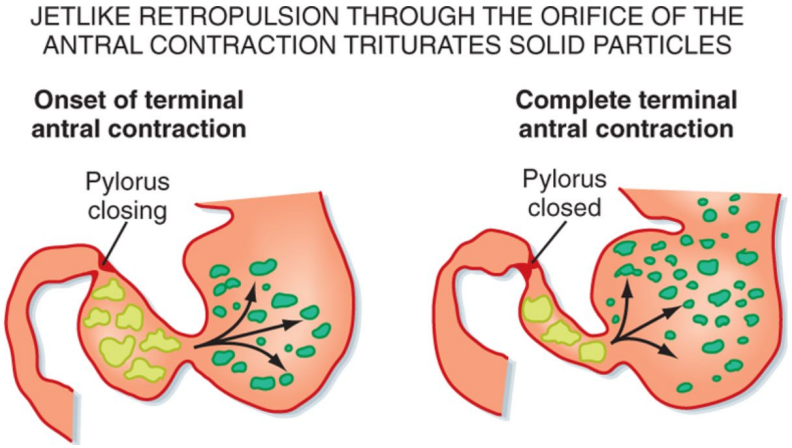

Figure 3: Contraction of the Antrum, Koeppen & Stanton: Berne and Levy Physiology, 6th edition

VI. Clinical Implications for Gastroenterology and Nuclear Medicine

Understanding these processes is crucial in gastroenterology and surgery. Disruptions to the terminal antrum or pylorus can lead to altered gastric emptying patterns, potentially causing symptoms such as nausea, vomiting, and/or early satiety. Surgical procedures involving the distal stomach, such as distal gastrectomy or sleeve gastrectomy, may affect these mechanisms and potentially impact digestion and gastric emptying.

Overall, trituration and jet-like retropulsion are fundamental processes in gastric function, particularly in the antrum. They work in concert to ensure thorough mixing and mechanical

breakdown of food, preparing it for further digestion and absorption in the small intestine. The intricate coordination between antral contractions and pyloric function is essential for these processes to occur effectively.

Normal gastric emptying of most of the solid food contents of the stomach usually occurs between 1.5 and 3 hours. Delayed gastric emptying is a digestive disorder in which the gastric emptying process is abnormally slowed down (*see Figure 4*). As discussed above, it is well established and documented in the medical literature that GLP-1 RAs cause delayed gastric emptying.

GLP-1 agonists have been shown to have significant inhibitory effects on gastric motility, including trituration and jet-like propulsion. Based on prior studies (Maselli, 2021) (Marathe, 2011) (Goyal, 2019), we know that:

1. GLP-1 and its agonists significantly slow gastric emptying in both healthy individuals and those with conditions such as obesity and type 2 diabetes. This slowing effect is likely to impact the overall process of trituration and jet-like propulsion;

2. Exogenous GLP-1 has been shown to reduce antral motility (motility of the lower stomach). Since the antrum plays a crucial role in trituration and jet-like propulsion, this reduction in motility would be expected to decrease the efficiency of these processes; and

3. GLP-1 infusion alters the distribution of a meal within the stomach, causing a greater proportion to be retained in the distal stomach (the lower two parts of the stomach: antrum and pylorus). This redistribution adversely affects the trituration process by changing the way food particles interact with the antral walls

The overall effect of GLP-1 drugs appears to be a general slowing and modulation of gastric motility, which would likely result in a reduction in the intensity and frequency of both trituration and jet-like propulsion. This aligns with the primary effect of GLP-1 agonists in slowing gastric emptying and contributing to glycemic control in managing patients with diabetes.

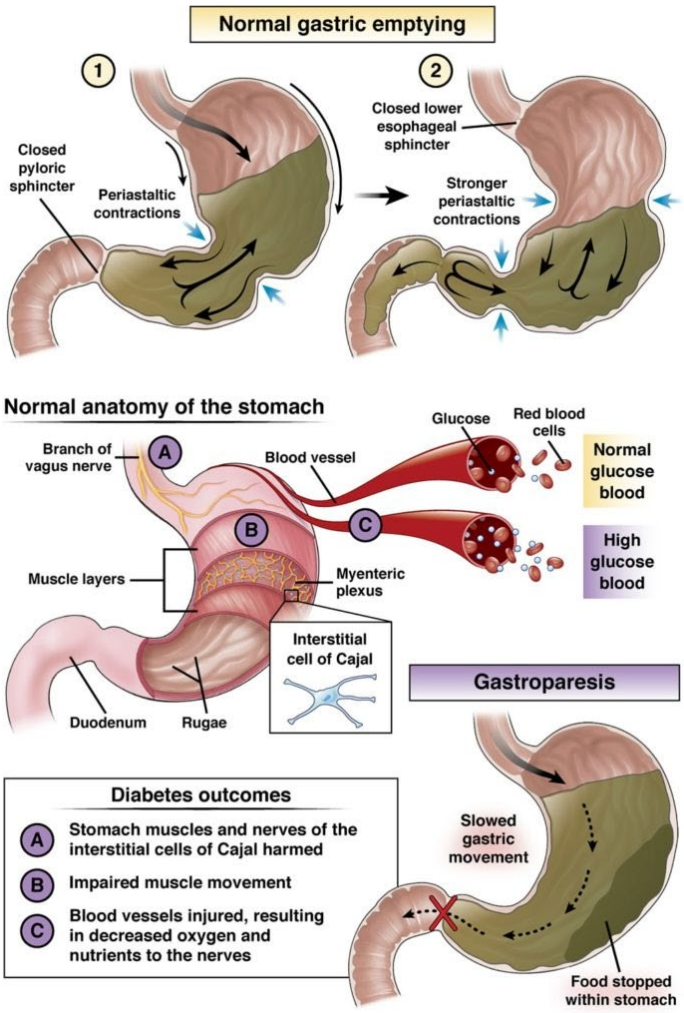

Figure 4: Delayed Gastric Emptying: AGA GI Patient Center

VII. GASTROPARESIS

Gastroparesis is a condition characterized by abnormal gastric motility with delayed gastric emptying in the absence of a mechanical (anatomic, such as stenosis) outlet obstruction. (Waseem, 2009) (Lacy, 2022). It is a digestive disorder defined by three elements. Although specific formulations vary, it is consistently defined as: 1) being associated with gastrointestinal symptoms, most commonly nausea, vomiting, postprandial fullness, and abdominal pain; 2) occurring in the absence of a mechanical obstruction of the pylorus; and 3) occurring in the presence of delayed gastric emptying. (Lacy 2022) (Camilleri 2022). It has an estimated prevalence per 100,000 persons of 37.8 for women and 9.6 for men, with approximately 5 million U.S. adults suffering from gastroparesis-like symptoms. (Lacy, 2022).

The etiology of gastroparesis is diverse with more than 50 recognized causes including diabetes, medication-induced gastroparesis, connective tissue disease, and post-surgical gastroparesis. When there is no clear cause, the term "idiopathic" is used. In epidemiological studies prior to the clearance of GLP-1 agonists, medication-induced gastroparesis accounted for 11% to 22% of cases. (Jung 2009; Ye 2021; Ye 2022).

Gastroparesis can develop as a result of a singular pathology, such as a medication-induced etiology, or as a combination of pathologies that could also include nerve damage from diabetes, surgical procedures, viral infections, muscle dysfunction of the stomach, immune dysregulation which can result in damage to stomach nerves, or loss of Interstitial Cells of Cajal, the specialized cells that regulate muscle contractions.

VIII. DIAGNOSIS OF GLP-1 RA INDUCED GASTROPARESIS

The clinical manifestations of GLP-1RA induced gastroparesis vary from patient to patient and require evaluation of the full clinical presentation. History, symptoms, assessment of co-morbidity, and review of relevant available test results comprise components of this complete clinical picture. Gastroparesis is not a "one size fits all" diagnosis and, consequently, each work-up needs to be customized to a particular patient, the care setting (e.g., ER v. outpatient setting), and that patient's specific history and findings.

Differential diagnosis is the technique by which a physician distinguishes among alternative diagnoses with similar clinical features to arrive at a specific diagnosis. A physician considers likely alternative, or different, diagnoses throughout the diagnostic process. Specific findings in the clinical workup make certain diagnoses more or less likely and guide decisions for further testing. Using the differential diagnosis method, a physician ultimately rules out unlikely potential causes and arrives at a diagnosis through process of elimination.

A. Tools for Clinical Assessment

a. Starting Point: History and Physical Exam

The most basic tools of clinical assessment are patient history and physical exam. In assessing a patient, it is important to gather details related to the onset of the present illness, the chronology of all symptoms, past illnesses, treatments and surgical procedures, drug, alcohol and tobacco use, family history, and all current medications and supplements.

The steps taken beyond the patient history and physical exam will vary based on the specific circumstances of that patient. Clinicians will request different tests depending on the clinical context. For instance, for a patient presenting to the emergency room after several days of severe nausea and vomiting, a basic metabolic panel might be required to identify conditions such as hyper/hypoglycemia or hypokalemia that would require immediate supportive care or diagnostic imaging studies, especially CT scans, to search for injuries or disease processes that would require immediate care, such as an obstructing gastric cancer, a gastrointestinal bleed, pancreatitis or a bowel obstruction. However, in the context of an office visit where the patient presents with less acute symptoms, these kinds of tests may not be ordered first as a matter of course when other, more obvious conditions are listed at the top of the differential.

b. Imaging Studies Can Be Obtained Depending on Clinical Presentation

Clinicians order imaging tests in a variety of clinical contexts. In the diagnosis of gastroparesis in particular, these include computed tomography (CT), ultrasound, conventional x-ray studies, upper GI series, esophagogastroduodenoscopy (EGD), magnetic resonance imaging (MRI) and nuclear medicine gastric emptying studies also known as gastric emptying scintigraphy. These can enable a physician to rule out alternative causes within the differential diagnosis. These tests may provide useful data to reach a diagnosis, particularly in the case of diabetic, idiopathic, connective tissue disease related, or post-surgical gastroparesis and in patients with mechanical obstruction such as might be caused by gastric cancer but are not crucial in the diagnosis of drug-induced gastroparesis, for the reasons discussed in more detail elsewhere herein.

Smart Pill/Wireless Motility Capsule: Although not widely available or commonly conducted, an alternative imaging study of the stomach is one in which a camera in capsular form is swallowed and takes sequential images of the stomach and small and large intestines as it passes through the GI tract. The rate that these pills/capsules transit through the stomach is typically different from that of either liquids such as water or food such as a scrambled egg meal and these do not stimulate hormones and enzymes such as gastrin and pepsin.

Gastric Emptying Breath Test: This is a non-radioactive test used to measure gastric emptying rates over a four-hour period, measuring the solid phase of gastric emptying. As is the case with gastric emptying scintigraphy, a standardized meal of dried egg mix with 13C-Spirulina is administered with crackers and water and breath samples are collected at 45, 90, 120, 150, 180, and 240 minutes. The ^{13}C Spirulina is metabolized in the GI tract producing $^{13}CO2$ which is exhaled and can be measured using gas isotope radio mass spectrometry with changes over time indicating the rate of gastric emptying. One advantage of this study is that it can be performed in clinician's offices or even patient's homes. As the FDA (who cleared it in 2015) points out, GEBT results may be inaccurate in patients with significant small bowel, pancreatic, liver and/or lung disease. Another limitation is that it is contraindicated in patients with severe lactose intolerance or hypersensitivity to Spirulina, egg, milk or wheat allergens (ABDiagnostics, 2013). Bharucha et al found that the GEBT can accurately measure gastric emptying when compared with gastric emptying scintigraphy (Bharucha, 2013).

Esophagogastroduodenoscopy (EGD): An EGD, also known as an upper endoscopy, involves the use of a camera attached to a small flexible tube that a physician inserts into a patient's upper gastrointestinal tract through the patient's mouth.

Electrogastrography (EGG): EGG presents an interesting alternative in the work-up of patients with suspected gastric motility issues. Hobson (Hobson, 2021) et all describe EGG as "non-invasive measurement of gastric myoelectrical activity (GMA) using cutaneous electrodes placed on the abdomen". They point out that while not a new technique, and that EGG "has been reinvigorated with advances in artificial intelligence software, such as high-resolution and body surface mapping". EGG records the pacemaker activity of the interstitial cells of Cajal which act as pacemakers throughout the GE tract. These cells generate slow waves at a frequency of about 3 cycles per minute (cpm). Hobson describes gastric emptying studies as having "limited sensitivity and specificity and poorly predict symptom severity and outcomes in patients with

gastroparesis and FD" (functional dyspepsia) (Chokshi, 2022). He believes that on the other hand, that by identifying subsets of patients with abnormal gastric slow waves and pyloric dysfunction, EGG could potentially provide greater insight into the pathophysiological mechanisms in symptoms of gastroparesis, and even tailor treatment in comparison to gastric emptying studies.

Conventional Radiograph X-Ray: This study is very limited due to its relatively poor ability to demonstrate soft tissues such as the stomach but will often occasionally demonstrate an abnormally very distended stomach when there is severe retention of gastric contents. This study is very easy and fast to obtain in both an inpatient and outpatient setting but is relatively insensitive to mild gastric distention.

Upper GI Series: One variant of a conventional x-ray study of the abdomen is an "upper GI series" in which a patient typically drinks barium, and a radiologist observes the course of the barium through the esophagus into the stomach and then obtains images of the esophagus, stomach and duodenum using the barium and air/gas as contrast materials which allow much more detailed information than a conventional x-ray study. This allows the radiologist to observe anatomic abnormalities including obstruction and stenosis and the presence of inflammatory or neoplastic processes. The radiologist is also able to observe and obtain images in multiple projections (perspectives) of the function of the stomach and record in cine/movie format the passage of barium as it moves into, through and from the stomach into the duodenum. This dynamic study is typically performed within a 5-to-15-minute period and can be suggestive of gastroparesis if there is evidence of a relatively large amount of retained food or fluid within the stomach or if there is very slow passage of barium during the study interval. Overall, radiation for this study is typically tens to hundreds of times greater than that of a single x-ray.

Computed Tomography (CT): A CT study uses x-rays (approximately 10 times the radiation of an abdominal radiograph) to create a three-dimensional imaging of the abdomen and is able to delineate the anatomy of the stomach in exquisite detail including the volume of the stomach, contents of the stomach (solid or liquid or gas), evaluate for an outlet obstruction and localize a partial or full mechanical obstruction and its complications such as perforation. As is the case for an x-ray study, a CT scan generally captures an image of the stomach at a single point in time, unlike an upper GI series or an ultrasound study or a nuclear medicine gastric emptying study. Patients could be imaged multiple times over the course of several minutes or 4 hours or more, but this is usually impractical given scheduling issues associated with most CT scanners where patients are often scheduled in 15-minute to 30-minute time intervals. The wide availability of CT and rapid scanning (often the scan is complete in less than 20 seconds), makes CT a common first line imaging study in the emergency department and clinic.

Magnetic Resonance Imaging (MRI): An MRI study uses electromagnetic signals generated by changing magnetic fields to produce three-dimensional, cross-sectional images of the entire abdomen and lower chest and upper pelvis. MRI studies do not generate radiation to patients but take longer by a factor of 10 to 100 to obtain resulting in images times that can range from 20 minutes to an hour for abdominal imaging. As is the case with CT, MRI can demonstrate excellent anatomic detail of the stomach and its contents with even better detail in the muscle of the stomach and gastric contents. It is more subject to patient breathing and motion which can cause the equivalent of blurring of MRI images. Given the time required for the study and additional safety

precautions related to ferromagnetic materials in or on the patient and greater cost, MRI is usually not a first line study in a patient with gastric symptoms in comparison to CT.

A promising variant of MRI is functional MRI in which multiple cine (movie) images are obtained over time to obtain high resolution and highly reproducible assessment of gastric motility and emptying. Functional MRI allows for simultaneous assessment of contractile activity as well as gastric emptying and patterns of mobility. Specific patterns such as reduced antral peristaltic wave propagation and a reduced gastric motility index on MRI are suggestive of gastroparesis. Unlike ultrasound this technique is technologist independent, meaning that it does not require special technologist skills. As with MRI and CT, functional MRI allows for very accurate volume assessment of the stomach. This study is not generally available in most imaging facilities.

Ultrasound: Ultrasound utilizes sound waves and can also produce cross sectional images of the stomach although air/gas in the stomach and colon and small bowel present challenges since air represents an impediment to these sound waves. As with MRI, ultrasound does not utilize x-rays and is very safe. It is inexpensive and can be performed portably outside of the radiology department in an ER setting or in other point of care settings. Ultrasound tends to be more operator dependent with regard to quality of the study than other cross-sectional studies in which image acquisition is more standardized. Due to the requirement for a high level of expertise and challenges presented by air in the stomach and bowel, ultrasound is very much underutilized as a methodology to observe and quantify gastric emptying. Ultrasound can be very effective in non-invasively, without radiation, evaluating the degree of distension of the stomach, evaluating its contents for fluid or air or food and allowing serial imaging over time to determine gastric emptying and to observe the dynamic motion of the stomach. Ultrasound is not currently the standard of care because of a lack of training for radiologists and technologists and more so, clinicians in its application to gastric imaging and is rarely performed for either acute or chronic symptoms.

B. Differential Diagnosis

As discussed above, the first step in a differential diagnosis is to first consider reasonably likely causes, which are based, in part, on a patient history and initial physical examination. For instance, in a patient who presents with gastrointestinal symptoms and discloses that they are a recovering alcoholic and have a family history of cancer, gastric cancer would be a reasonably likely potential cause. Because of the inclusion of stomach cancer as a reasonably likely potential cause, logical next steps would include an upper endoscopy, to visualize potential tumors in the gastric lining, a CT scan, to look for tumors and spread of disease to adjacent and distant structures such as the liver or lungs that might not be apparent on endoscopy, and a complete blood count, to assess for biomarkers for cancer and infection and other possibilities. As another example, in a female patient of childbearing age who is sexually active, pregnancy is a reasonably likely explanation for GI symptoms, so a pregnancy test would be in order. Although that patient's specific history would require a physician to consider pregnancy as a potential cause, and then to conduct testing to refute or confirm pregnancy, that does not mean we conduct pregnancy tests in all women with GI symptoms. The testing conducted as part of the differential diagnosis is based on the reasonably likely potential causes identified as part of the patient history and physical exam.

Because the symptoms of gastroparesis are nonspecific and overlap to a greater or lesser degree with many conditions, it is important to consider and rule out a variety of alternative diagnoses before concluding that a patient does indeed have gastroparesis. As discussed above, the inclusion of potential causes in a specific patient's differential diagnosis depends upon whether those possible causes are reasonably likely based upon the patient's history and the physical examination. Below I briefly list some of the more common potential alternative diagnoses to gastroparesis, before discussing the application of these diagnostic techniques in the context of suspected drug-induced gastroparesis:

1. Functional dyspepsia: This condition may only be diagnosed in patients "with one or more of four symptoms (postprandial fullness, early satiation, epigastric pain, epigastric burning) that are unexplained after a routine clinical evaluation according to the Rome IV criteria. The Rome IV criteria further requires that symptoms must have been present for at least 3 months prior to diagnosis and the onset of symptoms must have occurred at least 6 months before the diagnosis is made. FD can be classified into two subgroups; postprandial distress syndrome which can have symptoms similar to gastroparesis and epigastric pain syndrome which is characterized as epigastric pain or burning that is not exclusively postprandial and is less difficult to distinguish from gastroparesis (Kim, 2019). According to Kim et al, slow gastric emptying occurs in 25% of patients with FD and a 4-hour solid phase gastric emptying scan does not correlate with patient symptoms despite being able to quantitatively assess the percentage of retained meal over time. This makes a gastric emptying study of very limited value in distinguishing FD from gastroparesis.

2. Mechanical gastric outlet obstruction: This is more often a partial obstruction but can be complete as well. This represents a "blockage" caused by a narrowing or complete closure of a portion of the stomach or its outflow tract caused by intrinsic narrowing such as a gastric cancer or extrinsic compression such as from pancreatic cancer. Malignancy is the most common cause of gastric outlet obstruction with 50-80% of outlet obstructions related to gastric cancer (up to 35% due to distal gastric cancer and 15-25% due to pancreatic adenocarcinoma) (Kumar, 2022). Other causes include peptic ulcers, non-steroidal anti-inflammatory drugs, Helicobacter pylori related inflammation, polyps, ingestion of corrosive substances, gastric tuberculosis, post-surgical strictures, Crohn's disease, gastric volvulus, Crohn's disease, eosinophilic gastroenteritis, gall stone impaction in the pylorus or proximal duodenum (Bouveret syndrome), annular pancreas and pancreatitis (Kumar, 2022). Mechanical obstruction may present similarly to gastroparesis. It is important to note that gastric outlet obstruction will lead to delay in gastric emptying, but it does so by physically blocking the passage of food out of the stomach, rather than as a result of causing abnormal motility of the stomach.

3. Cyclical vomiting syndrome (CVS) (Cooper, 2014): Characterized by recurrent episodes of intense nausea and vomiting lasting hours to days. This is considered to be a neurological disorder with neuronal hyperexcitability particularly in the amygdala and insular cortex. These patients often have autonomic nervous system

disorders. Up to 70% (24=70%) of adult CVS patients have personal or family history of migraines and CVS can be triggered as is the case with migraines by stress, sleep deprivation, and hormonal changes. Chronic cannabis use has been implicated as a cause with a tendency to seek relief through hot showers. (Chang, 2009); CVS can be differentiated from gastroparesis in multiple ways. It often begins in childhood and is typically associated with accompanying headache, vertigo and photophobia unlike gastroparesis. Unlike gastroparesis where symptoms are more chronic and persistent, CVS has distinct acute episodes with symptom-free periods.

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4. Psychiatric disorders: Including anxiety, anorexia nervosa, or bulimia, which can cause persistent upper GI symptoms;

5. Rumination syndrome: A rare behavioral disorder, most often diagnosed in children but also diagnosed in adults, involves regurgitation of food within minutes of meal intake;

6. Chronic pancreatitis: Can cause similar symptoms of nausea, vomiting, and abdominal pain;

7. Other GI disorders: Including peptic ulcer disease, inflammatory bowel disease, and esophageal disorders like achalasia or gastroesophageal reflux disease (GERD);

8. Endocrine disorders: Such as diabetic ketoacidosis, thyroid disorders, or parathyroid abnormalities; and

9. Neurological conditions: Including increased intracranial pressure or CNS tumors.

C. How the History, Physical, Imaging and GES are Used to Diagnose Gastroparesis, and Specifically Medication-induced Gastroparesis

When gastroparesis is based on a permanent (or unknown) underlying condition, it should be confirmed by GES and upper endoscopy. (Camilleri 2022) (Lacy 2022). It is important to understand the extent of delay in order to evaluate treatment options, which can range from lifestyle modification to surgery. In many contexts, particularly diabetes, I would expect the symptoms of gastroparesis to develop gradually over time, with patients only seeking care once they become intolerable. Because it can be difficult to distinguish from other conditions, especially functional dyspepsia, it is important to use confirmatory diagnostic testing.

Drug-induced gastroparesis on the other hand has features that are likely to be obvious from history and physical examination. Delayed gastric emptying is associated with gastrointestinal symptoms that can be caused by retained food in the stomach, including nausea, vomiting, early satiety/fullness, abdominal pain and bloating. (Vijayvargiya 2019). Gastrointestinal complaints will only begin after the drug is started and begins to induce delayed gastric emptying and may be amplified with increasing doses. Furthermore, first-line treatment for

drug-induced gastroparesis is simply to withdraw the drug suspected to be delaying gastric emptying. If the gastric emptying effect of the drug is responsible for the patient's symptoms, they should begin to resolve as the drug clears his or her system. The symptom resolution will also help rule out partial mechanical obstruction of the pylorus, because if a patient has such an obstruction, the symptoms will not resolve from withdrawing the drug (which is not known to cause mechanical obstruction) and therefore symptoms will persist. Accordingly, where induction or titration of medication known to cause delayed emptying is temporally related to the classic symptoms of gastroparesis, a diagnosis can be made without the need to order a GES or other imaging.

It has been suggested that GES is always required to confirm delayed gastric emptying because it cannot be conclusively determined whether delayed gastric emptying is responsible for gastrointestinal symptoms in a given patient. (Jalleh 2024). There is evidence that suggests that not all patients who experience symptoms associated with abnormal gastric emptying, in fact, have delayed gastric emptying as measured by GES. (Balan 2011). There is also one study, reported only in a non-peer reviewed abstract, of patients treated with GLP-1RAs that reported similar results. (Lupianez-Merly 2024).[3] These studies have important limitations however, because among other things they are based on population studies and do not provide information about the specific symptoms, their severity and timing and so have limited applicability to a specific patient presenting to a physician who is able to capture this information in detail through the clinical workup. In a prospective observational study where the researchers were able to capture more detailed data for analysis, authors found an association between certain gastrointestinal symptoms and found that patients with more severe symptoms were more likely to have delayed gastric emptying. (Dibaise 2016). There are also clinical studies of GLP-1RA drugs that found patients who had delayed gastric emptying but did not report serious gastrointestinal symptoms. (Jalleh 2020) (Linnebjerg 2008) (Quast 2020). These studies do not suggest however that patients who in fact have severe gastrointestinal symptoms will have normal gastric emptying on GES and they do not suggest that reported symptoms are not associated with underlying delayed gastric emptying.

When faced with suspected drug-induced gastroparesis, I go about evaluating whether the diagnosis is appropriate in a number of ways: 1) obtain a thorough history, determine the patient's baseline before the taking the drug, rule out other causes, perform a physical examination and based on that history and findings, would likely withdraw the suspect drug(s), 2) Depending on the history of onset of symptoms and their severity, I would consider performing in imaging study such as a CT scan to evaluate for abnormalities of the stomach including gastric wall thickening, a mass lesion, compression or displacement of the stomach by an abdominal mass, post-surgical changes, and for partial or complete mechanical obstruction associated with neoplasm or gastric ulcer disease or other etiology. Additionally, based on the history and findings on physical exam, I would consider requesting an upper endoscopy study to help evaluate for several other etiologies that may be difficult to discern otherwise such as an inflammatory process. If symptoms persisted after the patient was off his/her medications for an appropriate period of time to allow clearance of the medication, I would consider a nuclear medicine gastric emptying study. This study would not be utilized in the acute setting and is not indicated by current guidelines in patients who are currently on medications that impede gastric emptying such as opioids or GLP-1 RAs. If there is

[3] I note that while this study indicates that not all patients with at least one symptom of gastroparesis had the condition after GES, it certainly found that many did.

no obvious cause, or if symptoms fail to resolve after the suspect drug(s) is withdrawn, a broader, more comprehensive analysis may be required.

IX. GASTRIC EMPTYING STUDY (GES)

A. What is a Gastric Emptying Study (GES)?

A gastric emptying study is a nuclear medicine test that measures how quickly food leaves the stomach and enters the small intestine. It involves ingesting a meal containing a small amount of a radioactive substance, which allows for visualization and quantification of stomach emptying over time using a specialized camera.

The American College of Gastroenterology (ACG) (Camilleri, ACG Clinical Guideline: Gastroparesis, 2022) and the American Gastroenterological Association (AGA) (Lacy, 2022) both provide guidelines for diagnosing gastroparesis in general. Both recognize the gastric emptying study as the most reliable method for objectively assessing gastric emptying and confirming the diagnosis of gastroparesis but differ in their recommendations for gastric emptying studies. There are no specific recommendations for gastroparesis induced by medications by either group.

The ACG guidelines emphasize the importance of a 4-hour (at least 3 hour) solid phase GES as the gold standard for diagnosis while the AGA guidelines do not specify a preferred duration for the study acknowledging greater flexibility and variability in the performance of these studies. The ACG guideline emphasizes that "shorter studies, especially gastric emptying studies which are only 90 minutes long, should not be used because they may produce false negative results." (Camilleri, ACG Clinical Guideline: Gastroparesis, 2022). However a large multicenter study performed by Zuckier et al (Zuckier, 2015) found that using the "Bonta criteria" (Bonta, 2011), they were able to shorten the duration of the study in 75% of the patients. The Bonta criteria suggest that using gastric emptying of less than 35% at 2 hours as positive for delayed gastric emptying and emptying at 2 hours greater than 55% for normal gastric emptying maintains study accuracy.

The AGA guidelines, on the other hand, additionally put more emphasis on the importance of patient symptoms as the major diagnostic criteria for gastroparesis. They suggest discontinuation of any medications or agents that might delay or speed up the emptying process before conducting the study. In an AGA clinical practice uptake, Lacy et al point out that "although delayed gastric emptying is the defining motor abnormality, the complex pathophysiology of gastroparesis includes impaired gastric accommodation, electrical dysrhythmias, antroduodenal dyscoordination, pyloric dysfunction, vagal nerve injury and disorders of visceral sensation". They suggest that lack of consistent reproducible relationships between global gastroparesis symptoms and gastric emptying delay results in complications in treatment decisions, and also in part because gastric emptying scans are not always performed correctly (Lacy, 2022)(Camilleri 2022)

The criterion for 10% retention at 4 hours was first proposed in a 2000 study by Tougas et al (Tougas, 2000) who suggested standardization of the gastric emptying study technique/protocol using an egg substitute low fat meal. He used 123 volunteers not taking any medication aged 19-

73 from 11 centers with images taken at 60, 120, and 240 minutes after ingestion of the meal. He found that only 1.2% of patients had 10% or more gastric activity in their stomach after four hours and suggested this level of retention in the stomach or greater at four hours as a criterion for gastroparesis. Vijayvargiya (Vijayvargiya, 2019) and colleagues performed a systemic review (meta analysis) for the use of gastric emptying studies as a criteria for objective evaluation of upper gastrointestinal symptoms and found a "significant association" between the results of the gastric emptying study and clinical symptoms of nausea (odds ratio 1.6), vomiting (2.0), abdominal pain (1.5), and early satiety/fullness (1.8). Gastric emptying studies using 3 hours of data collection or more and "optimal methods" had higher correlations with clinical symptoms than those performed with suboptimal gastric emptying methods (less than 3 hours) (Vijayvargiya, 2019) (Pathikonda, 2012). However, Camilleri et al question the validity of gastric emptying studies using 10% retention or more at 4 hours as a criteria for the diagnosis of gastroparesis (Camilleri, ACG Clinical Guideline: Gastroparesis, 2022), suggesting that "Further studies are required to appraise the optimal meal composition and cutoff to define normality to address the reported significant overlap between GP and FD, which may be confounded by the low calorie and fat content of the meal and the use of .10% retention at 4 hours to define delayed GE".

B. How Do Nuclear Medicine Studies Differ from other Types of Medical Imaging Studies?

Unlike x-ray and CT (computed tomography), ultrasound and MRI studies which send x-rays or sound waves or a changing magnetic field into a patient's body and measure the returning signal, in nuclear medicine, a dose of radioactive material is injected or as in the case of gastric emptying studies, is ingested by the patient. Nuclear medicine departments are typically outside of clinical areas and are separated due to the need to sequester patients undergoing nuclear medicine studies from other patients due to potential exposure to radioactive materials. Nuclear medicine studies, almost without exception, are performed in the nuclear medicine department unlike CT and ultrasound studies which are often performed in areas within or adjacent to an emergency room.

Radioactive materials are injected into or ingested by the patients who undergo nuclear medicine studies rather than x-rays or sound waves or magnetic pulses being sent into the patient. The radioactivity from these substances are emitted by the body in the form of gamma rays which come from atomic nuclei (gamma photons are virtually identical to x-ray photons differing slightly in energy) and can be detected and used to create an image of where the radioactive material is distributed in the body. Nuclear medicine cameras can acquire images of a patient using the radiation coming from the patient's body. For a gastric emptying study, a radiopharmaceutical, Technetium 99m, which has a half-life of 6 hours is combined with sulfur colloid and then mixed into water accompanying the meal that is ingested by a patient. Imaging is typically performed for up to four hours with numerous images representing snapshots in time of the progress of the food and radioactive technetium sulfur colloid mixture as it passes from the esophagus to the fundus, body, antrum, and out through the pylorus of the stomach into the duodenum.

The radiation dose delivered to the patient is dependent on the amount of radioactive material ingested rather than the amount of time that the patient is imaged and is approximately the equivalent of 27 frontal chest x-ray studies or about 80% of a very lose dose CT screening

study for lung cancer. It is approximately one fifth of the natural radiation that most people get during the course of a year.

In summary, nuclear medicine utilizes radioactive materials that decay over time. Most nuclear medicine studies currently utilize Technetium 99m which has a six-hour half-life (half of the radioactive is reduced every six hours). One of many advantages of nuclear medicine is that images can be obtained at multiple timepoints without any additional radiation associated with the image acquisition. After ingestion of a meal with radioactive Technetium in water and egg whites and toast and jelly, images can be obtained either continuously to create a cine or movie images made up of images obtained over time or a patient can be asked to wait in a waiting area and delayed images at intervals such as one, two, four or other time periods can be obtained. This continuous and discrete imaging can be performed without any additional injection of radioactive materials and multiple images can be obtained to allow for numerous measurements of activity in the stomach at various timepoints. Software that is included with nuclear medicine cameras is utilized to create a plot of activity in the stomach over time. These images are typically obtained from both the front and back of the patient using systems that have multiple cameras to obtain data from these two perspectives.

C. How is a GES Performed?

1. Patient Preparation:

Fasting: Patients are typically instructed to fast for at least 4-6 hours prior to the study to ensure the stomach is empty. Diabetic patients should have their blood sugar less than 200 mg/dL Pre-menopausal women should be studied during days 1-10 of their menstrual cycle to avoid the effects of hormonal variation on the prescribed meal. Prokinetic agents such as metoclopramide should be stopped two days before the study. (Donohoe, 2009).

Medication Review: Certain medications, especially those that influence gastric motility (e.g., prokinetics, anticholinergics, opioids and GLP-1 agonists (Weber, 2024), should be adjusted or temporarily withheld before the test, as per physician guidance. Discontinuing medications that impact gastric emptying is recommended by multiple guidelines including those published by the Society of Nuclear Medicine and Molecular Imaging.

2. Procedure:

a. Ingestion of Radiolabeled Meal for a solid gastric emptying study:

i. The patient consumes a standardized meal, with the recommended meal consisting of 120 gm liquid egg white (e.g. Egg Beaters), 2 slices of white toast, 30 gm strawberry jelly, 120 ml of water which is labeled with 0.5 to 1.0 mCi of technetium -99m sulfur colloid. (Donohoe, 2009); and

ii. A radioactive tracer (commonly Technetium-99m sulfur colloid) is mixed into the meal. This tracer emits gamma rays, allowing for external imaging.

b. Image Acquisition:

i. The patient lies on a table, and a (nuclear medicine) gamma camera captures images of the lower chest and abdomen at specific time intervals (typically 0, 1, 2, and 4 hours after meal ingestion); and

ii. These images show the distribution of the radioactive tracer within the stomach and intestines (figures 5-7).

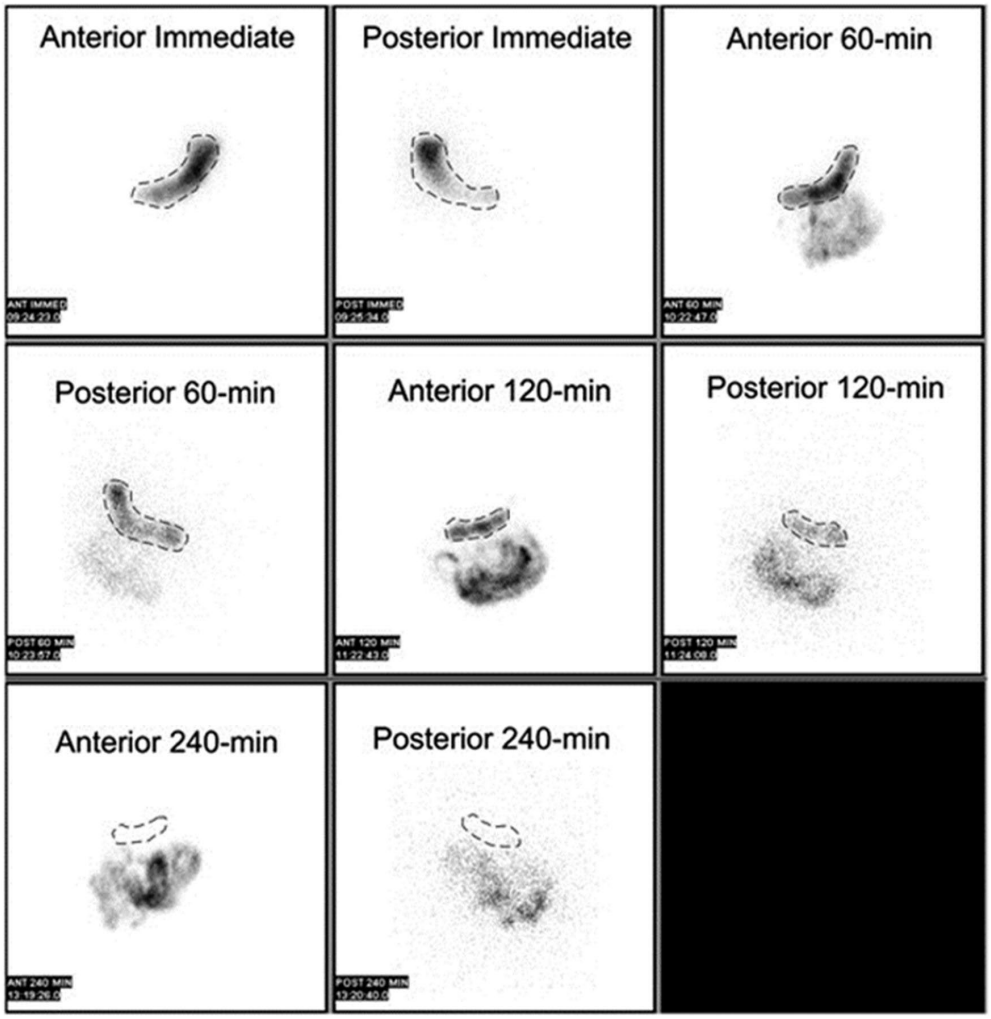

Figure 5: Normal gastric emptying study (Farrell, Gastric Emptying Scintigraphy, 2019) demonstrating correct regions of interest in both the anterior and posterior projections on initial, 1-hour, 2-hour, and 4-hour images. *This image was originally published in* JNMT. *Vijayakumar V. Assessment of the Practical Role of a Radionuclide Low-Fat-Meal Solid Gastric Emptying Study.* J Nucl Med Technol. *2006; 34:82–85. © SNMMI.*

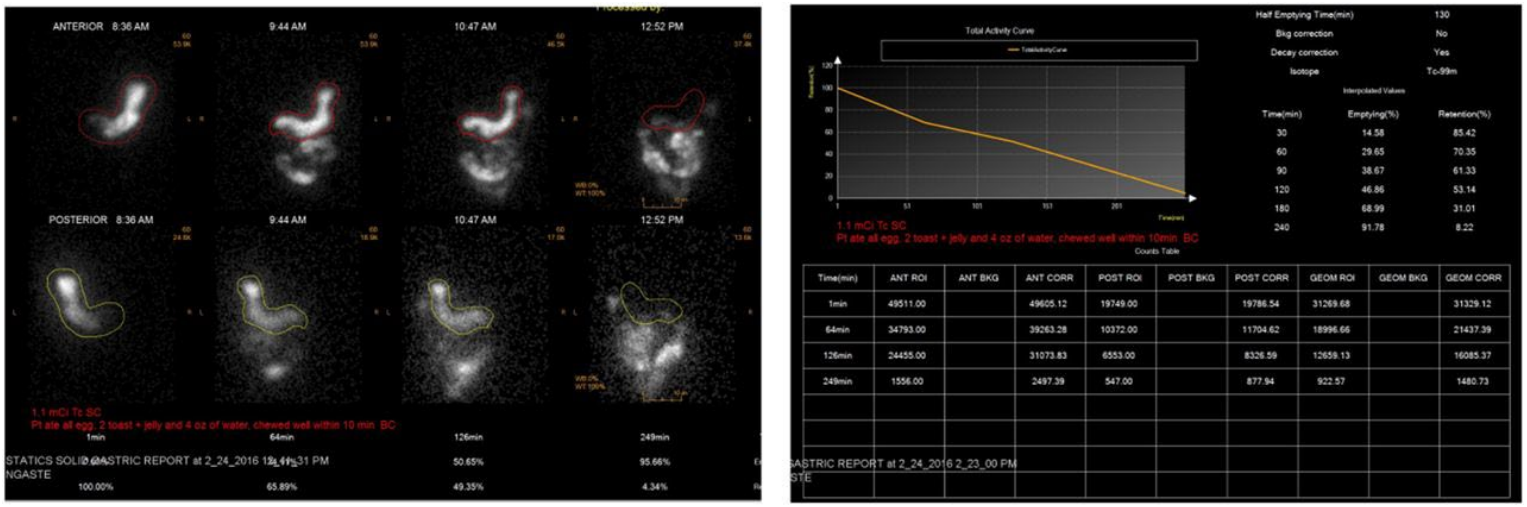

Figure 6: Normal solid gastric emptying study (Farrell, Gastric Emptying Scintigraphy, 2019). (Top) Anterior and posterior images at 0 and approximately 1, 2 and 4 hours. (Bottom) Region counts from the anterior and posterior images and geometric mean. The percent retention at 4 hours is 8.2%. *Images courtesy of Leonie L. Gordon, MD, FACNM Medical University of South Carolina, Charleston, SC.*

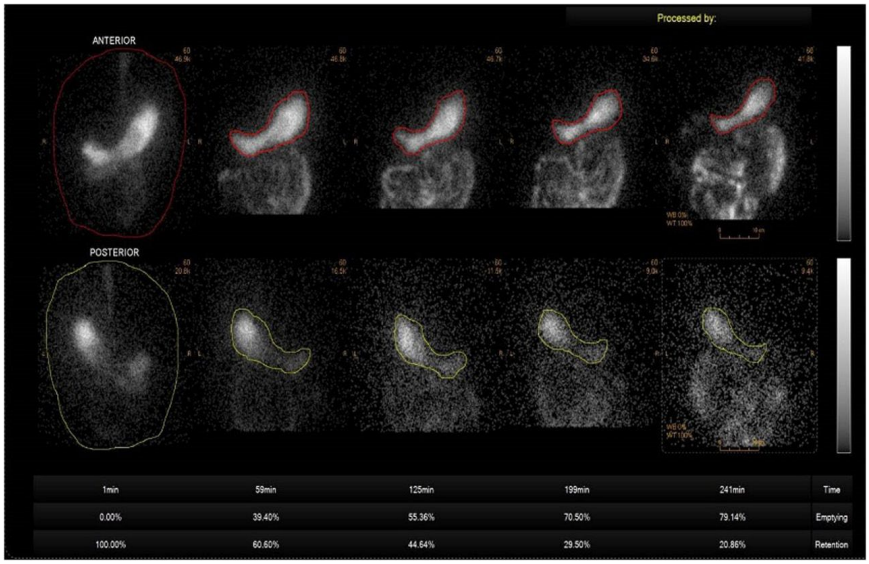

Figure 7: Abnormal solid gastric emptying study (Farrell, Gastric Emptying Scintigraphy, 2019) delayed emptying with 20.9% retention at 4 hours. At top, anterior images; at bottom, posterior images. *Images courtesy of Jon A. Baldwin, MD, University of Alabama at Birmingham, Birmingham, AL.*

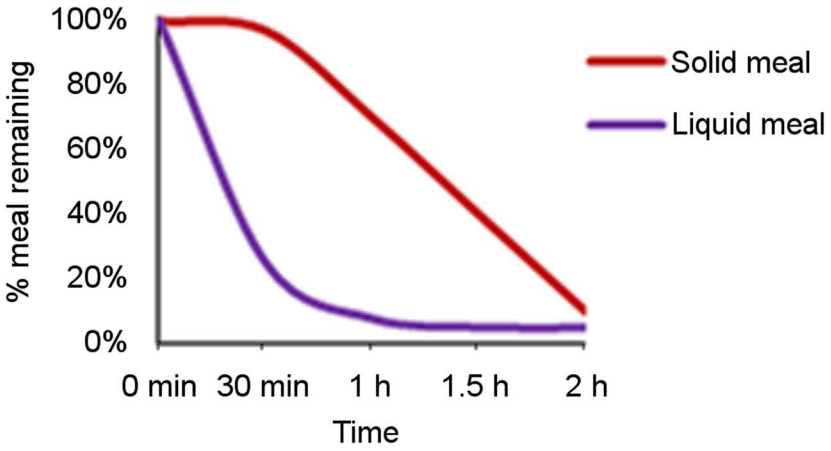

Figure 8: Normal gastric emptying curves (Farrell, Gastric Emptying Scintigraphy, 2019). For solid meal (red), there is an initial 20-30 m lag period as the antrum reduces meal particle size and mixes with gastric acid. After the lag period, the solid material empties from the stomach in a linear fashion. The liquid meal (purple) immediately begins to leave the stomach and empties in an exponential pattern.

3. Data Analysis and Interpretation:

The images are analyzed to determine the percentage of radioactivity remaining in the stomach at each time point as demonstrated in figure 6 and figure 8 with regions of interest drawn over the stomach. These data is used to calculate the gastric emptying half-time (T1/2), which represents the time it takes for half of the meal to empty from the stomach. The results are compared to established normal values to assess whether gastric emptying is delayed.

The GES provides a quantitative measure of how slow gastric emptying is compared to a normal range. This helps determine the severity of gastroparesis. A gastric emptying study measures the percentage of the radioactive meal remaining in the stomach at different time points, allowing for tracking of emptying over time and estimation of a clearance half-time.

D. Limitations of Gastric Emptying Studies:

Gastric emptying studies have a few limitations, including but not limited to patient variability with baseline rates of gastric emptying, external factors that may influence gastric emptying rates—such as medications like opioids or GLP-1s and/or medical conditions like diabetes—and inconsistent standard protocols for how a GES is performed.

With respect to inconsistent standard protocols, different hospitals and/or imaging centers will typically follow imaging guidelines such as recommendations from the Society of Nuclear Medicine and Molecular Imaging for performing procedures, though not every hospital / facility may apply them uniformly. For gastric emptying studies, this routinely includes inquiries about any medications that might impact the results of a gastric emptying study. Specifically, if a study is requested for a patient who is taking medications that interfere with gastric emptying such as opioids or GLP-1 agonists, the person scheduling or protocoling the study will ask the requesting

practitioner to discontinue these medications if clinically not contraindicated and schedule the study when these medications are "cleared" from the patient.

In my own practice at the University of Maryland and the VA Maryland Healthcare System, nuclear medicine or radiology residents create a protocol or plan for each imaging study to be performed prior to the patients being scheduled. That protocoling process is under my supervision. The residents review the patient's history in the electronic medical record and review prior examinations and the results of those studies. They then determine whether the study is indicated or whether another study would be more appropriate. They also direct the scheduler with instructions for the study that might include whether a patient should be taken off certain medications prior to an examination being performed. The nuclear medicine technologists will collaborate in this process based on their understanding of current departmental policies and guidelines.

Typical waiting times for CT scans in most facilities is the same day for urgent studies, especially from the ER, and a few days for other studies. However, waiting times for gastric emptying studies are typically substantially longer, more on the order of a week or two and potentially considerably longer when patients need to be off certain medications.

Access to GES can vary depending on geographic location and the availability of nuclear medicine facilities and trained personnel. GES is not typically performed in emergency room settings due to the time required and the need for specialized equipment and personnel. This imaging study requires one of the longest durations for the patient and department of any of the imaging studies performed in a radiology and nuclear medicine department. The test will take more than 4 hours to complete, as images are acquired at specific intervals plus the time required for patient evaluation in the department, meal preparation and the time required for the patient to consume the meal, equipment set-up checking the images to ensure adequate image quality.

Additionally, factors such as anxiety, recent food intake, certain medications and many others can influence GES interpretation. Technical factors, such as patient motion, can lead to inaccurate results. As has been demonstrated with gastric endoscopy, significant retained food is commonly seen and is not thought to necessarily represent a pathological process. (Bi, *infra*). In comparison to other lab studies, GES can be relatively expensive, and insurance coverage may vary.

E. Gastric Emptying Study - Conclusion

The GES can be a valuable tool for evaluating gastric emptying and aiding in the diagnosis of gastroparesis. However, as stated above, it is not essential to a diagnosis of medicine induced gastroparesis. Clinicians should consider factors such as symptom patterns, medical history, and other diagnostic tests when making a diagnosis and developing a treatment plan. In my practice, we occasionally contact referring clinicians about patients who are on medications that can reduce gastric emptying to discuss discontinuation of the medications prior to performing the study.

X. SUMMARY OF OPINIONS

To a reasonable degree of medical and scientific certainty:

1. GLP-1 RA-induced gastroparesis can be diagnosed based on patient history, differential diagnosis, current symptoms, and physical exam.

2. Imaging, endoscopy, or a GES can provide an additional datapoint for the diagnosis of GLP-1 RA-induced gastroparesis but is usually not necessary. This should be done in a personalized, patient-specific manner rather than a "one size fits all" approach.

3. A GES is not required to diagnose GLP-1 RA-induced gastroparesis.

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Appendix A

Materials Considered

I include by reference all materials listed in the body of my report.

Peer Reviewed Literature, Medical References, and Books

Year	Author	Title
2013	A. Ardila-Hani, et al.	Severity of dyspeptic symptoms correlates with delayed and early variables of Gastric Emptying
2019	A. Bharucha, et al.	Diabetic Gastroparesis
2014	A. Bharucha, et al.	Relationship Between Clinical Features and Gastric Emptying Disturbances in Diabetes Mellitus
2012	A. Bharucha, et al.	Comprehensive assessment of gastric emptying with a stable isotope breath test
2013	A. Bharucha, et al.	Comprehensive assessment of gastric emptying with a stable isotope breath test
2024	A. Chaudhry, et al.	Tendency of semaglutide to induce gastroparesis: a case report
2018	A. Desai, et al.	Reproducibility of Gastric Emptying Assessed with Scintigraphy in Patients with Upper GI Symptoms
2013	A. Flint, et al.	The once-daily human GLP-1 analogue liraglutide impacts appetite and energy intake in patients with type 2 diabetes after short-term treatment
2021	A. Hobson, et al.	Gastroparesis and functional dyspepsia. A chicken and EGG situation, from *The Functional Gut Clinic* (2021)
1997	A. House, et al.	National survey of radionuclide gastric emptying studies
2022	A. Kumar, et al.	Gastric Outlet Obstruction, from *StatPearls* (2022)
2020	A. Maurer, et al.	Appropriate use criteria for gastrointestinal transit scintigraphy
2018	A. Notghi, et al.	National survey of gastric emptying studies in the UK
2016	A. Perlas, et al.	I-AIM framework for point-of-care gastric ultrasound

Year	Author	Title
2024	A Razak, et al.	Role of Point-of-Care Gastric Ultrasound in Advancing Perioperative Fasting Guidelines
2021	A. Saxena, et al.	Energy intake as a short-term biomarker for weight loss in adults with obesity receiving liraglutide: A randomized trial
2021	A. Syed, et al.	Epidemiology and diagnosis of gastroparesis in the United States - a population-based study
2018	A. Tseng, et al.	Clinical utility of gastric emptying scintigraphy: Patient and physician perspectives
2023	NSW Agency for Clinical Innovation.	Gastric Emptying Scintigraphy, in *Clinical Practice Guide: Agency for Clinical Innovation* (2023)
2023	B. Goodman	They took blockbuster drugs for weight loss and diabetes. Now their stomachs are paralyzed, from *CNN* (2023)
2024	B. Hiramoto, et al.	Quantified Metrics of Gastric Emptying Delay by Glucagon-LikePeptide-1 Agonists: A Systematic Review and Meta-Analysis With Insights for Periprocedural Management
2019	B. Kim	Gastroparesis and Functional Dyspepsia: A Blurring Distinction of Pathophysiology and Treatment
2022	B. Lacy, et al.	AGA clinical practice update on management of medically refractory gastroparesis: expert review
2022	B. Lacy, et al.	Approach to the Patient with Nausea and Vomiting, in *Yamada's Textbook of Gastroenterology* (2022)
2021	B. Lacy, et al.	Controversies in gastroparesis: discussing the sticky points
2021	B. Moshiree, et al.	Clinical presentations of gastroparesis
2008	Berne & Levy, et al.	The Gastric Phase of the Integrated Response to a Meal
2024	C. Sousa et al.	When the Stomach Takes a Vacation: The Unseen Battles of Gastroparesis
2014	C. Cooper, et al.	Rapid or Normal Gastric Emptying as New Supportive Criteria for Diagnosing Cyclic Vomiting Syndrome in Adults

Year	Author	Title
2021	C. Gibbons, et al.	Effects of oral semaglutide on energy intake, food preference, appetite
2024	C. Lupianez-Merly, et al.	Real-World Effects of GLP-1 Receptor or Dual GLP-1/GIP Receptor Agonists on Gastrointestinal Symptoms and Gastric Emptying: Results From a Large Clinical Practice Database
2024	C. Lupianez-Merly, et al.	Effects Of GLP-1 Receptor or a Dual GLP-1/GIP Receptor Agonists on Gastrointestinal Symptoms and Gastric Emptying: Results From a Large Clinical Practice Database
2011	C. Marathe, et al.	Effects of GLP-1 and Incretin-Based Therapies on Gastrointestinal Motor Function
2019	C. Rayner, et al.	Is making the stomach pump better the answer to gastroparesis?
2010	D. Sfarti	Prevalence of gastroparesis in type 1 diabetes mellitus and its relationship to dyspeptic symptoms
2020	C. Zhang, et al.	Area postrema cell types that mediate nausea-associated behaviors
2024	S. Garg	Increased Risk of Gastroparesis Associated with GLP-1RA Use in Type 2 Diabetes Patients, from *Cleveland Clinic* (2024)
2021	D. Bi, et al.	Food Residue During Esophagogastroduodenoscopy Is Commonly Encountered and Is Not Pathognomonic of Delayed Gastric Emptying
2011	D. Bonta	Shortening the 4-hour gastric-emptying protocol
2023	D. Cangemi, et al.	Misdiagnosis of gastroparesis is common: a retrospective review of patients referred to a tertiary gastroenterology practice
2008	D. Cassilly, et al.	Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy
2019	D. Daniels, et al.	Glucagon-Like Peptide 1 in the Brain: Where Is It Coming From, Where Is It Going?

Year	Author	Title
2008	D. Drucker, et al.	Exenatide once weekly versus twice daily for the treatment of Type 2 Diabetes: a randomised open-label non-inferiority study
2018	D. Drucker, et al.	Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1
2016	D. Drossman, et al	Rome IV Functional Gastrointestinal Disorders: Disorders of Gut-Brain Interaction
2017	D. Hinnen	Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes
2021	D. Maselli, et al.	Effects of GLP-1 and Its Analogs on Gastric Physiology in Diabetes Mellitus and Obesity
2022	D. Maselli, et al.	Effects of liraglutide on gastrointestinal functions and weight in obesity: A randomized clinical and pharmacogenomic trial
2021	D. Quast, et al.	Macronutrient intake, appetite, food preferences and exocrine pancreas function after treatment with short- and long-acting glucagon-like peptide-1 receptor agonists in type 2 diabetes
2004	D. Revicki, et al.	Gastroparesis Cardinal Symptom Index (GCSI): Development and Validation of a Patient Reported Assessment of Severity of Gastroparesis Symptoms
2015	D. Sandoval, et al.	Physiology of Proglucagon Peptides: Role of Glucagon And GLP-1 In Health and Disease
2024	D. Yang, et al.	The goals for successful development of treatment in gastroparesis
2014	D. Boltin, et al.	Vomiting and dysphagia predict delayed gastric emptying in diabetic and nondiabetic subjects
2013	E. Bouras, et al.	Gastroparesis: From Concepts to Management
2023	E. Fujino et al.	Anesthesia Considerations for a Patient on Semaglutide and Delayed Gastric Emptying

Year	Author	Title
2024	E. Kazzi, et al.	In Case You Missed It: 2022 ACG Clinical Guideline Gastroparesis: Limited Evidence-Based Options, from *The American College of Gastroenterology* (2024)
2024	E. McCleskey	Study Challenges Seven-Day Hold on GLP-1 Agonists Before Surgery
2012	E. Rey	Prevalence of Hidden Gastroparesis in the Community: The Gastroparesis "Iceberg"
1994	F. Azpiroz	Control of Gastric Emptying by Gastric Tone
2022	F. Carbone, et al.	Relationship Between Gastric Emptying Rate and Simultaneously Assessed Symptoms in Functional Dyspepsia
2023	F. Mandarino, et al.	Imaging in Gastroparesis: Exploring Innovative Diagnostic Approaches, Symptoms, and Treatment
2024	F. Wu, et al.	Association of glucagon-like peptide receptor 1 agonist therapy with the presence of gastric contents in fasting patients undergoing endoscopy under anesthesia care: a historical cohort study
2019	F. Wuestenberghs, et al.	Association Between Symptoms, Quality of Life, and Gastric Emptying in Dyspeptic Patients
2024	G. Barakat, et al.	Satiety: a gut–brain–relationship
2006	G. Lim, et al.	Glucagon-Like Peptide 1 Secretion by the L-Cell: The View from Within
2024	G. Mammoser	Ozempic, Wegovy Users More Likely to Develop "Stomach Paralysis", Retrieved from Healthline: Health News
2003	G. Sarnelli	Symptoms Associated With Impaired Gastric Emptying of Solids and Liquids in Functional Dyspepsia
2000	G. Tougas, et al.	Standardization of a simplified scintigraphic methodology for the assessment of gastric emptying in a multicenter setting
2000	G. Tougas, et al.	Assessment of gastric emptying using a low-fat meal: establishment of international control values

Year	Author	Title
2011	G. Umpierrez, et al.	The effects of LY2189265, a long-acting glucagon-like peptide-1 analogue, in a randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: the EGO study
2024	H. Brent, et al.	Quantified Metrics of Gastric Emptying Delay by Glucagon-Like Peptide-1 Agonists: A Systematic Review and Meta-Analysis With Insights for Periprocedural Management
2017	H. Halawi, et al.	Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial
2009	H. Jung, et al.	The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006
2012	H. Kusunoki, et al.	Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: randomized controlled study evaluation by real-time ultrasonography
2021	H. Kuwata, et al.	Effects of glucagon-like peptide-1 receptor agonists on secretions of insulin and glucagon and gastric emptying in Japanese individuals with type 2 diabetes: A prospective, observational stud
2024	H. Parkman, et al.	Glucagon like peptide-1 receptor agonists: the good, the bad, and the ugly - benefits for glucose control and weight loss with side effects of delaying gastric emptying
2023	H. Parkman, et al.	Glucagonlike Peptide-1 Receptor Agonists: The Good, the Bad, and the Ugly—Benefits for Glucose Control and Weight Loss with Side Effects of Delaying Gastric Emptying
2022	H. Parkman, et al.	Postprandial symptoms in patients with symptoms of gastroparesis roles of gastric emptying and accommodation
2023	H. Silver, et al.	Effect of the glucagon-like peptide-1 receptor agonist liraglutide compared.
2022	H. Soliman	Gastric Electrical Stimulation: Role and Clinical Impact on Chronic Nausea and Vomiting

Year	Author	Title
2009	H. Ziessman, et al.	The Added Diagnostic Value of Liquid Gastric Emptying Compared with Solid Emptying Alone
2024	J. Araujo-Duran, et al.	Gastroparesis for the non-gastroenterologist
2017	J. Blundell, et al.	Effects of once-weekly semaglutide on appetite, energy intake, control of eating
2016	J. Dibaise, et al.	The relationship among gastroparetic symptoms, quality of life, and gastric emptying in patients referred for gastric emptying testing
2007	J. Holst	The Physiology of Glucagon-like Peptide 1
2015	J. Meier, et al.	Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial
2024	J. Nasser, et al.	Food Retention at Endoscopy Among Adults Using Glucagon-Like Peptide-1 Receptor Agonists
2021	J. Schol, et al.	United European Gastroenterology (UEG) And European Society For Neurogastroenterology And Motility (ESNM) Consensus On Gastroparesis
2011	J. Seok, et al.	How to Interpret Gastric Emptying Scintigraphy
2014	J. van Can, et al.	Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults
2020	J. Wise, et al.	Gastric emptying scans: poor adherence to national guidelines
2022	J. Yu, et al.	GLP-1 receptor agonists in diabetic kidney disease: current evidence and future directions
2011	K. Balan	Clinical significance of scintigraphic rapid gastric emptying
2023	K. Banks, et al.	Gastric Emptying Scan, from *StatPearls*
2021	K. Dahl, et al.	Oral semaglutide improves postprandial glucose and lipid metabolism, and delays gastric emptying

Year	Author	Title
2009	K. Donohoe, et al.	Procedure guideline for adult solid-meal gastric-emptying study 3.0
1997	K. Jones, et al.	Relation between postprandial satiation and antral area in normal subjects
2019	K. Jones, et al.	Effects of lixisenatide on postprandial blood pressure, gastric emptying and glycaemia in healthy people and people with type 2 diabetes
2016	K. Katsurada, et al.	Neural effects of gut- and brain-derived glucagon-like peptide-1 and its receptor agonist
2020	K. Van den Houte, et al.	The Role of GI Peptides in Functional Dyspepsia and Gastroparesis: A Systematic Review
2014	L. Baggio	Glucagon-like peptide-1 receptors in the brain: controlling food intake and body weight
2024	L. Catanese	GLP-1 diabetes and weight-loss drug side effects: "Ozempic face" and more, Retrieved from Harvard Health Publishing
2024	L. Collins, et al.	Glucagon-Like Peptide-1 Receptor Agonists, from *NCBI Bookshelf* (2024)
2023	L. Raven, et al.	Delayed Gastric Emptying with Perioperative Use of Glucagon-like Peptide-1 Receptor Agonists
2018	L. Szarka, et al.	Evaluation of patients with suspected gastroparesis
2018	L. Watson, et al.	A whey/guar “preload” improves postprandial glycaemia and glycated haemoglobin levels in type 2 diabetes: A 12-week, single-blind, randomized, placebo-controlled trial
2018	M. Bekkelund et al.	Pathophysiology of Idiopathic Gastroparesis and Implications for Therapy
2023	M. Camilleri	Abnormal gastrointestinal motility is a major factor in explaining symptoms and a potential therapeutic target in patients with disorders of gut–brain interaction

Year	Author	Title
2024	M. Camilleri	Prevalence and variations in gastric emptying delay in response to GLP-1 receptor agonist liraglutide
2012	M. Camilleri, et al.	What are the important subsets of gastroparesis?
2022	M. Camilleri, et al.	Effects of GLP-1 and other gut hormone receptors on the gastrointestinal tract and implications in clinical practice
2022	M. Camilleri, et al.	ACG clinical guideline: gastroparesis
2013	M. Camilleri, et al.	Clinical Guideline: Management of Gastroparesis
2022	M. Camilleri, et al.	Effects of GLP-1 and Other Gut Hormone Receptors on the Gastrointestinal Tract and Implications in Clinical Practice
2024	M. Camilleri, et al.	Gastroparesis
2021	M. Drella	Diagnostic Coding for Gastroparesis, A Chronic Gastrointestinal Disorder.pdf
2016	M. Farrell, et al.	Variability in Gastric Emptying Meals Used in Clinical Practice… Seriously?, from *The Journal of Nuclear Medicine* (2016)
2019	M. Farrell, et al.	Gastric Emptying Scintigraphy
2024	M. Georgiou, et al.	Gastric Emptying Scintigraphy Protocol Optimization Using Machine Learning for the Detection of Delayed Gastric Emptying
2019	M. Grover, et al.	Gastroparesis: A turning point in understanding and treatment
2021	M. Hompesch, et al.	Effects of efpeglenatide versus liraglutide on gastric emptying, glucose metabolism and beta-cell function in people with type 2 diabetes: an exploratory, randomized phase Ib study
2012	M. Horowitz, et al.	Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in Type 2 Diabetes
1989	M. Horowitz, et al.	Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus

Year	Author	Title
2022	M. Kalas, et al.	Frequency of GLP-1 receptor agonists use in diabetic patients diagnosed with delayed gastric emptying and their demographic profile
2021	M. Kalas, et al.	Medication-Induced Gastroparesis: A Case Report
2021	M. Klinge, et al.	Gastric Emptying Time and Volume of the Small Intestine as Objective Markers in Patients With Symptoms of Diabetic Enteropathy
2018	M. Nauck, et al.	Incretin Hormones: Their Role in Health and Disease
2011	M. Nauck, et al.	Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down?
1997	M. Nauck, et al.	Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans
2012	M. Pathikonda	Gastric Emptying Scintigraphy: Is Four Hours Necessary?.
2015	M. Pelletier-Galarneau, et al.	Multicenter Validation of a Shortened Gastric-Emptying Protocol
2015	M. Plummer, et al.	Hyperglycemia Potentiates the Slowing of Gastric Emptying Induced by Exogenous GLP-1
2003	M. Samsom, et al.	Prevalence of Delayed Gastric Emptying in Diabetic Patients and Relationship to Dyspeptic Symptoms
2023	M. Sodhi, et al.	Risk of Gastrointestinal Adverse Events Associated with Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss
2014	M. Umapathysivam, et al.	Comparative Effects of Prolonged and Intermittent Stimulation of the Glucagon- Like Peptide 1 Receptor on Gastric Emptying and Glycemia
2024	M. Weber	Trust the Gold Standard: All Glucagon-like Peptide-1 Receptor Agonists Can Delay Gastric Emptying, from *The American Society of Anesthesiologists* (2024)
2020	N. Bergmann, et al.	No acute effects of exogenous glucose-dependent insulinotropic polypeptide on energy intake, appetite, or energy expenditure when added to treatment with a long

Year	Author	Title
		acting glucagon-like peptide 1 receptor agonist in men with type 2 diabetes
2023	N. Goelen, et al.	Do prokinetic agents provide symptom relief through acceleration of gastric emptying? An update and revision of the existing evidence
2001	N. Talley, et al.	Can symptoms discriminate among those with delayed or normal gastric emptying in dysmotility-like dyspepsia?
2006	N. Talley, et al.	Functional dyspepsia, delayed gastric emptying, and impaired quality of life
2024	P. Nathani, et al.	Sa1964 Incidence Of Gastrointestinal Side Effects In Patients Prescribed Glucagon-Like Peptide-1 (GLP-1) Analogs: Real-World Evidence
2021	P. Pasricha, et al.	Functional dyspepsia and gastroparesis in tertiary care are interchangeable syndromes with common clinical and pathologic features
2018	P. Rai	Liraglutide-induced acute gastroparesis
2011	P. Rhee, et al.	Analysis of pacemaker activity in the human stomach
2022	P. Silver, et al.	Proximal and distal intragastric meal distribution during gastric emptying scintigraphy: Relationships to symptoms of gastroparesis
2020	P. Usai-Satta	Gastroparesis: New insights into an old disease
2018	P. Vijayvargiya, et al.	Association between delayed gastric emptying and upper gastrointestinal symptoms: a systematic review and meta-analysis
2019	P. Vijayvargiya, et al.	Correction: Association between delayed gastric emptying and upper gastrointestinal symptoms: a systematic review and meta-analysis
2019	P. Vijayvargiya, et al.	Effects of Promotility Agents on Gastric Emptying and Symptoms: A Systematic Review and Meta-analysis

Year	Author	Title
2024	Q. Liu	Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists
2022	R. Chokshi, et al.	Is It Time to Abandon Gastric Emptying in Patients With Symptoms of Gastroparesis and Functional Dyspepsia?
2019	R. Cogliandro, et al.	Is gastroparesis a gastric disease?
2023	R. Gilbert, et al.	Reconsideration of the gastroparetic syndrome
2019	R. Goyal, et al.	Advances in the physiology of gastric emptying
2020	R. Haas, et al.	Evaluation of 4 hour vs 2 hour gastric emptying procedure
2016	R. Hammersjo, et al.	Esophageal and Gastric Dysmotilities are Associated with Altered Glucose Homeostasis and Plasma Levels of Incretins and Leptin
2011	R. Hejazi, et al.	Does Grading the Severity of Gastroparesis Based on Scintigraphic Gastric Emptying Predict the Treatment Outcome of Patients with Gastroparesis?
2024	R. Jalleh, et al.	Clinical consequences of delayed gastric emptying with GLP-1 receptor agonists and tirzepatide
2024	R. Jalleh, et al.	Gastrointestinal Effects of GLP-1 Receptor Agonists: Mechanisms, Management, and Future Directions
2022	R. Jalleh, et al.	Normal and disordered gastric emptying in diabetes: recent insights into (patho)physiology, management and impact on glycaemic control
2024	R. McCoy, et al.	Effectiveness of Glucose-Lowering Medications on Cardiovascular Outcomes in Patients with Type 2 Diabetes at Moderate Cardiovascular Risk
2023	R. Mishra et al.	Adverse Events Related to Tirzepatide
2024	R. Reddivari	Gastroparesis, from *NCBI Bookshelf* (2024)
2020	S. Almustanyir, et al.	Gastroparesis with the initiation of liraglutide: a case report
2019	S. Brandstater, et al.	Mechanics of the Stomach: a Review of an Emerging Field of Biomechanics

Year	Author	Title
2019	S. Chakraborty, et al.	GI dysfunctions in diabetic gastroenteropathy, their relationships with symptoms, and effects of a GLP-1 antagonist
2022	S. Egboh, et al.	Gastroparesis: A Multidisciplinary Approach to Management
2019	S. Ishida, et al.	Quantification of gastric emptying caused by impaired coordination of pyloric closure with antral contraction: a simulation study
2021	S. Kato, et al.	Effects of GLP-1 receptor agonist on changes in the gut bacterium and the underlying mechanisms
2021	S. Kuwelker, et al.	Relationship between symptoms during a gastric emptying study, daily symptoms and quality of life in patients with diabetes mellitus
2015	S. Madsbad	Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists
2023	S. Mehdi, et al.	Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent
2024	S. Singh, et al.	Impact of GLP-1 Receptor agonists in gastrointestinal endoscopy: An updated review
2015	S. Trapp, et al.	PPG neurons of the lower brain stem and their role in brain GLP-1 receptor activation
2020	S. Urva, et al.	The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists
2019	S. Vavricka, et al.	Gastroparesis and Dumping Syndrome: Current Concepts and Management
2009	S. Waseem, et al.	Gastroparesis: Current diagnostic challenges and management considerations
2008	T. Abell, et al.	Consensus Recommendations For Gastric Emptying Scintigraphy: A Joint Report Of The American

Year	Author	Title
		Neurogastroenterology And Motility Society And The Society Of Nuclear Medicine
2006	T. Abell, et al.	Treatment of gastroparesis: a multidisciplinary clinical review
2020	T. Al-Mahrouqi, et al.	Cyclic Vomiting Syndrome: A Case Report and Mini Literature Review
2020	T. Borner, et al.	GIP receptor agonism blocks chemotherapy-induced nausea and vomiting
2021	T. Borner, et al.	GIP Receptor Agonism Attenuates GLP-1 Receptor Agonist-Induced Nausea and Emesis in Preclinical Models
2023	T. Heise, et al.	Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes
2024	T. Qapaja, et al.	Gastroparesis Risk In Patients With Type 2 Diabetes Prescribed GLP-1 Receptor Agonists
2021	T. Zheng et al.	Management of gastroparesis
2010	U. Khayyam, et al.	Assessment of symptoms during gastric emptying scintigraphy to correlate symptoms to delayed gastric emptying
2023	V. Martinez	Clinician Insights on How to Manage Semaglutide-Induced Gastroparesis
2024	V. Nail, et al.	Medication reconciliation enhances the accuracy of gastric emptying scintigraphy
2020	V. Rangan, et al.	Gastroparesis in the hospital setting
2021	V. Shami, et al.	Is Gastroparesis Truly Different From Functional Dyspepsia?
2003	V. Stanghellini, et al.	Predictors of gastroparesis in out-patients with secondary and idiopathic upper gastrointestinal symptoms
1996	V. Stanghellini, et al.	Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia
1990	V. Van den Maegdenbergh, et al.	Visualization of the Gastric Mechanical Systole Using a New Scintigraphic Technique

Year	Author	Title
2010	W. Hasler, et al.	Psychological Dysfunction Is Associated With Symptom Severity but Not Disease Etiology or Degree of Gastric Retention in Patients With Gastroparesis
2011	W. Hasler, et al.	Bloating in gastroparesis: severity, impact, and associated factors
2024	W. Latif, et al.	Compare and Contrast the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs), from *NCBI Bookshelf* (2024)
2012	W-J Guo, et al.	Relationship between symptoms and gastric emptying of solids in functional dyspepsia
2024	X. Wang, et al.	Extensive scintigraphic gastric motor function testing with concurrent symptom recording predicts prospectively measured daily dyspeptic symptoms
2017	Y. Nakatani, et al.	Effect of GLP-1 receptor agonist on gastrointestinal tract motility and residue rates as evaluated by capsule endoscopy
2011	Y. Ron, et al.	Early Satiety Is the Only Patient-Reported Symptom Associated With Delayed Gastric Emptying, as Assessed by Breath-Test
2022	Y. Ye, et al.	Epidemiology, etiology, and treatment of gastroparesis: real-world evidence from a large US national claims database
2021	Y. Ye, et al.	Epidemiology and outcomes of gastroparesis, as documented in general practice records, in the United Kingdom
2014	Y-C Chiu, et al.	Decreased Gastric Motility in Type II Diabetic Patients
2009	YH. Chang, et al.	Cannabinoid Hyperemesis Relieved by Compulsive Bathing
2023	Z. Zhang	GLP-1RAs caused gastrointestinal adverse reactions of drug withdrawal: a system review and network meta-analysis

Drug and Device Labeling

GEBT Package Insert for FDA Revised

Zepbound Package Insert

Mounjaro Package Insert
Wegovy Package Insert
Ozempic Package Insert
Trulicity Package Insert
Saxenda Package Insert
Victoza Package Insert

Appendix B
Search Terms

- 5-HT receptor agonists
- Abdominal discomfort
- Abdominal pain
- Abdominal X-ray
- Acupressure
- Acupuncture
- Advocacy organizations
- American Gastroenterological Association (AGA)
- Anorectic agent
- Anticholinergics
- Antidepressants
- Antiemetics
- Antrum
- Artificial intelligence (AI)
- Autonomic neuropathy
- Azithromycin
- Bacterial infections
- Bezoars
- Biomarkers
- Biopsy
- Bloating
- Botulinum toxin
- Breath test
- Calcium channel blockers
- Cannabis hyperemesis syndrome
- Causes and Risk Factors
- Chronic nausea and vomiting
- Clinical trials
- Cologastric reflexes
- Connective tissue disorders
- CT scan
- Cyclic vomiting syndrome
- Dehydration
- Delayed gastric emptying
- Diabetes
- Diabetic gastroparesis
- Diabetic gastroparesis
- Diagnostic criteria
- Diagnostic Tests
- Dietary modifications
- Dietician
- Differential diagnosis
- Distension

- Domperidone
- Drug-induced gastroparesis
- Dumping syndrome
- Duodenum
- Early satiation
- Early satiety
- Ehlers-Danlos syndrome
- Electroacupuncture
- Electrogastrography (EGG)
- EndoFLIP
- Endoscopic therapy
- Enteral nutrition
- Enterogastrone
- Enterra gastric electrical stimulator
- Epigastric pain
- Epigastric pain syndrome (EPS)
- Erythromycin
- Esophageal retention
- Feeling full quickly
- Food aversion
- Functional dyspepsia
- Functional dyspepsia patient support groups
- Functional dyspepsia subtypes
- Fundal wrap
- Fundic accommodation
- Fundus
- G -POEM - gastric peroral endoscopic myotomy
- Gastric bypass revision
- Gastric bypass surgery
- Gastric electrical stimulation
- Gastric emptying half-time (T1/2)
- Gastric emptying scintigraphy
- Gastric emptying study
- Gastric manometry
- Gastric motility
- Gastroenterologist
- Gastroparesis
- Gastroparesis Cardinal Symptom Index (GCSI)
- Gastroparesis patient education
- Gastroparesis severity
- Genetics
- Ghrelin
- GLP-1
- GLP-1 receptor agonists
- glucagon
- Glucagon Like Peptide Hormone (GLP-1)

- Glycemic control
- Gut-brain axis
- Harris-Benedict equation
- Healthcare Professionals and Organizations:
- Heineke-Mikulicz pyloroplasty
- Hiatal hernia
- Hypothalamus
- Idiopathic gastroparesis
- Ileal brake
- Imaging studies
- Immune markers
- Incretin
- Indigestion
- Indirect calorimetry
- Infections
- Inflammation
- insulin
- International Foundation for Functional Gastrointestinal Disorders (IFFGD)
- Laparoscopic pyloroplasty
- Leptin
- Liquid meals
- Loss of appetite
- Low-fat diet
- Machine learning
- Malnutrition
- Management strategies
- Medications
- Metoclopramide
- Microbiome
- Mirtazapine
- Motility specialist
- MRI
- Multiple sclerosis
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Nausea
- Neurological disorders
- New treatment targets
- Nucleus tractus solitarii (NTS)
- Nutritional support
- Ondansetron
- Online forums
- Opioids
- Pain management
- Pancreatic alpha-cells
- Pancreatic beta-cells
- Parenteral nutrition

- Parkinson's disease
- Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM)
- Patient Resources and Support:
- Peristalsis
- Postprandial distress syndrome
- Postprandial distress syndrome (PDS)
- Postprandial fullness
- Postpyloric feeding
- Postsurgical gastroparesis
- Preproglucagon (PPG) neurons
- Prochlorperazine
- Prokinetic medications
- Prokinetics
- Psychologist
- Pyloroplasty
- Pylorospasm
- Pylorus
- Rapid gastric emptying
- Refeeding syndrome
- Reflux
- Regurgitation
- Research and Emerging Concepts:
- Research updates
- Retching
- Rome IV criteria
- Roux stasis syndrome
- Roux-en-Y stasis syndrome
- Rumination syndrome
- Saxenda
- Scintigraphy
- Scleroderma
- Small bowel bacterial overgrowth
- Small frequent meals
- Specific Conditions and Subtypes
- Stomach emptying
- Stroke
- Surgery
- Symptoms
- Tachyphylaxis
- Technetium 99m
- Terminal antral contraction
- Treatment options
- Tricyclic antidepressants
- Trituration
- Type 2 diabetes mellitus (T2DM)
- Upper abdominal pain

- Upper endoscopy
- Upper gastrointestinal symptoms
- Vagal nerve stimulation
- Vagotomy
- Venting gastrostomy
- Viral gastroenteritis
- Vomiting
- Wegovy
- Weight loss
- Wireless motility capsule

Appendix C

CURRICULUM VITAE

Eliot L. Siegel, M.D.

Date November 2024

Contact Information

Business Address:	Advanced Molecular Imaging and Therapy 331 Oak Manor Drive, Suite 201 Glen Burnie, MD 21061
Phone Number:	410-371-8009
Fax Number:	410-866-6991
E-Mail:	esiegel@unithera.com; uncleeliot@gmail.com

Education

1974-1977	Physiology of Human Perception Undergrad and Grad Computer Science Minor University of Maryland, College Park College Park, MD
08/1978-05/1982	M.D. Medicine University of Maryland School of Medicine Baltimore, MD

Post Graduate Education and Training

07/1982-06/1986	Diagnostic Radiology Residency University of Maryland Baltimore, MD
07/1986-06/1987	Nuclear Medicine Fellowship University of Maryland Baltimore, MD

Employment History

03/2024-Present	Professor (Part-Time), Department of Diagnostic Radiology University of Maryland School of Medicine, Baltimore, MD
07/2023–Present	Physician, Nuclear Medicine, and Diagnostic Radiology Advanced Molecular Imaging and Therapy, Glen Burnie, MD
07/2003–02/2024	Professor, Department of Diagnostic Radiology Vice Chairman, Information Systems University of Maryland School of Medicine, Baltimore, MD
06/2022–02/2024	ICC Lead, Diagnostic Radiology & Nuclear Medicine VISN 5 (VA Capitol Health Care Network), Linthicum, MD
07/2019–06/2022	Chief, Imaging Services & ICC Lead VA Maryland Health Care System, Baltimore, MD
07/1987–06/2019	Chief, Imaging Services VA Maryland Health Care System, Baltimore, MD

CURRICULUM VITAE
Eliot L. Siegel, M.D.

