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Rosita D. Frazier & William L. Hasler

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Impact of GLP-1 receptor agonists on gastrointestinal function and symptoms

Rosita D. Frazier[1] and William L. Hasler[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic Arizona, Scottsdale, AZ

Rosita D. Frazier (ORCID 0009-0006-8874-921X)

William L. Hasler (ORCID 0000-0002-6158-2871)

Corresponding author:

William L. Hasler

Mayo Clinic Arizona

Division of Gastroenterology and Hepatology

13400 E. Shea Blvd.

Scottsdale, AZ 85259

Telephone: (480) 342-3538

E-mail: Hasler.William@mayo.edu

Abstract

Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are approved for diabetes, obesity, and metabolic liver disease, but are also used off-label for other conditions. Adverse events associated with GLP-1RAs have become evident with their increased use.

Areas Covered: This review characterizes GLP-1 physiology and GLP-1RA effects on gastrointestinal (GI) function and symptoms. A comprehensive literature search was conducted accessing PubMed and EMBASE databases from July 1987 through August 2025. Effects of GLP-1RAs on parameters of dysfunctional GI transit and motility and symptoms potentially associated with these impairments are highlighted. The additional impact of GLP-1RA induced gastric food retention on the risk for pulmonary aspiration during anesthesia is a focus of concern. Extraintestinal complications including biliary tract disease and pancreatitis are discussed. Management of GLP-1RA adverse events is reviewed including adjustment of dosing protocols, dietary modifications, and pharmacotherapy to target GI symptoms, however these recommendations lack evidence-based support. New GLP-1RAs are in testing, many with action on other incretin pathways, but these may have adverse consequences similar to existing agents.

Expert Opinion: Prospective investigations of multicenter databases are advocated to transform management approaches of these GLP-1RA induced GI functional consequences and adverse symptoms from empiric treatments to more evidence-based protocols.

Keywords: Anesthesia, diabetes mellitus, gastrointestinal motility, incretin, nausea and vomiting, pulmonary aspiration, tachyphylaxis

Article highlights

- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are incretin therapies which have documented benefits in type 2 diabetes, obesity, and other conditions by virtue of central nervous system and peripheral actions in the gastrointestinal (GI) tract and other organs.
- GLP-1RAs elicit prominent emptying delays and altered accommodation in the stomach and possible inhibitory actions on small intestinal and colonic function as well.
- Adverse symptom consequences include abdominal pain, nausea, vomiting, bloating, abnormal bowel function, and manifestations of gastroesophageal reflux as well as increased risks for cholecystitis and pancreatitis.
- GLP-1RAs have been extensively reported as causing gastric food retention and possible pulmonary aspiration in individuals undergoing anesthesia prior to GI endoscopy and surgery.
- Although data are limited, managing GLP-1RA adverse events has focused on adjusting GLP-1RA dosing, discontinuing other therapies with overlapping side effects, avoiding high fat and high residue foods that are emptied slowly from the stomach, and judicious use of pharmacotherapies targeting the various GI symptoms elicited by this medication class.
- The literature has highlighted a diverse range of adverse GI consequences of these agents, but case reports and small investigations hint at potential benefits of GLP-1RAs in other disorders of GI function including dumping syndrome and irritable bowel syndrome which warrant further study.

1. Introduction

The use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) has increased dramatically over the past decade, catalyzed by evidence supporting efficacy in glycemic control, weight reduction, and cardiovascular risk modification. Originally developed to manage type 2 diabetes, GLP-1RAs also occupy central roles in treating obesity and other metabolic syndromes. Their use has expanded into off-label indications including polycystic ovary syndrome and alcohol use disorder. GLP-1RAs currently available in the United States (US) include semaglutide (trade names Ozempic, Rybelsus, Wegovy), liraglutide (Victoza, Saxenda), dulaglutide (Trulicity), exenatide (Byetta, Bydureon), and tirzepatide (Mounjaro, Zepbound). The Wegovy formulation of semaglutide was recently approved by the Food and Drug Administration (FDA) in August 2025 for metabolic dysfunction-associated steatohepatitis.

Semaglutide prescriptions increased 442% between January 2021 and December 2023, at which time it was filled 2.6 million times at retail pharmacies. Significant growth in semaglutide prescriptions began after approval for obesity in June 2021 and surged with public awareness of its weight-loss benefits in late 2022 [1].

As their use has increased in endocrinology and primary care settings, gastroenterologists are often encountering individuals with GLP-1RA related gastrointestinal (GI) side effects which limit their use, impair quality of life, and mimic or unmask pre-existing GI disorders thereby posing diagnostic and therapeutic dilemmas for clinicians. Clinical trial data highlight the impact of GLP-1RAs on GI function and the burden of GI side effects. Many GI adverse events are dose-dependent, but also show variability across different agents within this drug class.