07/1997–06/2003	Associate Professor, Department of Diagnostic Radiology University of Maryland Medical School, Baltimore, MD
07/1986–06/1997	Assistant Professor, Department of Diagnostic Radiology University of Maryland Medical School, Baltimore, MD
07/1986–06/1987	Chief, Cross-Sectional Imaging and Nuclear Medicine Veterans Administration Hospital, Baltimore, MD

Medical Licensures
State of Maryland (D30836), Medicine, Active
State of Florida (ME169717), Medical Doctor, Active
State of New Jersey (25MA12321900), Medical Doctor, Active

Certifications
Medical Specialist in Maryland, Recognized by the Maryland Board of Physician Quality Assurance
05/1983 Diplomate, National Board of Medical Examiners
06/1986 Diplomate, Diagnostic Radiology, American Board of Radiology
06/1987 Diplomate, Nuclear Medicine, Special Competence certified by the American Board of Radiology

Major Clinical Tasks

1987-2022	Chief, Imaging Service VA Maryland Health Care System
1987-2/2024	Nuclear Medicine Attending Physician University of Maryland School of Medicine
1987-2/2024	Nuclear Medicine Attending Physician Baltimore VA Medical Center
1987-2/2024	Attending Physician Medical Center Midtown Campus
2003-2/2024	Professor and Vice Chairman, Department of Radiology University of Maryland School of Medicine
2018-2/2024	Attending Physician UM Charles Regional Medical Center US Capital Region Medical Center
2019-2/2024	Lead ICC Radiology and Nuclear Medicine VISN 5 ICC
2022-2/2024	Chief Nuclear Medicine, VA Maryland Healthcare System

Professional Memberships

1987-2/2024	VA Chiefs of Radiology Association
1987-Present	American Medical Association
1987-Present	Association of University Radiologists
1987-Present	Maryland Radiological Society
1987-Present	Radiological Society of North America
1987-Present	American Roentgen Ray Society
1987-Present	American College of Radiology
1990-2/2024	Association of Veterans Administration Nuclear Medicine Chiefs

1992-Present	Society of Imaging Informatics in Medicine
1993-Present	Society of Photo-optical and Industrial and Electrical Engineers
1995-Present	Maryland Radiological Society - Executive Council
1995-1996	VA Chiefs of Radiology Association - Secretary/Treasurer
1996-2/2024	VA Chiefs of Radiology Association - President Elect
1996-Present	American Telemedicine Association
2008-Present	ACR-National Radiology Data Registry (NRDR)
2019-Present	Society of Nuclear Medicine and Molecular Imaging

Honors and Awards

1993	Department of Veterans Affairs Commendation for Excellence
1998	Smithsonian Award: Laureate Improving Health Care Operations through High-Speed Network
2000	Diagnostic Imaging Magazine's International Editor's and Readers Award for Innovation in Radiology
2001	Aunt Minnie Runner up (International) Educator of the Year Award
2002	Aunt Minnie Top 5 (International) Research of the Year Award
2002	Diagnostic Imaging Magazines Top Twenty Most Influential People in Radiology
2003	Aunt Minnie Most Influential Researcher of the Year Award
2003	Society of Computer Applications in Radiology, Fellowship Award
2006	Medical Imaging Magazine Top Ten Radiologists in the World Category
2006	Outstanding Teaching Achievement
2007	University of Maryland School of Medicine Mentor of the Year
2007	Medical Imaging Magazine Top Ten - Radiologist Category
2008	Outstanding Teaching Achievement
2009	American College of Radiology Fellow
2020	RSNA Honored Educator Award
2023	Society for Imaging Informatics in Medicine Gold Medal for the Society Award

Institutional Service

VA Maryland Health Care System/VISN 5

1987-1993	Biohazards Committee
1987-2007	Utilization Review Committee
1987-2015	Automated Data Processing Committee
1987-2015	Cancer Committee
1987-2022	Clinical Executive Board
1987-2/2024	Chairman, Radiation Safety Committee
1987-2/2024	Research and Development Committee
1990-1994	Activation Equipment Committee
1990-1994	Activation ADP Committee
1990-2007	Chairman, VA Radiology Chesapeake Integration Workgroup
1991-1992	Search Committee for Chairman of Surgery
1992-1993	Search Committee for Chairman of Psychiatry
1992-2007	Eastern Region Representative, VA Radiology Advisory Group
1996-2007	Chairman, Asynchronous Transfer Mode (ATM) Subcommittee
1996-2012	Chairman, VISN 5 Telemedicine Committee

1996-2022	VISN 5 Information Management Task Force
1997-2022	Executive Committee of the Medical Staff
1998-2022	Clinical Privileges Committee
1998-2022	Professional Standards Board
2005-2008	Radiology Informatics Subcommittee of the Education Exhibits Committee

University of Maryland School of Medicine/Medical System

1990-2007	University of Maryland/Veterans Administration Radiology Sharing Task Force
1991-1993	Research Coordinating Committee
1994-2/2024	Continuing Medical Education Committee
1995-2/2024	Telemedicine Advisory Committee
2001-2007	Telemedicine Clinical Advisor
2002-2/2024	Radiology Chairman's Section Chief Meetings
2002-2/2024	Radiology Chairman's Section Chief Quality
2002-2/2024	Nuclear Medicine Subcommittee for P&T
2002-2/2024	Clinical Research Working Group
2006-2/2024	University of Maryland School of Medicine Mentoring Program
2007-2/2024	Dual Appointment, Professor, Department of Radiology, University of Maryland School of Medicine Bioengineering Department, University of Maryland College Park

State Service

1995-2007	Chairman Telemedicine Task Force for VA Eastern Region Network
1995-2012	Chairman Maryland VA Health Care System Computerized Patient Record (OE/RR) Committee
2017-2022	Chair CRISP Imaging Committee (Regional Imaging and information exchange)

National Service

1989-1991	National Academy of Sciences Subcommittee on Medical Records
1990-1992	SCAR/CAR June 1992 Conference Organizing Committee and Program Committee
1990-2022	Veterans Administration National Field Advisory Group for Diagnostic Imaging
1991-2007	Program Director, Society of Photo-Optical and Industrial Engineers Medical Imaging Conference - PACS
1991-2007	National Institutes of Health National Prostate Multicenter Trial Grant Review Panel
1992-2007	National Veterans Affairs Imaging Expert Panel
1992-2012	Session Chair, Society of Computer Applications in Radiology Annual Meeting

CURRICULUM VITAE
Eliot L. Siegel, M.D.

1993-1994	Secretary/Treasurer, Veterans Administration Merit Review, Washington, D.C.
1994-2007	Councilor, SCAR Program Committee Minicourse Scar University
1994-2007	Intersociety Commission American College of Radiology
1994-2012	Veterans Affairs Multimedia Expert Panel
1994-2018	Veterans Affairs MRI and CT Specifications Committee Expert Panel
1995-2007	Department of Defense Radiology Business Process Re-engineering Committee
1995-2012	Picture Archive and Communication System Technical Advisory Committee
1995-2012	Telemedicine Expert Panel and Task Force Veterans Administration
1995-2012	Grant Reviewer
1996-2007	President, VA Chiefs of Radiology Association
1996-2007	Society of Photo-Optical Instrumentation Engineers 1997 Scientific Committee (PACS and Digital Imaging)
1996-2014	Radiological Society of North America Electronics Communication Committee Medical Devices Committee
1996-2007	Program Committee, SPIE Imaging Conference
1997-2012	VA National Telemedicine Field Advisory Group
1997-2012	VA National Telemedicine Field Advisory Group
1997-2014	National Institutes of Health - National Cancer Institute Image Archive Management Workshop
1997-Present	Society of Photo-Optical and Instrumentation Engineers Scientific Committee (PACS and Digital Imaging)
1998-2007	Co-Director, Society of Computer Applications in Radiology University
1998-2007	SCAR Program Committee Chair Local Arrangements
1999-2007	ARRS Scientific Program Committee - PACS/Computers Subcommittee
1999-2007	SCAR Education Committee
1999-2007	Dean, Society of Computer Application in Radiology
1999-2007	Chairman, VA Chiefs of Radiology
1999-Present	Executive Committee of the Maryland Radiological Society
2001-Present	Society of Computer Applications in Radiology Publications Chairman Program Committee
2001-2007	NASA New Partnerships in Medical Diagnostic Imaging Panelist Advanced Technology Workshop
2002-2007	ARRS Scientific Program Chairman - PACS/Computers
2002-2014	National Cancer Institute Biomedical Imaging Program Cancer Imaging Informatics Workshop American College of Radiology
2015-2/2024	Chair, (Conference on Machine Intelligence in Medical Imaging (C-MIMI)
7/2023-2/2024	Veterans Administration National Field Advisory Group for Nuclear Medicine
7/2023-2/2024	Veterans Administration National Field Advisory Group for Theranostics
7/2023-2/2024	Veterans Administration National Field Advisory Group for Artificial Intelligence

7/2023-2/2024 Veterans Administration National Field Advisory Group for Low Dose Lung Nodule Screening

Teaching Responsibilities

1987-2/2024 Medical Student Instructor
Radiology Elective and Digital Imaging
University of Maryland School of Medicine

1987-2/2024 Director, Resident and Fellow Training
Diagnostic Radiology and Nuclear Medicine
VA Maryland Health Care System

1987-2/2024 Teacher/Participant
Medical Grand Rounds, Clinicopathologic Correlation Course, Tumor Board, Nuclear Cardiology
University of Maryland School of Medicine

1990-1995 Co-Supervisor
Journal Club Residents, Fellows, and Faculty
University of Maryland School of Medicine

1993-2/2024 Mentor, Research and Development
Digital Imaging Projects
VA Maryland Health Care System

1994-2/2024 Cardiology Fellow Instructor
Department of Nuclear Medicine
University of Maryland Medical System

2000-2015 Lecturer and Instructor
Radiology Residency Program
Johns Hopkins University

2005-2/2024 Mentor, Medical Students, Residents, Fellows
Department of Nuclear Medicine
University of Maryland School of Medicine

2008-2/2024 Lecturer and Instructor
Radiology and Nuclear Medicine Residents
University of Maryland School of Medicine

Completed Grants

11/2010-11/2014 (PI)
caBIG Imaging Workspace Knowledge Center
University of Maryland School of Medicine
National Cancer Institute
Grant Number: ZIHCO020005-06
Total Direct Costs: $2,024,000+($506,000/y)

1/2009-1/2014 (PI: 1.0%)
Creation and Evaluation of a CT Quality Assessment Network to Optimize Quantitative Imaging for Clinical Trials

National Institutes of Health
Completed Grant Funding

9/2009-9/2013 (PI)
Radiological Society of North America Internet-Based Network for Patient-Controlled Medical Image Sharing
University of Maryland School of Medicine
National Heart, Lung, and Blood Institute
Grant Number: NHLBI-PB(EB)-2009-134-RCO-1
Total Direct Costs: $344,368.00

10/2009-2013 (PI)
Diagnostic Imaging CT Data Analysis and Development Liaison
University of Maryland School of Medicine/National Institutes of Standards and Technology
National Institute of Standard and Technology, NIST-2009-MSE-01

5/2010-5/2012 (Co-PI)
Deep QA Project
University of Maryland School of Medicine
IBM Watson Research Center
Total Direct Costs: $132,000

1/2005-12/2012 (Co-PI 8%)
Multiple Sclerosis Center of Excellence
Department of Veterans Affairs
Total Direct Costs: $25,000

10/2008-12/2009 (Co-PI 10%)
Combined Multimodality Multispectral Ultra Low-Dose X-Ray and Photon- Selective Imaging Technology for Non-Contrast Agent Differentiation of Vasculatures, Tissues, and Abnormalities.
Intramural Seed Grant-UMB/UMCP
Total Direct Costs: $74,696

1/2001-1/2006 (Co-PI 1%) PI: Andrew P. Goldberg, M.D.
Claude D. Pepper Older Americans Independence Center.
Department of Veterans Affairs
National Institutes of Health/National Institute on Aging
Grant Number: 2P60AG12583-06A1
Total Direct Costs: $1,480,959

1/2003-1/2006 (PI 1%)
Lung Nodule Detection: Relative Sensitivity and Specificity of

Conventional CT, Ultra-low Dose CT, Direct Radiography and Dual Energy Subtraction Direct Radiography
GE Medical Systems
Total Direct Costs: $270,000

1/2003-1/2006 (Technical Coordinator 10%)
Multiple Sclerosis Center of Excellence Telemedicine Project
Department of Veterans Affairs
MS Center of Excellence

1/2003-1/2004 (PI 1%)
Improving access to Digital Imaging Expertise Informatics grant to establish online expert system for repository of information related to computer applications in diagnostic imaging.
National Library of Medicine
Grant Number: G08LM7875
Total Direct Costs: $11,654

1/2002-12/2003 (PI 1%)
Development of Core Curriculum for PACS Administration
Educational Program Education Committee Chairman
Society for Computer Applications in Radiology
Total Direct Costs: $35,000

1/1998-1/2003 (Co-PI 1%)
Hypertension, Cognition, and the Brain in Older Adults Study
Examines the Relation of Hypertension to Brain Structure and Function and Cognitive Function.
National Institutes of Health/National Institute on Aging
Grant Number: 1R29AG015112-01
Total Direct Costs: $305,471

1/1997-1/2003 (Co-PI 1%)
Hypertension, Cognition, and the Brain in Older Adults Study
Examines the Relation of Hypertension to Brain Structure and Function and Cognitive Function.
Bristol Myers Squibb Medical Imaging, Inc.
Grant Number: CG94055

1/2002-12/2002 (PI 1%)
Multi-Center Study on Technologist Productivity: Comparison of Computed and Direct Radiography
Fuji Medical Systems U.S.A
Total Direct Costs: $50,000

1/2002-12/2002 (PI 1%)

Utility of Dual Energy Subtraction for Lung Cancer Screening
GE Medical Systems
Total Direct Costs: $130,000

1/2001-12/2001 (PI 1%)
Longitudinal Survey on Technologist Productivity: Effect of Computer Applications on Productivity and Utilization
Society for Computer Applications in Radiology
Total Direct Costs: $25,000

1/2000-12/2000 (PI 1%)
Development of Pro Forma Economic Model for Cost Analysis of Filmless Imaging
GE Medical Systems
Total Direct Costs: $20,000

1/1999-12/1999 (PI 1%)
Architectural Design Optimization for the Filmless Radiology Reading Room
GE Medical Systems
Total Direct Costs: $180,000

1/1999-12/1999 (PI 1%)
Disease Specific Processing Image Enhancement using Computed Radiography
Fuji Medical Systems
Total Direct Costs: $840,000

1/1995-12/1995 (Collaborator 1%)
MRI Evaluation of the Effect of exercise on Muscle Fibers of the Thigh
Department of Veterans Affairs

1/1995-12/1995 (PI 1%)
Neuroanatomical, Neurophysiological, and Neuropsychological Correlates of Essential Hypertension in the Elderly
DuPont
Total Direct Costs: $20,000

1/1995-12/1995 (Co-PI 1%)
Hypertension and the Brain. Geriatric Leadership Academic Award (GLAA).
National Institute on Aging
Grant Number: IK07AG00608
Total Direct Costs: $5,000

1/1995-12/1995 (PI 1%)
Evaluation of DICOM PACS to Radiology Information Systems Interface
Department of Veterans Affairs - Veterans Administration
Hybrid Open Systems Technology
Total Direct Costs: $25,000

1/1995-12/1995 (PI 1%)
Comparison and Determination of Relative Efficacy Between High Performance Commercial and PC-based Imaging Workstations
Department of Veterans Affairs - Veterans Administration Hybrid Open Systems Technology
Total Direct Costs: $20,000

1/1995-12/1995 (PI 1%)
Economics of PACS: Development of an Economic Model
Department of Veterans Affairs - Veterans Administration Hybrid Open Systems Technology
Total Direct Costs: $43,000

1/1994-12/1994 (Collaborator 1%)
Pepper Center Grant
Department of Veterans Affairs
Total Direct Costs: $180,000

1/1994-1/1996 (Collaborator 1%)
The Effect of Therapy on the Tissue Burden of Disseminated MAC Infection as Measured by Quantitative Bone Marrow Culture and Correlation with Quantitative Blood Culture in HIV-Infected Patients
National Institutes of Health
Grant Number: NO1AI15123
Total Direct Costs: $537,765

1/1994-1/1996 (Collaborator 1%)
Depleted Uranium Longitudinal Study
Department of Veterans Affairs
Total Direct Costs: $40,000

1/1993-1/1994 (PI)
Picture Archiving and Communications Systems - Evaluation of\
Clinical and Practical Utility

Siemens Medical Systems
Total Direct Costs: $20,000

Patents, Inventions & Copyrights

2023 – Siegel, Eliot. Carestream Health, Inc.
US 2023/0371912 A1
Remote and Automated Intensive Care Unit
Filed: 10/20/2021
Received: 11/23/2023

2023 – Siegel, Eliot. Carestream Health, Inc.
US 2023/0027305 A1
System and Method for Automated Projection Radiography
Filed: 11/18/2020
Received: 1/26/2023

2022 – Siegel, Eliot. Carestream Health, Inc.
WO 2022/216532 A1
Personalized Critical Care Imaging
Filed: 4/1/2021
Received: 10/13/2022

2019 – Siegel, Eliot. Carestream Health, Inc.
US 10,413,268 B2
Hybrid Imaging Apparatus and Methods for Interactive Procedures
Filed: 2/26/2016
Received: 9/17/2019

2016 – Siegel, Eliot. Yyesit, LLC.
US 2016/0203699 A1
Method and Apparatus of Surveillance System
Filed: 3/23/2016
Received: 7/14/2016

2012 – Siegel, Eliot. University of Maryland, Baltimore
US 8,180,126 B2
Detecting Meniscal Tears in Non-Invasive Scans
Filed: 8/12/2008
Received: 5/15/2012

2008 – Siegel, Eliot. Morita, Mark.
US 2008/0120548 A1
System and Method for Processing User Interaction Information from Multiple Media Sources

CURRICULUM VITAE
Eliot L. Siegel, M.D.

Filed: 11/22/2006
Received: 5/22/2008

Current Publications

Peer Reviewed Journal Articles: *Over 300 articles published 1988-2020.*

1. Enzmann DR, Arnold CW, Zaragoza E, **Siegel E**, Pfeffer MA. Radiology's Information Architecture Could Migrate to One Emulating That of Smartphones. Journal of the American College of Radiology. 2020 Oct;17(10)1299-1306.
2. Dreizin D, Zhou Y, Fu S, Wang Y, Li G, Champ K, **Siegel E**, Wang Z, Yuille AL. A Multiscale Deep Learning Method for Quantitative Visualization of Traumatic Hemoperitoneum at CT: Assessment of Feasibility and Comparison with Subjective Categorical Estimation. Radiology: Artificial Intelligence. 2020 Nov;2(6).
3. B. Gajera B, Kapil SR, Ziaei D, Mangalagiri J, **Siegel E**, Chapman D. CT-Scan Denoising Using a Charbonnier Loss Generative Adversarial Network. Institute of Electrical and Electronic Engineers. 2021;9:84093-84109.
4. Juluru K, Shih HH, Murthy K, Elnajjar P, El-Rowmeim A, Roth C, Genereaux B, Fox J, **Siegel E**, Rubin DL. Integrating AI Algorithms into the Clinical Workflow. Radiology: Artificial Intelligence. 2021 Aug;3(6).
5. Saboury B, Morris MA, **Siegel E**. Future Directions in Artificial Intelligence. Radiologic Clinics. 2021 Nov;59(6):1085-1095.
6. Trevino M, et al. Advancing Research on Medical Image Perception by Strengthening Multidisciplinary Collaboration. JNCI Cancer Spectrum. 2021 Dec;6(1).
7. Yi PH, Kim TK, **Siegel E**, Yahyavi-Firouz-Abadi N. Demographic Reporting in Publicly Available Chest Radiograph Data Sets: Opportunities for Mitigating Sex and Racial Disparities in Deep Learning Models. Journal of the American College of Radiology. 2022 Jan;19(1B);192-200.
8. Saboury B, Bradshaw T, Boellaard R, Buvat I, Dutta J, Hatt M, Jha A, Quanzheng L, Liu C, McMeekin H, Morris MA, Scott P, **Siegel E,** Sunderland J, Wahl R, Zuehisdorff S, Rahmim A. Artificial Intelligence in Nuclear Medicine: Opportunities, Challenges, and Responsibilities. The Journal of Nuclear Medicine. 2022 Jun;63 Suppl 2:2733.
9. Saboury B, Bradshaw T, Boellaard R, Buvat I, Dutta J, Hatt M, Ha AK, Li Q, Liu C, McMeekin H, Morris MA, Scott PJ, **Siegel E,** Sunderland JJ, Pandit-Taskar N, Wahl RL, Zuehisdorff S, Rahmim A. Artificial Intelligence in Nuclear Medicine: Opportunities, Challenges, and Responsibilities Toward a Trustworthy Ecosystem, The Journal of Nuclear Medicine. 2023 Feb;64(2):188-196.
10. Adams SJ, Madtes DK, Burbridge B, Johnston J, Goldberg IG, **Siegel EL,** Babyn P, Nair VS, Calhoun ME. Clinical Impact and Generalizability of a Computer-Assisted Diagnostic Tool to Rish-Stratify Lung Nodules with CT. Journal of the American College of Radiology. 2023 Feb;20(2)232-242.
11. Huang EP, O'Connor JPB, McShane LM, Giger ML, Lambin P, Kinahan PE, **Siegel EL**, Shankar LK. Criteria for the translation of radiomics into clinically

useful tests. Nat Rev Clin Oncol. 2023 Feb;20(2):69-82.

12. Bradshaw TJ, McCradden MD, Jha AK, Dutta J, Saboury B, **Siegel EL**, Rahmin A. Artificial Intelligence Algorithms Needs to Be Explainable – or Do They? The Journal of Nuclear Medicine. 2023 Jun;64(6):976-977.
13. Florence X. Doo FX, Cook T, **Siegel E**, Joshi A, Parekh V, Elahi A, Yi P. Exploring the Clinical Translation of Generative Models Like ChatGPT: Promise and Pitfalls in Radiology, From Patients to Population Health. Journal of the American College of Radiology. 2023 Sep;20(9):877-885.
14. Florence X, Doo FX, Cook T, **Siegel E**, Joshi A, Parekh V, Elahi A, Yi P. Exploring the Clinical Translation of Generative Models Like ChatGPT: Promise and Pitfalls in Radiology, From Patients to Population Health. Journal of the American College of Radiology. 2023 Sep;20(9):877-885.
15. Doo FX, Kulkarni P, **Siegel E**, Toland M, Yi PH, Carlos RC, Parekh VS. Economic and Environmental Costs of Cloud for Medical Imaging and Radiology Artificial Intelligence. Journal of the American College of Radiology. 2024 Feb;21(2):248-256.
16. Doo FX, **Siegel E**. Conflicts of Interest in Radiology Publishing, Journal of the American College of Radiology, 2024 Mar 26 (in press); ISSN 1546-1440.
17. **Siegel E**, Morris M. Artificial Intelligence in Nuclear Medicine: Counterpoint—More Hype Than Reality Today. American Journal of Roentgenology. 2024 Apr 24 (printed online).
18. Sari H, Teimoorisichani M, Pyka T, Viscione M, Shi K, Morris M, **Siegel E**, Saboury B, Rominger A, Ultra-Low-Dose PET Imaging in Long Axial Field-of-View PET Scanners with LSO Transmission-Based Attenuation Correction. Journal of Nuclear Medicine. Jun 2024, 65 (supplement 2) 241061.
19. Saboury B, Farhadi F, Brosch-Lenz J, Morris M, Veziroglu E, Pogue A, Rahmim A, Ghesani M, **Siegel E**. 2024. Heptathlon of Sustainable Meaningful Access to Radiopharmaceutical Therapy (RPT 3.0), Journal of Nuclear Medicine June 2024, 65 (supplement 2) 241904.

Non-Peer Reviewed Journal Articles*: Over 250 articles published 1978-2020.*

1. Abdullah S, Rothenberg S, **Siegel E**, Kim W. School of Block-Review of Blockchain for the Radiologists. Academic Radiology. 2020 Jan; 27(1):47-57.
2. Gozes O, Frid-Adar M, Greenspan H, Browning PD, Zhang H, Ji W, Bernheim A, **Siegel E.** Rapid AI Development Cycle for the Coronavirus (COVID-19) Pandemic: Initial Results for Automated Detection & Patient Monitoring Using Deep Learning CT Image Analysis. arXiv preprint arXiv:2003.05037, 2020 Mar.
3. Gangopadhyay A, Morris M, Saboury B, **Siegel E**, Yesha Y. IDIOMS: Infectious Disease Imaging Outbreak Monitoring System. Digital Government: Research and Practice. 2020 Nov;2(1).
4. Greenspan H, Estepar RSJ, Niessen WJ, **Siegel E**, Nielsen M. Position Paper on COVID-19 Imaging and AI: From the Clinical Needs and Technological Challenges to Initial AI Solutions at the Lab and National Level Towards a New Era for AI in Healthcare. Medical Image Analysis. 2020 Dec;66:101800.
5. Manesh R, **Siegel EL**, Schatzlein J, Mackowiak PA. St. Francis of Assisi's Fatal Illness: A Diagnosis Based on Alternative Forms of Intelligence. The Pharos.

Summer 2021;15:14-18.
6. Park CJ, Yi PH, **Siegel EL**. Medical Student Perspectives on the Impact of Artificial Intelligence on the Practice of Medicine. Current Problems in Diagnostic Radiology. 2021 Sep-Oct;50(5):614-619.
7. Toosi A, Bottino AG, Saboury B, **Siegel E**, Rahmim A. A Brief History of AI: How to Prevent Another Winter (A Critical Review). PET Clinics. 2021 Oct;16(4):449-469.
8. Saboury B, Rahmim A, **Siegel E**. PET, and AI Trajectories Finally Coming into Alignment. PET Clinics. 2021 Oct;16(4):XV-XVI.
9. Siegel E. Imaging Informatics: Waking Up to 50 Years of Progress. Applied Radiology. 2021 Nov;50(6):27-29.
10. Saboury B, Morris MA, **Siegel E**. Future Directions in Artificial Intelligence. Radiologic Clinics of North America. 2021 Nov;59(5)1085-1095.
11. Hasani N, Morris MA, Rahmim A, Jones E, **Siegel E**, Saboury B. Trustworthy Artificial Intelligence in Medical Imaging. PET Clinics. 2022 Jan;17(1):1-12.
12. Hasani N, Farhadi F, Morris MA, Jones E, **Siegel E**, Saboury B. Artificial Intelligence in Medical Imaging and its Impact on the Rare Disease Community: Threats, Challenges, and Opportunities. PET Clinics. 2022 Jan;17(1):13-29.
13. Beegle C, Hasani N, Maass-Moreno R, Saboury B, **Siegel E**. Artificial Intelligence and Positron Emission Tomography Imaging Workflow-Technologists' Perspective. PET Clinics. 2022 Jan;17(1):31-39.
14. Saboury B, Rahmim A, **Siegel E**. Taming the Complexity: Using Artificial Intelligence in a Cross-Disciplinary Innovative Platform to Redefine Molecular Imaging and Radiopharmaceutical Therapy. PET Clinics. 2022 Jan;17(1): PXVII-XIX.
15. Liu T, **Siegel E**, Shen D. Deep Learning and Medical Imaging Analysis for COVID-19 Diagnosis and Prediction. Annual Review of Biomedical Engineering. 2022 Mar;24(1):179-201.
16. Huang EP, O'Connor JP, McShane LM, Giger ML, Lambin P, Kinahan PE, **Siegel EL**, Shankar LK. Criteria for the Translation of Radiomics into Clinically Useful Tests. Nature Reviews Clinical Oncology. 2022 Nov;20:69-82.
17. Santomartino SM, **Siegel E**, Yi PH. Academic Radiology Departments Should Lead Artificial Intelligence Initiatives. Academic Radiology. 2023 May;30(5):971-974.
18. Kulkarni P, Kanhere A, **Siegel E**, Yi PH, Parekh VS. One Copy Is All You Need: Resource-Efficient Streaming of Medical Imaging Data at Scale. arXiv preprint arXiv:2307.00438, 2023 Jul.
19. Kulkarni P, Garin S, Kanhere A, **Siegel E**, Yi PH, Parekh VS. High-Throughput AI Inference for Medical Image Classification and Segmentation using Intelligent Streaming. arXiv preprint arXiv:2305.15617, 2023 Jul.
20. Beheshtian E, **Siegel E**, Mezrich J. Caveat Emptor: Medicolegal Issues May Arise from the Opaque and Unpredictable Nature of Current Large Language Models Used in Diagnostic Imaging. Academic Radiology. 2024 Jan (In Press).
21. Smith-Bindman R, Wang Y, Stewart C, Luong J, Chu PW, Kohli M, Westphalen AC, **Siegel E**, Ray M, Szczykutoicz TP, Bindman AB, Romano PS. Improving the Safety of Computed Tomography Through Automated Quality Measurement.

Investigative Radiology. 2024 Jan.

Books

1. **Siegel EL**, Kolodner R. Filmless Radiology, New York, NY: Springer-Verlag New York Inc., 1999.
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CURRICULUM VITAE
Eliot L. Siegel, M.D.

Major Invited Speeches or Presentations

Over 1,000 invited speeches or Presentations 1988-2020

1. Using AI Imaging Tools During COVID-19, Diagnostic Imaging, 9 April 2020.
2. A Multimodality Approach to AI in Diagnostic Imaging, Educational Symposia, 12 August 2020.
3. Radiology AI: Past, Present, and Future, RSNA Radiology: AI Podcast, 27 November 2020.
4. Clinical Workflow of Portable MR Imaging: Hyperfine Portable MR Imaging, 2020 RSNA Annual Meeting, 3 Dec 2020, Chicago, IL.
5. Journey to the Cloud with Change Healthcare, 2020 RSNA Annual Meeting, 1 December 2020, Chicago, IL.
6. Radiology and AI in 2020, Canon Medical Systems, 15 April 2021.
7. Webinar, Fireside Chat, Hyperfine Portable MR Imaging, 19 July 2021.
8. COVID-19 Crisis: How Medical Imaging and AI Can Answer the Call. RADlogics, 23 August 2021.
9. AI/Machine Learning Hype, Hope, and Reality. University of Miami, Institute for Data Science and Computing, Data Citizens: A Distinguished Lecture Series Presents Series, 11 November 2021.
10. Intelligent Healthcare: AI Today and Beyond, Canon Medical Systems Europe, 23 November 2021.
11. The State of AI in Radiology Today, A Roundtable Discussion Webinar, Canon Medical Systems, 4 April 2022.
12. Elevating a Patient's Radiology Journey with ML and the Cloud, AWS Summit 2022, Washington DC, 14 June 2022.
13. Emerging CT Imaging Trends: Evolution in Computed Tomography, RadSite, 26 October 2022.
14. Imaging Follow-Up Management in 2023, Online Expert Panel, Agamom Webinar, 1 February 2023.
15. The Past, Present, and Future of AI in Radiology, Artificial Intelligence in Radiology Education (AIRE) AI Literacy Course, 12 October 2023.
16. Empowering Radiology to Elevate Patient Adherence in Follow-Up Care; RSNA Annual Meeting, Chicago, IL, 28 November 2023.
17. Radiologists and Theranostics. RSNA 2023 Interview with AuntMinnie.com, 30 November 2023.
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20. Artificial Intelligence in Nuclear Medicine Point/Counterpoint, American Journal of Radiology Webinar, 19 June 2024.
21. Debate on Utilization of Data – Opportunities, Ethics, and Patient Perspectives, Society of Imaging Informatics, Society for Imaging Informatics in Medicine Annual Meeting, National Harbor, MD, 27 June 2024.
22. Advocating for AI Adoption and Deployment in Radiology and Leveraging Platforms for Operational Efficiency, Society for Imaging Informatics in Medicine

Annual Meeting, National Harbor, MD, 28 June 2024.

23. AI In Radiology, Now and Tomorrow: Moving the Needle, American Association of Physicists in Medicine 66th Annual Meeting, Los Angeles, CA, 24 July 2024.
24. Visiting Professor, Hot Seat Conference, University of Alabama at Birmingham, 13 August 2024.

Appendix D

Testimony List

I have provided no trial or deposition testimony in the previous 4 years.

Exhibit C

Evaluation of Gastroparesis
Expert Opinion

By Daniel L. Raines, MD, FACG

I. Introduction

I serve as Chief of Gastroenterology and Professor of Clinical Medicine for Louisiana State University Health Sciences Center (LSUHSC). Since its founding in 1931, LSUHSC has led medical education in Louisiana. It has developed over time to include six professional schools (Medical, Dental, Nursing, Allied Health, Public Health, and Graduate Studies) with an annual enrollment of over 2,800 students. LSUHSC is one the largest providers of healthcare in the Gulf South, caring for over one (1) million patients annually. My role as Chief of Gastroenterology is comprised of responsibilities involving patient care, medical education, and clinical research. I care for over 2,000 unique patients annually and have done so each year following graduation from my gastroenterology fellowship in 2007. These clinical experiences were supplemented prior to and during my gastroenterology fellowship by the mentorship of my father, Dr. David Raines, who was also a gastroenterologist. My clinical practice within LSUHSC is complimented by a subspecialty expertise in disorders of gastrointestinal motility, small bowel bleeding, chronic diarrhea, and obesity medicine. The majority of patients currently seen in my clinic are referred by other gastroenterologists for further evaluation of complex cases or rare diseases including patients previously diagnosed with gastroparesis.

As Chief of Gastroenterology, in May of 2018, I collaborated with members of the LSU Department of Surgery to establish the LCMC Center for Weight Loss and Bariatric Surgery. This center provides care to thousands of patients each year through a multidisciplinary approach to obesity, which involves nutritionists, behavioral therapists, gastroenterologists, and surgeons. In October of 2022, we earned national accreditation from the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP). This accreditation confirms compliance with all requirements for essential staffing, training, facility infrastructure, and patient care pathways for obesity medicine. In September of 2024, our program was expanded through the recruitment of additional surgeons and creation of a dedicated hospital unit. Glucagon-like peptide-1 receptor agonist (GLP-1RA) agents are commonly utilized in our patient population in the treatment of obesity as well as diabetes.

My educational activities as an academic professor are integrated within LSUHSC at multiple levels. They include didactic as well as clinical education of medical students, physician assistant (PA) students, medical residents, and gastroenterology fellows. I served as Program Director for the LSUHSC Gastroenterology Fellowship Program from May 2012 until June 2024. Over the past 20 years, I have provided individual instruction to over 500 trainees and served as a mentor to 48 gastroenterology fellows in the diagnosis and management of gastrointestinal disorders, including gastroparesis. My educational activities routinely extend into other educational institutions, such as Tulane University School of Medicine and Ochsner Medical Center, as an adjunctive faculty. My clinical research pursuits have been recognized by the National Institutes of Health (NIH), the New England Journal of Medicine (NEJM), the American Society of Gastrointestinal Endoscopy (ASGE), and the American College of Gastroenterology (ACG).

As Program Director at LSUHSC, I developed enduring teaching materials for the benefit of future trainees in our fellowship as well as other fellowship programs. In 2012, I collaborated with the American College of Gastroenterology (ACG) to publish a training course in capsule

endoscopy accompanied by textbook titled, "Capsule Endoscopy by Case Study." The majority of gastroenterology fellowship programs in the United States utilize this training course for training in capsule endoscopy. In October of 2024, the ACG Board of Governors elected to commission a 2nd edition of "Capsule Endoscopy by Case Study" under my direction. The LSUHSC Gastric and Esophageal Motility Curriculum is a recent example of my enduring teaching materials. This curriculum was developed to ensure competency in the evaluation of gastric and esophageal motility disorders. It includes reading materials, virtual lectures, and patient case studies. Our fellowship program intends to disseminate this curriculum to other gastroenterology fellowships in the United States following validation as a method to achieve competency in the diagnosis of upper gastrointestinal motility disorders.

I am frequently invited to speak to local, regional, and national audiences on a variety of topics in the field of gastroenterology, including gastrointestinal motility disorders and wireless motility capsule (WMC) technology. I have been an active member of all three major U.S. gastroenterology societies, the American Society for Gastrointestinal Endoscopy (ASGE), the American College of Gastroenterology (ACG), and the American Gastroenterological Association (AGA) since the start of my gastroenterology fellowship in 2004. I was elected as a Fellow of the ACG in 2012 and served as President of the Louisiana State Gastroenterology Society from 2016 to 2017. I became certified in Gastroenterology by the American Board of Internal Medicine in 2008 and recertified in 2018.

II. Question Presented

I have been asked to describe the accepted/standard of care methods used to diagnose gastroparesis in clinical practice in the United States. Although literature pertaining to GLP-1RA drugs is included in my review, I was not asked to provide an opinion as to whether these drugs cause gastroparesis.

III. Summary of Methodology and Materials Considered

Decades of education, training, and clinical experience serve as a foundation for the opinions expressed in my report. As a practicing gastroenterologist, I regularly diagnose and manage patients with gastroparesis while keeping abreast of evolving medical knowledge pertaining to this condition. I have prepared this report using the same scientific rigor and methodologies used in my role as an academic clinician. My opinions are expressed to a reasonable degree of medical and scientific certainty. I reserve the right to supplement or amend my opinions if new information becomes available, to respond to Defendants' expert(s), and to use graphics and demonstratives to explain or illustrate information discussed in this report.

In preparing this report, I conducted a literature review to serve as a supplement to my existing knowledge base and clinical experience. This review was conducted in the same manner as I conduct research when preparing scholarly works for publication. My literature search originated with a PubMed database search of the body of literature published to date (as of November 2024). The Medical Subject Heading (MeSH) term "gastroparesis" was used to obtain a comprehensive list of the articles in which gastroparesis is one of the main topics discussed (MeSH Major Topic).

I surveyed the results of this search to identify relevant articles, including (but not limited to) review articles, society guidelines, consensus statements, epidemiologic studies, studies pertaining to gastroparesis pathophysiology, and articles related to the diagnosis of gastroparesis. Careful review of these articles through references and footnotes led to identification of further sources of information. Additional articles were incorporated through searches for publications which I have cited those I found relevant. Specific references are cited in my opinion and listed in the bibliography. A list of additional materials considered is attached as Exhibit A.

IV. Gastroparesis Pathophysiology

Gastroparesis (GP) is characterized by symptomatic delay in gastric emptying in the absence of mechanical obstruction. (Quigley 2015) (Camilleri 2021). Typical symptoms include nausea, vomiting, abdominal pain/bloating and early satiety. (Quigley 2015) (Camilleri 2021). As impairment of gastric motility is fundamental to this condition, the physiology of normal gastric function and mechanisms for dysfunction must be reviewed.

A. Normal Gastric Function

The stomach serves as a vessel to grind food into a liquid which is injected into the small intestine in tiny, 1mm portions. Thick layers of muscle in the stomach push food into the channel at the end of the stomach (pylorus) in rhythmic, propulsive waves. The stomach contains specialized nerve cells, or Interstitial Cells of Cajal (ICC), which function as pacemakers for coordinated waves of muscular contraction. (Figure 1). The strength and frequency of these waves are regulated through a complex system of nerves embedded within the gastrointestinal tract (enteric nervous system or ENS), which is influenced by signals exchanged with the central nervous system. The ICC convey messages between nerves and smooth muscle cells using specialized chemicals called neurotransmitters. In the gastrointestinal tract, acetylcholine (Ach) is the primary neurotransmitter used to stimulate muscular contraction, while nitric oxide (NO) and vasoactive peptide (VIP) promote relaxation.

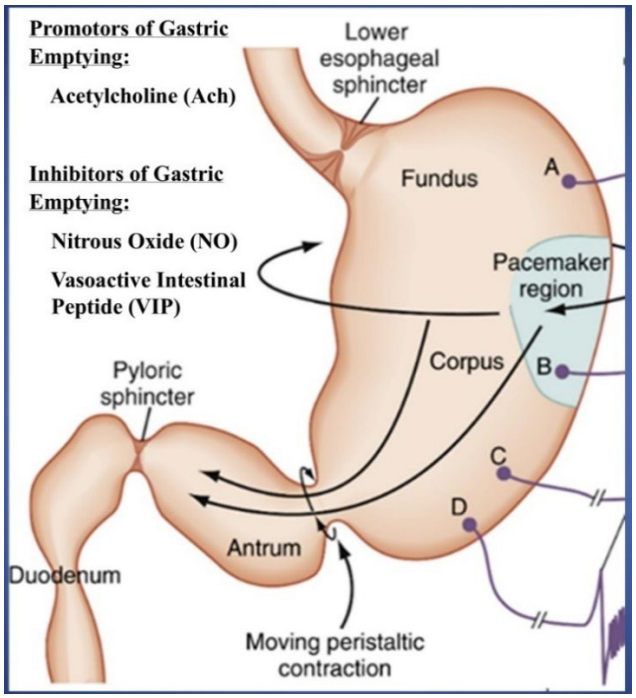


Figure 1: Structure and function of the upper gastrointestinal tract (Netter Collection of Medical Illustrations)

Physiologic emptying of gastric contents varies by type of contents. The stomach normally empties liquids within three (3) hours of ingestion and solids within four (4) hours of ingestion. (Figure 2).

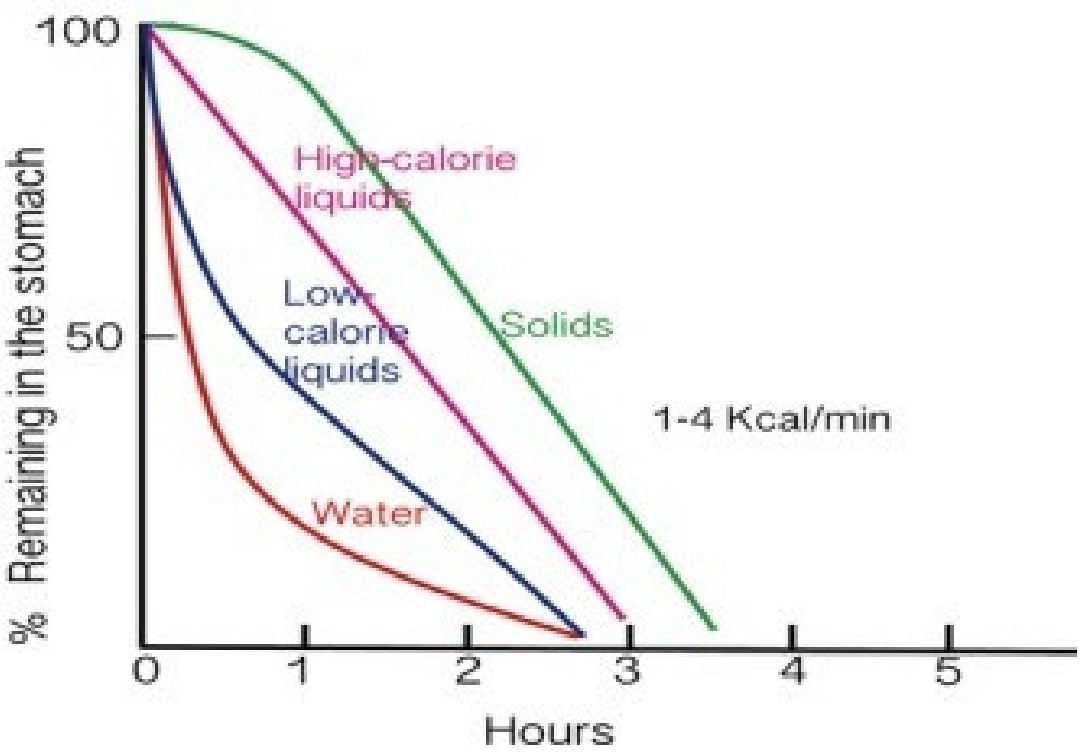


Figure 2: Physiologic emptying of gastric contents over time (adapted from Goyal 2019)

B. Etiologies of Gastroparesis

The term gastroparesis literally translates to "paralysis of the stomach." This condition may develop as the result of any pathology which interferes with normal gastric motor function. Specific pathologies may contribute to injury or dysfunction of gastric smooth muscle, nerves which serve the stomach, or both. Depending on the underlying cause, gastric motility may be temporary or permanently impaired. Patients with diabetes mellitus may develop gastroparesis due to injury to the enteric nerves (enteric neuropathy). Connective tissue disorders, such as scleroderma, may result in injury to the enteric nerves and gastric smooth muscle resulting in gastroparesis. The primary nerve which connects the brain to the stomach (Vagus nerve) may be injured due to trauma or surgery resulting in gastroparesis due to loss of communication between the central nervous system and the enteric nervous system. (Quigley 2015). In some cases of gastroparesis, the etiology may be undefined or "idiopathic."

Certain medications may interfere with gastric motility, resulting in drug-induced gastroparesis. (Galvez 2023) (Camilleri 2011) (Bekkelund 2018) (Patrick & Epstein 2008). Studies regarding the prevalence of gastroparesis in the United States estimate that drug-induced gastroparesis accounts for 11.8% to 22% of all cases of gastroparesis. (Jung 2009) (Ye 2022). Opioids are known to cause gastroparesis through inhibition of gastric motility and stimulation of the pyloric sphincter. (Bagnol 1997) (Bayguinov 1993). GLP-1RAs may delay gastric emptying by mimicking the actions of endogenous glucagon-like peptide-1 (GLP-1). (Maselli 2020) (Halawi 2017) (Imeryüz N 1997) (Schirra 2002) (Delgao-Aros 2002) (Schirra 2009). Endogenous GLP-1 is released after a meal to suppress appetite and slow gastric emptying. It is cleared from the blood stream within a few minutes, while GLP-1RA drugs remain active for multiple days. (Nauck 2021). Delay in gastric emptying is included in labeling for the drugs. (Mounjaro Label, July 28, 2023) (Saxenda Label, April 20, 2023) (Trulicity Label, Nov 17, 2022) (Wegovy Label, March 8, 2024).

Other medications which have been associated with drug-induced gastroparesis include anticholinergic agents, levodopa, lithium, tricyclic antidepressants, phenothiazines, somatostatin, calcium channel blockers, beta agonists, immune checkpoint inhibitors, progesterone, aluminum antacids, sucralfate, nicotine, glucagon, and isoniazid. (Bi 2021) (Szarka & Camilleri 2019) (Ahuja 2020).

V. Diagnosis of Gastroparesis

A. Principles of Medical Diagnosis

Medical evaluations begin with a detailed history and physical examination. This information is used to develop a list of potential diagnoses, or "differential diagnoses," which may explain a patient's symptoms. These diagnoses are typically organized by likelihood then reordered or excluded based upon evidence accumulated through diagnostic testing, clinical course, and response to therapy. A final diagnosis is made by the treating physician based upon their judgement of which diagnosis is most likely. Although some medical diagnoses rely more heavily upon clinical history, exam findings, or testing results, they are rarely made by a single

piece of evidence. (Bickley & Szilagyi 2021) (Harrison's Principles of Internal Medicine, Chapter 4: Decision-Making in Clinical Medicine 2021).

B. Differential Diagnosis for Gastroparesis

Patients with gastroparesis typically present with symptoms of nausea, vomiting, abdominal pain, and early satiety. Chronic nausea and vomiting are predominant in the majority of cases. The differential diagnosis for patients with chronic nausea and vomiting (>7 days) includes medication-related nausea, post-operative nausea/vomiting, neurologic conditions, functional disorders, motility disorders, mechanical obstruction, mucosal inflammation, pregnancy, and chemotherapy-related nausea/vomiting.

I will provide an overview of the most common pathologies which result in symptoms of chronic or recurrent nausea and vomiting and may also include abdominal pain and/or early satiety.

- **Gastroparesis** is a motility disorder characterized by recurrent nausea and vomiting combined with abdominal pain/bloating (present in 80% of patients) and early satiety (present in 60%). (Yamada). Vomiting of undigested food is a cardinal symptom which may be considered pathognomonic for delay in gastric emptying if the food was ingested >4 hours prior. Patients with gastroparesis commonly experience frequent or persistent nausea which limits their ability to work or function independently and is associated with a lower quality of life. (Parkman 2016). Patients with severe symptoms may require treatment in an emergency room or hospital for dehydration. A diagnosis of gastroparesis may be supported by the presence of a condition known to contribute to delay in gastric emptying, such as diabetes, scleroderma, or vagal nerve injury. In cases in which onset of symptoms correlate with initiation of a drug known to induce delay in gastric emptying, a diagnosis of drug-induced gastroparesis is more likely.

- **Organic pathologies**, which may present with similar symptomology to gastroparesis, include peptic ulcer disease, gastric cancer, gallstone disease, and pancreatitis. Patients with peptic ulcer disease (*i.e.*, gastric ulcers) primarily complain of recurrent upper abdominal pain which is worse on an empty stomach. They may also experience symptoms of early satiety, nausea, and vomiting. (Kavitt 2019). Gastric cancer may result in upper abdominal pain with eating accompanied by nausea, vomiting, and progressive weight loss. Gallbladder disease, such as symptomatic gallstones, typically produces symptoms of recurrent pain in the right upper abdomen which occurs within 30-60 minutes following a meal. Inflammation of the pancreas (pancreatitis) is characterized by "penetrating" upper abdominal pain which persists for days or weeks.

- **Functional disorders** (now termed "Disorders of Brain Gut Interaction" or DBGIs) are characterized primarily by abnormal central processing of signals from the intestine, intestinal inflammation, and/or abnormal motility. (Drossman 2016) (Rome IV). Identified risk factors for DGBIs include history of childhood abuse or trauma, psychological stress, anxiety, depression, and/or chronic fatigue. Patients with DGBIs

often experience lifelong symptoms beginning in adolescence or early adulthood. (Zia 2022). They are classified by identifiable symptoms which occur together in a syndrome. (Cheng 2013). The classification system for DGBIs is developed and published by the Rome Foundation, an independent non-profit organization dedicated to research and education in the field of functional disorders/DBGIs, such as irritable bowel syndrome (IBS). (Rome IV). Functional Dyspepsia (FD) is characterized by abdominal pain and early satiety but may be complicated by nausea and/or vomiting. (Rome IV). FD consists of two subtypes: epigastric pain syndrome (EPS) and post-prandial distress syndrome (PDS). EPS is defined by recurrent epigastric pain and/or epigastric burning. PDS is defined by recurrent symptoms of bothersome fullness after eating and/or early satiety which prevents finishing a standard meal. Chronic Nausea and Vomiting Syndrome (CNVS) is defined by recurrent symptoms of nausea and vomiting without a defined etiology after complete evaluation. This may include psychogenic vomiting. Patients who experience discrete episodes of nausea with persistent vomiting may meet criteria for either Cyclical Vomiting Syndrome (CVS) or Cannabinoid Hyperemesis Syndrome (CHS). Rumination syndrome is characterized by effortless regurgitation and re-swallowing of recently ingested food without retching or nausea.

- **Psychiatric Disorders**, which may present with some symptoms associated with gastroparesis, include anorexia and bulimia. Anorexia is typically characterized by abnormally low body weight, a fear of weight gain, and a distorted perception of one's body weight or shape. Patients with anorexia may engage in purging, or self-induced vomiting. Bulimia is characterized by binge eating accompanied by behavior to prevent weight gain, including purging and/or abuse of laxatives. A detailed history and physical exam is commonly revealing in these cases.

C. Diagnostic Testing

In the context of evaluation of gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and early satiety, the choice of diagnostic tests is heavily dependent upon the initial impression of likely diagnoses based upon history and physical exam. Symptom qualifiers such as quality, severity, duration, timing, context, modifying factors, or associated symptoms are instrumental in focusing attention on a short list of conditions. A review of previous medical diagnoses, medications, and social history is often revealing for information which excludes some diagnoses (*e.g.*, gallbladder disease in a patient with previous gallbladder removal) while increasing the likelihood of other diagnoses (*e.g.*, history of alcoholism as a risk factor for pancreatitis).

When ordering a diagnostic test (lab tests, imaging studies, etc.), it is a best practice to do so after confirming an initial impression rather than ordering tests in a broad or indiscriminate manner. The choice of diagnostic testing is also influenced by availability. For example, laboratory studies and imaging by CT scan may be readily accessible in an emergency room setting. Some tests, such as gastric emptying scintigraphy (GES), are only available in centers with a nuclear medicine department and only performed on outpatients following insurance authorization. History and physical examination may be diagnostic in cases of drug-induced gastroparesis;

functional disorders, such as CVS, CHS and rumination syndrome; and psychiatric disorders, such as anorexia and bulimia.

The following table includes a concise description of the common alternative diagnoses included in the differential diagnoses for patients with symptoms suggestive of gastroparesis. For each diagnosis, cardinal symptoms and risk factors are listed along with specific tests which may be ordered to confirm a suspected diagnosis. Following this table, I have included a list of diagnostic tests which may be considered in all patients with nausea, vomiting, abdominal pain, and early satiety.

Table 1: Common Etiologies of Gastrointestinal Symptoms Observed in Gastroparesis

*Routine lab studies include: complete metabolic panel (CMP), complete blood count (CBC), lipase level

Diagnosis	Cardinal Symptoms	Risk Factors	Confirmatory Testing
Gastric ulcer	Recurrent upper abdominal pain	NSAID use H. pylori infection	Upper endoscopy (EGD)
Gastric cancer	Upper abdominal pain after eating Weight loss	Smoking Family history of gastric cancer	Upper endoscopy (EGD)
Gallstones	Recurrent upper abdominal pain 30 min after eating	Female sex Obesity	Lab studies of liver enzyme levels Ultrasound of the gallbladder
Pancreatitis	Constant upper abdominal pain with abdominal tenderness	Heavy alcohol use	Serum lipase level CT scan
Epigastric pain syndrome (EPS)	Chronic symptoms of epigastric burning and/or bloating	Female sex Anxiety	Routine lab studies* CT scan Upper endoscopy (EGD) GES **not** recommended
Post-prandial distress syndrome (PDS)	Chronic symptoms of fullness after eating and/or early satiety	Female sex Anxiety	Routine lab studies* CT scan Upper endoscopy (EGD) GES **not** recommended

Chronic nausea & vomiting syndrome (CNVS)	Chronic nausea and/or vomiting which is unexplained	All other causes excluded	Routine lab studies* CT scan Upper endoscopy (EGD) GES
Cyclic vomiting syndrome (CVS)	Discrete episodes of nausea with persistent vomiting	History of migraines	None (diagnosis based upon history)
Cannabinoid hyperemesis syndrome (CHS)	Discrete episodes of nausea with persistent vomiting	Frequent use of cannabis/THC	None (diagnosis based upon history)
Rumination syndrome	Persistent, effortless regurgitation of recently ingested food	History of mental illness	None (diagnosis based upon history)
Anorexia	Severe restriction of food intake, often accompanied by purging	Female sex Distorted body image	None (diagnosis based upon history)
Bulimia	Periods of overeating followed by purging Abuse of laxatives	Female sex Family history of bulimia	None (diagnosis based upon history)

Imaging studies (plain x-ray, CT scan, MRI, ultrasound) allow for visualization of internal structures, including the gastrointestinal tract, liver, pancreas, and gallbladder. Imaging of the abdomen by CT scan or MRI may be useful in evaluating for mechanical obstruction of the gastrointestinal tract. CT or MRI imaging of the abdomen may also reveal organic pathology, such as peptic ulcer disease, gastric cancer, pancreatitis, or gallbladder disease. Abdominal ultrasound may be diagnostic for disease of the gallbladder as well as other intra-abdominal organ pathology. Imaging study findings which support a diagnosis of gastroparesis include gastric distension and/or retained gastric food.

Upper endoscopy (esophagogastroduodenoscopy or EGD) involves insertion of a lighted tube with a camera through the mouth and down into the esophagus, stomach, and duodenum. In patients with a history of nausea, vomiting, or abdominal pain, upper endoscopy may be utilized to evaluate for esophageal disease, gastric ulcers, and gastric cancer. The discovery of retained gastric food (RGF) on upper endoscopy is highly suggestive of delayed gastric emptying. (Coleski 2016). In a large retrospective review of patients evaluated by both upper endoscopy and GES, RGF on upper endoscopy was predictive of delayed GES in 55% of cases. In patients with type I diabetes, the finding of RGF was highly predictive (79%) of an abnormal GES. In patients taking drugs associated with delay in gastric emptying, the overall positive predictive value of RGF for abnormal GES was 62%. Patients taking a GLP-1RA were 5.3 times more likely to have RGF compared to controls, more than any other drug. (Bi 2021). The authors of this study concluded that GES was unnecessary to confirm a diagnosis of gastroparesis in cases in which RGF correlates closely with abnormal GES, as observed in patients with Type I diabetes. (Bi 2021).

Gastric emptying scintigraphy (GES) is the test most commonly used to evaluate delay in gastric emptying. A GES is the most accurate test of gastric emptying currently available; it is considered

as the "gold standard" by which other tests are validated. Correct performance of the GES, though, requires strict adherence to a standardized protocol. Patients preparing for a GES must hold all medications which may affect gastric motility for a time period equal to 3-6 times the drug half-life. (Abell 2008). On the day of the exam, the imaging facility must prepare a standardized meal consisting of four (4) ounces of scrambled egg whites mixed with technetium-99m sulfur colloid radioactive tracer. The eggs are served with two slices of white bread, 30gm of strawberry jam, and 120ml of water. Images are obtained immediately following ingestion, and at one (1) hour, two (2) hours, and four (4) hours post-meal. Delayed gastric emptying is classically defined as retention of >60% of the meal at two (2) hours or >10% at four (4) hours. (Abell 2008). Retention of >30% of a standard meal at three (3) hours has also been accepted in the criteria for an abnormal GES. (Tougas 2000).

Although GES is considered the best available test to evaluate for delay in gastric emptying, it is far from perfect. Rates of gastric emptying vary significantly between healthy individuals. The normal ranges for gastric emptying were developed to be accurate in 90-95% of healthy adults, leaving a 5-10% risk of a false positive GES. Previous studies have also identified issues with reproducibility of the GES. In one study, GES yielded a different result (normal, delayed, or rapid) in 30% of patients when performed on two occasions, with an average interval of 15 days between studies. (Arts 2005). Additionally, adherence to the standardized protocol for GES varies greatly across institutions. This variability is likely related to the complexity of the protocol and responsibilities assigned to the imaging center staff to prepare the standardized meal. (Wise 2020). The performance of GES is limited to centers with nuclear medicine imaging capability and should only be performed in an outpatient setting.

Gastric emptying breath test (GEBT) involves the ingestion of eggs labeled with a non-radioactive carbon isotope (^{13}C-Spirulina). As the eggs are digested, carbon^{13} is released in the form of carbon^{13} dioxide which is detected in the patient's breath. GEBT is 89% sensitive for delayed emptying of solids. (Szarka 2008). This test is considered by current guidelines to be accurate in the evaluation of gastric emptying but is not widely available.

Wireless motility capsule (WMC) or "Smartpill" transmits data, including pH and pressure, as it transits through the gastrointestinal track. This study has been validated compared to a GES as a reasonably accurate test in the diagnosis of delayed gastric emptying. However, WMC has been criticized as a non-physiologic test which evaluates the emptying of a foreign particle rather than food. (Lee 2019). Like GEBT, this test has practical advantages over GES but is not widely available.

D. Diagnoses Associated with Delayed Gastric Emptying

Delayed gastric emptying is a defining feature of all subtypes of gastroparesis but is also observed in 25-40% of patients with functional dyspepsia. Evaluation of these diagnoses may be specific for drug-induced gastroparesis, other gastroparesis (non drug-induced), and functional dyspepsia.

- Drug-Induced Gastroparesis

Drug-induced gastroparesis may be considered in cases in which symptoms of nausea, vomiting, abdominal pain, and/or early satiety develop following the initiation of a medication, such as a GLP-1 RA, known to inhibit gastric motility. Recurrent nausea and/or vomiting are key historical findings. These symptoms should be qualified in order to confirm a pattern consistent with gastroparesis rather than other disorders of nausea/vomiting such as CVS, CHS, or Rumination Syndrome. Vomiting of undigested food consumed over four (4) hours prior is a clear indicator of delay. Historical elements which may assist in excluding alternative diagnoses include fever, blood in stool, diarrhea, history of NSAID use, history of alcohol abuse, or use of cannabis. A medical history review should be performed to identify any prior history of reflux esophagitis, peptic ulcer disease, pancreatitis, or abdominal surgery. Physical examination in patients with drug-induced gastroparesis may be revealing for abdominal distension. The presence of findings such as an elevated temperature, jaundice, or severe abdominal tenderness are suggestive of organic pathology.

In cases in which a patient's history and physical exam are consistent with a diagnosis of drug-induced gastroparesis and negative for evidence of alternative diagnoses, I assign a diagnosis of drug-induced gastroparesis. The next step in management should be withdrawal of the offending drug. A diagnosis of drug-induced gastroparesis may be further supported in patients who experience resolution of symptoms after medication withdrawal. Symptom resolution also indicates a lack of mechanical obstruction. Patients who experience continued symptoms following drug withdrawal require further evaluation including imaging and/or upper endoscopy followed by formal measurement of gastric emptying by GES, GEBT, or WMC. This approach is consistent with various diagnostic algorithms proposed in the literature which recognize that evaluation of drug-induced gastroparesis varies from non-drug induced forms of gastroparesis. (Camilleri 2022) (Bi 2021) (Szarka & Camilleri 2019). See Appendix A.

In patients with a clinical diagnosis of drug-induced gastroparesis, results from prior laboratory studies, imaging or endoscopy, may be supportive if they show evidence of delayed gastric emptying and/or are negative for evidence of mechanical obstruction. Additional supportive findings include gastric distention per imaging, retained gastric food visible on endoscopy, or a positive GES, GEBT, or WMC.

I have reviewed the limited data regarding the association between gastric emptying and gastrointestinal symptoms in patients on GLP-1RA therapy. One database analysis compared patients diagnosed with any gastrointestinal symptom and who had been prescribed a GLP-1RA. (Lupianez-Merly 2024). Of these, 696 patients had completed a GES, and 241 patients (35%) were found to have delayed emptying. In the delayed GES group, 127 of 241 patients had preexisting GI symptoms. The authors failed to exclude patients with preexisting symptoms prior to GLP-1RA therapy. The criteria for inclusion were overly broad with addition of patients with only one (1) symptom, including symptoms which are not typical for gastroparesis, such as diarrhea and constipation. These weaknesses preclude a valid comparison of patients with normal GES vs delayed GES in this analysis.

Delayed GES in the absence of reports of gastrointestinal symptoms can be found in the medical literature. (Linnebjerg 2008) (Jalleh 2020) (Jalleh 2024). These publications relied upon voluntary patient reports which likely underestimate the presence of symptoms. I would not assign a diagnosis of gastroparesis in these cases without evidence of symptoms. Therefore, they have limited applicability to GLP-1RA patients who present with symptomatic delay in gastric emptying.

After considering the relevant literature, drug-induced gastroparesis can be diagnosed clinically. The recommendations for next step in management of suspected drug-induced gastroparesis is drug withdrawal. GES is not recommended for hospitalized patients or in the setting of medications which influence gastric motility. GLP-1 RAs are known to delay gastric emptying.

- Other forms of Gastroparesis (non drug-induced)

Patients with gastroparesis which is not drug-induced present with the same symptoms and physical exam findings observed in drug-induced gastroparesis. Most presentations are accompanied by a risk factor for gastroparesis, such as long-standing diabetes, connective tissue disease, or surgery complicated by Vagal nerve injury. Diagnostic testing should include routine lab studies followed by either upper endoscopy or CT imaging to exclude mechanical obstruction. A GES, GEBT, or WMC should be ordered to document delay in gastric emptying and assess for severity.

In the field of gastric motility, some experts have expressed concern regarding the diagnosis of gastroparesis based upon symptoms and in the absence of a GES. When considering the diagnostic utility of symptoms in gastroparesis, findings reported in the medical literature are mixed. Some studies report symptoms as predictive of a positive GES while others have found this correlation to be unreliable. (Balan 2011) (Vijayvargiya 2019). One report from a tertiary referral center estimated that only 20% of patients referred for gastroparesis were “correctly diagnosed” due to lack of documentation of a GES study performed per the standardized protocol. This estimate illustrates a perspective gastroparesis cannot exist without a positive GES. (Cangemi 2023). As no test is 100% accurate, including GES, the possibility of a true diagnosis of gastroparesis must be considered in patients with typical gastroparesis symptoms and an emptying study which falls withing normal limits.

- Functional Dyspepsia

Approximately 25-45% of patients with functional dyspepsia may have a delayed emptying by GES. These patients may meet criteria for a diagnosis of gastroparesis by society guidelines but do not have gastroparesis. (Park 2017). FD and GP can often be differentiated based upon symptoms. Epigastric pain is typically the predominant symptom in cases of FD. Unlike patients with gastroparesis, the character of the pain is often described as either “burning” (EPS) or fullness after eating which prevents finishing a meal (PDS). Patients with functional dyspepsia sometimes experience nausea and occasionally vomiting, but these are rarely dominant symptoms. Patients

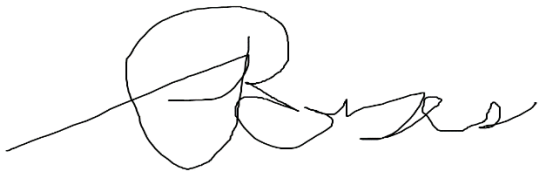
with functional dyspepsia commonly experience symptoms over many years which wax-and-wane. By definition, cases of FD cannot be attributed to a specific injury or medication. (Rome IV).

VI. Summary and Conclusions

I commonly diagnose and manage patients with gastroparesis, including drug-induced gastroparesis, in my practice. In patients who experience symptoms of gastroparesis which correlate with GLP-1RA therapy, my first step is to withdraw the drug. Improvement in symptoms following withdrawal of an offending drug supports a diagnosis of drug-induced gastroparesis and obviates the need for additional testing. In patients with other forms of gastroparesis, I routinely order an upper endoscopy and/or imaging to evaluate for organic pathology and mechanical obstruction. I utilize GES studies to document delay in gastric emptying and assess severity of delay. When interpreting GES studies, I remain open to the possibility of a false negative or false positive result. In patients with symptoms most consistent with functional dyspepsia, I commonly order an upper endoscopy and/or imaging studies but do not commonly utilize GES.

In summary, I hold the following opinions to a reasonable degree of medical and scientific certainty:

- Gastroparesis is a clinical diagnosis defined by symptomatic delay in emptying of the stomach due to abnormal gastric motility.
- Drug-induced gastroparesis is a subtype of gastroparesis which accounts for an estimated 11.8% to 22% of all cases of gastroparesis in the United States.
- In cases of drug-induced gastroparesis, withdrawal of the offending drug is recommended as the first step in management.
- Drug-induced gastroparesis may be diagnosed in the absence of a GES study.
- A diagnosis of drug-induced gastroparesis may be supported by imaging studies, including plain x-ray, CT scan, MRI and/or abdominal ultrasound.
- A positive GES may also support a diagnosis of drug-induced gastroparesis.
- Patients with symptoms of gastroparesis who fail to improve following drug withdrawal require additional testing including upper endoscopy, imaging, and/or GES.



Opinion Executed

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Exhibit A

Materials Considered

I incorporate by reference all materials cited in my report.

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Drug Labeling

Zepbound Package Insert
Mounjaro Package Insert
Wegovy Package Insert
Ozempic Package Insert
Trulicity Package Insert
Saxenda Package Insert
Victoza Package Insert

Exhibit D

Clinical Gastroenterology and Hepatology 2023;21:2670–2672

RESEARCH LETTERS

Misdiagnosis of Gastroparesis is Common: A Retrospective Review of Patients Referred to a Tertiary Gastroenterology Practice

Gastroparesis (GP) and functional dyspepsia (FD) are the 2 most common sensorimotor disorders of the stomach. Symptoms of abdominal pain, nausea, early satiety, and vomiting characterize both disorders.[1,2] GP is defined by delayed gastric emptying, although 20%–30% of patients with FD also have delayed gastric emptying.[3] This overlap makes the diagnosis difficult for many health care providers. No study has described diagnostic outcomes in patients referred to a tertiary referral center for the evaluation of suspected GP. We hypothesized that GP is frequently incorrectly overdiagnosed in the community and that FD, along with other disorders that mimic GP, are underdiagnosed.

We assembled a retrospective cohort population consisting of adult patients referred to Mayo Clinic Jacksonville specifically for the evaluation of GP between January 2019 and July 2021. Demographics, medical comorbidities, medications, diagnostic tests, and laboratory studies were collected. A final diagnosis was determined by review of clinical notes, communications, and tests by experts in the field (DJC, BEL). The primary outcome of interest was patients' final diagnoses. Additional information pertaining to study methods can be found in Supplementary Methods.

A total of 339 patients referred for tertiary evaluation of GP were identified, most of which were female (82.1%) and White (85.6%) (Supplementary Table 1). Seventy-two patients (21.7%) had diabetes; most had type II diabetes mellitus (43 patients; 59.7%). Many patients (71.7%) had been previously diagnosed with gastroesophageal reflux disease. Nineteen patients (5.6%) had been diagnosed with *Helicobacter pylori*. Anxiety (56.9%) and depression (38.8%) were prevalent. Forty-nine patients (14.5%) were taking opioids and 65 patients (19.2%) were using cannabis. One hundred and forty patients (41.3%) had undergone cholecystectomy and 23 patients (6.8%) had undergone a fundoplication procedure.

Nausea was the most common presenting symptom, reported by 302 patients (89.1%). This was followed by abdominal pain (76.4%), constipation (70.5%), vomiting (65.8%), bloating (37.5%), and early satiety (34.5%). Pertinent medications are listed in Supplementary Table 1. Forty-four patients (13%) had undergone at least 1 pyloric injection of botulinum toxin, 8 patients (2.4%) had a gastric electrical stimulator implanted, and 9 patients (2.7%) underwent gastric peroral endoscopic myotomy (Supplementary Table 2). Prior diagnostic evaluation included esophagogastroduodenoscopy (EGD) in 278 patients (82.5%); 127 (45.6%) were normal. A prior EGD could not be definitively confirmed for 61 (18%) patients. Importantly, only 196 patients (57.8%) had definitively been evaluated with a gastric emptying study (GES); 130 of these patients (38.3%) had undergone a 4-hour GES but only 23 patients (6.8%) ingested radiolabeled eggs as the test meal. Sixty-six patients (19.5%) were ultimately confirmed to have GP, whereas 273 (80.5%) received an alternative diagnosis (Figure 1); FD was the most common alternative diagnosis (44.5%).

Compared with patients with GP, patients with alternative diagnoses were younger (median age, 44 [range, 18–83] vs 52 [18–90]; $P = .001$) and had a lower median body mass index (median, 24.9 vs 28.5; $P = .017$) (Supplementary Table 1). Patients correctly diagnosed with GP more often had diabetes (40% vs 17.2%; $P < .001$), and had a history of Barrett's esophagus (12.1% vs 4.8%; $P = .042$); they were less likely to have chronic kidney disease (2.9% vs 9.1%; $P = .036$) and rheumatoid arthritis (4.4% vs 12.1%; $P = .035$). Confirmed GP patients were more likely to have had cholecystectomy (56.1% vs 37.7%; $P = .008$), appendectomy (24.2% vs 13.6%; $P = .038$) or fundoplication (13.6% vs 5.1%; $P = .025$). Proton pump inhibitor use was more prevalent among patients with confirmed GP (71.2% vs 48.7%; $P < .001$). Patients with confirmed GP were less likely to use cannabis (9.1% vs 22.1%; $P = .034$). In terms of endoscopic findings, patients with GP more often had retained food in the stomach on EGD (22.7% vs 8.8%; $P = .004$), and more often had been treated with botulinum toxin injection of the pylorus (22.7% vs 10.6%; $P = .013$). Importantly, there was no difference in gastrointestinal symptoms on presentation between the patient groups.

Treatments recommended after tertiary evaluation differed among patients correctly diagnosed with GP and those with alternative diagnoses. Patients with confirmed GP were more often treated with metoclopramide (19.7% vs 0%; $P < .001$), prucalopride (16.7% vs 1.5%; $P < .001$), ondansetron (28.8% vs 13.2%; $P = .005$), promethazine (12.1% vs 5.1%; $P = .05$), and diet interventions (30.3% vs 17.2%; $P = .024$). Patients with

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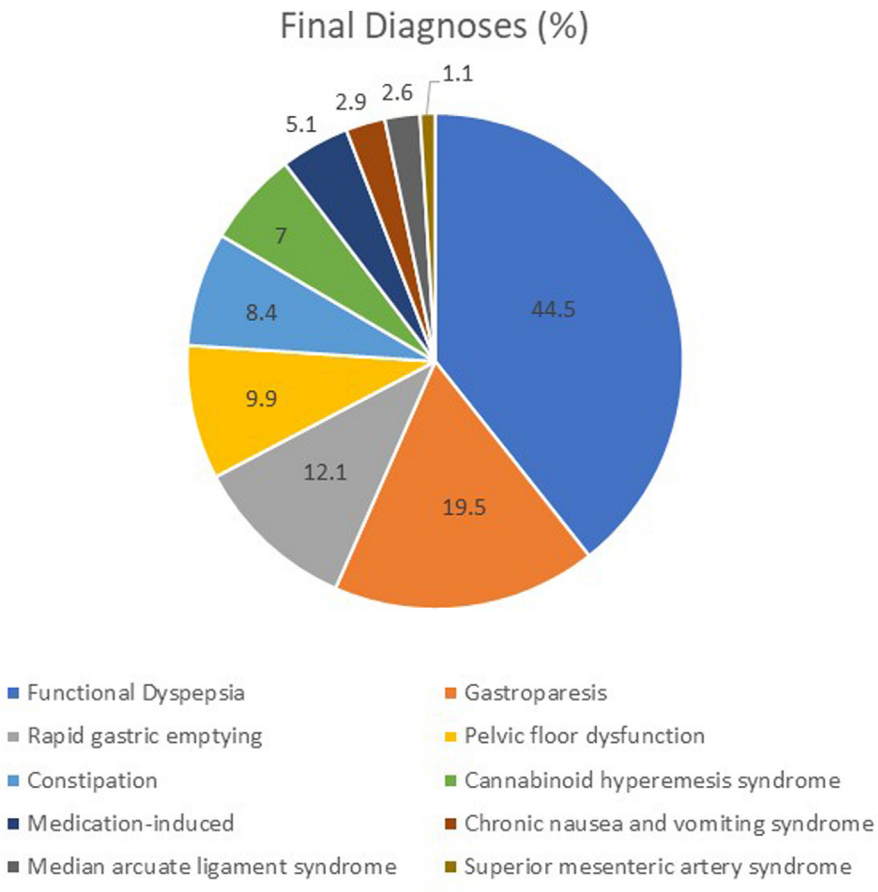

Figure 1. Study cohort final diagnoses.

alternative diagnoses were more often treated with a tricyclic antidepressant (9.5% vs 1.5%; $P = .039$) and advised to discontinue cannabis (5.5% vs 0%; $P = .05$).

In this retrospective study of 339 patients referred for evaluation of GP at our tertiary gastroenterology practice, we determined that most (80%) patients did not have GP but rather an alternative diagnosis; notably almost half of these patients (44.5%) were diagnosed with FD. Importantly, there was no difference in symptom presentation between the 2 groups. This highlights the fact that FD and GP frequently overlap, a finding increasingly recognized among experts in the field.[1,4] Interestingly, only 58% of patients believed to have GP had undergone GES before referral and only 23 patients (6.5%) were known to have undergone a 4-hour GES with a test meal of radiolabeled eggs. Our findings highlight the results of a recent study demonstrating low compliance with GES protocol guidelines among US medical institutions.[5] Although findings of retained gastric food on upper endoscopy were seen more commonly in patients correctly diagnosed with GP in our study, it is important to highlight that the presence of retained food on EGD is not diagnostic of GP.[6]

Study limitations include the retrospective and observational nature, the modest sample size, and the inherent potential for referral bias. Despite these limitations our study presents practical and novel data with respect to diagnosing GP.

In summary, more than 80% of patients referred for further evaluation of GP ultimately received alternative diagnoses; most were diagnosed with FD. Less than 10% of patients referred for GP evaluation had undergone definitive assessment of gastric emptying using the recommended, validated scintigraphy test protocol. Symptom presentation between the 2 groups was similar. Our findings reaffirm guidelines noting that GP cannot be diagnosed based on symptoms alone. FD, which is more prevalent than GP, should be considered first in patients with characteristic upper GI symptoms. Improperly performed GES seems to play a critical role in misdiagnosis of GP.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical*

Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.01.024.

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Lilly Stephens (Data curation: Supporting; Writing – review & editing: Supporting)

Brian E. Lacy (Conceptualization: Supporting; Data curation: Supporting; Formal analysis: Supporting; Methodology: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting)

Conflicts of interest

This author discloses the following: Brian E. Lacy is a consultant for Ironwood, Urovant, Salix, Sanofi, and Viver. The remaining authors disclose no conflicts.

Supplementary Methods

If a gastric emptying scintigraphy study was recommended by the consulting provider, it was performed according to standardized protocol,[1] and results were interpreted in the context of the patients' symptoms and medical history to determine a final diagnosis. For example, a mild delay in gastric emptying on gastric emptying scintigraphy may been determined to represent a diagnosis of functional dyspepsia instead of gastroparesis. Functional dyspepsia, and other disorders of gut-brain interaction, such as chronic nausea and vomiting syndrome, were diagnosed according to Rome IV criteria.[2] The primary outcome of interest was patients' final diagnoses. Continuous variables were summarized with median and range, and categorical variables were summarized with frequency and percentage. Differences between misdiagnoses and correct diagnoses of gastroparesis were evaluated using the Kruskal-Wallis rank sum test for continuous measures and the Fisher exact test for categorical measures.

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Supplementary Table 1. Demographic and Historical Data for Patients Diagnosed With Gastroparesis and Those With Alternative Diagnoses

	Patients with alternative diagnoses (n = 273)	Patients with gastroparesis (n = 66)	Total (n = 339)	*P* value
Age, *y*	44 (18–83)	52 (18–90)	46 (18–90)	.001
Body mass index	24.9 (13.1–51.3)	28.5 (15.7–42.8)	25.3 (13.1–51.3)	.017
Sex				1.000
Female	224 (82.1)	54 (81.8)	278 (82.0)	
Male	49 (17.9)	12 (18.2)	61 (18.0)	
Race				.842
White	231 (85.6)	57 (87.7)	288 (86.0)	
Non-White	39 (14.4)	8 (12.3)	47 (14.0)	
Diabetes				< .001
Type I	18 (6.7)	11 (16.9)	29 (8.7)	
Type II	28 (10.5)	15 (23.1)	43 (13.0)	
Gastroesophageal reflux disease	195 (71.4)	48 (72.7)	243 (71.7)	.880
Barret's esophagus	13 (4.8)	8 (12.1)	21 (6.2)	.042
Helicobacter pylori	17 (6.2)	2 (3.0)	19 (5.6)	.549
Depression	110 (40.4)	21 (31.8)	131 (38.8)	.208
Anxiety	157 (57.5)	36 (54.5)	193 (56.9)	.680
Cholecystectomy	103 (37.7)	37 (56.1)	140 (41.3)	.008
Fundoplication	14 (5.1)	9 (13.6)	23 (6.8)	.025
Appendectomy	37 (13.6)	16 (24.2)	53 (15.6)	.038
Proton pump inhibitor use	133 (48.7)	47 (71.2)	180 (53.1)	< .001
Nonsteroidal anti-inflammatory drug use	50 (18.4)	11 (16.7)	61 (18.0)	.859
Antiemetic use				
Ondansetron	115 (42.3)	30 (45.5)	145 (42.9)	.670
Promethazine	56 (20.5)	15 (22.7)	71 (20.9)	.736
Other	17 (6.2)	2 (3)	19 (5.6)	.549
Prokinetic use				
Metoclopramide	30 (11)	3 (4.5)	33 (9.7)	.163
Domperidone	6 (2.2)	3 (4.5)	9 (2.7)	.385
Erythromycin	10 (3.7)	4 (6.1)	14 (4.1)	.487
Prucalopride	11 (4)	9 (13.6)	20 (5.9)	.007
Anxiolytic use				
Alprazolam	29 (10.6)	12 (18.2)	41 (12.1)	.096
Lorazepam	21 (7.7)	5 (7.6)	26 (7.7)	1.000
Clonazepam	21 (7.7)	8 (12.1)	29 (8.6)	.324
Diazepam	14 (5.1)	2 (3)	16 (4.7)	.747
Other	9 (3.3)	0 (0)	9 (2.7)	.215
Antidepressant use				
Tricyclic antidepressant	24 (8.8)	8 (12.1)	32 (9.4)	.480
Serotonin-norepinephrine reuptake inhibitor	38 (13.9)	6 (9.1)	44 (13)	.414
Selective serotonin reuptake inhibitor	63 (23.1)	15 (22.7)	78 (23)	1.000
Mirtazapine	29 (10.6)	7 (10.6)	36 (10.6)	1.000
Buspirone	10 (3.7)	5 (7.6)	15 (4.4)	.182
Other	23 (8.4)	9 (13.6)	32 (9.4)	.238
Opioid use	41 (15.0)	8 (12.1)	49 (14.5)	.697
Cannabis use (current)	59 (21.7)	6 (9.1)	65 (19.2)	.034
Alcohol use (current)	103 (37.7)	19 (28.8)	122 (36.0)	.256
Tobacco use (current)	37 (13.6)	4 (6.1)	41 (12.1)	.241

NOTE. Values are n (%) or median (range).

Supplementary Table 2. Presenting Symptoms and Prior Testing Results and Treatments in Patients With Gastroparesis and Those With Alternative Diagnoses

	Patients with alternative diagnoses (n = 273)	Patients with gastroparesis (n = 66)	Total (n = 339)	*P* value
Nausea	241 (88.3)	61 (92.4)	302 (89.1)	.388
Vomiting	174 (63.7)	49 (74.2)	223 (65.8)	.114
Satiety	98 (35.9)	19 (28.8)	117 (34.5)	.314
Abdominal pain	209 (76.6)	50 (75.8)	259 (76.4)	.873
Bloating	104 (38.1)	23 (34.8)	127 (37.5)	.672
Prior upper endoscopy	220 (80.9)	58 (89.2)	278 (82.5)	.145
Esophagitis	27 (9.9)	5 (7.6)	32 (9.4)	.814
Gastritis	37 (13.6)	11 (16.7)	48 (14.2)	.555
Retained gastric food	24 (8.8)	15 (22.7)	39 (11.5)	.004
Prior gastric emptying scintigraphy[a]	150 (54.9)	46 (70)	196 (37.2)	
Delayed gastric emptying[b]	120 (44)	41 (62.1)	214 (82.9)	
Prior contrast-based study[c]	25 (9.3)	10 (15/2)	35 (10.4)	.178
Prior pyloric Botox injection	29 (10.6)	15 (22.7)	44 (13.0)	.013
Gastric pacemaker	7 (2.6)	1 (1.5)	8 (2.4)	
Gastric peroral endoscopic myotomy	6 (2.2)	3 (4.5)	9 (2.7)	

NOTE. Values are n (%).