The most publicized GI consequences of GLP-1RA use include nausea and vomiting as well as the purported risks of pulmonary aspiration secondary to GLP-1RA induced gastric food retention in individuals undergoing anesthesia for endoscopy or surgery. GLP-1RA use is also associated with a broader spectrum of GI and extraintestinal complications. This evolving landscape necessitates a nuanced understanding of the pharmacology, physiological effects, and clinical implications of GLP-1RAs on GI function.

In this review, we describe GLP-1 physiology including gut and central nervous system (CNS) mechanisms of action and review deleterious and beneficial effects of GLP-1RAs on GI function and symptoms. This goal of this article is to provide a framework for gastroenterologists to recognize, manage, and collaborate with endocrinology and obesity medicine colleagues in caring for individuals using GLP-1RAs. A literature review was conducted using PubMed and Embase from July 1987 to August 2025 to identify randomized controlled trials, meta-analyses and systematic reviews, evidence-based consensus statements, neurobiological and physiological investigations, and relevant case series. Combinations of keywords were searched including 'GLP-1 agonists', 'glucagon-like peptide-1 agonists', 'gastric emptying', 'gastrointestinal transit', 'gastrointestinal motility', 'gastrointestinal symptoms', 'gastroparesis', 'disorders of gut-brain interaction', 'adverse events', 'side effects', 'gastrointestinal endoscopy', 'anesthesia', and 'aspiration pneumonia'. Additional publications were selected from reference lists of articles identified during these initial searches.

2. GLP-1 pharmacology, mechanism of action, and clinical utility

2.1 Biology of GLP-1 and Other Incretins:

Glucagon-like peptide-1 (GLP-1) is a 30-amino acid incretin hormone derived from post-translational processing of proglucagon released by enteroendocrine L-cells of the distal ileum and colon [2]. Incretins are hormones defined by their abilities to stimulate pancreatic insulin release in glucose-dependent fashion, thereby protecting against development of hypoglycemia [3]. GLP-1 secretion is biphasic with an early phase beginning 5-15 minutes after meal ingestion mediated by neural and vagal inputs and a later phase 30-90 minutes after eating occurring in response to luminal nutrient exposure, particularly carbohydrates and fats [4, 5]. The native form of GLP-1 has a short half-life of 1.5-3 minutes because of rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) [6]. Consequently, the physiologic form of GLP-1 has no clinical benefits when administered exogenously. In the development of clinically effective GLP-1RAs, molecular modifications made to the native GLP-1 molecule permits their evasion of renal elimination.

2.2 GLP-1 Receptor Agonists:

Clinically available GLP-1 receptor agonists (GLP-1RAs) are synthetic peptides or peptide analogs which exhibit molecular modifications that help resist DPP-4 degradation, thereby extending their biological activity (Table 1). Semaglutide is a long-acting analog modified by fatty acid conjugation and albumin binding with a half-life of 7 days that is available in injectable and oral formulations [7]. Liraglutide is an acylated product with a half-life of 13 hours. Dulaglutide, with fusion to the Fc fragment of human immunoglobulin, allows weekly dosing [8]. Exenatide is an exendin-4 analog with a half-life of 2.4 hours requiring twice-daily

dosing. An extended release, polymer-based form of exenatide is available. Tirzepatide, with a 5-day half-life, is the first GLP-1RA with a second action as a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist [9]. Although tirzepatide acts on two receptor pathways, its side effects are mostly consequences of its GLP-1RA action. These diverse GLP-1RA products permit prescription of agents with daily or weekly administration and subcutaneous or oral delivery options with variable pharmacokinetics and distribution.

2.3 CNS and Neurohumoral Mechanisms of Action of GLP-1 and GLP-1 Receptor Agonists:

GLP-1 binds to the GLP-1 receptor, a G-protein–coupled receptor expressed on pancreatic β-cells, vagal afferent neurons, the nodose ganglia, area postrema, the GI tract, cardiac tissue, kidneys, and several CNS regions inside the blood brain barrier including the hypothalamus, medulla, hypothalamus, and parietal cortex [10, 11]. This distribution permits the main physiologic actions of GLP-1 to promote glucose-dependent insulin secretion from pancreatic β cells, inhibit pancreatic glucagon release, delay gastric emptying, promote satiety, and modulate cardiovascular and renal function (Table 2) [12]. GLP-1 receptors on vagal afferent nerves and central emetic centers also underpin the GI and neurologic side effect profiles of GLP-1RA therapy. Most but not all GLP-1RAs do not penetrate the blood-brain barrier. It is believed that CNS activation by most GLP-1RAs occurs via binding to GLP-1 receptors on vagal pathways in the nodose ganglia, which lie outside of the blood-brain barrier and then project to the nucleus tractus solitarius and area postrema [13]. GLP-1 receptor activation has impact on several neurohumoral pathways independent of actions on gastric emptying including increased glutamate release, altered dopamine signaling, and stimulation of pro-opiomelanocortin neurons