[a]Any gastric emptying scintigraphy, regardless of test meal or length of study, was included.

[b]Determination of delayed gastric emptying reported per the individual test parameters, which varied according to different gastric emptying scintigraphy protocols.

[c]Esophogram, upper gastrointestinal series, small bowel follow-through, and magnetic resonance enterography studies were considered contrast-based studies.

Exhibit E

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ORIGINAL ARTICLE

Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials

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Aim: GLP-1 receptor agonists (RAs) may cause nausea, vomiting or diarrhoea. The aim of this study was to assess the risk of adverse events (AEs) with GLP-1 RAs and their relation to dose, background medication and duration of action.

Research design and methods: The PubMed database was searched and 32 clinical trials with GLP-1 RAs (phase 3) were selected. We performed a systematic analysis and compared the proportion of patients reporting nausea, vomiting or diarrhoea, for different doses and glucose-lowering background medications, and relative to a reference compound within the subclasses of short- (exenatide b.i.d.) and long-acting (liraglutide) GLP-1 RAs, calculating the relative risks ± 95% confidence intervals.

Results: The risk of nausea was dose-dependent for long-acting (P = .0063) and across all GLP-1 RAs (P = .0017), and a similar trend was observed for vomiting (P = .23). Diarrhoea was dose-dependent (P = .031). Background treatment with metformin was associated with more nausea (P = .04) and vomiting (P = .0009). Compared to exenatide b.i.d., there was less nausea and diarrhoea with lixisenatide. Compared to liraglutide, there was a similar risk associated with dulaglutide, and less with exenatide q.w. and albiglutide. Long-acting GLP-1 RAs were associated with less nausea and vomiting, but with more diarrhoea than short-acting agents.

Conclusions: GLP-1 RAs are associated with gastrointestinal AEs that are related to dose and background medications (especially metformin) and may vary in a compound-specific manner. Long-acting agents are associated with less nausea and vomiting but with more diarrhoea.

KEYWORDS

gastrointestinal adverse events, GLP-1 analogues, GLP-1 receptor agonists, incretin mimetics, side effects

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are mimetics of the gut incretin hormone glucagon-like peptide-1 (GLP-1), stimulating GLP-1 receptors and thereby exerting glucose-lowering actions in subjects with type 2 diabetes and hyperglycaemia.[1,2] The first GLP-1 RA, exenatide b.i.d.,[3] was approved for use to treat patients with type 2 diabetes in 2006, and a number of agents of this class are in use today. Based on their pharmacokinetic characteristics, they have been sub-divided into short-acting agents, which reach peak drug concentrations within a few hours after subcutaneous injection, but fall to low or even 0 levels 6 to 10 hours later. This leads to repeated exposure to effective drug concentrations with intermittent troughs.[4] Typically, these agents (exenatide b.i.d.[3] and lixisenatide, usually recommended as a once-daily injection[5,6] have marked activity on glycaemic excursions following meals ingested immediately

after injection,[7] with little effect on meals not covered by injections; and the deceleration of gastric emptying seems to be the main mechanism preventing post-meal glycaemic increments.[7] Long-acting GLP-1 RA, at their recommended dosing schedules, lead to permanently elevated drug concentrations with limited fluctuations between injections (liraglutide, daily[8]; exenatide q.w.,[9] taspoglutide,[10] dulaglutide,[11] albiglutide,[12] all once weekly). Through this permanent exposure of GLP-1 receptors to stimulating ligands, tachyphylaxis for the deceleration of gastric emptying seems to be triggered,[13] leading to minor residual effects on gastric motility after a few days to weeks.[7,9]

Basically, all GLP-1 RA trials report so-called gastrointestinal side effects (mainly nausea, vomiting, diarrhoea) as the most frequent adverse events.[1] It is not entirely clear whether these sensations are mediated by an influence of GLP-1 RA on gastrointestinal functions (eg, gastric emptying, intestinal motility, secondary changes in the secretion of other gastrointestinal peptide hormones) or mainly by a direct interaction with the central nervous system,[14] either by accessing the brain through areas devoid of a blood-brain barrier,[15–18] or indirectly through receptors on afferent parasympathetic nerve branches.[19–21] Based on such reasoning, it can be assumed that the important differences between various GLP-1 RAs may translate into a different proportion of patients being affected by such side effects. From head-to-head comparisons of short- and long-acting GLP-1 RAs, a reduced long-term incidence of nausea, for example, with liraglutide (long-acting) vs exenatide (b.i.d.; short-acting) has been claimed.[22] This, however, was not confirmed when comparing lixisenatide (short-acting) and liraglutide (long-acting).[7] Furthermore, a GLP-1 RA studied in a phase 3 program, but not approved for clinical use, taspoglutide, appeared to have prominent gastrointestinal side effects,[10] whereas albiglutide (eg, when compared to liraglutide) elicited fewer such side effects.[23]

Therefore, we aimed to study nausea, vomiting and diarrhoea as reported in clinical trials with GLP-1 RAs in a systematic manner, that is, to see whether these adverse events are dose-related, depend on background glucose-lowering medications, and whether they potentially manifest differently between short-acting and long-acting GLP-1 RAs in broader terms, or within the subclasses of short-and long-acting agents, when compared to a reference compound (exenatide b.i.d. for short-acting and liraglutide for long-acting GLP-1 RAs as the first ones to be approved). (Preliminary data have been communicated in abstract form.[24])

2 | RESEARCH DESIGN AND METHODS

The present study was performed in accordance with the PRISMA (Preferred reporting items for systematic review) statement guidelines.[25]

2.1 | Data sources and searches

Publications on clinical trials with GLP-1 RAs were retrieved from the PubMed database with the help of EndNote version X7.1 (Thomson Reuters). The generic names of GLP-1 RA (exenatide, lixisenatide, liragutide, taspoglutide, dulaglutide and albiglutide) were used as search terms together with the terms "glycaemic/glycemic," "clinical," "trial," "HbA1c," "glycated haemoglobin/hemoglobin." References were screened for other reports on GLP-1 RA trials. The search was last updated March 31, 2016.

2.2 | Study selection

We performed a systematic meta-analysis of adverse events reported from clinical trials with all GLP-1 RAs from a phase 3 program. The studies were selected by KB and MAN. Inclusion criteria were (1) a comparison of a GLP-1 RA (only approved doses) and a comparator drug/placebo, (2) either a GLP-1 RA monotherapy or a background medication with metformin or insulin and (3) a minimum duration of 12 weeks. Since the prevalence of gastrointestinal adverse events may be lower with longer-term exposure to such drugs, shorter studies were disregarded. Subgroup studies of specific ethnic groups were excluded. This applies particularly to Asian populations, because of differences in the pathophysiology of their type 2 diabetes, differences in body measures (height, weight, etc.) with resulting impact on exposure to drugs, and because different doses of GLP-1 RAs are sometimes used.

2.3 | Data extraction and quality assessment

The included studies were screened for data of interest (proportion of patients reporting nausea, vomiting or diarrhoea; withdrawal from the study for any reason or because of adverse events) and information about the GLP-1 RA(s) studied, dosages, comparator drugs and patient numbers, as well as baseline characteristics (age, gender, body-mass index, duration of known diabetes, HbA1c) were extracted in predefined forms. Details can be found in Tables S1 and S2, File S1. A quality assessment of the studies was done according to the Jadad score (Table S3, File S1).[26] All studies contributing to the present analysis were checked for evidence of selective reporting or publication bias. A funnel plot relating study size (patients treated with GLP-1 RA) to the proportion of patients reporting nausea, vomiting or diarrhoea (Figure S2, File S1) did not provide any evidence for publication bias.

2.4 | Data synthesis and analysis

The proportion of patients treated with various GLP-1 RAs experiencing nausea, vomiting or diarrhoea and those withdrawing from the trials for any reason or because of side effects were compared between different compounds, or summarized for the subclasses of short-acting and long-acting GLP-1 RAs, or for all GLP-1 RAs taken together.

2.5 | Analysis of gastrointestinal adverse events and withdrawals in clinical trials with GLP-1 RAs

For each arm of the studies in which a GLP-1 RA was employed (within one trial, different doses and/or different compounds), the number of patients studied (safety population) and the number reporting nausea, vomiting or diarrhoea, and the number withdrawing from the study for any reason or because of adverse events was recorded. The proportion of patients exposed to this drug dose

reporting these adverse events was calculated. In a second step, data from all treatment arms reporting results with the same compound and dose were combined.

2.6 | Dose-dependency

For exenatide b.i.d., (5 or 10 μg b.i.d.), lixisenatide (10 or 20 μg q.d.) liraglutide (1.2 and 1.8 mg/d), dulaglutide (0.75 and 1.5 mg/wk) and albiglutide (30 and 50 mg/wk) 2 doses are approved or have been studied in the phase 3 trials. Thus, the proportion of patients reporting adverse events was compared for the higher vs lower dose for each compound. The relative risks (and their 95% confidence intervals, as well as *P* values for the significance of the differences) were calculated for an increased risk of adverse events with the higher dose.

2.7 | Dependency on the glucose-lowering background medications

Clinical trials of GLP-1 RA were grouped according to the glucose-lowering background medication employed in the studies. Monotherapy studies (least likely to be confounded by effects of other drugs) were compared to studies where metformin treatment was mandatory as a baseline therapy, which was maintained throughout the exposure to GLP-1 RA. This analysis was of interest, because metformin itself can cause gastrointestinal side effects such as abdominal pain or cramps, increased bowel movements and diarrhoea. In trials were metformin was a mandatory background medication, some patients also took thiazolidinediones. Studies reporting combinations with sulfonylureas were excluded since, in these studies, metformin was used concomitantly (except for one dedicated study with a sulfonylurea-only background).[27]

Another aspect considered specifically were trials of GLP-1 RAs on top of (basal) insulin treatment with insulin glargine or insulin degludec. In this case, the additional treatment with (any) oral glucose-lowering drug is common practice and was not a reason to exclude a study from the present analysis.

For these analyses, only the highest dose for each GLP-1 RA was analysed, to rule out confounding through dose-dependent differences in outcomes. Again, the proportion of patients reporting adverse events or withdrawals was compared for a metformin or basal insulin background medication vs monotherapy. The relative risks (and their 95% confidence intervals, as well as *P* values for the significance of the differences) were calculated for a difference in risk with these background medications.

2.8 | Comparison within the class (to an arbitrarily chosen reference medication)

To potentially identify compounds within the sub-classes of short- and long-acting GLP-1 RA swith a particularly low or high risk of gastrointestinal adverse events, all compounds were compared to either exenatide (b.i.d.), chosen as a reference within the short-acting compounds, or with liraglutide, determined to be the reference compound within the long-acting subclass. Both compounds were the first to be approved and provided data for the highest number of patients treated relative to other compounds (Figure 1).

Again, only the highest dose for each GLP-1 RA was analysed, to rule out confounding through dose-dependent differences in outcomes. The proportions of patients reporting adverse events or withdrawals were compared for each compound compared to the reference compound. The relative risks (and their 95% confidence intervals, as well as *P* values for the significance of the differences) were calculated for a difference in risk compared to the reference compound.

2.9 | Differences between short- and long-acting GLP-1 RA

For this analysis, all data within the short- and long-acting sub-classes of GLP-1 RA were pooled and compared to each other. Again, only the highest dose for each GLP-1 RA was analysed, to rule out confounding through dose-dependent differences in outcomes. The relative risks (and their 95% confidence intervals, as well as *P* values for the significance of the differences) were calculated relative to the short-acting class.

2.10 | Association of the proportion of patients reporting nausea, vomiting or diarrhoea with withdrawal rates

The proportion of patients reporting nausea, vomiting or diarrhoea with each compound within each study was related to either the withdrawal rate for any reason or the withdrawal rate because of adverse events by linear regression analysis.

2.11 | Calculations and statistical analysis

Contingency table analysis was performed using GrapPad Prism, version 6.05 (GraphPad Software Inc., La Jolla, California), also providing relative risks and their 95% confidence intervals and p-values for comparisons. Baseline characteristics of patients examined in clinical trials were expressed as means ± standard deviations (SD) and efficacy results were expressed as change vs baseline ± standard error of the mean (SEM). Linear regression analysis was performed using GraphPad Prism, version 6.05 and results are reported as the regression equation, the correlation coefficient squared (r^2) and the *P* value indicating the significance of the association.

3 | RESULTS

Among 336 publications retrieved from the literature, 304 could not be analysed further because (1) they were reviews or secondary analyses of studies already reported earlier; (2) they were extensions of studies in which the primary endpoint was reached and reported after a shorter study duration; (3) the duration of the clinical trial was less than 12 weeks; (4) the report was on fixed-dose combinations of GLP-1 RA with insulin analogues (so that any adverse events could not be ascribed to the GLP-1 RA alone); (5) the study reported was

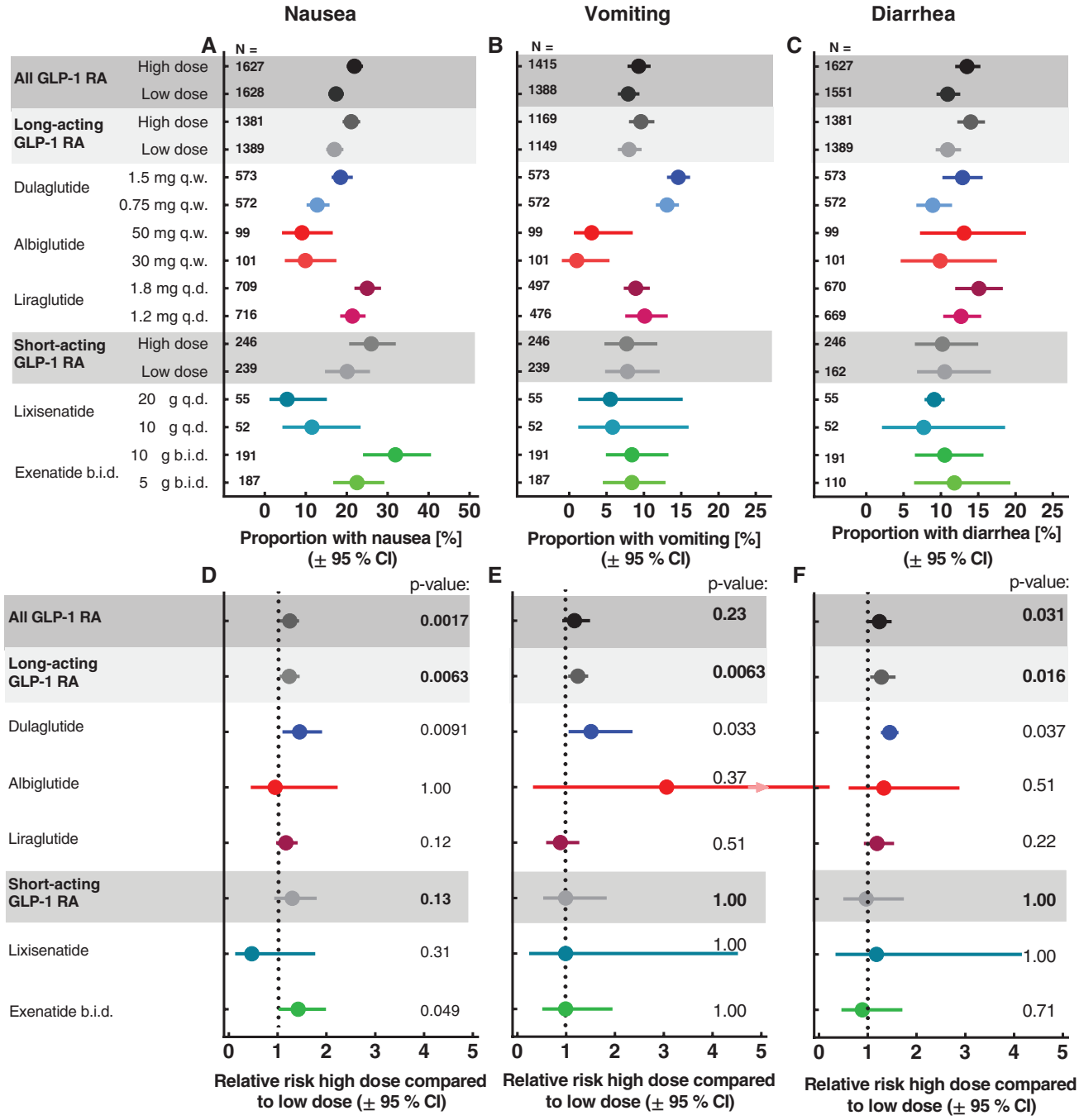

FIGURE 1 Proportions of patients participating in clinical trials with GLP-1 receptor agonists (GLP-1 RAs) reporting nausea (A), vomiting (B) or diarrhoea (C) and their 95% confidence intervals, depending on whether a high or low dose was administered. In panels D, E, and F, the relative risks for nausea, vomiting and diarrhoea and their 95% confidence intervals, respectively, are depicted for the higher vs lower dose administered. This is shown for each compound, and for short-acting GLP-1 RAs combined (exenatide b.i.d. and lixisenatide; light green background), as well as long-acting GLP-1 RAs combined (liraglutide, albiglutide and dulaglutide; light orange background), and all GLP-1 RAs combined (light grey background). In addition, the numbers of patients contributing to the analysis in each study and *P* values for an elevated risk of gastrointestinal adverse events with the higher dose are presented. Exenatide once weekly could not be analysed because only one dose has been reported in clinical trials.

not a randomized prospective trial of a GLP-1 RA in at least one arm of the study; (6) adverse events and/or withdrawals from the study (for any reason or because of adverse events) were not documented as the proportions of patients reporting nausea, vomiting or diarrhoea and as the proportions withdrawing from the study for any reason or because of adverse events. A flow diagram depicting all publications retrieved by the literature search and those finally analysed, as well as the reasons publications could not be used for the present analysis, is available in Figure S1, File S1.

A total of 10 367 patients from 32 individual studies were included in the meta-analysis. The risk of bias within studies and across studies was considered to be low. The parameters of interest were uniformly reported in all trials analysed, with no hint of selective reporting or publication bias.

3.1 | Dose-dependency

For those GLP-1 RAs that have been studied at different doses, taken together, nausea and vomiting, but not diarrhoea, were reported at significantly higher frequencies with higher doses (Figure 1). For nausea and vomiting, this was consistent for the long-acting compounds taken together, and for the single compounds within this sub-class, with the exception of liraglutide and albiglutide. A non-significant trend along the same lines was observed for liraglutide and the frequency of nausea, as well as for albiglutide and the frequency of vomiting. Within the short-acting sub-class, there was a significant dose-dependency for exenatide, but not for lixisenatide. It should be noted that the results for 10 and 20 μg of lixisenatide were from the same study, with a similar number of patients studied in both arms.[28] The frequency of diarrhoea was similar with the lower and higher doses with the exception of dulaglutide, which caused more diarrhoea at 1.5 than at .75 mg/wk (Figure 1D).

As a sensitivity analysis, a similar analysis was performed, expressing the patients' reports of adverse events as a multiple of rates reported with placebo treatment. Although this analysis was based on lower study and patient numbers (since not all studies had a placebo arm), the results of the original analysis were confirmed (Figure S3, File S1). Regarding withdrawals for any reason or withdrawals because of adverse events, no clear dose-dependency was observed, except for albiglutide (Figure S4, File S1).

As a sensitivity analysis, a similar analysis was performed expressing the patients withdrawing from the studies as a multiple of rates reported with placebo treatment. Although this sensitivity analysis was based on a lower number of studies and of patients available (since not all studies had a placebo arm), the results of the original analysis were confirmed by and large (Figure S5, File S1).

3.2 | Dependency on the glucose-lowering background medications

More nausea, vomiting and diarrhoea were reported on a background of metformin medication. This was largely driven by effects within the short-acting sub-class, namely more nausea, vomiting and diarrhoea on a metformin background with exenatide b.i.d. (Figure 2). Insulin as a background medication led to an overall change in the frequency of reporting nausea and increased the frequency of nausea, vomiting and diarrhoea with short-acting GLP-1 RA, namely exenatide b.i.d. (Figure 2). Some effects could not be analysed because no studies reported such results.

A background medication with metformin, as well as with insulin, increased the risk of withdrawals from the study for any reason in the case of short-acting GLP-1 RA, namely lixisenatide, whereas such background medication reduced the risk of withdrawals with long-acting GLP-1 RA. Thus, no significant effect was found, when all GLP-1 RAs were considered together (Figure S6, File S1). For withdrawals because of adverse events, both a metformin and a basal insulin background medication increased the risk concerning short-acting GLP-1 RA (Figure S6, File S1).

3.3 | Comparison within the class (to an arbitrarily chosen reference medication)

Lixisenatide, compared to exenatide b.i.d., was associated with a significantly reduced relative risk of nausea and diarrhoea, but a similar risk for vomiting (Figure 3). Relative to liraglutide, exenatide q.w. displayed a significantly lower risk of nausea, but only trends towards a reduced risk of vomiting and diarrhoea (Figure 3). Albiglutide was associated with a significantly lower risk of nausea, vomiting and diarrhoea compared to liraglutide. Dulaglutide showed a lower risk of diarrhoea, whereas the risks of nausea and vomiting were similar to those of liraglutide (Figure 3).

The overall proportion of patients withdrawing from trials was not significantly related to the background medication, but both a metformin and an insulin background increased withdrawals, only in the case of short-acting GLP-1 RA (Figure S7, File S1). Lixisenatide treatment was associated with fewer patients withdrawing from the studies compared to exenatide b.i.d. The other long-acting GLP-1 RAs did not significantly differ from liraglutide in this respect (Figure S7, File S1).

3.4 | Differences between short- and long-acting GLP-1 RA

Long-acting GLP-1 RAs (not including taspoglutide) were associated with less nausea and vomiting, but more diarrhoea (Figure 4). Withdrawals for any reason occurred less frequently with long-acting GLP-1 RA. There was no significant difference concerning withdrawal because of AEs.

3.5 | Association of nausea, vomiting and diarrhoea with withdrawal rates for any reason or because of adverse events

A regression analysis relating nausea, vomiting and diarrhoea to withdrawals for any reason or because of adverse events showed significant associations in most instances (Figure 5). These associations were closer when adverse events were related to withdrawals because of adverse events. Information available from the publications used did not allow an analysis of incidence rates of episodes of nausea, vomiting, and diarrhoea.

4 | DISCUSSION

This pooled analysis of gastrointestinal adverse events with GLP-1 RA showed that side effects are related to the dose of GLP-1RAs (Figure 1), to metformin and/or basal insulin as a background medication (Figure 2), and that there are characteristic differences among individual compounds within the class of GLP-1 RAs, within the subclasses of short- and long-acting GLP-1 RAs (Figure 3), and between short- and long-acting GLP-1 RAs in more general terms (Figure 4). Thus, our analysis may provide information that may be helpful in choosing therapeutic agents from the class of GLP-1 RA when making individualized treatment decisions. This certainly would require a

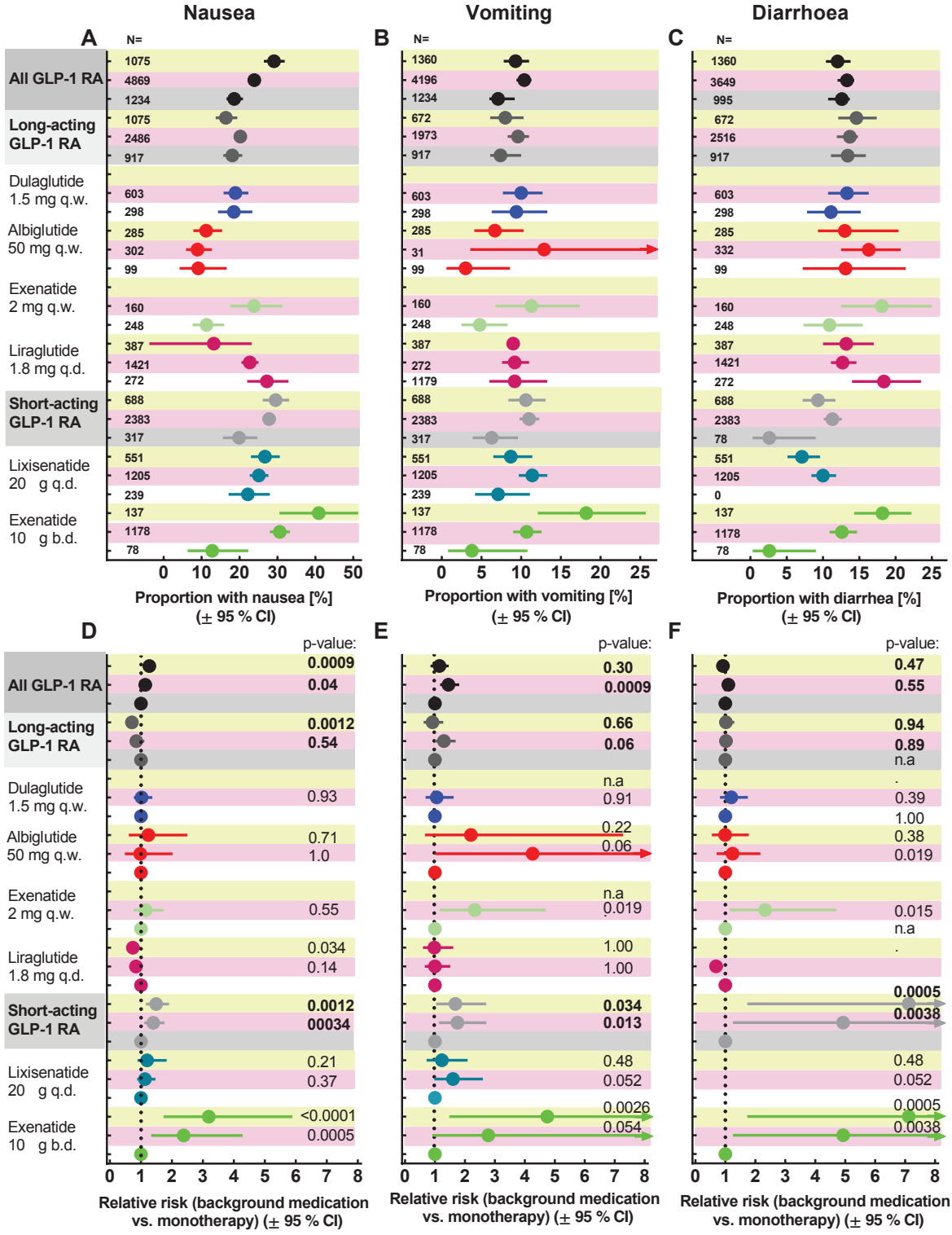

FIGURE 2 Proportions of patients participating in clinical trials with GLP-1 RAs reporting nausea (A), vomiting (B) or diarrhoea (C) and their 95% confidence intervals, depending on whether the study drug was administered as monotherapy (no other glucose-lowering medications, white background) or on a background of metformin (pink background), or in addition to basal insulin (± other oral glucose-lowering agents; yellow background). Only results reporting the higher approved dose are depicted for compounds available at different doses. In panels D, E and F the relative risks of nausea, vomiting and diarrhoea (and their 95% confidence intervals), respectively, are depicted for metformin or insulin as background glucose-lowering medications. This is shown for each compound, and for short-acting GLP-1 RAs combined (exenatide b.i.d. and lixisenatide), as well as long-acting GLP-1 RAs combined (liraglutide, exenatide once weekly, albiglutide and dulaglutide; light orange background), and all GLP-1 RAs combined (light grey background). In addition, the numbers of patients contributing to the analysis in each study and *P* values for an elevated risk of gastrointestinal adverse events with the higher dose are presented.

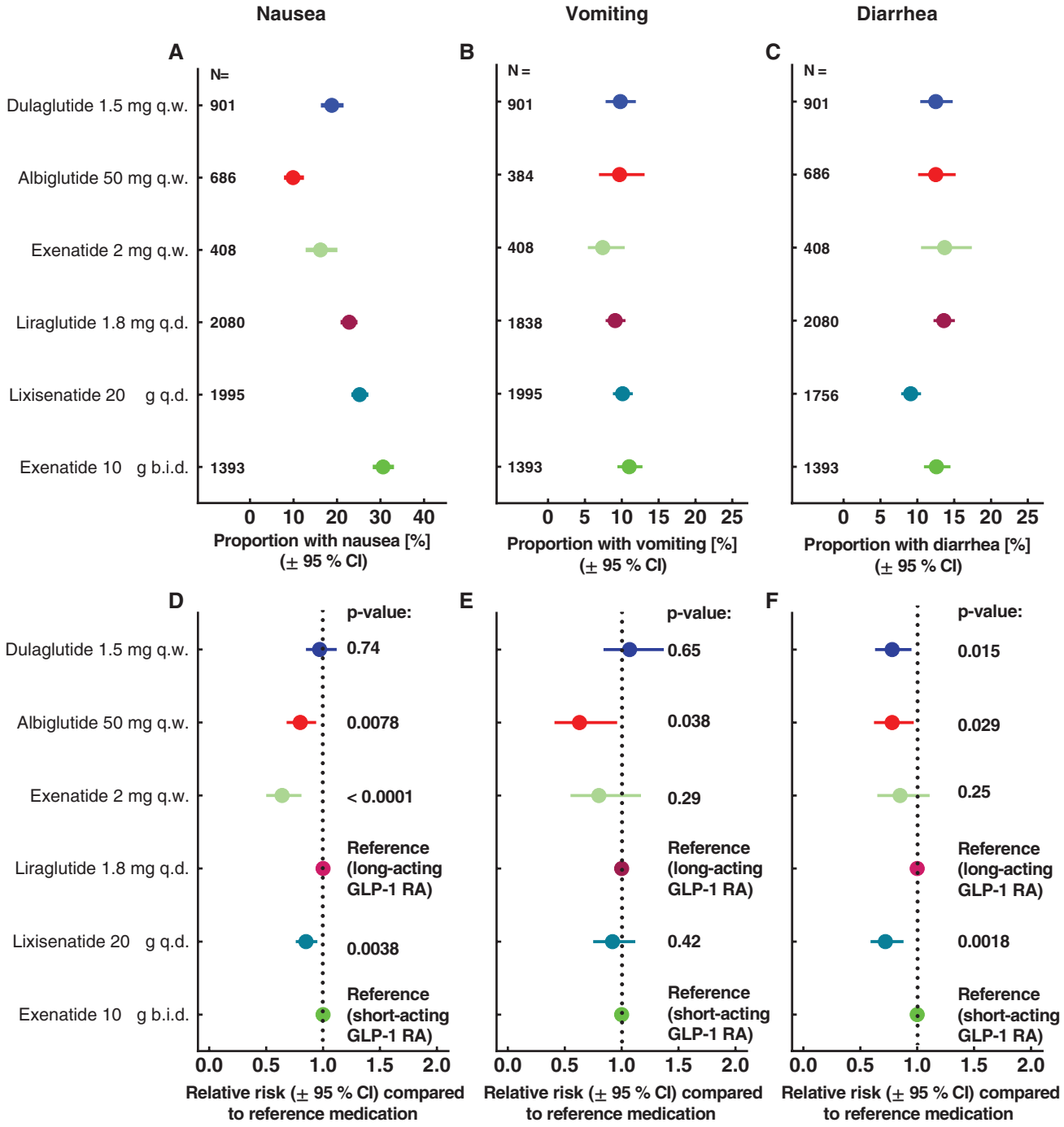

FIGURE 3 Proportions of patients participating in clinical trials with GLP-RAs reporting nausea (A), vomiting (B) or diarrhoea (C) and their 95% confidence intervals, depending on the use of specific compounds. Only results reporting the higher approved dose are depicted for compounds available at different doses. In panels D, E and F the relative risks of nausea, vomiting and diarrhoea (and their 95% confidence intervals), respectively, are depicted relative to an arbitrarily defined reference compound within the spectrum of short-acting GLP-1 receptor agonists (exenatide b.i.d.) or long-acting GLP-1 RAs (liraglutide). In addition, the number of patients contributing to the analysis in each study and *P* values for an elevated risk of gastrointestinal adverse events with the higher dose are presented.

broader view, also taking into consideration therapeutic effectiveness and the risk of adverse events.

In head-to-head comparisons of GLP-1 RA belonging to the short- and long-acting subclasses on a background of oral glucose-lowering medications (eg, exenatide b.i.d. vs liraglutide[22]; exenatide once weekly vs exenatide b.i.d.[9]; dulaglutide vs exenatide b.i.d.[29]), glycemic control was uniformly better with the long-acting agents; however, this was without significant differences in bodyweight reduction. Nevertheless, in our analysis, short-acting agents were associated with more nausea (Figure 4) but with less diarrhoea, and with higher withdrawal rates for any reason. These examples show that short-acting GLP-1 RAs may have a lower benefit-risk

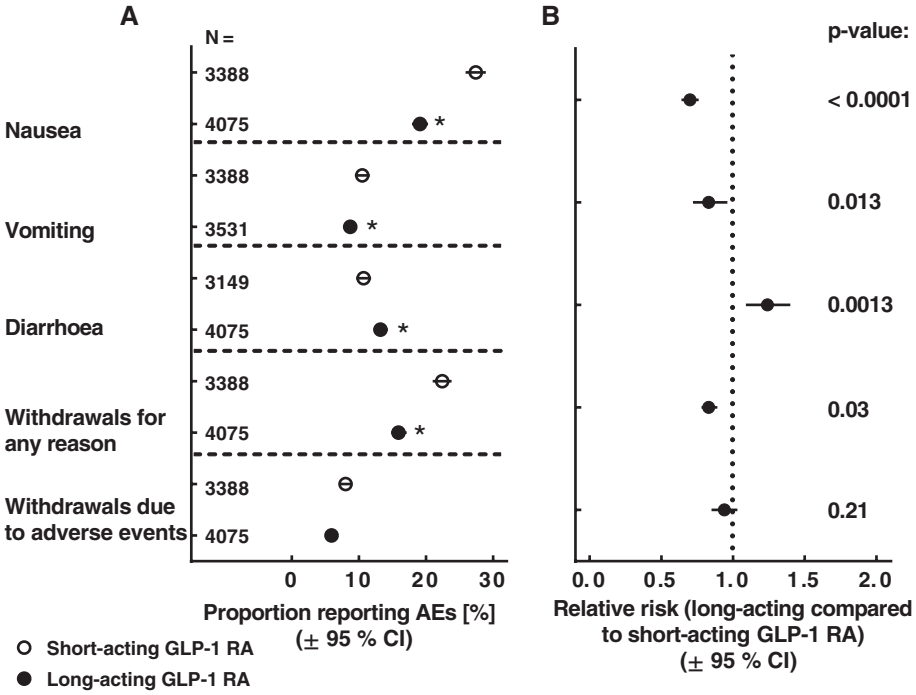

FIGURE 4 Proportions of patients reporting nausea, vomiting or diarrhoea and those withdrawing from the study for any reason or because of adverse events with short- vs long-acting GLP-1 RA (±95% confidence intervals; left panel; A). In the right panel (B) the relative risk of reporting nausea, vomiting or diarrhoea and of withdrawing from the study for any reason or because of adverse events is shown (± 95% confidence intervals) for long-acting vs short-acting GLP-1 RA. The dotted line marks a relative risk of 1. *P* values were derived from contingency table analysis (Fisher's exact test). Asterisks indicate a significant difference ($P < .05$) between pooled short- and long-acting GLP-1 RA.

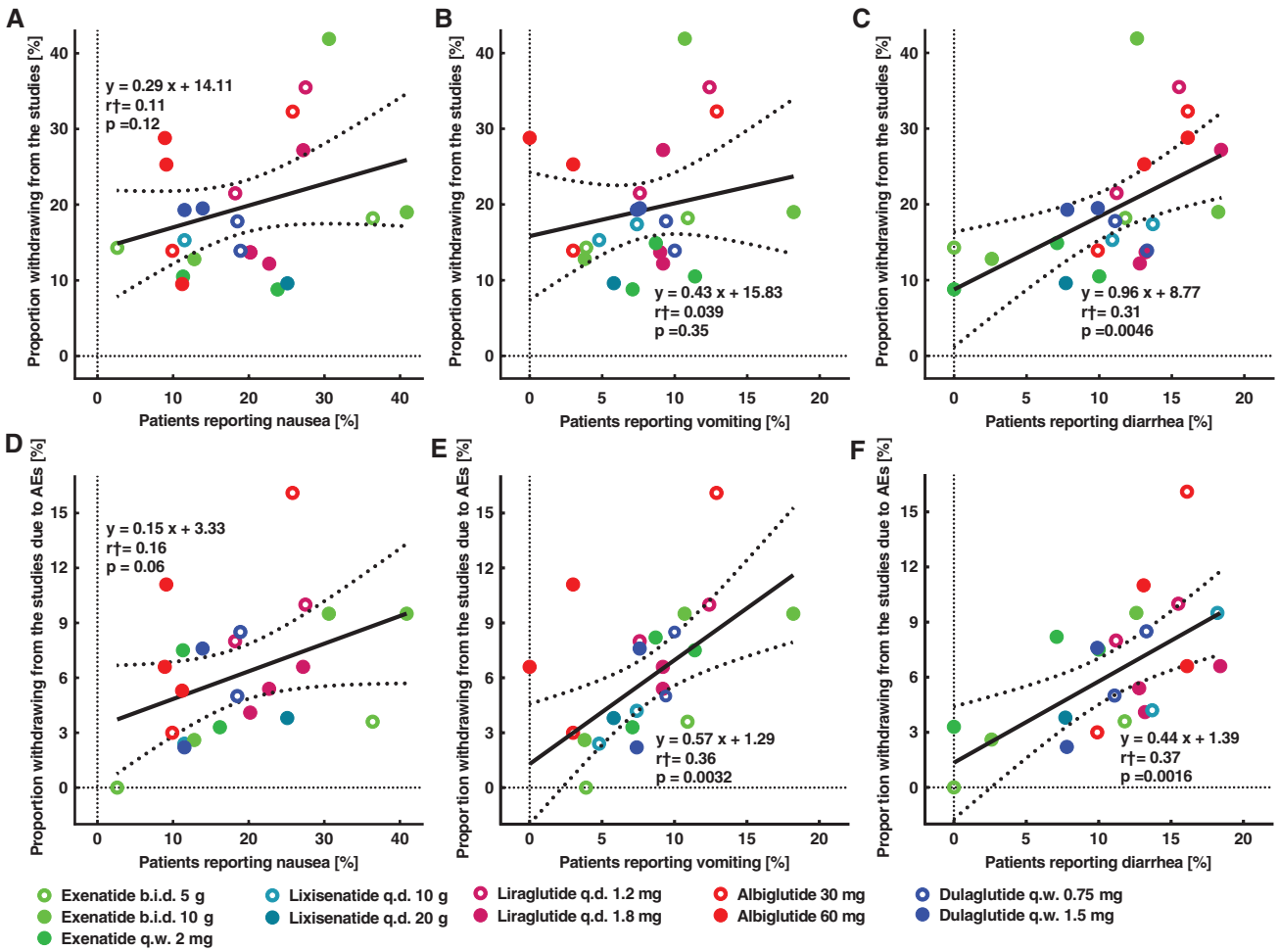

FIGURE 5 Linear regression analysis relating the proportion of patients reporting nausea (A, D), vomiting (B, E) or diarrhoea (C, F) to withdrawal from study medication for any reason (A-C) or because of adverse events (D-F). Each compound is shown with a specific colour. High doses are depicted as filled symbols; lower doses are depicted as open symbols (see colour code). For each relationship, the regression equation is presented as well as r^2 (which explains the proportion of variation related to the factor presented on the x-axis), and the *P* value indicating a potentially significant relationship. The regression equation and its 95% confidence interval are also shown.

relationship than long-acting GLP-1 RAs, if HbA1c and bodyweight control and gastrointestinal adverse events, as well as withdrawals from clinical trials, are consiered. Certainly, other considerations, such as potential accelerations in heart rate,[7] cardiovascular safety in more general terms,[30] potential differences in the risk of acute pancreatitis[31] or of pancreatic cancer[32] and other malignancies will play an important role when estimating the overall benefit-risk relationship.

It should be noted that such considerations may be entirely different when using the same agents on a background of basal insulin (employed to control fasting glucose concentrations) because, in this situation, differences in the ability to control post-meal rises matter for the choice of GLP-1 RAs.[4,7] Short-acting compounds such as exenatide b.i.d. and lixisenatide may have advantages under these circumstances, although no head-to head studies on a basal insulin background are available to prove such an advantage. Theoretically, a potentially greater effectiveness may, in such cases, justify the use of agents with a higher risk of causing nausea. On the other hand, positive outcomes of cardiovascular trials with long-acting GLP-1 RAs,[33,34] but not with short-acting GLP-1 RA lixisenatide[35] can be used to justify preferential prescription of liraglutide for those at risk of such complications (semaglutide[33] has not yet been approved).

There are other examples of head-to-head comparisons, where clinical effectiveness and adverse events are congruent: dulaglutide and liraglutide have similar effectiveness and a similar adverse event profile,[36] and exenatide once weekly vs liraglutide[37] and albiglutide vs liraglutide[23] were both less effective and associated with fewer adverse events. This may point to non-equivalences of the doses used, as a consequence of dose-finding studies that did not examine the full range of doses from ineffective to maximally effective, and complicated by an inacceptable side-effect profile. For both exenatide once weekly[38] and for albiglutide,[39] the phase 2 studies may not have identified the optimum dose. In both cases, the doses tested in phase 3 trials appear to be less effective than, for example, 1.8 mg of liraglutide daily; on the other hand, they are associated with fewer gastrointestinal side effects.

A third comparison worth mentioning is between compounds that appear to be similarly effective but are associated with widely varying risks of adverse events. Taspoglutide seems to be an example of a GLP-1 RA that is as effective in controlling glycaemia and bodyweight as other long-acting GLP-1 RAs[10,40] but is associated with a higher proportion of nausea and vomiting, as well as withdrawals, than that seen with any other GLP-1 RA (File S1, page 13). This, together with the severe hypersensitivity reactions observed with use of taspoglutide, explains why this compound was never approved for the treatment of type 2 diabetes. There is no obvious explanation for these peculiarities, but one may assume that they may be related to differences in access to the central nervous system. GLP-1 and GLP-1 RAs, in principle, can get access to the central nervous system,[15–18] where certain areas are devoid of a fully functioning blood-brain barrier (eg, the circum-ventricular organs.[41]) In addition, various brain functions may be influenced by interacting with afferent nerves of the autonomic nervous system equipped with GLP-1 receptors.[19–21] Different GLP-1 RAs may have properties that explain different abilities to access the brain and to elicit therapeutic actions (eg, weight reduction) as well as explaining adverse events (eg, nausea and vomiting), and taspoglutide may be special along these lines. The converse may be the case with albiglutide, although no published data are available regarding access to the central nervous system for this particular compound. Therefore, we mention data from taspoglutide studies, although it is not available in clinical practice; thus, we can show the full spectrum of risk of adverse events as evident from clinical trials.

Gastrointestinal diseases can cause nausea, vomiting and diarrhoea and, conventionally, these adverse events, if caused by GLP-1 RAs, are called gastrointestinal. They may, rather, be caused by a direct effect on the central nervous system. GLP-1 RAs change gastrointestinal motility[42,43]; namely, they decelerate gastric emptying, but this is subject to tachyphylaxis,[13,44] if effective drug concentrations are maintained for prolonged periods of time, as is the case with continuous infusions or with the subcutaneous injection of long-acting GLP-1 RAs. This means that gastrointestinal motility effects of GLP-1 RAs will be preserved during long-term treatment with short-acting agents, but not with long-acting agents. The fact that short-acting GLP-1 RAs are associated with more nausea could be related to this difference, but nausea with GLP-1 RAs has also been observed in the fasting state,[45] when gastric fullness and/or emptying should not play any role. Diarrhoea, on the other hand, may be caused by a direct influence of GLP-1 RAs on the gut, either mediated through the intramural autonomic plexus, or directly affecting smooth muscle activity.[46] This may explain the different effects of short- and long-acting GLP-1 RAs in this respect.

The fact that more nausea, vomiting and diarrhoea was observed on a background of metformin may be explained by the known side-effect profile of metformin,[47,48] which alone can provoke such symptoms. The enhanced risk with insulin under some circumstances may be associated with metformin and other oral glucose-lowering medications administered in conjunction with basal insulin, as is typically prescribed with “bedtime” insulin therapy.[49] Moreover, insulin-treated patients are more likely to have a longer duration of diabetes, more diabetic complications, including autonomic neuropathy, and thus may be more susceptible to gastrointestinal adverse events.

It is obvious from the correlations found that nausea, vomiting and diarrhoea are associated with withdrawals from clinical trials for any reason as well as because of adverse events, the latter association being stronger than the former, as expected. One may interpret the findings to suggest that withdrawals for other reasons (eg, withdrawal of consent) may still, at least partly, be caused by such side effects.

Our study has weaknesses and limitations. The study programmes for different GLP-1 RAs did not provide a similar set of studies, with protocols for all background medications that we were interested in. In other respects, the information provided by different publications was not homogeneous. For some agents, the number of studies and patients in the trials was small, resulting in wide confidence intervals, thus precluding firm conclusions. Also, the symptoms were assessed as self-reported adverse events, and authors did not use a structured questionnaire, as would be available.[50] In future trials, more may be learned about gastrointestinal adverse events when using such a validated instrument. Next, gastrointestinal

symptoms may fluctuate over time, both in a type 2 diabetic and a more general population.[51] In addition, we have not been able to describe the time course of the prevalence of gastrointestinal adverse events with prolonged exposure to GLP-1 RAs, as only few studies provided this information.[22,52,53] Another weakness of our study is that we performed multiple statistical analyses without adjusting *P* values.

On the other hand, our study is the first systematic analysis of nausea, vomiting and diarrhoea as adverse events in clinical trials with GLP-1 RAs, and it yielded some important conclusions. (1) Short- and long-acting GLP-1 RAs display characteristic differences in the risk of nausea, vomiting and diarrhoea, and in the risk of withdrawals for any reason or because of adverse events. (2) The risk is related to the dose of the GLP-1 RA. (3) A background medication involving metformin may enhance the risk of such adverse events. (4) There are important differences among compounds, even when belonging to the same sub-class of either short- or long-acting GLP-1 RAs, which determine the risk of nausea, vomiting and diarrhoea, as well as as the risk of withdrawal from clinical trials with GLP-1 RAs. This may have an equivalent in the clinical use of GLP-1 RAs, where discontinuation of such treatment is commonly observed. The results of our analysis should provide a rationale to pay attention to differences in the risk of nausea, vomiting and diarrhoea associated with particular GLP-1 RAs when choosing an agent from this class according to the concept of individualized treatment choices.

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Conflict of interest

K. B. and M. K. have nothing to disclose. M. S. A. has received travel grants from MSD and Novo Nordisk. M. A. N. was a member of an advisory panel for Berlin Chemie AG, Amylin Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, Ingelheim, Germany, Eli Lilly and Company, GlaxoSmithKline, MSD GmbH, Merck Sharp & Dohme Limited, Novo Nordisk Pharma GmbH, Mainz, Germany, Sanofi-Aventis Deutschland GmbH, Versartis, Inc., Intarcia Therapeuticals, Inc.; and has received consultancy fees from Amylin Pharmaceuticals, Inc., AstraZeneca, Mjölndal, Sweden, Berlin Chemie AG, Boehringer Ingelheim, Ingelheim, Germany, Diartis Pharmaceuticals, Inc., Redwood City, California, Eli Lilly and Company, GlaxoSmithKline, Hoffman La Roche, Basel, Switzerland, Intarcia Therapeutics, Inc., MSD GmbH, Novartis Pharmaceuticals Corparation, Janssen Global Services, Titusville, NJ, USA, Novo Nordisk A/S, Sanofi-Aventis Pharma, Baden Soden, Germany, Versartis, Inc.; and has received research support from Berlin Chemie AG, Boehringer Ingelheim, Ingelheim, Germany, Novartis Pharma, Basel, Switzerland/Nürnberg, Germany, MSD GmbH, Metacure, AstraZeneca, Södertälje, Sweden, GlaxoSmithKline, Roche Pharma AG, Grenzach/Wyhlen, Germany, Novo Nordisk Pharma GmbH, Mainz, Germany, and ToleRx; has received speaking honoraria from AstraZeneca, Mjölndal, Sweden, Berlin Chemie AG, Boehringer Ingelheim, Ingelheim, Germany, Lilly Deutschland GmbH, Bad Homburg, Germany, MSD GmbH, Novartis Pharma, Basel, Switzerland, Novo Nordisk A/S, and Roche Pharma AG, Grenzach/Wyhlen, Germany; and has other relations with Diabate/Boehringer Ingelheim, Ingelheim, Germany, MSD GmbH, Incretin Expert Program/Lilly Deutschland GmbH, Bad Homburg, and Medscape LLC, New York, USA. J. J. M. has served on advisory boards for, has received honoraria or consulting fees from, or has received research funding from AstraZeneca, Berlin-Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Novartis, Roche and Sanofi-Aventis.

Author contributions

K. B. and M. A. N. designed the protocol, K. B., M. K., J. J. M., and M. A. N. selected suitable publications and extracted and analysed data. All authors made substantial contributions to the conception and design of the study, to acquisition of data or analysis and interpretation of data, participated in drafting the article or revising it critically for important intellectual content, and were involved in final approval of the version to be published. M. A. N. is the guarantor of the present manuscript and takes full responsibility for the integrity of the work.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Exhibit F

Expert Report of Linda Nguyen, M.D.

I. Experience, Training and Education

I am currently a Clinical Professor of Medicine at Stanford University and Interim Chief of Gastroenterology & Hepatology. Prior to assuming the role of Interim Chief, from 2008-2021, I was Director of Neurogastroenterology and Gastrointestinal (GI) Motility in Stanford's Division of Gastroenterology. During my tenure as Director of Neurogastroenterology and Motility at Stanford, we became one of the largest motility programs in the United States. My area of clinical and research expertise focuses on gastroparesis and disorders of the stomach. Over the past 19 years, I have cared for thousands of patients with gastroparesis or gastroparesis-like symptoms.

I completed medical school at UCLA School of Medicine and my GI fellowship training at California Pacific Medical Center in San Francisco, CA, where I was formally trained in Neurogastroenterology and Motility, with research focused on gastroparesis. I am an internationally recognized gastroenterologist who specializes in the field of Neurogastroenterology and Motility.

I have had numerous invited speaking engagements and visiting professorships nationally and internationally on the topic of gastroparesis. I have lectured and regularly present on topics such as What is Gastroparesis, Vagal Nerve Stimulation for Gastroparesis, The Role of Diet in the Care of Patients with Gastroparesis, Gastroparesis Updates from the American College of Gastroenterology (ACG) Guidelines, and Gastric Motility Testing. My research has been funded by the National Institutes of Health / National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK), as well as philanthropy and industry grants, and I have published over 90 peer-reviewed original research papers, review articles and 8 book chapters focused predominantly on gastroparesis and gastroparesis-like disorders. My research includes understanding the role and impact of physiologic testing on clinical care, exploring novel therapies for gastroparesis, and expanding the role of neuromodulation in the treatment of GI motility disorders and pain.

In recognition of my expertise on the topic of gastroparesis, in 2021, I was invited to be a content expert co-author of the ACG Clinical Guideline on Gastroparesis. I also have been chosen as one of two delegates from the United States to work on the "Rome Foundation and International Neurogastroenterology and Motility Societies' Consensus on Idiopathic Gastroparesis." Only two GIs are selected from each of the international societies that have contributed to this international consensus statement work, and I was selected to represent the American Neurogastroenterology and Motility Society (ANMS). The consensus guideline was published online in December 2024.[1]

[1] Schol J, Huang I-H, Carbone F, et al. Rome Foundation and International Neurogastroenterology and Motility Societies' Consensus on Idiopathic Gastroparesis. *The Lancet Gastroenterology & Hepatology*, Vol. 10, Issue 1, 68-81, January 2025.

In addition to my experience in gastroparesis, I am dedicated to developing successful cross-disciplinary collaborations to advance the understanding of chronic digestive disorders. This has led to research exploring the overlap between gastroparesis and migraine, gastroparesis and autonomic dysfunction, small intestinal bacterial overgrowth and chronic fatigue syndrome and chronic abdominal pain and widespread pain. This also has led to the creation of multidisciplinary clinics in collaboration with pain specialists, neurologists, psychologists and dietitians. I spearheaded efforts which resulted in the creation of the first Autonomic Neurogastroenterology Fellowship in the US, which is a joint neurology and GI motility fellowship. In recognition of my expertise, I was invited to participate as a committee member for the Institute of Medicine's Committee on the Development of a Consensus Case Definition for Chronic Multisystem Illness in 1990-1991 Gulf War Veterans from 2012-2013 and again on the National Academies of Sciences, Engineering, and Medicine's Committee on Health Care Utilization in Adults with Disabilities from 2016-2018.

My commitment to patient-centric care and application of cutting-edge science earned me the "Master Clinician Award" for the Stanford Department of Medicine and "Distinguished Investigator Award for Women in Neurogastroenterology" from the ANMS.

I have held many national scientific society appointments over the course of my career and am currently Vice Chair of the Clinical Practice Section of the American Gastroenterological Association (AGA). I also serve as a Member of the Board of Directors for the ACG Institute. In 2019, I co-founded the ANMS Women in Neurogastroenterology Program, and I currently serve as co-chair of that program. I am co-editor of the "Neurogastroenterology and Motility Disorders of the Gastrointestinal Disorders" section of the journal, *Current Gastroenterology Reports*.

Finally, I have initiated and championed numerous programs locally and nationally to support women and those underrepresented in medicine, including junior faculty mentoring programs, midcareer career development awards and wellness workshops.

My full CV is attached as Exhibit A. I am being compensated for my time at a rate of $650 per hour. I have not previously testified as an expert in any litigation.

II. Assignment

I was asked by counsel for Defendants to offer my expert opinion as to the standard of care for diagnosing patients presenting with symptoms potentially consistent with gastroparesis (such as nausea, vomiting, abdominal pain, and bloating), including the specific testing requirements. In addition, I was asked to provide a general overview of gastroparesis, including what is known about its causes and pathophysiology. My opinions, as presented below, are based on my knowledge, training, research activities, and long experience as a GI motility physician and as a co-author on the current ACG gastroparesis guidelines. My reliance materials are listed in Exhibit B.

III. Background on Gastroparesis

Gastroparesis is a chronic medical condition characterized by symptomatic delayed gastric emptying in the absence of a mechanical obstruction. Known causes of gastroparesis include, for

example, diabetes, surgery (with injury to the vagus nerve), hypothyroidism, dysautonomia, certain autoimmune and connective tissue disorders (e.g., scleroderma, Ehlers-Danlos Syndrome, lupus), certain nervous system disorders (e.g., Parkinson's, multiple sclerosis, cerebral palsy), and certain viral infections. Diabetes itself is the number one known cause of gastroparesis. Gastroparesis also can be idiopathic, which means the underlying cause is known.

While gastroparesis has long been described in the medical literature, our understanding of the condition has advanced significantly over the past 20 years. In 2006, the National Institutes of Health (NIH), through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), established the Gastroparesis Clinical Research Consortium. The Consortium is made up of several leading research centers across the country with the common goal of performing research to advance our understanding of the etiology, natural history, diagnosis, and treatment of gastroparesis. Stanford University Medical Center has participated as a member of the Consortium, and I personally have served as a Principal Investigator of NIH Consortium-funded research studies.

A discussion of the symptoms, pathophysiology, and prevalence of gastroparesis is included below as context for discussion of the diagnostic approach to patients presenting with symptoms potentially consistent with gastroparesis.

A. Symptoms

Symptoms of gastroparesis include nausea, vomiting, postprandial fullness, early satiety, and possibly bloating and abdominal pain. Symptoms of gastroparesis are nonspecific, meaning that they frequently overlap with the symptoms of other disorders, such as functional dyspepsia, dumping syndrome, rumination syndrome, gastritis, cyclic vomiting syndrome, cannabinoid hyperemesis, cannabis withdrawal, peptic ulcer, narcotic bowel syndrome, anorexia nervosa, bulimia nervosa, median arcuate ligament syndrome, superior mesenteric artery syndrome, postural orthostatic tachycardia syndrome, gastric outlet obstruction, biliary colic, and chronic pancreatitis, amongst others.

In 2023, Cangemi et al[2] conducted a retrospective cohort study of 339 adult patients referred to Mayo Clinic Jacksonville specifically for the evaluation and treatment of gastroparesis. In the cohort, nausea was reported by 89.1%, abdominal pain by 76.4%, constipation by 70.5%, vomiting by 65.8%, bloating by 37.5%, and early satiety by 34.5%. Patients were evaluated by the Mayo investigators, and a final diagnosis was made. After comprehensive assessment and objective testing, including gastric emptying scintigraphy, the study found that 80.5% of the patients referred for evaluation and management of gastroparesis did not have gastroparesis. Tellingly, the publication was titled, "Misdiagnosis of Gastroparesis is Common."

[2] Cangemi DJ, Stephens L, Lacy BE. Misdiagnosis of Gastroparesis is Common: A Retrospective Review of Patients Referred to a Tertiary Gastroenterology Practice. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2023;21(10):2670-2672.e3.

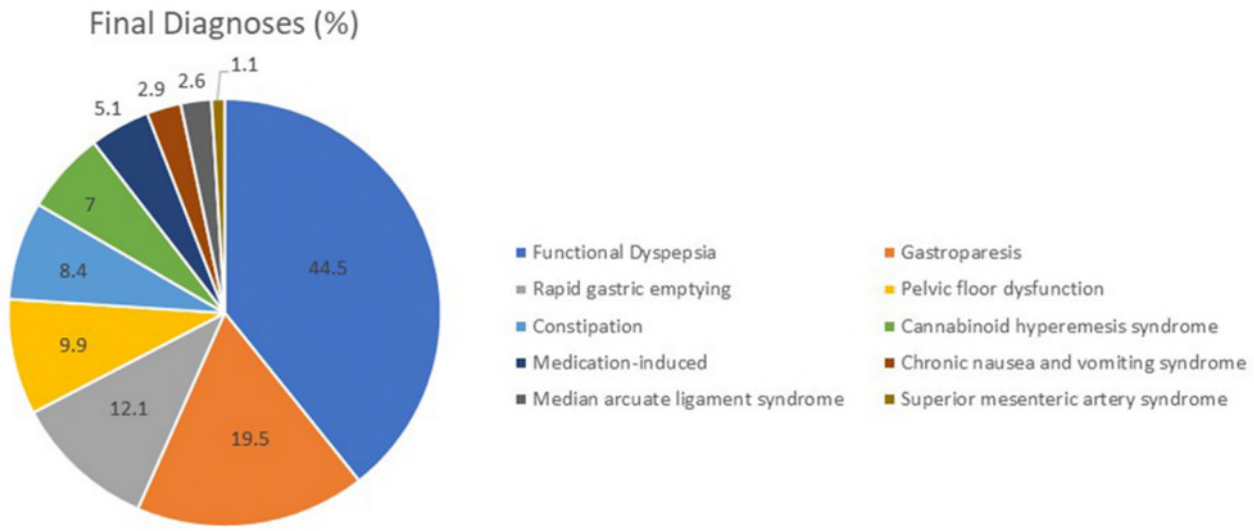

Figure 1. Source: Cangemi DJ, Stephens L, Lacy BE. Misdiagnosis of Gastroparesis is Common: A Retrospective Review of Patients Referred to a Tertiary Gastroenterology Practice. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2023;21(10):2670-2672.e3.

The Cangemi et al[3] study demonstrates why symptoms cannot reliably be used to diagnose gastroparesis, as such approach was associated with an 80% error rate. It specifically stated, "Our findings reaffirm guidelines noting that GP cannot be diagnosed based on symptoms alone." Indeed, as illustrated below, numerous physiologic mechanisms—ranging from gastric accommodation and sensation, central nervous system (CNS) processing to psychiatric conditions and small bowel disease—can present with GI symptoms similar to those associated with gastroparesis.

In addition to symptoms being non-specific, there is poor correlation between the severity of symptoms and the severity of delayed gastric emptying. Although generally patients with severely delayed gastric emptying are more likely to experience more severe symptoms, there is not always a direct correlation, with some patients experiencing significant symptoms with modest delays while some patients with significant delays experience only minor symptoms.[4] To help determine which gastric physiologic abnormality had the greatest correlation with symptoms in patients with idiopathic gastroparesis, the renowned team led by Professor Jan Tack found that abnormalities in gastric accommodation and sensitivity to gastric distention correlated better with symptoms than the severity of the delay in gastric emptying. They concluded "in patients with idiopathic

[3] Cangemi DJ, Stephens L, Lacy BE. Misdiagnosis of Gastroparesis is Common: A Retrospective Review of Patients Referred to a Tertiary Gastroenterology Practice. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2023;21(10):2670-2672.e3.

[4] Parkman HP, Hallinan EK, Hasler WL, et al. NIDDK Gastroparesis Clinical Research Consortium (GpCRC). Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. *Neurogastroenterol Motil*. 2017 Apr;29(4):10.1111/nmo.12981.

severely delayed gastric emptying, symptom pattern and symptom severity are determined by coexisting proximal stomach dysfunction rather than by the severity of delayed emptying".[5]

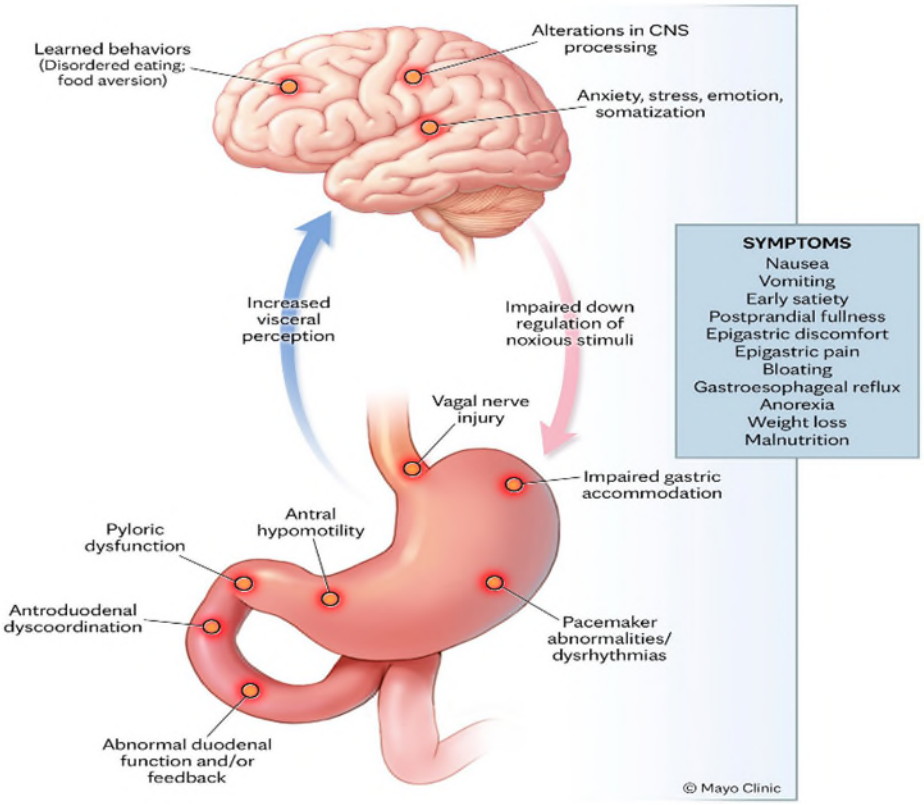

Figure 2. Source: Adapted from Lacy BE, Tack J, Gyawali CP. AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis: Expert Review. *Clinical Gastroenterology and Hepatology*, Volume 20, Issue 3, 491 – 500.

Although there is overlap in the treatment of these disorders, such as the use of anti-nausea medications for symptomatic nausea, the treatment approaches are fundamentally different. Having an appropriate diagnosis is critical to dictate the appropriate treatment for patients suffering from GI disease. For example, the symptoms of rapid gastric emptying and gastroparesis are similar. However, the treatments of these disorders are on the opposite spectrum. Therapies used in gastroparesis that further accelerate already rapid gastric emptying may worsen symptoms in patients who have rapid gastric emptying. Tricyclic antidepressants (TCAs) are a class of medications commonly used to treat chronic pain conditions such as fibromyalgia and migraine. TCAs are effective in treating functional dyspepsia and cyclic vomiting

[5] Karamanolis G, Caenepeel P, Arts J, et al. Determinants of symptom pattern in idiopathic severely delayed gastric emptying: gastric emptying rate or proximal stomach dysfunction? *Gut*. 2007 Jan;56(1):29-36.

syndrome.[6] However, TCAs are not effective in treating idiopathic gastroparesis.[7] Surgical therapies for medically refractory gastroparesis, such as pyloromyotomy and gastric electrical stimulation (Enterra), require documented delay in gastric emptying. The efficacy of these therapies in patients with normal gastric emptying is not known. Accordingly, the ACG Clinical Guideline and other gastroparesis guidelines (discussed below) require objective clinical testing to make a diagnosis of gastroparesis.

B. Pathophysiology

The pathophysiology of gastroparesis is complex and involves abnormalities of the intrinsic and autonomic nervous system, the connective tissue of the GI tract, gastric and duodenal myopathy (smooth muscle) and immune dysregulation. At a high level, gastroparesis results from damage to the nerves, muscles and/or connective tissue involved in the movement of food through the stomach, resulting in chronic impairment of gastric motility.

For example, in diabetic gastroparesis, chronically elevated blood sugar levels damage the nervous system resulting in abnormal myenteric neurotransmission (vagus nerve) and impaired inhibitory (nitric oxide) activity, and cause dysfunction in the smooth muscles and pacemaker cells of the stomach. Together, these effects lead to antral hypomotility, pyloric dysfunction, and ultimately delayed gastric emptying. Similar pathophysiologic changes can occur with autoimmune disorders and with viral infections, including COVID. These effects likely are related to immune-mediated injury to the vagus nerve and/or injury to the pacemaker cells (interstitial cells of Cajal (ICC)) that control the smooth muscles of the stomach. The diagram below provides an overview of some of the pathophysiologic mechanisms involved in gastroparesis.

[6] Ford AC, Moayyedi P, Black CJ, et al. Systematic Review and Network Meta-analysis: Efficacy of Drugs for Functional Dyspepsia. *Aliment Pharmacol Ther.* 2021 Jan;53(1):8-21.
[7] Parkman HP, Van Natta ML, Abell TL, et al. Effect of Nortriptyline on Symptoms of Idiopathic Gastroparesis: The NORIG Randomized Clinical Trial. *JAMA*. 2013 Dec 25;310(24):2640-9.

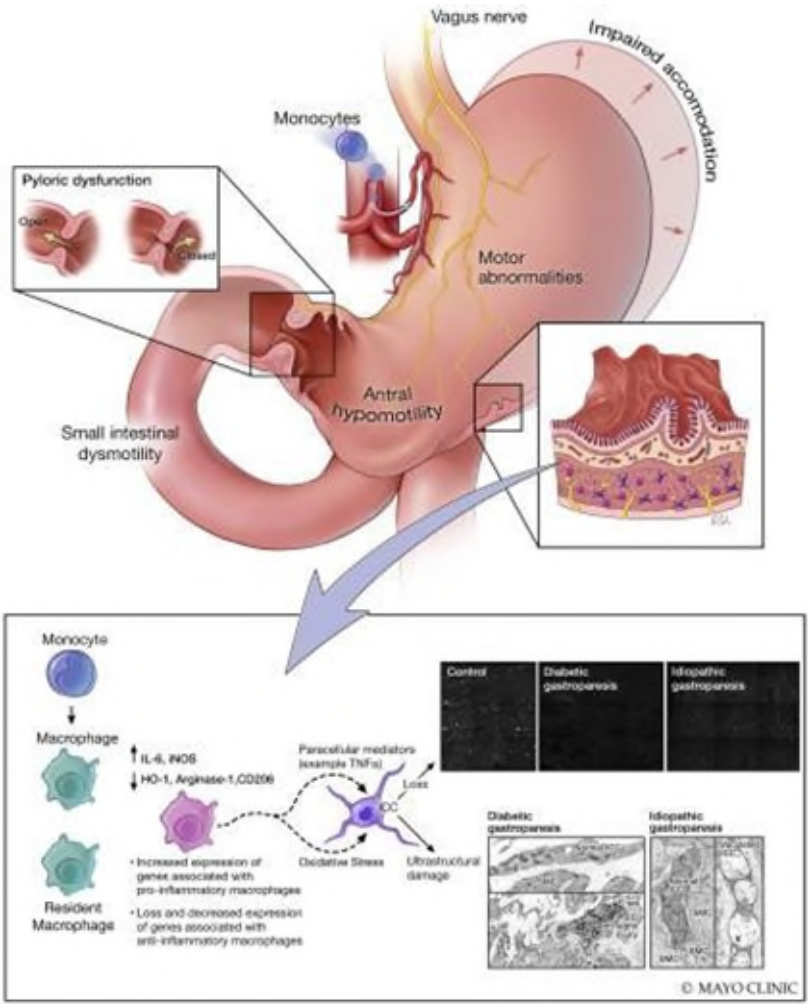

Figure 3. Source: Grover M, Farrugia G, Stanghellini V. Gastroparesis: a turning point in understanding and treatment. *Gut*. 2019 Dec;68(12):2238-2250.

C. Prevalence

Gastroparesis-like symptoms (e.g., nausea, vomiting, abdominal pain, bloating) are frequently reported by patients, and for that reason alone, its prevalence is difficult to estimate. The most representative population-based study to date to estimate prevalence was conducted by Ye et al.[8] In the study, based on ICD-9 and ICD-10 codes for gastroparesis alone, the authors estimated prevalence of gastroparesis in the US to be 267.7 per 100,000 persons (or 0.27%). However, the prevalence dropped more than 10-fold—to 21.5 per 100,000 persons (or 0.02%)—when the researchers applied a more stringent criteria that included symptoms of gastroparesis and a

[8] Ye Y, Yin Y, Huh SY, et al. Epidemiology, Etiology, and Treatment of Gastroparesis: Real-World Evidence From a Large US National Claims Database. *Gastroenterology*. 2022;162(1):109-121.e5.

gastric emptying test (consistent with ACG and other clinical guidelines). Another study by Jung et al. reported similar results, with a prevalence of 24.2 per 100,000 adults.[9]

IV. Appropriate Diagnosis of Gastroparesis

Due to the non-specific nature of gastroparesis symptoms and the high error rate of symptom-based approaches discussed above, a diagnosis of gastroparesis cannot be made based on clinical presentation alone. Rather, a reliable diagnosis requires three criteria to be met: (1) symptoms consistent with gastroparesis; (2) exclusion of mechanical obstruction with esophagogastroduodenoscopy (EGD) or a radiographic study; and (3) objective evidence of delayed gastric emptying of solids.

At this time, two gastric emptying tests, when properly performed, are accepted for use in the diagnosis of gastroparesis: gastric emptying scintigraphy and the stable isotope gastric-emptying breath test. The wireless capsule motility (WCM) test (SmartPill) was FDA approved in 2006 as an alternative to scintigraphy for the diagnosis of gastroparesis. Although scintigraphy and WCM measured different aspects of gastric emptying, the WCM test offered the additional benefit of measuring small bowel and colonic motility. The technology was acquired by Medtronic, which discontinued production in 2023. In the US, gastric emptying scintigraphy remains the most widely used test of gastric motor function.

The requirements for objective testing have been adopted and codified into guidelines by all major clinical societies involved in the evaluation and management of gastroparesis. Failure to comply with these diagnostic requirements frequently can lead to misdiagnosis, with significant potential clinical and psychosocial impact for the patient.[10] Beyond the ramifications of wrong diagnosis and wrong therapy, the diagnosis of gastroparesis is associated with significant stigmatization associated with poor outcomes across disease-related and psychosocial domains. We conducted a qualitative survey in patients with gastroparesis and found that they experienced stigmatization from healthcare providers and others. Patients also may internalize negative stereotypes about chronic digestive diseases like gastroparesis.

A. Clinical Guidelines Overview

In general, clinical guidelines are recommendations meant to guide clinicians so that patients receive optimal care. Guidelines are based on the most current scientific evidence. Recommendations are graded based on the quality of the evidence and strength of the recommendation.[11] Guidelines can and do evolve over time based on the emergence of new data.

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[9] Jung HK, Choung RS, Locke GR 3rd, et al. The Incidence, Prevalence and Outcomes of Patients with Gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology*. 2009; 136(4):1225-1233; *see also* Jaafari H, Houghton LA, West RM, et al. The national prevalence of disorders of gut brain interaction in the United Kingdom in comparison to their worldwide prevalence: Results from the Rome foundation global epidemiology study. *Neurogastroenterol Motil.* 2023 Jun;35(6):e14574; Syed AR, Wolfe MM, Calles-Escandon J. Epidemiology and Diagnosis of Gastroparesis in the United States: A Population-based Study. *J Clin Gastroenterol*. 2020;54(1):50-54.

[10] Taft TH, Craven MR, Adler EP, et al. Stigma experiences of patients living with gastroparesis. *Neurogastroenterol Motil.* 2022 Apr;34(4):e14223.

[11] Guyatt GH, Oxman AD, Vist GE, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6.

Likewise, gastroparesis guidelines have evolved; however, the diagnostic requirements for gastroparesis have remained unchanged.

In 2004, the AGA issued one of the first reviews on the diagnosis and treatment of gastroparesis.[12] In this early review, the AGA noted that "Gastroparesis is a symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction"; that "Symptoms of gastroparesis are nonspecific and may mimic structural disorders such as ulcer disease, partial gastric or small bowel obstruction, gastric cancer, and pancreaticobiliary disorders"; and that "There also is an overlap between the symptoms of gastroparesis and functional dyspepsia." The AGA outlined a diagnostic approach to gastroparesis, premised on "demonstrating delayed gastric emptying" and "exclusion of other potential etiologies of symptoms."

Table 1. Evaluation of Patients Suspected to Have Gastroparesis

1. Initial investigation
   - A. History and physical examination
   - B. Blood tests
     - Complete blood count
     - Complete metabolic profile, including glucose, potassium, creatinine, total protein, albumin, calcium
     - Amylase, if abdominal pain is significant symptom
     - Pregnancy test, if appropriate
   - C. Abdominal obstruction series, if vomiting or pain is acute or severe
2. Evaluate for organic disorders
   - A. Upper endoscopy to evaluate for mechanical obstruction or mucosal lesions (alternative: barium upper gastrointestinal series, often with small bowel follow-through)
   - B. Biliary ultrasonography if abdominal pain is a significant symptom
3. Evaluate for delayed gastric emptying
   - A. Solid-phase gastric emptying test
   - B. Screen for secondary causes of gastroparesis
     - Thyroid function tests (thyroid-stimulating hormone)
     - Rheumatologic serologies (eg, antinuclear antibody, scleroderma antibody [ScI70])
     - Glycosylated hemoglobin (HbA_{1C})
4. Treatment trial with prokinetic agent and/or antiemetic agent
5. If no clinical response, consider further investigation
   - A. EGG
   - B. Antroduodenal manometry
   - C. Small bowel evaluation with enteroclysis or small bowel follow-through
   - D. Further laboratory tests, if indicated
     - ANNA, tissue transglutaminase antibody

Figure 4. Source: Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association. American Gastroenterological Association Technical Review on the Diagnosis and Treatment of Gastroparesis. *Gastroenterology*. 2004 Nov;127(5):1592-622.

[12] Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association. American Gastroenterological Association Technical Review on the Diagnosis and Treatment of Gastroparesis. *Gastroenterology*. 2004 Nov;127(5):1592-622.

In 2013, the ACG issued its first clinical guideline for the evaluation and management of patients with gastroparesis.[13] The guideline was published in the *American Journal of Gastroenterology* and was authored by leading gastroparesis experts from the Mayo Clinic, Temple University, MD Anderson, the University of Mississippi, and Stanford University. With respect to the diagnosis of gastroparesis, the 2013 ACG guideline stated:

> Documented delay in gastric emptying is required for the diagnosis of gastroparesis. Scintigraphic gastric emptying of solids is the standard for the evaluation of gastric emptying and the diagnosis of gastroparesis . . . Alternative approaches for assessment of gastric emptying include wireless capsule motility testing and ^{13}C breath testing . . . Medications that affect gastric emptying should be stopped at least 48 hours before diagnostic testing.

In 2021, the United European Gastroenterology ("UEG") and European Society of Neurogastroenterology and Motility ("ESNM") issued their own consensus on gastroparesis utilizing the Delphi method, which was based on input and voting from 40 experts from 19 European countries.[14] Statements were endorsed if there was at least 80% agreement among the experts. Again, with respect to diagnosis, the guidelines stated:

- Upper gastrointestinal endoscopy is mandatory for establishing a diagnosis of gastroparesis. STATEMENT ENDORSED, overall agreement 93% . . . GRADE A.
- The presence of food in fasting state during endoscopy is diagnostic for gastroparesis. STATEMENT NOT ENDORSED, overall agreement 40% . . . GRADE B.
- An abnormal GE [gastric emptying] test is mandatory for establishing a diagnosis of gastroparesis. STATEMENT ENDORSED, overall agreement 95% . . . GRADE A.
- Gastric ultrasound assessment is a valid test for diagnosing gastroparesis. STATEMENT NOT ENDORSED, overall agreement 18% . . . GRADE B.

Later that same year, an initial North American perspective on the UEG/ENSM guidelines was published in *Neurogastroenterology & Motility*.[15] With respect to diagnosis, the authors stated:

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[13] Camilleri M, Parkman HP, Shafi MA, et al. Clinical Guideline: Management of Gastroparesis. *American Journal of Gastroenterology* 108(1):18-37, January 2013.

[14] Schol J, Wauters L, Dickman R, et al. ESNM Gastroparesis Consensus Group. United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis. *United European Gastroenterol J.* 2021 Apr;9(3):287-306.

[15] Camilleri M, Dilmaghani S, Vosoughi K, et al. A North American perspective on the ESNM consensus statement on gastroparesis. *Neurogastroenterol Motil.* 2021 Aug;33(8):e14174.

> We agree with the endorsements by the ESNM working group regarding the diagnosis of gastroparesis, specifically, exclusion of gastric or small intestinal obstruction, upper gastrointestinal endoscopy, and gastric emptying testing (by scintigraphy or breath test, but not by wireless motility capsule or ultrasound) being mandatory for establishing a diagnosis of gastroparesis, although the presence of food in the fasting state during endoscopy is not sufficient for diagnosis.

The following year, in 2022, the ACG issued new guidelines intended to "document, summarize, and update the evidence and develop recommendations for the clinical management of gastroparesis, updating the 2013 ACG guideline on gastroparesis."[16] I was privileged to be invited to join as a co-author in the preparation and publication of those guidelines.

Around the same time, the AGA issued a clinical practice update on the management of medically refractory gastroparesis.[17] Consistent with the ACG guidelines, the AGA recommended that clinicians evaluating patients with refractory gastroparesis:

- "review symptoms and evaluate physical examination findings to exclude disorders that can mimic medically refractory gastroparesis," and
- "verify appropriate methodology of the gastric emptying study to ensure an accurate diagnosis of delayed gastric emptying."

Also around the same time, the Rome Foundation initiated the process of developing consensus guidelines on idiopathic gastroparesis and invited the major international neurogastroenterology and motility societies to participate. These included the Australasian Neurogastroenterology and Motility Association, the Asian Neurogastroenterology and Motility Association, the American Neurogastroenterology and Motility Society, the European Society for Neurogastroenterology and Motility, and Sociedad Latinoamericana de Neurogastroenterología. Group meetings were held in 2022 and 2023, and the final consensus statement was published online in *The Lancet* in December 2024.[18] I was honored to be selected as one of the two representatives from the American Neurogastroenterology and Motility Society.

Like the other guidelines discussed above, the Consensus group acknowledged that "By definition, gastroparesis implies an objective delay in gastric emptying in the absence of mechanical obstruction, and requires both an assessment of gastric emptying and confirmation of the absence of gastric outlet obstruction or another mechanical factor, most commonly through an upper endoscopy." The Consensus group further noted that "symptoms of gastroparesis lack specificity" and that "a demonstration of delayed gastric emptying is necessary

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[16] Camilleri M, Kuo B, Nguyen L, et al. ACG Clinical Guideline: Gastroparesis. *Am J Gastroenterol.* 2022 Aug 1;117(8):1197-1220.

[17] Lacy BE, Tack J, Gyawali CP. AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis: Expert Review. *Clin Gastroenterol Hepatol.* 2022 Mar;20(3):491-500.

[18] Schol J, Huang I-H, Carbone F, et al. Rome Foundation and International Neurogastroenterology and Motility Societies' Consensus on Idiopathic Gastroparesis. *The Lancet Gastroenterology & Hepatology*, Vol. 10, Issue 1, 68-81, January 2025.

for diagnosis." To this point, the Consensus group explained that numerous conditions can "mimic" symptoms of gastroparesis, including diabetes, thyroid disease, kidney failure, and electrolyte abnormalities.

With respect to diagnosis, the group adopted several key consensus positions, including as most relevant here, that:

- "An upper gastrointestinal endoscopy is mandatory for establishing a diagnosis of idiopathic gastroparesis" (100% agreement, Grade A);
- "An abnormal gastric emptying test is mandatory for establishing a diagnosis of idiopathic gastroparesis" (92% agreement, Grade A); and,
- "Ceasing medications that could interfere with gastric transit before gastric emptying investigations is required to ensure an accurate diagnosis of gastroparesis"[19] (100% agreement, Grade A).

B. 2022 ACG Guidelines

The 2022 ACG guidelines are the most current domestic clinical guidelines addressing the diagnosis and management of gastroparesis, and they represent the official practice recommendations of the ACG.[20] The guidelines include a specific diagnostic algorithm for gastroparesis, intended to support accurate diagnosis of gastroparesis and to allow clinicians to differentiate other gastrointestinal conditions, such as functional dyspepsia. The algorithm outlines critical aspects of the proper diagnostic approach to patients presenting with symptoms potentially associated with gastroparesis.

As an initial matter, symptoms consistent with gastroparesis—such as nausea, vomiting, postprandial fullness, bloating and upper abdominal discomfort—must be present. Generally, symptoms should be present for a prolonged period before a diagnosis of gastroparesis should be considered. Initially, a detailed evaluation should be conducted to determine other causes of these symptoms, including a thorough review for medications with GI side effects, medical conditions that can manifest with GI symptoms and objective testing to exclude a mechanical obstruction. Medications identified as potential agents that can cause GI symptoms should be discontinued. Next, the clinician should conduct objective studies to rule out mechanical obstruction and evaluate gastric motility. Either an EGD or other radiologic study should be performed to rule out mechanical obstruction (or blockage) that is preventing normal movement of food through the stomach. Importantly, the presence of retained food at the time of EGD is not diagnostic of gastroparesis.

If symptoms persist, the next step is to perform an optimized gastric emptying test to confirm objective delay in gastric emptying. An optimized gastric emptying test is defined as a test that measures emptying of a solid meal over a duration of at least 3 hours for which medications that

[19] The Consensus group noted that certain classes of medicines including prokinetic agents, opiates, anticholinergics/antispasmodics, and GLP-1RAs potentially can have an "impact on gastric motility".
[20] ACG has a membership of 18,000+ physicians from 86 countries and is one of the most preeminent gastroenterological societies in the world.

can impact gastric emptying have been discontinued and hyperglycemia treated. Hyperglycemia (glucose > 275 mg/dL) and medications can temporarily delay gastric emptying; thus, they should be avoided prior to the gastric emptying study.[21]

Tests endorsed by the ACG include scintigraphy and the ^{13}C-spirulina breath test. Studies assessing extra-gastric dysmotility (i.e., motility issues in other parts of the GI system) such as Wireless Motility Capsule (WMC) or whole gut scintigraphy can also be considered if patients have symptoms suggestive of a more diffuse dysmotility such as constipation. Only after these steps have been completed can a reliable diagnosis of gastroparesis be made.

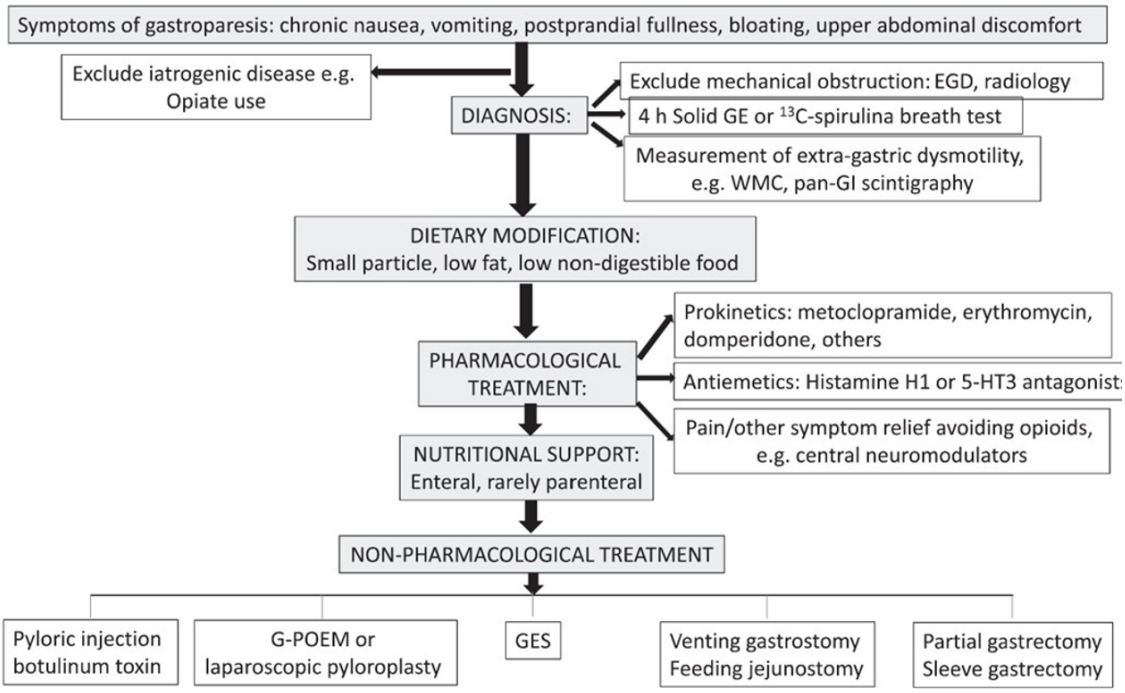

Figure 5. Source: Camilleri M, Kuo B, Nguyen L, et al. ACG Clinical Guideline: Gastroparesis. *Am J Gastroenterol.* 2022 Aug 1;117(8):1197-1220.

The 2022 ACG algorithm, illustrated above, is broadly consistent with recommendations of other societies in this space and reflects the clinical standard of care for the diagnosis of gastroparesis, including the definitive requirement for objective gastric emptying testing.[22]

[21] Camilleri M, Kuo B, Nguyen L, et al. ACG Clinical Guideline: Gastroparesis. *Am J Gastroenterol.* 2022 Aug 1;117(8):1197-1220.

[22] See e.g., BMJ Best Practice (US): Gastroparesis – Symptoms, diagnosis, and treatment *available at* https://bestpractice.bmj.com/topics/en-us/642 (last visited December 3, 2024).

C. Gastric emptying scintigraphy

Although breath testing and wireless capsule motility are accepted tests for the diagnosis of gastroparesis, they are generally limited to academic referral centers; therefore, I will focus my discussion on gastric emptying scintigraphy which is widely available and the most common modality used in the US.

Gastric emptying scintigraphy ("GES") is considered the gold standard test for assessing gastric motility. A standardized protocol for performing GES was published in 2008 by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine.[23] In short, the protocol involves a patient consuming a low-fat, egg-white meal after an overnight fast. The meal is radiolabeled with 0.5–1 mCi ^{99m}Tc. Imaging is performed at 0, 1, 2, and 4 hours after the meal, and computer measurements are taken at each image interval as to the amount of the meal that remains in the patient's stomach. Each image typically takes less than two minutes to perform, and a patient can relax and leave the testing room between images. After four hours, less than or equal to 10% of the meal should remain in the patient's stomach. Patients should stop medications affecting gastric motility prior to the test, and the test should not be performed if a patient's blood sugar is over 275 mg/dL.

It is important to highlight that GES (and other diagnostic testing for gastroparesis) should not be performed in the emergency department, or while a patient is acutely ill. Multiple factors associated with hospitalization can impact the test results: acute stress, immobility, dehydration, electrolyte abnormalities and medications (ondansetron, benzodiazepines, metoclopramide, opiates). Additionally, when patients are actively vomiting, they may be unable to complete the solid gastric emptying test meal. Patients with suspected gastroparesis should be referred for outpatient evaluation and testing after stabilization and treatment of significant symptoms.[24]

GES is widely available in the US. The studies are conducted in nuclear medicine units in Radiology departments along with commonly used nuclear medicine studies such as PET scans for cancer, nuclear cardiac stress test (Thallium stress test) and ventilation-perfusion tests, etc. ^{99m}Tc is the most commonly used medical radioisotope in the world, used in tens of millions of medical procedures annually and is safe for patients who are not pregnant.[25]

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[23] Abell TL, Camilleri M, Donohoe K, et al.; American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Consensus Recommendations for Gastric Emptying Scintigraphy: A Joint Report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol*. 2008 Mar;103(3):753-63.

[24] A 2002 study by Cremonini et al. found that 4-hour gastric emptying on scintigraphy was highly reproducible on repeat testing.[24] In this study of 21 healthy volunteers who underwent gastric emptying scintigraphy 3 weeks apart, the intra-subject variation observed in gastric emptying test results at 4 hours was only 4%. The variance was less than 10% in the majority (86%) of participants. This study demonstrates the reproducibility of gastric emptying scintigraphy over time when testing once patients are more stable and not in an emergency department setting. Cremonini F, Mullan BP, Camilleri M, et al. Performance characteristics of scintigraphic transit measurements for studies of experimental therapies. *Aliment Pharmacol Ther.* 2002 Oct;16(10):1781-90.

[25] Mahesh M, Ansari AJ, Mettler FA Jr. Patient Exposure from Radiologic and Nuclear Medicine Procedures in the United States and Worldwide: 2009-2018. *Radiology*. 2023 Apr;307(1):e221263.

V. Clinical Experience and Perspectives

I have been taking care of patients with gastroparesis for almost 20 years. I have spent the past 16 years at Stanford Health Care, where I take care of patients with GI motility disorders, particularly related to gastric motility disorders. Patients are typically referred to me by other gastroenterologists, predominantly in California; however, I also see patients from around the country. My practice as a specialist is similar to that reported by Cangemi et al., which now often involves "un-diagnosing" patients who do not actually have gastroparesis. In fact, some days I spend more time correcting prior misdiagnoses of gastroparesis than I do diagnosing gastroparesis.

In a study by Tanner et al., examining the therapeutic trends in gastroparesis from 2010 to 2020, they found that only 16% of patients diagnosed with gastroparesis underwent a prior gastric emptying test. Additionally, patients were frequently taking medications known to delay gastric emptying prior to the diagnosis of gastroparesis: opioid analgesics (52.6%), anticholinergic medications (74.0%), and calcium channel blockers (36.0%). Despite this, approximately 5% of patients underwent an invasive procedural or surgical intervention, including total gastrectomy in 2% of patients.[26] This trend is concerning, as misdiagnosis of gastroparesis leads to inappropriate therapies that result in persistent symptoms, side effects from medications, and unnecessary procedures (such as jejunal tube feeds or total parenteral nutrition).[27] It is also the reason why I have dedicated so much of my time and effort to establishing diagnostic guidelines and educating other physicians on gastroparesis.

Additionally, my research on stigma in gastroparesis was inspired by my observation over the years that patients when diagnosed with gastroparesis are often deemed "too complicated" and referred on to academic medical centers with minimal guidance. Gastroparesis is a chronic condition that is associated with significant morbidity and should be differentiated from disorders that may have similar symptoms but different disease course.

A. Diagnostic Approach

When a patient is referred to me for suspected gastroparesis, I spend a significant amount of time reviewing the patient's chart, including their past medical history and testing. In addition, I take an independent history and perform a thorough physical examination. I then determine whether additional testing is needed to confirm and/or rule out a gastroparesis diagnosis.

In particular, I will not make a diagnosis of gastroparesis in a patient without first ruling out mechanical obstruction, either with an EGD or other radiographic techniques. In addition, I will not make a diagnosis without a gastric emptying study (typically scintigraphy) performed consistent with the consensus methodology established by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. In particular, I will not make a diagnosis

[26] Tanner SE, Kurin M, Shahsavari D, et al. Trends in Gastroparesis Management: A United States Population-based Study From 2010 to 2020. *J Clin Gastroenterol*. 2023 Sep 1;57(8):789-797.
[27] Fosso CL, Quigley EMM. A Critical Review of the Current Clinical Landscape of Gastroparesis. *Gastroenterol Hepatol (NY)*. 2018 Mar;14(3):140-145.

if the GES was performed while a patient was on medications that can affect gastric motility or if the patient had blood sugar levels above 275 mg/dL at the time of the study. I also will not make a diagnosis without first ruling out other conditions that may "mimic" gastroparesis. Once a diagnosis of gastroparesis is confirmed, the history is re-reviewed and additional testing is performed to evaluate the cause of gastroparesis, including thyroid, neurologic, autoimmune, cardiac or connective tissue disorders, or prior surgeries. This diagnostic approach is consistent with the clinical guidelines discussed above and the approach used by my colleagues at Stanford.

VI. Conclusion

Gastroparesis is a complex disorder involving abnormalities of the intrinsic and autonomic nervous system, the connective tissue of the GI tract, gastric and duodenal myopathy (smooth muscle) and immune dysregulation. Symptoms of gastroparesis are nonspecific and there is poor correlation between the severity of symptoms and the severity of delayed gastric emptying, though patients with severely delayed gastric emptying are more likely to experience more severe symptoms.[28] For this reason, over two decades of consensus recommendations confirm that the diagnosis of gastroparesis requires chronic symptoms, normal endoscopy and objective confirmation of delayed gastric emptying using a gastric emptying study. Correctly diagnosing gastroparesis is important as it helps to guide treatment, especially nutritional support and more invasive therapies such as surgery.

VII. Comments to the Reports of Dr. Fass, Dr. Raines, and Dr. Siegel

I have reviewed the reports of Drs. Fass, Raines, and Siegel. As all three reports touch on many of the same topics, I have combined my comments on all three reports in the key points below.

(1) Medication effects on gastric emptying are temporary.

Dr. Fass and Dr. Raines both state in their reports that "drug-induced gastroparesis" is unique and different from all other forms of gastroparesis in that symptoms cease when medication is stopped. I agree to the extent that certain medicines (including GLP-1RAs) can transiently delay gastric emptying resulting in symptoms that mimic (but are not equivalent to) the medical condition known as gastroparesis and that resolve upon treatment cessation. As I discussed above, gastroparesis is a chronic disease. It results from injury or damage to the muscles and/or nerves involved in the movement of food through the stomach. As both Dr. Fass and Dr. Raines appear to acknowledge, medicines (such as GLP-1RAs) do not cause injury or damage to those muscles or nerves. Rather, they have a temporary physiologic effect on the rate of movement of food (delayed gastric emptying) through the stomach that resolves upon cessation of the medicines. In the case of GLP-1RAs, transient delayed gastric emptying is part of the intended mechanism of action of the medicines.

[28] Nguyen L, Wilson LA, Miriel L, et al. Autonomic function in gastroparesis and chronic unexplained nausea and vomiting: Relationship with etiology, gastric emptying, and symptom severity. *Neurogastroenterol Motil*. 2020;32(8):e13810.

(2) Symptoms alone are not sufficient to conclude a patient has delayed gastric emptying, much less true gastroparesis.

Resolution of GI symptoms after stopping a medication may confirm, at most, that a patient had a GI side effect of the medication. It does not confirm that a patient had delayed gastric emptying or that delayed gastric emptying caused their symptoms. The premise—underlying the opinions offered by plaintiffs' experts—that symptoms alone are sufficient to diagnose a patient with gastroparesis and/or to establish that they have delayed gastric emptying is false and contradicted by the scientific literature. Indeed, I agree with Dr. Fass that "the symptoms of gastroparesis are relatively common and not specific to the condition." I also agree with Dr. Raines that "[w]hen considering the diagnostic utility of symptoms in gastroparesis, findings reported in the medical literature are mixed" at best. As noted above, recent studies indicate that symptom-based diagnoses are incorrect well over 50% of the time. That also is consistent with my clinical experience.

(3) While GI symptoms are quite common with GLP-1RAs, clinically delayed gastric emptying is relatively rare.

An abstract by Lupianez-Merly et al.[29] that both Dr. Raines and Dr. Siegel discuss in their reports is illustrative of this. A full, peer-reviewed article on this research has not yet been published so these results should be viewed as preliminary. However, looking at the entirety of the population of GLP1-RA users studied (86,682 patients), 14,658 patients (17.9%) experienced at least one GI symptom. Within the same population, 696 patients were suspected of having delayed gastric emptying such that a GES was ordered. Among those patients suspected of having delayed gastric emptying and for whom scintigraphy was ordered, 241 actually had delayed gastric emptying. That means, in total, only 0.28% of patients taking GLP-1RA medications had documented delayed gastric emptying. Even among the subset of patients who were suspected of having delayed gastric emptying based on their symptoms, only 35% had an objective delay in gastric emptying. In other words, (1) GI symptoms are quite common with use of GLP-1RA medications; (2) delayed gastric emptying is relatively rare among patients who are taking a GLP-1RA medication; and (3) even when doctors suspected a patient had delayed gastric emptying sufficient to warrant a gastric emptying study, their suspicions were confirmed only 35% of the time.

(4) It is true that "no test is 100% accurate" but that does not mean clinicians can ignore the established, guideline-recommended methods for diagnosing gastroparesis and treating patients.

Dr. Fass notes that "GES tests by their nature can only offer a snapshot of the patient's gastric motility on the day of the test." But this is true of many of the medical diagnostic tests that we use in practice. Moreover, for chronic medical conditions like gastroparesis, a person's baseline rate of gastric emptying is not likely to fluctuate widely from day-to-day. Also, in treating patients with

[29] Lupianez-Merly C, Dilmaghani S, Blundo R, et al. Effects of GLP-1 Receptor or A Dual GLP-1/GIP Receptor Agonists on Gastrointestinal Symptoms and Gastric Emptying: Results From a Large Clinical Practice Database. AGA Abstracts. 2024:S-1066-S-1067.

true gastroparesis, it is not uncommon to order repeat gastric emptying studies over time to determine whether nutritional modifications and other interventions have had an impact on improving their rates of gastric emptying.

All of the methods for imaging referenced in Dr. Siegel's report have strengths and limitations, and as Dr. Raines mentions, as with all tests, there is the possibility of a false negative or positive when interpreting gastric emptying studies. Nonetheless, a gastric emptying study (either scintigraphy or the breath test) is the most reliable method available to assess gastric emptying. Further, as consistently reflected across all diagnostic guidelines, a gastric emptying study is required to make a reliable diagnosis of gastroparesis.

Finally, it is unfortunately true, as plaintiffs' experts suggest, that not all physicians follow clinical guidelines for gastroparesis diagnosis in their clinical practice. Indeed, as I noted above, I now spend a substantial portion of my time un-diagnosing patients who were "diagnosed" with gastroparesis without appropriate clinical testing.

Dated this 23rd day of December 2024

Linda Anh B. Nguyen, MD, FACG, AGAF

Exhibit G

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF PENNSYLVANIA

IN RE: GLUCAGON-LIKE PEPTIDE-1
RECEPTOR AGONISTS (GLP-1 RAs)
PRODUCTS LIABILITY LITIGATION — CIVIL ACTION
MDL 3094
2:24-md-03094-KSM

THIS DOCUMENT RELATES TO:
ALL ACTIONS/ALL CASES:

CONFIDENTIAL

VIDEO DEPOSITION OF: ELIOT SIEGEL, M.D.

DATE: JANUARY 31, 2025

TIME: 9:06 A.M. - 5:30 P.M.

PLACE: 20 N. ORANGE AVENUE
SUITE 1600
ORLANDO, FLORIDA

REPORTED BY: TAMARA MASCI TANNEN, RPR, FPR-C
STENOGRAPHIC COURT REPORTER
NOTARY PUBLIC, STATE OF FLORIDA

A. Yes.
Q. Where you didn't supervise it directly?
A. Where I didn't supervise it directly, yeah, both, when I supervised it and when I didn't supervise it.
Q. Okay. And then if you look -- if you do look at Page 4 of your report --
A. Mm-hmm. Or yes.
Q. The top paragraph.
A. Okay.
Q. You note that you have interpreted tens of thousands of nuclear medicine examinations?
A. Correct.
Q. And that's correct?
A. It is.
Q. That's a true statement?
A. It is a true statement.
Q. And then you note that you have interpreted over 1,000 gastric emptying studies. Do you see that?
A. I do, yes.
Q. Gastric emptying studies is and have been over the course of your career available to patients, obviously?
A. Yes.
Q. If we take not just interpret gastric emptying studies, but either interpret them or supervise them or recommend them, how many gastric emptying studies have you

been involved with over the course of your career?

A. As I said in the report, it's over 1,000. I don't have a way to remember exactly how many it was. And so, that's an estimate. I would -- if I erred on one side or the other, it would be underestimating the number of gastric emptying studies that I've done.

And the reason for that is that in general, my observation anecdotally, although I don't have statistics related to this, is that fewer gastric emptying studies are being done in recent years than there were years ago. More patients are getting EGD than they did back in the 1980s, for example. And so --

Q. Was EGD available in the 1980s?

A. I think it was available in the late 1980s, as I recall.

Q. That's when it first became available?

A. Yeah, I think in the 1980s, it became available and much more widely used. But we used to do more -- a higher percentage of the studies that we did in a greater number of gastric emptying studies were done in the past than are done currently.

And so, that estimate of a thousand was really sort of related to how many have been done within the last several years, but I bet that the rate of gastric emptying studies being done per day or per period of time was

significantly greater in years past. So I would bet that it's well over a thousand gastric emptying studies.

Q. Okay. You've been involved in potentially many thousands of gastric emptying studies?

A. I would say maybe somewhere between 1,000 and 3,000.

Q. Okay. Gastric emptying studies have been around for decades?

A. Yes.

Q. It's a well-established medical procedure?

A. It is, yes.

Q. Now, if you go to Page 10. Do you see the heading 7, Gastroparesis?

A. I do, yes.

Q. You give a definition of gastroparesis in here, right?

A. I give a definition of gastroparesis and then a reference to that definition.

Q. Okay.

A. Two references, actually.

Q. And you say gastroparesis has three elements, right, numbered?

A. Correct.

Q. Okay. And that's consistent across the medical literature, those three elements, right?

A. Yes.
Q. The first element of gastroparesis is gastrointestinal symptoms, true?
A. True.
Q. The second is the absence of mechanical obstruction of the pylorus?
A. True.
Q. And the third is the presence delayed gastric emptying?
A. True.
Q. All three elements are required for the definition of gastroparesis to be met?
A. I think that is the most common definition of all of the things that I've read, correct.
Q. And specifically, gastroparesis requires the presence of delayed gastric emptying, true?
A. Correct.
Q. If you only have GI symptoms, so element one, and absence of mechanical obstruction, element two, do you agree that the definition of gastroparesis is not met?
A. If you have element one symptoms and then two, a lack of mechanical obstruction, then I do agree with that. I believe that one needs to have -- in order to diagnose gastroparesis, I think one needs to have evidence suggesting that it is likely that there's delayed gastric emptying.

Q. The symptoms for the first element, gastrointestinal symptoms, you say those include most commonly --

A. Mm-hmm.

Q. -- nausea --

A. Yes.

Q. -- vomiting, postprandial fullness and abdominal pain, right?

A. Right.

Q. Those are all gastrointestinal symptoms?

A. They are a subset of gastrointestinal symptoms.

Q. What is postprandial fullness?

A. It means the sensation of fullness after a patient or subject ingests a meal.

Q. And this is not the exclusive list of gastrointestinal symptoms of gastroparesis, right?

A. Correct.

Q. There could be others?

A. There can be others.

Q. Okay. Other symptoms could be diarrhea, right?

A. Other symptoms can be fairly broad. I don't think diarrhea would be near the top of my list as most common symptoms associated with gastroparesis.

Q. Okay. But it does appear with gastroparesis sometimes?

Q. -- much, much greater than the prevalence of gastroparesis itself, right?

MR. BUXNER: Object to form.

THE WITNESS: I don't know how much greater it is. But I would imagine that it is a -- one is a subset of the other.

BY MS. FITZPATRICK:

Q. Do you know how many -- there's about 350,000,000 people in the U.S., right?

A. About.

Q. Okay. And 5 million U.S. adults, that's a prevalence number, right? That's at any given time?

A. Correct.

Q. Okay. So 5 million adults?

A. Yeah.

Q. Over 350 million adults?

A. Yeah.

Q. I'll withdraw that because I actually don't have an adult number.

But you agree with me that the prevalence of gastrointestinal symptoms like nausea, vomiting, postprandial fullness and abdominal pain is much, much higher than the prevalence of gastroparesis, right?

A. I agree that fewer people have gastroparesis than the number that have -- well, I actually don't know the

number of patients who have -- who have one or the other.

But I believe that the number of patients who have symptoms of -- like gastroparesis is greater than the number of patients who have gastroparesis. I think that's what's you asked.

Q. The symptoms associated with gastroparesis are common, right?

MR. BUXNER: Object to form.

THE WITNESS: I think that symptoms that we listed as being characteristic of gastroparesis are common. I think it really depends on the severity of those symptoms. And the etiology of those symptoms is really important also.

And so, you know, one can have nausea associated with so many different types of things. And so, each one of these symptoms, you know, may have a very different pattern of presentation than the pattern for gastroparesis.

And so, I think it's really important not to generalize and to look specifically at any particular patient and the constellation of findings that they have.

BY MS. FITZPATRICK:

Q. My question is: You agree with me that nausea, vomiting, postprandial fullness and abdominal pain are

common?

A. I think each one of them are relatively common --

Q. Okay.

A. -- in that millions of people likely suffer from those during the course of a year.

Q. And the symptoms of -- these symptoms: Nausea, vomiting, postprandial fullness and abdominal pain, they are not specific to gastroparesis, true?

A. Correct. One cannot diagnose gastroparesis from any one of those symptoms. And it really -- again, the diagnosis of gastroparesis really depends on a constellation of findings from a temporal perspective and constellation of findings as far as multiple different things that a patient has over time, including severity of those findings, et cetera.

Q. If you go to Page 15.

A. Uh-huh. Yes.

Q. The top paragraph.

A. Okay.

Q. You note -- doctor, you note that the symptoms of gastroparesis are non-specific, right?

A. Correct. The report says that because the symptoms of gastroparesis are non-specific.

Q. Yes. That was my question.

A. Yes.

A. I do.
Q. All of these conditions have GI symptoms, true?
A. All of these symptoms can be associated with GI symptoms. For example, endocrine disorders. There's a wide variety of endocrine disorders, such as thyroid disorders, for example, and most of those do not have GI symptoms associated with them in most cases.
And so, these would all be things in the differential because of the fact that there are subsets of these conditions, such as endocrine disorders, for example, that can have GI manifestations, but they certainly don't all have GI manifestations.
Q. So all of the conditions listed on 15 to 16 of your report, if I understand you correctly, can have GI manifestations. That's what you just told me, true?
MR. BUXNER: Object to form.
THE WITNESS: All of these entities can have GI symptoms associated with a subset of those disorders. So neurologic conditions tend not to have GI symptoms, but a small subset do.
BY MS. FITZPATRICK:
Q. But some of them can; is that fair?
A. Correct. It is fair.
Q. Okay. And the endocrine disorders you called out, those can have GI symptoms, right?

A. Correct.
Q. The neurological conditions you called out, those can have GI symptoms, right?
A. Correct.
Q. Rumination syndrome, that can have GI symptoms, true?
A. It can have GI symptoms, although that also has fairly characteristic GI symptoms that would allow me to distinguish that from gastroparesis.
Q. Chronic pancreatitis can have GI symptoms, true?
A. Yes, frequently has GI symptoms.
Q. And the GI disorders you called out can have GI symptoms, obviously?
A. Yes.
Q. All of these conditions can occur in people taking GLP-1 Receptor Agonists, true?
A. GLP-1 Receptor Agonists do not prevent one from having this set of symptoms or diseases, that is correct.
Q. It's fair to say that not everyone with chronic nausea or vomiting has gastroparesis, true?
MR. BUXNER: Object to form.
THE WITNESS: It is fair to say that.
BY MS. FITZPATRICK:
Q. And it's fair to say that --
A. Yes.

Q. And it's fair to say that not everyone taking a GLP-1 receptor agonist with chronic nausea or vomiting has gastroparesis, true?

A. I think that it is fair to say not everyone does, but I believe the majority -- vast majority of patients who are taking GLP-1 agonists do in fact have delayed gastric emptying and the subset that have symptoms do indeed have drug-induced gastroparesis.

Q. You're telling me that everyone taking a GLP-1 agonist that has GI symptoms has drug-induced gastroparesis?

MR. BUXNER: Object to form.

THE WITNESS: I'm telling you that patients who are taking GLP-1 agonists are likely to have delayed gastric emptying. And that's from the information in the labels and from a preponderance of the literature. And so they meet the criteria for probable delayed gastric emptying.

And so since the majority of them don't have a gastric outlet obstruction, the subset of those that have symptoms I would diagnose drug-induced gastroparesis.

BY MS. FITZPATRICK:

Q. And so, for the subset of people taking GLP-1 Receptor Agonists that have GI symptoms, you would diagnose drug-induced gastroparesis, right?

whether or not the patient had gastroparesis.

Q. But you agree that -- as you wrote in your report, that if the gastric emptying effect of the GLP-1 receptor agonist is responsible for the patient's symptoms, they should begin to resolve as the drug starts to clear his or her system, right?

A. That's correct. I'm not sure I would have stated it that way, but yes.

Q. In your report, you note that GLP-1 receptor agonist medications can have half-life of a few hours up to as many as seven days, right?

A. Correct.

Q. That's the time for fully half of the drug to be cleared from the body, right? That's what a half-life means?

A. It -- it may be a more technical definition from that, but I think that's one definition. It's really how much activity is there. Some of that activity gets cleared from the body in different ways. And so that t 1/2 may have a more precise pharmacologic definition than that.

But I think in general, the idea is that t 1/2 is the time when half of the drug is still within the patient's body.

Q. The time to clear less than half of the drug from the body is even less than that range, right?

A. Correct.

Q. So you expect to see symptoms resolve within a day or two of drug withdrawal, right, for GLP-1 Receptor Agonists?

MR. BUXNER: Object to form.

THE WITNESS: It would depend on whether it was long-acting or short-acting in the half life. And so I think the patients are variable as far as how they end up responding to withdrawal. And so, some may respond, you know, more quickly than others. Some may never respond, or some may not, you know, respond indefinitely.

And so, I don't believe that there's any hard and fast rules about determining whether or not it was due to gastric emptying based on how a patient responds after the medication is withdrawn.

BY MS. FITZPATRICK:

Q. Your -- you -- are you aware that anesthesiologists recommend to stop GLP-1 Receptor Agonists five days before surgery?

MR. BUXNER: Object to form.

BY MS. FITZPATRICK:

Q. Are you aware of that?

A. So -- no. What I am aware of is the fact that anesthesiologists are concerned about GLP-1s. And because

anesthesiologists in their literature do believe that it -- GLP-1 Receptor Agonists cause delayed gastric emptying, there's a concern about aspiration in a patient essentially vomiting associated with it.

But it really would depend for an anesthesiologist on which specific GLP-1 agonist. And there are different recommendations and different ideas within the anesthesiology literature about how long one should wait or whether one should wait prior to procedures.

Q. You're not aware of surgical consensus guidelines that say stop five days before surgery?

MR. BUXNER: Object to form.

THE WITNESS: I am not aware of one. And I would feel uncomfortable with a guideline that generalized GLP-1 Receptor Agonists to any one particular recommendation for how long without considering which GLP-1 agonist it was and other specific information about the patient.

BY MS. FITZPATRICK:

Q. If you go -- still on Page 17 --

A. Okay.

Q. -- further down. Hold on. Let me find it. At the -- all the way at the bottom, last couple sentences, there's one that starts "if symptoms persisted."

A. Okay.

Q. Do you see that it says: "If symptoms persisted after the patient was off his/her medication for an appropriate period of time to allow clearance of the medication, I would consider a nuclear medicine gastric emptying study."

Do you see that?

A. I do, yes.

Q. And then if you go down 17 to 18, it says: "If there is no obvious cause, or if symptoms fail to resolve after the suspect drugs is withdrawn, a broader more comprehensive analysis may be required."

Do you see that?

A. I do.

Q. That's because if the symptoms fail to resolve after the suspect drug is withdrawn, it doesn't appear to be drug-induced gastroparesis, true?

MR. BUXNER: Object to form.

THE WITNESS: It's not true. It just changes the probability.

BY MS. FITZPATRICK:

Q. Makes the probability less, true?

A. I believe it's true that if one withdraws a GLP-1 agonist and the patient continues to have the same symptoms, then it raises larger questions about what is the probability that it was caused by gastric emptying. So I

think that's what you were asking. And the answer to that is yes.

Q. And the probability is less. If the symptoms persist after the drug is out of their system, the probability that the symptoms are caused by the drug is less, right? We can agree on that?

A. We can agree on that. It may still be the most likely cause, but it would trigger me to look into other causes more deeply than I had previously.

Q. And at that point, if the symptoms persist after withdrawal of the drug, you would consider a gastric emptying study, true?

A. I would consider a gastric emptying study once I was able to perform it within the guidelines suggested by the Society of Nuclear Medicine, which are to wait until the patient has had the drug cleared from their system.

Q. That's the premise of my question. If symptoms persist after they're off them in enough time for the drug to clear and they still have symptoms, you would do a gastric emptying study, true?

MR. BUXNER: Object to form. Asked and answered.

THE WITNESS: That's not true. In other words, I would consider a gastric emptying study, but we just talked about a large number of different studies that could be done, including an EGD, including taking

additional patient history. And so I'd really want to know the context of the patient.

So if you're asking would I do a gastric emptying study in every patient that still has symptoms after the medications are withdrawn, which I think you're asking, the answer is, no, I would not do it in every patient. I would probably do it in only a small minority of those patients.

BY MS. FITZPATRICK:

Q. If you look at Page 16 of your report?

A. Sure.

Q. Under C. You wrote in your report that: "When gastroparesis is based on a permanent or unknown underlying condition, it should be confirmed by gastric emptying study and upper endoscopy."

Do you see that?

A. I do. I was quoting --

Q. And you have --

Do you see it?

A. I do see it, yes.

Q. And you have two citations, correct?

A. Correct. And I was really quoting both of those citations.

Q. And you agree with those citations; that's why you put them in your report, true?

MR. BUXNER: Object to form.

THE WITNESS: I wanted to detail what was in the literature. And so both of those authors believe that it should be confirmed by -- by another study. I don't agree that one needs to do upper endoscopy and a GES study in those patients. And I think it really depends on the specific patient.

And so they mention that. I would not have made that particular statement because I think it's too much of a blanket statement.

So even though I wanted to quote those two authors in what they had said, I don't believe that the majority of patients need to have a gastric emptying study if there are other studies that have provided that information, such as an EGD or history or other things. So again, I'd want to go back to the individual patient.

BY MS. FITZPATRICK:

Q. Did you write your report?

A. Yes.

Q. And you said you quoted those two authors, but there's no quote marks, right? It's just a sentence.

A. Right. The reason I didn't put quote marks is --

Q. I'm not asking. There's no quote marks, correct?

A. True.

Q. It's not a quote, true?

A. I -- I don't know that I would have put a quotation mark if it were a quote. In other words, this is not a scientific paper. So I don't recall. I'd have to look back to see whether or not that specific sentence was in there.

But I wanted to do was make sure that that sentence was attributed to those two authors so I could reflect what their opinion was in those articles.

Q. If you go to Page 19 --

A. Okay.

Q. -- the paragraph right above heading B.

A. Nineteen, paragraph above heading B. Okay.

Q. Here you're also referring to Camilleri's 2022 paper?

A. Okay.

Q. Same as what we were just looking at on Page 16, right?

A. I don't know if --

Q. Page 19 immediately above heading B.

A. Camilleri wrote multiple articles. And so I don't know if this is the same one or not because there's so many Camilleri articles that I refer to. So I don't know whether this is the same one.

I think this one, the Camilleri one, is the ACG

clinical guideline that was gastroparesis in '22. I don't know if the other one is that same article or not.

Q. Your bibliography contains a single publication by first author Camilleri, true?

A. Right. But that --

Q. True?

A. It's -- to my knowledge, that is correct.

Q. Okay.

A. I'd have to look and verify that.

Q. And on Page 19 when you quote Camilleri 2022, you use quotation marks, true?

A. I'd have to look back.

MR. BUXNER: Hold on for one second. Hold on one second, Doctor, before you answer.

I just want to make sure I'm where you are because I've lost you.

MS. FITZPATRICK: We're on Page 19.

MR. BUXNER: 19.

MS. FITZPATRICK: We're on the sentence above heading B.

MR. BUXNER: Okay. Gotcha.

BY MS. FITZPATRICK:

Q. You see there's a quote from Camilleri 2022?

A. Right. Now -- now I'm lost too. In other words, I quoted it saying further studies are required to appraise.

That's in quotes.

Q. Yes.

A. And so, I know that that is a quote. I don't know whether the other one is a quote or not. I may have not put the quotation marks in it but still used it as a quote. I probably would have been more careful if it had been a scientific paper.

But I'd have to go back and see whether or not I'm summarizing or extrapolating or I'm quoting him directly. I just don't know the answer to that.

Q. If you look back at Page 16 --

A. Okay.

Q. -- there are not -- we've established no quotation marks, right, for the statement --

A. We've established in the report that there are no quotation marks.

Q. Yes. And also, no disagreement with that statement is in the report, true? You don't follow up that statement by pointing out any disagreement with it, right?

MR. BUXNER: Object to form.

THE WITNESS: I don't disagree with that -- with my own statement. But as the author -- I mean, you asked me who wrote the report. I wrote the report, so I'm telling you that when I wrote the report, I was trying to refer to those two authors and what their

opinion was, not to express my own opinion.

BY MS. FITZPATRICK:

Q. But the statement: "When gastroparesis is based on a permanent or unknown underlying condition, it should be confirmed by GES and under endoscopy" is your own statement, true?

A. It is. But I wish that I had essentially had the opportunity to -- I mean, I want to clarify that by saying that I was quoting these two authors and that I believe it should be confirmed based on a patient-by-patient basis. That's really the theme of what I'm trying to convey.

And so, I hope that the report as a whole conveyed that information. When I said one size does not fit all, I was really referring to why it's so important to individualize it to the patient.

And so, this particular statement was not in any way meant to essentially deny the theme of establishing this in each and every patient. I always teach my residents and fellows essentially that there should not be overarching rules, but that one needs to determine that on a patient-by-patient basis.

So I personally don't agree with that particular statement myself based on my reading. But that's what was contained in Camilleri and Lacy's 2022 papers.

Q. If you look at the last sentence in that

paragraph, it says: "Because it can be difficult to distinguish from other conditions."

And you're referring to gastroparesis, true?

A. Correct.

Q. So "because it can be difficult to distinguish gastroparesis from other conditions -- "

A. Yeah.

Q. " -- especially functional dyspepsia --"

A. Yes.

Q. You say: "It is important to use confirmatory diagnostic testing." True?

A. True. But that doesn't refer to a gastric emptying study necessarily.

Q. There's other imaging studies we talked about besides gastric emptying studies, right?

A. Yeah, CT, ultrasound. Quite a variety.

Q. And it's important to use some form of imaging study because it can be difficult to distinguish gastroparesis from other conditions, true?

A. No, I didn't say imaging.

MR. BUXNER: Object to form.

THE WITNESS: I said confirmatory diagnostic testing. So that would mean lab values. It would mean a variety of different diagnostic tests. I'm not implying --

BY MS. FITZPATRICK:

Q. What lab values distinguish gastroparesis from functional dyspepsia?

A. It may be -- I can't tell you what the specific ones are that would make that distinction. It may be -- I don't know. In other words, I can't tell you a specific lab value off the top of my head that would do that.

But I specifically mentioned other diagnostic testing that could be confirmatory of one or the other.

The challenge is, is that functional dyspepsia is a diagnosis of exclusion. You see that in the literature over and over again.

And so, it's really important essentially to be able to, you know, understand that's a diagnosis of exclusion. There's the Rome criteria specifically for it. And so, the idea would be to do other testing, but not necessarily a gastric emptying study.

Q. Because it can be difficult to distinguish gastroparesis from other conditions, as you write --

A. Yeah.

Q. -- especially functional dyspepsia --

A. Yeah.

Q. -- it's important to use some kind of objective evidence. True? Whatever that form is?

A. Objective or subjective --

THE REPORTER: Wait, wait, wait.
THE WITNESS: Sure.
MR. BUXNER: Doctor, let her finish the question.
THE WITNESS: Oh okay.
MR. BUXNER: You're in the middle of her and then I can't get the objection.
THE WITNESS: Sorry.
BY MS. FITZPATRICK:
Q. I'll restate. Because it can be difficult to distinguish gastroparesis from other conditions, especially functional dyspepsia, it's important to use confirmatory objective evidence, whatever the form, whether that's diagnostic testing or imaging testing, it's important to have objective evidence, true?
MR. BUXNER: Object to form.
THE WITNESS: Either objective or subjective confirmatory diagnostic testing. It doesn't have to be objective.
BY MS. FITZPATRICK:
Q. What is a subjective diagnostic test?
A. Subjective diagnostic test might be palpation of a patient to determine whether or not there's bloating. It might be essentially listening for gastric sounds. It might be any number of different things that might not provide a specific number that's associated with it.

A. Correct.
Q. And the AGG -- AGA, right?
A. AGA, correct.
Q. And you make the point that not just the ACG, but the AGA also recognized the gastric emptying study as the most reliable method for objectively assessing gastric emptying, true?
A. I believe that's true.
Q. And the most reliable method for confirming the diagnosis of gastroparesis, true?
MR. BUXNER: Object to form.
THE WITNESS: I don't believe that it goes beyond assessment of gastric emptying. And so I don't believe that one can extrapolate that because it's the gold standard, which I believe it is for determining gastric emptying, that it is essentially the gold standard for making the diagnosis of gastroparesis. I think it's an important distinction.
BY MS. FITZPATRICK:
Q. Do you see where you wrote in your report just two months ago that both the ACG and the AGA recognize the gastric emptying study as the most reliable method for objectively assessing gastric emptying and confirming the diagnosis of gastroparesis; do you see that?
A. Assuming that one wants to have an objective

measurement to confirm gastroparesis, I believe gastric emptying is the best study. But that doesn't imply that I believe that gastric emptying is required to make the diagnosis of -- or a gastric emptying study is required to make the diagnosis of gastroparesis.

Q. But you recognize that the ACG and AGA do require objective evidence of gastric emptying for a diagnosis of gastroparesis, true? They use the word "objective."

MR. BUXNER: Object to form.

Go ahead, Doctor.

THE WITNESS: Right. I believe that when they're using the term "objective," that they are not restricting that to a gastric emptying study or a study that essentially gives you quantitative data, that I believe when they are using objective, that objective would also relate to information in the history and physical, patient presentation, temporal aspects as well.

BY MS. FITZPATRICK:

Q. Are you aware that the American College of Radiology published practice parameters for the performance of gastrointestinal scintigraphy?

A. Yes.

Q. You're a member of the American College of Radiology?

A. Yes. I'm a fellow of the American College of Radiology.

Q. The American College of Radiology is a credible, reputable organization, right?

A. I believe so.

Q. And the practice parameters from them are authoritative, right?

MR. BUXNER: Object to form.

THE WITNESS: I don't --

BY MS. FITZPATRICK:

Q. In the sense you gave before?

A. In the sense that I gave before that there can be multiple authoritative sources, but they are one authority that people look to essentially for guidelines.

Q. I'm handing you now what I've marked as Exhibit 4.

A. Do I have that?

THE WITNESS: I think I want to take a stretch break.

MR. BUXNER: Have we been going for an hour; do you know?

MS. FITZPATRICK: We could take a break.

MR. BUXNER: If it's good for you.

MS. FITZPATRICK: Yeah, that's fine.

MR. BUXNER: Great.

THE WITNESS: I'm not in the middle -- you're not

in the middle of a question, are you?

MS. FITZPATRICK: No.

THE WITNESS: Okay.

THE VIDEOGRAPHER: Off record, 11:22 A.M.

(Deposition Exhibit Number 4 marked for identification.)

THE VIDEOGRAPHER: On record, 11:35 A.M.

BY MS. FITZPATRICK:

Q. Doctor, do you see Exhibit 4? I've handed you Guidelines from the American College of Radiology on the performance of scintigraphy.

A. I do, yes.

Q. Okay. These are not guidelines on how to diagnose gastroparesis, true?

A. True.

Q. I've shown you guidelines from the Rome Foundation, from the American College of Gastroenterologists and from the AGA on gastroparesis, true?

A. You have.

Q. Those are all organizations of -- or that include gastroenterologists?

A. Yes.

Q. Can you point me to any guidelines from a radiology organization on how to diagnose gastroparesis?

A. No, there are no guidelines that I'm aware of that

specifically talk about diagnosing gastroparesis.

Q. From radiologists, right?

A. From radiologists. That would not be the type of guideline that radiology would typically issue.

Q. That's not the expertise of radiologists, true?

MR. BUXNER: Object to form.

THE WITNESS: The expertise of radiologists is very much in the area of diagnosis. But in general, the ACR guidelines are more specific to how to perform studies rather than comprehensively going into detail. The guidelines would be so incredibly expansive because there are so many different specialties that we cover.

So in general, they tend to limit themselves to guidelines on how to perform the study rather than how to make specific diagnoses with the study.

BY MS. FITZPATRICK:

Q. Radiologists can be experts in how to use imaging studies to diagnose diseases, right?

A. Right.

Q. Radiologists are not experts in diagnosing diseases without imaging studies, right?

A. I disagree with that.

MR. BUXNER: Object to form.

THE WITNESS: Oh sorry. I'll try to wait.

BY MS. FITZPATRICK:

Q. If you look at the guidelines that you have in front of you, these are done in conjunction -- not just the American College of Radiology, but also with the American College of Nuclear Medicine?

A. Correct.

Q. That's a credible, reputable organization?

A. I believe so.

Q. Are you a member of that one too?

A. I'm in the process of joining. There's another society called the Society of Nuclear Medicine and Molecular Imaging that I'm a member of. And I'd like to become a member of that society as well. ACNM.

Q. If you go to Page 7 --

A. In Exhibit 4, you mean?

Q. Yes. Under the heading Gastric Emptying, do you see that?

A. I do.

Q. Do you see that it says: "Evaluation of gastric motility utilizing a radiolabeled meal provides functional information that is indispensable in the management of patients presenting with various upper gastrointestinal signs and symptoms."

Do you see that?

A. I do.

Q. And the radiolabeled meal, they're describing a

gastric emptying study, true?

A. They are.

Q. And so what the American College of Radiology guidelines state is that gastric emptying studies provide information that is indispensable in the management of patients presenting with upper GI symptoms, true?

A. It is true that this -- that sentence that you just read is in the guideline.

Q. And you disagree because you think the gastric emptying study is not necessary, not indispensable, true?

MR. BUXNER: Object to form.

THE WITNESS: I believe that -- that a) they're not talking -- when they talk about indispensable in the management of patients presenting with various upper GI signs and symptoms, number one, they're not talking specifically about gastroparesis.

But number two, I would interpret this as a member of the American College of Radiology, as meaning that in managing patients who present with those, that a gastric emptying study is the study that would be best to determine gastric motility if that is thought to be required in the workup.

And so, I think this is really a statement that it's an indispensable study once the decision is made that a study is actually needed. That's how I would

and do interpret that.

BY MS. FITZPATRICK:

Q. You understand that indispensable means absolutely necessary, right?

MR. BUXNER: Object to form.

THE WITNESS: I don't understand that it means absolutely necessary. I think what they're saying is that other studies, such as a Capsule Study or a breath test study, et cetera, are not what they believe is the preferred study. And those other studies are dispensable, but that they believe and they agree with the other standards that you mentioned, in my own opinion, that it is the best and arguably indispensable gold standard for determining rate of gastric emptying.

BY MS. FITZPATRICK:

Q. So patients presenting with various upper GI signs and symptoms. That would include people with gastroparesis, true?

A. It would.

Q. Okay. And when they say that a gastric emptying study is indispensable to the management of those patients, you think they mean indispensable only if you've already decided to do some kind of study?

A. I know they mean that because otherwise, they would be suggesting that every one of those millions of

Q. If you turn back to your report, Exhibit 1, Page 17 --

A. Yes.

Q. -- in the first full paragraph a sentence in, do you see the sentence that starts -- two sentences in -- I apologize, one sentence in -- do you see the sentence that reads: "There is evidence that suggests that not all patients who experience symptoms associated with abnormal gastric emptying in fact have delayed gastric emptying as measured by gastric emptying study."

Do you see that?

A. I do.

Q. And you agree there is a evidence that not all patients treated with GLP-1 Receptor Agonists who experience GI symptoms in fact have delayed gastric emptying as measured by a gastric emptying study?

A. I believe that --

MR. BUXNER: Object to form.

THE WITNESS: Oh sorry. I believe that's the case.

BY MS. FITZPATRICK:

Q. I'm handing you now what I'll mark as Exhibit 8.

(Deposition Exhibit Number 8 marked for identification.)

BY MS. FITZPATRICK:

Q. Do you recognize this as a publication by a Dr. Lupianez-Merly among others that you cite in your report?

A. Yes.

Q. This publication by Dr. Lupianez-Merly is a piece of evidence that not all patients treated with GLP-1 Receptor Agonists who experience GI symptoms in fact have delayed gastric emptying as measured by a gastric emptying study?

MR. BUXNER: Object to form.

THE WITNESS: I'm not sure I understood the question. Sorry.

BY MS. FITZPATRICK:

Q. We looked at your report --

A. Right.

Q. -- where you made the statement that there's evidence that suggests that not all patients on GLP-1 RAs who experience GI symptoms actually in fact have delayed gastric emptying once they go get a gastric emptying study. We saw that in your report, right?

A. Right.

Q. You cite this publication by Dr. Lupianez-Merly, right?

A. I do.

MR. BUXNER: Object to form.

BY MS. FITZPATRICK:

Q. And so, I'm just confirming that this publication by Dr. Lupianez-Merly is the evidence you're pointing to or some of the evidence you're pointing to that not all patients on GLP-1 RAs who experience GI symptoms in fact have delayed gastric emptying?

MR. BUXNER: Object to form.

THE WITNESS: I think you're asking the question about whether or not this was the study that I was -- and paper, even though it's not peer-reviewed that I was referring to in my report. The answer is yes.

BY MS. FITZPATRICK:

Q. And so, this paper is evidence that not all people taking GLP-1 Receptor Agonists who have GI symptoms actually have delayed gastric emptying, right?

MR. BUXNER: Object to form.

THE WITNESS: I think it really depends. I think there are a lot of limitations of this particular paper. But I was citing this as one of the articles in the literature that support that suggestion, yes.

BY MS. FITZPATRICK:

Q. And you understand that this paper looked at 696 patients on GLP-1 Receptor Agonists who had GI symptoms and a standard gastric emptying study, right?

A. Right.

Q. And only -- scratch that.

455 out of those 696 turned out to have normal gastric emptying studies, true?

A. I -- I'd have to make sure that that's -- those figures are right, but -- so maybe we could do that again because I'd have to look at the numbers. I didn't memorize the numbers.

Q. So if you look in the results -- do you see the Results section?

A. Uh-huh. 80,000 patients --

Q. Yeah.

A. -- were prescribed.

Q. So they start with a bigger population and then whittle it down, right?

A. Yeah.

Q. That's common, right?

A. Uh-huh.

Q. Is that a "yes"?

A. Yes, I'm sorry.

Q. And then, they write: Among these -- "Among those 696 underwent validated gastric emptying study."

Do you see that?

A. I do.

Q. So they're talking about 696 patients who had been prescribed a GLP-1 RA and developed at least one GI symptom suggestive of gastroparesis. Do you see that?

A. I do.

Q. Okay. And then, of those 696 only 35 -- I'm sorry. Only 35 percent of them had a delayed gastric emptying at four hours by study, right?

A. Right. In other words, the numbers that you're quoting from the paper are what is indeed in the paper. I don't believe the paper is valid or changes my mind significantly. But it is evidence that is supportive of that idea, which is why I cited it in my report.

Q. Okay.

A. I think there are multiple major limitations to the study.

Q. This is the only study that you cite of patients on GLP-1 Receptor Agonists with symptoms getting tested for delayed gastric emptying, true?

MR. BUXNER: Object to form.

THE WITNESS: To my knowledge, that's the only one that I included.

BY MS. FITZPATRICK:

Q. And it's the only --

A. I'm not sure if I included any other. I'd have to look. But this is a paper that I really think is fundamentally flawed.

Q. So my question is: You cite one paper and one paper only of people on GLP-1 Receptor Agonists with GI

But I believe that I would be able to write guidelines about the diagnosis just looking at the diagnostic part, not the therapeutic part, as well as gastroenterologists.

Q. You reviewed Dr. Cangemi's 2023 study --

A. Yes.

Q. -- titled: "Misdiagnosis of Gastroparesis is Common." Do you remember that?

A. I do. That was Mayo Jacksonville. Was it? It was Mayo.

Q. It was Mayo, correct.

A. Yes.

Q. I'm handing you what I'll mark as Deposition Exhibit 7 or 8.

(Deposition Exhibit Number 9 marked for identification.)

THE WITNESS: Thank you.

BY MS. FITZPATRICK:

Q. This is the paper we just referred to, correct?

A. Right. They refer to it as a research letter, but yes.

Q. Mayo Clinic is a prestigious medical institution, true?

MR. BUXNER: Object to form.

THE WITNESS: Very true.

BY MS. FITZPATRICK:

Q. Do you know Dr. Cangemi personally?

A. No.

Q. Do you know him by reputation?

A. Yes.

Q. You agree he's a well-respected gastroenterologist?

A. I do agree with that.

Q. And you agree there's been reports that gastroparesis is misdiagnosed, true?

A. True.

Q. And that misdiagnosis of gastroparesis is common; you've seen that literature?

A. I have seen that literature. I don't know how common it is because one really needs to have a consensus of what gastroparesis actually is. But I would not be surprised if gastroparesis is misdiagnosed in some cases.

Q. You wouldn't be surprised if misdiagnosis was common of gastroparesis?

MR. BUXNER: Object to form. Misstates.

THE WITNESS: I think it depends on based on my own definition or somebody else's definition or -- I do believe that gastroparesis is often misdiagnosed based on what I've read.

BY MS. FITZPATRICK:

Q. If you look at the first page on the left, do you see that it says: "We assembled a retrospective cohort population -- "

A. Yes.

Q. " -- consisting of adult patients referred to Mayo Clinic Jacksonville -- "

A. Yeah, it was Jacksonville, okay.

Q. " -- specifically for the evaluation of gastroparesis." And then it gives the dates.

A. Yes.

Q. Okay. You understand that Dr. Cangemi and his co-authors looked at the files of 339 patients referred to the Mayo Clinic in Jacksonville who all had gastroparesis diagnoses before their referral, right?

A. Actually, on a careful reading of the paper, it's not clear that they all did have that. In other words, it actually specifically says 339 patients were referred for tertiary evaluation of gastroparesis.

That doesn't necessarily mean to me -- it just stuck out in my mind when I read it that it really doesn't mean that they were already carrying a diagnosis, but they were referred for evaluation. And so, it's not clear to me in the paper that they actually had a diagnosis of gastroparesis when they came.

Q. If you look at the supplementary table -- if you

to bear out on what was in the article.

BY MS. FITZPATRICK:

Q. So your argument that I'm hearing is that --

A. If I had to bet, I would bet --

Q. You think that -- sorry.

MR. BUXNER: You guys are talking over each other.

BY MS. FITZPATRICK:

Q. You think the title of this research letter does not correspond to the actual content of the study that was done?

A. I think --

MR. BUXNER: Object to form.

THE WITNESS: I think, as is true of so many articles that I've read, casual reading of the title does not really necessarily hold up into a deeper understanding of the methodology. And I would really be surprised if all of these patients essentially had been diagnosed as having gastroparesis and they were just sent to Mayo Clinic to reevaluate them to see whether they had gastroparesis or not.

I believe that they were referred for -- I believe they were referred to Mayo Clinic with the question still about their final diagnosis, knowing how things work.

BY MS. FITZPATRICK:

Q. You agree, though, that a reasonable inference of reading this paper is that 339 people received diagnosis of gastroparesis before they ever got to Mayo?

A. Unfortunately --

Q. You --

MR. BUXNER: Hold on for one second, Doctor.

Are you done with your question?

MS. FITZPATRICK: Yes.

MR. BUXNER: Object to form.

Go ahead.

THE WITNESS: Unfortunately, I believe that -- that people may infer that. But on carefully reading the article, I'm not convinced that that's the case.

BY MS. FITZPATRICK:

Q. You see that Dr. Cangemi found that only 19.5 percent, he writes, if you look at that section where we were --

MR. BUXNER: Where were we? Can you orient? Do you mind?

MS. FITZPATRICK: Yeah.

BY MS. FITZPATRICK:

Q. If you go back to Page 2 on the right, the paragraph starting "In summary." Do you see that, Doctor?

A. Two on the right starting "In summary," yeah.

Q. It says: "In summary, more than 80 percent of

patients referred for further evaluation of gastroparesis ultimately received alternative diagnoses."

Do you see that?

A. I do. And it's interesting. When it says further evaluation, that suggests to me that a diagnosis was not made actually because it wasn't for treatment of gastroparesis. It was for further evaluation.

So that would support my suspicion that the title actually is -- that inference that you would have made from the title is actually not accurate.

Q. You agree that the Mayo Clinic people refer them to try to figure out a treatment for gastroparesis?

A. And to diagnosis, both.

Q. Okay. So these could be people who were referred to them to evaluate them for treatment, and in the course for evaluation, they did a more careful gastric emptying study, true?

MR. BUXNER: Object to form.

BY MS. FITZPATRICK:

Q. That's entirely possible?

A. I think it's possible, but not likely.

Q. Do you see that Dr. Cangemi writes: "Our findings reaffirm guidelines noting -- " down further in that paragraph.

A. I do.

Q. "Our findings reaffirm guidelines noting that gastroparesis cannot be diagnosed based on symptoms alone."

Do you see that?

A. I see that sentence, yes.

Q. You agree that gastroparesis cannot be diagnosed based on symptoms alone?

MR. BUXNER: Object to form.

THE WITNESS: That's what I've been pretty much saying all day, yes, absolutely. I don't believe that symptoms alone without any other information would allow one to make that the diagnosis.

The other thing that I think is really important to point out is that this is --

BY MS. FITZPATRICK:

Q. There's no question pending.

MR. BUXNER: No, no, he's -- there is a question. He's explaining his answer. He has a right to explain it as an expert.

Go ahead, Doctor.

MS. FITZPATRICK: You will have your own opportunity.

MR. BUXNER: No, he's in the middle of a sentence and you cut him off in response to your question.

MS. FITZPATRICK: Because it was a non-responsive sentence. The other thing I think is important to note

is literally what he was saying.

MR. BUXNER: Right. He's explaining it.

You can finish your answer, Doctor.

BY MS. FITZPATRICK:

Q. Let's hear it. Let's hear how responsive it is.

A. Right. So what I was going to say is that it's important to point out that my understanding of this study was that it was not conducted on a patient population with GLP-1 Receptor Agonists, but it was conducted on a patient population that had general symptomatology associated with it without mention in here of this being a GLP-1 receptor agonist study.

Q. What was my question, Doctor?

A. It's been awhile since we talked, so I'd be happy to have that played back.

Q. If you turn back to the supplementary material in the Supplementary Methods; do you see that section?

A. Supplementary Methods. The several sentences on -- I guess what's that, Page 2672.e1?

Q. Yes.

A. Yes.

Q. First, you understand these are patients referred to Mayo and Mayo's been asked to consult. Whatever they've been asked to do, it definitely falls under the word "consult," right?

A. Correct.
Q. Okay. So the Mayo doctor's the consulting provider, right?
A. Correct.
Q. Okay. And do you see that it says: "If a gastric emptying scintigraphy Study was recommended by the consulting provider." Do you see that?
A. I do.
Q. Okay. And so you understand that Mayo did their own scintigraphy of the patients who had been referred to them, true?
A. True. I would infer that from the paper or the, I guess, letter.
Q. Doctor, you're not aware in your experience of any patient with gastroparesis diagnosed without some kind of study that you categorized in your report as an imaging study, right? In your personal experience, that hasn't happened?
MR. BUXNER: Objection to form.
THE WITNESS: I'm sorry, I don't understand that question.
BY MS. FITZPATRICK:
Q. Sure. You have no personal experience of a patient being diagnosed with gastroparesis without one of the studies that you categorized as imaging studies in your

occasions."

Do you see that sentence, Doctor?

A. I do.

Q. Okay. My first question, Doctor: Generally speaking, what was your role in diagnosing those 100-plus patients that you discuss in that paragraph?

MR. BUXNER: Object to form.

Go ahead.

THE WITNESS: My role is as a nuclear medicine physician and radiologist.

BY MR. PRZYMUSINSKI:

Q. Well, okay. I understand that's your specialty and your training, but specifically in the context of these patients, what was -- what aspect of diagnosis were you engaged in when you said you have diagnosed gastroparesis in these 100-plus occasions?

MR. BUXNER: Object to form.

THE WITNESS: I think what you're asking is -- and tell me if I'm wrong -- what information did I use in order to diagnose gastroparesis? The answer really is information that's provided in the clinical indication for the study, plus information that's in the patient's chart, plus information that we have in discussion with patients when we have additional questions, plus the results of the gastric emptying study that I

interpreted.
BY MR. PRZYMUSINSKI:
Q. Okay. So in all 100 -- or 100-plus of these occasions, you would have been relying on information that was provided to you by the treating physician and other information that you had and then interpreting the results of the gastric emptying study; is that correct?
MR. BUXNER: Object to form.
THE WITNESS: I would have been relying on information from the chart, the patient, the referring physician and any information that I would get from my technologist, my radiology resident or radiology fellow, plus the study that I'm interpreting, plus all the studies that the patient had in the department, plus any previous gastric emptying studies that the patient may have had.
BY MR. PRZYMUSINSKI:
Q. Okay. But in all of the at least 100 occasions we are talking about, there would have been a gastric emptying study conducted that you in your role as a radiologist and nuclear medicine specialist would have been interpreting; is that correct?
A. Correct. That's how I would have had those patients referred to me by their providers.
Q. Okay. So none of the 100 cases or at least 100

cases we are talking about here involve a diagnosis of a patient with gastroparesis without conducting a gastric emptying study, correct?

A. That's correct. Pretty much, by definition, since they find their way to me because I perform that interpretation and that diagnostic study and service, then yes. I don't see patients outside of that context. Or at least I haven't.

I changed my career, as you may have heard early -- earlier in the day, but up until when I quote/unquote retired from University of Maryland and the VA, even though I still work for of them to some extent, in general the patients referred to me came by way of diagnostic studies that were interventional studies that I performed on patients.

Q. So Doctor, is it also fair for me to conclude from that that you have never personally diagnosed a patient with drug-induced gastroparesis; is that correct?

MR. BUXNER: Object to form.

THE WITNESS: I'm not sure what you mean by personally. So let's talk a little bit about personally. So I mean, anytime I make a diagnosis, it's personally.

I think what you may be saying is have I diagnosed patients outside of my role interpreting gastric

emptying studies? Because when you say personally, please help me understand what you mean by that.

BY MR. PRZYMUSINSKI:

Q. Well, let's back up then. In your report, you describe that you've diagnosed gastroparesis on at least a hundred occasions, correct?

A. Correct.

Q. And I thought what you told me that is in every one of those cases, you diagnosed gastroparesis in the context of conducting a gastric emptying study or Scintigraphy. Am I wrong?

A. You are correct.

Q. Okay. Are you saying there's some other subset of gastroparesis diagnosis beyond these you discuss here that you have made as well?

A. Yes. So -- so I have. But I just want to say that I consider that I diagnosed all of those patients personally when I do of gastric emptying studies. But I've also diagnosed gastroparesis on CT scans, I've diagnosed gastroparesis on X-ray studies, on ultrasound studies, and on MR studies as well.

Q. Are those in addition to the 100 occasions you describe here or is that part of the at least hundred occasions you discuss here?

A. In addition to.

Q. Okay. Have you ever diagnosed a patient, diagnosed, given a formal diagnosis to a patient of drug-induced gastroparesis?

A. Of drug-induced gastroparesis. I have not because patients who are essentially on drugs would not be referred to me for nuclear medicine studies.

Q. Okay. So you have never diagnosed a patient as having GLP-1 Receptor Agonists or GLP-1 RA-induced gastroparesis; is that correct?

A. I have. But it's been in the context of imaging studies and in the context of my practice as an interventional radiologist and in the context of gastrointestinal studies and other studies that I've done.

Q. Just a second ago you told me you have never diagnosed a patient with drug-induced gastroparesis because that's not how patients come to you.

A. For -- for a Gastric Scintigraphy.

Q. How then are you --

THE REPORTER: Um-umm.

THE WITNESS: Oh I'm sorry.

THE REPORTER: Wait, wait. Stop.

BY MR. PRZYMUSINSKI:

Q. How then did you diagnose a patient with GLP-1 RA-induced gastroparesis?

MR. BUXNER: Lucas, it's Evan. Can you restate

that because there was talking here right while you were talking.

MR. PRZYMUSINSKI: I sure will, Evan. Let me strike that question and start again.

BY MR. PRZYMUSINSKI:

Q. You told me, Doctor, that you have never formally diagnosed a patient with drug-induced gastroparesis in your practice. How is that statement consistent with you now telling me that you have diagnosed patients with GLP-1 RA-induced gastroparesis?

A. The way it's consistent is that I don't always know when I'm doing a X-ray study or a CT scan or an MR what the patient's medications are. I just know that in the context of doing gastric emptying studies where the purpose of the study is specifically to come up with an objective number to be able to quantify gastric emptying.

In those other studies, we don't have the same requirement that patients be off their medications.

And so, I believe that there are patients who have been referred to me where I've read their CT scans or other studies where they've been on a GLP-1 agonist. But there are no cases that I can recall of where the indication for a study was a patient with GLP-1 -- on a GLP-1 agonist to find out whether or not they had delayed gastric emptying for those other types of studies. Does that make sense?

differential?

A. Yes.

Q. You need to do some additional testing to evaluate the cause of what you saw on the scan, correct?

A. Correct. But I would not have suggested a gastric emptying study because the CT has established that there is a huge amount of food and fluid within the stomach. I think a gastric emptying study would be contraindicated in that particular patient.

Q. All right. Outside of that one example, Doctor, can you recall any other example where you diagnosed -- formally diagnosed, i.e. called the patient or called the treating physician or their resident and said I diagnosed your patient with GLP-1 RA-induced gastroparesis?

A. You mean with a gastric emptying scintigraphy Study or a non-gastric emptying scintigraphy Study?

BY MR. PRZYMUSINSKI:

Q. In any way, Doctor.

A. Yeah. So I can recall times when we've called and mentioned that we thought the diagnosis or our diagnosis was gastroparesis. But I don't recall patients who are on GLP-1 Receptor Agonists being referred to us.

The clinicians who refer patients to us do not refer patients for evaluation of GLP-1 Receptor Agonists for all the reasons we've been talking about today, I believe.

Q. So the answer to my question is "no," correct?
MR. BUXNER: Object to form.
THE WITNESS: If you could restate your question.
BY MR. PRZYMUSINSKI:
Q. Sure. What I --
A. I'm just trying to --
THE REPORTER: Wait, wait, wait.
THE WITNESS: I'm sorry. Go ahead, please.
THE REPORTER: One at a time.
BY MR. PRZYMUSINSKI:
Q. I was going to restate the question, if that's okay. The question I had was: Have you ever formally diagnosed a patient with GLP-1 RA-induced gastroparesis? And you gave me an answer. And I thought that answer was "no." Is that correct?
A. That's correct.
Q. Okay. Now, Doctor, in your report and this morning with -- over the course of, I don't know, three, three and a half hours of this deposition, you talked about the fact, in part at least, that it's your opinion that drug-induced gastroparesis can be diagnosed without the use of objective diagnostic testing, including specifically without the use of scintigraphy; is that correct?
MR. BUXNER: Hold on for a second. Can you repeat it, Lucas? I apologize. I just had trouble hearing

you. It got muddled in the middle.

MR. PRZYMUSINSKI: Okay. Let's try again.

BY MR. PRZYMUSINSKI:

Q. Doctor, in the morning section of your deposition and certainly in your report, we talked about the fact that part of the opinion you're offering, perhaps the main part, is that the diagnosis of gastroparesis can be made without the need for specific diagnostic testing, including specifically without the need for performing gastric emptying study, correct?

A. Correct.

Q. And I assume part of that opinion is that you believe that a diagnosis of drug-induced gastroparesis can be made in a similar manner, correct?

A. I believe that a diagnosis of drug-induced gastroparesis can be made looking at the temporal proximity of a drug and all of the other signs, symptoms and studies that are available to us in the patient's history, yes.

Q. Yes. So it can be made without the need for diagnostic testing, including specifically without the need of scintigraphy, correct?

A. Specifically, scintigraphy. As far as diagnostic testing, that really would vary from patient to patient. I don't want to make a blanket statement that I want to diagnose gastroparesis without any diagnostic studies of any

type imaging or otherwise. I think that would be too sweeping.

Q. Fair enough.

At least within the context of drug-induced gastroparesis, it's your opinion that you can reliably make that diagnosis without some form of gastric emptying study, correct?

A. Correct.

Q. Okay. And presumably, that opinion also applies specifically to GLP-1 RA-induced gastroparesis, correct?

A. It would apply to others, but it would also apply to GLP-1 Receptor Agonists.

Q. It's part of the subset, right? Part of the subset of what you view as gastroparesis, correct?

A. Correct.

Q. Okay. But you also agree with me, Doctor, that at least in your own practice, you've never actually diagnosed drug-induced gastroparesis in this manner, correct?

A. I'm constantly diagnosing drug -- I'm constantly diagnosing gastroparesis. I don't always -- I don't have the history of whether or not a patient is on a GLP agonist, but I still diagnose gastroparesis.

And so, in the case where I'm doing a gastric emptying study, those questions are explicitly asked. And so for those studies, I don't have studies that I diagnose

because those patients do not get gastric emptying studies.

Q. Ultimately, Doctor, the methodology that you describe for diagnosing drug-induced gastroparesis, whatever your opinion is about the reliability of it, it's not a methodology you've ever actually done to formally diagnose a patient, correct?

MR. BUXNER: Object to form.

THE WITNESS: Yeah. I guess -- I think what you're saying is similar to the questions you've been asking; and that is, I work in the context of my role as a radiologist and nuclear medicine physician. And so, the patients that I see in that particular role until now that I've changed to become an oncologist, in that particular role are exclusively patients who have been referred for either one type of imaging study or the other or a consultation related to those imaging studies.

BY MR. PRZYMUSINSKI:

Q. Doctor, I think you talked a little bit about the fact that it's important to understand the history and physical for patients and sort of their global medical history when making a diagnosis, correct?

A. Correct.

Q. Okay. Now, I think from the discussion we just had, you also would acknowledge that when a radiologist

receives information on the history and physical findings of a patient, it's often incomplete. For example, as you said, you may not know specifically what medications they're on, correct?

A. It is often incomplete, which is why I ask my residents and fellows to look through the chart and to talk with the referring physicians to make that as complete as possible.

Q. But you yourself acknowledge a lot of the time you don't even know whether a patient was on a GLP-1 medication when you were doing the study, correct?

MR. BUXNER: Object to form.

THE WITNESS: So I think we are -- I'm trying to find out whether we are focusing on gastric emptying scintigraphy or all imaging studies that one may perform.

BY MR. PRZYMUSINSKI:

Q. I'm just asking about your job as a radiologist and what information you're provided when you're making your own assessment of the radiographic study, regardless of if it's a GES, an X-ray, a CT scan, MRI, a PET scan. In any of the situations, you don't have the full physical history information that the treating physician has, correct?

MR. BUXNER: Object to form.

THE WITNESS: So the type of information I have

depends on the type of study that I'm doing. And so, we actually have a much more structured mechanism for being able to obtain that type of information on patients where there's a referral for quantitative gastric emptying studies that goes above and beyond the type of history that I might take if I'm doing abdominal radiographic, for example.

And so, it really varies depending on the type of study.

So if you're asking the question do I have as much information available to me as my colleagues, the answer is yes from the Electronic Medical Record. If you ask me, have I talked with the patient before the patient came to the imaging department, as much as the gastroenterologist, the answer in most cases is probably no.

But I think the histories that we are able to get nowadays, given that we have access to the Electronic Medical Record is probably comparable to what the referring physicians have access to.

BY MR. PRZYMUSINSKI:

Q. That actually brings up a point that I wanted to ask about.

So let's talk about these patients that came to your radiology department for a gastric emptying

scintigraphy study. Okay?

A. Yes, okay.

Q. And I think you mentioned that for most of the actual procedure is being done by technicians, correct?

A. So the procedure itself as far as injecting the radiopharmaceutical, as far as putting the patient under the imaging system, as far as scanning and obtaining the image and sending the images, that's all done by the -- they prefer to be referred to as technologists.

Q. Okay. So for the 100 patients or so you describe as having diagnosed with gastroparesis in your report, for any of those patients, did you yourself put your hands on the patient and actually do a physical examination?

A. So in a subset of those patients, I've talked with the patient. But it's a relatively small subset. In a larger subset of the patients, my resident or fellow has talked with the patients. And in a hundred percent of the cases, our technologist has talked with the patients in detail. And so, any --

Q. Well, I asked about performing a physical exam, Doctor, not talking to them.

So the question on the table was: How many of those 100-plus cases did you actually perform a physical examination of the patient?

MR. BUXNER: Object to form.

THE WITNESS: It would be a tiny number of those when I was doing interventional radiology as an interventional radiologist. Then I did do a physical examination prior to performing procedures on the patient.

BY MR. PRZYMUSINSKI:

Q. Well, but I wasn't asking about procedures. I was asking about the patient you said you diagnosed with gastroparesis.

Of those patients, how many did you perform a physical examination on, put your hands physically on the patient and examine the patients?

MR. BUXNER: Object to form. Asked and answered.

Go ahead, Doctor.

THE WITNESS: I did not perform a physical examination on any of those patients.

BY MR. PRZYMUSINSKI:

Q. Okay. What percentage or those 100-plus patients do you think you personally took a medical history from?

A. I would say probably closer to 5 percent. But I had access to the medical history and the physical results on all the patients. I just didn't do the exam myself.

But I don't believe that my physical exam and history would necessarily be better than the one that's documented in the chart by my fellow clinician colleagues.

Q. Doctor, for those 100-plus patients that you describe as having diagnosed with gastroparesis, after you reviewed their results of the scintigraphy study, did you then go talk to the patients and inform them of your diagnosis?

MR. BUXNER: Object to form.

THE WITNESS: The answer is in the majority of cases, those patients had already left the imaging department by the time that I reviewed the study. So I would have talked to them before my resident would have talked with them before, the technologist would have talked with them until they -- until they left the department.

BY MR. PRZYMUSINSKI:

Q. What I'm asking, Doctor, would you have after you did the study called the patients, reached out to the patient, say, hey, I reviewed your history, your physical examination, findings and your study results and I diagnosed you as your doctor with gastroparesis? How often did you do that?

A. I'm not sure what you mean by as your doctor.

But the answer is, if we have findings that are significant or important to the patient, then we have the fellow or resident call the referring physician. When we are not able to contact the referring physician, then we

THE WITNESS: It doesn't change my opinion that long-acting GLP-1 Receptor Agonists also cause delayed gastric emptying.

BY MR. PRZYMUSINSKI:

Q. Okay. Doctor, slight shift, but still in the same area. So we've been talking about delayed gastric emptying, right, and we've been talking about your opinions with respect to the effect of GLP-1 medicines on gastric emptying.

I want to go a little bit broader than that and ask you the following question: Is it your opinion that any medication that prolongs gastric emptying or slows gastric emptying is capable of causing gastroparesis?

MR. BUXNER: Object to form.

THE WITNESS: I don't know exactly what you mean by any medication. But I would say in general that medications that slow down gastric emptying would fall into the criteria that I would have for a drug-induced gastroparesis without it necessarily being limited to GLP-1 Receptor Agonists.

For example, opioid medications, one could have -- and the literature has consistently essentially mentioned opioids as one of the causes of drug-induced gastroparesis.

BY MR. PRZYMUSINSKI:

Q. Is there any distinction in your mind then, Doctor, between a medication causing a delay in gastric emptying and a medication causing gastroparesis?

MR. BUXNER: Object to form.

THE WITNESS: Yes, I think they're two different things because you can -- a medication can delay gastric emptying without being associated with significant GI symptoms. And so, I don't -- I would not equate gastroparesis with a delay in gastric emptying.

BY MR. PRZYMUSINSKI:

Q. How would a medication delay gastric emptying but not cause gastric symptoms?

A. I believe that the delay in gastric emptying is a huge spectrum from one medication to the other. That -- that spectrum changes over time. You mentioned the idea of being on the medication, reducing the amount of delay in gastric emptying. And so, I believe that it really depends and that there's a significant spectrum.

Q. Okay. So the -- I'll use a loose term and you can make it more precise. The magnitude of the -- (inaudible)

THE REPORTER: Wait, wait, wait. We've got to start that over.

MR. PRZYMUSINSKI: Do you want me to start over?

THE REPORTER: Yeah.

MR. PRZYMUSINSKI: Okay. That's not a problem.
BY MR. PRZYMUSINSKI:
Q. So I used the looser term -- and you can make it more precise -- use better language than I can because you're the expert. But is it fair to say that the magnitude or the nature of the impact on gastric emptying that an individual medication has may make it more or less likely to result in GI symptoms related to that effect?
MR. BUXNER: Object to form.
THE WITNESS: Yes, I think that's fair.
BY MR. PRZYMUSINSKI:
Q. Okay. And so, just the fact that a medication delays gastric emptying alone is not sufficient to conclude that it causes gastroparesis; is that correct?
MR. BUXNER: Object to form.
THE WITNESS: Not in isolation, but in each individual patient, when considering the patient's symptoms, history, other medications that they're on, co-morbidities, et cetera.
BY MR. PRZYMUSINSKI:
Q. Doctor, please tell me if this is not something you're familiar with. But with respect to symptoms like nausea and vomiting, are you familiar with the fact that medications can have impacts that are essentially mediated, meaning at the brain level, that can cause nausea and

vomiting in patients without actually having direct effects or the stomach or musculature or nerves?

A. I'm not aware of specific medications. For example, I'm aware that there are medications that have an impact on CNS in addition to actually delaying gastric emptying, such as the GLP-1 agonists. If there are medications that only operate at a CNS level, then I'm not clear on specifically what those are.

For example, opioids operate at multiple different levels. So you'd have to have something that would be specific to CNS. But yet, there are neural cells throughout the body. And so, I think it would be very difficult to find an isolated medication that would only impact the central nervous system without having an impact on the peripheral nervous system now that we know even with a gut biome, essentially that there's so many quote/unquote aspects of the peripheral nervous system that are mediated.

Q. Well, this is why I go to the expert who said it a lot better than I did. So let's take the example of GLP-1s which you just brought up that can have affects on gastric emptying, but they can also have affects essentially within the brain, correct?

A. I wouldn't make that necessary distinction. In other words, I think that what you're saying is correct, but in addition to that, they can have an impact on the brain

that secondarily has an impact on gastric emptying mediated, say, by the say vagus nerve, for example.

Q. So there's a number of options. You can have a direct effect on gastric emptying. You could have the stomach and muscular nerve level. You could have an effect that's central that's independent of gastric emptying. You have an effect on the central level that could then have a downstream effect on the stomach itself on gastric motility or some combination of all of those, correct?

MR. BUXNER: Object to form.

THE WITNESS: One thing I want to be really careful about is that I don't get into causation. And the questions that you're asking are sounding increasingly like causation. You may disagree with that, but to me -- and maybe I just don't understand causation.

BY MR. PRZYMUSINSKI:

Q. No, no, no. I'm not asking causation at all, Doctor. So sorry. It's really about the question really boils down to, we are talking about how medications can have -- and I said it could be anything. I don't care about GLP-1s.

THE REPORTER: Wait, wait, wait, Lucas.

MR. BUXNER: Court reporter lost you.

MS. FITZPATRICK: Start over.

MR. BUXNER: We all did.
BY MR. PRZYMUSINSKI:
Q. Okay. So I don't want to adopt the causation. I think we've done that already. That's why I said I don't need to pick GLP-1s. You mentioned GLP-1. That's the only reason I came to it. I was just talking about medication is generally.
And the concept I'm trying to make sure I understand is, is it fair to say that certain medications can have an impact on gastric emptying directly, can have an impact potentially at the CNS at the brain level, and potentially then, as you said, as the third option, the effect at the CNS level could then feed back to the stomach directly through the vagus nerve or otherwise. Is that fair?
MR. BUXNER: Object to form.
THE WITNESS: You're asking about drugs or medications in general. And I believe the answer to that --
BY MR. PRZYMUSINSKI:
Q. In general.
A. -- is yes.
Q. Okay. And so, if there are multiple ways which a medication can contribute to GI symptoms, such as nausea and vomiting, and if you said just the fact that a medication

delays gastric emptying is not enough to conclude that it's causing gastroparesis, how can you conclude just based on the fact that you have a medication that doesn't delay gastric emptying and you have symptoms, that those symptoms relate to gastric emptying and not have some other effect of the medication that's contributing to nausea and vomiting?

MR. BUXNER: Object to form and scope.

THE WITNESS: You're asking about all drugs; is that correct?

BY MR. PRZYMUSINSKI:

Q. Any drugs.

A. Or are you asking about --

Q. Any drugs that's got multiple effects at different levels related to nausea and vomiting.

MR. BUXNER: Object to the form of the question. And I think it's outside the scope of his report. It seems like you're asking pharmacology.