in the hypothalamus coupled with inhibition of neuropeptide Y and agouti-related peptide neuronal function which reduce appetite, promote satiety, and impair food intake [14]. Other consequences of GLP-1 receptor activation include reductions in leptin resistance in the hypothalamus and circulating ghrelin, a gut hormone involved in appetite stimulation [15].

2.4 Gastrointestinal Mechanisms of Action of GLP-1 and GLP-1 Receptor Agonists:

Slowing of gastric emptying by GLP-1 is a consequence of activation of negative feedback from the distal small bowel, a phenomenon known as the ileal brake [16]. Exogenous GLP-1 delays gastric emptying similarly in healthy humans and individuals with type 2 diabetes [17]. One study of liraglutide observed correlation of weight reduction with degrees of gastric emptying slowing, suggesting these delays may be a biomarker of clinical responsiveness to GLP-1RA therapy [18]. In another investigation, the GLP-1RA lixisenatide induced gastric emptying delays that inversely correlated with early insulin secretory responses suggesting an important role for its GI motility effects in regulating glyemia [19]. However, numerous other therapies elicit pronounced gastric emptying delays including opioids, cannabinoids, and anticholinergic agents yet these medications do not consistently promote weight loss nor do they improve glycemic control. Thus, it is probable that these mechanisms involving the CNS neurohumoral pathways are responsible for many of the therapeutic benefits of GLP-1RAs in type 2 diabetes and obesity rather than inhibition of gastric emptying.

2.5 Clinical Utility of GLP-1 Receptor Agonists:

Initially approved for glycemic control in type 2 diabetes, GLP-1 RA use has extended to treatment of obesity with several controlled trials demonstrating durable weight loss and improved cardiometabolic parameters [20, 21]. In one review, tirzepatide 15 mg weekly reduced body weight 17.8% after 72 weeks, while semaglutide 2.4 mg weekly promoted weight loss up to 13.9% at 68 weeks and liraglutide decreased weight up to 5.8% after 26 weeks in non-diabetics [22]. In addition to injectable GLP-1RAs, oral semglutide reduced body weight and A1c levels in type 2 diabetics while increasing proportions of individuals reducing A1c values below 7% [23]. Phase II trials show histologic liver improvement in individuals with metabolic liver disease (formerly termed nonalcoholic steatohepatitis) [24]. GLP-1RAs enhance insulin sensitivity as a consequence of weight loss and may restore ovulatory function in polycystic ovary syndrome [25]. Individuals who have undergone bariatric surgery but regained significant weight post-operatively are also candidates for GLP-1RAs [26]. A recent review reported benefits of GLP-1RAs to decrease ethanol consumption and cravings as well as ethanol-related hospitalizations in alcohol use disorder [27]. Other observed benefits of GLP-1RAs include improvements in blood pressure and lipid profiles and reductions in sleep apnea.

2.6 Other Potential Incretin-Based Therapies:

Incretins other than GLP-1RAs are also prescribed for glycemic control in type 2 diabetes. As described above, the dual agonist tirzepative also serves as an agonist of GIP which increases glucose-dependent insulin secretion, glucagon release during euglycemia or hypoglycemia, lipogenesis, and bone formation with associated inhibition of bone resorption after meal intake [28, 29]. However, GIP does not cause gastric emptying delays. Additionally,

several DPP-4 inhibitors available in the US include sitagliptin, saxagliptin, linagliptin, and alogliptin which improve glycemic control by inhibiting endogenous GLP-1 breakdown.

3. Effects of glp-1 receptor agonists on gastrointestinal motility

GLP-1RAs have established effects to delay gastric emptying, but actions on other GI motility parameters are described (Figure 1). The following sections characterize these impairments and risk factors for their development.

3.1 Effects on Gastric Emptying and Other Stomach Functions:

While GLP-1RA induced delays in gastric emptying may be beneficial for glycemic control, they can pose challenges especially for individuals with GI motility disorders. In a systematic review and meta-analysis of 5 scintigraphic studies, gastric emptying half times were greater on versus not on GLP-1RAs with a pooled difference of 36 minutes (95% CI 17-55, P<0.01) [30]. In a different investigation of short acting GLP-1RAs (exenatide, lixisenatide), emptying half times were delayed up to 3.4 fold often to greater degrees than with longer acting agents [31, 32]. It is proposed that GLP-1RA delays gastric emptying by an interplay of GLP-1 activated pathways in the gut and CNS. Exogenously administered GLP-1 slows gastric emptying by inhibiting antro-duodenal motility through vagal pathways, increasing pyloric tone, and inducing isolated pyloric pressure waves [33].

Studies raise the possibility that gastric emptying impairments on GLP-1RAs exhibit different features when prescribed for type 2 diabetes versus obesity. In one report, 24% of

individuals with diabetes and delayed gastric emptying were taking GLP-1RAs [34]. This observation does not confirm a causative inhibitory effect on stomach motility as diabetes itself may be complicated by gastroparesis. Inhibition of gastric emptying by native GLP-1 is blunted in individuals with diabetes and vagal neuropathy suggesting mediation of emptying delays by vagal pathways [35]. In individuals with pre-existing gastroparesis, GLP-1RA administration only elicited further delays in 2 of 20 individuals with diabetes in one study [36].

Other factors that relate to delayed gastric emptying on GLP-1RAs have been assessed. In a National Institutes of Health (NIH) cross-sectional analysis of 10,328 adults in the All of Us cohort, emptying delays were less prevalent for semaglutide versus dulaglutide, liraglutide, or exenatide [37]. Conversely, another study reported higher prevalence of delayed gastric emptying with semaglutide versus other GLP-1RAs [38]. In one report, all individuals with gastric emptying delays also had pre-existing gastroparesis or were on other medications with inhibitory action on gastric motility including opioids [39].

Several reports have observed tachyphylaxis to the slowing effects of GLP-1RAs on gastric emptying. In healthy individuals, repeated tirzepatide or dulaglutide administration led to diminishing gastric emptying delay compared to those observed after the first dose [40]. Tolerance to inhibitory effects of GLP-1 on gastric motility appears to be dose-dependent [41]. Likewise among obese individuals given semaglutide, delayed emptying was noted with short-term treatment (8-16 weeks) while 2 studies of 20 weeks duration did not observe persistent emptying delays [42, 43]. In a post hoc investigation with serial gastric emptying determinations in 67 individuals with obesity receiving liraglutide, 57% developed gastric emptying delays at 5 weeks (Figure 2) [44]. However, only 30% exhibited persistent delays at 16 weeks providing evidence for tachyphylaxis. This inconsistent tolerance to delaying actions of GLP-1RAs

indicates tachyphylaxis is not universal, with some individuals exhibiting persistent gastroparesis after 6 months of therapy. The unpredictability of tachyphylaxis development does not guarantee that symptoms will resolve with continued GLP-1RA use—particularly among individuals with existing gastroparesis. Some suggest tachyphylaxis to GLP-1RA therapy is more prominent with long-acting formulations likely from sustained receptor exposure rather than short-acting agents like exenatide which which exert briefer inhibitory actions by vagal pathways [41].

Another concern relating to GLP-1RA induced emptying delays is the theoretical risk of altering intestinal medication absorption. This has been prominently observed in Parkinson's disease in which emptying delays impair absorption of oral therapies that mitigate movement manifestations of this condition [45]. A similar worry was raised for individuals undergoing cardiac interventions who are on medications to improve heart function that could be unpredictably absorbed on GLP-1RAs [46]. However in healthy subjects, oral semaglutide had limited impact on plasma lisinopril, warfarin, digoxin, or metformin concentrations [47].

GLP-1RAs also affect other measures of gastric function. Exogenous GLP-1 administion increases fasting and fed gastric volumes, enhances gastric accommodation after eating, and alters food distribution in the stomach in healthy humans by activating afferent vagal signaling, which can be impaired in diabetes [17]. Using single photon emission computed tomography, liraglutide increased fasting gastric volumes 16 weeks after initiating therapy [48]. This action was absent in diabetic subjects with impaired vagal functioning suggesting dependence on vagal integrity [49]. Another report observed 21% reductions in gastric acidity on liraglutide and lixisenatide [32].

3.2 Effects on Small Intestine and Colon Transit:

GLP-1RAs also exert multifaceted effects on motility and secretion in the small intestine and colon. Exogenous GLP-1 suppresses the fasting small bowel migrating motor complex, the physiologic contractile pattern which clears bacteria and retained intestinal food residue between meals [50]. GLP-1RAs also attenuate peristalsis and inhibit transit in the colon via nitric oxide-mediated pathways [51].