If you understand it, go ahead, Doctor. But --

MR. PRZYMUSINSKI: Well, not really, Evan. Because what I'm asking about is a methodology that purports to be able to diagnose gastroparesis based solely on symptoms without direct evidence of delayed gastric emptying. And so, I'm trying to understand how he diagnosed gastroparesis based purely on a general understanding that these medicines may delay gastric

in that particular way and get the gastric emptying studies. And one would also have to have a nuclear medicine department. I mean, it's one thing to get the IRB approval, but then you'd have to have a nuclear medicine department that would be willing for quote/unquote research purposes to essentially violate what the guidelines suggest and all the reasons that one would not do that in that department.

So theoretically, if one could find the right IRB to approve it, theoretically if one could find a department that would actually do the study, then the answer is one could do that research project. But I know I would not have an easy time.

Q. Didn't the Mayo Clinic do exactly that study, Doctor?

A. So Mayo Clinic did that with liraglutide, but Mayo Clinic is a much more captive, essentially -- in other words, it's an internal system. At the VA, for example, we have University of Maryland that makes decisions about IRB.

So I just think logistically it would be difficult. I don't know how hard it was and how many years it took them to their IRA to actually approve to that -- of that. I don't know -- if the researchers were part of the nuclear medicine department, then that may have made it easier to get that done.

So I think hypothetically, what you're saying is a

study that could be done. I just know that if I wanted to do that study, I would have a very difficult time in 2025 in doing that and finding the department.

Q. And that's fair, Doctor.

But we also I think agreed that you're not aware of any study that has taken your diagnostic methodology predicated on symptoms and history and tested how reliable it is in predicting the extent of delay in gastric emptying, correct?

A. Correct. I mean, I would, through inference of other data that I've seen and what I've read, you know, believe that that study would be of limited value. But I have not seen that particular study done, nor would I feel as though I would want to conduct it.

Q. So because the study hasn't been done, we actually cannot predict what the error rate is of your methodology, meaning how many times out of a hundred -- if the physician says I think this patient has drug-induced gastroparesis based on their presentation, how many times of out of a hundred they're actually right and how many times out of a hundred they're wrong, correct?

A. So without doing the study, would one would not be able to come up with that quantitative data. I can tell you our gastroenterologists at the University of Maryland and Department of Veterans Affairs are not asking us for gastric

emptying studies clinically. They're making the decision themselves -- not me, they're making the decision that they can take the patients off the medications without doing a gastric emptying study.

And so, you know, to answer your question, if you wanted that -- the quantitative data, you'd need to do the study, you're right.

Q. Also, Doctor, tell me if I'm wrong, right? So clinical medicine, right? Let's say you are -- let's say I'll see a patient, right? And I put that patient on some medication. Let's not talk about GLP-1 so we don't get into causation. All right? And I give the patient a medication. And a week later they come back and they have a side effect. Right? Or they report a side effect. They have some experience, whatever it is, right? Then as a physician, what I would do, right, is I would say, okay, is this a side effect that potentially could be related to this medication? If the answer to that is no, in my experience and everything I read, no, that's one thing. But if I think it could potentially be related, then I say, okay, maybe we will stop the medication, I'll reduce the dose and see what happens, right? That's a pretty common thing physicians do?

A. Agree.

Q. Okay. And if the symptom resolves, right, goes away, either with dose reduction or cessation, you say,

well, probably whatever your side effect you acknowledge was related to the medication. If it doesn't, you say maybe it wasn't the medication, maybe it's something else, correct?

MR. BUXNER: Object to form.

THE WITNESS: And you would write a note in the chart based on your best diagnostic acumen as far as what you believed was the reason that the patient's symptoms improved when you withdrew the drug.

In most cases, I would assume you would document in the chart that you believe that it was drug-induced for whatever -- if we are looking at gastric emptying or whatever. And so --

BY MR. PRZYMUSINSKI:

Q. Yeah. Here's the thing, Doctor, patients don't come in to you complaining of delayed gastric emptying. They come in to you saying I'm nauseous and I'm vomiting. Right? And so, as a physician, you stop the medication and say if they have nausea and vomiting, if it goes away, I could care less what the cause of the nausea and vomiting was, they're better and they're happier. I'm not diagnosing them with drug-induced gastroparesis. I'm just saying the cause of their symptom is better. I don't need to do a test because it doesn't matter what the cause of it was. They're not saying I concluded that they had drug-induced gastroparesis, and therefore, that's the cause of their

don't believe that there is enough data that's out there to be able to draw a distinction of at which time.

I can just say that from a clinical perspective, the longer out a patient is -- for example, if a patient were years out, then I would be more likely to more vigorously pursue other possibilities rather than taking the patient off the medication. If the patient had been on the same medication and it had been stable and on the same dose, then the longer out it is, the more I'd consider other possibilities.

BY MR. PRZYMUSINSKI:

Q. Okay. Doctor, something you said earlier before we switched was that you could write guidelines on diagnosis of gastroparesis. Is that correct? That's within your experience and your qualifications?

MR. BUXNER: Object to form.

THE WITNESS: I believe that I would be qualified to make recommendations for guidelines either in my department at University of Maryland or the VA or to the -- essentially to present a paper to the Society of Nuclear Medicine with rational recommendations or recommendations about GLP-1s and gastroparesis. It would be very much along the lines of what we've been talking about all day today.

BY MR. PRZYMUSINSKI:

Q. So let's be more general and talk about diagnostic guidelines -- guidelines for diagnosis of gastroparesis.

Have you authored any guidelines for the diagnosis of gastroparesis from any organization?

A. No.

Q. Have you been invited to participate in the drafting of diagnostic guidelines for gastroparesis by any organization?

A. No.

Q. Okay. Has anyone ever approached you and say, Dr. Siegel, we would love you to come participate in the publication of a guideline on how to diagnose patients with gastroparesis?

A. No.

Q. Okay. And Doctor, I'm guessing that you've also never published anywhere a methodology that you describe in your report whereby you can diagnose drug-induced gastric emptying without conducting a gastric emptying study, correct?

MR. BUXNER: Object to form.

THE WITNESS: I have not published anything related to diagnosis of gastroparesis.

BY MR. PRZYMUSINSKI:

Q. So in fact, this is the first time you've really

put together or written an opinion on the topic in this litigation, correct?

A. Correct. This litigation gave me the opportunity to do a fairly deep literature search that I had not done before in order to create this report which has information in it that I think would be valuable to nuclear medicine physicians and radiologists in general. But I don't think that I -- my name has been associated with expertise in that particular area.

Q. Okay. Doctor, on Page -- on Page 5 of your report --

A. Page 5.

Q. -- there's a section on Methodology; do you see that?

A. Yes, I do.

Q. Okay. In the second paragraph in that section, you describe what you did at the onset of generating this report, you created a list of search terms and then you started doing searches on Google Scholar, PubMed, backward and forward searches. And is that the process you undertook to do the literature search you've been referring to today?

A. Yes.

Q. Doctor, how many studies did you identify or articles or publications did you identify through this search?

A. So I list a large number in my Materials Considered. In those materials that I read, there were a number of citations. I did a number of searches for articles that -- where I read an abstract but didn't believe that I needed to include that. I just tried to do ones that were as responsive as possible to the reason for the report, the ones that I thought, you know, were the -- some of the reviews that best summarized what was in the literature.

But in my Materials Considered List, it does not have an exhaustive list of all of the websites, all of the articles. These were ones that I focused on in order to create the report. That's what I mean by Materials Considered.

Q. That makes sense.

Ballpark, can you estimate for me how many articles you actually -- not scanned, but actually read that came out from this -- this search that you conducted as part of your report preparation process?

A. You mean materials considered plus ones that I didn't list as materials considered?

Q. No, no. Here's my question: So you established you did a pretty comprehensive search. And presumably, that search identified a lot of different things that you probably then filtered to things that you thought were relevant to your opinion. I assume some of those you

Q. All I asked is, have you seen the sentence? I'm asking you about it more broadly. Do you see the sentence?

A. I do see the sentence.

Q. Okay. And the citation you have there is from Jalleh 2024, right?

A. Correct.

Q. I don't know if I'm pronouncing that right, but we will have to go with that.

Now, here's the question, Doctor: Do you agree with the statement that: GES is always required to confirmed delayed gastric emptying because it cannot be conclusively determined whether delayed gastric emptying is responsible for gastrointestinal symptoms in a given patient?" Here's your opportunity.

MR. BUXNER: Object to -- object to form.

THE WITNESS: I don't agree with that.

BY MR. PRZYMUSINSKI:

Q. The next sentence you say: "There is evidence that suggests that not all patients who experience symptoms associated with abnormal gastric emptying in fact have delayed gastric emptying as measured by gastric emptying scintigraphy." Do you see that?

A. Yes.

Q. And this reference there you have is Balan 2011; do you see that?

A. I do, yes.

Q. Now, is it -- will you agree with me at a minimum, that there is at least some evidence suggesting that not every patient who experiences symptoms associated with abnormal gastric emptying in fact has delayed gastric emptying as measured by GES?

MR. BUXNER: Object to form. Asked and answered.

THE WITNESS: Yeah, I'm not sure I understand that question.

BY MR. PRZYMUSINSKI:

Q. Well, I'm just asking: Do you agree that there is at least some evidence, and then I read the sentence, that suggests that not all patients who experience symptoms associated with abnormal gastric emptying in fact have delayed gastric emptying as measured by GES?

MR. BUXNER: Object.

BY MR. PRZYMUSINSKI:

Q. Agree with that or not?

A. Agree.

MR. BUXNER: Sorry. Let me just --

THE WITNESS: Sorry.

MR. BUXNER: I want to object as asked and answered.

But go ahead.

THE WITNESS: Okay.

BY MR. PRZYMUSINSKI:

Q. The next sentence talks about the Lupianez-Merly 2024 study, which we talked a little bit about. I know Ms. Fitzpatrick talked to you a little bit about it earlier today.

A. Yes.

Q. And that's the Mayo Clinic abstract, correct?

A. That is one of the abstracts that came out of Mayo Clinic, correct.

Q. It's the one we marked as Exhibit 8, correct?

A. Let me look at my list of exhibits. Yes.

Q. Okay. And with respect to that study, what you said there's also one study reported only in a non-peer-reviewed abstract that patients treated with GLP-1 RAs report similar results, right? That's what you said.

MR. BUXNER: Object. Asked and answered.

THE WITNESS: Correct.

BY MR. PRZYMUSINSKI:

Q. Is that correct?

A. Correct.

Q. Okay. So is it fair for me to say the following: at least with respect to the data that you summarized from Jalleh 2024, Balan 2011 and Lupianez-Merly 2024, which are the first three sentences of this paragraph, those studies call into question whether the presence of symptoms can be

CERTIFICATE OF OATH

STATE OF FLORIDA

COUNTY OF PALM BEACH

I, TAMARA MASCI TANNEN, RPR, Notary Public, State of Florida, certify that ELIOT SIEGEL, M.D. personally appeared before me on the 31st day of January 2025 and was duly sworn.

Signed this 31st

_____

TAMARA MASCI TANNEN, RPR, FPR-C
Notary Public
State of Florida
My Commission #HH 621542
Expires March 7, 2029

REPORTER'S DEPOSITION CERTIFICATE

STATE OF FLORIDA)

COUNTY OF PALM BEACH)

I, TAMARA MASCI TANNEN, Registered Professional Reporter, certify that I was authorized to and did stenographically report the video deposition of ELIOT SIEGEL, M.D.; that a review of the transcript was requested; and that the foregoing transcript, pages 1-325, is a true and complete record of my stenographic notes.

I FURTHER CERTIFY that I am not a relative, employee, attorney or counsel of any of the parties, nor am I a relative or employee of any of the parties' attorney or counsel connected with the action, nor am I financially interested in the action.

DATED this 2nd day of February 2025.

_____

TAMARA MASCI TANNEN, RPR, FPR-C

Exhibit H

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAs) PRODUCTS LIABILITY LITIGATION	)	CIVIL ACTION
THIS DOCUMENT RELATES TO: ALL ACTIONS/ALL CASES	)	MDL No. 3094 2:24-md-03094-KSM

CONFIDENTIAL

WEDNESDAY, JANUARY 29, 2025

_ _ _

Videotaped Deposition of DANIEL RAINES, M.D., taken pursuant to notice and conducted at The Ritz-Carlton, 901 Canal Street, New Orleans, Louisiana, at 8:56 a.m. CST, on the above date, before Jennifer A. Dunn, Registered Merit Reporter; Certified Realtime Reporter; California, Illinois & Texas Certified Shorthand Reporter; and Missouri Certified Court Reporter.

Job No. 7130405

GOLKOW, a Veritext Division

my questions today?

A Yes.

Q Dr. Raines, you issued an expert report in this matter?

A Yes.

Q And I noticed that you've got some documents in front of you. Is one of those a copy of your expert report?

A It is.

MR. PREMO-HOPKINS: All right. I'm going to hand to you what we're going to mark for the record as Exhibit 1 to your deposition.

(Raines Exhibit 1 marked.)

MR. PREMO-HOPKINS: If it's easier for you to refer to the one that's bound, that's fine, but we need to have one for the record.

BY MR. PREMO-HOPKINS:

Q Can you just confirm for me, Dr. Raines, that Exhibit 1 is a complete and accurate copy of your expert report in this matter?

A It is.

Q Great. And Exhibit 1, your expert report, that contains all of the opinions that you've been asked to render at this point in time in this case; is that right?

A Yes.

Q And it includes all the materials you considered

that are referenced in there?

A It does.

Q And you haven't issued any updates or supplements to that report thus far, correct?

A No. There's one typo I noticed last night on page 12.

Q All right.

A In the middle of the page.

Q So we're going to go to page 12 on Exhibit 1 with you.

All right. And can you direct me to where you found the typo?

A Yeah. There's four paragraphs. The second paragraph, last sentence.

There's a "See Appendix A."

Q Yes.

A But that's a typo. The Appendix A is the materials considered.

So there's not -- so that's just a typo that needs to be removed.

Q I see. So just on page 12 of Exhibit 1, the "See Appendix A" referenced in the second full paragraph there, you would omit that?

A Correct.

Q Okay. Any other changes?

A No.
Q Did you write this report yourself, Dr. Raines?
A I did.
Q And all of the opinions in the report are yours?
A Yes.
Q And you hold them to a reasonable degree of medical and scientific certainty?
A Yes.
MR. PREMO-HOPKINS: I'm going to hand you what we've premarked as Exhibits 2 through 6, which are documents that we received last night, and I think from your materials it looks like you may have in the -- with you, but I'm not sure.
So we'll start with Exhibit 2.
THE WITNESS: Okay.
(Raines Exhibits 2 through 6 marked.)
BY MR. PREMO-HOPKINS:
Q Do you recognize Exhibit 2 as a presentation entitled: "Esophageal Motility Disorders Achalasia," and it has your name on the front?
A Yes.
Q And did you -- is this your presentation?
A Yes.
Q And do you know how it came to be produced to me last night?

A I submitted it to Parvin for submission and printing out for this meeting.

Q And is there anything in -- tell me what is Exhibit 2, what's the purpose of this presentation?

A This is a presentation for our fellowship lecture series.

Q And what is the fellowship lecture series?

A So, I'm a gastroenterology fellow program director. I spent 20 years training gastroenterology fellows, and so we cover different topics.

Each year, typically nine years of topics in the field of gastroenterology. A gastroenterology fellowship is three years long, and so we cover 270 topics over the course of three years in the different areas of gastroenterology, for, you know, part of our didactic series, as a supplement to procedural training.

Q So the audience for the presentation that's Exhibit 2 would be gastroenterology fellows at LSU?

A Yes.

Q And when is the last time you gave this presentation?

A I think it was two years ago.

Q So sometime in the first -- the spring of 2023, you think?

A Yeah.

A If they're in the United States and they manage patients with common gastrointestinal disorders and that's comfortable for them.

Generally, it would be an internal medicine doctor and generally somebody that specializes in gastrointestinal disease.

Q So the descriptions that you apply, or that you describe with regard to the diagnosis of gastroparesis in clinical practice in the United States, would be applicable to a doctor who has to diagnose gastroparesis, true?

A Yeah. Well, doctors that see patients with gastrointestinal disorders. So it wouldn't be applicable to an orthopedic surgeon that doesn't see those type of patients.

Q Got it. So you're not going to hold the orthopedic surgeon to this standard of care with regard to gastroparesis, but for doctors who see patients with gastroparesis?

A Yes.

Q You would apply your standard of care here?

A If that's what they like consider within the purview of their practice.

Q And what if they don't consider it in the purview of their practice?

A Then I would expect them to not necessarily make

that diagnosis if they don't feel comfortable in that area, like the orthopedic surgeon.

Q In the background section of your report, just above the Question Presented, you mention some societies that you're a part of?

A Yes.

Q It says you're an active member of all three major U.S. gastroenterology societies. Is that still true?

A Yes.

Q And one of those is the American Society for Gastrointestinal Endoscopy?

A It is.

Q Can we call that the ASGE today?

A We do.

Q And if I say that today, you'll not what I'm talking about?

A Yes.

Q Another gastroenterology society of which you're a member is the American College of Gastroenterology, or the ACG?

A Yes.

Q And then the third is the American Gastroenterological Association, or the AGA, right?

A Yes.

Q And if we talk about the ACG and the AGA, you'll

know what we're talking about today?

A I will.

Q Are there any of those three societies that you think is, you know, presents more compelling or more reliable material than the other?

MS. AMINOLROAYA: Object to form.

THE WITNESS: I wouldn't make such a generalization.

BY MR. PREMO-HOPKINS:

Q Is there any society that you go to more often with regard to gastric motility issues if you're looking for a reference?

A Not really some preferential society.

Q It says that you were selected as a fellow of the ACG in 2012. What is a fellow of the ACG?

A That is someone that's -- has specific or a certain amount of time allocated to meetings with the ACG, at least three annual meetings, and has recommendations from other fellows, the ACG, that kind of documents more involvement or particular involvement with that society to a certain degree and has been assessed by the society as somebody that's particularly engaged.

Q And are you still a fellow of the ACG?

A Yes.

Q Do you still engage with the ACG in the way you

just described today? In other words, did it start in 2012 and continue to today?

A Boy, it started in like maybe 2000. And then -- and then I'm currently writing a book, a second edition, of my capsule endoscopy book with the ACG, and so that's really a big portion of my relationship with them, with the staff.

Q You say the majority of your relationship with the ACG staff relates to your work on capsule endoscopy?

A Mm-hmm.

Q Is that yes?

A Yes.

Q As a doctor in clinical practice in the United States, what materials would be significant to consider when evaluating what constitutes a standard of care for a diagnosis of gastroparesis?

A It would be clinical training. So we train in certain areas, and as a doctor I would consider myself a gastroenterologist who trained in digestive disorders, so the standard of care is what most physicians do and, you know, in our field or specialty and situation.

And so I reference publications. I reference lecture materials, opinions, my own clinical experience, the mentorship of the physicians that train me.

Q In considering and evaluating what constitutes of standard of care in your report, one of the things you would

consider would be your clinical training?

A Yes.

Q Another thing that you would consider would be, you said reference or lecture materials, yes?

A Yes.

Q And publications?

A Yes.

Q And the mentorship of physicians that trained you?

A Yes.

Q And I think you said the standard of care is what most physicians do; is that right?

A Yes.

Q What is the significance, if any, of consensus guidelines published by groups like the medical societies you referenced in understanding the standard of care?

MS. AMINOLROAYA: Object to form.

THE WITNESS: We use guidelines as -- as also another data point or a reference point.

BY MR. PREMO-HOPKINS:

Q Does the fact that they are consensus guidelines make them any more or less important in your evaluation of the standard of care?

A It depends on the topic.

Q Why?

A Because sometimes there's lack of consensus

between individuals, groups. Like sometimes different societies and different specialties, so if there's no consensus or there's a lot of conflict between different societies or different experts, then if you can get them all to agree on something, then it's more significant than, you know, a case in which there is no disagreement or there's not much debate about something.

Q If physicians in these societies are coming to agreement on certain points, with regard to reaching a consensus on certain points, that would be something that you would -- I think you said that would be more significant to you; is that right?

A It's a factor.

MS. AMINOLROAYA: Object to form.

THE WITNESS: Yeah.

BY MR. PREMO-HOPKINS:

Q And the more consensus there is, the more significance it would be to you, right, with regard to the standard of care?

A I would say it's significant as far as a reference point and still I'm making my standard of care determination based on all those other data points.

Q Have you ever previously departed from a consensus guideline in reaching an opinion with regard to the standard of care in any of your litigation consulting?

MS. AMINOLROAYA: Object to form.

THE WITNESS: No.

MR. PREMO-HOPKINS: We've been going for about an hour, Dr. Raines, do you want to take a quick break?

THE WITNESS: I'm good.

BY MR. PREMO-HOPKINS:

Q Okay. So you also mention in your report an organization called The Rome Foundation?

A Yes.

Q What's The Rome Foundation?

A It's a collaboration of physicians that talk about the disorders of brain-gut axis, and I think probably for -- in your reading and everybody in this room, it's a bit confusing because it started many years ago and you originally think of it as like irritable bowel syndrome and then over time the terminology we use has changed significantly from irritable bowel syndrome to functional disorders to disorders of the brain-gut axis.

So when they changed the terminology or name of the conditions that they address, it makes it hard for people to follow.

Q So you understand The Rome Foundation to be an organization focused on disorders of brain gut function?

A Brain gut interaction, really.

Q Interaction, thank you.
A Yeah.
Q And are you -- are you -- I'm not exactly sure how people get selected to be part of The Rome Foundation's -- are you a member of The Rome Foundation?
A No.
Q Have you ever been asked to participate in any proceedings of The Rome Foundation?
A No.
Q Is gastroparesis a disorder of brain gut interaction?
A No.
Q Why do you say that?
A It's a motility disorder and The Rome Foundation disorders are disorders defined and addressed by The Rome Foundation don't have a clear or definable path of physiology, and that's one of the ways that we differentiate those orders from other disorders.
Q Would you look to The Rome Foundation ever for guidance on the standard of care with regard to diagnosing gastroparesis?
A I think there's some useful data points in The Rome Foundation publications. So I think it's a useful reference.
There's a lot of information published by them,

You write in the middle of page 7 there: "The differential diagnosis for patients with chronic nausea and vomiting (greater than seven days), includes" -- and then you list a number of conditions, yes?

A Yes.

Q What are you relying on to conclude that chronic nausea and vomiting means nausea and vomiting greater than seven days?

A That's the textbook definition that we get from the Yamada Textbook of Gastroenterology.

Q Is the Yamada textbook a reliable source for information about gastroparesis and gastroenterology?

A It's a useful data point.

MS. AMINOLROAYA: Object to form.

BY MR. PREMO-HOPKINS:

Q And when you talk about the Yamada textbook, are you talking more specifically about the chapter written by Dr. Cangemi, and -- oh, gosh, the two doctors at the Mayo Clinic?

A I'd have to look. Because the textbook's obviously a whole textbook.

Q Yeah. We have -- I have a chapter, we can look at it later. You don't have to -- it's not a memory test.

A Yeah, it's, you know, regarding the differential diagnosis portion of the book, and if that's the portion

that they're authoring then, yes, but I don't recall -- this is a reference to that kind of specific portion of the book.

Q Got it. And so when you say -- you would consider a differential diagnosis for gastroparesis if a patient presented with nausea and vomiting for more than seven days?

A Yes.

Q Not everyone who has chronic nausea and vomiting for greater than seven days has gastroparesis, right?

A Correct.

Q The symptoms of recurrent nausea and vomiting can be caused by many different conditions other than gastroparesis, right?

A Correct.

Q Put another way, would you agree that the symptoms of gastroparesis are nonspecific?

MS. AMINOLROAYA: Object to form.

THE WITNESS: I would say that the symptoms of gastroparesis -- I wouldn't say they're overall nonspecific. They certainly correlate with the disease.

BY MR. PREMO-HOPKINS:

Q Would you agree with me that the symptoms of gastroparesis overlap with many other conditions?

MS. AMINOLROAYA: Object to form.

THE WITNESS: The symptoms of chronic nausea

and vomiting overlap with all the other differential diagnosis on this table.

BY MR. PREMO-HOPKINS:

Q So one of the things that you list in the paragraph we were just looking at for the differential diagnosis, actually the very first thing you list is medication-related nausea.

Do you see that?

A Yes.

Q What is medication-related nausea?

A That's a side effect from a medication where a patient has nausea after ingesting medication. We think it's -- it's often like a centrally mediated nausea, meaning like they have nausea from something in the CNS, or a receptor in the CNS potentially, the nausea center, causing nausea.

Q What does centrally mediated in the CNS mean?

A In the brain.

Q How would you distinguish or differentiate between medication-related nausea or drug-induced gastroparesis?

A I'd probably review the symptom of vomiting, especially vomiting undigested food, would be a good example.

Q When you talk about medication-related nausea, are you referring to nausea that's not caused by delayed gastric

emptying?

A I think there certainly is a centrally mediated or brain related -- brain receptor mediated nausea that's seen with multiple medications.

Q Are you aware, one way or the other, about whether or not there's a centrally mediated or brain-related nausea and vomiting seen with GLP-1 RA medications?

A I haven't seen any literature to support that theory.

Q If we turn to page 11 of your report.

One of the necessary conditions for diagnosing gastroparesis is delayed gastric emptying, yes?

A Yes.

Q And delayed gastric emptying alone, though, isn't sufficient to diagnose gastroparesis, would you agree with that?

A I would.

Q So of the conditions that you mention on page 9 and 10 of your report in the table?

A Yes.

Q Are patients who take GLP-1 RA medications, are they how immunized or protected from any of those conditions?

In other words, would they suffer them at a lower prevalence than the general population?

A Are GLP-1s decreasing the risk of any of these disorders? I guess if you extrapolate, if you -- if somebody took GLP-1 and lost weight, then their risk of gallstones may decrease.

And then GLP-1s are associated with pancreatitis, so their risk would increase, but a decrease.

Q Patients on GLP-1 RA medications can suffer from all of the conditions you list in the table on pages 9 and 10, irrespective of whether they're taking a GLP-1 RA, true?

MS. AMINOLROAYA: Object to form.

THE WITNESS: I can't imagine a scenario where somebody with anorexia would be given a GLP-1, or certainly shouldn't be.

So if you're asking that any patient -- any human can have any of these disorders then, yes, including patients that are given GLP-1, or really any other medication.

BY MR. PREMO-HOPKINS:

Q You talked about that history point with regard to vomiting of undigested food, and I can direct you to page 7, that's where that's referred to in your report.

A Yeah.

Q You say: "Vomiting of undigested food is a cardinal symptom which may be considered pathognomonic" --

A Yeah.

Yes, I can. In those classic cases.

And then cases that are more complicated and patients have previous diagnosis of pancreatitis or other, you know, other history, it makes it difficult and that's when you have to kind of drill into the individual case as far as how you would evaluate that specific patient.

Q Can you describe for me what you would call a classic case that can be diagnosed as drug-induced gastroparesis based on history and physical alone?

A Yes. So a patient with no history of any other illness, especially like no other like pre-existing symptoms, completely asystematic, no medical problems, not on any other medicines, that suddenly started a drug, like a GLP-1, and then developed severe nausea and vomiting, with vomiting food within four hours after ingestion, that was kind of persistent for more than seven days or recurrent over the course of seven days.

No fever. No weight loss. Other than like acute weight loss with dehydration, no abdominal tenderness necessarily, so that kind of classic story.

Q If you see a patient that presents with symptoms consistent with gastroparesis, they're on a GLP-1 RA medication, those symptoms, the onset of those symptoms correlates with the initiation of the GLP-1 RA?

A Yeah.

Q And the history is negative for alternative diagnoses, you're diagnosing drug-induced gastroparesis?

A It depends on the case, but if we have a hypothetical scenario of a classic case that I've just described, then, yes, I can diagnose drug-induced gastroparesis.

Q What would complicate a case such that you can't diagnose drug-induced gastroparesis based on history and physical alone?

A Too many things to talk about.

Q Can you name some of them for me?

A So like a pre-existing history of gastroparesis. A pre-existing history of pancreatitis. A pre-existing history of abdominal surgery with like a gastrectomy or some change in anatomy would be kind of examples.

Q Diabetes?

A That would be a factor. It depends on like the severity of the diabetes and how longstanding, if they have other features or features of end organ damage from their diabetes.

Q And in order to make a diagnosis under your standard of care with regard to drug-induced gastroparesis, you don't require the cessation of symptoms after withdraw of the medication?

MS. AMINOLROAYA: Objection to form.

THE WITNESS: I would -- there's a threshold where I would assign a diagnosis, and so I want to assign a diagnosis at that time before I withdrew the drug, and then I would withdraw the drug.

BY MR. PREMO-HOPKINS:

Q And if you withdraw the drug and the symptoms persist, you would consider alternative diagnoses?

A I would.

Q If you have a patient that presents with what you called the cardinal symptoms of gastroparesis and they're taking a GLP-1 RA in correlation with those symptoms, you reach the conclusion they have drug-induced gastroparesis?

A It depends the presentation, but in the classic presentation I described, I would.

Q And you understand that gastroparesis requires a delayed gastric emptying, yes?

A Correct. Gastroparesis has two requirements.

One is symptoms related to delay in emptying from the motility disorder.

Q How do you know that patient that we just described that presents with symptoms and tells you that they're taking a GLP-1 RA has delayed gastric emptying?

A Like vomiting food more than four hours after ingestion is certainly an indicator.

Q What if there's no food vomited more than four

hours before?

A It depends on the case. So if they don't have a classic presentation or if you want to pick out variations from the classic, then I'd really have to see the patient and kind of tease out their story.

Q I guess I'm trying to understand. In your diagnosis, is it sufficient that the patient is taking a GLP-1 RA in correlation with symptoms to reach the conclusion that they're suffering from delayed gastric emptying?

A All I can say is it depends on the case, except for if we describe a classic case, then, yes, I can make that diagnosis, and then if we generalize that to every patient, then that's a different story.

Q So only in some cases is it sufficient for you to reach a diagnosis of drug-induced gastroparesis if a patient is taking a GLP-1 RA in correlation with symptoms consistent with gastroparesis, true?

MS. AMINOLROAYA: Object to form.

THE WITNESS: Yes. I would say it's not all cases that I would assign a diagnosis of drug-induced gastroparesis with somebody that's taking a GLP-1 RA and has symptoms of nausea and vomiting.

BY MR. PREMO-HOPKINS:

Q You need something else?

patient by patient. But, in general, there are some patients that I can diagnose with drug-induced gastroparesis based on history alone.

Q And those patients need to have symptoms of gastroparesis for more than seven days?

A I would say more than seven days, just because the late of like acute infection gastritis is -- when we talk about symptoms less than seven days or nausea and vomiting that's less than seven days, the differential diagnosis that I describe in my report is a lot different.

So there's different pathologies, and included in the differential diagnosis is acute infectious gastritis or a stomach virus or a stomach bug, and that's pretty common.

So if I see a patient in the ER that has nausea and vomiting just for one day, then, you know, I would not diagnose that person with gastroparesis or drug-induced gastroparesis, or any form of gastroparesis, just with like a short duration of symptoms, just because of the prevalence of like other diseases and, namely, like a stomach virus.

Q Given the potential for alternative causes, you would not diagnose a patient who's been suffering from GI symptoms for less than seven days with gastroparesis, true?

A True.

Q And to diagnose a patient with nausea and vomiting secondary to delay in gastric emptying, you would expect, I

think you said, more than just a little nausea, right?

A Yes.

Q You would expect a patient that has to present to the emergency room unable to eat, those types of things?

A Those would be examples, yeah.

Q That's the level of severity you're talking about, though?

A Those are examples of severity.

Q Are they on the high end?

A I don't know, I never graded them, but I can give you examples.

Q So you don't have a grading of the severity of symptoms that would be required to diagnose drug-induced gastroparesis in the absence of scintigraphy, true?

A I never created a grading system for diagnosis of drug-induced gastroparesis based on the symptoms.

Q You just know it when you see it?

A Yeah.

MS. AMINOLROAYA: Object to form.

THE WITNESS: It's more like it depends on the individual case.

BY MR. PREMO-HOPKINS:

Q And it depends on how severe their symptoms are, yes?

A It does. And in general, it depends like how much

we do for a patient. It depends on how severe their symptoms are.

Q The more severe the GI-related symptoms, the more likely you are to conclude that they're suffering from drug-induced gastroparesis?

A The more classic their presentation is for drug-induced gastroparesis, the more likely.

Q It seems circular to me, sir.

A I know, me, too. So it's like -- there's a certain threshold, like, yes. They have to have symptom onset with the drug.

Q Okay. So the first step, they would need symptom onset with the drug, yes?

A Yes. It's got to correlate with the drug.

Q Okay. Which symptoms should correlate with the drug?

A So typically it would be nausea and vomiting is the symptoms that I would want to see to make the diagnosis of drug-induced gastroparesis, so.

Q So you want -- in order to make a clinical diagnosis without a gastric emptying study, you would want to see onset of nausea and vomiting that correlates with use of GLP-1 RA?

A Yeah. Or, you know, maybe if they change their dose or increase their dose.

I understand it's like there's got to be some kind of criteria, so the criteria would be correlation with the drug and then symptoms of gastroparesis, namely, nausea and vomiting, more than seven days.

And then when we talk about severity, there's a lot of ways to grade severity. So it's hard to like create a threshold for severity.

Examples of severity would be dehydration, coming to the ER, hospitalization, you know, if they're not able to get out of bed, you know, it's kind of those -- those components, and those are kind of nuanced for the patient as far as severity.

So it's hard to set like a number as far as severity. I can give kind of examples of severity.

Q Are you done with that answer?

A Yes.

Q You didn't say anything about gastric emptying, which I thought was a necessary criteria for diagnosing gastroparesis.

A I said nausea and vomiting, yeah.

Q Is it your opinion that nausea and vomiting in the context of onset of GLP-1 RA medication can only be caused by delayed gastric emptying?

A I think it would be wrong to say only like 100 percent.

MS. AMINOLROAYA: Objection. Asked and answered.

THE WITNESS: Yeah. I think we'd have to go through this discussion of papers that talk about GLP-1-induced gastroparesis, and we could look for phrases that talk about, it seems like this might be the cause of their gastroparesis, and the next step would be -- or the intervention would be to withdraw the drug and, you know, we'd have to look for a phrase or a comment like that.

BY MR. PREMO-HOPKINS:

Q So you're looking for a phrase that says: "Withdraw of the drug."

A Would be the next step in management, yeah.

Q Management of what?

A Somebody that's presenting -- like that typical case of somebody in the ER with no other reason to have gastroparesis that's vomiting that just started the drug.

Q As you sit here today, can you -- you can look at your report, look at your Materials Considered List, can you name for me any peer-reviewed or published literature that says you can diagnose delay in gastric emptying based on symptoms alone?

MS. AMINOLROAYA: Objection. Asked and answered. He's asked the question for the third time.

THE WITNESS: Okay. I can't quote a peer-reviewed article that contains that specific phrase that says you can diagnose drug-induced gastroparesis by symptoms alone.

BY MR. PREMO-HOPKINS:

Q Can you identify for me, whether you're quoting or not, peer-reviewed published literature that says you can diagnose delay in gastric emptying based on symptoms alone?

MS. AMINOLROAYA: Objection. Asked and answered for a fourth time.

THE WITNESS: I think we can look through and find things that say examples of GLP-1s are associated with gastroparesis, and when you suspect that's the reason of their symptoms, then the next step is to withdraw the drug.

And so that phrasing of they drug-induced gastroparesis, it's from a GLP-1, and the management is to withdraw the drug. Like I think that's pretty straightforward, but I don't think --

BY MR. PREMO-HOPKINS:

Q You just said -- you just said that you've looked at papers that say patients suffer from drug-induced gastroparesis caused bay GLP-1?

A Yeah. Let's look at some of those. So I'm sure you're very familiar with this.

Q You're looking in your black binder, yes?
A I am.
Q What's the paper that you're looking at?
A So probably start with the Maselli article that's in my reference list from 2022.
Q And what would you rely on there to reach the conclusion that the standard of care in the United States is that one can diagnose delay in gastric emptying based on symptoms alone?
A It's a study that demonstrates that GLP-1s are associated with significant delay in gastric emptying, that's symptomatic, and that the follow-up study by Dr. Camilleri from Obesity Medicine in 2023, talks about how that delay varies between individuals, with about 50 percent experience symptomatic delay and then 50 percent of those patients have improvement or resolution and some have kind of persistent symptoms. So it's more of a documentation of GLP-1s.

There's evidence that they induce delay that's symptomatic and that sometimes it resolves and sometimes it doesn't. Some people have significant delay and some don't, but I think that -- you're searching for me to say somebody made a statement somewhere that kind of fits your specific statement that you once stated somewhere, but I don't know a specific article that makes the exact statement that you're

really fit very well with the diagnosis or they're not responding to the standard treatment for that diagnosis. You know, their case isn't proceeding as you would expect, or they're not getting better.

And so that's what we see in referral centers is, we see preferentially people that aren't getting better. They have an unusual case. They have a complicated case. They're not improving. They're not responding to the standard therapy.

So when you look at that population of patients that's different than a population of patients that we would see, you know, say, in a general practice diagnosed with gastroparesis.

So we call that tertiary referral bias, and that's what you see -- they kind of quote that in the limitations of the study.

MS. AMINOLROAYA: Mark, we've been going a little over an hour.

Can we go off the record and take a short break?

MR. PREMO-HOPKINS: Yeah. It was going to go quicker if he stops giving speeches. Yes, we can go off the record and take a break.

THE VIDEOGRAPHER: We are going off the record at 1:16 p.m.

(Recess taken at 1:16 p.m.)

THE VIDEOGRAPHER: We're now back on the record. The time is 1:26 p.m.

BY MR. PREMO-HOPKINS:

Q Dr. Raines, we just took a break.

Are you ready to begin again?

A I am.

Q So before the break, we were looking at the -- what I'm calling the Cangemi study, but the 2023 study in Clinical Gastroenterology and Hepatology that's titled: "Misdiagnosis of Gastroparesis is Common."

Do you have that in front of you?

A I do.

Q And your opinion in this case is that -- in this litigation, is that in a classic presentation of gastroparesis symptoms, that correlates with the initiation or increase of GLP-1 RA medication, you can diagnose delayed gastric emptying in gastroparesis based on those facts alone, right?

A The description that I gave for a classic presentation, I can diagnose drug-induced gastroparesis based on all those factors combined alone.

Q And that is the classic symptoms and the use of the GLP-1 RA medication and what I think you said was exclusion of alternative diagnoses, right?

MS. AMINOLROAYA: Object to form.
THE WITNESS: No evidence of.
BY MR. PREMO-HOPKINS:
Q No evidence of. Thank you.
A Yeah. And then seven days.
Q Right.
A And then, you know, more severe symptoms, and I can't define like every severe symptom criteria, but I could give examples, as we discussed.
Q You don't require there to be vomiting of undigested food more than four hours after a meal in order to diagnose?
A No.
Q If we -- have you ever presented that -- this theory about the diagnosis of drug-induced gastroparesis for publication?
MS. AMINOLROAYA: Object to form.
THE WITNESS: A theory of diagnosing gastroparesis?
BY MR. PREMO-HOPKINS:
Q Have you ever presented this idea that you can diagnose drug-induced gastroparesis based on symptoms, a history and physical alone, for publication?
MS. AMINOLROAYA: Object to form.
THE WITNESS: No.

BY MR. PREMO-HOPKINS:

Q And you're not -- you haven't published it anywhere, not only have you not presented it for publication, it hasn't been published anywhere, right?

A It's not really like a theory. It's kind of a generally-accepted practice, and so that's why it's referenced in my standard of care.

Q It's a generally-accepted practice that clinical practitioners in the United States can diagnose drug-induced gastroparesis based on history and physical alone?

MS. AMINOLROAYA: Object to form.

THE WITNESS: It's a generally-accepted practice that patients fitting that classic presentation of onset of symptoms with the onset of a drug that's known to cause gastroparesis, with no other evidence of any other pathology that's chronic over seven days and severe, that most physicians would make the diagnosis of the drug is the cause of their symptoms, and so their next step would be to withdraw the drug.

And I would call that drug-induced gastroparesis, and so where withdrawing the drug is like the next step rather than ordering a scintigraphy.

BY MR. PREMO-HOPKINS:

Q I'm sorry. Are you here offering opinions today

about the causation of gastroparesis?

A I'm saying the GLP-1 RAs are associated with drug-induced gastroparesis, and there's evidence that they delay gastric emptying.

Q Do you have an opinion, to a reasonable degree of medical or scientific certainty, that any particular GLP-1 RA causes gastroparesis?

MS. AMINOLROAYA: Object to form.

THE WITNESS: I referenced articles in my report and have some today that we can discuss that talk about the association between GLP-1 RAs and delay in gastric emptying.

BY MR. PREMO-HOPKINS:

Q Do you have an opinion to a reasonable degree of medical or scientific certainty that any particular GLP-1 RA causes gastroparesis, yes or no?

MS. AMINOLROAYA: Same objection. Asked and answered.

THE WITNESS: Yeah. I think as I describe in my report, I'm not here to provide -- I haven't been asked to provide an opinion an all of the literature related to causation.

So I'm here to talk about diagnosis of gastroparesis and different subtypes and presentations in different subtypes.

Q Do you agree with that statement that gastroparesis cannot be diagnosed based on symptoms alone?

A I disagree, because it's a generalization. It's -- it doesn't apply to all subtypes of gastroparesis.

So drug-induced gastroparesis can be diagnosed based on symptoms alone and physical in a classic presentation, or hypothyroidism-induced gastroparesis.

And there's -- the guidelines and this letter, they just don't include information about all the different subtypes, including those subtypes. And I don't think that these doctors would recommend doing a -- like a scintigraphy study in somebody with hypothyroid gastroparesis, rather than just kind of treating their hypothyroidism, for example.

Q You disagree with the statement that the Cangemi article reaffirms guidelines noting that gastroparesis cannot be diagnosed based on symptoms alone?

MS. AMINOLROAYA: Objection.

BY MR. PREMO-HOPKINS:

Q You disagree with that?

MS. AMINOLROAYA: Objection. Asked and answered.

THE WITNESS: This is a statement that they reaffirm the guidelines. And the guidelines are based on a typical patient.

BY MR. PREMO-HOPKINS:

Q Do you know what guidelines they're referring to that note that gastroparesis cannot be diagnosed based on symptoms alone?

A There are several.

Q Okay. What are the several guidelines that note that gastroparesis cannot be diagnosed based on symptoms alone?

A So, there's the ACG 2022 that recommended scintigraphy in a typical patient, and I would consider that a diabetic or idiopathic would be common examples.

So in those common groups, then we do scintigraphy commonly to diagnose gastroparesis.

And then the AGA clinical practice update in 2022.

Let's see. I don't know if that article specifically makes that statement, but it's kind of inferred.

And then the other one was the Rome publication in The Lancet 2025.

Q Okay. So the ACG 2022, the AGA 2022, and the Rome Lancet 2025, all support the proposition that gastroparesis cannot be diagnosed based on symptoms alone, true?

A These guidelines state that in these typical presentations, in a typical patient presentation then -- which I infer is diabetic and idiopathic gastroparesis, that

they should get a scintigraphy study, which I would agree with.

Q And so you're inferring a lot from these articles in terms of what the authors of the articles meant about what type of gastroparesis they were talking about, yes?

MS. AMINOLROAYA: Objection to form.

BY MR. PREMO-HOPKINS:

Q Wouldn't you agree with me?

A I think they don't mention the subtypes. So they don't mention how to manage somebody with hypothyroid gastroparesis.

And so like, you know, they're missing out on parkinsonian gastroparesis, or they're missing out on drug-induced gastroparesis. And sometimes -- and rather than just not mentioning it, they mention it, but they're not really clear about, you know, the term that they use.

Sometimes they use drug-induced gastroparesis and sometimes they say -- like this ACG article in 2022, like exclude iatrogenic disease, which is -- seems like a vague statement about stopping the drug that's the cause of their gastroparesis or the cause of their symptoms.

Q Have you ever published in any peer-reviewed literature the view that the ACG guidelines are vague or unclear?

A I think they make that statement in the guideline

gastroparesis, as you describe it, without the need for a gastric emptying study, based on your history and physical examination; is that fair?

A Yes.

Q Okay. Now, I think I understood from the questions earlier that that methodology, that approach, that diagnostic approach that you describe --

A Yeah.

Q -- is not a diagnostic approach that you can point to as being spelled out specifically in any of the guidelines we reviewed; is that correct?

MS. AMINOLROAYA: Objection.

THE WITNESS: I would disagree.

BY MR. PRZYMUSINSKI:

Q Okay. Why do you disagree?

A Because the inference, especially the example the ACG guideline describes in the table, like exclude iatrogenic disease, and so if that means, stop the drug, that's the cause of the drug-induced gastroparesis, then it is in the guideline and that's actually demonstrated in the algorithm.

Q So you're making an inference, right, you're saying --

A Yeah.

Q -- I'm seeing. Let me finish my question.

A Sure.

Q I'm seeing them discuss exclude iatrogenic causes, and you're then drawing the inference that that implies that they are then adopting an assumption that those cases are drug-induced gastroparesis, correct?

A It's hard to say because it's not spelled out.

Q Well, and I think that's my point.

A Sure.

Q So in none of the guidelines -- and I think we already talked about this, but I want to go back to it for a different reason.

My understanding was, at least within the guidelines we talked about, the AGA 2022, the ACG 2022, and the Rome 2025, there was no specific discussion of the methodology you are proposing today; is that correct?

A I think the guidelines talk about discontinuing the drug as drugs that are potential causes of the patient's presentation, so.

Q Again, that's different from diagnosing them with gastroparesis, correct?

MS. AMINOLROAYA: Let Dr. Raines finish his answer, please.

MR. PRZYMUSINSKI: Fair enough.

THE WITNESS: Yeah. Yeah.

You know what I don't see is if a patient is

on a drug like a GLP-1 that's suspected to be the cause of their symptoms is to recommend doing a scintigraphy study on their drug, and then diagnosing them with drug-induced gastroparesis. I don't see that.

MR. PRZYMUSINSKI: Okay.

THE WITNESS: And so -- and it doesn't really talk about like how to manage those patients as a specific subtype. It doesn't talk about subtypes of hypothyroidism-induced gastroparesis either.

So again, it's not that the guidelines are wrong. It's just they don't cover every particular scenario.

BY MR. PRZYMUSINSKI:

Q And, Doctor, I'm not asking whether you think the guidelines are right or wrong.

A Okay.

Q The simple point is that the methodology you are describing today for diagnosing some subset of patients with drug-induced gastroparesis is not specifically described or adopted in any of these guidelines; that's fair, correct?

MS. AMINOLROAYA: Objection. This is duplicative of questioning that was covered earlier today.

THE WITNESS: I think it's depends on how we interpret things like the figures in tables, like you

causation.

THE WITNESS: I'm saying what the standard of care is. What would most gastroenterologists do?

So when gastroenterologists see people in the ER that were asymptomatic, started a drug that's known to delay gastric emptying and they come to the ER vomiting, vomiting residual food, most gastroenterologists would say: "I think that your symptoms are related to the drug," and they would stop this drug.

BY MR. PRZYMUSINSKI:

Q So there's a difference, Doctor, between saying symptoms are related to the drug and saying the symptoms are related to the drug and your diagnosis is drug-induced gastroparesis.

You see the difference, right?

MS. AMINOLROAYA: Objection.

THE WITNESS: I see the difference, and I would use the term "drug-induced gastroparesis," and it's obviously that you have a different opinion that you wouldn't use that term.

BY MR. PRZYMUSINSKI:

Q Well, it's not about my opinion. My opinion doesn't matter. No one cares what my opinion is. We care to hear about what your been is.

A Sure.

Q So here's the question. So the methodology that you have, right, the methodology that encompasses, in some substantive patients, taking a temporal correlation between initiation of therapy or a change in dose with a GLP-1 --

A Yeah.

Q -- in combination with the presence of nausea and vomiting for some version of over seven days --

A Yes.

Q -- in combination of whatever level of severity that you assign to it.

A Yeah.

Q Have you tested that methodology in any scientific way?

A I haven't done like a research study or something like that to evaluate that practice pattern. That's kind of a standard of practice that people do.

Q Well, I know you keep saying it's the standard of practice, but --

A Sure.

Q -- I'm trying to understand how reliable it is.

So have you done any study to test -- "when I have these symptoms and I make a diagnosis of drug-induced gastroparesis, how often am I right and how often am I wrong?"

Have you done a study to evaluate that?

A I haven't done a formal research study. I just have my personal experience of, say, maybe 100 cases like that and about 90 percent improve with time.

And of the people that don't have resolution of their symptoms, then I may be skeptical of their individual diagnosis, kind of depending on their course, and if they're slowly getting better or not, or if they have -- like other reasons to have those symptoms or not.

Q And I appreciate that, Doctor, but it's a little bit different from what I'm asking.

A Sure.

Q The question -- what you're telling me, as I understand, correct me if I'm wrong, is that, in your experience of about 100 patients who have been on a GLP-1 that had nausea and vomiting, after stopping the medication, 90 percent had resolution in a few weeks, correct?

A Yes.

Q Okay. My question is not about resolution of nausea and vomiting. My question is about the presence of gastroparesis.

A Okay.

Q Which is a different concept, right?

A It's a -- one cause of nausea and vomiting, so sure.

Q One of many causes of nausea and vomiting, correct?

A Correct.

Q All right. So my question is this: Have you done any study to assess whether your methodology, history, physical, symptoms, correlation, all the stuff you talked about throughout the day, how often that methodology actually results in the right answer, meaning the patient actually has real gastroparesis, meaning there is evidence of delayed gastric emptying sufficient to meet criteria to make a diagnosis of delayed gastric emptying and gastroparesis?

MS. AMINOLROAYA: Objection. Asked and answered.

MR. PRZYMUSINSKI: I don't think so.

THE WITNESS: I think if somebody's vomiting solid food, like that they ate 10 hours ago in the ER, I would call that objective evidence that they're not emptying their stomach.

And so if you're asking if I did a research study with an IRB protocol to publish, I haven't done a research study like that.

BY MR. PRZYMUSINSKI:

Q Do you know of any data that's been published in the peer-reviewed literature that reports on the positive

predictive value, meaning the likelihood that the result is accurate for the methodology you propose, versus gastroparesis as a diagnosis?

A I'm not aware of any particular study like with that specific design.

Q So if I wanted to know how reliable your methodology is for predicting gastroparesis based on symptoms and presentation, I can't go find any literature anywhere that would tell me how accurate it is and how often it's wrong, can I?

MS. AMINOLROAYA: Objection. Asked and answered.

THE WITNESS: I think for a lot of questions there's not a specific research study to answer that specific question, and there may never be.

BY MR. PRZYMUSINSKI:

Q I'm not asking about lot of other issues, I'm asking about this one --

A In this particular --

Q Let me finish my question.

A Sure.

Q In the context of this methodology, which you're putting forward as a standard of care in your report, I want to know, is there any peer-reviewed literature, published literature, that I can go to to determine whether the method

A Yeah. So it's a description of a recent trial, it's called: "The prevalence and variations on the gastric emptying delay in response to GLP-1 receptor agonist liraglutide."

Q Okay. What --

A It kind of has a table that describes this analysis of patients that most had a delay in gastric emptying on therapy and some of them had a persistent delay and some did not.

So that was -- 57 percent developed a very significant delay, and those patients who developed delay, 51 percent had persistent delay, and the remaining had normalization in 16 weeks.

So --

Q Does it correlate that delay with symptoms?

A There was an actually interesting analysis that we looked at. There's not a lot of great data that describes the delay and symptoms and how they correlate.

There was a study that we discussed in my opinion that was -- just published in abstract form on the bottom of page 12.

So I'm sure you're familiar with the Lupianez-Merly 2024 data.

Q Mm-hmm.

A So this is some data -- it's not really

high-quality data, and it's still in abstract form, it's a retrospective review.

And Dr. Nguyen, I recall, kind of also discusses this study or abstract that was published, and so it infers that gastric emptying studies were done on patients that had symptoms on GLP-1 RA in kind of a deliberate manner. But it was a chart review of patients that had symptoms, and those symptoms included nausea, constipation, bloating, not necessarily the symptoms that we normally see and -- or normally consider to be typical for gastroparesis.

And in this analysis -- and they just did a retrospective chart review. They found that 34 percent of patients were found to have delayed emptying.

Q Doctor, are you talking about the poster presentation by Camille Lupianez-Merly, spelled L-u-p-i-a-n-e-z?

A Yeah.

Q Dash M-e-r-l-y; is that correct?

A Yeah.

MR. PRZYMUSINSKI: Well, let's mark that as Exhibit 12, just so we have it in the record.

(Raines Exhibit 12 marked.)

BY MR. PRZYMUSINSKI:

Q This is the document, Doctor, that we're talking about; is that right?

A Yeah.

Q Okay. Now, as I understand, you said poster presentation. I understand you said limited data, but if you -- and I think this is what you just said.

If you look at the second bullet underneath the little flowchart, it says: "One-third of patients who underwent gastric emptying study were found to have delayed gastric emptying." Correct?

A Yeah.

Q All right. So what it's telling you in this study is that of the patients who had GI symptoms while on a GLP-1 drug, only a third of them actually had delayed gastric emptying, correct?

A Yeah. And it's kind of misleading, though. It kind of gives you the impression that they didn't have the symptoms before, but this includes patients that had GI symptoms before.

So like half of them had GI symptoms before they started the drug, and then half didn't. And they didn't separate out which patients were which, so they just kind of blended them together, and so it's kind of hard to interpret. And when they say they average everything together, there's not much difference.

But I think the issue is that they took patients that had GI symptoms before they started the drug, and then

they lumped them in with the patients that had symptoms that began after they started with the drug.

Q And that's fair. I understand there's limitations, Doctor, and we can talk about that another time, but the question that I had asked that prompted you to pull this out was -- it started with a question of whether every patient who has nausea and vomiting on a GLP-1 develops that as a result of delayed gastric emptying and you said: "No."

And then I asked whether you had data to -- to predict reliable data to tell us what percentage of patients who have GI symptoms while on a GLP-1 actually also had delayed gastric emptying.

A Sure.

Q And you pointed me to this as the best data you could identify.

If this data were correct, Doctor, that would mean that 67 percent, or two-thirds of patients have GI symptoms on a GLP-1, do not have delayed gastric emptying, correct?

A I didn't say this was the best data I could identify. It was a data point that I could recall, that's when I review all the medical literature, like that was an example of a piece of medical literature.

Q Okay. What is the best piece of medical literature you can identify for me --

A Sure.

Q -- sitting here today, that provides us with an estimate of the rate of delayed gastric emptying in patients who have nausea and vomiting while taking a GLP-1?

A The incidence of nausea and vomiting on a GLP-1 overall?

Q No, let me do it again.

A Okay.

Q So what is the best piece of evidence of data, of scientific data, that you believe is available, sitting here today, that you know of, that reports on the percentage of patients who have delayed gastric emptying among the full body of patients on GLP-1s, who experience symptoms such as nausea and vomiting?

A I don't know if there's a lot of literature pertaining to that specific data point.

Q Well, if there's not a lot of literature --

A Sure.

Q -- how do you know that the majority of patients have nausea and vomiting while on a GLP-1 have delayed gastric emptying as the cause of that nausea and vomiting?

A I think pathophysiologically that's a mechanism. So first that there's an explanation for biopathophysiology that's -- it seems fairly well-established these drugs cause delay in gastric emptying, and so if that's a known

mechanism, then I think it makes sense that that's -- the symptoms are related to that mechanism.

Q So if I understand that correctly, Dr. Raines, because you're aware that GLP-1 medication is delayed gastric emptying, you then conclude that a patient who experiences nausea and vomiting at or around the time when they start the medication or increase their dose, their symptoms must be a result of delayed gastric emptying; is that correct?

MS. AMINOLROAYA: Object to form.

THE WITNESS: I think using "must" makes it sounds like it's so absolute. So it's like it makes sense or that -- it's more likely than not that that's why they have those symptoms.

BY MR. PRZYMUSINSKI:

Q So the more likely than not part comes from your belief that the effect of gastric emptying of these medications is more likely than not the reason why patients develop nausea and vomiting when they're on these medicines; is that correct?

MS. AMINOLROAYA: Object to form.

THE WITNESS: When I see a patient -- well, it's when patients that started a medication like this, or a GLP-1, present with nausea and vomiting, I feel like the most likely explanation, it's related to the

of impossible to get an objective test.

And that kind of speaks to their complications of, you know, how these people are really complicated.

Q Okay. Doctor, in terms of patients who come to you, right, and they have a presumptive diagnosis of gastroparesis, they refer to you for evaluation, whatever it is that you end up doing your end, you eventually presumably try to do your best to give them an accurate diagnosis, right?

A That's kind of a general statement. Like I generally try to assess patients, diagnose them, and treat them.

Like I've never heard anybody say like "I try to give them an accurate diagnosis." Sure, like.

Q But you want to do your best, right, to make sure you get the diagnosis correct?

A I want to practice within my field of expertise and like provide the best care to the patient.

Q Okay. And, Doctor, why would it be important, for example, to be able to distinguish a patient who's got gastroparesis from a patient who's got a different etiology of the GI symptoms?

MS. AMINOLROAYA: Objection to form.

THE WITNESS: I think what you're inferring is like there's discussion in the literature about

people being assigned a diagnosis of gastroparesis who may have a different disorder, like chronic nausea and vomiting disorder, and they may undergo treatment, like a surgical treatment, like a POEM surgery or a Botox injection, and how there's morbidity and mortality associated with those procedures, and that makes sense.

BY MR. PRZYMUSINSKI:

Q In fact, in your own practice, right, you say there's 30 percent of patients who are misdiagnosed, correct?

A Yeah.

Q That's a substantial number of people who, based on external evaluation by physicians, who presumably are good clinicians, still get the wrong diagnosis before coming to see an expert like yourself, correct?

MS. AMINOLROAYA: Object to form.

THE WITNESS: I see that in my small bowel bleeding practice, too.

BY MR. PRZYMUSINSKI:

Q You see that in what? I'm sorry.

A Like my small bowel bleeding practice. So it's like -- that's what you get in a referral center, as a lot of patients that come, they don't have a straightforward case and they're not getting better with the standard treatment or they're not following the expected course.

And so that referral bias, you know, really expresses itself at a tertiary care center. So we see that in a lot of different conditions.

Q No, I get that.

A Yeah.

Q But it is important to you, right, to get the right diagnosis, because you want to ensure that patients are not receiving unnecessary and inappropriate treatments, correct?

MS. AMINOLROAYA: Object to form. Asked and answered.

THE WITNESS: Sure. I understand the concern that patients that are labeled with a diagnosis of gastroparesis may get procedures and -- like a POEM surgery or medications that are not going to benefit them if they don't really have gastroparesis, and like I understand that concern.

MR. PRZYMUSINSKI: Okay. Doctor, a couple more things and then maybe we'll be close to done.

(Raines Exhibit 13 marked.)

BY MR. PRZYMUSINSKI:

Q Here you go, Doc.

So what I've marked as 13 is the ASGE 2011 guideline that's titled: "The role of endoscopy in gastroduodenal obstruction and gastroparesis."

presentation, and the same goes for cannabinoid hyperemesis, cyclical vomiting syndrome, rumination syndrome.

BY MS. AMINOLROAYA:

Q When would you perform -- when would you perform a test or order a test in a patient with symptoms of nausea and vomiting who were on a GLP-1 drug?

A It depends on the presentation. So the classic presentation we described where patients got no previous symptoms, no risk factors for any other pathology, their symptoms are typical or classic for gastroparesis, following set of symptoms correlates closely with like the initiation of the drug, then I would make that diagnosis and remove the drug.

In somebody with a very complicated history, and, say, a history of pre-existing diabetic gastroparesis or pre-existing pancreatitis, I may or may not make a conclusion that the patient's symptoms are related to the GLP-1, especially with lack of temporal correlation, where their symptoms were present before they started the drug.

Q Thank you. Turning to a different topic.

You were asked some questions about some rare or differential diagnoses for chronic nausea and vomiting, including median arcuate ligament syndrome, or MALS?

A Yes.

Q Superior mesenteric artery syndrome. Do you recall those questions?

A I do.

Q And you didn't include these in your chart. Is that because they are very rare causes of nausea and vomiting?

MR. PRZYMUSINSKI: Objection to form. Leading.

THE WITNESS: I didn't include every possible cause of chronic nausea and vomiting, just because they're too exhaustive, including those rare diseases.

So I included the most common disorders that we see, and kind of described the common disorders we consider and the kind of mechanism by which we evaluate patients by history and physical before we decide on doing tests, or sometimes not doing tests.

So basically including a list of kind of common or prevalent disorders and not -- this list is not meant to be exhaustive for every possible cause of chronic nausea and vomiting.

BY MS. AMINOLROAYA:

Q And for MALS and superior mesenteric artery syndrome, can you distinguish them from drug-induced gastroparesis?

A It's not so much that if they didn't have any risk

factors for those disorders, or their presentation doesn't fit, I wouldn't consider them.

So it's more like the patient's history is classic for drug-induced gastroparesis and that I'm making that diagnosis and then withdrawing the drug.

You can imagine that it's possible that another diagnosis might be present, but, you know, we go with what's by far most likely and then manage them accordingly.

Q And would you run tests for these conditions if you suspected them?

A Of course. So if there's a specific presentation, say, of SMA syndrome, would be a patient that's had dramatic weight loss, say of 100 pounds over the last couple months, and then has nausea and vomiting after eating, then that story is kind of consistent with or suspicious for SMA syndrome, and we would order a CAT scan as a specific test.

MS. AMINOLROAYA: Okay. Thank you, Doctor.

No further questions.

MR. PRZYMUSINSKI: Let's go off the record and give us one minute, please.

THE VIDEOGRAPHER: We are off the record. The time is 4:46.

(Off the record at 4:46 p.m.)

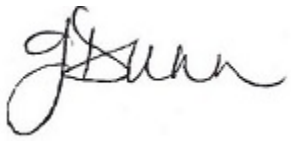
THE VIDEOGRAPHER: We're now back on the record. The time is 4:46 p.m.

CERTIFICATE

I, Jennifer A. Dunn, NCRA Certified Realtime Reporter, NCRA Registered Merit Reporter, Missouri Certified Court Reporter, Certified Shorthand Reporter in California, Illinois and Texas, do hereby certify that prior to the commencement of the examination, DANIEL RAINES, M.D., was duly remotely sworn by me to testify to the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony as taken stenographically by me at the time, place, and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.



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Dated: January 29, 2025

Exhibit I

Review

MOLECULAR METABOLISM

GLP-1 receptor agonists in the treatment of type 2 diabetes — state-of-the-art

Michael A. Nauck*, **Daniel R. Quast, Jakob Wefers, Juris J. Meier**

ABSTRACT

Background: GLP-1 receptor agonists (GLP-1 RAs) with exenatide b.i.d. first approved to treat type 2 diabetes in 2005 have been further developed to yield effective compounds/preparations that have overcome the original problem of rapid elimination (short half-life), initially necessitating short intervals between injections (twice daily for exenatide b.i.d.).
Scope of review: To summarize current knowledge about GLP-1 receptor agonist.
Major conclusions: At present, GLP-1 RAs are injected twice daily (exenatide b.i.d.), once daily (lixisenatide and liraglutide), or once weekly (exenatide once weekly, dulaglutide, albiglutide, and semaglutide). A daily oral preparation of semaglutide, which has demonstrated clinical effectiveness close to the once-weekly subcutaneous preparation, was recently approved. All GLP-1 RAs share common mechanisms of action: augmentation of hyperglycemia-induced insulin secretion, suppression of glucagon secretion at hyper- or euglycemia, deceleration of gastric emptying preventing large post-meal glycemic increments, and a reduction in calorie intake and body weight. Short-acting agents (exenatide b.i.d., lixisenatide) have reduced effectiveness on overnight and fasting plasma glucose, but maintain their effect on gastric emptying during long-term treatment. Long-acting GLP-1 RAs (liraglutide, once-weekly exenatide, dulaglutide, albiglutide, and semaglutide) have more profound effects on overnight and fasting plasma glucose and HbA_{1c}, both on a background of oral glucose-lowering agents and in combination with basal insulin. Effects on gastric emptying decrease over time (tachyphylaxis). Given a similar, if not superior, effectiveness for HbA_{1c} reduction with additional weight reduction and no intrinsic risk of hypoglycemic episodes, GLP-1RAs are recommended as the preferred first injectable glucose-lowering therapy for type 2 diabetes, even before insulin treatment. However, GLP-1 RAs can be combined with (basal) insulin in either free- or fixed-dose preparations. More recently developed agents, in particular semaglutide, are characterized by greater efficacy with respect to lowering plasma glucose as well as body weight. Since 2016, several cardiovascular (CV) outcome studies have shown that GLP-1 RAs can effectively prevent CV events such as acute myocardial infarction or stroke and associated mortality. Therefore, guidelines particularly recommend treatment with GLP-1 RAs in patients with pre-existing atherosclerotic vascular disease (for example, previous CV events). The evidence of similar effects in lower-risk subjects is not quite as strong. Since sodium/glucose cotransporter-2 (SGLT-2) inhibitor treatment reduces CV events as well (with the effect mainly driven by a reduction in heart failure complications), the individual risk of ischemic or heart failure complications should guide the choice of treatment. GLP-1 RAs may also help prevent renal complications of type 2 diabetes. Other active research areas in the field of GLP-1 RAs are the definition of subgroups within the type 2 diabetes population who particularly benefit from treatment with GLP-1 RAs. These include pharmacogenomic approaches and the characterization of non-responders. Novel indications for GLP-1 RAs outside type 2 diabetes, such as type 1 diabetes, neurodegenerative diseases, and psoriasis, are being explored. Thus, within 15 years of their initial introduction, GLP-1 RAs have become a well-established class of glucose-lowering agents that has the potential for further development and growing impact for treating type 2 diabetes and potentially other diseases.

Keywords Glucagon-like peptide-1 receptor agonists; Exenatide; Lixisenatide; Liraglutide; Dulaglutide; Albiglutide; Semaglutide; Type 2 diabetes; Cardiovascular disease; Body weight

1. DEVELOPMENT OF GLP-1 RAS

The identification of gut-derived glucagon-like peptide-1 (GLP-1), putatively belonging to the family of incretin hormones (i.e. gastrointestinal hormones released after nutrient intake with the ability to glucose-dependently augment insulin secretory responses during periods characterized by hyperglycemia) triggered the development of GLP-1 receptor agonists (GLP-1 RAs). The groups around Jens Holst (Copenhagen, Denmark) [1] and Joel Habener (Boston, MA, USA) [2] were the first to correctly identify "truncated" GLP-1 (GLP-1 [7—36 amide], the amidated form [1], or GLP-1 [7—37], the glycine-extended form [2]), as the product(s) of proglucagon translational processing in mammalian gut mucosa (L cells) as published in 1987. Based on the proglucagon nucleotide sequence, prior assumptions regarding processing enzymes led to an erroneous GLP-1 sequence longer by 6 N-terminal amino acid residues [3]. However, "truncated" GLP-1 was

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clearly insulinotropic at much lower (picomolar) concentrations compared to the extended GLP-1 sequence [1,2]. Initial studies with rodent models indicated that GLP-1 is highly effective as an insulinotropic agent in non-diabetic, metabolically healthy animals, but shared substantially reduced biological activity in diabetic animals with the previously identified incretin glucose-dependent insulinotropic polypeptide (GIP) [4]. Nevertheless, studies in human subjects with type 2 diabetes surprisingly showed well-preserved insulinotropic activity of both GLP-1 [7—36 amide] [5] and GLP-1 [7—36] that was accompanied by a short-term reduction in plasma glucose in the normal fasting range in patients previously characterized by persistent hyperglycemia [6,7]. However, GLP-1 was found to be proteolytically degraded and inactivated by the ubiquitous protease dipeptidyl peptidase-4 (DPP-4) [8] and both the intact GLP-1 molecule and DPP-4-generated metabolites (GLP-1 [9—36 amide] or [9—36]) were subject to rapid elimination from the circulation, with an elimination half-life of approximately 2 min [9]. Therefore, GLP-1 allowed the "proof-of-principle" that GLP-1 receptor stimulation is a suitable method of reducing plasma glucose in subjects with type 2 diabetes. It also helped clarify the three main mechanisms leading to reductions in plasma glucose concentrations: (a) glucose-dependent insulinotropic actions [5], (b) suppression of glucagon hypersecretion [7] except during episodes characterized by hypoglycemia [10], and (c) a deceleration of gastric emptying, which was found to be associated with marked effects on post-meal glycemic excursions [11]. Relatively early acute changes in appetite, satiety, and prospective food consumption by pharmacological doses of GLP-1 were described, resulting in a corresponding reduction in caloric intake [12], thus increasing the motivation to develop compounds mimicking the physiology of GLP-1 resistant to the proteolytic inactivation by DPP-4 and with slower elimination kinetics to allow for reasonable administration frequencies. As a product of serendipity, the peptide exendin-4 from the saliva of a venomous lizard (*Heloderma suspectum*, the Gila monster) was found to be homologous to mammalian GLP-1 and able to bind and activate GLP-1 receptors [13,14]. Synthetic exendin-4 was named exenatide and, without further modification, was the first GLP-1 receptor agonist approved to treat type 2 diabetes. The detailed background of the (patho)physiology of the incretin system and the history of the development of incretin-based glucose-lowering medications have recently been reviewed [15,16].

2. GLP-1 RAS AVAILABLE IN 2020 AND THEIR PHARMACOKINETIC PROPERTIES (TABLE 1)

Following the approval of exenatide to treat type 2 diabetes (USA: 2005; Europe: 2006), several pharmaceutical companies started diverse developments aiming at GLP-1 receptor stimulation with greater effectiveness and longer duration of action. Exenatide needs to be injected at least twice daily, which mainly provides active circulating concentrations covering two major meals every day, with low levels between the two injections. Liraglutide, approved in 2009, was designed to provide a nearly unchanged amino acid sequence compared to mammalian GLP-1. A free fatty acid side chain was coupled to the peptide, which promotes binding to albumin in plasma and interstitial fluid. Only a minor proportion (estimated 1—2%) of liraglutide circulates in a free (non-albumin-bound) form, ready to diffuse into tissues and bind receptors. The albumin-bound bulk forms a reservoir promoting prolonged action. Overall, the elimination half-life is approximately 13 h, making it a suitable preparation for once-daily injection. The next step was aiming at once-weekly injections of GLP-1 RAs. Exenatide was developed as a novel preparation with the active ingredient slowly released after subcutaneous injection from a matrix dissolving over time. Thus, the onset of action was very much delayed, and a steady state was not reached until 8—10 weeks of treatment [17,18]. Other approaches followed the strategy to couple (modified) GLP-1 to large proteins such as an immunoglobulin Fc fragment (dulaglutide or efpeglenatide) or albumin (albiglutide). These compounds appear to slowly degrade, with half-lives of approximately one week. After subcutaneous injection, they reach effective circulating concentrations relatively early, thus beginning to lower plasma glucose soon after initiating such treatment. Semaglutide is another compound with a structure generally similar to liraglutide (GLP-1 with a free fatty acid side chain) but with a much longer half-life, apparently mediated by even tighter coupling to albumin. Semaglutide is presently available for once-weekly subcutaneous injection. More recently, semaglutide was co-formulated with sodium N-(8-(2-hydroxybenzoyl) amino) caprylate (SNAC) for oral treatment. To account for the relatively low bioavailability of semaglutide when absorbed through the gastrointestinal tract, oral semaglutide needs to be administered daily. This is the first GLP-1 RA approved for oral administration. At equivalent doses, subcutaneous and oral semaglutide seem to have similar effects on HbA_{1c}, body weight, and adverse events [19]. Details regarding the molecular structures of various GLP-1 RAs and additional pharmacokinetic information were summarized by Nauck and Meier in 2019 [20].The time between subcutaneous (or oral) administration and the occurrence of peak concentrations is displayed in Figure 1.

2.1. Recommendations for initial up-titration (Figure 2)

All GLP-1 RAs developed to date have been designed for standardized dosage recommendations applicable to most if not all patients. Nausea and vomiting were noticed as common side effects, mainly occurring after the initiation of injection treatment or after increasing the dose. Peak plasma concentrations may determine the time when these symptoms most likely occur. In the early stages, a strategy of starting exenatide with a lower than maintenance dose, slowly increasing to the desired steady state, was found to reduce problems with gastrointestinal adverse events. Since then, recommendations have been developed for such an up-titration (dose escalation) approach to induce tolerance before patients are exposed to higher doses of GLP-1 RAs (Figure 2). Whether or not initial up-titration has to be recommended for a given compound/preparation depends on these agents' pharmacokinetic properties. This is not necessary for preparations such as once-weekly exenatide because the protracted action is the result of slow absorption, while the elimination of circulating exenatide follows the same kinetics as known for un-retarded (b.i.d.) exenatide (Table 1). Among those agents that have a long duration of action mainly through their slow elimination (long elimination half-life, see Table 1), those with a relatively rapid time to peak concentration ($T_{max} < 24$ h; applies to short-acting GLP-1 RAs, liraglutide, and semaglutide [20]) are those with recommended dose escalation schedules, while those with slower absorption (dulaglutide and albiglutide; $T_{max} \geq 48$ h) (Figure 1) can be initiated at their final dose. This could be explained by the fact that the GLP-1 RAs characterized by a free fatty acid side chain are injected as "free" (non-albumin-bound) compounds and that it takes some time to reach a steady—state equilibrium for binding to albumin. Only after reaching this equilibrium, most of the compound is bound to albumin, and, as such, is unable to diffuse into tissues and elicit effects (including adverse events).

Choosing the appropriate initial dose escalation schedule can have consequences for dose selection in phase 2 of clinical development programs, since doses carried on into phase 3 and suggested for

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Table 1 — Characteristics of GLP-1 RAs that have been approved to treat type 2 diabetes as of 2020.

GLP-1 RA	First approved (date)	Molecular weight (Da)[c]	Reference amino acid sequence	Other important components	Elimination half-life	Administration schedule	Pharmaceutical company	Reference
For subcutaneous injection								
Short-acting compounds								
Exenatide b.i.d.	2005 (USA); 2006 (Europe); Byetta	4186.6	Exendin-4	None	3.3–4.0 h	Twice daily	AstraZeneca[i]	[21]
Lixisenatide	2013 (Europe); Lyxumia; 2016 (USA); Adlyxin	4858.5	Exendin-4	Poly-lysine tail	2.6 h	Once daily	Sanofi	[22]
Long-acting compounds/preparations								
Liraglutide	2009 (Europe); 2010 (USA); Victoza	3751.2	Mammalian GLP-1	Free fatty acid[e]	12.6–14.3 h	Once daily	Novo Nordisk	[23]
Once-weekly exenatide	2012; BYDUREON[a]	4186.6	Exendin-4	Active ingredient encapsulated in microspheres of poly-(D,L-lactide-co-glycolide)	3.3–4.0 h[f]	Once weekly	AstraZeneca[i]	[21]
Dulaglutide	2014; Trulicity	59670.6	Mammalian GLP-1	Immunoglobulin Fc fragment	4.7–5.5 d	Once weekly	Eli Lilly and Company	[24]
Albiglutide	2014 (Europe); Eperzan Tanzeum (USA)[b]	72971.3	Mammalian GLP-1	Albumin	5.7–6.8 d	Once weekly	GlaxoSmithKline	[25]
Semaglutide	2017 (USA); 2019 (Europe); Ozempic	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7–6.7 d	Once weekly	Novo Nordisk	[26]
For oral administration								
Semaglutide (long-acting)	2020; Rybelsus	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7–6.7 d	Once daily	Novo Nordisk	[27]
Fixed-dose combinations								
With basal insulin (for subcutaneous injection)								
Liraglutide/ insulin degludec (iDegLira)	2014 (Europe); 2016 (USA); Xultophy	3751.2[d]	Mammalian GLP-1	Basal insulin	12.6–14.3 h	Once daily (anytime[g])	Novo Nordisk	[28]
Lixisenatide/ insulin glargine (iGlarLixi)	2016 (USA); Soliqua 100/33; 2017 (Europe); Suliqua	4858.5[d]	Exendin-4	Basal Insulin	2.6 h	Once daily[h]	Sanofi	[29]

[a] Improved once-weekly auto-injector BYDUREON BCise was approved in 2018.
[b] Marketing was discontinued in 2018.
[c] Mammalian GLP-1: 3297.7.
[d] For the GLP-1 RA component only.
[e] Promoting binding to albumin.
[f] Identical to the short-acting preparation.
[g] Approximately the same time every day.
[h] Before meals with the highest expected glycemic excursion.
[i] Previously Amylin Pharmaceuticals, Eli Lilly and Company, and Bristol Myers Squibb.

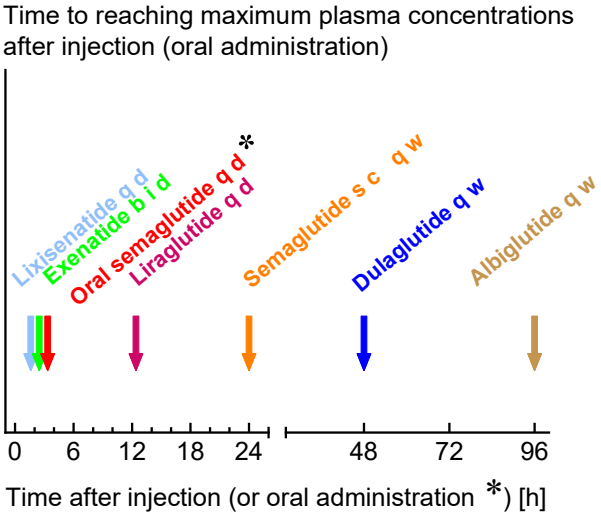

Figure 1: Arrows indicate the time from injection (or oral administration in the case of oral semaglutide) to peak plasma concentrations (C_{max}) for GLP-1 RAs (T_{max}). For references, please see [20]. Peak plasma concentrations may determine the time when nausea and vomiting are observed with GLP-1 RA treatment. The extremely slow absorption of once-weekly exenatide does not allow identification of a peak.

approval have to be effective as well as tolerable and safe. Less than optimal up-titration regimens may lead to (avoidable) side effects and will most likely limit the upper dose range that is considered to have a beneficial efficacy-side effect relationship.

Another question related to initial up-titration is whether it is needed when switching from one agent to another (e.g., for increasing efficacy or avoiding side effects). This is an issue that is not normally clarified by dedicated clinical trials. Therefore, recommendations mainly based on pharmacokinetic modeling are available [30].

2.2. Injection devices (Figure 3)

All GLP-1 RAs are delivered from pre-filled, dedicated pen injection devices developed for each particular product. However, details are considerably different for various products. They vary with respect to one time (mainly once-weekly GLP-1 RAs) vs multiple usage and in their ability to deliver one predetermined dose or whether it can be used to choose between several dose settings. For once-weekly exenatide, the microspheres containing the active drug need to be resuspended in buffer. Originally, this meant reconstitution of the active ingredient in vehicle solutions, which are stored in different vessels. An improved dual-chamber device has simplified this procedure. The dulaglutide pen injection device has received attention

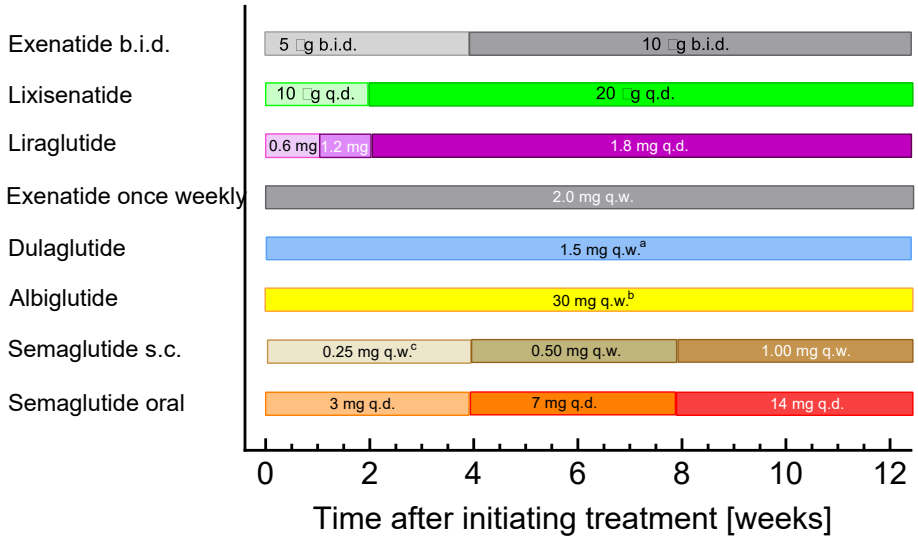

Figure 2: Recommendations issued in official package inserts regarding the necessity for slow up-titration of approved GLP-1 receptor agonists.

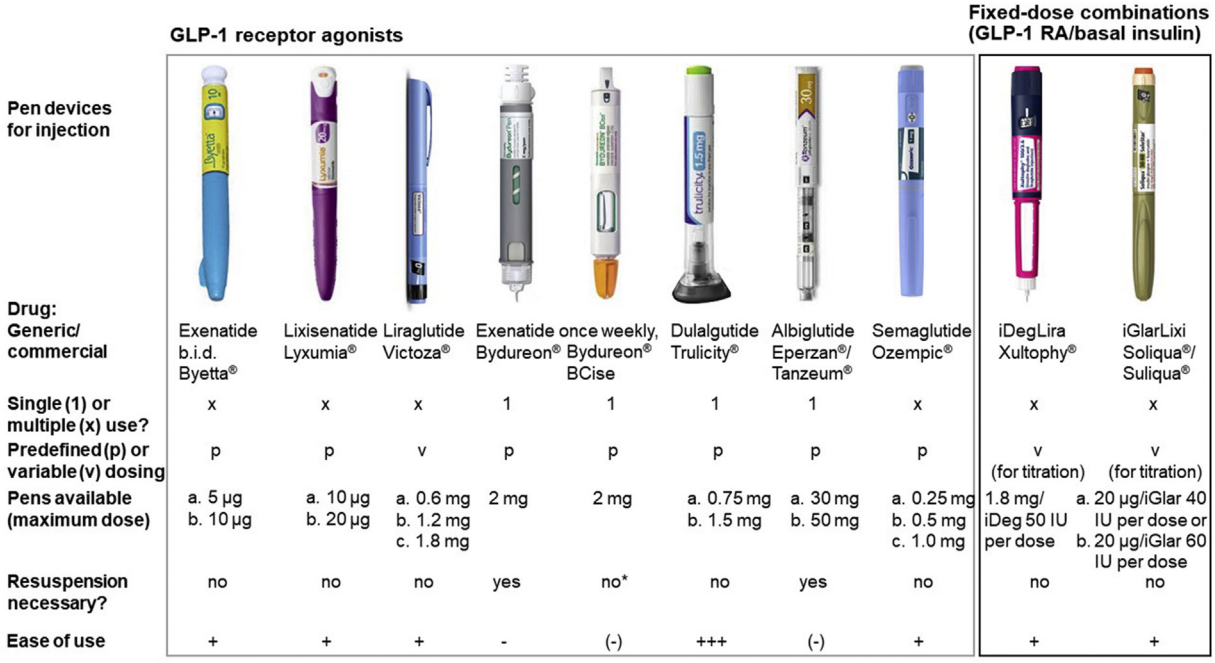

Figure 3: Optical appearance and properties of pen injection devices for approved GLP-1 receptor agonists (as mono substances or fixed-dose combinations with basal insulin). Modified from Nauck and Meier 2019 [20]. *Thorough shaking was necessary to evenly resuspend the active ingredient. The ease of use was estimated semi-quantitatively based on informal feedback from patients using these pen injection devices.

because of its single-use design and the needle, which is never visible throughout the injection procedure. Figure 3 depicts the visual appearance and some essential properties as well as the authors' evaluation of their ease of use of all available pen injection devices for GLP-1 RAs (free and fixed-dose combinations).

2.3. Classification as short- and long-acting GLP-1 RAs

Since the parent compound of GLP-1 RAs, GLP-1, has a very short elimination half-life that precluded its clinical use outside settings characterized by continuous administration, compounds/preparations with longer intervals between injections have been developed over time (Table 1). While this at first was thought to be mainly relevant with respect to the injection frequency, thus representing a convenience issue, essential pharmacological differences were later identified that suggested that both short- and long-acting GLP-1 RAs may have specific advantages and indications [31]. By definition, short-acting GLP-1 RAs (exenatide b.i.d. and lixisenatide) are characterized by short-lived peaks in plasma drug concentrations following each injection, with intermittent periods of near-zero concentrations. Thus, the time—action profile changes between periods (lasting a few hours) during which patients are exposed to effective circulating drug concentrations, and "resting" periods, during which GLP-1 receptors are

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not activated. In contrast, long-acting GLP-1 RAs, once at a steady state, are characterized by constantly elevated drug concentrations in a range leading to substantial GLP-1 receptor stimulation and only minor fluctuations between injections (e.g., a 24-h period for liraglutide and a week-long period for semaglutide). Of note, this definition does not rest on the injection frequency alone but on the pharmacological kinetics. Consequently, once-daily lixisenatide is a short-acting compound, whereas once-daily liraglutide is a long-acting GLP-1 RA (Table 1).

One obvious consequence of the different temporal patterns of short- and long-acting GLP-1 RAs with reduced exposure during the night in short-acting compounds is the ability of long-acting GLP-1 RAs to more profoundly lower fasting plasma glucose than short-acting GLP-1 RAs. This was best exemplified by a study comparing un-retarded (b.i.d.) and long-acting release (once-weekly) exenatide [18], although the differences were valid for the comparison of any short- and long-acting GLP-1 RA (Figure 4).

Another peculiarity relates to the effectiveness of GLP-1 RAs to slow gastric emptying in light of tachyphylaxis: while intermittent stimulation of GLP-1 receptors (short-acting GLP-1 RAs) is associated with preserved effects on gastric motility, even long-term continuous stimulation leads to desensitization, which probably begins early (within 4—24 h) and reaches its full expression after several weeks or months [32]. Since the velocity of gastric emptying is tightly coupled to the absorption of nutrient carbohydrates, slowed gastric emptying means reduced and/or delayed glycemic increases after meals. For short-acting GLP-1 RAs, delayed gastric emptying is the main mechanism for post-meal reductions in plasma glucose rises [33]. It has been claimed that short-acting GLP-1 RAs act preferentially on post-meal glycemic rises through their effect on gastric emptying, which are preserved over time [18,33,34], while there is substantial tachyphylaxis for long-acting compounds [18,34]. First, long-acting GLP-1 RAs reduce post-prandial glucose as well, mainly through increasing insulin and suppressing glucagon [31]. The effect on gastric emptying relates only to meals, before which the short-acting GLP-1 RA has been administered (once daily with lixisenatide and twice daily with exenatide b.i.d.), with minor effects at most for other meals [33]. Whether this translates into a net advantage is far from clear. In a recent meta-analysis comparing short- and long-acting GLP-1 RAs on a basal insulin background, post-prandial glucose increases were not significantly different [35]. Conditions under which a reduction in post-

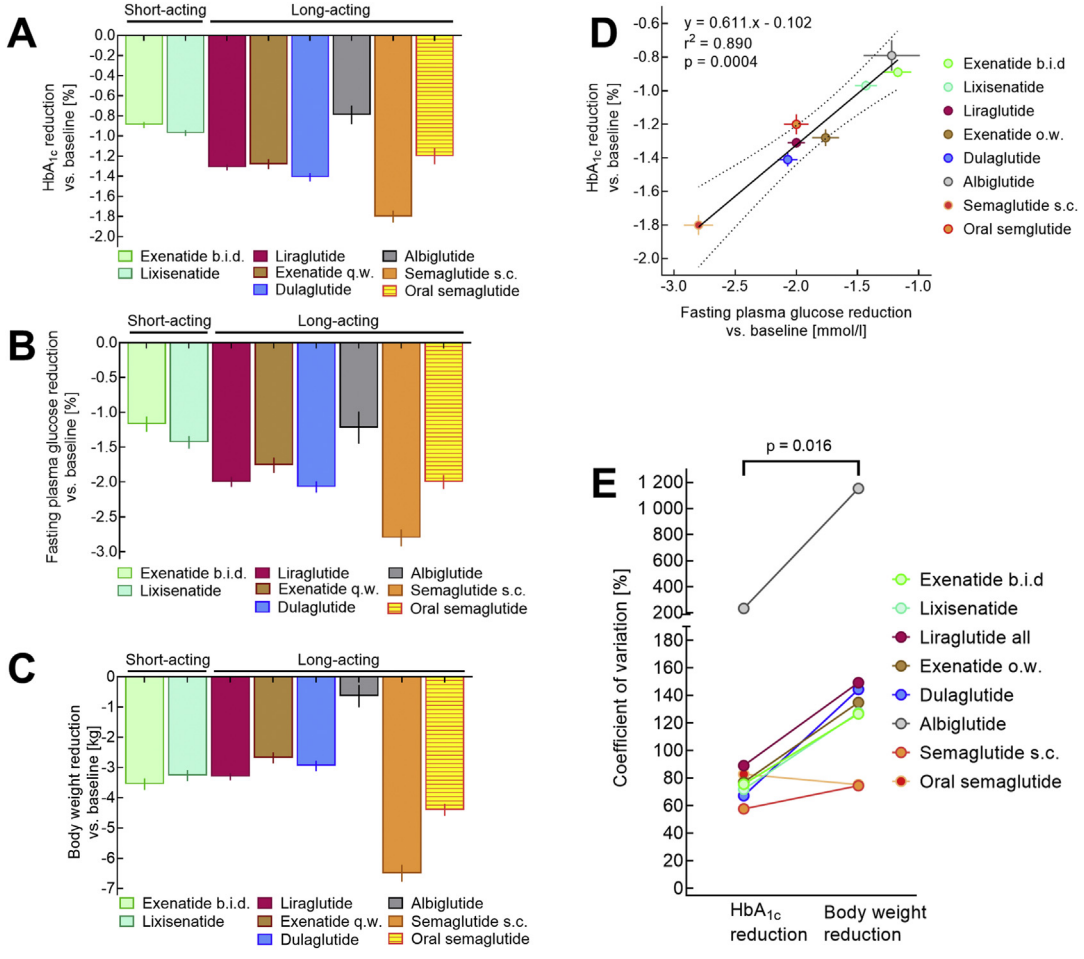

Figure 4: Comparison of approved GLP-1 RAs with respect to their effectiveness in reducing HbA_{1C} (A), fasting plasma glucose (B), and body weight (C). A linear regression analysis relating reductions in fasting plasma glucose to reductions in HbA_{1c} is shown in panel D. A comparison of the reported coefficients of variation for reducing HbA_{1c} and body weight is displayed in panel E. All data are from clinical trials reporting head-to-head comparisons between various GLP-1 RAs (exenatide b.i.d. vs lixisenatide [36], exenatide b.i.d. vs liraglutide [37], lixisenatide vs liraglutide [38], exenatide once-weekly vs liraglutide [39], albiglutide vs liraglutide [40], dulaglutide vs liraglutide [41], subcutaneous semaglutide vs dulaglutide [42], and oral semaglutide vs liraglutide [43]) on a background of oral glucose-lowering agents. Data concerning the same GLP-1 RA were pooled using conventional equations to calculate common means and their standard deviations.

meal glycemic excursions through a lasting deceleration of gastric emptying cause an obvious advantage of short-over long-acting GLP-1 RAs still need to be defined.

The effectiveness of short- and long-acting GLP-1 RAs for controlling fasting plasma glucose and HbA_{1c} in patients with type 2 diabetes otherwise treated with oral glucose-lowering agents was compared in relatively large head-to-head comparison trials conducted in patients receiving oral glucose-lowering medications as background therapy. Figure 5 shows representative data from these clinical trials. The reduction in fasting plasma glucose was systematically more pronounced with long-acting compounds. Consequently, HbA_{1c} values were reduced significantly more by long-acting GLP-1 RAs (since the overnight period represented one-third of the 24 h period). Efficacy regarding reductions in fasting plasma glucose and HbA_{1c} were highly correlated (Figure 4D), underscoring the importance of controlling fasting plasma glucose to achieve acceptable overall glycemic control based on commonly recommended target ranges. Similar conclusions were derived from specifically assessing 4 head-to-head clinical trials comparing short- and long-acting GLP-1 RAs (depicted in Nauck and Meier 2019 [20]).

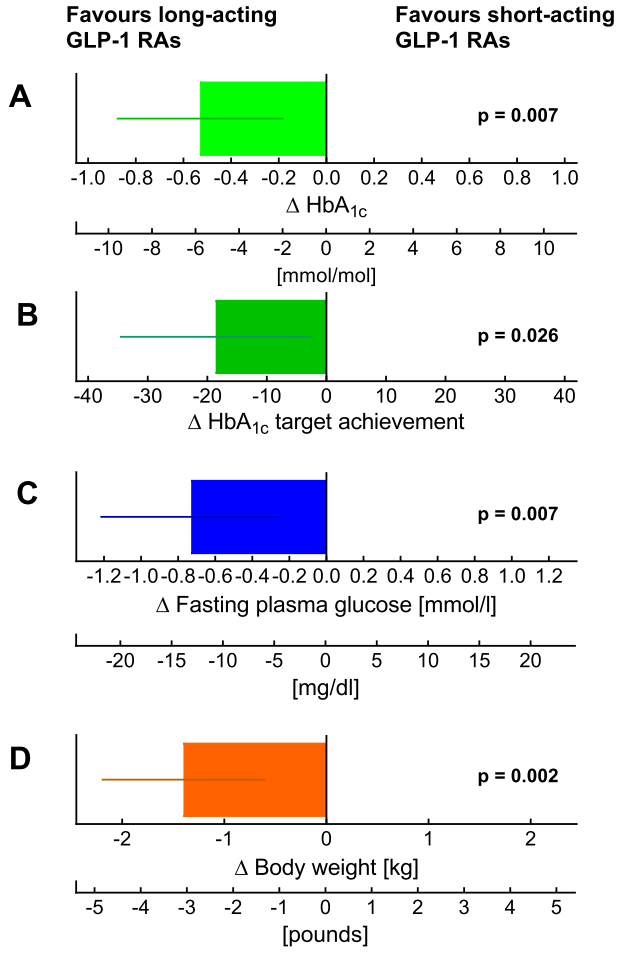

Figure 5: Meta-analysis comparing effects of short- and long-acting GLP-1 receptor agonists added to basal insulin in HbA_{1c} (A), HbA_{1c} target ($\leq$7.0%) achievement (B), fasting plasma glucose (C), and body weight (D). For each variable, the results were significantly better for long-acting compounds (liraglutide, once-weekly exenatide, dulaglutide, and semaglutide based on 6 studies) compared to short-acting compounds (exenatide b.i.d. and lixisenatide based on 8 studies). Both studies with free and fixed-dose combinations were analyzed. Modified from [50].

2.4. Comparison between GLP-1 RA and insulin therapy

According to current recommendations, recently diagnosed type 2 diabetes should be treated with patient education instructing in favor of a healthy lifestyle including nutrition avoiding excess calories and rapidly absorbed carbohydrates and physical exercise. At this early stage or later, single (mostly metformin) or combination therapy with oral glucose-lowering agents is recommended until injectable therapy with more effective drugs (insulin or GLP-1 receptor agonists) becomes necessary. It was surprising that when meta-analyzing studies directly comparing insulin treatment (mainly basal insulin combined with oral agents) with any of the GLP-1 receptor agonists, there was, at most, a minor difference in glycemic effectiveness [44,45]. If anything, GLP-1 receptor agonist had a slightly better effect on reducing HbA_{1c}. In addition, they uniformly led to some weight loss, and were only associated with hypoglycemic episodes when combined with sulfonylureas or insulin. As a factor contributing to more convenience, GLP-1 RAs can be employed using more or less standardized dosing instructions (including initial up-titration), while insulin needs to be individually titrated, with effective doses spread across a wide range. Some features of (basal) insulin and GLP-1 RA therapy in combination with oral glucose-lowering agents are summarized in Table 2. Of note, basal insulin and GLP-1 RAs are similarly effective in patients starting at very high baseline HbA_{1c} values (although patients selected by this criterion often fail to reach conventional target ranges for HbA_{1c}) [46]. Overall, these reasons form the basis of the ADA/EASD recommendation to preferentially use GLP-1 RAs in type 2 diabetes patients failing on oral agents alone [47]. Exceptions are circumstances suggesting type 1 diabetes or latent autoimmune diabetes in adults (LADA) with severe insulin deficiency.

2.5. Combination with (basal) insulin therapy

Therapy with basal insulin may fail because it may be successful in controlling fasting plasma glucose but does not sufficiently limit post-prandial glycemic excursions. Treatment intensification can mean adding one to three prandial insulin injections per day or adding a GLP-1 RA to ongoing insulin treatment. Nevertheless, GLP-1 RA therapy with a background of oral glucose-lowering medications may fail to achieve glycemic targets as well. In this case, combining it with insulin (mainly basal insulin) is a well-documented method of improving fasting, post-prandial, and overall (HbA_{1c}) glycemic control [51—57]. The combination of (basal) insulin with a GLP-1 RA is a highly effective treatment even for advanced stages of type 2 diabetes. It should only be used in patients needing a combination of two injectable treatments, especially considering the costs of such a combination.

When a GLP-1 RA is added to (basal) insulin, the combination is as effective as an intensified (basal bolus) insulin regime in terms of HbA_{1c} control, but with a much lower risk of hypoglycemia and weight gain [58].

When insulin is added to a GLP-1 RA, it helps control fasting plasma glucose. In combination with post-prandial effects of GLP-1 RAs (through decelerating gastric emptying, stimulating insulin, or suppressing glucagon secretion [31]), this provides excellent chances to achieve the target ranges for fasting, post-prandial, and overall (HbA_{1c}) glycemic control. In studies comparing basal insulin and GLP-1 RAs alone and in combination with each other, the combination achieved the lowest HbA_{1c} or highest HbA_{1c} reduction and a body weight transformation in between GLP-1 RA alone (lowest) and insulin alone (highest) [59]. There is a risk of hypoglycemic episodes with this combination, which is higher than treating with GLP-1 RAs alone, but lower compared to insulin treatment alone [59].

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Table 2 — Comparison of injectable treatments for type 2 diabetes with basal insulin or GLP-1 receptor agonists (based on meta-analyses of head-to-head comparisons [44,45]).

Criterion	Treatment with		Commentary
	Basal insulin	GLP-1 receptor agonists	
Glycemic control			
Fasting plasma glucose (FPG)	After meticulous titration, FPG concentrations in the target range (for example, 80 −110 mg/dl) can often be reached	Substantial reduction can be achieved. Overall, slightly less effective than insulin	An exception is semaglutide for once-weekly injection, which lowered FPG more than insulin glargine [48]
Prandial glycemic excursions	Can be reduced with appropriately dosed basal insulin	Reduced through deceleration of gastric emptying (short-acting GLP-1 RAs) and the influence on insulin and/or glucagon secretion [31]	Short-acting GLP-1 RAs maintain their effect on gastric emptying with continued administration, while there is tachyphylaxis over days/weeks with long-acting GLP-1 RAs [18]
HbA_{1c}	Substantial reduction, often into the target range	Substantial reduction, often into the target range	A slightly better reduction was shown with GLP-1 RAs, which might have been caused by insufficient titration of basal insulin; long-acting GLP-1 RAs achieve lower HbA_{1c} concentrations [44]
Dosing	By titration, often starting with approximately 10 IU/d. Effective doses are somewhere between 15 and 200 IU/d and cannot be precisely predicted based on clinical characteristics (for example, BMI)[a]	Standard dosage recommendations are available for individual GLP-1 RAs (often including some slow up-titration during the initial period)	Hypoglycemia may be dose-limiting for insulin, while nausea and vomiting may suggest using lower doses than generally recommended for GLP-1 RAs
Frequency	Usually once daily ("bedtime" insulin)	Between twice daily (exenatide b.i.d.) and once weekly	Variable for GLP-1 RAs because of their differing elimination kinetics
Changes in body weight	Increases by 1 −2.5 kg on average	Decreases by 2−6 kg on average	Within the range typical for each GLP-1 RA, individual weight loss is highly variable
Risk of hypoglycemic episodes	Hypoglycemic episodes are reported in approximately 43% of patients, in part depending on the proportion receiving sulfonylurea treatment [44]	Hypoglycemic episodes are reported in approximately 23% of patients, very much depending on the proportion receiving sulfonylurea treatment [44]	Clinically meaningful hypoglycemia with GLP-1 RAs heavily depends on a co-medication with sulfonylureas [44]
Nausea and vomiting as adverse events	Rare	Nausea (up to 20%) and vomiting (up to 10%) mainly occur after initiating treatment or associated with increases in dosage	Gastrointestinal side effects lead to medication withdrawal in approximately 5 −10% [49]

[a] Algorithms are available that aid the titration process.

The fact that a combination of a GLP-1 RA with basal insulin is a highly efficacious glucose-lowering treatment regime for advanced stages of type 2 diabetes has led to the development of fixed-dose combinations. GLP-1 RAs that are usually injected once daily (liraglutide or lixisenatide) were combined with basal insulin designed for once-daily injection (insulin degludec or insulin glargine), resulting in the fixed-dose combinations iDegLira [28,59] and iGlarLixi [60,61]. Since insulin must be titrated slowly as part of the dose-finding process, the GLP-1 RA component of these fixed-dose combinations is titrated slowly as well. This approach for introducing GLP-1 RA therapy has resulted in fewer problems with nausea, vomiting, or diarrhea. Apparently smaller steps of increasing GLP-1 RA exposure better support an adaptation process increasing patients' tolerance to such adverse reactions.

It has been postulated that short-acting GLP-1 RAs are particularly suited for combination with basal insulin because the strength of long-acting compounds, a greater effect on fasting plasma glucose, is not needed in this combination since the role of basal insulin would be to control fasting plasma glucose. However, the effect of slowing gastric emptying leading to slower absorption of nutrients (which is preserved over time with short-acting GLP-1 RAs) is a mechanism limiting post-meal glycemic excursion [31]. Notably, with short-acting GLP-1 RAs, this effect only applies to the meal before which the agent has been injected. A recent meta-analysis described the advantages of combining long-acting GLP-1 RAs (compared to short-acting GLP-1 RAs) with basal insulin [50]. This applied to free combinations (dosage determined separately for the GLP-1 RAs and basal insulin) as well as fixed-dose combinations [50]. As depicted in Figure 5, not only HbA_{1c} was lowered significantly more and HbA_{1c} targets were achieved in a higher proportion of patients, but also fasting plasma glucose concentrations and body weight were controlled better with long-acting GLP-1 RAs [50]. In addition, the risk of hypoglycemic episodes and gastrointestinal side effects was slightly, but significantly lower with long-acting GLP-1 RAs [50].

2.6. Weight loss induced by GLP-1 RAs

Intracerebroventricular [62] and peripheral administration of GLP-1 [12] and GLP-1 RAs [20,63] reduces appetite and prospective food consumption, increases satiety and a feeling of abdominal fullness, and limits caloric intake under conditions of ad libitum feeding. All GLP-1 RAs after longer-term treatment lead to weight loss but in varying degrees (Figure 4). Thus, GLP-1 RAs are unique in promoting weight loss while reducing the glycemia level, which in turn limits glucosuria (energy lost through urinary glucose excretion) and therefore should be associated with weight gain. Most other glucose-lowering agents, except for sodium/glucose cotransporter-2 (SGLT-2) inhibitors, usually lead to some weight gain (sulfonylureas, insulin, or thiazolidinediones) or are weight neutral (metformin, DPP-4 inhibitors, or α-glucosidase inhibitors) [47]. Liraglutide (at doses somewhat higher than used to treat diabetes mellitus) is also approved for pharmacological obesity therapy [64,65]. Semaglutide, the GLP-1 RA with the highest efficacy regarding weight loss in clinical trials of type 2 diabetes patients (Figure 4), is also undergoing evaluation as a weight-loss agent in obese subjects without diabetes mellitus [66−68].

The quantitative differences in body weight reduction typically achieved with different GLP-1 RAs critically depend on the respective doses selected in phase 2 studies. Since the primary indication for using GLP-1 RAs is type 2 diabetes, dose selection has mainly addressed glycemic control (HbA_{1c} reduction). Some data suggest that while HbA_{1c} reduction plateaus at relatively lower doses, higher doses may still be more effective for weight loss [69,70]. This is one

important reason for testing higher doses, for example, dulaglutide [71], to seek approval for more effective, higher doses of GLP-1 RAs for those who tolerate them.

The fact that some GLP-1 RAs have particularly weak effects with respect to body weight (e.g., albiglutide), whereas other compounds seem to have more pronounced effects (e.g., semaglutide) even if their glucose-lowering effects are similar, has sparked interest in characterizing the mechanism of action. It is obvious that appetite-and weight-reducing effects involve uptake into specific brain regions and interaction with CNS neural circuits involved in the homeostatic or hedonic [77] regulation of energy household and food intake. Table 3 summarizes recent insights gained from comprehensive studies characterizing semaglutide's (and liraglutide) effects on diet-induced obesity in rodents [72,73]. These findings point to a role of the arcuate nucleus within the hypothalamus, area postrema (AP), and nucleus tractus solitarii (NTS) for the influence of systemically administered GLP-1 RAs on appetite, satiety, calorie intake, and body weight as schematically summarized in Figure 6. In this model, GLP-1 RAs seem to be effective at preventing meal initiation by suppressing the activity of NPY/agouti-related peptide (AgRP) producing neurons in the arcuate nucleus and inducing meal termination in the lateral parabrachial nucleus (PB). Signals reaching the PB originate from the arcuate nucleus of the hypothalamus and brain stem (AP and NTS). POMC/CART neurons expressing GLP-1 receptors activate PB neurons and directly or indirectly suppress NPY/AgRP neurons [72,73], leading to disinhibition of suppressive signals to the PB (Figure 6). Recent data indicated subtle differences in how the brain interacts with liraglutide and semaglutide [73], which may help explain why these two GLP-1 RAs differ in their efficacy to reduce body weight (Figure 4). This information may guide the design of GLP-1 RAs or related pharmacological agents with even more pronounced weight loss efficacy. It still remains unclear why albiglutide has a weaker weight-lowering efficacy than other GLP-1 RAs (Figure 4).

Human studies have confirmed the ability of GLP-1 RAs to influence food choices (toward a selection of less energy-dense healthier foods) [66,78]. However, in contrast to some recent findings in rodents [73], studies in human subjects did not observe any interference of semaglutide treatment with a reduction in energy expenditure that usually accompanies weight loss (as one important mechanism for maintaining body weight close to a pre-determined "set point") [66,79]. Twelve weeks may not be sufficient to reach a steady state of weight reduction and possibly compensatory mechanisms. Of interest are the results of questionnaires indicating that obese subjects had fewer food cravings and could better resist food cravings while treated with semaglutide [66]. The answers point to the fact that eating was considered less pleasurable during treatment with semaglutide [66]. This could be in line with functional magnetic resonance imaging showing that GLP-1 R activation decreases anticipatory food reward (the anticipated pleasure of eating certain meals) and increases consummatory food reward (the pleasure offered by eating a meal) [80]. The regulation of energy intake thus is not only subject to homeostatic regulation (nervous system circuits attempting to maintain unchanged body weight), but also interacts with the brain reward system [80–84].

The robust effects of GLP-1 RAs to reduce body weight, usually by 2–7 kg (or % of initial body weight) on average in type 2 diabetes, have led to the exploration of GLP-1 RAs as a novel pharmacological treatment in obese but non-diabetic subjects often with impaired fasting glucose or glucose tolerance ("prediabetes"). Based on the observation that dose–response relationships have shown a plateau for glycemic control at lower doses than for body weight reduction,

Table 3 – Mechanisms involved in GLP-1 RA-associated appetite and weight reduction as reported in a recently published comprehensive study focusing on the effects of semaglutide (compared to liraglutide) on diet-induced obesity in mice (based on Secher et al., 2014 and [72] and Gabery et al., 2020 [73]).

Aspects of the mechanism of GLP-1 RA-induced weight loss	Findings	Explanation/ commentary
Access of peripherally circulating GLP-1 RAs into the central nervous system	• No transport across the blood–brain barrier (BBB) • Uptake of liraglutide and semaglutide into selected brain areas: (a) not protected by the BBB (circumventricular organs); (b) protected by the BBB: for example, nucleus arcuatus (hypothalamus), area postrema, nucleus tractus solitarii, and dorsal motor nucleus of the vagus nerve (brain stem) • A potential role of tanycytes in mediating uptake of semaglutide into some brain areas	• Absence of GLP-1 Rs in brain endothelial cells • Uptake of liraglutide and semaglutide into selected brain areas is similar, but not fully identical (e.g., semaglutide had a distribution extending more laterally and into posterior portions of the nucleus arcuatus)
Access of GLP-1 RAs to GLP-1 receptors in the brain	• Brain areas with a high uptake of semaglutide are equipped with GLP-1 receptors (mainly in the hypothalamus and hindbrain)	• Uptake of fluorescently labeled semaglutide is substantially reduced in GLP-1 $R^{-/-}$ animals
Direct effects of GLP-1 RAs on the hypothalamus (nucleus arcuatus)	• POMC/CART neurons are depolarized (stimulated); NPY/AgRP neurons are hyperpolarized (inhibited)	• As previously shown for liraglutide
Neuronal activation in brain areas accessible for GLP-1 RAs	• C-Fos activation observed in the area postrema and nucleus tractus solitarii (brain stem)	• Immediate consequence of GLP-1 R engagement
Neuronal activation in brain areas not directly accessible for GLP-1 RAs ("secondary activation")	• C-Fos activation in the bed nuclei of the stria terminalis, central amygdala nucleus, midline group of the dorsal thalamus, parasubthalamic nucleus, and parabrachial nucleus (CGRP-expressing neurons)	• These are brain regions that have been identified as part of an appetite-regulation pathway related to meal termination [74]
Food intake and body weight	• Reduced (strong initial effect and some attenuation over time); substantial weight reduction compared to placebo treatment	• Reduced caloric intake is the main mechanism leading to weight loss with GLP-1 RAs
Food preference	• Semaglutide reduced intake of chocolate bars in favor of chow	• These results suggest that GLP-1 RAs may promote healthier food choices
Energy expenditure	• Weight loss induced by caloric restriction leads to a compensatory reduction in energy expenditure • Weight loss induced by semaglutide only transiently did so: energy expenditure returned to baseline levels within a week	• Interferes with an effective compensatory mechanism counteracting weight loss; needs to be confirmed in human studies

BBB: blood–brain barrier, GLP-1 R: glucagon-like peptide-1 receptor, GLP-1 RA: GLP-1 receptor agonist, POMC/CART: proopiomelanocortin/cocaine- and amphetamine-regulated transcript, NPY/AgRP: neuropeptide Y/agouti-related peptide.

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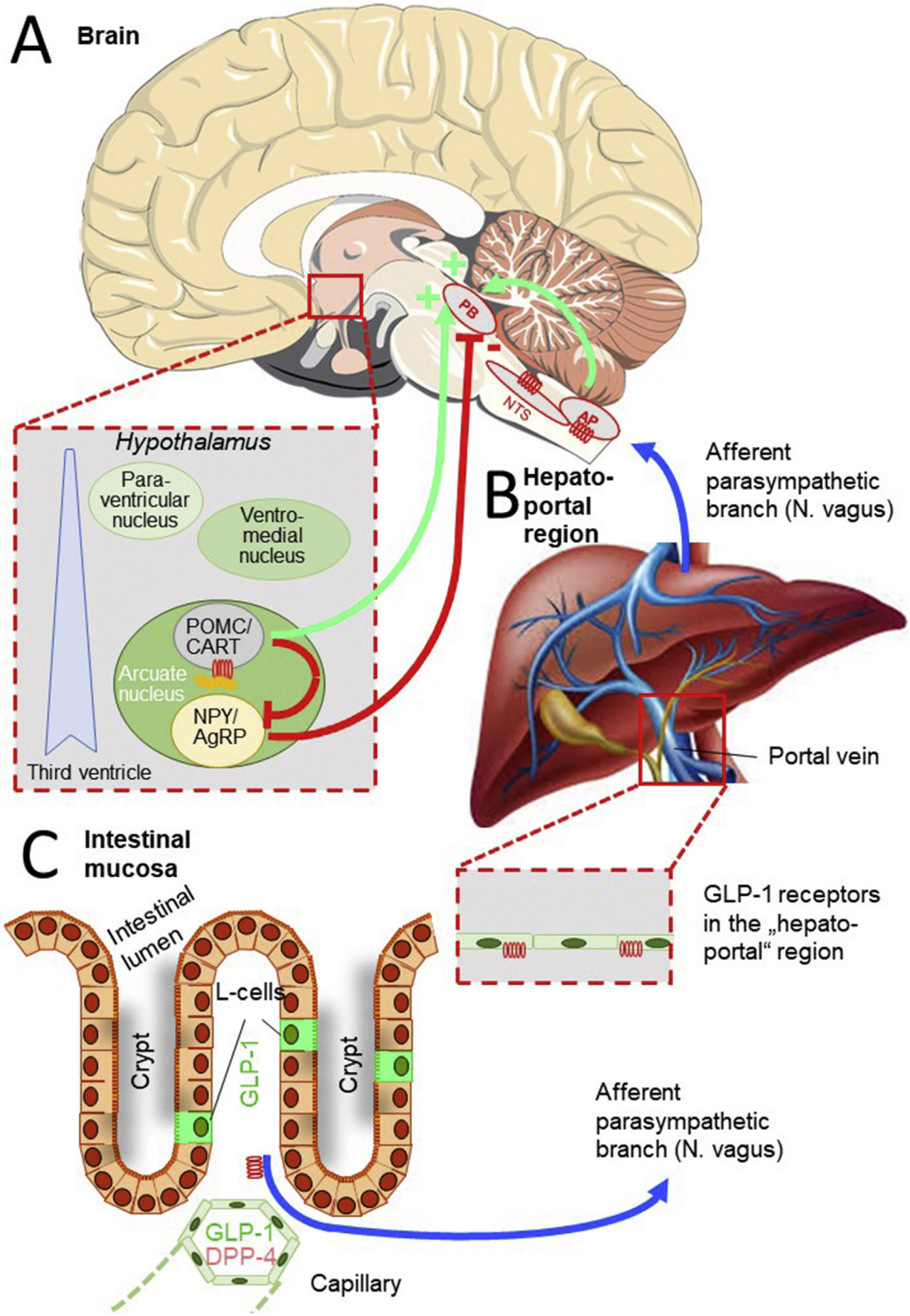

Figure 6: Schematic diagram demonstrating how various methods of GLP-1 or GLP-1 RA administration into the general circulation can reach and influence brain areas involved in the regulation of energy intake and expenditure [72,73]. (A) Evidence also suggests that GLP-1 receptors in the hepatoportal region [75] (B) and on afferent parasympathetic nerve endings in the intestinal mucosa (C) [76] may generate central nervous system signals influencing insulin secretion and metabolism. Stimulatory signals (+) are shown in green, inhibitory (−) signals are depicted in red, and afferent parasympathetic (vagal) signals are denoted in blue. See the text for a more detailed explanation of the mechanisms.

higher doses have been employed to treat obese subjects. Daily doses up to 3.0 mg are approved for liraglutide (1.8 mg is the maximum dose for treating type 2 diabetes) [65], and clinical trials have tested semaglutide at up to 0.4 mg per day (that is, corresponding to 2.8 vs 1.0 mg per week for type 2 diabetes) [68]. Doses of up to 4.5 mg per week (vs a maximum of 1.5 mg for type 2 diabetes) are being explored for dulaglutide [85]. In subjects tolerating these higher doses of GLP-1 RAs, substantially greater reductions in body weight were observed than with "conventional" doses typically employed to treat type 2 diabetes. Impaired glucose tolerance often improves while subjects receive this type of treatment, most likely explained by the glucose-lowering properties of GLP-1 RAs [65,86]. Whether this means a true interference with or a delay in the progression to diabetes needs to be studied in trials assessing the long-term consequences of withdrawing GLP-1 RA treatment. GLP-1 RAs need to be continuously administered after induction of weight loss. After discontinuation of this pharmacological treatment, body weight will revert to baseline values or at least close to baseline values within a few months [87].

It has often been overlooked that the individual weight reduction response of patients with type 2 diabetes treated with GLP-1 RAs is more variable than the reduction in HbA_{1c}. This is obvious when treatment-related weight and HbA_{1c} changes are plotted individually [18,88]. It can also be concluded from a higher coefficient of variation (the standard deviation divided by the mean value expressed as a percentage) depicted in Figure 4E. Why some patients do not reduce their body weight at all when treated with GLP-1 RAs while others respond with weight loss very much exceeding the mean values reported in clinical trials (for example, Figure 4) can only partially be answered with current knowledge. Schlogel et al. [89] examined responders and non-responders (with respect to exenatide's effect on energy intake) and found hypothalamic effects only in responders. This hints at a biological reason most likely related to the mechanisms summarized in Table 3 and could be the result of genetic polymorphisms, for example, regarding GLP-1 receptors or other components of the signal transduction pathway.

However, the weight-lowering effects of GLP-1 RAs can probably be modulated by lifestyle measures aiming at reduced calorie intake [90], although a systematic examination of the combined efficacy of initiating treatment with GLP-1 RAs and patient education aiming at optimizing the weight-reducing effects of GLP-1 RAs is still lacking (or has failed to provide convincing benefits [91]). Obese patients with type 2 diabetes often tried various dietary approaches to lose weight and failed. One possible explanation for the wide spectrum of weight loss observed with initiating treatment with GLP-1 RAs could be that some patients feel motivated for further attempts to improve their eating behavior and lifestyle because of a realistic chance of success. Other patients may instead believe that the GLP-1 RA will ameliorate their obesity problem without them contributing by willingly restricting caloric intake and engaging in physical activity. This is a hypothesis worth sparking clinical studies, as would be developing a dedicated patient education program aiming at optimizing weight reduction with GLP-1 RAs in type 2 diabetes and in particular when using them in obese, prediabetic subjects to prevent progression to type 2 diabetes [68,86,92].

2.7. Gastrointestinal and other adverse events

Side effects most reported with GLP-1 RAs are nausea, vomiting, and diarrhea, often summarized as gastrointestinal adverse events. They are typically most prominent when initiating treatment with (any) GLP-1 RA or after increasing the dose (e.g., during recommended up-titration regimens). Since these symptoms can occur in fasting subjects, they are probably not related to the effects of GLP-1 RA treatment on gastrointestinal functions (e.g., deceleration of gastric emptying) but instead are caused by direct interactions with CNS GLP-1 receptors (Figure 6) most likely located in the brain stem (area postrema). Nausea is typically reported in up to 25% and vomiting or diarrhea in up to 10% of subjects treated with GLP-1 RAs [20,49]. For most patients, these are short, self-limited episodes that cease spontaneously, even with continued treatment. The time point of occurrence is probably related to the time characterized by maximum drug concentrations typically occurring at T_{max} following several hours to days after each injection (Figure 1). The probability of these side effects varies with sudden incremental exposure to GLP-1 RAs. An often-used recommendation to avoid these adverse events is a standardized, slowly increased exposure through up-titration regimens (Figure 2), which have been shown to mitigate gastrointestinal side effects. Experience with fixed-dose combinations with basal insulin (which must be titrated much more slowly) underscore the effectiveness of this approach.

Summarizing adverse event reporting from clinical trials examining GLP-1 RAs discloses subtle differences in the risk of these side effects depending on the short- (worse) vs long-acting nature (better) background medication (worse in combination with metformin or insulin) that are also related to the individual compound/preparation [49].

In part related to adverse events, patients randomized to GLP-1 RA treatment often discontinue this medication. Table 4 shows reported figures from cardiovascular (CV) outcome trials with GLP-1 RAs, the largest trials available reporting the longest durations of exposure to

Table 4 — Proportions of patients randomized to GLP-1 RA treatment in CV outcome trials discontinuing study drug treatment, proportion of the follow-up period during which patients were exposed to the study drug, and proportions discontinuing due to adverse events.

GLP-1 RA	Proportion of patients permanently discontinuing the study drug [%][a]	Proportion of follow-up period during which the study drug was taken [%]	Proportion of patients discontinuing the study drug because of adverse events [%]	Trial/reference
Lixisenatide	27.5	90.5	11.4	ELIXA [95]
Liraglutide	n.p.	84	9.5	LEADER [96]
Once-weekly exenatide	43.0	76	4.5[c]	EXSCEL [97]
Dulaglutide	26.8	82.2	9.1	REWIND [98]
Albiglutide	24.5	87	8.6	HARMONY Outcomes [99]
Semaglutide s.c.	21.3	86.5	13.2	SUSTAIN-6 [100]
Oral semaglutide	15.3	n.p.[b]	11.6	PIONEER-6 [101]

n.p.: Not presented.

[a] Not counting transient "drug holidays."

[b] 75% received the study medication for more than 1 year (total follow-up of 15.3 months).

[c] Counting only gastrointestinal adverse events. No CV outcome trial has been reported for exenatide b.i.d. (approved before these studies became mandatory).

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GLP-1 RAs. The proportions of patients reporting adverse events were not generally different from shorter clinical trials [49]. This indicates that while the frequency and severity of side effects can be successfully modulated through optimized up-titration regimens, a certain percentage of patients does not tolerate this treatment with the current regimens of initiating GLP-1 RA. Interestingly, in a recent study allowing individual titration of oral semaglutide, most patients discontinuing this treatment did so after exposure to the lowest (initial) dose of 3 mg per day [93]. This may indicate that the sensitivity of patients toward developing gastrointestinal adverse events is considerably heterogeneous, such that some patients fail to tolerate low doses, while for others, higher doses than currently used may offer better effectivity without increasing side effects. Along these lines, higher doses of some GLP-1 RAs are being explored, especially to further reduce body weight [65,67,68,71,86]. The reported nausea, vomiting, and diarrhea rates are generally lower in Japanese than Caucasian populations, suggesting that the cultural background and eating behaviors may also have an impact on the induction of nausea with GLP-1 RAs [94].

When GLP-1 RAs were introduced as novel agents to treat type 2 diabetes, there was uncertainty about several potential adverse effects such as acute pancreatitis, pancreatic cancer, and thyroid cancer [102,103]. The availability of large databases from randomized CV outcome studies that defined pancreatitis, pancreatic cancer, and thyroid cancer as "adverse events of special interest" with protocols carefully adjudicating suspected cases has reduced these concerns since they uniformly reported hazard ratios of these adverse events not significantly different from 1.0 [104]. In retrospect, an elevation in amylase and/or lipase activity commonly observed with GLP-1 RAs [105,106] together with abdominal symptoms typically triggered by GLP-1 RAs may have led to the suspicion of pancreatitis. Since 2 diagnostic criteria are sufficient for this diagnosis, pancreatitis may have been diagnosed even in the absence of imaging results supporting this diagnosis [105]. Nevertheless, thyroid C cells express GLP-1 receptors [107], and subjects at risk of (rare) medullary thyroid cancer (e.g., based on personal or family history or genetic testing) should not be treated with GLP-1 RAs. These subjects were consequently excluded from clinical trials with GLP-1 RAs.

3. CARDIOVASCULAR OUTCOME STUDIES

All GLP-1 RAs were approved for treating type 2 diabetes patients after 2008 (except for exenatide b.i.d., which was approved in 2005). Therefore, all of the compounds/preparations had to provide results of dedicated cardiovascular outcome studies supporting at least the cardiovascular safety of these medications in the target population and compared to placebo both on a background of standard of care (allowing any additional glucose-lowering medication necessary to meet targets recommended by current guidelines). The typical primary endpoint was major adverse cardiovascular events (MACE: time to first event of either CV death or non-fatal myocardial infarction or stroke). According to guidelines by the US Food and Drug Administration, definite proof of CV safety would be a hazard ratio for MACE near or below 1.0 with a confidence interval not exceeding 1.3 (equivalent to a 30% elevation in risk). If a study provides preliminary proof of safety (upper limit of the confidence interval below 1.8), another CV outcome study aiming at definite proof is required. Depending on the ambitions, studies with different patient numbers and durations are needed. This explains the heterogeneity in study designs, sample sizes, and follow-up periods between the trials summarized in Figure 7 [20,108]. Another differentiator is the proportion of patients with pre-existing cardiovascular damage, albeit defined by previous events or supported by functional testing and/or imaging, which ranged from 31% (REWIND [98]) to 100% (ELIXA [95] and HARMONY Outcomes [99]) and obviously had an important impact on the CV event rate observed during the trials.

3.1. Heterogeneity regarding principal results from CV outcome trials comparing GLP-1 RAs with placebo

Figure 7A displays hazard ratios (active treatment vs placebo) for MACE and their 95% confidence intervals for all published CV outcome trials with GLP-1 RAs. With the exception of lixisenatide, all other GLP-1 RAs at least show a trend of a reduced incidence of MACE events, which was significant in four studies and not significant in 2 additional studies. Hence, the results are, from a clinical perspective, quite heterogeneous and suggest that some GLP-1 RAs are more suitable to prevent CV events than others. Assessing heterogeneity mathematically as part of the meta-analysis, however, resulted in I^2 values suggesting at most moderate heterogeneity. Our interpretation is that comparing the various trials indicates a common mechanism of action, but important differences related to pharmacokinetic properties (one injection per day of lixisenatide does not fully cover a 24 h period), optimized dosages as a result of phase 2 dose-finding studies (probably applies to 2 mg per week of once-weekly exenatide), and drug discontinuation rates impact the degree of CV benefit that can be achieved with individual compounds/preparations as suggested by Caruso et al. [109]. Remarkably, the reduction in MACE events with albiglutide is very much comparable if not more pronounced than with other effective GLP-1 RAs (Figure 7A) despite its reduced ability to lower HbA_{1c}, fasting plasma glucose, and body weight in clinical trials (Figure 4) [40]. When choosing a GLP-1 RA to prevent CV events, one of the compounds significantly reducing MACE should be selected. Liraglutide (LEADER trial) was unique in not only significantly reducing MACE events, but also CV and all-cause mortality [96]. Semaglutide (subcutaneous, SUSTAIN-6 [100], and oral, PIONEER-6 [101]) trials showed impressive results, especially considering their small sample sizes and short durations. This was due to their primary ambition to demonstrate safety, the minimum requirement for approval, which requires smaller patient numbers, a shorter trial duration, and fewer events. This preliminary nature makes additional larger trials necessary to fully characterize the potential to prevent CV complications of type 2 diabetes (oral semaglutide: SOUL, ClinicalTrials.gov NCT 03914326) or obesity (once-weekly semaglutide s.c.: SELECT ClinicalTrials.gov NCT03574597).

Individual CV outcome trials were not powered to assess single CV endpoints, but a composite endpoint such as MACE. However, a meta-analysis pooling results from all individual trials provided some insight that CV events can generally be prevented by GLP-1 RA treatment [108]. As shown in Figure 7B, across all of the trials, significant reductions by 9–16% in the incidence of acute myocardial infarction, stroke, cardiovascular, and even all-cause death could be achieved for the GLP-1 RA class as a whole, while in the individual trials, these effects on individual cardiovascular outcomes were only occasionally significant. However, the number of such events (myocardial infarction, stroke, CV death, etc.) in individual trials was too low to provide the power to detect significant differences. This also applied to a reduction in the hospitalization for heart failure, which was not significant in any of the individual trials, but in the meta-analysis (hazard ratio, 0.91; 95% confidence interval, 0.83–0.99). This figure contrasts with the consistent ≈35% risk reduction for hospitalization for heart failure in all studies employing SGLT-2

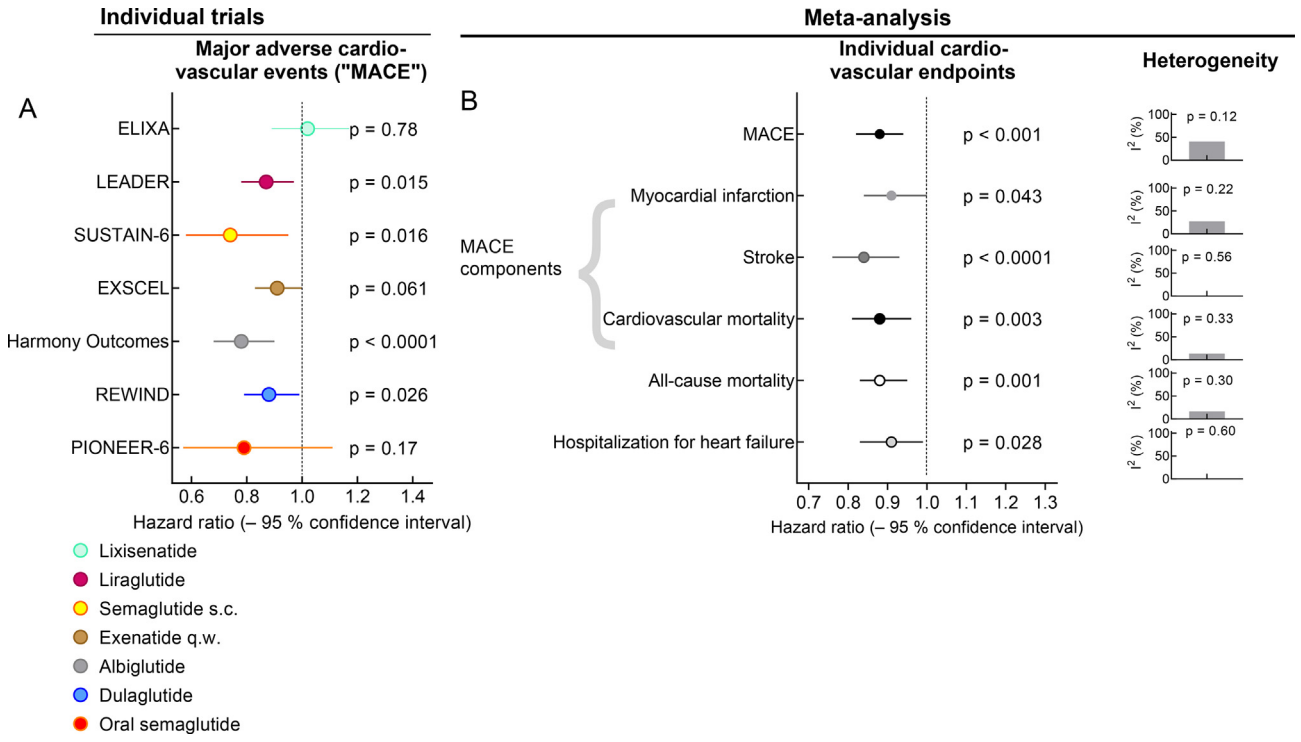

Figure 7: Results of cardiovascular outcome studies comparing GLP-1 RAs with placebo on a background of standard of care. (A) Reduction in major adverse cardiovascular events (MACE: time to first event) in published individual clinical trials. (B) Results of a published meta-analysis [108] analyzing various cardiovascular endpoints across all of the clinical trials shown in panel A. MACE (a combination of either cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was the primary endpoint in all studies. Meta-analysis results are supplemented with I^2 and related p values indicating the heterogeneity of the analysis of individual endpoints (column of panels to the far right) as reported in [108].

inhibitors [110,111]. Of note, patients with NYHA IV heart failure were excluded from the CVOTs with GLP-1 RAs, such that no firm conclusions could be drawn regarding these patients. In light of the dedicated studies of liraglutide in patients with advanced heart failure, which not only failed to prove benefits, but suggested some potential for harm caused by GLP-1 RAs [112,113], GLP-1 RAs are usually not recommended as first choice if the objective is to prevent heart failure complications. Indeed, the small increase in heart rate observed with GLP-1 RA treatment may represent an unfavorable mechanism in patients with advanced (NYHA III/IV) heart failure [34]. Instead, the pattern of effects observed in CV outcome trials suggests a primary mode of action preventing complications of atherosclerosis such as ischemic events (myocardial infarction and stroke) and associated mortality (vide infra).

Most CV outcome trials with GLP-1 RAs recruited patients with type 2 diabetes characterized by established CV disease (e.g., previous CV events) or indicators of a high risk of CV events. These studies were originally primarily designed as safety trials, and accruing a large number of CV events in high-risk patients was one strategy to limit the sample size and duration of these trials. Therefore, the results of these trials cannot be extrapolated to the general population of type 2 diabetes patients including those with short disease duration and lack of CV comorbidities. The REWIND study (employing dulaglutide as the GLP-1 RA) was exceptional in having recruited a mixed population with 31.5% with and 68.5% without pre-existing atherosclerotic vascular damage [98]. Subgroup analyses of the REWIND trial (dulaglutide vs placebo, both on a background of standard of care) highlighted that dulaglutide was able to induce a significant MACE reduction in the overall study population and quantitatively similar regardless of the patients' history of CV events (p for interaction was 0.97). Those with or without CV co-morbidities at baseline had identical risk reductions (that for both subgroups just missed statistical significance) [98]. These data suggest a potential to prevent CV complications even in lower-risk type 2 diabetes patients, yet fall short of definite proof.

Along the same lines, a subgroup analysis within the meta-analysis by Kristensen et al. [108] identified no statistically significant heterogeneity for the effect of GLP-1 RAs on MACE between primary vs secondary prevention ($p = 0.24$) The more recent meta-analysis by Marsico et al. [114] strengthened this conclusion. However, since the absolute risk reduction was smaller in the primary prevention population, it remains to be ascertained whether this intervention would be cost-effective in lower-risk patients.

3.2. Mediation analyses aiming to define the mechanism(s) leading to beneficial cardiovascular effects of GLP-1 RAs

As previously demonstrated in detail [115], GLP-1 RAs modify a number of risk factors for cardiovascular complications, including body weight reduction, lower systolic blood pressure, reduced plasma LDL cholesterol and triglyceride concentrations, and improved glycemic control (reductions in fasting and post-meal plasma glucose resulting in lower HbA_{1c}; see Figure 4). Thus, a reduction in the incidence of ischemic events could be the consequence of a more beneficial risk profile under treatment with GLP-1 RAs. Mediation analysis is an approach to identify potential mediators that might explain the findings observed in terms of endpoints. While several mathematical approaches have been developed, their common aim is to show that taking into account the changes in a potential mediator reduces the

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effect size with respect to the endpoint of interest. Potential mediators are variables measured in the trial that are differentially affected by active drugs and placebo. For example, GLP-1 RAs reduce systolic blood pressure by 2—4 mmHg compared to placebo treatment [115]. Considering this reduction in systolic blood pressure, if the difference in MACE outcomes is reduced, it can be concluded that a reduction in systolic blood pressure mediates the prevention of MACE. If the effect is nullified, this mechanism is responsible for 100% of the effect, but partial mediation is also possible.

Using slightly different approaches, mediation analyses have been published on the effects of liraglutide in the LEADER trial [116] and the effects of dulaglutide in the REWIND study [117]. Interestingly, both analyses concluded that HbA_{1c} reduction was a potential mediator, responsible for up to 82% of the total effect. A reduction in urinary albumin excretion was found to be another potential mediator in the LEADER trial (responsible for up to 33% of the total effect). Of note, any potential mechanism that does not leave a measurable trace or has not been assessed in a given trial will never be identified as a potential mediator using this approach. This applies to intravascular changes associated with the progression of atherosclerosis unless they are accompanied by, for example, inflammatory responses, which can be identified by measuring C-reactive protein or inflammatory cytokines (which was not done in any of the CV outcome trials of GLP-1 RAs). Hence, identifying HbA_{1c} reduction as a potential mediator of CV benefits induced by GLP-1 RAs leaves a number of open questions, especially since it has been difficult to establish a relationship of HbA_{1c} reduction with cardiovascular benefits in other glucose-lowering medications [118].

For CV outcome studies of GLP-1 RAs, a relationship that links the magnitude of the HbA_{1c} reduction achieved (versus placebo) to the hazard ratio for major adverse CV events was suggested by Caruso et al. [119]. In particular, they identified a relationship between the mean reduction in HbA_{1c} in individual trials and the corresponding hazard ratio for stroke [119]. Figure 8 presents a similar analysis, however, including CV outcome studies with DPP-4 and SGLT-2 inhibitors. Remarkably, these additional data points were positioned along the same regression lines, and the relationship between the reduction in HbA_{1c} and MACE (Figure 8A) or stroke (Figure 8C) remained significant. Similar trends of non-fatal acute myocardial infarction and CV death were non-significant. A significant reduction in hospitalizations for heart failure was restricted to SGLT-2 inhibitors and independent from reductions in HbA_{1c} (Figure 8F). Such an analysis may not only confirm the relationship initially observed by Caruso et al. [119], but may also explain why DPP-4 inhibitors and SGLT-2 inhibitors did not consistently reduce MACE [110,111,115]. Given that all of the CV outcome trials aimed at glycemic equipoise (similar if not identical glycemic control for active drug and placebo treatment), only trials with potent glucose-lowering medications such as GLP-1 RAs, which failed to achieve glycemic equipoise, underscored the potential for a CV benefit.

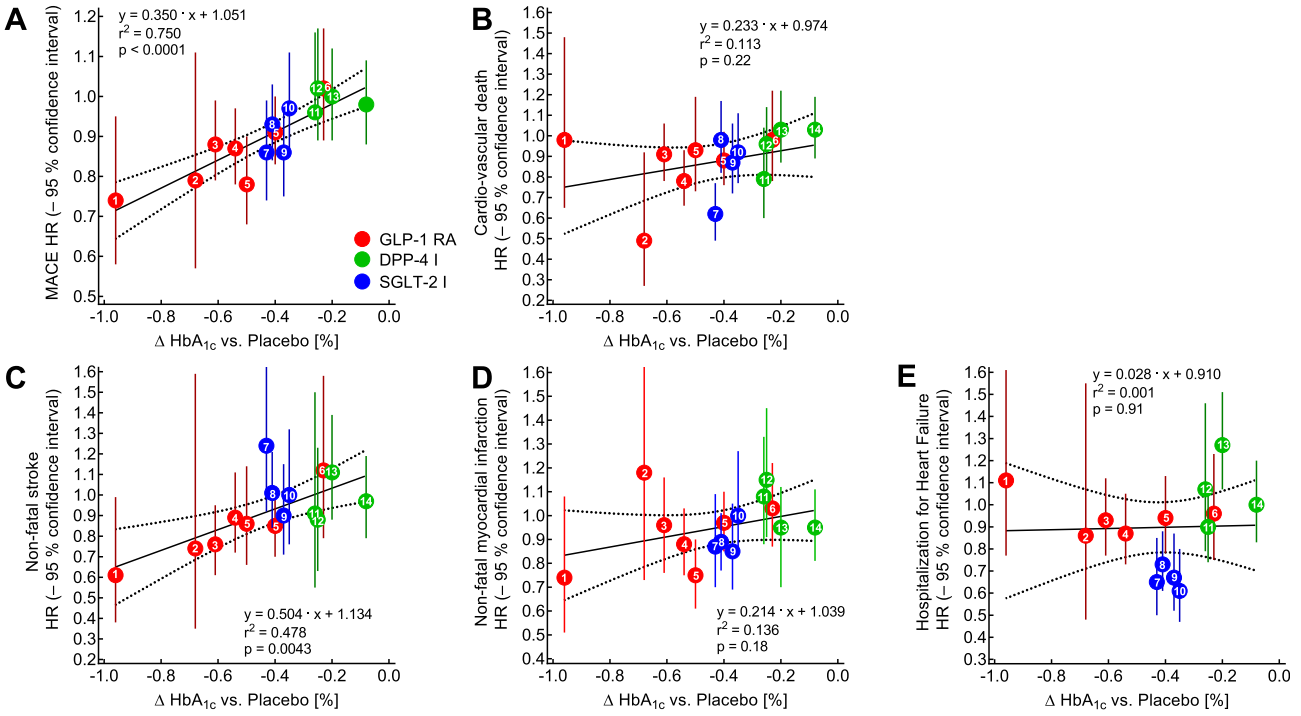

Figure 8: Regression analysis of differences achieved in HbA_{1c} concentrations between patients treated with placebo and active drug vs hazard ratios for major adverse cardiovascular outcomes (MACE; A), cardiovascular death (B), non-fatal stroke (C), non-fatal myocardial infarction (D), and hospitalization for heart failure (E) reported from cardiovascular outcome studies with GLP-1 receptor agonists (red), SGLT-2 inhibitors (blue), and DPP-4 inhibitors (green). Significant associations are shown for MACE (A) and non-fatal stroke (C) with similar slopes of the regression lines, while for cardiovascular death (B) and non-fatal myocardial infarction (D), a less prominent, non-significant correlation resulted from the analysis. Regarding hospitalization for heart failure (E), hazard ratios did not vary with HbA_{1c} reduction. Analyzing GLP-1 receptor agonists only resulted in significant correlations for MACE and stroke as well as previously reported by Caruso et al. [119] but not for the other endpoints. Numbers in symbols identify the clinical trials: 1: SUSTAIN-6 (subcutaneous semaglutide) [100], 2: PIONEER-6 (oral semaglutide) [101], 3: REWIND (dulaglutide) [98], 4: LEADER (liraglutide) [96], 5: EXCSEL (once-weekly exenatide) [97], 6: ELIXA (lixisenatide) [95], 7: EMPA-REG Outcomes (empagliflozin) [120], 8: DECLARE-TIMI-58 (dapagliflozin) [121], 9: CANVAS program (canagliflozin) [122]; 10: VERTIS-CV (ertugliflozin, presented at the 80th scientific session of the American Diabetes Association); 11: EXAMINE (alogliptin) [123], 12 CARMELINA (linagliptin) [124], 13: SAVOR-TIMI-53 (saxagliptin) [125], and 14: TECOS (sitagliptin) [126].

3.3. Mechanisms explaining cardiovascular benefits

Understanding the robust interference of GLP-1 RAs with the progression and complications of atherosclerosis requires detailed knowledge of the pathomechanisms involved and consequences of GLP-1 receptor stimulation. Various steps and mechanisms involved in atherogenesis [127] are displayed in Figure 9A, while the effects of GLP-1 receptor stimulation in arterial vessel walls are shown in complementary Figure 9B.

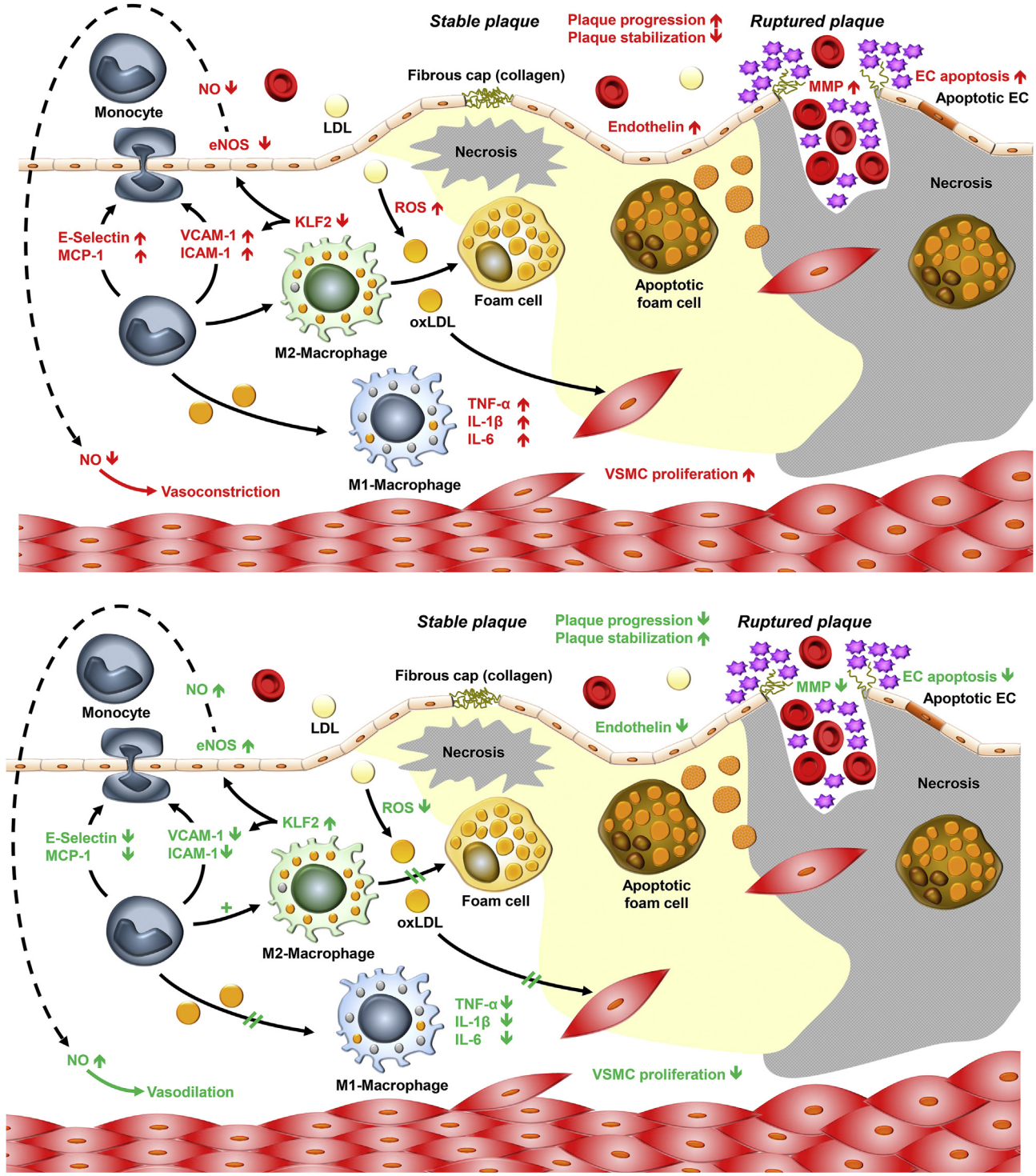

Figure 9: Mechanisms driving the development of atherosclerotic lesions in patients with type 2 diabetes (A) and effects of GLP-1 RAs on the progression of atherogenesis and the development of its complications (B). See the text for further details on the mechanisms involved and references to the supporting literature. EC: endothelial cell, eNOS: endothelial nitrous oxide synthase, ICAM-1: intercellular adhesion molecule-1, IL: interleukin, KLF-2: Krüppel-like factor-2, LDL: low-density lipoprotein, MCP-1: monocyte chemoattractant protein-1, NO: nitrous oxide, oxLDL: oxidized low-density lipoprotein, ROS: reactive oxygen species, TNF-α: tumor necrosis factor, VCAM-1: vascular cell adhesion protein 1, VSMC: vascular smooth muscle cell.

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3.4. Atherogenesis in patients with type 2 diabetes (Figure 9A)

LDL cholesterol is transported across the intima layer of arterial blood vessels and in part oxidized to oxidized LDL particles (oxLDL) through reactive oxygen species (ROS). Contact of monocytes and macrophages with oxLDL and ROS promotes further infiltration of monocytes by secreting adhesion molecules such as vascular cell adhesion protein 1 (VCAM-1), monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), and E-selectin. Stimulated by oxLDL, monocytes transform into macrophages. M1 macrophages produce pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, and IL-1β. M2 macrophages take up lipid particles through phagocytosis and suppress the formation of Krüppel-like factor 2 (KLF-2), which in turn suppresses endothelial NO synthase (eNOS), leading to lower NO production and preventing vasodilation through NO-mediated vascular smooth muscle relaxation. In an environment dominated by ROS and oxLDL, M2 macrophages transform into foam cells that can undergo apoptosis and release their lipid content into the lipid core of nascent atherosclerotic plaques. Stable plaques are characterized by a dense fibrous cap mainly composed of collagen that helps prevent rupture. However, as atherogenesis progresses, larger necrotic areas form, endothelial cells (EC) undergo apoptosis, and matrix metalloproteinases (MMP) proteolytically destroy the fibrous cap. This results in plaque rupture, thrombus formation, and bleeding into necrotic plaque areas.

3.5. Interference of GLP-1 RAs with the atherogenesis process (Figure 9B)

As demonstrated in animal studies and experiments using human cells, GLP-1 receptors expressed in endothelial cells, monocytes, macrophages, and vascular smooth muscle cells produce numerous effects potentially interfering with the process of atherosclerotic plaque formation or rupture. First, ROS production is reduced by GLP-1 [128—130], exenatide [131], liraglutide [130,132—136], and semaglutide [137]. The oxLDL-mediated activation of monocytes and macrophages and the consecutive activation of adhesion molecules such as VCAM-1, MCP-1, E-selectin, and ICAM-1 is successfully reduced by GLP-1 receptor stimulation (e.g., GLP-1 [138], exenatide [138—140], dulaglutide [141], and liraglutide [142]). This results in a reduction of monocyte accumulation in the vascular wall, as shown for example with exenatide [143]. Endothelial cells express more eNOS, produce more NO, and suppress endothelin formation that overall lead to vascular smooth muscle relaxation and endothelium-derived vasodilation (e.g., GLP-1 [130,144], exenatide [144], and liraglutide [130,133,145]). M2 macrophages instead of M1 macrophages preferentially form from monocytes (e.g., lixisenatide [146] and liraglutide [147]) and the otherwise suppressed KLF-2 formation instead increases (e.g., by lixisenatide [146], liraglutide [147], and dulaglutide [141]). The reduced exposure to ROS after GLP-1 receptor stimulation slows the process of foam cell formation (e.g., GLP-1 [148,149] and liraglutide [150]) and reduces caspase-mediated apoptosis of foam cells (e.g., GLP-1 [151] and semaglutide [152]) and the formation of necrosis in the core of atherosclerotic plaques (e.g., GLP-1 [153] and lixisenatide [154]). Furthermore, GLP-1 receptor stimulation reduces vascular smooth muscle proliferation (e.g., exenatide [155] and liraglutide [156]) and possible migration into plaques (liraglutide [157]). The integrity of endothelial cells was shown to be stabilized by exenatide [158,159]. Plaque hemorrhage was reduced by semaglutide [160]. The reduced expression of MMP preserves intact fibrous caps and prevents plaque rupture (e.g., GLP-1 [153], exenatide [161] and semaglutide) [160]. The overall result is a slowing of plaque progression and plaque stabilization. The formation, extent, and vulnerability of atherosclerotic lesions in animal models characterized by rapidly progressive atherosclerosis was substantially reduced by GLP-1 RA [160]. Studies in humans have partially confirmed anti-inflammatory [162] and anti-atherosclerotic actions of GLP-1 RAs [163].

4. RENAL EFFECTS OF GLP-1 RAS

The discovery of beneficial renal effects using GLP-1 RAs is a recent achievement mainly based on the observations that GLP-1 RAs prevented new-onset macroalbuminuria [99,164,165], reduced urinary albumin excretion [164,165], or slowed the decline in the estimated glomerular filtration rate (eGFR) over time [164—166]. The mechanisms leading to these renal benefits are largely unknown. While significant reductions in achieving renal composite outcomes were reported [99,164,165], they heavily relied on dominating effects preventing new-onset persistent macroalbuminuria. Clinical events indicating progression to end-stage renal disease (doubling in serum creatinine, major reduction by 30—50% in eGFR, achieving eGFR below 15 ml/min per 1.73 m^2, necessary to initiate renal replacement therapy or perform renal transplantation, or death due to renal causes) have rarely been reported in numbers allowing a meaningful analysis. This is due in part to the fact that the populations studied had fairly good renal function at baseline. Studies of selected patients with prominent or advanced renal disease are lacking. A dedicated trial studying the effects of semaglutide on renal outcomes in type 2 diabetic patients with chronic kidney disease is underway to clarify these issues: FLOW (ClinicalTrials.gov NCT03819153). Since most GLP-1 RAs can be used in chronic kidney disease, while SGLT-2 inhibitors lose some of their glucose-lowering efficiency with reduced glomerular filtration rates, further studies appear to be needed, especially since patients with reduced eGFR at baseline seem to benefit most in terms of preventing rapid declines in eGFR [164]. For the time being, more robust effects have been reported for SGLT-2 inhibitors, which are preferred glucose-lowering medications interfering with the progression of diabetic renal disease even in patients with moderately reduced eGFR [110,111,167].

5. ADHERENCE AND PERSISTENCE (OBSERVATIONAL STUDIES)

While initiating GLP-1 RA treatment in clinical practice is already discrepant from current guidelines, suboptimal treatment persistence and adherence are additional important issues [168]. A recent study suggested that HbA_{1c} reductions with GLP-1 RAs observed in real-world studies were $\sim$0.5% below those observed in controlled clinical trials [169]. The authors attributed approximately three-fourths of this gap to poor medication adherence in clinical practice. In a retrospective analysis comparing different GLP-1 RAs, once-weekly injectable dulaglutide demonstrated greater adherence rates than once-weekly exenatide or once-daily injectable liraglutide [170]. Of note, over a six-month treatment period, 26.2% of dulaglutide and 48.4% of once-weekly exenatide patients discontinued treatment, and in a direct comparison of dulaglutide and liraglutide, the respective discontinuation rates were 28.0% and 35.6% [170]. When the proportion of days covered (PDC) was compared between once-weekly exenatide and liraglutide, the proportions of patients with good adherence (PDC $>$ 0.80) after 6 months were 53.4% and 48.1%, respectively [171]. Likewise, an analysis of Medicare recipients in the US reported a PDC $>$80% of 43.2% in patients receiving exenatide

QW, 39.0% in patients receiving exenatide b.i.d., and 35% in patients receiving liraglutide [172]. Hence, no consistent data on differences in adherence between short- and long-acting GLP-1 RAs could be found. A recent real-world retrospective observational study showed that dulaglutide users were less likely to interrupt treatment than semaglutide and exenatide BCise users [173]. In a pairwise meta-analysis comparing treatment adherence and persistence between GLP-1 RAs and long-acting insulin analogues, the odds ratio for non-adherence was 1.95, suggesting better adherence with the insulin analogs [174]. As a general trend from these comparisons, adherence to GLP-1 RAs seems to be better with lower injection frequencies.

However, these studies must be interpreted with caution because of the retrospective study designs and partially incomplete data assessment. Furthermore, observation periods of 6–12 months are still too short to judge the long-term adherence to GLP-1 RAs.

6. DISCONTINUATION RATES IN RANDOMIZED CV OUTCOME TRIALS

As presented in Table 4, some patients randomized to GLP-1 RA treatment discontinued the assigned medication. The proportion withdrawing from GLP-1 RA treatment in CV outcome trials ranged from 15% (oral semaglutide) to approximately 25%; an exceptionally high withdrawal rate was observed with once-weekly exenatide (43%), possibly related to the less comfortable pen injection device requiring resuspension of the active ingredient in buffer (Figure 3) or the occurrence of subcutaneous nodules at injection sites [175]. Approximately one-half of the discontinuations were reported to be associated with adverse events (Table 4). In the trials reporting discontinuation because of any adverse events and those specifically due to gastrointestinal side effects, the latter were responsible for approximately one-half of the withdrawals. Another potential reason contributing to withdrawals was a perception of ineffective glycemic and body weight control achieved (including a suspicion to have been randomized to placebo), perhaps as a consequence of the progression of the type 2 diabetes mellitus disease process [176]. Whether or not GLP-1 RA treatment counters this progression (e.g., through β cell-preserving effects [177]) remains an open question. In rodents, these effects are restricted to earlier periods in life [178] when β cells have a propensity to proliferate, which they lose in adult animals [179]. Overall, randomized controlled clinical trials showed that high persistence regarding GLP-1 RA treatment could be maintained for periods up to 5 years, which contrasts with data from observational studies (as previously described). Efforts to encourage persistent use of GLP-1 RA, as successful in clinical trials, may be necessary to achieve better persistence in clinical practice as well.

7. GUIDELINE RECOMMENDATIONS AND CLINICAL REALITY

The current ADA/EASD consensus algorithm suggests that GLP-1 RAs should be preferentially used after metformin failure in (a) patients with established atherosclerotic cardiovascular disease and (b) patients without established cardiovascular disease with high-risk indicators, such as age $\geq$ 55 years, carotid, lower extremity or coronary artery stenosis >50%, left ventricular hypertrophy, eGFR < 60 ml/min, or albuminuria [180]. GLP-1 RAs may also be used to prevent hypoglycemia or weight gain. The ESC guidelines have gone even further in recommending GLP-1 RAs (or SGLT-2 inhibitors) as first-line therapy in patients with established atherosclerotic cardiovascular disease or in those at high or very high risk (that is, three or more major risk factors or diabetes duration $\geq$ 10 years without target organ damage, plus any other additional risk factors) [181]. According to these international recommendations, ~30–60% of patients with type 2 diabetes would qualify for a GLP-1 RA. However, in clinical reality, the percentage of patients receiving GLP-1 RA treatment remains low, ranging between 1% and 10% in different countries [182].

The reasons for this apparent gap between guideline recommendations and clinical reality are heterogeneous: first, the cost of treatment with GLP-1 RAs is considerably higher than most oral glucose-lowering drugs, but instead comparable to the cost of an intensified insulin treatment regimen (including glucose-monitoring costs). Although various cost-effectiveness analyses suggested that the overall benefits associated with GLP-1 RA treatment outweigh the direct treatment costs [183], the price of the currently available GLP-1 RAs remains a major barrier in most countries. Second, the need for daily or weekly injections discourages some patients from initiating GLP-1 RAs [184]. Third, contraindications (i.e., history of pancreatitis, diabetic retinopathy, or medullary thyroid cancer) may prevent the use of GLP-1 RAs in affected patients [185]. Finally, gastrointestinal adverse events remain an important limitation of GLP-1 RA treatment [49].

8. OPPORTUNITIES FOR FUTURE DEVELOPMENT OF GLP-1 RAS

Since 2005, when exenatide was first approved, rapid development began that has yielded progress with respect to GLP-1 RAs pharmacokinetics, with the obvious consequence that instead of 2 (or more) injections per day, now once-weekly injections are available. While advances making GLP-1 RA treatment more comfortable are welcome, it should not be overlooked that the effectiveness of GLP-1 RAs has increased in large steps (e.g., going from exenatide to liraglutide, the first long-acting GLP-1 RA, but also advancing to semaglutide, which clearly has superior efficacy than other GLP-1 RAs, especially with respect to body weight reduction as depicted in Figure 4). These significant advances, occurring in substantial leaps, suggest that this development has not yet come to an end.

8.1. Oral administration of GLP-1 RAs

One development worth noting is that, despite the peptide nature of all of the GLP-1 RAs, semaglutide is now available for oral administration. An absorption enhancer molecule (SNAC; see Section 2) must be part of the oral preparation to promote absorption through the gastric mucosa. Low bioavailability after oral administration makes daily administration of a semaglutide tablet necessary to avoid wide fluctuations in drug exposure. It must be taken on an empty stomach, and for 30 min after taking oral semaglutide, no other food, drink, or medication should be administered to allow undisturbed absorption. With these precautions, in principle, quantitatively similar effects can be achieved with respect to glycemic control and lowering body weight [19]. The phase 3 PIONEER program, however, was conducted with somewhat lower doses (maximum, 14 mg/d) than would be necessary to match the effectiveness of subcutaneous semaglutide at 0.5 or 1.0 mg/week [43].

In addition to developing peptide-based GLP-1 RAs for oral administration, some reports described small molecules with GLP-1 receptor agonist properties that should be suitable for oral administration without additives and/or sensitive procedures. To date, the binding affinities of these compounds has been too low to support further development as clinically effective drugs [186–189].

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8.2. Use in patients with type 1 diabetes

Effects of GLP-1 or GLP-1 RAs on residual insulin secretion [190], glucagon suppression [190,191], gastric emptying delay [190], and plasma glucose [192,193] in type 1 diabetic subjects were described starting in the early stages of GLP-1 discovery. Clinical trials employing liraglutide or exenatide (un-retarded preparation usually administered b.i.d.) in addition to intensified insulin regimens, however, did not demonstrate convincing benefits (e.g., with respect to optimized glycemic control or the frequency of hypoglycemic episodes) or described potential adverse outcomes such as a higher risk of ketoacidosis. Only body weight and insulin doses were consistently reduced [194—197]. However, these results do not rule out benefits for specific subgroups (e.g., obese patients with type 1 diabetes or subjects at high risk of cardiovascular complications) or with dosage recommendations that may differ from those used to treat type 2 diabetes.

8.3. Individualized use in well-defined type 2 diabetes subtypes

Cluster analysis was applied to define subgroups within the type 2 diabetes population that differ with respect to insulin secretory capacity, insulin sensitivity, age at diagnosis, and the presence of autoimmune markers [198—200]. These subgroups display significant differences in the development of CV and renal complications [198—200]. Thus, given the beneficial actions of GLP-1 RAs on preventing CV events (and on the progression of nephropathy), they may turn out to be particularly effective in those presenting a high a priori risk of these complications. Identifying a central pathophysiological defect (e.g., reduced insulin secretory capacity) may also help select a specific therapy addressing this point (e.g., GLP-1 RAs augmenting insulin secretion triggered by hyperglycemia). While prospective studies comparing various therapies in type 2 diabetes patients belonging to different subgroups are lacking, this sub-classification promises to be a helpful tool assisting in a more individualized approach toward selecting glucose-lowering medications for a given patient.

8.4. Combination treatment with GLP-1 RAs plus SGLT-2 inhibitors

In addition to GLP-1 RAs, SGLT-2 inhibitors are another class of glucose-lowering medications that have proven beneficial CV effects, especially regarding the prevention of heart failure complications (Figure 6 [110,111]). This raises the question of differential indications [201]. Based on the pattern of effects on various CV endpoints, GLP-1 RAs seem to better prevent ischemic events potentially resulting from anti-atherogenic effects (as previously described). The mechanisms of action of SGLT-2 inhibitors differ and aim to prevent heart failure complications (using hospitalization as an indicator) and the progression toward end-stage renal failure [110,111]. Therefore, if a patient seems to be at risk of ischemic events (e.g., because of previous events), GLP-1 RAs appear to be the better option. However, if the risk of congestive heart failure complications is considered the primary problem, SGLT-2 inhibitors are the better choice.

Since the severalfold elevated risk of CV events that type 2 diabetes demonstrates is only partially reduced by both GLP-1 RAs and SGLT-2 inhibitors, it may be necessary to combine medications from both classes to further improve their effectiveness. Combining dapagliflozin with exenatide once weekly lowers plasma glucose and body weight more than any of the single agents alone [202], even for prolonged periods of time [203]. Similar results were observed after adding empagliflozin to liraglutide in Japanese patients [204] and when adding canagliflozin to liraglutide treatment [205]. The weight loss induced by the combination compared to the single agents appeared to be additive, but HbA_{1c} reduction was less than additive. When adding dulaglutide to pre-existing treatment with SGLT-2 inhibitors, HbA_{1c} decreased substantially, while body weight declined by only 1 kg (at a higher dose of 1.5 mg) [206]. Systolic blood pressure was also lowered substantially by this combination [204—208]. The effects of combining GLP-1 RAs with SGLT-2 inhibitors were corroborated in a meta-analysis by Castellana et al. [209], confirming this combination's potential.

This leads to the essential question, will combining GLP-1 RAs and SGLT-2 inhibitors result in even better CV outcomes? No data are available to estimate the effects on CV outcomes using this combination. It is uncertain whether a large enough clinical trial addressing this question will ever be conducted. Real-world studies analyzing existing databases documenting medication use and clinical outcomes may help in this respect, but no such analysis seems to be currently available.