In addition to these physiologic actions, GLP-1RAs may have clinically important pathophysiologic actions on distal gut regions. Using video capsule endoscopy, one group observed prolongation of small bowel transit from 4.2±0.4 to 6.6±3.9 hours in 14 subjects with type 2 diabetes and peripheral neuropathy as well as individuals without neuropathy [52]. As a consequence of its proposed inhibitory actions in the colon, liraglutide increased the prevalence of inadequate bowel preparation prior to colonoscopy among subjects with type 2 diabetes with peripheral neuropathy [53]. Although less frequently reported, diarrhea may also occur during GLP-1RA treatment possibly secondary to disrupted bile acid absorption, osmotic effects from unabsorbed nutrients, or gut microbiome alterations.

3.3 Symptoms Potentially Referable to GLP-1 Induced GI Dysmotility:

GLP-1RAs elicit significant GI symptoms even in healthy individuals. In one study in 30 normal controls, semaglutide produced bothersome stomach fullness in 75% versus 7% with placebo [54]. Similar increases on semaglutide versus placebo were observed for early satiety (67% vs. 0%), anorexia (67% vs. 0%), and nausea (47% vs. 7%).

GI side effects also are commonly reported by individuals on GLP-1RAs for diabetes or obesity. It was proposed that these adverse symptoms might be an important contributor to weight loss on these agents. However, one study observed that weight reductions on weekly semaglutide were nearly independent of GI symptoms [55]. In a systematic review of 26 randomized controlled trials including 15,491 individuals, GI side effects were more prevalent with GLP-1RAs (47-84%) compared to placebo (13-63%) [22]. Adverse events necessitating treatment cessation were more common on GLP-1RAs (0-26% vs. 0-9%).

Symptoms referable to both the upper and lower GI tracts are reported. In the retrospective NIH cross-sectional analysis of 10,328 adults in the All of Us cohort, side effects on semaglutide, dulaglutide, liraglutide, or exentatide included abdominal pain in 57.6% of adverse event reports, constipation in 30.4%, diarrhea in 32.7%, and nausea and vomiting in 23.4% [37]. The US FDA Adverse Event Reporting System (FAERS) database observed increases in GI disorders with an odds ratio of 1.46 (95% CI 1.44-1.49), which were more prominent with liraglutide, dulaglutide, and semaglutide [56]. In 130 individuals presenting to emergency departments after GLP-1RA exposure, 92% reported nausea and 76% noted vomiting, intravenous fluids were required by 56%, and antiemetic medications were administered to 51% [57]. As with gastroparesis and related conditions, nausea severity in individuals taking GLP-1RAs shows poor correlation with gastric emptying suggesting that many symptoms are driven by CNS mechanisms [58]. Gastroesophageal acid reflux disease (GERD) is prominent in some individuals on GLP-1RAs, which may partly relate to delayed gastric emptying. Among individuals with type 2 diabetes, GLP-1RAs were associated with erosive esophagitis (HR 1.15 95% CI 1.09-1.22), esophageal stricturing (HR 1.284 95% CI 1.135-1.453), and Barrett's metaplasia without or with dysplasia [59]. Recently in an active-comparator cohort study,

24,708 individuals on GLP-1RAs exhibited increased risks of GERD (relative risk [RR] 1.27, 95% CI 1.14-1.42) and GERD complications (RR 1.55, 95% CI 1.12-2.29) versus those on sodium-glucose co-transporter-2 inhibitors [60]. However in another diabetes study, liraglutide and lixisenatide did not increase numbers of reflux episodes on 24 hour pH testing [32].

Factors contributing to GI symptom induction by GLP-1RAs have been examined. GI side effects, especially nausea and diarrhea, are dose-dependent. Long-acting agents are generally linked to less nausea and vomiting versus short-acting formulations, but may be more often associated with diarrhea [61]. Female sex is associated with greater nausea and vomiting, potentially from hormonal effects, heightened visceral sensitivity, or slower gastric emptying [62]. Younger age and lower BMI predict increased symptom burden on GLP-1RAs [63]. In the NIH All of Us cohort, individuals who were white had higher rates of diarrhea, nausea, and vomiting versus Asians, while those who black more often reported constipation [37]. In this study, cardiac and renal disease increased odds ratios for all GI side effects.

Combining GLP-1RAs with other diabetes therapies can have additive side effects. In a systematic review and meta-analysis of 8 studies with 1895 individuals with type 2 diabetes, combining GLP-1RAs with sodium-glucose cotransporter-2 inhibitors (e.g. empagliflozin, dapagliflozin, canagliflozin) led to greater nausea, vomiting, and diarrhea versus monotherapy [64]. In a different meta-analysis, increased nausea and vomiting was observed when GLP-1RAs were combined with metformin [65].

It is recognized that GI symptoms associated with GLP-1RA use mimic those of various dysmotility syndromes as well as disorders of gut-brain interaction (DGBI). Bothersome nausea, vomiting, early satiety, and fullness on GLP-1RAs are not different from reports in gastroparesis or gastroduodenal DGBIs including functional dyspepsia and chronic nausea vomiting

syndrome. Symptoms similar to constipation-predominant irritable bowel syndrome (IBS) are reported in randomized GLP-1RA trials mostly with high dose semaglutide or liraglutide [21].

3.4 Agent-Specific Side Effect Profiles of GLP-1 Receptor Agonists:

Available literature suggests that adverse symptoms may differ between different GLP-1RAs, although some reports provide conflicting information. Adverse events for each agent are discussed below.

Semaglutide: In trials and post-marketing surveillance, semaglutide often but not uniformly leads to high rates of nausea, vomiting, abdominal pain, constipation, diarrhea, and flatulence [38]. FAERS data report the highest risks for semaglutide for nausea (OR 7.41, 95% CI 7.10-7.74), vomiting (OR 6.67, 95% CI 6.32-7.05), constipation (OR 6.17, 95% CI 5.72-6.66), and diarrhea (OR 3.55, 95% CI 3.35-3.77) [56]. Similar increases in GI side effects on oral semaglutide were observed in other FAERS data [66]. In other controlled studies, nausea is reported in over 20% of users, vomiting in 10-20%, and constipation and diarrhea in about 15% [67]. Consequently, some suggest this agent may be less suitable for individuals with established gastrointestinal illnesses [38].

Liraglutide: Liraglutide is also associated with substantial GI intolerance. In FAERS analyses, liraglutide was associated with the highest risks of upper abdominal pain (OR 4.63, 95% CI 4.12-5.21) [56]. In the retrospective NIH cross-sectional analysis of 10,328 adults, abdominal pain, bowel disturbances, and nausea and vomiting were more prevalent on liraglutide than semaglutide or exenatide [37]. Nearly 60% of individuals experience nausea and >20% develop vomiting when liraglutide is used for weight reduction [68].

Dulaglutide: Meta-analyses rank dulaglutide and exenatide among the best tolerated agents with low rates of treatment discontinuation because of GI side effects [69]. However in the retrospective NIH cross-sectional cohort, abdominal pain, bowel disturbances, and nausea and vomiting were more prevalent with dulaglutide versus semaglutide or exenatide [37]. However in other studies, dulaglutide had more favorable GI tolerability, causing nausea in 10–12% and vomiting in fewer than 5% of individuals [70].

Exenatide: Gradual dose titration of exenatide has been advocated to minimize development of nausea, supporting the importance of careful dosing strategies. In one report, exenatide given twice-daily was associated with nausea in up to 36% and vomiting in 18% of cases [71]. However, the extended-release exenatide formulation may be better tolerated.

Tirzepatide: Although it exerts additional action on GIP receptors, tirzepatide shares similar GI adverse event profiles as other GLP-1RAs. In a systematic review of 9 trials with 9818 participants, higher rates of nausea were noted at 10 and 15 mg tirzepatide doses versus the 5 mg dose [72]. In another controlled trial, 20-22% of individuals experienced nausea, 10-12% reported vomiting, 20% noted diarrhea, and 9% noted constipation [73].

3.5 Beneficial GI Effects of GLP-1RAs in Selected Clinical Settings:

Although usually considered to be undesired consequences of therapy, the inhibitory effects of GLP-1RAs on gastric function and hormonal activity may have benefits in some settings. In a 46 year old woman who developed GI and vasomotor symptoms after sleeve gastrectomy, tirzepatide decreased meal-induced reactive hypoglycemia and reduced

postprandial bloating and diarrhea showing its potential utility in treating early and late dumping syndrome [74].

Similarly, GLP-1RAs exert beneficial action on extragastric function raising the possibility they may have a potential therapeutic use in some lower GI disorders including IBS. ROSE-010 is a GLP-1RA that inhibits fasting small intestinal contractile complexes and leads to generalized decreases in motor activity in individuals with IBS [75]. In one controlled study, ROSE-010 produced abdominal pain reductions that were greater in women and individuals with constipation-predominant and mixed IBS versus those with diarrhea-predominance [76]. In a systematic review, ROSE-010 reduced pain intensity in individuals across all IBS subtypes versus placebo (OR 2.30 95% CI 1.53-3.46) [77]. In a small case series, exenatide reduced stool frequency and improved stool form in 5 individuals with short bowel syndrome, permitting discontinuation of parenteral nutrition in 3 individuals [78].