8.5. Unimolecular oligo-hormonal agonists address more than just GLP-1 receptors

One avenue of further increasing the potency of GLP-1 RAs is developing molecules that address not only GLP-1 receptors, but a second (co-agonist) or even a third (tri-agonist) receptor (choosing from glucagon, glucose-dependent insulinotropic polypeptide [GIP], or peptide YY [PYY] receptors). Preliminary findings suggest that highly effective compounds (e.g., tirzepatide [210]) can be developed this way, in particular providing weight loss far exceeding that reported with pure GLP-1 RAs. These developments will be the focus of another manuscript on the present supplement volume (Baggio et al. [211]).

8.6. Pharmacogenomics

Since GLP-1 RAs exert their biological effects by interacting with the GLP-1 receptor, interindividual differences in the expression of these receptors or polymorphisms at the GLP-1 receptor gene may modify biological responses [212—215]. Along these lines, certain polymorphisms regarding the TCF7L2 gene (probably involved in determining β cell mass and the expression of GLP-1 receptors) impair insulin responses to exogenous GLP-1 [216]. One study described a modification of the in vitro effects of GLP-1 RAs for the GLP-1 receptor variant T149M (methionine instead of threonine in position 149) on β cells [217]. However, a preliminary clinical study did not describe differences in pharmacological effects in response to short-term treatment with exenatide [218]. Given the potential of selecting patients with a predicted greater clinical effectiveness [219], the issue of pharmacogenomics regarding GLP-1 RA still appears to be an understudied research area. Furthermore, patients not responding to GLP-1 RAs as expected, either when initially exposed to GLP-1 RAs (primary non-responders) or after a satisfactory response period (secondary non-responders), have often been observed in clinical practice. Systematic studies elucidating the mechanisms of a potential non-response to GLP-1 RA treatment (such as genetics or lifestyle issues) remain lacking.

8.7. Potential novel indications: neurodegenerative diseases and psoriasis

Interest in using GLP-1 RAs to treat neurodegenerative diseases emerged from preclinical studies showing that GLP-1 receptor signaling is involved in cognitive functions [220] and GLP-1 RAs can induce neuronal growth and synaptic plasticity and reduce apoptosis and oxidative stress [221].

In Alzheimer's disease, the most prevalent form of dementia, animal studies have shown the positive effects of GLP-1 RAs on cognitive impairment [222,223]. In a clinical trial of patients with prediabetes and type 2 diabetes, memory function improved after 4 months of

liraglutide administration [224]. However, there was no placebo control. In another trial with non-diabetes subjects at increased risk of Alzheimer's disease, administration of liraglutide for 3 months improved brain region connectivity (assessed by functional MRI), but cognitive functions did not improve [225]. Another trial in non-diabetes patients with Alzheimer's disease found that 6 months of liraglutide treatment prevented a further decline in brain glucose uptake (assessed by positron emission tomography), but did not change cognitive function tests [226]. A larger clinical trial is currently ongoing that is investigating the effects of liraglutide on mild Alzheimer's disease using comprehensive neurological and cognitive assessment [227].

Parkinson's disease is another neurodegenerative disease for which GLP-1 RAs are being explored as treatment options [221,228]. In a mouse model of Parkinson's disease, a novel GLP-1 RA protected dopaminergic neurons and ameliorated behavioral deficits, most likely by blocking the formation of a neurotoxic astrocyte variant [229]. In clinical trials, exenatide improved the MDS-UPDRS score (a standardized assessment scale for patients with Parkinson's disease) [230,231]. Nevertheless, a recent systematic Cochrane Database review declared the evidence of improved motor impairment in GLP-1 RA-treated patients with Parkinson's disease as "low certainty" [232].

In an animal model of Huntington's disease, mice treated with exendin-4 for 9 weeks presented with reduced huntingtin protein aggregates in the cortex compared to placebo and had longer life spans [233]. We are not aware of any clinical trials in human patients with Huntington's disease.

Psoriasis is associated with type 2 diabetes [234]. Two case reports generated interest in using GLP-1 RAs as a potentially novel treatment option for psoriasis [235,236]. Two subsequent prospective studies found positive effects on psoriasis severity scores in type 2 diabetes patients treated with GLP-1 RAs [237,238], a finding that could not be confirmed in non-diabetes subjects [239]. This possibly suggests a clinical effectiveness that may differ in diabetes and non-diabetes patients.

9. CONCLUSIONS

Clinical research conducted over the past 30 years has established GLP-1 RAs as a widely recommended class of glucose-lowering agents. The best representatives of this class are capable of lowering plasma glucose comparable to insulin regimens, but with a lower risk of hypoglycemia and the added benefit of weight loss. The ability to prevent CV events in high-risk patients has re-emphasized the particular benefits that GLP-1 RAs may generate in type 2 diabetes therapy. Despite these past achievements, there is a potential for further increasing effectivity, optimizing molecules and dosing regimens, and exploring specific patient groups that will particularly benefit from GLP-1 RAs.

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CONFLICT OF INTEREST

M.A.N. has been a member of advisory boards or consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and Novo Nordisk. He has received grant support from AstraZeneca, Eli Lilly and Company, Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and Novo Nordisk. He has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and Novo Nordisk. J.J.M. has received consulting and speaker honoraria from AstraZeneca, Eli Lilly and Company, Merck, Sharp & Dohme, Novo Nordisk, Sanofi, and Sevier. He has received research support from Boehringer Ingelheim, Eli Lilly and Company, Merck, Sharp & Dohme, Novo Nordisk, and Sanofi. J.W. and D.Q. have nothing to declare.

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Exhibit J

Abstract Discussion Forum (0)

Number: Mo1637

EFFECTS OF GLP-1 RECEPTOR OR A DUAL GLP-1/GIP RECEPTOR AGONISTS ON GASTROINTESTINAL SYMPTOMS AND GASTRIC EMPTYING: RESULTS FROM A LARGE CLINICAL PRACTICE DATABASE

Society: AGA
Track: Functional GI and Motility Disorders

Background: There has been a considerable increase in the use of GLP-1 receptor agonists or dual agonists (collectively identified as GLP-RA) for indications of obesity and diabetes mellitus. At least one mechanism of action of these agents is to cause delay in gastric emptying (GE), which can cause profound symptoms and even increase the risk of complications. There is currently no robust real-world data on the impact of GLP-RA on gastrointestinal (GI) symptoms and GE. Our **aim** was to determine the prevalence of delayed GE and characteristics of GI symptoms following GLP-RA. **Methods:** Using diverse prescribing and health record data from the Mayo Clinic Platform (including primary care and referral patients), an initial 79,925 patients were found to have been prescribed GLP-RA. Of these, we studied a cohort of 839 who developed a relevant GI symptom and had a gastric emptying scintigraphy (GES). GES was performed using a standard, validated 320 kilocalorie, 30% fat egg meal in 696 patients. Demographics, clinical symptoms (using ICD-10 codes), GLP-RA type and doses, concomitant medications, and symptoms were recorded. **Results:** Of the ~80,000 patients prescribed a GLP-RA, 14,658 developed at least 1 GI symptom suggestive of gastroparesis, 3,993 developed at least 2 symptoms. Among those, 696 underwent validated GES, of which 35% (241/696) had delayed GE at 4hr; 134/696 fulfilled criteria of delayed GE at 2hr; however, 9 of them had a normal GE at 4hr. Of the 241 with delayed GE, 127 had preexisting GI symptoms and 38 had documentation of a prior delayed GES. Females were overrepresented in the group with delayed GE; however, the rest of the characteristics including the type and duration of GLP-RA used were similar between the groups with normal or delayed GE except for higher dosing for dulaglutide in patients with delayed and exenatide in patients with normal GE (**figure**). The distribution of GI symptoms among those with and without delayed GE was similar except for constipation which was more common in those with delayed GE (**table**). **Conclusions**: In this study, 18% of patients receiving GLP-RA developed at least 1 new GI symptom suggestive of gastroparesis, but only a third of those who underwent GES were found to have gastroparesis. This resembles findings from a prospective study of 67 patients treated with liraglutide (PMID:37927173). Females and symptom of constipation were more prevalent in those with delayed GE. These real-world data suggest that GI symptoms are prevalent in those treated with GLP-RA. However, not all these patients had impaired GE; symptoms likely represent a spectrum of mechanisms impacted by these drugs. Further characterization is needed to determine risk factors associated with bothersome GI symptomatology, as well as to identify patients at higher risk of complications like malnutrition and aspiration.

Patient demographics and gastrointestinal symptoms for those who underwent gastric emptying scintigraphy (N=696)

EFFECTS OF GLP-1 RECEPTOR OR A DUAL GLP-1/GIP RECEPTOR AGONISTS ON GASTROINTESTINAL SYMPTOMS AND GASTRIC EMPTYING: RESULTS FROM A LARGE CLINICAL PRACTICE DATABASE

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Abstract Discussion Forum (0)

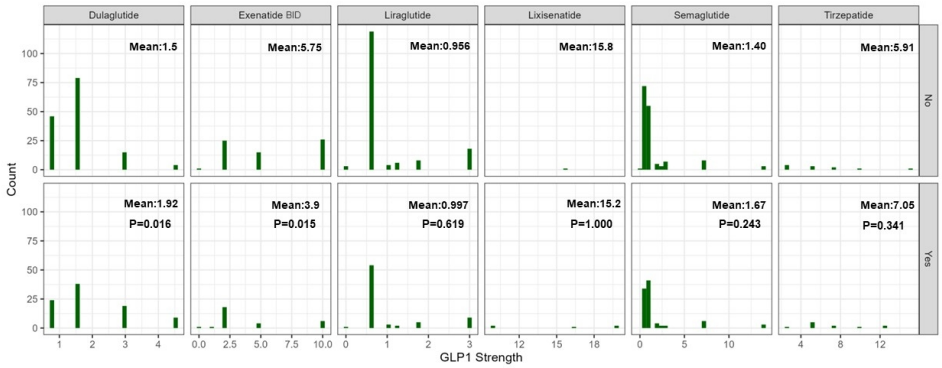
Number: Mo1637

EFFECTS OF GLP-1 RECEPTOR OR A DUAL GLP-

Characteristics (Mean)	Normal GE (4hr) N=455	Delayed GE (4hr) N=241	p-value (F-exact)
Age (years)	49.6 (36-53)	49.9 (40-53)	0.087
Male	154 (33.8%)	59 (24.6%)	0.012
Female	301 (66.2%)	181 (75.4%)	0.012
BMI	33.90kg/m^2	34.32kg/m^2	0.660
Race			0.210
White	404 (88.8%)	207 (85.9%)	
Black	21 (4.6%)	17 (7.1%)	
Asian	8 (1.8%)	4 (1.7%)	
Native Hawaiian/Pacific Islander	1 (0.2%)	1 (0.4%)	
American Indian/Alaskan native	3 (0.7%)	6 (2.5%)	
Other/unknown	18 (4.0%)	6 (2.5%)	
GLP-RA medication Rx			0.219
Dulaglutide	126 (27.7%)	76 (31.5%)	
Exenatide	50 (11.0%)	19 (7.9%)	
Liraglutide	133 (29.2%)	58 (24.1%)	
Lixisenatide	1 (0.2%)	2 (0.8%)	
Semaglutide	134 (29.5%)	76 (31.5%)	
Tirzepatide	11 (2.4%)	10 (4.1%)	
Time between GLP-RA Rx and GES study (days)	366	299	0.159
Symptoms			
Nausea	70%	66%	0.3
Vomiting	55%	56%	0.7
Constipation	40%	50%	**0.01**
Diarrhea	46%	47%	0.8
Bloating	28%	28%	0.99
Abdominal pain	48%	54%	0.13

BMI=body mass index; GE=gastric emptying; GES=gastric emptying scintigraphy; Rx=prescription

Mean maximum dose of most recent GLP-RA prescribed in those with delayed (yes) and normal (no) GES using non-parametric Wilcoxon rank sum test. P-value represents comparison between two groups: delayed vs non-delayed GES.



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ACG Clinical Guideline: Gastroparesis

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Abstract

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

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MC: Single-center research studies: Allergan, Takeda, and Vanda; Consulting with compensation to his employer: Takeda, Alpha Sigma Wasserman
TA: Investigator: Censa, Clndome, Vanda, Allergan, Neurogastrix; Consultant: Censa, Nuvaira, Takeda, Medtronic; Speaker: Takeda, Medtronic; Reviewer: UpToDate; Writer: Med Study; Editorial: *Neuromodulation, Wikistim*; ADEPT-GI: IP for autonomic/enteric diagnosis and therapies
BK: Clinical trials with Takeda, Vanda, Alpha Sigma Wasserman, GSK; Consulting with Takeda, Cindome, Neurogastrix; Speaking for Medtronic
LN: Investigator: Allergan, Vanda; Consultant: Abbvie, Ironwood, Alnylam, Eli Lilly, Gemelli, Neurogastrx, Pendulum, Phathom, RosVivo, Salix, Takeda. Scientific Advisory Board: Gemelli, RosVivo
VMV: Nothing to disclose
JP: Nothing to disclose
KG: Nothing to disclose
RY: Consultant through Institutional Agreement: Medtronic, Ironwood Pharmaceuticals, Diversatek, StatLinkMD; Research support: Ironwood Pharmaceuticals; Advisory Board: Phathom Pharmaceuticals; RJS Mediagnostix

INTRODUCTION

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

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

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

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

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

in gastroparesis. However, the review addresses the use of central neuromodulators and cannabis in gastroparesis.

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

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

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

METHODS

Key Questions

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

Literature Search

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

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

Screening

Between February 2019 and July 2021, a team of five content experts (DA, TA, MC, BK, LN) screened a total of 1908 distinct references retrieved by the original and updated searches.

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

While no restriction was placed on publication dates during the retrieval process, emphasis was placed during screening by content experts on studies published after the searches included in the previous guideline, and tables from the 2013 guideline were updated with more recent evidence from the literature. Similarly, searches were not limited by age range within the databases, but any retrieved studies on an exclusively pediatric population were manually excluded during screening. Review articles, correspondence, and other publications without original data were excluded from analysis, though relevant reviews were retained for hand search of their included references.

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

Assessment

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process (Table 2) (21) was used to assess the quality of evidence for each question, by two formally trained GRADE methodologists (RHY & KG) to evaluate the quality of the evidence and strength of the recommendations. The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence and precision of the estimate of effect. A strength of recommendation is given as either strong (noted as “recommendations,” and meaning that most patients should receive the recommended course of action) or conditional (noted as “suggestions,” and meaning that many patients should have this recommended course of action, but different choices may be appropriate for some patients) based on the quality of evidence, risks versus benefits, feasibility, and costs, taking into account perceived patient and population-based factors. Furthermore, a narrative

evidence summary for each section provides important details for the data supporting the statements. The panel have additionally highlighted “key concepts” that were not included in the GRADE assessment. Key concepts are statements to which the GRADE process has not been applied and often include definitions and epidemiological statements rather than diagnostic or management recommendations.

NARRATIVE REVIEW OF EVIDENCE

Risk Factors

Recommendation

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

Optimal glucose control reduces the future risk of aggravation of the gastroparesis.—Acute hyperglycemia delays gastric emptying in patients with diabetes and, in the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, delayed gastric emptying was associated with gastrointestinal symptoms and with measures of early and long-term hyperglycemia (22). However, it was unknown if better glycemic control increases the risk of hypoglycemia or improves hemoglobin A1c levels and gastrointestinal symptoms in diabetic gastroparesis.

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

Diagnostic Testing

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

Recommendation

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

Optimal duration of gastric emptying tests.—It is customary to recommend cessation for 48 hours prior to the test of medications including opioids, cannabinoids, prokinetics, antiemetics, and neuromodulators with potential impact on the results of the GE test.

Based on a systematic review and meta-analysis (26) of the literature from 2007 to 2017 that included studies evaluating the association between GE (in 92 studies: 26 breath test, 62 scintigraphy, 1 ultrasound and 3 wireless motility capsule) and nausea, vomiting, early satiety/postprandial fullness, abdominal pain and bloating, 25 studies provided quantitative data for meta-analysis (15 scintigraphy studies enrolling 4056 participants and 10 breath test studies enrolling 2231 participants). Meta-regression demonstrated a significant difference between optimal and suboptimal GE test methods when comparing delayed GE with nausea and vomiting. Studies using optimal GE test methodology (that is solid meal and at least 3 hours of data collection) showed significant associations between GE and nausea (OR: 1.6; 95% CI: 1.4 to 1.8), vomiting (OR: 2.0; 95% CI: 1.6 to 2.7), abdominal pain (OR: 1.5; 95% CI: 1.0 to 2.2), and early satiety/fullness (OR: 1.8; 95% CI: 1.2 to 2.6) for patients with upper gastrointestinal symptoms. Among patients with diabetes, the most significant association with delayed GE was with the symptom of early satiety and fullness, but not with nausea and vomiting (26). Therefore, systematic review and meta-analysis supports an association between optimally measured delayed gastric emptying and upper gastrointestinal symptoms. It is worth noting that scintigraphic assessment should be ideally performed up to 4 hours unless it is documented that more than 90% of the solid meal has emptied at 3 hours (27).

Potential Confounding between Gastroparesis and Functional Dyspepsia

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

has been emphasized that the distinction between the two diagnoses is relevant because of the better prognosis of FD in contrast to the persistence of gastroparesis (28).

Diagnosis of gastroparesis using scintigraphy

Recommendation

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

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

Recommendation

4. Wireless motility capsule testing may be an alternative to the scintigraphic gastric emptying assessment for the evaluation of gastroparesis in patients with upper GI symptoms. (conditional recommendation, low quality of evidence)

Compared to wireless motility capsule (WMC).—The results from measurements by SGE and WMC differ. Overall agreement in results between the two methods was 75.7% (kappa=0.42). In subjects without diabetes, the WMC detected a higher proportion of subjects with delayed GE (33.3%) than SGE (17.1%) (P<.001); in contrast, a higher proportion of subjects with diabetes had delayed GE detected by SGE (41.7%) than by WMC (17.1%) (P=.002). Severe delays in GE were observed in a higher proportion of subjects by WMC (13.8%) than by SGE (6.9%) (P=.02). Rapid GE was detected in a higher proportion of subjects by SGE (13.8%) than by WMC (3.3%) (P<.001) (35,36). Research supports WMC testing as an alternative test to SGE for the evaluation of gastroparesis in patients with upper GI symptoms, and one advantage is that it provides a measure of gastric contractile amplitude and this can correspond to the timing of capsule emptying documented by the change in pH measured as the capsule traverses the pylorus.

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

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

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

Diagnosis of gastroparesis using stable isotope breath test and comparison with scintigraphy

Recommendation

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

The stable isotope gastric emptying breath test (GEBT) using 13-carbon spirulina has been validated in simultaneous measurements performed with the gold standard scintigraphy and a solid test meal. This has been validated both in patients with upper gastrointestinal

symptoms and healthy controls as well as in pharmacologically induced slowing or acceleration of GE (43,44). Though the kappa statistic is not provided, a validation study of 38 healthy volunteers and 129 patients with clinically suspected delayed GE showed that, at 80% specificity, the 45- and 180-minute samples combined were 93% sensitive to identify accelerated GE, and 150- and 180-minute combined were 89% sensitive for delayed GE (43). The test is also approved for use in children.

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

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

Using high-resolution electrical mapping (256 electrodes; 36 cm^2) (51), it was shown that 9 patients with chronic unexplained nausea and vomiting had slow-wave dysrhythmias, with only 1 of 9 controls showing these dysrhythmias. Dysrhythmias included abnormalities of initiation (stable ectopic pacemakers, unstable focal activities) and conduction (retrograde propagation, wavefront collisions, conduction blocks, and re-entry) across slow, normal, or fast frequencies; dysrhythmias also showed velocity anisotropy (mean, 3.3 mm/s longitudinal vs 7.6 mm/s circumferential; $P < .01$). Such high resolution, spatial mapping is recommended, especially because of the evidence that abnormalities of slow-wave initiation aberrant conduction and low amplitude activity in gastroparesis often occur at normal frequency, which could be missed by tests that lack spatial resolution (52).

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

Other Tests for Gastroparesis Based on Full-Thickness Biopsies

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

MANAGEMENT OF GASTROPARESIS

Small particle diet and nutrition interventions

Recommendation

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

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

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

Pharmacologic agent use in gastroparesis

Recommendation

7. In patients with idiopathic and diabetic gastroparesis, pharmacologic treatment should be considered to improve GE and gastroparesis symptoms, considering benefits and risks of treatment. (conditional recommendation, low quality of evidence)

8. In patients with gastroparesis, we suggest treatment with metoclopramide over no treatment for management of refractory symptoms. (conditional recommendation, low quality of evidence)

9. In patients with gastroparesis where domperidone is approved, we suggest use of domperidone for symptom management. (conditional recommendation, low quality of evidence)

10. In patients with gastroparesis, we suggest use of 5–HT4 agonists over no treatment to improve gastric emptying. (conditional recommendation, low quality of evidence)

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

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

Regulatory authorities issued restrictions and recommendations regarding long-term use of metoclopramide at oral doses exceeding 10 mg 3–4 times daily because of the risk for development of tardive dyskinesia; the restrictions include use for <12 weeks and age <65 years. Studies in the last decade have addressed the risk of tardive dyskinesia in contrast to reversible involuntary movements on treatment with metoclopramide. First, the relative risk (69) of tardive dyskinesia in metoclopramide users in a VA medical center was not significantly greater than in non-user controls (RR: 1.67; 95% CI: 0.93 to 2.97). Second, it was estimated that the risk of tardive dyskinesia from metoclopramide use is likely to be <1% (70). The most comprehensive assessment (71) showed that the risk of tardive dyskinesia from metoclopramide is in the range of 0.1% per 1000 patient years, below a previously estimated 1%–10% risk suggested in treatment guidelines by regulatory authorities. High-risk groups are elderly females, diabetics, patients with liver or kidney failure, and patients with concomitant antipsychotic drug therapy which reduces the threshold for neurological complications.

The FDA package insert on metoclopramide specifies that restlessness, drowsiness, fatigue, and lassitude occurred in approximately 10% of patients who received 10 mg four times daily. No other quantitative data are provided in the FDA approved insert on the prevalence of other, reversible central nervous system disorders with metoclopramide. One study (72) that documented the epidemiology of extrapyramidal reactions to metoclopramide was studied by examining reports in the Adverse Reactions Register of the Committee on the Safety of Medicines in the United Kingdom in the period 1967–82. Out of an estimated 15.9 million prescriptions, there were 479 reports of extrapyramidal reactions (455 of dystonia-dyskinesia, 20 of parkinsonism, and 4 of tardive dyskinesia). A more recent study of metoclopramide adverse events in the FDA Adverse Event Reporting System (FAERS)

for the period 2004–2010 yielded reports of 4,784 neurological reactions and 944 reports were for tardive dyskinesia; the total number of prescriptions was almost 40.5 million (73). These data suggest that 0.1% of prescriptions are associated with non-tardive dyskinesia neurological symptoms, which seem to be low estimates and may reflect the fact that medication cessation with reversal of the neurological symptoms may not be reported to regulatory agencies.

Domperidone is available for treatment of gastroparesis under a special program administered by the Food and Drug Administration. Table 4 provides a summary of clinical trials with domperidone (74–86). Domperidone has been tested in studies that involved patients with IG, DG, or post-surgical gastroparesis (PSG), and it has been associated with symptom improvement manifested as lower overall scores or reduction in frequency and intensity of symptoms of gastroparesis. Four studies have also documented acceleration of GE compared to control or baseline.

Table 5 summarizes efficacy of other prokinetic agents (5-HT_4 and ghrelin receptor agonists) on symptoms or GE (64,87–100). As a group of medications, prokinetics have the most substantive clinical trials, and overall evidence suggests that they provide symptomatic benefit. For all the medications, the recommendation is conditional for use of treatment over no treatment to improve gastric emptying. The methodological assessment for the 5-HT4 agonists concluded that there was inconsistent data for symptom improvement.

Another class of agents is the motilin agonists which are used in the treatment of gastroparesis in adults and children. These medications include erythromycin, clarithromycin, and azithromycin. These medications are generally used in the short term (1–4 weeks) because of development of tachyphylaxis to motilides (101). Based on a systematic review and network meta-analysis of 33 studies and data on 22.6 million subjects, macrolide use was not associated with the risk of arrhythmia or cardiovascular mortality (102).

Antiemetics, central neuromodulators in gastroparesis

Recommendation

11. In patients with gastroparesis, use of antiemetic agents is suggested for improved symptom control; however, these medications do not improve GE. (conditional recommendation, low quality of evidence)

12. Central neuromodulators are not recommended for management of gastroparesis. (strong recommendation, moderate quality of evidence)

13. Current data do NOT support the use of ghrelin agonists for management of gastroparesis. (strong recommendation, moderate quality of evidence)

14. Current data do NOT support the use of haloperidol for treatment of gastroparesis. (conditional recommendation, low quality of evidence)

Table 6 summarizes efficacy of antiemetics and central neuromodulators in gastroparesis (103–109). These are therapies commonly used for symptom relief in gastroparesis. The central neuromodulator studied with the highest level of evidence was the tricyclic antidepressant, nortriptyline, in IG (105). In this randomized, placebo-controlled trial, nortriptyline was no better than placebo in relieving global symptoms of gastroparesis, but some improvement in abdominal pain was noted. In a study of amitriptyline, 50mg/day, there was no retardation of GE in patients with FD (110). Further RCTs are needed to determine the efficacy of other central neuromodulators. Although there are no formal randomized trials, experience with use of haloperidol in emergency room treatment of patients presenting with gastroparesis has led to reduced need for morphine treatment and admission to hospitals (111), rather than documenting effect on gastroparesis symptoms.

Other drug therapies for gastroparesis

A recent study has targeted previously described impaired nitric oxide metabolism and an abnormal tetrahydrobiopterin (BH-4) pathway in gastroparesis patients with diabetes mellitus. This phase II study needs confirmation in other larger controlled studies (112).

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

Use of pharmacotherapy to reduce the future aggravation of gastroparesis

Based on a referral center experience, predictors of responsiveness to pharmacotherapy (113) were identified. A good response to pharmacological agents can be expected in the viral and dyspeptic subgroups of idiopathics, Parkinson’s disease, and the majority of diabetics; whereas a poorer outcome to prokinetics can be expected in post-vagotomy patients, those with connective tissue disease, a subgroup of diabetics (e.g., with evidence of vagal neuropathy), and the subset of IG dominated by abdominal pain and history of physical and sexual abuse (113). The comprehensive NIH Gastroparesis Consortium database of 748 patients (86) showed 181 (24%) on domperidone and 567 not receiving domperidone; 63% had IG. Compared to patients not receiving domperidone, those patients who were receiving domperidone (median time on domperidone following initiation of 32 weeks, 95% CI: 25–35 weeks) experienced moderate, but significantly more improvement in gastroparesis outcome measures of the Gastroparesis Cardinal Symptom Index (GCSI) total score, nausea and fullness subscales, upper abdominal pain score, gastroesophageal reflux disease (GERD) score, and the patient assessment of upper gastrointestinal disorders – quality of life (PAGI-QOL) score.

In a systematic review (114) of 14 studies that evaluated GE and upper GI symptoms, including IG or DG, and including only studies with optimal GE test methods being evaluated, there was a significant positive association between improvements in GE and upper GI symptoms in response to prokinetic agents.

Immunological therapies

There is insufficient evidence to support routine clinical use of autoimmune therapies in management of gastroparesis. A retrospective analysis of 11 female patients (115) with drug and device resistant gastroparesis with coexisting positive autoimmune profiles who were treated for 8–12 weeks with diverse immunomodulatory treatment showed that total symptom score improved in 6 of 11 patients, with maximum GI symptom improvement with IVIg (2 of the 3 patients treated). In a subsequent open-label study, 14 patients (3 DG, 1 PSG, and 10 IG) with serological and/or tissue evidence of immunological abnormality, IVIg therapy (400 mg/kg infusion weekly for 12 weeks) was associated with significant improvement in symptoms scores for nausea, vomiting, early satiety, and abdominal pain, and 9/14 patients were responders to this open-label treatment (116). This study built upon the retrospective medical record review suggesting a positive experience among 11 patients treated with IVIg or combined mycophenolate mofetil with methylprednisolone, or only mycophenolate mofetil therapy (115).

Non-pharmacological therapy for gastroparesis: gastric electrical stimulation (GES), acupuncture, and herbal medicines

Recommendation

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

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

Table 7 shows efficacy of several bioelectric treatments including vagal nerve stimulation, spinal cord stimulation and GES (117–142). A recent randomized, crossover trial of ON vs. OFF GES in patients with medically refractory vomiting with or without delayed GE, GES decreased the vomiting frequency. Severity of nausea and appetite improved while ON compared to OFF. However, there were no differences in GI quality of life, nutritional parameters, or GE (121). Randomized crossover trials of GES for medically refractory DG or IG have shown mixed results which may reflect the variation in trial designs with differing timing of the ON vs. OFF randomization and crossover (120–124). Other modalities of electrostimulation (vagal and spinal cord) appear promising; however, larger randomized, sham-controlled trials are needed to determine the efficacy. However, documented clinical usefulness in both IG and DG (documented in Table 7) suggests there is a role for GES in accordance with its HUD approval.

Recommendation

16. Acupuncture alone or acupuncture combined with prokinetic drugs may be beneficial for symptom control in patients with DG. Acupuncture cannot be recommended as beneficial for other etiologies of gastroparesis. (conditional recommendation, very low quality of evidence)

17. Herbal therapies such as Rikkunshito or STW5 (Iberogast) should NOT be recommended for treatment of gastroparesis. (conditional recommendation, low quality of evidence)

Table 8 summarizes information on effects of electro-acupuncture, acupuncture, and herbal medicines in gastroparesis (143–154). The evidence available does not support their use in clinical practice.

Pyloric Interventions: Diagnostic and Therapeutic

Recommendation

18. In patients with gastroparesis, EndoFLIP evaluation may have a role in characterizing pyloric function and predicting treatment outcomes following peroral pyloromyotomy. (conditional recommendation, very low quality of evidence)

19. Intrapyloric injection of botulinum toxin is not recommended for patients with gastroparesis based on randomized, controlled trials. (strong recommendation, moderate quality of evidence)

20. In patients with gastroparesis with symptoms refractory to medical therapy, we suggest pyloromyotomy over no treatment for symptom control. (conditional recommendation, low quality of evidence)

Table 9 shows results of EndoFLIP for selection of patients for pyloromyotomy or pyloric botulinum toxin injection (155–161). Current evidence suggests that such measurements of pyloric diameter and distensibility index or compliance are associated with greater gastric retention, and that the measurements may predict response to therapy, particularly, significant enlargement of the post-G-POEM pyloric diameter (159). It is reasonable to consider such pyloric interventions in a clinical trial and to include assessments of pyloric physiology to appraise the impact of pyloric dysfunctions on outcomes. Thus, whereas intrapyloric injection of botulinum toxin is not recommended for patients with gastroparesis based on randomized, controlled trials (162), a recent large multicenter study from France documents the efficacy of botulinum toxin injection, particularly for the relief of vomiting, when patients are selected based on measurements of pyloric distensibility (161).

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

Table 10 shows efficacy of G-POEM for gastroparesis based on open-label studies (163–181). Overall, these open-label studies suggest there is benefit in terms of symptom improvement and improved GE, though most studies were of only 3–6 months' duration. A 12-month study showed 56% patients improved at 1 year (173). Symptom control after endoscopic pyloromyotomy is comparable to surgical myotomy; however, endoscopic myotomy has been associated with fewer post–procedural complications and shorter length of hospital stay. A recent study has identified benefit in relief of symptoms as well as improved GE with G-POEM procedure followed for 6 months in a sham-controlled study (174). Other pylorus-directed procedures are also available such as surgical pyloroplasty,

though there is more evidence on G-POEM. Heineke-Mikulicz pyloroplasty involves longitudinal incision across the pylorus, which is then closed transversely, and this results in division of both longitudinal and circular muscle layers. In 177 patients with gastroparesis, laparoscopic pyloroplasty achieved improved GE in 90% of patients and induced short-term improvement of nausea, vomiting, bloating, and abdominal pain. However, morbidity rate was 6.8%, with problems such as confirmed leaks or further surgical interventions including jejunostomy and subtotal gastrectomy (182).

CONCLUSION AND A LOOK TO THE FUTURE

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS USED

AE	adverse event
CGM	continuous glucose monitoring

CSII	continuous subcutaneous insulin infusion
DB	double blind
DM	diabetic
DG	diabetic gastroparesis
EEG	electroencephalogram
EGG	electrogastrography
ESNM	European Society of Neurogastroenterology and Motility
FD	functional dyspepsia
GCSI	Gastroparesis Cardinal Symptom Index
GCSI-DD	Gastroparesis Cardinal Symptom Index-Daily Diary
GE	gastric emptying
GEBT	gastric emptying breath test
GERD	gastroesophageal reflux disease
GES	gastric electrical stimulation
GCSI	gastroparesis cardinal symptom index
GI	gastrointestinal
GIQLI	gastrointestinal quality of life index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
G-POEM	gastric per oral endoscopic myotomy
HC	healthy control
HV	healthy volunteer
HR-QOL	health-related quality of life
HUD	humanitarian use device
IG	idiopathic gastroparesis
IV	intravenous
LP	laparoscopic pyloroplasty
NICE	National Institute for Health and Care Excellence
NA	not available

NS	not significant
PAC-QOL	patient assessment of constipation – quality of life
PAGI-QOL	patient assessment of upper gastrointestinal disorders – quality of life
PAGI-SYM	patient assessment of upper gastrointestinal disorders – symptoms
PC	placebo-controlled
PG	parallel-group
PICO	Patient Intervention Comparison and Outcomes
po	oral
PSG	post-surgical gastroparesis
RCT	randomized controlled trial
ROM	radiopaque marker
Rx	treatment
SGE	gastric emptying by scintigraphy
SRMA	systematic review and meta-analysis
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEA	transcutaneous electrical acupuncture
TSS	total symptom score
WMC	wireless motility capsule
XO	crossover

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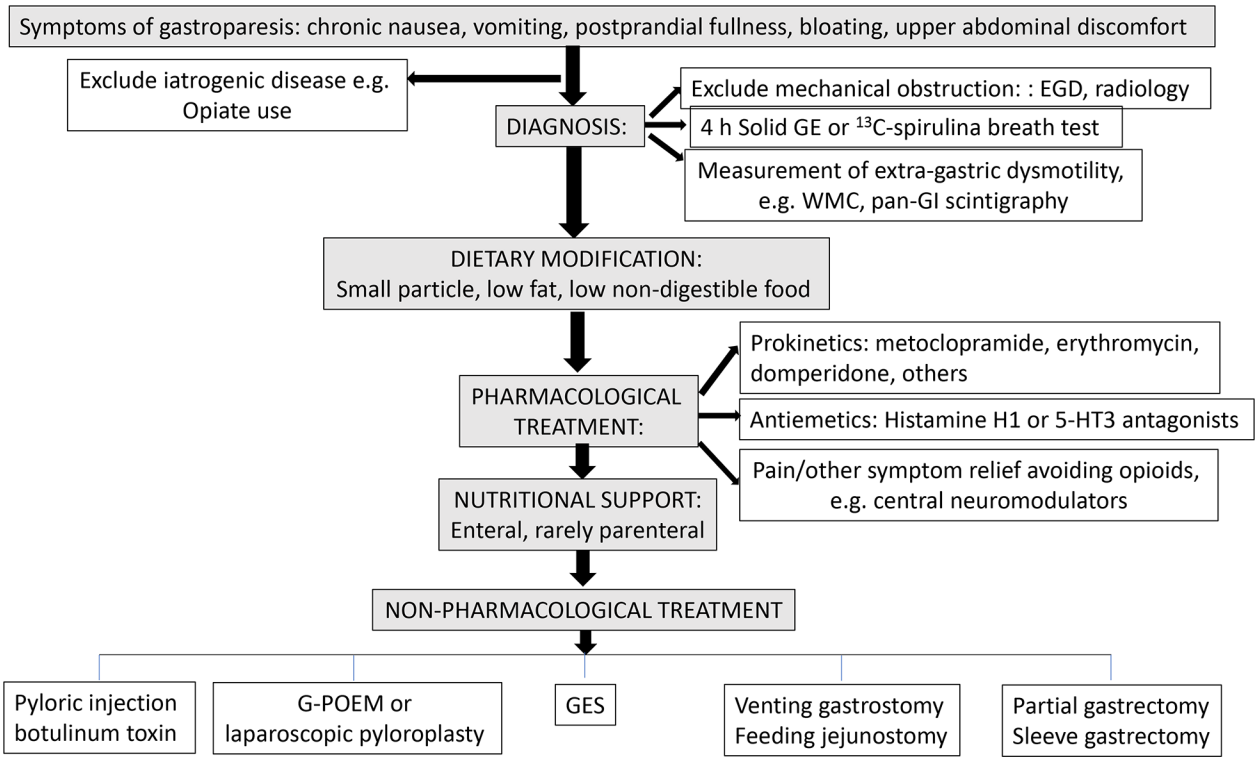

Figure 1.
This algorithm updates the algorithm from the 2013 ACG guideline on gastroparesis (1).

Table 1.

Gastroparesis Recommendations

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

Table 2.

GRADE quality criteria (GRADE=Grading of Recommendations Assessment, Development and Evaluation) (21)

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

Table 3.

Trials of metoclopramide for gastroparesis

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

(Updated from ref. 1, Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical Guideline: Management of Gastroparesis. Am J Gastroenterol 2013;108:18–37); GE=gastric emptying; T1DM = type 1 diabetes mellitus AE=adverse event; DB=double-blind; DG=diabetic gastroparesis; DM=diabetic; GE=gastric emptying; GI=gastrointestinal; HC=healthy controls; IG=idiopathic gastroparesis; NA=not available; PC=placebo- controlled; PG=parallel group; PS=post-surgical gastroparesis; RCT=randomized controlled trial; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TSS=total symptom score; XO=crossover

Table 4.

Summary of clinical trials with domperidone

Type of Study	N, etiology	Dose	Duration	Symptom improvement vs. baseline (OPEN) or vs. placebo (RCT)	Δ Gastric emptying	Adverse effects	Reference
Open, po	3 DM	10mg qid	1 wk	Yes, not quantified	Improved, not quantified	NA	Watts 1985, ref. 74
Open, po	12 IG, 3 DM, 2 PS	20mg qid	48 mo	68.3% ($P < 0.05$)	34.5% ($P < .05$)	↑ prolactin (100%), symptoms (17.6%)	Soykan 1997, ref. 75
Retrospective, p°	57 DM	Max. dose 80mg/day	377 days	70% patients improved	NA	16%	Kozarek 1990, ref. 76
Open,	6 DM	20mg qid	6 mo	79.2% ($P < 0.01$)	26.9% (NS)	NA	Koch 1989, ref. 77
Open	12 DM	20mg tid	Single oral dose 40mg	chronic oral administration 20mg tid (35–51 days) reduced symptoms	↑ solid and liquid emptying	NA	Horowitz 1985, ref. 78
RCT, PG, PC, withdrawal study	208 DM	20mg qid	4 wk	53.8% lower overall score with domperidone ($P = 0.025$)	NA	2–3% ↑ prolactin, similar to placebo	Silvers 1998 ref. 79
RCT, PC, XO + open label 1yr	13 DM	NA	8 wk	↓ in symptom frequency and intensity ($P < 0.03$); symptomatic improvement averaging >1y	NA	NA	Braun 1989, ref. 80
RCT, PC, XO	6 DM	10mg i.v.	Single	NA	↑ homogenized solid emptying	NA	Heer 1983, ref. 81
RCT, PC, XO cisapride (C) or DOM (D)	8 IG; 3 DM	0.8mg/kg (C) tid or 0.9mg/kg (D) tid	4 wk	No overall benefit over placebo; 2 of 3 DM improved	NA	Gas pains, skin rash	Franzese 2002, ref. 82
RCT, PC, XO	11 upper GI distress: 3 DM + severe gastric retention	10mg qid	4 wk each Rx	2/3 diabetics improved with DOM Rx; among total 11 patients, no superiority of DOM over placebo	NA	Abdominal gas pains, skin rash, itching, sweating, dizziness, constipation	Nagler 1981, ref. 83
RCT, PG, DOM vs. metoclopramide	93 DM	DOM 20mg qid; metoclopramide 10 mg qid	4 wk	41.19% improved vs. baseline (NA); NS vs. metoclopramide	NA	Somnolence 49% metoclopramide, 29% DOM	Patterson 1999, ref. 84
RCT, PG, PC in second phase among initial responders over 4weeks	208 DM responders to initial single-blind treatment with same dose	20mg domperidone qid	4 wk	Symptom severity increased in both groups, worse with placebo. For HRQOL (SF-36), improvement in physical component score, borderline in physical functioning, but no difference in 7/8 other HRQOL subscales	NA	Not reported in study	Farup 1998, ref. 85
Cohorts in NIH gastroparesis consortium (63% IG)	181 in DOM group, 567 in non-DOM group	Not standardized	Up to 96 weeks	DOM patients: moderate but significantly more improvement in gastroparesis outcomes: GCSI,	NA	No significant cardiovascular or other DOM-related complications	Sarosiek 2021, ref. 86

Type of Study	N, etiology	Dose	Duration	Symptom improvement vs. baseline (OPEN) or vs. placebo (RCT)	Δ Gastric emptying	Adverse effects	Reference
				nausea, fullness, upper abdominal pain, GERD scores, and PAGI-QOL			

(Reproduced from ref. 1, Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical Guideline: Management of Gastroparesis. Am J Gastroenterol 2013;108:18–37) DM=diabetic; DOM=domperidone; GCSI=Gastroparesis Cardinal Symptom Index; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HR-QOL=health-related quality of life; IG=idiopathic gastroparesis; NA=not available; NS=not significant; PC=placebo-controlled; po=oral; PAGI-QOL=Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; PG=parallel-group; PS=post-surgical gastroparesis; RCT=randomized, controlled trial; Rx=treatment; XO=crossover

Table 5.

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

Medication/trial design	N, Etiology	Dose (p.o.)	Duration	Efficacy	Reference
				5-HT4 agonists	
Clebopride PC, DB, RCT	**76 with dyspeptic syndromes and x-ray proven delayed GE**	**0.5 mg tid**	**3 months**	**Clebopride was more effective than placebo in reducing or relieving symptoms**	**Bavestrello 1985, ref. 87**
Prucalopride PC, DB, XO, RCT	13 DM, 2 connective tissue disease	4mg/day	Two 4-wk treatments with 2 wks washout	GE faster on prucalopride; GCSI scores were lower than baseline but not different between treatment arms. Meal-related symptom scores over time or cumulative score were not significantly different between groups. GE was more rapid in the prucalopride treatment period,	Andrews 2021, ref. 88
Prucalopride PC, DB, XO, RCT	28 IG, 6 DG	2mg/day	Two 4-wk treatments with 2 wks washout	Prucalopride significantly improved the total GCSI, subscales of fullness/satiety, nausea/vomiting, and bloating/distention, overall PAC-QOL score and gastric emptying $T_{1/2}$; also all efficacies were shown only in the idiopathic group	Carbone 2019, ref. 89
Revexepride: PG, DB, PC, stratified, repeated dose RCT	62 non-DM; 30 DM (55 female, 37 male); gastroparesis symptoms, and slower baseline GEBT $T_{1/2}$ in placebo group	0.02, 0.1, or 0.5 mg tid	4 weeks	Large inter-individual differences in GEBT with no significant treatment effect; GCSI and PAGI-SYM scores decreased at Week 2 and decreased further at Week 4 in all groups including placebo. Quality of life improved in all treatment groups after 4 weeks of treatment.	Tack et al 2016, ref. 90
Velusetrag: DB, PC, RCT; 3-period XO	18 DG, 16 IG	5, 15 or 30 mg po daily	7 days each period	GE $T_{1/2}$ numerically reduced with all 3 doses of velusetrag vs placebo. Efficacy was similar between subjects with diabetic and idiopathic gastroparesis.	Kuo 2021, ref. 91
Felcisetrag: DB, PC, RCT	36: 22 IG, 14 DG	0.1, 0.3 or 1.0mg i.v., daily	3 days	Felcisetrag significantly accelerated GE, small bowel transit, ascending colon emptying ($T_{1/2}$) and colonic transit at 48 hours	Chedid 2021, ref. 92
			Ghrelin Agonist		
Relamorelin RCT, PC, XO	10 T1DM with previous delayed GE	100 μg SQ	Single dose	Decreased gastric retention of solids at 1h and 2h and decreased GCSI-DD scores and nausea/vomiting/fullness/pain scores	Shin 2013, ref. 93
Relamorelin RCT, PC, PG	204 DG + moderate to severe symptoms and delayed GE	10 μg SQ daily or 10 μg SQ bid	12 weeks	Relamorelin (10 μg bid) significantly accelerated GE and significantly reduced vomiting vs. placebo. Among patients with baseline vomiting, relamorelin accelerated GE, reduced vomiting and improved other symptoms	Lembo 2016, ref. 94
Relamorelin RCT, PC, PG	393 DM with moderate to severe gastroparesis symptoms	10 μg, or 30 μg or 100 μg or placebo SQ bid	12 weeks	75% reduction in vomiting frequency vs baseline (NS compared with placebo). All 4 symptoms of DG (composite or individual symptoms) significantly reduced over 12-wk in all 3 relamorelin doses and accelerated GE vs. placebo. Adverse effect: impaired glycemic control with relamorelin	Camilleri 2017, ref. 95
Relamorelin and TZP-101 or TZP 102: 6 RCTs in SRMA	DG (N=557)	Diverse doses		Significantly improved overall gastroparesis symptoms (standardized mean difference, −0.34; 95% CI, −0.56 to −0.13)	Hong 2020, ref. 96

Medication/trial design	N, Etiology	Dose (p.o.)	Duration	Efficacy	Reference
				5-HT4 agonists	
Clebopride PC, DB, RCT	**76 with dyspeptic syndromes and x-ray proven delayed GE**	**0.5 mg tid**	**3 months**	**Clebopride was more effective than placebo in reducing or relieving symptoms**	**Bavestrello 1985, ref. 87**
				and significantly improved symptoms, including nausea, vomiting, early satiety, and abdominal pain	
Motilin Agonists					
Erythromycin RCT, PC, XO	10 T1DM	200mg iv; 250mg p.o. tid	4 weeks	Solid meal retention at 2h: 63±9% with placebo; 4±1% with erythromycin; no effects on the symptoms	Janssens 1990, ref. 97
Erythromycin open trials of i.v. and p.o.	10 IG and 4 DG; 4 patients dropped out	6 mg/kg i.v. 500 mg tid-ac and qhs	Single dose; 4 wk and open 8.4 mo	Solid meal retention at 2h: 85±11% (SD) at baseline; 20±29% on iv erythromycin ($p < 0.001$); 48±21% after 4 wk of oral therapy ($p < 0.01$). Reduction in total symptom scores and a significant reduction in global assessment scores	Richards 1993, ref. 98
Erythromycin vs metoclopramide RCT, XO	13 DG	p.o. 250 mg tid erythromycin; p.o.10 mg tid metoclopramide	3 weeks each period	Compared with baseline, improved GE parameters after both erythromycin and metoclopramide, with improved total GI symptom scores, more pronounced with erythromycin	Erbas 1993, ref. 64
Erythromycin RCT, PC, XO	20 IG (functional dyspepsia + delayed GE)	200mg i.v.	Single dose	Erythromycin accelerated (breath test) solid GE T½=146 (27) vs 72 (7) min, and liquid GE T½=87 (6) vs 63 (5) min; no overall symptom improvement except for bloating	Arts 2005, ref. 99
Erythromyin vs azithromycin retrospective case-control analysis	120 patients (27 DM) underwent SGE with provocative testing	250mg i.v. of each drug	Single dose	Both treatments accelerated gastric emptying with no difference between the 2 treatments: erythromyin GE T½=166±68min baseline to 11.9±8.4min; azithromycin GE T½=178±77min baseline to 10.4±7.2min	Larson 2010, ref. 100

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

Table 6.

Efficacy of antiemetics and central neuromodulators in gastroparesis

Medication/trial design	N, Etiology	Dose	Duration	Efficacy	Reference
Aprepitant PC, PG, DB, RCT	126 pts with at least moderate chronic nausea and vomiting	p.o. 125mg/day	4-weeks	Aprepitant did not reduce symptoms of nausea (primary outcome measure) but significantly reduced secondary outcomes: in symptom severity for nausea, vomiting and overall symptoms. Adverse events (mild or moderate severity) commoner in aprepitant (35%) vs placebo (17%).	Pasricha 2018, ref. 103
Tradipitant PC, PG, DB, RCT	152 adults with IG (91) or DG (61)	p.o. 85 mg bid	4 weeks	Significant decrease in nausea score (reduction of 1.2) at week 4; significant increase in nausea-free days at week 4 with even greater effects in patients with nausea and vomiting at baseline (n = 101). A >1-point improvement in GCSI score in 46.6% on tradipitant compared with 23.5% on placebo.	Carlin 2021, ref. 104
Nortriptyline PG, PC, DB RCT	130 IG	dose escalation at 3-week intervals (10, 25, 50, 75 mg) to 75 mg at 12 weeks	15 weeks	No difference in primary outcome measure (decrease from the patient's baseline GCSI score of at least 50% on 2 consecutive 3-week GCSI assessments during 15 weeks of treatment); more treatment cessation in nortriptyline group (29%) than placebo group (9%); numbers of adverse events not different.	Parkman 2013, ref. 105
Haloperidol PC, RCT	33 Emergency Dept. patients with acute exacerbation of diagnosed gastroparesis	5mg vs. placebo both + conventional therapy (selected by treating physician)	Single dose	One hour after therapy, the mean pain and nausea scores in the haloperidol group were 3.13 and 1.83 compared to 7.17 and 3.39 in the placebo group (symptoms on 10-point scale). No adverse events were reported.	Roldan 2017, ref. 106
STW5 or STW5-11 vs. cisapride DB, double dummy, RCT	186 dysmotility type of FD	NA	NA	The lower limit of the confidence interval for both herbal preparations was above the pre-defined lower limit of the equivalence border and hypothesis of non-inferiority was proven for STW 5 & STW 5-II.	Rosch 2002, ref. 107
STW 5 PC, PG, DB, RCT	103 patients with FD and gastroparesis	20 drops tid	4 weeks	Improvement of the GIS (P=0.08) and the proportion of patients with a treatment response (P=0.03) were more pronounced in the STW 5 group compared to placebo. No effect on GEBT.	Braden 2009, ref. 108
Survey questionnaire of treatment of nausea in in clinical practice	102 patients: gastroparesis 43.1%, FD 27.5%, PSG 8.8%, other 2.0%, undetermined multiple 10.8%.			Patient-reported best treatments were marijuana, ondansetron, and promethazine. Least effective treatments were erythromycin, diphenhydramine, buspirone, gabapentin, pregabalin, acupuncture, and Iberogast. Promethazine was more effective in patients with a higher GCSI.	Zikos 2018, ref. 109

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

Table 7.

Efficacy of several bioelectric therapies in gastroparesis

Device/trial design	Patients	Efficacy	Reference
Vagal Stimulation			
Open-label pilot study: short-term noninvasive cervical vagal nerve stimulation in patients with drug-refractory gastroparesis	23 patients with gastroparesis for 3 weeks and 7 of these for 6 weeks.	Response rates were 35% at 3 weeks and 43% for 3–6 weeks. Improvements in mean total GCSI and subscales were noted.	Paulon 2017, ref. 117
Open-label pilot study: noninvasive vagal nerve stimulation for 4 wks improves symptoms and gastric emptying in patients with IG	15 patients with mild to moderate IG	Improvement in total GCSI symptom scores and three subscales, with 40% participants meeting primary endpoint; therapy also associated with a reduction in GE T1/2.	Gottfried-Blackmore 2020, ref. 118
Spinal Cord Stimulation			
Open-label study of spinal stimulation in patients with abdominal pain, with the majority having gastroparesis	23 patients, 96% Caucasian and 79% women, with gastroparesis in 63%	After 12 months of 10-KHZ spinal cord stimulation, 78% of patients had >50% reduction in pain and 64% remitted in pain. Other outcomes improved in most patients.	Kapural 2020, ref. 119
Controlled Trials in Gastric Electric Stimulation (GES)			
Temporary GES			
RCT, PC, XO trial of two consecutive, 4-day sessions of temporary GES	58 patients (47 females) with gastroparesis symptoms: 38 IG; 13 DG, 7 PSG	Overall slight, NS daily decrease in average vomiting scores First session was significant, but not significant after XO. Temporary GES may improve symptoms such as vomiting.	Abell T 2011, ref. 120
Permanent GES			
GES reduces refractory vomiting in a randomized, XO trial	218 patients in 19 centers, 97 with DG and 121 with IG were included and 46 were excluded, thus 172 patients were implanted and analyzed	A randomized, XO trial for 4 months of GES decreased vomiting in DG and IG, irrespective of baseline GE.	Ducrotte 2020, ref. 121
Multicenter, DB, XO, RCT of GES	17 DG and 16 IG	Self-reported vomiting frequency significantly reduced in the on vs. off period and consistent with the significant patient preference for the on vs. off period; vomiting frequency decreased, and symptom severity and quality of life improved at 6 and 12 months. Once unblinded, the symptom improvement continued at one year.	Abell T 2003, ref. 122
Randomized XO study of GES with all patients turned on for 6 weeks and then with consecutive 3-month XO periods with device on or off	55 patients with DG	6 weeks of GES therapy significantly reduced vomiting and gastroparetic symptoms in patients with DG.	McCallum R 2010, ref. 123
Prospective, DB, randomized, XO study of GES with all patients initially having device on for 6 weeks followed by DB consecutive 3-month XO periods with device either on or off.	32 patients with IG	GES implanted with on stimulation was shown to decrease vomiting symptoms in the initial 6-week on period. NS reduction in vomiting symptoms in on vs. off period. Sustained decrease in vomiting and days of hospitalization at 12 months in the on group.	McCallum R 2013, ref. 124

Device/trial design	Patients	Efficacy	Reference
Two separate but related studies of the effect of GES on pancreatic function in gastroparesis patients: single-blinded, RCT compared to normal controls	9 patients with gastroparesis and GES and 9 healthy controls	Pancreatic elastase was significantly different for GES on vs. off: 508 on vs. 378 off. Total GI symptoms were significantly lower on vs. off. Pancreatic polypeptide and heart rate were borderline improved with on vs. off.	Luo 2004, ref. 125
DB, prospective, single-arm, RCT Study of GES in DG	7 DG patients	No evidence was found for GES-induced modulation of the visceral sensory system and central excitability. Some changes in symptoms noted with GES.	Frokjaer 2009, ref. 126
Propensity score matching. Effect of GES in gastroparesis with prospective data	319 patients with gastroparesis symptoms, of which, 81 had GES and 231 without GES	Patients treated with GES had clinically significant improvement in gastroparesis symptoms. When adjusted by propensity scoring only nausea remained significant	Abell T 2019, ref. 127
Controlled with medical arm but not randomized study with 1 year of baseline and 3 years of treatment with two groups: GES vs intensive medical therapy	9 GES patients and 9 similar patients in an outpatient medical program	GES was found to be more effective in improving long-term GI symptoms, decreased costs, and less use of healthcare resources than intensive medical therapy.	Cutts 2005, ref. 128
Meta-analyses Assessing Effectiveness of Gastric Electrical Stimulation			
NICE Guidance on GES for gastroparesis	Several studies reviewed, 2 metanalysis, 2 RCT, XO	Diabetics with severe symptoms may benefit from therapy.	Kong 2015, ref. 129
SRMA 13 studies, 12 lacked controls and 1 blinded and randomized	13 studies, 12 lacked controls and 1 blinded and randomized	Following GES, improvements in TSS score (3/13 studies), vomiting severity (4/13), nausea severity (4/13), SF-36 physical composite score (4/13), SF-36 mental composite score (4/13), requirement for enteral or parenteral nutrition (8/13), and 4-h gastric emptying (5/13). Weight gain (in 3/13) did not reach overall significance, 3 Device removal or reimplantation rate was 8.3%. Beneficial in improving symptoms in patients with gastroparesis	O'Grady 2009, ref. 130
SRMA 5 studies randomly allocated patients to periods with or without GES	5 randomized trials 16 open-label studies	TSS scores did not differ between these periods with or without GES in randomized trials. Open-label studies showed a significant decrease in TSS scores, which was also shown with medical therapy or placebo arms, or botulinum toxin. Meta-regression analysis showed that significant differences in baseline TSS ratings impacted TSS ratings during treatment. Argues against the use of GES outside of strict clinical trials as viable treatment option.	Levinthal 2017, ref. 131
SRMA	21 studies	GES appears to offer significant improvement in symptom control in a subset of patients.	Lal 2015, ref. 132
SRMA	10 studies	GES is an effective modality for treating gastroparesis refractory to less invasive treatment.	Chu 2012, ref. 133
Selected Open-Label Trials of Gastric Electrical Stimulation			
Multicenter, open-label GES experience in France	142 patients (60 diabetic, 82 non-diabetic) and medico-economic data were available for 96 patients (36 diabetic, 60 non-diabetic)	24 months after implantation. GIQLI score increased, with a more significant improvement in non-diabetic than in diabetic patients. Proportion of patients vomiting less than once per month increased by 25.5%. GES decreased mean overall healthcare costs (saving of average $3348/patient/year), with. savings greater for diabetic patients (4096 US$/patient/year).	Gourcerol 2020, ref. 134
Open-label GES study	16 patients with PSG refractory to medical therapy	Severity and frequency of all 6 upper GI symptoms, TSS, physical composite score, and mental composite score significantly improved after 6 months and sustained at 12 months; 4/7 stopped jejunal feeding; mean number of hospitalization days significantly reduced by a mean 25 days compared with prior year. No effect on GE.	McCallum 2005, ref. 135

Device/trial design	Patients	Efficacy	Reference
Open-label GES study	37 gastroparesis patients preop. and 1y post-GES implant	8/27 off prokinetics; 9/26 off antiemetics at 1y; mean TSS significantly reduced, overall SF-36 scores (HR-QOL) significantly improved, and hospitalizations decreased from 50 ± 10 days for the year prior to GES therapy to 14 ± 3 days. GE was not significantly improved.	Lin 2005, ref. 136
Open-label GES study	55 patients with gastroparesis with follow-up information for over 3y	Of the 55 patients, 10 died of unrelated complications, 6 had devices removed and 2 could not be reached. 37 patients had activated GES for mean 45 months: TSS, hospitalization days and the use of medications all significantly reduced at 1 and 3 y. Among 15/37 patients requiring nutritional support, only 5 continued beyond 3y. Mean HbA1c in diabetics reduced from 9.5 to 7.9% at 3y.	Lin 2006, ref. 137
Open-label GES study	15 patients with gastroparesis	Four patients (4 idiopathic) failed to improve more than 20% on multiple assessments after a year of therapy. All diabetic patients experienced a durable symptomatic improvement with GES. GES non-responders had less severe vomiting preoperatively.	Musunuru 2010, ref. 138
Open-label GES clinical experience	221 patients with gastroparesis: 142 (64%) DG, 48 (21%) IG, 31 (14%) PSG	At follow-up of at least 1 year, there was association of symptom improvement with improved GE in DG, not in IG. Patient age, gender, baseline TSS score, and baseline gastric retention had no significant effect on clinical improvement in response to GES.	Hou 2012, ref. 139
Open-label experience	4 patients with gastroparesis	Mean length of hospital stay in the year pre-GES was 81.75 days and 62.25 days in the year post-GES; also no improvement in glycemic control following GES.	Hannon 2011, ref. 140
Open-label follow-up study of GES after successful initial temporary GES	IG 9, DG 3 with long duration symptoms (7.3 years)	Short-term: improved TSS, body weight, BMI, and serum albumin by 3 to 6 months. Intermediate (1 to 2 years) and long-term (5 year) data: continued improvement in TSS, weekly vomiting frequency score, QOL measures, and maintained weight gain.	Abell T 2003, ref. 141
Open-label GES study	Refractory gastroparesis: DG 39, PSG 9, IG 7	TSS and the physical and mental composite scores of QOL improved significantly; GE did not change; BMI and body weight increased; days spent in hospital admissions significantly decreased.	Forster 2003, ref. 142

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

Table 8.

Effect of electro-acupuncture, acupuncture, and herbal medicines in gastroparesis

Electro-acupuncture			
Device/trial design	**Patients**	**Efficacy**	**Reference**
Multicenter sham-controlled, XO, 4-week RCT of transcutaneous electroacupuncture (TEA) via surface ECG electrodes at acupoints PC6 and ST36.	26 DG patients, 18 completed study; TEA performed using pulse trains self-applied for 2 hrs. post-lunch/dinner	4-wk TEA, not sham-TEA, significantly improved 5 of 9 gastroparesis symptoms: nausea by 29.7%, vomiting by 39.3%, abdominal fullness by 21.4%, bloating by 20.6%, and retching by 31.1%. A significant change in pain was also noted with TEA.	Xu 2015, ref. 143
Acupuncture			
Device/trial design	**Patients**	**Efficacy**	**Reference**
Single-blind, RCT, XO trial of acupuncture for 1 week vs sham acupuncture with 1-month washout period	25 DG patients	Real acupuncture was associated with significantly greater reductions in gastric retention at 2h and 4h and in GCSI score with no differences in fasting blood glucose or HbA1c	Li 2015, ref. 144
Single-center, DG comparison of acupuncture to control	Acupuncture treatment group (n=16 (5M/11F), 5 times per week 40 minutes each for 10 days, and a control group (n=16 (7M/9F).	Compared to control group, acupuncture resulted in the clinically significant improvement of the severity of symptoms and the GCSI nausea by 68,4%, retching by 76,8%, vomiting by 86,7%, stomach fullness by 62,5%, not able to finish a normal-sized meal by 21,2%, stomach visibly larger by 13,4%, loss of appetite by 12,8%, feeling excessively full after meals by 64,7% and bloating by 22.5%	Kostitska 2016, ref. 145
Single-center, RCT of acupuncture applied to Zusanii once per day and other acupoints compared to metoclopramide 20mg tid i.m.	Acute PSG in 63 patients	Significant differences in gastric drainage volume, cure rate and number of treatments with cure rate was 90.6% with acupuncture and 32.3% with metoclopramide	Sun 2010, ref. 146
Single-center comparison of 6-day Rx with acupoint stimulation (bilateral TEA) at Neiguan, PC-6 or prokinetic (metoclopramide, cisapride, erythromycin)	30 mechanically-ventilated neurosurgical ICU patients with delayed GE [gastric residual volume (GRV) >500 mL for ≥2 days]	After 5 days of treatment, 80% of patients in the acupoint group successfully developed feeding tolerance (GRV <200mL/24h) versus 60% in the prokinetic group; benefit was documented from day 1 of treatment. Similarly, feeding balance improved significantly on all days of treatment with acupoint vs. prokinetic therapy.	Pfab 2011, ref. 147
Single-center, open-label treatment with needleless TEA	11 patients with DG evaluated with visual stimulation (VS) to evoke nausea and EEG	TEA improves gastric dysrhythmia and ameliorates nausea. TEA treatment of nausea provoked by VS resulted in a change of dominance from right to left inferior frontal lobe activity on EEG.	Sarosiek 2017, ref. 148
RCT of acupuncture points: group A Zhongwan (CV 12) and Zusanli (ST 36); group B, Neiguan (PC 6) and Zusanli (ST 36); group C, non-acupoint and Zusanli (ST 36).	99 patients with gastroparesis at 3 clinical centers	Treatment was performed for 30 minutes every day, 5 days as a course of treatment. GCSI scores of each group after treatment and at follow-up were significantly lower than those before treatment (P <0.01), and the reduction in group A (Zhongwan (CV 12) and Zusanli (ST 36)) was greater than that of groups B and C (P <0.01). SF36 scores similar in the three groups.	Xuefen 2020, ref. 149
SRMA of acupuncture either manually stimulated (24 studies) or electrically stimulated (8 studies).	32 studies with a total of 2601 participants: DG (31 studies) or PSG (1 study)	There was low-certainty evidence that symptom scores of participants receiving acupuncture did not differ from those receiving sham acupuncture at 3 months when measured by a validated scale. There was very low-certainty evidence that acupuncture had ‘improved’ symptoms compared to gastrokinetic medication (4–12 weeks) (12 studies; 963 participants).	Kim 2018, ref. 150
SRMA of 14 RCTs of acupuncture	14 RCTs of DG	Acupuncture treatment had a higher response rate than controls (RR, 1.20 [95% confidence interval (CI), 1.12 to 1.29], P < 0.00001), and significantly improved dyspeptic symptoms compared with the control group.	Yang 2013, ref. 151

Open-label treatment with behavioral technique, autonomic training with directed imagery (verbal instructions)	26 patients with chronic nausea and vomiting	Gastrointestinal symptoms decreased by >30% in 58% of the treated patients; responders manifested mild to moderate delay in baseline GE; the sympathetic adrenergic measure (change in the foot cutaneous blood flow in response to cold stress) predicted improvement in autonomic training outcome.	Rashed 2002, ref. 152
Chinese Herbal Medicine			
SRMA Banxiaxiexin decoction for DG	16 RCTs involving 1302 patients	Effect of Banxiaxiexin decoction (BXXD) for DG was superior to the control group (n = 1302, RR 1.23, 95% CI 1.17 to 1.29). Methodological quality of included studies was low, and long-term efficacy and safety are still uncertain.	Tian 2013, ref. 153
SRMA in comparison to conventional treatment (Western medicine treatment [metoclopramide, mosapride, cisapride, domperidone]), placebo, and no treatment (blank) for DG	Ten RCTs involving 867 patients (441 in the experimental groups [herbs alone], and 426 in the control groups [all prokinetic])	Effects of Xiangshaliujunzi Decoction (XSLJZD) for the treatment of DG were superior to the control group (n=867, RR=1.33, 95% CI: 1.24–1.42) based on symptoms and gastric emptying. Evidence remains weak due to the poor methodological quality of the included studies.	Tian 2014, ref. 154

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

Table 9.

EndoFLIP for Selection of Patients for Pyloromyotomy or Pyloric Botulinum Toxin Injection

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

(CSA=cross-sectional area; DI =distensibility index; DG=diabetic gastroparesis; GIQLI=Gastrointestinal Quality of Life Index; HC=healthy controls; IG=idiopathic gastroparesis; NA=not available; PSG=post-surgical gastroparesis; TSS=total symptom score

Table 10.

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

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

# Pts	Types of gastroparesis pts	Changes in GE	Changes in symptoms	Duration follow up	Adverse events	Ref. #
9	5 PSG, 2 DG, 1 IG, and 1 PSG and diabetic		Mean GSCI decreased from 3.16 to 0.86 (3 months), 0.74 (6 months), 1.07 (12 months) and 1.31 (24 months [ns]) after the procedure. GIQLI improved from baseline at 12 months; not significant at 24 months	median follow-up was 23 (range 12–31) months	1 delayed bleeding from gastric ulcer	Hustak 2020, ref. 174
76	Gastroparesis with median duration 48 months; median gastric retention at 4h 45% and median GCSI 3.6	High rate of gastric retention at 4h was significantly associated with clinical failure	Clinical success in 65.8% of patients at 1 year, with median of reduction in GCSI score of 41 %; high preop GCSI satiety score predicted clinical success	At least 1 y		Ragi 2021, ref. 175
SRMA	14 studies with total 276 patients	Pooled GE scintigraphy normalization rate was 61.3% (95% CI, 51.5–70.8%)	Clinical symptom improvement rate was 88.2% (95% CI, 83.6–93.1%). Mean GCSI score improvement rate: 90.2% at 1 month, 83.3% at 3 months, 70.3% at 6months, 52.4% at 12 months and 57.1% at 18 months.	Up to 18 months	Intra-operative complications were found in about 3.2% and postoperative adverse events in 2.1%	Zhang 2019, ref. 176
SRMA	6 studies	GE scintigraphy not improved	Improvement in GCSI score after 3 months of G-POEM as compared with pre-G-POEM GCSI scores.	3 months	Pooled rate of total adverse events was 9% (95% C.I. 2.7–25.9).	Garg 2020, ref. 177
SRMA	272 patients in 8 studies	The pooled results of 4h GE scintigraphy were 41.89% (95% CI, 32.75–51.03%) pre-G-POEM and 16.48% (95% CI, 9.83–23.14%) post-G-POEM	Pooled rates of GCSI were 3.25 (95% CI, 2.75–3.75) pre-procedure, 1.80 (95% CI, 1.10–2.49) at 1–3 months, 1.56 (95% CI, 0.45–2.68) at 6 months, and 1.10 (95% CI, 0.75–1.45) at 12 months	1, 3, 6, and 12 months	Pooled adverse events rate was 12% (95% CI, 6–19%)	Li 2021, ref. 178
SRMA	10 studies, 292 patients	GE scintigraphy, significant decrease of the residual percentage at 2 and 4 hours	Significant symptomatic improvement was achieved after 83.9% of procedures	Mean follow-up, 7.8 ± 5.5 months).	The overall adverse events rate was 6.8%.	Spadaccini 2020, ref. 179
Laparoscopic pyloroplasty compared to G-POEM procedure						
60	Retrospective comparison lap pyloroplasty (LP) vs. G-POEM, Single-center, 30 per group (19 IG, 6 PSG, 5 DG), matched by propensity scoring	LP and G-POEM both resulted in similar, significant improvements in GCSI scores (overall and each of 3 subscales) with no differences between treatment groups	LP and G-POEM both resulted in similar, significant improvements in objective GE with no differences between treatment groups	1-month outcome (28 G-POEM, 22 LP) 3-month outcome (25 G-POEM, 21 LP)	Longer length of stay, operative time, more estimated blood loss and complications in the LP group (surgical site infection, pneumonia, and unplanned ICU admission	Landreneau 2019, ref. 180
SRMA	G-POEM (332 in 11 studies) vs. surgical pyloroplasty (375 in 7 studies	4h GE scintigraphy success results: G-POEM 85.1% (95% CI 68.9–93.7) and surgical pyloroplasty 84% (95% CI 64.493.8) with no significant difference	Clinical success, based on GCSI score: G-POEM 75.8% (95% CI 68.1–82.1) and surgical pyloroplasty 77.3% (95% CI 66.4–85.4), with no significant difference		Overall adverse events were comparable	Mohan 2020, ref. 181

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

Exhibit L

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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis: Expert Review

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DESCRIPTION: **Delayed gastric emptying on objective testing defines gastroparesis, but symptoms overlap with functional dyspepsia and do not correlate well with gastric emptying delay. This review outlines a strategy for defining, diagnosing, and managing refractory gastroparesis.**

METHODS: **The Best Practice Advice statements presented here were developed from review of existing literature combined with expert opinion to provide practical advice. Because this was not a systematic review, formal rating of the quality of evidence or strength of recommendations was not performed.**

BEST PRACTICE ADVICE:

1. **Clinicians should review symptoms and evaluate physical examination findings to exclude disorders that can mimic medically refractory gastroparesis.**
2. **Clinicians should verify appropriate methodology of the gastric emptying study to ensure an accurate diagnosis of delayed gastric emptying.**
3. **Clinicians should classify patients with gastroparesis into mild, moderate, or severe based on symptoms and the results of a properly performed gastric emptying study.**
4. **Clinicians should identify the predominant symptom and initiate treatment based on that symptom.**
5. **Clinicians should be aware of the multiple treatment options to treat nausea and vomiting.**
6. **Clinicians should consider the use of neuromodulators to treat gastroparesis associated abdominal pain but should not use opioids.**
7. **Clinicians can consider gastric electrical stimulation for gastroparesis patients with refractory/intractable nausea and vomiting who have failed standard therapy and are not on opioids.**
8. **Clinicians can consider G-POEM for select refractory gastroparesis patients with severe delay in gastric emptying, using a thoughtful team approach involving motility specialists and advanced endoscopists at a center of excellence.**

Keywords: Gastroparesis; Nausea and Vomiting; Abdominal Pain.

Gastroparesis is a syndrome defined by symptomatic delay in gastric emptying in the absence of mechanical obstruction.[1] Typical gastroparesis symptoms of nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and/or weight loss (Figure 1) overlap to a significant degree with functional dyspepsia (FD).[1–5] With an estimated prevalence per 100,000 persons of 37.8 for women and 9.6 for

Abbreviations used in this paper: FD, functional dyspepsia; FDA, Food and Drug Administration; FLIP, functional lumen imaging probe; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric electrical stimulation; G-POEM, gastric per-oral endoscopic myotomy; 5-HT_3, 5-hydroxytryptamine$_3$; NK-1, neurokinin-1; RCT, randomized controlled trial; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

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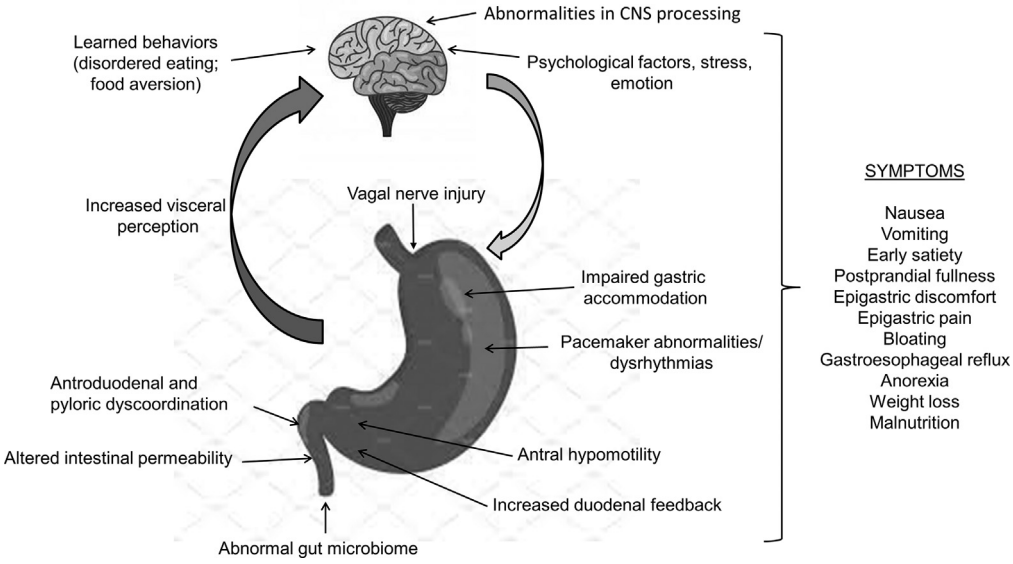


Figure 1. Putative factors involved in the generation of refractory gastroparesis symptoms. Both central processes and local gastroduodenal mechanisms may participate in symptom generation. Exaggerated visceral perception, altered central processing, learned behaviors including food aversion, and ongoing psychological distress may all potentially contribute to clinical presentation and symptom intensity. CNS, central nervous system.

men,[6] approximately 5 million U.S. adults suffer with gastroparesis-like symptoms,[7] and 7.2% of the global population report FD symptoms,[8] making gastroparesis and FD 2 of the most common sensorimotor disorders of the stomach.[2,3,9] The etiology of gastroparesis is diverse, with more than 50 recognized causes. Diabetes accounts for 25%, medications (eg, opioids, glucagon-like peptide-1 agonists), vascular disorders, connective tissue disorders, and postsurgical causes are other common causes, but the largest etiologic group is idiopathic.[1,2,4,7,10,11] Gastroparesis negatively impacts quality of life and is a significant economic burden to the health care system.[12,13]

Although delayed gastric emptying is the defining motor abnormality, the complex pathophysiology of gastroparesis includes impaired gastric accommodation, electrical dysrhythmias, antroduodenal dyscoordination, pyloric dysfunction, antral hypomotility, vagal nerve injury, and disorders of visceral sensation.[1,2,4,7,11] Lack of consistent reproducible relationships between global gastroparesis symptoms and gastric emptying delay complicates treatment decisions,[14,15] in part because gastric emptying scans are not always performed correctly. Simply accelerating gastric emptying may not improve global gastroparesis symptoms. Furthermore, the gastroparesis-FD overlap clouds interpretation of treatment response, because some patients with FD may be treated as if they had gastroparesis.[2,5,14,16,17] This overlap was highlighted by the recent finding that as many as 42% of gastroparesis patients were reclassified as having FD, and 37% of FD patients were reclassified as gastroparesis over the course of a year.[18] These factors explain why no single treatment has proved uniformly effective at treating global gastroparesis symptoms.

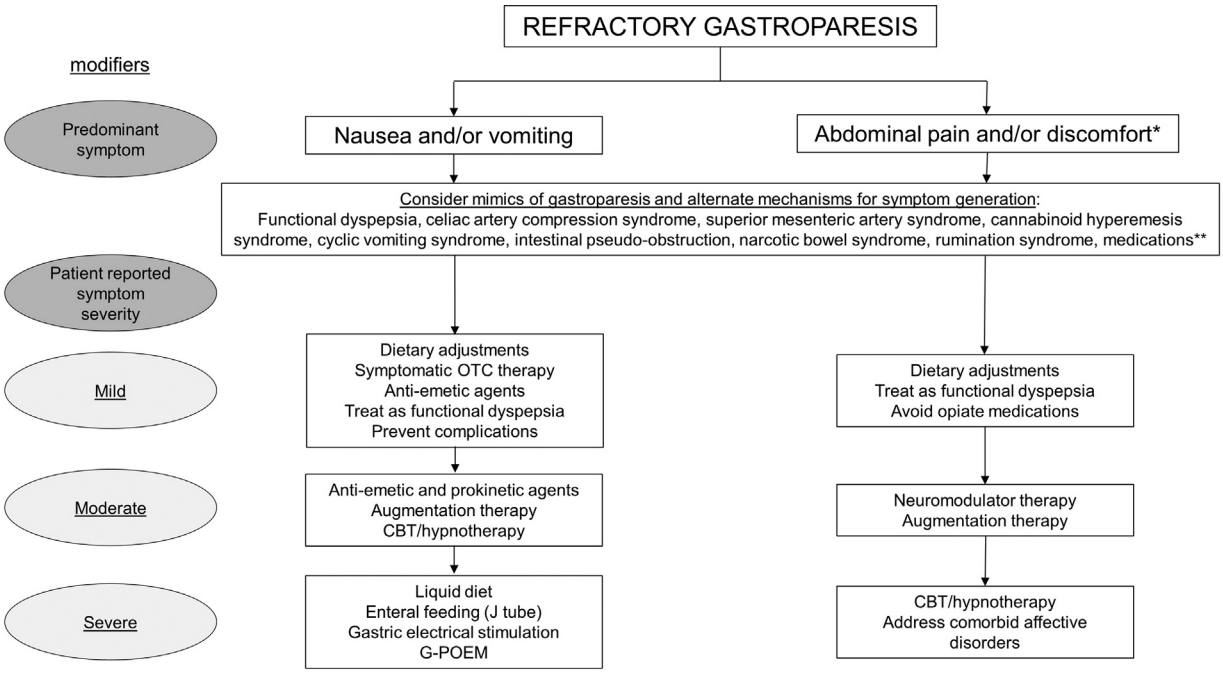
When gastroparesis symptoms persist, patients are often labeled as having medically refractory gastroparesis, despite the fact that no precise definition or dedicated treatment algorithm for this diagnosis exists in the literature. This review outlines a strategy for defining, diagnosing, and managing medically refractory gastroparesis. This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the Clinical Practice Updates Committee as well as external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. This clinical practice update is not intended to be a comprehensive review on gastroparesis and will not focus on etiology, pathophysiology, or diagnostic testing.

Definition of Medically Refractory Gastroparesis

Medically refractory gastroparesis can be defined as persistent symptoms in the context of objectively confirmed gastric emptying delay, despite the use of dietary adjustment and metoclopramide as a first-line therapeutic agent. Inherent to this definition is the proviso that symptoms are not medication induced (eg, opioids, glucagon-like peptide-1 agonists). Generally, nausea and vomiting are the predominant persistent symptoms, although all symptoms should be considered.[1,5,9] On the basis of a single trial that formally studied dietary manipulation in patients with gastroparesis,[19] a small particle size, reduced fat diet should be used for a minimum of 4 weeks. A reasonable trial of metoclopramide, the only Food and Drug Administration (FDA) approved medication for gastroparesis, is a minimum of 10 mg three times daily before meals and at bedtime for at least 4 weeks, which is based on limited data and no agreed upon standards.[1] Evidence to support longer interventions from randomized controlled

trials (RCTs) is not available. Clinicians should familiarize themselves with the black box warning associated with metoclopramide use, although the risk of tardive dyskinesia from chronic metoclopramide use may be lower than previously estimated by regulatory authorities. Because there are no prospective, randomized controlled studies comparing different management strategies (eg, a central anti-emetic vs a prokinetic agent), initiating treatment based on the predominant presenting symptom is a reasonable first approach.