4. Other intraabdominal complications of glp-1 receptor agonists

In a systematic review and meta-analysis of 76 trials, GLP-1RAs were associated with increased risks of cholelithiasis (RR 1.27, 95% CI 1.10-1.47), cholecystitis (RR 1.36 95% CI 1.14-1.62), and other biliary disease (RR 1.55 95% CI 1.08-2.22) which were prominent with higher GLP-1RA doses [79]. This study reported that risks for gallbladder and biliary disease were significantly elevated only after 26 weeks of GLP-1RA therapy. Oral semaglutide showed similar increases in cholecystitis and gallstone risks [66]. This association is believed to result from a combination of factors. Significant weight loss, similar to that after bariatric surgery, can increase bile lithogenicity. GLP-1 RAs may also have direct effects on bile composition or

gallbladder motility. It also should be recognized that risks for biliary disease are higher among individuals with diabetes or obesity irrespective of GLP-1RA prescription.

An increased risk of pancreatitis has been observed in large observational studies. In the retrospective NIH All of Us cross sectional analysis, pancreatitis represented 3.4% of adverse events associated with semaglutide, dulaglutide, liraglutide, or exentatide use [37]. The FAERS database analysis from 2007 to 2023 observed the highest risk for pancreatitis with liraglutide, although others report greater risks with exenatide [38]. A different study analyzing FAERS data between 2019 and 2023 reported increases in pancreatitis on oral semaglutide with a reporting odds ratio (ROR) of 23.12 (95% CI 19.23-27.78) [66]. Times for development of acute pancreatitis averaged 2.5 months in one series and ranged from 0 days to 3 years [80]. It is recognized that some patients who are prescribed GLP-1RAs, including those with long-standing diabetes, are at increased risk of pancreatitis due to preexisting gallstone disease.

Other GLP-1RA complications are seen. In the NIH All of Us analysis, GI bleeding represented 15.9% of adverse events [37]. GLP-1RAs have been associated with elevated risks of small bowel obstruction, apparently distinct from their inhibitory actions on intestinal transit. The FDA released a boxed warning which recommended avoiding GLP-1RA use in those with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 based on rodent studies in which these agents elicited thyroid C-cell tumors. These risks in humans remain debated.

5. Management considerations for individuals on glp-1 receptor agonists

Relationships between GLP-1RAs and motility disorders are increasingly recognized in clinical practice. While transient nausea or altered bowel function may be anticipated during GLP-1RA dose escalation, a subset of individuals experiences sustained, clinically significant symptoms that mimic or unmask primary GI motility disorders or DGBIs. Differentiating adverse reactions from underlying intrinsic comorbidities can be challenging.

A multidisciplinary expert consensus article was recently published which offered recommendations on managing GI side effects of GLP-1RAs, however little controlled data exist and evidence-based guidance to manage these adverse effects remains limited [81]. Randomized trials have not included structured protocols for addressing side effects, aside from delayed dose escalation or dose reductions in some studies. Thus, management approaches in the following sections are largely informed by recommendations from the aforementioned expert consensus article coupled with publications by neurogastroenterologists who manage similar symptom presentations in individuals with dysmotility syndromes or DGBIs.

5.1 Decisions Regarding Prescription of GLP-1 Agonists:

Initiation of GLP-1RA therapy should be guided by individualized risk assessments. Detailed clinical histories are essential to identify individuals who may be susceptible to treatment-related adverse effects, with particular attention to pre-existing nausea, early satiety, postprandial fullness, bloating, and changes in bowel habits. Key factors warranting attention include known diagnoses of gastroparesis or DGBIs like functional dyspepsia or IBS, as these conditions share symptom overlap with GLP-1RA–associated GI adverse events. Some individuals with type 2 diabetes, especially with A1c levels >8.5%, may have unsuspected

autonomic neuropathy which may become apparent upon initiating GLP-1RA therapy. Concomitant use of medications that impair GI motility (including opioids and anticholinergics) should be reviewed as these agents may have additive effects to increase GLP-1RA intolerance. Prior operative procedures (e.g. fundoplication, bariatric surgery) can influence gastric motility potentially degrading the efficacy and tolerability of GLP-1RA therapy.

Once this information is acquired, a range of management decisions can be considered including pre-therapy motility testing with gastric scintigraphy in high risk individuals and careful selection of the appropriate GLP-1RA. It is recognized that performing gastric emptying testing while on GLP-1RAs may identify delays that are a consequence of treatment with this drug class rather than an intrinsic dysmotility syndrome. However, it may not be necessary to withhold GLP-1RAs in individuals with documented gut motility or sensation disorders. In a study of individuals with preexisting gastritis and/or GERD, GLP-1RAs were well tolerated and dose escalation was permitted at standard intervals [82].