Gastroparesis is heterogeneous, and symptom expression—frequency, intensity, severity, and duration—varies between patients, making an accurate diagnosis essential at the outset. A careful history, thoughtful physical examination, and prudent diagnostic tests can distinguish conditions that mimic refractory gastroparesis (Figure 2). Important physical examination findings include a succussion splash (suggestive of delayed gastric emptying or gastric outlet obstruction), a bruit on auscultation of the right upper quadrant (celiac artery compression syndrome), digital ulcers and telangiectasia (scleroderma) and ascites, a mass or enlarged lymph nodes (underlying malignancy). If not recently performed, a complete blood count, liver chemistries, and a basic metabolic profile should be checked. Electrolyte derangements are common in patients with persistent nausea and vomiting and should be corrected. A thyroid stimulating hormone level can be checked if hypothyroidism is a concern. Hyperkalemia and metabolic acidosis may indicate adrenal insufficiency, which can be initially evaluated by measuring a fasting cortisol level. Upper endoscopy should be performed to rule out an organic cause of symptoms. Gastric emptying can be measured by using several techniques (scintigraphy, ^{13C}spirulina breath test, wireless motility capsule); most U.S. centers perform gastric scintigraphy, albeit often incorrectly with short measurement times, leading to misdiagnosis and mismanagement.[20,21] Joint American Nuclear Medicine Society and American Neurogastroenterology and Motility Society guidelines outline key protocol requirements for performing an accurate 4-hour test,[22] optimally performed off opioid medication. Repeating scintigraphy may change the pathophysiological and diagnostic categorization from gastroparesis to FD and vice versa in as many as 37%–42% within the course of a year.[18] Because the wireless motility capsule, an inanimate object, identifies the phase III activity front of the migrating motor complex rather than overall gastric emptying, a meal-based test provides better physiological assessment of gastric emptying and is thus



GES: gastric emptying study; OTC: over the counter; CBT: cognitive and behavioral therapy; G-POEM: gastric per oral endoscopic myotomy
*Abdominal pain is present in many, but not all patients with gastroparesis. Data from tertiary care centers reveal a higher prevalence of pain compared to the general community.
**see references 1,5,31 for a comprehensive list of gastroparesis mimics and a differential diagnosis

Figure 2. Proposed algorithm for management of refractory gastroparesis symptoms. Patients can be phenotyped into 2 categories on the basis of presenting symptoms: nausea/vomiting predominant, and abdominal pain/discomfort predominant symptoms. This pathway assumes that anatomic/organic causes for symptoms have been ruled out with upper endoscopy and selective imaging, if clinically indicated. In the appropriate patients, celiac artery compression syndrome can be initially evaluated with a mesenteric duplex, and superior mesenteric artery syndrome can be evaluated with radiologic imaging (eg, small bowel follow through or computed tomography enterography). Intestinal pseudo-obstruction can be diagnosed by symptoms, laboratory tests, and imaging studies. In particular, cyclic vomiting syndrome and cannabinoid hyperemesis syndrome need to be differentiated from nausea/vomiting predominant gastroparesis. Management options depend on the degree of patient-reported symptoms and/or the degree of gastric emptying delay (mild, moderate, and severe) on a 4-hour gastric emptying scan.

recommended as the first-line test of gastric emptying over the wireless motility capsule.[5]

Clinical Manifestations of Refractory Gastroparesis

Symptoms and objective data can help drive treatment choices, starting with identification of the predominant or most bothersome symptom (Figures 1 and 2) using a validated symptom scoring system such as the Gastroparesis Cardinal Symptom Index (GCSI); however, overlap with FD makes this less reliable than previously thought.[16] Although not validated in large, prospective studies, some investigators categorize gastroparesis severity on the basis of the extent of gastric emptying delay[1] into mild (10%–15% retention at 4 hours on scintigraphy), moderate (15%–35% retention at 4 hours), and severe (>35% retention at 4 hours), which may potentially guide management. Because gastric emptying scans are commonly performed incorrectly, patients should be preferentially referred to centers that adhere to guidelines on properly performing a scintigraphic study.[20–22]

Pathophysiology of Refractory Gastroparesis

The pathophysiology of refractory gastroparesis is complex (Figure 1), and it is not always possible or feasible to identify all underlying pathophysiological abnormalities. For example, prokinetic therapy may be appropriate for predominant antral hypomotility, and pylorus-directed therapies can be considered for pyloric dysfunction. Abnormalities of visceral sensation, conditioned responses, eating disorders, alterations in central nervous system processing, and coexisting psychological disorders are often neither considered nor addressed during diagnostic evaluation, which is further compounded by the fact that these can be difficult to evaluate clinically.[23]

Management of Refractory Gastroparesis

Management goals consist of identifying and improving the predominant symptom, reducing the potential for complications (eg, reflux esophagitis, malnutrition, weight loss), reducing health care utilization, and improving quality of life (Table 1, Figure 2).

Medications for Nausea and Vomiting

For patients who fail metoclopramide, a variety of treatment options exist, although many of these agents have not been evaluated in large RCTs (Table 1). Whenever available, we will present data from gastroparesis studies.

Domperidone, a dopamine D_2-receptor antagonist, does not readily cross the blood-brain barrier; although QT prolongation and ventricular tachycardia are risks, it has fewer central side effects than metoclopramide.[24] Availability in the United States is only through an FDA investigational drug application. The recommended starting dose is 10 mg 3 times a day; although escalation to 20 mg 4 times a day has been reported, this should probably be avoided for cardiovascular safety considerations.[1] Published studies reveal modest efficacy, although patients studied were not defined a priori as having refractory gastroparesis.[25] A single-center cohort study of gastroparesis patients (n = 115) showed that 68% had improvement in symptom scores, although 7% had cardiac side effects requiring drug cessation.[26]

5-Hydroxytryptamine$_3$ (5-HT_3) receptor antagonists (eg, ondansetron, granisetron) block serotonin receptors in the chemoreceptor trigger zone and inhibit vagal afferents, thereby improving nausea and vomiting. These agents have similar efficacy; selection can be determined by price, availability, and mode of delivery. Ondansetron is available in both parenteral and enteral forms; granisetron is available as a liquid, tablets, and a transdermal patch. Studies have reported efficacy of transdermal granisetron (3.1 mg/24 h) in decreasing symptom scores by 50% in patients with refractory gastroparesis symptoms.[6,27]

Neurokinin (NK-1) receptor antagonists (eg, aprepitant, tradipitant, casopitant, rolapitant) block substance P in critical areas involved in nausea and vomiting, including the nucleus tractus solitarius and the area postrema.[28] An RCT of 126 gastroparesis patients randomized to aprepitant (125 mg/day) or placebo reported improvement of nausea and vomiting using the GCSI, but not when using visual analog score assessment of nausea intensity.[29] Another RCT comparing tradipitant (85 mg) with placebo in diabetic or idiopathic gastroparesis over 4 weeks demonstrated improvement in nausea, especially in idiopathic gastroparesis; vomiting and overall GCSI scores also improved.[30] Although NK-1 receptor antagonists appear to improve nausea and vomiting, these symptoms improved regardless of the presence (gastroparesis) or absence (FD) of significantly delayed emptying,[16 29] and symptoms do not necessarily correlate with gastric emptying time in many patients.[14] Nevertheless, up to one-third of patients with troublesome nausea may benefit from these agents, provided costs are affordable.

Phenothiazine antipsychotics (eg, prochlorperazine, chlorpromazine) reduce nausea and vomiting by inhibiting dopamine receptors in the brain,[31] but these agents have not been studied in gastroparesis or compared prospectively with other anti-emetics. A controlled trial using the substituted benzamide antipsychotic levosulpiride, which also has dopamine-2 blocking effects, in 40 diabetic gastroparesis patients showed significant

Table 1. Treatment Options for Refractory Gastroparesis Symptoms

Treatment	Dose
Medications for nausea and vomiting	
Ondansetron	4–8 mg bid or tid
Granisetron	1 mg bid
Granisetron patch	34.3 mg patch weekly
Prochlorperazine	5–10 mg qid
Chlorpromazine	10–25 mg tid or qid
Meclizine	12.5–25 mg tid
Scopolamine	1.5 mg patch every 3 days
Dimenhydrinate	25–50 mg tid
Diphenhydramine	12.5–25 mg tid
Trimethobenzamide	300 mg tid
Aprepitant	80 mg/day
Ginger	1 g bid
Medications to accelerate gastric emptying	
Metoclopramide	5–20 mg tid–qid
Domperidone	10–20 mg tid–qid[a]
Medications for visceral pain	
Tricyclic agents[b]	
Amitriptyline	25–100 mg/day
Imipramine	25–100 mg/day
Desipramine	25–75 mg/day
Nortriptyline	25–100 mg/day
Serotonin and norepinephrine reuptake inhibitors	
Duloxetine	60–120 mg/day
Anticonvulsants	
Gabapentin	>1200 mg/day in divided doses
Pregabalin	100–300 mg/day in divided doses
Other antidepressants	
Mirtazapine	7.5–30 mg/day
Other interventions	
Endoscopic injection of botulinum toxin A	
Gastric per-oral endoscopic myotomy (G-POEM)	
Gastric electrical stimulation	
Enteral feeding	
Cognitive and behavioral therapy, hypnotherapy	

NOTE. Metoclopramide is the only FDA approved medication for gastroparesis; all other agents are considered off-label use. Gastric electrical stimulation is approved under a Humanitarian Device Exemption (HDE).
bid, twice a day; FDA, Food and Drug Administration; qid, 4 times a day; tid, 3 times a day.
[a]Only available for use in the U.S. via FDA investigational drug protocol. Doses above 10 mg tid not recommended for risk of QT prolongation.
[b]Amitriptyline and imipramine are tertiary amines and are more likely to have side effects (eg, sedation) than secondary amines (desipramine and nortriptyline). Nortriptyline was not found to be effective in idiopathic gastroparesis, although it has not been tested prospectively in patients with diabetic gastroparesis. Tricyclic antidepressants also suppress nausea and vomiting.

improvement of symptoms as well as gastric emptying.[32] Scopolamine, a muscarinic cholinergic receptor antagonist, is used off-label in gastroparesis despite lack of supporting clinical studies. Although synthetic cannabinoids (eg, dronabinol, nabilone) are approved for chemotherapy-related nausea and vomiting, their use in gastroparesis has not been formally evaluated, with the potential to slow gastric emptying.[33] Ginger improves nausea and vomiting but has not been prospectively evaluated in refractory gastroparesis.[34]

Medications to Accelerate Gastric Emptying

Erythromycin, a macrolide antibiotic, accelerates gastric emptying by binding to motilin receptors, thereby stimulating cholinergic activity in the antrum, and initiating phase III contractions of the migrating motor complex.[35] Erythromycin, used intravenously in hospitalized patients (3 mg/kg every 8 hours)[1] or orally in outpatients (50–100 mg 4 times a day given 30–45 minutes before each of the 3 main meals and at bedtime), is associated with tachyphylaxis that limits effectiveness.[1,31] Higher oral doses may cause early satiation and pain and may exacerbate nausea and vomiting. Although azithromycin also accelerates gastric emptying in gastroparesis, it may prolong the QT interval and increase risk of cardiac arrhythmias, similar to erythromycin.[36]

5-HT_4 receptor agonists stimulate peristalsis through release of acetylcholine from the myenteric plexus.[37] Cisapride appeared to be effective in some patients despite lack of RCT data but was removed from the

market because of adverse cardiac effects.[38] Velusetrag, a highly selective 5-HT_4 receptor agonist, accelerated gastric emptying in a large phase 2 RCT, without apparent cardiac side effects,[39] but no phase 3 RCTs have been announced to date. Prucalopride, another selective 5-HT_4 receptor agonist, accelerated gastric emptying and improved symptoms and quality of life in both diabetic and idiopathic gastroparesis in a small RCT.[40] Large multicenter trials are needed to confirm these findings.

Relamorelin, a selective ghrelin agonist with prokinetic activity, improved core symptoms and accelerated gastric emptying in RCT of 393 diabetics with gastroparesis diagnosed using a ^{13}C-spirulina breath test,[41] but without improvement in vomiting compared with placebo; further prospective trials have been placed on hold. Whether the small change in gastric emptying is clinically meaningful remains unanswered.

Medications for Visceral Pain

Abdominal pain, common in refractory gastroparesis, markedly impairs quality of life.[12,42] The pathophysiology likely varies on the basis of underlying etiology, duration of symptoms, comorbid conditions, and associated psychological distress. Neuromodulators including tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) can reduce perception of pain at different levels of the brain-gut axis via multiple mechanisms.[43]

High-quality evidence for neuromodulator use in refractory gastroparesis is limited to a single placebo controlled RCT (NORIG trial) that studied the effects of nortriptyline, a secondary tricyclic amine.[44] Using a strict primary outcome of $\geq$50% reduction in 2 consecutive GCSI score assessments compared with baseline, there was no difference between a tailored nortriptyline dose (adjusted at 3-week intervals up to 75 mg at 2 weeks) and placebo. Because of the significant overlap between gastroparesis and FD,[18] more potent tertiary tricyclic amines (amitriptyline, imipramine) may potentially provide greater benefits, particularly in diabetic gastroparesis, although prospective RCT data in gastroparesis patients are lacking. However, amitriptyline improved FD patients in the FD treatment trial without slowing gastric emptying and was more effective than the selective serotonin reuptake inhibitor escitalopram, especially when epigastric pain was a relevant symptom and when gastric emptying was normal.[45] Other RCT data also support TCA benefit in FD with epigastric pain; although gastric emptying was not specifically evaluated in these studies, it is likely that TCA benefit would be independent of gastric emptying status. Noradrenaline reuptake inhibition, as provided by TCAs and SNRIs, is considered the main mechanism for controlling visceral pain.[45]

Selective serotonin reuptake inhibitors may improve coexisting anxiety and depression in patients with refractory gastroparesis but are unlikely to directly improve visceral pain because they do not block the reuptake of the key neurotransmitters involved in the perception of visceral pain, serotonin and norepinephrine.[43] Mirtazapine, a tetracyclic antidepressant with noradrenergic and specific serotonergic activity, improved refractory nausea and vomiting in a cohort of 30 gastroparesis patients[46] and improved weight loss, dyspeptic symptoms, and especially early satiation in a controlled trial in FD.[47]

Duloxetine, an SNRI that blocks reuptake of both serotonin and norepinephrine,[43] improved diabetic polyneuropathic pain compared with placebo at daily doses of 60–120 mg over 12 weeks in RCTs, although nausea or constipation can develop or worsen.[48] A systematic review provided second-tier evidence that more patients treated with the anticonvulsant gabapentin (>1200 mg daily in divided doses) for neuropathic pain achieved at least >50% reduction in pain compared with placebo,[49] although selective outcome reporting by industry sponsored trials for off-label use has called some of this evidence into question.[50] Pregabalin is structurally related to gabapentin but modulates calcium influx by binding to a subunit of voltage gated central nervous system calcium channels rather than gamma amino butyric acid receptors and inhibits release of excitatory neurotransmitter for anti-nociceptive and anticonvulsant effects. Pooled analysis from 7 RCTs enrolling 1510 patients with neuropathic pain indicated a statistically significant reduction in mean pain scores over 5–13 weeks at 150 mg, 300 mg, and 600 mg daily in divided doses, with dizziness, somnolence, weight gain, and peripheral edema reported as side effects.[51]

Finally, opioid analgesics (eg, morphine, oxycodone, hydromorphone, etc) should not be used to manage chronic visceral abdominal pain, because they further delay gastric emptying, increase the risk of narcotic bowel syndrome, and create the potential for addiction, tolerance, and overdose.

Gastric Electrical Stimulation

The FDA approved gastric electrical stimulation (GES) (Enterra Therapy) using high frequency (12 cycles per minute), low energy stimuli for the treatment of drug refractory nausea and vomiting due to gastroparesis in 2000. Although GES use continues to stimulate debate, some consistent themes have emerged from available literature. The precise mechanism of action remains unknown, but GES does not accelerate gastric emptying; its beneficial effects may occur via modulation of the gastric pacemaker, interstitial cells of Cajal, sensory afferents, other myoneural pathways, or the release of peptides.[52–57] However, GES does improve refractory nausea and vomiting in some patients with gastroparesis and may improve glycemic control, nutritional status, and quality of life, while reducing hospitalizations and medication use.[52–57] Even though one study reported a

reduction in self-reported "severe" pain,[58] persistent abdominal pain is not an indication for GES, and opioid use is a contraindication. Refractory symptoms of shorter duration are more likely to respond than prolonged intractable symptoms.[53] Whether patients with refractory diabetic gastroparesis respond better than those with idiopathic gastroparesis remains controversial.[54,57,59] Temporary electrical stimulation may predict response to GES and should be offered if available.[60] Thus, GES could be an option for gastroparesis patients with refractory/intractable nausea and vomiting who have failed standard therapy, are not on opioids, and do not have abdominal pain as the predominant symptom (Figure 2).

Pylorus Directed Therapies

The pylorus plays a critical role in the control of gastric emptying. Abnormalities of pyloric tone and pressure (eg, "pylorospasm") and dyscoordination between antral contractions and pyloric relaxation may impair gastric emptying and contribute to symptoms in some patients.[7,61] Deep pyloric biopsies have demonstrated that pyloric stenosis and reduced numbers of interstitial cells of Cajal may contribute to pyloric dysfunction.[62] Accurately measuring pyloric basal tone, phasic pressures, and relaxation is difficult, and endoscopy, fluoroscopy, and antroduodenal manometry all have significant limitations. The functional lumen imaging probe (FLIP) uses impedance planimetry to record cross-sectional area and minimum diameter of any hollow viscus, from which estimates of sphincter distensibility and compliance can be generated.[63] Although FLIP has primarily been used to study the esophagus, limited pyloric data are available,[63,64] with some studies showing diminished pyloric distensibility in select patients with gastroparesis.[63] However, FLIP has not been validated to segregate physiological from pathologic changes in pyloric distensibility across all causes of gastroparesis; it is also expensive, invasive, and not widely available.

Intrapyloric Botulinum Toxin Injection

Although early studies of intrapyloric botulinum toxin injection improved gastroparesis symptoms in diabetic patients,[65,66] two larger placebo-controlled studies showed no benefit over placebo.[67,68] No studies have focused on gastroparesis patients with severe emptying delay, which may be the population most likely to benefit. One study suggested benefit in gastroparesis with decreased pyloric distensibility on FLIP,[69] but this requires further confirmation before recommendation as a means to select patients. At present, although generally safe, available data argue against use of botulinum toxin in refractory gastroparesis, except in clinical trials.[70]

Transpyloric Stent Placement

Transpyloric stent placement should be considered investigational in refractory gastroparesis for the lack of data from prospective, sham-controlled trials and concerns over stent migration, despite limited case reports describing symptom improvement.

Gastric per Oral Myotomy

The success of per oral endoscopic myotomy (POEM) in achalasia spurred study of a similar endoscopic technique in refractory gastroparesis, termed gastric POEM (G-POEM) or gastric per oral pyloroplasty. Two separate multicenter trials noted improvement in symptoms and reduction in gastric emptying times.[71,72] Pooled analysis including 8 other open label and retrospective studies suggest a reduction in post-procedure GCSI scores and improved gastric emptying, with 6.8% overall adverse events.[73] Although technically feasible, randomized, sham-controlled studies do not exist, and long-term follow-up data are not available. Thus, although intriguing, G-POEM should not be considered first-line therapy and should only be performed at tertiary care centers using a team approach of experts (motility specialists, advanced endoscopists) with extensive experience in treating refractory gastroparesis patients. Finally, G-POEM has the theoretical potential to induce dumping syndrome, which has a deleterious effect on food tolerance and quality of life.[74]

Other Endoscopic and Surgical Interventions

Enteral nutrition may be required when nausea, vomiting, early satiety, and weight loss persist despite adequate trials of medications and endoscopic therapies. An endoscopic/surgical transjejunal tube or a combined gastrojejunostomy tube should be placed beyond the pylorus, and case series demonstrate weight recovery with acceptable morbidity and mortality, allowing removal after an average of 20 months.[75] In the occasional patient with nutritional compromise, parenteral nutrition may improve symptoms and provide a bridge to other therapies. The role of laparoscopic pyloroplasty or sleeve gastrectomy is unclear because of the absence of large, well-designed, sham-controlled trials. Partial or total gastrectomy is rarely required, carries a risk of dumping syndrome, and should be considered only after all available therapies have been exhausted, preferably at a tertiary care center.

Summary

In patients with foregut symptoms attributed to gastroparesis, a diagnosis of refractory gastroparesis requires persistent symptoms, particularly nausea and vomiting, in the context of reliably established gastric

emptying delay. Identification of the dominant refractory symptom directs management efforts, particularly escalation of medical management. Pursuing invasive therapeutic options on the basis of a single GES without clinical context may close the door on potentially effective management options targeting FD and other mimics of gastroparesis. Our knowledge gap remains vast, and areas for future research include study of pathophysiology and etiology, as well as identification of clinical and investigation-based (eg, FLIP) predictors of response to each management approach. Studies targeting gastroparesis phenotypes that benefit most from management options discussed in this review will help refractory gastroparesis patients.

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Clinical Practice Update
This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of Clinical Gastroenterology and Hepatology.

Conflicts of interest
The authors disclose the following: BL: Scientific advisory boards – Salix, Ironwood, Allergan, Arena, Allakos. JT: Ironwood (consulting). CPG: Medtronic, Diversatek, Takeda, Ironwood, Quintiles, IsoThrive (consulting and education).

Exhibit M

Review

Rome Foundation and international neurogastroenterology and motility societies' consensus on idiopathic gastroparesis

Jolien Schol, I-Hsuan Huang, Florencia Carbone, Luis Maria Bustos Fernandez, Guillaume Gourcerol, Vincent Ho, Geoffrey Kohn, Brian E Lacy, Aurelio Lopez Colombo, Hiroto Miwa, Baha Moshiree,Linda Nguyen, Greg O'Grady, Kewin T H Siah, Vincenzo Stanghellini, Jan Tack

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To establish a consensus on the definition and management of idiopathic gastroparesis, international experts (selected by neurogastroenterology and motility societies and initiated by the Rome Foundation) devised 144 statements using the Delphi method, with at least 80% agreement required. This consensus defined idiopathic gastroparesis as the presence of symptoms associated with delayed gastric emptying in the absence of mechanical obstruction. Nausea and vomiting were identified as cardinal symptoms. Frequently co-existing symptoms are early satiation and postprandial fullness. Diagnosis requires the presence of these symptoms alongside delayed gastric emptying, measured by a 4 h scintigraphy or gastric emptying breath test of a mixed composition meal in the absence of mechanical obstruction. Therapeutic options with proven efficacy were sparse. Dietary adjustments, nutritional support (per guidelines from the European Society for Clinical Nutrition and Metabolism for substantial weight loss or intractable vomiting), and opioid cessation were recommended by a consensus opinion. Antiemetic and prokinetic agents were also considered potentially beneficial. This consensus offers a global perspective on idiopathic gastroparesis.

Introduction

Historically, gastroparesis has been defined as a condition characterised by upper gastrointestinal symptoms and notably delayed gastric emptying in the absence of any mechanical obstruction, and is considered a major cause of potentially debilitating upper gastrointestinal symptoms.[1–4] Diabetes and upper gastrointestinal surgeries are two established and prevalent causes of gastroparesis, yet many cases of gastroparesis are categorised as idiopathic.[1–5] Over the past decade, the nature and definition of gastroparesis, the relevance of gastric emptying testing, and particularly the separation of idiopathic gastroparesis from functional dyspepsia and other upper gastrointestinal disorders have been topics of intense debate.[3–8]

At present, no therapies of established efficacy are available for idiopathic gastroparesis, and only *Helicobacter pylori* eradication and proton pump inhibitors (PPIs) have shown partial efficacy for functional dyspepsia.[2–4,7] Clinicians, drug developers, regulatory bodies, and people with idiopathic gastroparesis are all in need of clarification of existing diagnostic uncertainties.

The Rome Foundation, in collaboration with international neurogastroenterology and motility societies, gathered an international group of experts (the consensus group) with the aim of reaching a consensus on the definition, clinical characteristics, diagnosis, and management of gastroparesis. At the first meeting of the consensus group, members decided to limit the focus of this consensus project to idiopathic gastroparesis, given the size of the topic.

Methods

Professor Jan Tack, President of the Rome Foundation, initiated the process to develop consensus statements on different aspects of gastroparesis and its distinction from functional dyspepsia, which is one of the key disorders of gut–brain interaction and has been defined by the Rome criteria.[8] The presidents of each of the international neurogastroenterology and motility societies (the Australasian Neurogastroenterology and Motility Association, the Asian Neurogastroenterology and Motility Association, the American Neurogastroenterology and Motility Society, the European Society for Neurogastroenterology and Motility, and Sociedad Latinoamericana de Neurogastroenterología) were contacted in 2022 to establish their willingness to participate in this process and to nominate two members to serve on the panel of experts for the Delphi method. The Rome Foundation also nominated two members and a surgeon with expertise in gastroparesis was added to the group. The organisation of the process was supported by members of the Motility and Sensitivity research group at the Leuven Translational Research Centre for Gastrointestinal Disorders (Leuven, Belgium). All members of the consensus group are listed in the appendix (p 1).

The first meeting was held in person and online at Digestive Disease Week 2022, where decisions were made to focus on idiopathic gastroparesis, to avoid pathophysiology concepts in the consensus, and to use the Delphi method. The Delphi method, which combines the principles of evidence-based medicine and is supported by systematic literature reviews and a voting process, aims to determine a consensus for complex problems in medicine when evidence from controlled trials is insufficient.[9] A core group of four members (JT, JS, FC, and I-HH) drafted and finalised an initial list of statements covering several aspects of gastroparesis, which was sent to all members of the expert group for feedback and refinement. These statements were partly based on previous consensuses and guidelines.[1,3,4]

After discussion in the subsequent meetings (one held in person and virtually with all members in Leuven in

April, 2023, and another online meeting to review outcomes in August, 2023), a total of 144 statements were drafted (appendix pp 2–22). For each of the statements, the core group did a systematic literature search using relevant keywords to generate a narrative substantiation of the statement's content. The literature review and references were made available to all members. Each statement was presented with the evidence summary available on a separate file, and each member indicated their degree of agreement for the statement using a 6-point Likert scale (appendix p 23). Participants were masked to the votes of other participants. Consensus was defined as when at least 80% of the consensus group agreed (A+ or A) with a statement. The strength of evidence for each statement was scored with the GRADE system (appendix p 24).[10]

Results

Definition and concept

In most literature, the presence of symptomatic delayed gastric emptying is mandatory for a diagnosis of gastroparesis,[1–5] which was agreed upon by the current group. Consequently, the consensus does not include asymptomatic patients in the diagnosis of gastroparesis. The consensus also agreed that mechanical obstruction, which can also lead to delayed gastric emptying, should be excluded during the diagnostic evaluation. Theoretically, altering gastroduodenal motor function can trigger upper gastrointestinal symptoms, and some symptomatic patients do not have evident motor dysfunction, partly due to visceral sensitivity. Symptoms associated with delayed gastric emptying could also be associated with other gastroduodenal function alterations (eg, functional dyspepsia), which could contribute to the inconsistent relationship between symptom pattern and severity and a delay in gastric emptying.[2–6] In patients with idiopathic gastroparesis, other mechanisms have been implicated in symptom causation, such as impaired gastric accommodation, hypersensitivity to gastric distention, and altered duodenal or small bowel motility.[11–13] However, evidence for the role of these mechanisms and options for their assessment in clinical practice are sparse.

Symptom pattern

Many symptoms have been reported for patients with idiopathic gastroparesis, including nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, loss of appetite, and weight loss.[1–6,14] Nausea is present in nearly all patients with gastroparesis and has been associated with the severity of delays in gastric emptying.[1,4,15–19] Over 40% of patients in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) gastroparesis consortium database report that nausea and vomiting are the most troubling symptoms.[16] Nausea often precedes vomiting, which often relieves nausea.[17] When symptoms were evaluated during a gastric emptying test that covered the period of time between gastric emptying and symptom occurrence, the only symptom that achieved significantly higher ratings in people with delayed gastric emptying was nausea.[19] Nausea and vomiting were also included and validated in the Gastroparesis Cardinal Symptom Index.[20]

The European consensus on gastroparesis and American College of Gastroenterology clinical guidelines consider nausea and vomiting to be cardinal symptoms of gastroparesis.[3,4] In line with these concepts, the current international consensus group also identified nausea and vomiting as cardinal symptoms and requires the presence of nausea or vomiting for a diagnosis of idiopathic gastroparesis. Consequently, the symptom pattern of idiopathic gastroparesis is distinct from functional dyspepsia, which has early satiation, postprandial fullness, and epigastric pain or burning as cardinal symptoms.[7,8]

Based on the absence of correlation between symptoms and gastric emptying in a large, prospectively followed cohort study from the National Institutes of Health and NIDDK gastroparesis consortium, functional dyspepsia and gastroparesis were proposed to be indistinguishable conditions on the same spectrum.[6] The current international consensus group neither agreed nor disagreed with this statement, as symptoms of idiopathic gastroparesis overlap with those of functional dyspepsia, especially with postprandial distress syndrome. Both early satiety and postprandial fullness are common, severe symptoms in both diabetic and idiopathic gastroparesis.[14,21,22] A US study of 243 patients with idiopathic gastroparesis showed that 86% of patients fulfilled the Rome III criteria for functional dyspepsia, especially postprandial distress syndrome, which was present in 91% these of patients, compared with epigastric pain syndrome in 1·2% of patients.[23] Postprandial fullness and early satiation are also included and validated in the Gastroparesis Cardinal Symptom Index.[20]

Bloating is present in many disorders of gut–brain interaction and has been reported in up to 41% of patients with gastroparesis.[24] In the current consensus, there is a tendency to confirm that upper abdominal bloating, presumably originating from the stomach, also frequently occurs in idiopathic gastroparesis, but data are scarce on this specific statement and there are no data to distinguish bloating arising from the stomach versus the bowel. In addition, numerous studies reported epigastric pain in a large subset of patients with gastroparesis, but pain is less prevalent when patients who are receiving opioids are excluded.[16] Bloating and pain are not associated with the extent of delay in gastric emptying.[19]

In 2010, an American Neurogastroenterology and Motility Society task force distinguished three levels of severity of gastroparesis based on symptoms and impact.[1] In the development of the Gastroparesis Cardinal Symptom Index scoring system, clinician ratings of symptom severity were used in the validation process.[20]

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See **Online** for appendix

Outcomes of gastric emptying studies have also been used to score the severity of gastric retention in gastroparesis, but this measure is poorly linked to symptom severity and impact.[5,11,23] The current expert group does not consider the degree of gastric emptying delay to be an indicator of severity, but rather attributes gastroparesis severity to the severity of the reported symptoms.

Impact

Considerable health-care costs are associated with idiopathic gastroparesis, but most data are from the USA.[25–28] Although data from large prospective studies are needed, people with gastroparesis could incur both direct and indirect costs for over-the-counter medications, alternative therapies, dietary adjustments, medical consultations that are only partly covered, or co-financed treatments. Many people with gastroparesis report reduced working hours, are unemployed, or self-identify as disabled.[29–31]

In a systematic review, the quality of life of people with gastroparesis was significantly lower than population norms, with a negative relationship between quality of life and symptom severity.[32] Only a few studies have rigorously measured depression and anxiety in gastroparesis. A systematic review found three studies evaluating the presence of psychopathology in patients with gastroparesis, revealing anxiety and depression in up to 23% of participants, and somatisation in 50%.[32]

Although gastroparesis is often thought to lead to weight loss, this assumption is not substantiated by available cohorts, and in the National Institutes of Health and NIDDK consortium cohort, a large subset were patients with overweight or obesity.[6,16,17,23,33,34] Therefore, in the context of unintentional weight loss and because anorexia nervosa can be associated with delayed gastric emptying, an eating disorder should be ruled out in patients presenting with gastroparesis and weight loss.[35,36] In vomiting-predominant gastroparesis, other syndromes associated with vomiting should be ruled out, including cyclic vomiting syndrome, cannabinoid hyperemesis syndrome, and rumination. In contrast to gastroparesis, rumination typically does not present with nausea.[8,35,37]

Symptom severity would seem an obvious influence on health-care consulting behaviour in people with gastroparesis, but formal data are not available. Anxiety and depression scores are related to gastroparesis symptom severity and hospitalisation rates. Socio-economic differences also contribute to observed regional differences in management approaches and outcomes, such as hospital admissions, invasive procedures, and mortality in people with gastroparesis.[16,23,37–39]

Diagnosis

Most guidelines dictate that an upper endoscopy should be done before motility testing is considered in patients with upper gastrointestinal symptoms who have not responded to first-line therapy.[1,3,7,8] By definition, gastroparesis implies an objective delay in gastric emptying in the absence of mechanical obstruction, and requires both an assessment of gastric emptying and confirmation of the absence of gastric outlet obstruction or another mechanical factor, most commonly through an upper endoscopy.[2] Although the absence of a pyloric or small bowel obstructing factor is part of the diagnostic criteria for gastroparesis, none of the international or national guidelines recommend routine use of small bowel imaging.[1–4] Although median arcuate ligament syndrome can be a cause of nausea and vomiting, especially in women, routine use of a mesenteric duplex study is also not included in international or national guidelines.[1,3,4,40]

Some metabolic abnormalities (eg, diabetes, thyroid disease, kidney failure, and electrolyte abnormalities)[1,4,7,8,40] can mimic symptoms of gastroparesis or could be associated with delayed gastric emptying. A panel of laboratory tests, such as a glycaemia blood test, an serum electrolyte test, and kidney function testing might be helpful to rule out underlying disorders or to document consequences of vomiting.[35,37] This international consensus group supported a full blood count and glycaemia assessment, and showed support for kidney function and ionogram testing. There is no established role for *H pylori* in the pathogenesis of idiopathic gastroparesis,[1,3,4,7] underpinning the opinion of the international consensus group to not support routine testing for the presence of it in patients with suspected idiopathic gastroparesis, despite the contrasting recommendation for routine testing in patients with uninvestigated dyspepsia.[7,41,42]

As symptoms of gastroparesis lack specificity, a demonstration of delayed gastric emptying is necessary for diagnosis. Clinically, food retention in the stomach on endoscopy after an overnight fast has been used as a probable sign of gastroparesis. However, the one study correlating this retention with gastric emptying testing showed it lacks accuracy.[43] There are no data to support endoscopically observed hypocontractility as a marker of delayed gastric emptying.

To date, gastric emptying scintigraphy of a solid-phase meal is considered the gold standard for gastroparesis diagnosis.[3,4,44] An alternative is the gastric emptying breath test (GEBT), which incorporates a stable isotope (^{13}C) in a substrate in the meal, and uses the appearance of $^{13}CO_2$ in the breath to evaluate gastric emptying. Although GEBT has been widely used in clinical practice in Europe for many years,[45] it has only recently gained popularity in the USA after the 2015 approval of the ^{13}C-spirulina platensis breath test by the US Food and Drug Administration (FDA).[46] A systematic literature review found acceptable reproducibility of scintigraphy and GEBT measurements, and good correlation between both methods.[47]

The wireless motility capsule is an FDA-approved device for the evaluation of gastric emptying. As an indigestible solid, the wireless motility capsule leaves the

stomach—not with the test meal—but rather with the phase III activity front of the migrating motor complex. This occurence could explain some of the discrepancies with other types of emptying tests,[48,49] which is the likely basis for the international consensus group not supporting the diagnostic use of the wireless motility capsule. Gastric ultrasonography has been used to assess antral wall motion, patterns of transpyloric flow, and gastric emptying based on changes in the cross-sectional area or diameter of the gastric antrum. However, it is unsuitable to assess the emptying of solids, requires an experienced technician, is user dependent, could be influenced by the presence of intragastric air or posture, and is generally considered impractical for long-term observations.[50]

Existing guidelines and consensus statements on gastroparesis advocate for the use of solid meal gastric emptying tests, as these appear to provide the best assessment of gastric motor function.[1,3,4] In addition, American consensus on a scintigraphy test meal also uses a solid meal (Egg beaters [composed of pasteurised egg whites without fat of yolks]; ConAgra Foods, Omaha, NE, USA).[44] Meals with mixed composition (eg, carbohydrate, protein, and lipid) have been used in many studies.[12,19,33,45,51] The meal used should contain sufficient calories to interrupt interdigestive motility and induce a fed state pattern of motility. The calorific content of gastric emptying test meals in relevant literature ranges from 106 kcal and 420 kcal, and 150 kcal is sufficient to induce fed-state motility.[52] Although the American Neurogastroenterology and Motility Society and Society of Nuclear Medicine guidelines advocate for a low-calorie and low-fat meal (Eggbeaters),[44] such a meal has been argued to decrease the ability to distinguish functional dyspepsia from gastroparesis, as the lipid-induced release of cholecystokinin could be a pathophysiological factor in gastroparesis.[5]

Systematic reviews have shown a better correlation with symptoms and with symptom improvement of gastroprokinetics in gastroparesis when a gastric emptying test for at least 3 h is used.[14,53] Consensus statements and guidelines advocate a gastric emptying test of 4 h unless the entire meal ingested exits the stomach before 4 h.[40,44,54] When establishing cutoffs for standard gastric emptying, most studies have used the 95th percentile or two standard deviations from the mean in asymptomatic controls.[44,45] These cutoffs have been applied for the half gastric emptying time or, especially in scintigraphy studies, for the percentage retention of the meal at a given timepoint (2 h or 4 h). However, in some studies the 75th percentile has also been reported, which has also sometimes been used in trials or clinical practice.[45,55] The international consensus group supports a solid meal with mixed composition in a 4 h gastric emptying test. The international consensus group acknowledges the absence of and need for an international standardised and applicable gastric emptying test meal. Furthermore, one survey revealed poor adherence to recommendations for patients with gastroparesis to discontinue medications that could interfere with gastric transit before gastric emptying measurements.[56] The international consensus group acknowledges the importance of not taking medications (panel) to ensure an accurate diagnosis of gastroparesis.

Several studies have shown that delayed gastric emptying can be unstable over time.[5,57,58] On this basis, it was suggested that only patients with at least two atypical gastric emptying tests be recruited for studies on gastroparesis,[4] which has not yet happened. Most studies, including those with prokinetic drug interventions, kept the label of gastroparesis for patients who had an improvement in gastric emptying. Uniquely, in a follow-up study of the National Institutes of Health and NIDDK consortium cohort, patients whose gastric emptying rate had normalised over time were referred to as having functional dyspepsia.[5] The international consensus group did not reach agreement on the statement that patients whose gastric emptying rate normalises over time should receive a different diagnosis, but also the opposite statement did not receive a consensus vote.

Although electrogastrography and antroduodenal manometry were explored as potential tools for

Panel: **Medications by class with potential impact on gastric motility**

Prokinetic agents
- Domperidone
- Itopride
- Mosapride
- Metoclopramide
- Prucalopride

Opiate analgesic medications
- Oxycodone
- Hydrocodone
- Morphine
- Methadone

Anticholinergic or antispasmodic agents
- Atropine
- *Atropa belladonna*
- Dicycloverine
- Hyoscyamine
- Loperamide
- Promethazine

Antidiabetic medication
- GLP-1 agonists
  - Dulaglutide
  - Exenatide
  - Semaglutide
  - Liraglutide
  - Lixisenatide

investigating patients with symptoms that are suggestive of gastroparesis, the international consensus group determined that these tools are of limited use in the gastroparesis diagnostic pathway. As a result, these tests were not included in the current consensus. However, emerging modalities, such as body surface gastric mapping, might influence future diagnostic approaches.

Treatment

General

Idiopathic gastroparesis carries an increased risk of a calorie-deficient diet.[59] Nutritional consultation increases the likelihood that oral intake will meet total energy needs. Moreover, a small particle size diet reduces gastroparesis symptoms and reflux symptoms in patients with diabetic gastroparesis.[60] The international consensus group supports dietary intervention in the management of idiopathic gastroparesis.

Despite the high use of PPIs in patients with gastroparesis (≥70%), no data are available on the degree of efficacy of PPIs for gastroparesis symptoms. With up to 50% of patients having an overlapping gastro-oesophageal reflux disease (GERD) diagnosis, PPI use seems likely to target coexisting GERD symptoms.[61]

By inhibiting gastrointestinal motility, opioid use is associated with slower gastric emptying and could mimic gastroparesis.[62] Patients with gastroparesis who are taking opioids have a lower quality of life and face increased hospitalisation and the increased use of antiemetic and pain modulator medications.[63] Available guidelines therefore recommend opioid cessation in patients with gastroparesis, which was also supported by the international consensus group.[1–4,63] Concerns about delayed gastric emptying in patients with gastroparesis who take GLP-1 receptor agonists have emerged over the past few years.[64–66] However, data are insufficient on the benefits of discontinuing GLP-1 agonists in idiopathic gastroparesis, warranting further studies.

Antiemetics and prokinetics

As nausea and vomiting are cardinal symptoms of gastroparesis, a focus on antiemetic agents seems logical. However, formal evidence that antiemetic agents are effective in the treatment of nausea and vomiting associated with gastroparesis is sparse, although this strategy has been recommended as first-line symptomatic treatment.[35,67]

A broad range of antiemetics are available. Metoclopramide, a dopamine-2 receptor antagonist, is approved for the treatment of gastroparesis. However, it carries a black-box warning in the USA, due to possible extrapyramidal side-effects and potentially irreversible tardive dyskinesia, which has been reported in a small percentage of cases.[68] Domperidone is a peripherally acting dopamine-2 antagonist that decreases nausea, corrects gastric dysrhythmias, and increases gastric emptying. It does not readily cross the blood–brain barrier and is therefore less likely to cause extrapyramidal side-effects than metoclopramide. Formal studies with domperidone in idiopathic gastroparesis are sparse, but the drug has been evaluated for the treatment of diabetic gastroparesis.[69] However, domperidone is associated with prolongation of the cardiac QTc interval, for which the European Medicines Agency restricted its use.[70] In the USA, domperidone can only be obtained with an FDA Investigational New Drug application. More recently, a trial of trazpiroben (TAK-906; Takeda Oncology, Cambridge, MA, USA), a mixed D2/D3 receptor antagonist, did not show convincing efficacy over placebo in a phase 2b study.[71] In a network meta-analysis, dopamine-2 receptor antagonists as a class were superior to placebo in providing overall symptom relief in gastroparesis.[72] This outcome was also the case for the dopamine-2 receptor antagonist drugs domperidone and clebopride; clebopride is also a 5-HT_4 agonist.[72] Additionally, itopride, a drug with affinity for the dopamine D2 receptor used for functional dyspepsia in Asia, lacks data for its efficacy in the treatment of gastroparesis.[73]

Ondansetron and granisetron are 5-HT_3 receptor antagonists that are often prescribed for controlling nausea and vomiting. Although used as rescue therapy in some gastroparesis pharmacological trials,[71] there is little evidence to show the efficacy of 5-HT_3 antagonists in treating gastroparesis symptoms. In an open-label study, granisetron provided symptomatic benefits for nausea and vomiting in patients with gastroparesis.[74] However, in a network meta-analysis, 5-HT_3 receptor antagonists as a class were not superior to placebo in providing overall symptom relief in gastroparesis.[72]

Aprepitant, a neurokinin antagonist approved for the treatment of chemotherapy-induced emesis, was efficacious in the treatment of nausea in some patients with gastroparesis and related disorders.[75] In a dose-finding study, tradipitant (VLY-686; Vanda Pharmaceuticals, Washington, DC, USA), which is another selective NK-1 receptor antagonist, significantly improved nausea and vomiting in patients with gastroparesis.[76] In a network meta-analysis, neurokinin receptor-1 antagonists as a class were superior to placebo in providing overall symptom relief in gastroparesis.[72] However, in September 2024, the US Food and Drug Administration declined to approve the new drug application of tradipitant for the treatment of symptoms of gastroparesis.[77]

The international consensus group showed a tendency to support antiemetic therapy as first-line therapy and dopamine-2 antagonists as effective therapies, but did not reach the 80% consensus threshold.

Historically, prokinetic agents have been the primary focus of new drug development for gastroparesis. Prokinetics are defined as drugs that promote gastrointestinal motility, and therefore enhance gastric emptying. However, prokinetic agents are a heterogeneous group of agents, with different properties and pharmacological

modes of actions. To date, dopamine-2 antagonists, 5-HT_4 agonists, motilin receptor agonists, and ghrelin receptor agonists have all been studied.

Meta-regression analyses of the association between the improvement of gastric emptying and symptoms did not detect a significant relationship.[53,78] When the analysis was restricted to studies that used high-quality gastric emptying tests and a selection of agents, a significant correlation emerged.[53] These findings were confirmed in an updated analysis.[79] However, no single study reported a correlation between symptom improvement and gastric emptying. The closest temporal correlation between gastric emptying rate and symptoms occurs when symptoms are measured during the gastric emptying test.[19] Even when evaluating a series of controlled trials with assessment of symptoms during the gastric emptying test, no correlation was found between the degree of symptom improvement and the improvement of gastric emptying measured by GEBT.[80] Furthermore, the reported low compliance with gastric emptying protocol guidelines raises concerns about the potential for misdiagnosis, emphasising the need to verify test precision and consider a repeat test for accuracy.[56]

Cisapride was a previously preferred medication for the outpatient treatment of gastroparesis, but was withdrawn from many markets due to QT prolongation and risk of cardiac arrhythmias.[81] Tegaserod, a 5-HT_4 agonist, showed promising prokinetic effects in healthy volunteers but has also been associated with cardiovascular risks.[81] Other identified 5-HT_4 receptor agonists are naronapride (Dr Falk Pharma, Freiburg, Germany), velusetrag (Alfasigma, Bologna, Italy), renzapride, and prucalopride.[81] Prucalopride, a 5-HT_4 receptor agonist without a risk of QT prolongation, is approved in many countries for the treatment of chronic constipation. This drug also accelerates gastric emptying and was shown to relieve symptoms in a small crossover study of predominantly patients with idiopathic gastroparesis.[82] In a network meta-analysis, 5-HT_4 receptor agonists as a class were not superior to placebo in providing overall symptom relief in patients with gastroparesis.[72]

Several motilin receptor agonists have been studied as potential treatment for gastroparesis in the past 20 years, including camicinal (GSK962040; GlaxoSmithKline Pharmaceuticals, London, UK), raqualia (RQ-00201864; Raqualia Pharma, Nagoya, Japan), and mitemcinal (GM-611; Chugai Pharmaceuticals, Tokyo, Japan). Antibiotics with motilin receptor agonistic properties, such as azithromycin, erythromycin, and clarithromycin are clinically available and have been explored for use in gastroparesis.[83–85] However, the use of macrolide antibiotics to increase gastric motility includes risks and side-effects, such as drug resistance or tachyphylaxis, and QT prolongation. Although motilin receptor agonists exert the strongest stimulatory effect on gastric emptying rate, as a class they were not superior to placebo in providing overall symptom relief.[72]

The international consensus group showed a tendency to support prokinetic therapy as first-line therapy and as effective therapies, but did not reach the 80% consensus threshold.

Neuromodulators

Among visceral neuromodulators, only amitriptyline and nortriptyline have been studied in idiopathic gastroparesis. A controlled trial with nortriptyline in idiopathic gastroparesis did not show symptomatic benefit.[86] The neuromodulator amitriptyline was evaluated in an 8 week, multicentre, randomised, double-blind controlled study, which compared amitriptyline 50 mg, escitalopram 10 mg, and a placebo in patients with functional dyspepsia.[87] Overall, only amitriptyline provided symptom relief, which was to the subgroup of patients with ulcer-like functional dyspepsia. A gastric emptying test before randomisation allowed for evaluation of the subgroup with delayed emptying (ie, idiopathic gastroparesis), and no beneficial effect was observed with amitriptyline or escitalopram.[87] One randomised trial showed the efficacy of buspirone (10 mg three times a day) in patients with severe bloating.[88] However, there is are no studies with selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors in idiopathic gastroparesis.

A randomised, double-blind, placebo-controlled study found improvements in early satiety, nausea, quality of life, gastrointestinal-specific anxiety, nutrient tolerance, and weight loss with mirtazapine 15 mg once daily in functional dyspepsia with associated weight loss.[89] A prospective, uncontrolled study of mirtazapine 15 mg in gastroparesis showed an improvement in symptoms of nausea and vomiting and perceived loss of appetite compared with baseline.[90]

The international consensus group did not support the efficacy of any of the neuromodulators, but also did not support their lack of efficacy, indicating the need for additional research.

Although many reviews propose to reserve invasive therapies for patients with refractory gastroparesis, there are only a few definitions of medically refractory gastroparesis in relevant literature. In an American Gastroenterological Association clinical practice update, medically refractory gastroparesis was defined as a persistence of symptoms despite the use of dietary adjustment and metoclopramide as first-line therapies, reflecting the lack of other therapeutic options in the USA.[44] For a sham-controlled gastric peroral endoscopic pyloromyotomy (G-POEM) study, patients with gastroparesis were eligible if they had received at least one prokinetic drug that had not been successful.[91] A 2020 editorial proposed to reserve invasive therapy for patients with gastroparesis who had been exposed to a large range of antiemetic and prokinetic agents, including dopamine-2 antagonists, 5-HT_3 antagonists,

H1 antagonists, mirtazapine, 5-HT_4 agonists and aprepitant.[92]

The international consensus group considers patients to have idiopathic, medically refractory gastroparesis if they do not respond to antiemetic and prokinetic drugs, and have severe nutritional restriction or ongoing weight loss.

Gastric electrical stimulation

Several invasive therapies for gastroparesis have been developed, which can be considered in patients with refractory gastroparesis. Uncontrolled, long-term, cohort studies and two meta-analyses reported on the efficacy of gastric electrical stimulation in patients with gastroparesis to decrease gastroparesis symptomatic scores and to improve quality of life.[93–97] Subsequent randomised controlled trials did not confirm these findings.[98–100] However, one sham-controlled, multicentre study in France reported improvement in vomiting frequency, regardless of gastric emptying status.[101]

Pylorus-directed therapy

Numerous open-label studies reported short-term (<6 months) efficacy of intrapyloric botulinum toxin injection both on symptoms and gastric emptying in patients with gastroparesis.[102–106] However, two subsequent sham-controlled trials did not show an improvement in either symptoms or gastric emptying.[107,108] Patients with gastroparesis who have a higher likelihood or established hypercontractility of the pylorus have been proposed for selection in further studies. A sham-controlled, crossover study of botulinum toxin injection in patients with diabetic or post-surgical (fundoplication) gastroparesis did not show a benefit over placebo. The European Society for Gastrointestinal Endoscopy 2020 consensus recommends against the use of botulinum toxin injection in the treatment of patients with idiopathic gastroparesis in whom hypercontractibility of the pylorus has not been established.[109] A study of 35 patients with gastroparesis reported that decreased distensibility of the pylorus (measured with Endoflip [Medtronic, Minneapolis, MN, USA]) was a predictor of outcome for the botulinum toxin injection,[110] but studies selecting patients on pyloric distensibility criteria have not been reported to date.

Several open-label studies reported short-term and mid-term (<18 months) efficacy of endoscopic pyloric myotomy on symptoms, quality of life, and gastric emptying in patients with gastroparesis.[111] However, these open-label observations warrant further corroboration from randomised controlled trials. A sham-controlled G-POEM trial that enrolled 41 patients with gastroparesis (the largest subgroup had diabetes) showed that G-POEM was superior to the sham treatment and improved gastric emptying at 3 months and symptoms at 6 months.[91] As only 11 patients had idiopathic gastroparesis, the efficacy in this group needs to be studied in a larger cohort. In a preliminary report on 23 patients undergoing G-POEM treatment, pyloric distensibility and its change with treatment did not predict symptom benefit.[112] Only one study involving 28 patients reported symptomatic benefit of surgical pyloroplasty at 3 months.[113] One retrospective report observed that surgical pyloroplasty was associated with more complications (ie, surgical site or systemic infections, intensive care admissions) than endoscopic pyloric myotomy.[114] The G-POEM procedure in the sham-controlled trial was associated with increased distensibility of the pylorus.[91] However, to be able to select patients for pylorus-directed procedures, normal ranges of pyloric distensibility (measured by Endoflip) need to be established and prediction of efficacy needs confirmation.

Other management approaches

Only two studies evaluated near total gastrectomy with Roux-en-Y reconstruction and five studies investigated total or completion gastrectomy in patients with gastroparesis.[115–122] Symptomatic improvement was reported in 70–90% of patients but morbidity ranged from 17% to 40%, and all studies had a low number of patients included. In theory, pylorus-directed therapies could be at risk of inducing dumping syndrome, but there are only anecdotal reports in relevant literature.[91,122] A venting gastrostomy is intended to improve symptoms associated with gastric stasis and retention by allowing the escape of air and fluid through the venting tube.[123] However, there are no data from randomised controlled trials supporting this approach.

The international consensus group did not support the efficacy of any of these invasive therapies, even when reserved for patients with refractory gastroparesis. However, the group also did not support the statements of their lack of efficacy, indicating the need for additional research.

Studies on the prevalence of *H pylori* and gastroparesis are conflicting and little data are available on the effect of *H pylori* eradication in patients with gastroparesis.[1,2–4] The international consensus group recommends the eradication of *H pylori* when present, as it has been implicated in peptic ulcer and gastric cancer pathogenesis, but does not consider this effective for symptom improvement.

Several herbal therapies have been used for the treatment of functional dyspepsia, including peppermint oil (with or without carraway oil), ginger, Iberogast (Bayer AG, Leverkusen, Germany), Rikkunshito, and artichoke extract, but data from patients with gastroparesis are sparse.[124] Relevant literature also does not have specific reports on the effectiveness of hypnotherapy, cognitive behavioural therapy, or mindfulness-based therapy for patients with gastroparesis. Many case series suggest the benefit of acupuncture in patients with gastroparesis. A Cochrane systematic review found overall higher symptom improvement rates in patients with gastroparesis who received acupuncture compared

with those who received conventional medical therapy, but due to the heterogeneity and low quality of studies and the risk of bias, the conclusion is considered uncertain.[125] The international consensus group did not support the efficacy of any of the alternative or behavioural therapies.

According to practice guidelines from the European Society for Clinical Nutrition and Metabolism, nutritional supportive therapy should start with small, low-lactose, low-fibre, and low-fat meals six times per day, and with consideration of vitamin supplementation.[126] The next preferred step is home enteral nutrition if possible, but if

	Overall agreement	Likert scale scores*	Grade†
Idiopathic gastroparesis refers to a symptom or set of symptoms that are associated with delayed gastric emptying in the absence of mechanical obstruction	11/13 (85%)	A+ 9; A 2; A– 2; D– 0; D 0; D+ 0	A
Nausea and vomiting are cardinal symptoms in idiopathic gastroparesis	13/13 (100%)	A+ 10; A 4; A– 0; D– 0; D 0; D+ 0	B
Postprandial fullness is often present in patients with idiopathic gastroparesis	13/13 (100%)	A+ 9; A 4; A– 0; D– 0; D 0; D+ 0	B
Early satiation is often present in patients with idiopathic gastroparesis	12/13 (92%)	A+ 7; A 5; A– 1; D– 0; D 0; D+ 0	B
Symptoms in patients with idiopathic gastroparesis overlap mainly with postprandial distress syndrome and less with epigastric pain syndrome symptoms of functional dyspepsia	11/13 (85%)	A+ 4; A 8; A– 2; D– 0; D 0; D+ 0	A
Nausea or vomiting should be present for a diagnosis of idiopathic gastroparesis	11/13 (85%)	A+ 8; A 4; A– 1; D– 1; D 0; D+ 0	B
Idiopathic gastroparesis is a major source of health-care costs	12/13 (92%)	A+ 8; A 4; A– 0; D– 1; D 0; D+ 0	A
Idiopathic gastroparesis is a major source of self-costs to patients (health expenses made by patients and not covered by health insurance)	12/13 (92%)	A+ 8; A 4; A– 1; D– 0; D 0; D+ 0	B
Idiopathic gastroparesis is a major source of loss of work productivity	12/13 (92%)	A+ 8; A 4; A– 1; D– 0; D 0; D+ 0	B
Idiopathic gastroparesis is associated with a significant decrease in quality of life	13/13 (100%)	A+ 100%; A 0; A– 0; D– 0; D 0; D+ 0	A
In case of weight loss, eating disorders should be ruled out in patients with idiopathic gastroparesis	12/13 (92%)	A+ 8; A 4; A– 1; D– 0; D 0; D+ 0	B
In medically refractory cases of vomiting, other syndromes such as bulimia, rumination, neurological, or metabolic causes of vomiting should be considered	13/13 (100%)	A+ 11; A 2; A– 0; D– 0; D 0; D+ 0	B
Healthcare-consulting behaviour in idiopathic gastroparesis is driven by symptom severity and impact	11/13 (85%)	A+ 6; A 5; A– 1; D– 1; D 0; D+ 0	B
Limited laboratory tests are mandatory for establishing a diagnosis of idiopathic gastroparesis, which include a full blood count	11/13 (85%)	A+ 11; A 0; A– 0; D– 1; D 1; D+ 0	D
Limited laboratory tests are mandatory for establishing a diagnosis of idiopathic gastroparesis, which include glycaemia	12/13 (92%)	A+ 8; A 4; A– 0; D– 0; D 0; D+ 1	D
An upper gastrointestinal endoscopy is mandatory for establishing a diagnosis of idiopathic gastroparesis	13/13 (100%)	A+ 11; A 2; A– 0; D– 0; D 0; D+ 0	A
An abnormal gastric emptying test is mandatory for establishing a diagnosis of idiopathic gastroparesis	12/13 (92%)	A+ 10; A 2; A– 1; D– 0; D 0; D+ 0	A
Scintigraphic gastric emptying assessment is a valid test for diagnosing idiopathic gastroparesis	11/13 (85%)	A+ 10; A 1; A– 2; D– 0; D 0; D+ 0	A
^{13}C-octanoic acid breath test assessment is a valid test for diagnosing idiopathic gastroparesis	11/13 (85%)	A+ 4; A 8; A– 2; D– 0; D 0; D+ 0	A
^{13}C-spirulina breath test assessment is a valid test for diagnosing idiopathic gastroparesis	13/13 (100%)	A+ 1; A 12; A– 0; D– 0; D 0; D+ 0	A
A solid gastric emptying test is a valid test for diagnosing idiopathic gastroparesis	11/13 (85%)	A+ 8; A 4; A– 1; D– 1; D 0; D+ 0	A
An optimal gastric emptying test should measure for 4 h	13/13 (100%)	A+ 10; A 4; A– 0; D– 0; D 0; D+ 0	D
An optimal gastric emptying test should use a mixed composition meal (ie, proteins, carbohydrates, lipids)	12/13 (92%)	A+ 9; A 4; A– 1; D– 0; D 0; D+ 0	B
There is a need for a standardised gastric emptying test meal that can be used universally	12/13 (92%)	A+ 10; A 2; A– 0; D– 1; D 0; D+ 0	A
There is a need for a standardised gastric emptying test meal with well established diagnostic cutoffs	12/13 (92%)	A+ 10; A 2; A– 1; D– 0; D 0; D+ 0	A
Ceasing medications that could interfere with gastric transit before gastric emptying investigations is required to ensure an accurate diagnosis of gastroparesis	13/13 (100%)	A+ 5; A 8; A– 1; D– 0; D 0; D+ 0	A
Dietary adjustments are recommended for managing patients with idiopathic gastroparesis	13/13 (100%)	A+ 10; A 4; A– 0; D– 0; D 0; D+ 0	B
In patients with presumed idiopathic gastroparesis taking opioids, cessation of opioid therapy is indicated	12/13 (92%)	A+ 10; A 2; A– 1; D– 0; D 0; D+ 0	A
Idiopathic gastroparesis can be considered medically refractory in case of no response to antiemetic and prokinetic drugs, and severe nutritional restriction or ongoing weight loss	13/13 (100%)	A+ 10; A 4; A– 0; D– 0; D 0; D+ 0	C

(Table continues on next page)

	Overall agreement	Likert scale scores*	Grade†
(Continued from previous page)			
Eradication of *Helicobacter pylori* should be offered to all patients with idiopathic gastroparesis who are positive for *H pylori*	11/13 (85%)	A+ 9; A 2; A– 1; D– 0; D 0; D+ 1	B
In case of clinically significant weight loss or intractable vomiting, nutritional support should be recommended	13/13 (100%)	A+ 100%; A 0; A– 0; D– 0; D 0; D+ 0	B
Nutritional support (as per standard ESPEN guidelines on chronic intestinal failure) in idiopathic gastroparesis should preferentially use an oral or enteral, rather than a parenteral, route of administration	12/13 (92%)	A+ 10; A 2; A– 0; D– 0; D 0; D+ 1	B
Symptoms of idiopathic gastroparesis are persistent over years in most patients with idiopathic gastroparesis	12/13 (92%)	A+ 42%; A 50%; A– 1; D– 0; D 0; D+ 0	B

ESPEN=European Society for Clinical Nutrition and Metabolism. *For definitions see appendix p 23. †For definition see appendix p 24.

Table: **Statements endorsed by the international consensus on gastroparesis**

it is not sufficient, home parenteral nutrition can be considered.[127]

Nutritional support in the form of enteral or parenteral nutrition is featured in several algorithms for patients with refractory gastroparesis who have clinically relevant weight loss or nutritional deficiencies.[4,35,128] While short-term parenteral nutrition offers the ability to provide rapid weight or nutritional recovery, long-term parenteral nutrition should be avoided because of the associated risks of thrombosis, sepsis, and hepatotoxicity.[128] Enteral tube feeding is the preferred option for long-term nutritional support in patients with gastroparesis. According to a report of a retrospective series of patients with diabetic gastroparesis who received enteral feeding, the morbidity and mortality rates were low (less than 5% procedure-related mortality) and the feeding tube could be removed after 20 months on average.[129] Similar findings in 20 patients with idiopathic gastroparesis were reported in an abstract by the Leuven group.[130] The international consensus group agreed on the need for nutritional support in cases of severe weight loss or refractory vomiting, preferably through the oral or enteral route.

Prognosis

The natural history and outcome of patients with idiopathic gastroparesis is not well known. In a follow-up study of the National Institutes of Health and NIDDK gastroparesis consortium cohort, the majority of patients with gastroparesis did not improve across an average of 4 years of follow-up.[39] Data from a tertiary setting that covered 6 years of follow-up observed that 7% of patients with gastroparesis from the original cohort had died and 22% of patients from the original cohort needed long-term parenteral or enteral feeding, suggesting that gastroparesis is not a benign condition.[15] Based on follow-up of inpatients who underwent a gastric emptying test, delayed gastric emptying was an independent predictor of mortality.[51] Community studies of the outcomes of gastroparesis are rare, and studies done in tertiary referral centres might not reflect findings encountered in the general population. In a population-based study using the UK Clinical Practice Research Datalink database, mortality was significantly higher in people with diabetic gastroparesis than in patients with idiopathic gastroparesis.[131]

The international consensus group agreed that most patients with gastroparesis remain symptomatic for several years.

Discussion

Idiopathic gastroparesis is a challenging and controversial condition that is regularly encountered in gastroenterological practice. The outcome of this international consensus provides guidance for clinicians in diagnosing and managing patients with idiopathic gastroparesis, allowing for optimised outcomes. The statements for which a consensus was reached led to recommendations for understanding and managing gastroparesis (table, figure). The statements that did not reach consensus identify areas requiring further research.

In line with the majority of current definitions and guidelines, the consensus defines gastroparesis as the presence of upper gastrointestinal symptoms and delayed gastric emptying in the absence of mechanical obstruction.[1–5] Nausea and vomiting are established as the cardinal symptoms of gastroparesis. Despite agreement on the coexistence of postprandial distress syndrome symptoms, the focus on predominant nausea and vomiting proposes a shift toward differentiating (idiopathic) gastroparesis from postprandial distress syndrome, which has predominant symptoms of early satiation or postprandial fullness.[6,7]

The panel acknowledges the major impact on quality of life and the considerable health economic cost and individual cost of gastroparesis. The statement that gastroparesis could lead to unintended weight loss did not reach a consensus, but eating disorders need to be excluded in cases with declining bodyweight.

When making a diagnosis of gastroparesis, a selected panel of laboratory tests, an abnormal gastric emptying test, and a normal upper endoscopy are mandatory. Observations made from an endoscopy of the presence

of food after an overnight fast or an impression of low contractility are not regarded as reliable diagnostic markers. Radiological evaluation of the small bowel or large abdominal vasculature can be considered to eliminate persisting uncertainty regarding a mechanical obstructive factor or to rule out median arcuate ligament syndrome but are not required for all patients with gastroparesis.

The international consensus group agreed that scintigraphy and GEBT are reliable diagnostic tests, but no support exists for the wireless motility capsule or gastric ultrasound to detect delayed gastric emptying. There is a consensus that tests of 4 h are required for a reliable diagnosis, and that the meal should be a solid test meal with a mixed macronutrient composition, including lipids. This consensus statement has the major implication that the Eggbeater meal, which is a standard in North America, is not endorsed by the current international consensus group. The consensus identifies and supports the need for an internationally accepted and validated test meal for gastric emptying studies.

The section on the treatment of idiopathic gastroparesis displays the major lack of therapies of established efficacy. Of note, in gastroparesis trials, a high placebo response could overshadow a potentially positive therapeutic response to a drug.[132] Despite limited scientific evidence, the international consensus group supported dietary intervention as a key first step in the management of gastroparesis. PPI therapy is not considered effective or specific for the treatment of gastroparesis, and there is endorsement for the cessation of opioid use in patients with idiopathic gastroparesis. The group provided 77% support for antiemetic drugs (specifically dopamine-2 antagonistic therapy) and prokinetic therapy as first-line approaches for the treatment of idiopathic gastroparesis, but these did not reach the consensus threshold of 80%. This outcome could reflect the absence of widely available, safe, and effective agents in these categories.

The international consensus group also defined medically refractory gastroparesis as an absence of response to antiemetic and prokinetic drugs and severe nutritional restriction or ongoing weight loss. In refractory gastroparesis, alternative approaches or treatment options with potential side-effects or of a more invasive nature can be considered. However, there is no consensus on the use of neuromodulators, herbal therapies, acupuncture, or gut-directed behavioural

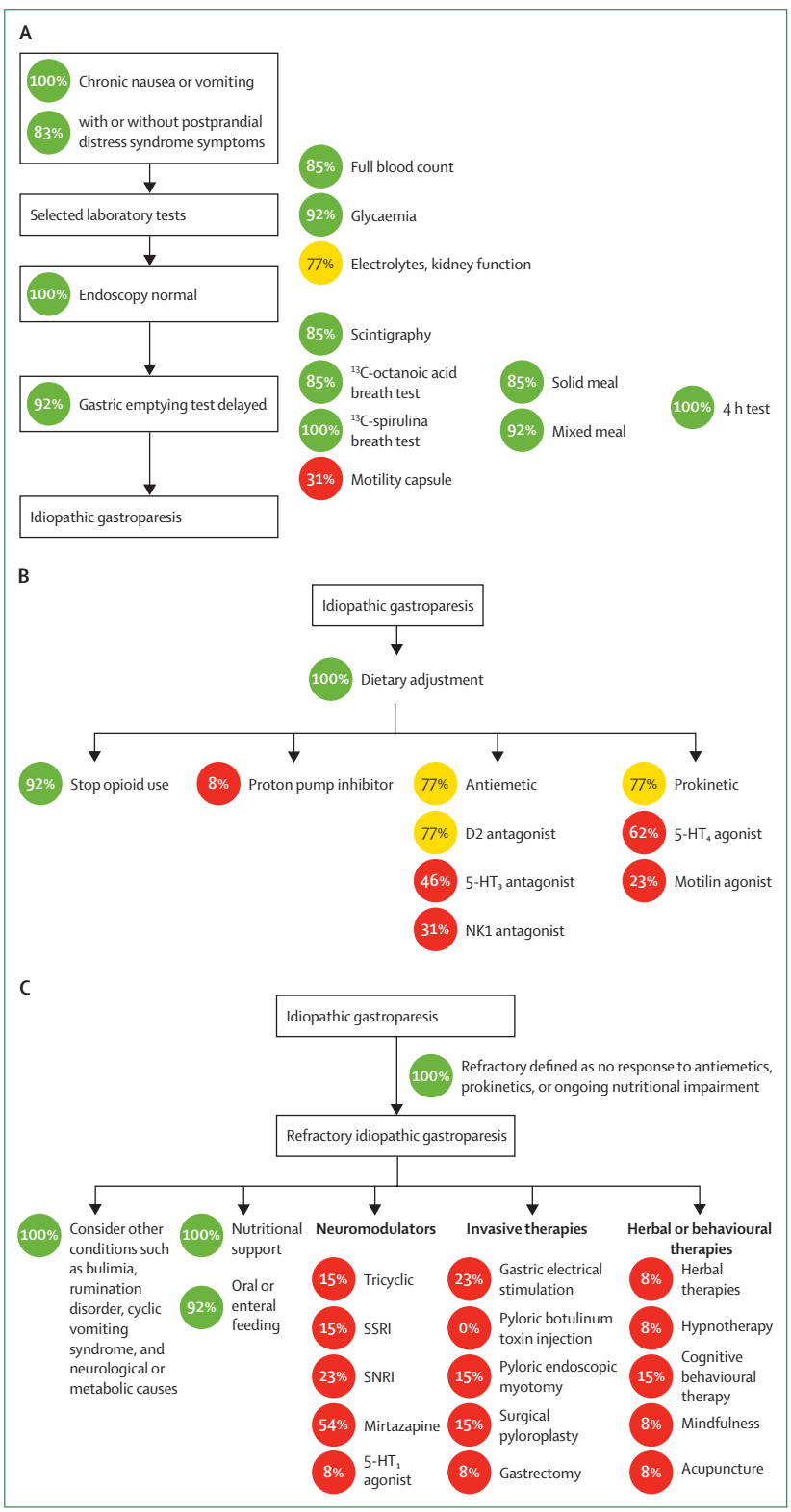

Figure: **Schematic representation of the outcome of the international consensus on idiopathic gastroparesis**

(A) Diagnostic approach, (B) initial management options, and (C) advanced management options for refractory patients. The arrows depict the diagnostic and therapeutic flow of the patient and the circles depict the percentage of consensus agreement. Low consensus is no strict indication of ineffectiveness, but rather reflects a lack of robust evidence for efficacy. SNRI=serotonin–norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

therapies for gastroparesis. More invasive therapies such as botulinum toxin injection, gastric electrical stimulation, pyloric endoscopic myotomy, or (partial) gastrectomy also received no support from the group. A lack of efficacy was also not established, indicating the need for further studies of these modalities. The group agreed on the use of nutritional support in cases of ongoing weight loss, focusing on enteral approaches rather than parenteral approaches. Finally, there is consensus that symptoms tend to persist over years in the majority of patients with idiopathic gastroparesis.

The most important outcome of this global consensus is the identification of a cardinal symptom pattern for gastroparesis (nausea or vomiting). The separation of gastroparesis from functional dyspepsia has been an ongoing and controversial issue. With two cardinal symptoms that are distinct from the symptom pattern in functional dyspepsia, the current consensus could outline a path towards a better differentiation of gastroparesis from functional dyspepsia, although the overlap with postprandial distress syndrome will continue to be present.

In addition to cardinal symptom patterns, documented delayed gastric emptying with a valid test in patients with normal results on endoscopy is mandatory for making a diagnosis of gastroparesis. The consensus also identified a need to develop an internationally applicable valid mixed test meal for gastric emptying testing, to be used in either scintigraphy or GEBT. Although the international consensus group can see potential for antiemetic and prokinetic use, their use did not reach a consensus, indicating that the efficacy of existing and newer therapies requires evaluation in well designed and appropriately powered studies.

This international consensus group, composed and endorsed by members of the Rome Foundation and the Australasian Neurogastroenterology and Motility Association, Asian Neurogastroenterology and Motility Association, American Neurogastroenterology and Motility Society, European Society for Neurogastroenterology and Motility, and Sociedad Latinoamericana de Neurogastroenterología (appendix p 1), used the Delphi method to establish the current state of consensus on definition, symptom characteristics, diagnosis, treatment, and prognosis of idiopathic gastroparesis. The group voted on several statements to guide clinicians, research organisations, regulatory bodies, and the pharmaceutical or medical device industry. Additionally, the statements aim to raise awareness of gastroparesis among clinicians globally.

Search strategy and selection criteria

For each of the statements, the core group of the international consensus group searched for literature using search terms specific to each statement to generate a narrative substantiation of the statement's content. The search identified relevant peer-reviewed articles in English published between Jan 1, 1980 and July 31, 2023, from Pubmed, MEDLINE, and EMBASE.

Contributors

JT conceived and designed the study, undertook the systematic literature review, data analysis, and interpretation, and provided critical revisions to the manuscript. JS, I-HH, and FC contributed to the systematic literature review, the development and refinement of consensus statements, data analysis, and interpretation. All other authors contributed to the development and refinement of consensus statements and provided critical revisions to the manuscript.

Declaration of interests

JT has given scientific advice to Aclipse, Adare, AlfaSigma, Bayer, Clasado, Danone, Falk, FitForMe, Ironwood, Kyowa Kirin, Menarini, Promed, Ricordati, Takeda, Truvion, Tsumura, and Zeria Pharmaceuticals; has received financial research support from Biohit, Kiowa Kirin, ProMed, Sofar, and Takeda; and has served on the speaker bureau for Abbott, Bio-Codex, Mayoly, Menarini, ProMed, Schwabe, Takeda, and Truvion Pharmaceuticals. BEL is on scientific advisory boards for Ironwood, Salix, Takeda, and Sanofi. VS is a consultant or speaker for AlfaSigma, Bayer, Coloplast, and Metagenics. HM has received speaking fees from Takeda, Viatris, EA Pharma, and Astra. GG has served as a consultant or speaker for Laborie, Medtronic, Kyowa Kirin, Lilly, and Enterra Medical. GO'G is a director and shareholder of Insides Company and Alimetry and holds patents and other intellectual property in the fields of gastrointestinal electrophysiology and neuromodulation (US11712566B2; US20230083795A1). BM has participated in the advisory board and received grant support from Atmo, and grant support from Takeda, Medtronic, and the Gastroparesis Consortium (NIDDK NIH UO1 grant). LN is a consultant for Enterra Medical, Ardelyx, Phathom, Evoke, and Takeda. All other authors have no competing interests.

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Exhibit N

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE MATTER OF:	
GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAS) PRODUCTS LIABILITY LITIGATION	MDL No. 3094 20-md-3094
THIS DOCUMENT RELATES TO:	
ALL ACTIONS/ALL CASES	

VIDEOTAPED DEPOSITION OF LINDA A. NGUYEN, M.D.

PALO ALTO, CALIFORNIA

Thursday, February 13, 2025

Stenographically Reported by:

HEATHER J. BAUTISTA, CSR, CRR, RPR, CLR
Realtime Systems Administrator
California CSR License #11600
Oregon CSR License #21-0005
Washington License #21009491
Nevada CCR License #980
Texas CSR License #10725

Job No.: 2114

A. It -- generally, it's one of my patients with gastroparesis who are in the hospital with nausea and vomiting, or other GI issues where they have a flare in their symptoms, and they ask my advice for any diagnostic testing or treatment recommendations and whether or not I think they need to be admitted to the hospital or if I can see them in the out-patient setting if they're able to be discharged home.

Q. And when -- and the patients with gastroparesis who are in the hospital, do they -- do they typically have one subtype of gastroparesis, or does it run a spectrum?

A. Can you clarify what you mean by a subtype of gastroparesis.

Q. Sure.

So diabetic gastroparesis; that's a form of gastroparesis; is that fair?

A. That's fair.

Q. Okay.

Let's see. Post-viral gastroparesis, is that another type of gastroparesis?

A. Yes, that's a -- a type of gastroparesis.

Q. Okay.

A. Yeah. So when I see patients in the hospital with gastroparesis, they run the gamut of all subtypes

of gastroparesis.

Q. Is it fair to say you are not a nuclear medicine doctor?

A. I am not a nuclear medicine doctor.

Q. You're not a radiologist?

A. I'm not a radiologist.

Q. Have you ever signed a gastric emptying study interpretation?

A. I have not signed a gastric emptying -- actually, I'll take that back. I have not signed a nuclear medicine scintigraphy gastric emptying. I have signed --

(Stenographer clarification.)

THE WITNESS: I have signed a wireless capsule motility gastric emptying study.

Q. (By Ms. Aminolroaya) Was that done in the context of a clinical trial or in the hospital?

A. It was done part of clinical care.

Q. Is that something that you do frequently?

A. I used to do it frequently. The wireless capsule motility study is no longer available.

Q. Thank you, Doctor.

I'd like to switch topics right now to talk about the diagnostic process.

Do you agree that arriving at a diagnosis is a

process?

A. Yes.

Q. Are you familiar with the differential diagnosis?

A. I'm very familiar with differential diagnosis.

Q. Is that -- do you use the differential diagnosis in your practice?

A. Every day.

Q. And is that something that you learned in medical school?

A. Yes.

Q. I didn't ask you about this before, and I should have.

Do you teach residents and fellows as part of your work at Stanford?

A. I do.

Q. And do you teach the differential diagnosis to residents and fellows at Stanford?

A. I do.

Q. Would you agree that the differential diagnosis is a systematic process where a health care provider will consider a list of possible medical conditions that could be causing a patient's symptoms and clinically evaluate the patient, and then develop a list of possible conditions that could explain those patient's

Q. (By Ms. Aminolroaya) You have looked at the label for the GLP-1 drugs?

A. I have looked at the label for GLP-1 drugs.

Q. Are you aware that they state that they delay gastric emptying?

MR. PRZYMUSINSKI: Objection to form.

THE WITNESS: I've looked at the label. I have not seen a label recently. Do you have a copy of a label for me to read to ensure that that's what it says?

Q. (By Ms. Aminolroaya) Sure. We have a copy of a label.

MS. AMINOLROAYA: We'll mark -- we'll mark as Exhibit 11, the prescribing information for Ozempic.

(Exhibit 11 was marked for identification.)

Q. (By Ms. Aminolroaya) And we'll go to Section 12, clinical pharmacology for the mechanism of action.

(Stenographer clarification.)

Q. (By Ms. Aminolroaya) Go to Section 12 of the label, which is on Page 12 of the document.

And do you see 12.1, Mechanism of Action?

A. I do see that.

Q. Do you see the last sentence there, "The mechanism of blood glucose lowering also involved a minor delay in gastric emptying in the early postprandial phase"?

Do you see that?

A. I do see that.

Q. Fair to say that there is -- a mechanism besides delayed gastric emptying is not mentioned here in the mechanism of action section of the drug?

MR. PRZYMUSINSKI: Objection to form.

THE WITNESS: I'm sorry. Can you repeat the question and how it pertains to the earlier question you had asked.

Q. (By Ms. Aminolroaya) Yeah. So my question was -- is what -- are you aware of a mechanism other than delayed gastric emptying that can explain how a patient can develop symptoms of nausea, vomiting, early satiety, by a mechanism other than delayed gastric emptying?

A. As I mentioned earlier, I have not looked into all the literature on the -- on GLP-1s and physiology and mechanisms. I do see that it says minor delay in gastric emptying in the -- that there is minor delay in gastric emptying.

The -- the challenge here is that although the label states it and we know that GLP-1s delay gastric emptying, what we don't know is whether or not that delay in gastric emptying actually leads to symptoms.

And you can -- I'm going to draw your attention

to Page 17 of my report here, and the reason we -- one of the reasons we can't draw that conclusion is if you go to 17, and it's the line marked 3, that says, "While GS symptoms are quite common with GLP-1 RAs, clinically delayed gastric emptying is relatively rare."

And in that paragraph, under that section there, and this is an abstract that was referenced both by Drs. Raines and Siegel, in that this large population of patients who were using GLP-1 RAs, who are -- if you just boil it down to the ones who were symptomatic and suspected that they had delayed gastric emptying, and then went on to have a gastric emptying, only 30 percent of those patients actually had delayed gastric emptying, which means 65 percent of the patients in that group that were having symptoms suspicious for gastroparesis did not have delayed gastric emptying.

So that goes back to, you know, the question earlier is that, you know, are there other mechanisms that are known to cause symptoms, the answer is I have not researched it, but based on this data here, I would have to conclude that there has to be a different mechanism that is driving these symptoms.

Q. But to be clear, you have not researched the literature on another mechanism that could explain GI symptoms while on a GLP-1; fair?

A. I'm sorry. I'm sorry. The question again?

MS. AMINOLROAYA: Can you please, Court Reporter, read back the question.

(Record read.)

THE WITNESS: I have not done that research, because that was not the reason -- I was not asked to look into that, so I'm just not prepared to address that question.

Q. (By Ms. Aminolroaya) And so you can't say whether there is any peer-reviewed literature that identifies another mechanism besides delay that explains GI symptoms while on a GLP-1.

MR. PRZYMUSINSKI: Objection to form.

THE WITNESS: What I can say is I have not done the research, so I cannot answer the question.

Q. (By Ms. Aminolroaya) Okay.

Turning to a different topic, you can put the label aside.

Would you agree that a fair number of patients with gastroparesis present with vomiting?

A. I'm sorry. The -- can you repeat the question.

Q. Would you agree that a fair number of patients with gastroparesis present with vomiting?

A. Patients with gastroparesis can present with vomiting, yes.

I, HEATHER J. BAUTISTA, CSR No. 11600, Certified Shorthand Reporter, certify:

That the foregoing proceedings were taken before me at the time and place therein set forth, at which time the witness declared under penalty of perjury; that the testimony of the witness and all objections made at the time of the examination were recorded stenographically by me and were thereafter transcribed under my direction and supervision;

That the foregoing is a full, true, and correct transcript of my shorthand notes so taken and of the testimony so given;

( ) Reading and signing was requested/offered.

(XX) Reading and signing was not requested/offered.

( ) Reading and signing was waived.

I further certify that I am not financially interested in the action, and I am not a relative or employee of any attorney of the parties, nor of any of the parties.

I declare under penalty of perjury under the laws of California that the foregoing is true and correct.

Dated: February 14, 2025

HEATHER J. BAUTISTA, CSR, CRR, RPR, CLR