A conservative strategy for initiating GLP-1RA therapy is advocated for individuals deemed to be at risk of GI adverse events, including starting at the lowest dose, extending titration intervals, and deferring dose escalation or reducing doses during periods of symptom exacerbations [81]. Starting at lower-than-standard doses (e.g., 0.25 mg weekly for semaglutide) and escalating doses no more frequently than every 6–8 weeks demonstrated improved tolerability in clinical practice [83]. These approaches can enhance tolerability and prevent unnecessary discontinuation of therapy.

Close monitoring is warranted to identify alarm symptoms that may necessitate dose adjustment or therapy interruption, including persistent or worsening vomiting after the titration phase, refractory early satiety or intolerance to solid foods, rapid or unintended weight loss,

findings suggesting bowel obstruction, or evidence of dehydration or nutritional compromise. In such scenarios, temporary discontinuation or dose de-escalation is appropriate. Reinitiating therapy may be considered after symptoms resolve, with adoption of a slower titration schedule or switching to a GLP-1RA with more favorable GI tolerability. However, switching routes of administration may be of little benefit as oral semaglutide and newer oral non-peptide GLP-RAs in testing (orforglipron) show similar GI side effect profiles as subcutaneous agents [84].

Genetic polymorphisms in GLP-1R and TCF7L2 may influence gastric emptying responses and tachyphylaxis to GLP-1RAs [85, 86]. These observations raise the possibility of future pharmacogenomic protocols that could be routinely performed before treatment to stratify candidates for GLP-1RA therapy by risks for developing adverse events.

Coordination of care with endocrinologists, bariatric specialists, dietitians, and primary care providers is essential while initiating GLP-1RA therapy in individuals at risk of GI side effects. Such collaborative approaches will ensure that benefits of GLP-1RAs are weighed against GI risks, allowing for shared management of symptom mitigation.

5.2 Practical Approach to Therapy of GLP-1 Agonist-Induced GI Side Effects:

Adjunctive approaches have been proposed to manage GI symptoms during GLP-1RA use which borrow from similar management plans for gastroparesis, chronic nausea, dyspepsia, or altered bowel function. Key challenges lie in discerning whether GI symptoms represent intolerable adverse effects of GLP-1RAs or if diet modifications or pharmacotherapies can ameliorate symptoms to permit continued therapy. This may hinge on provider recognition of

symptom severity profiles, responses to treatments targeting GI side effects, and the preference of the patient regarding GLP-1RA continuation.

Dietary counseling is essential, especially for nausea, vomiting, or bothersome early satiety suspicious for a gastric emptying delay. Ingestion of frequent small volume, low fat and low fiber meals with reduced residue can limit symptom provocation and should be a standard recommendation, especially for evening meals (Table 3) [81, 87]. Adequate fluid intake should be reinforced, especially with frequent vomiting or diarrhea.

Other therapies may increase GI symptoms in additive fashion when combined with GLP-1RAs. As an example, consideration can be given in diabetic individuals with adequate glycemic control to discontinuing metformin which can independently cause nausea or diarrhea (Table 3).

Symptom-directed interventions may be offered to reduce bothersome GI side effects of GLP-1RA therapy (Table 3). Antiemetic medications (e.g. ondansetron, promethazine) can reduce nausea, while neuromodulators such as mirtazapine, tricyclic agents, or buspirone may modulate visceral hypersensitivity or improve gastric accommodation to reduce early satiety or abdominal pain. Intravenous erythromycin showed efficacy in reversing gastric emptying impairments due to GLP-1RAs in healthy controls in one study [88]. Prokinetic agents targeting the stomach including metoclopramide or erythromycin may be considered, especially if gastric emptying is delayed and if individuals report symptoms of gastroparesis or dyspepsia [89]. Prucalopride may be helpful with GLP-1RA associated constipation and also accelerates gastric emptying. Diarrhea can be managed with loperamide on demand or on a scheduled basis.

5.3 Anesthesia Concerns for Endoscopy and Surgery While on GLP-1 Agonists:

The largest body of literature on adverse events associated with GLP-1RA use relates to anesthesia concerns about risks of gastric food retention and subsequent pulmonary aspiration. A systematic review and meta-analysis of 12 studies involving 105,515 subjects (32,144 on GLP-1RAs and 73,273 controls) found this medication class was linked to increased rates of retained gastric contents (OR 6.30, 95% CI 5.30-7.49), and greater needs to abort (OR 5.50, 95% CI 3.25-9.32) or repeat (OR 2.19, 95% CI 1.42-3.38) endoscopic testing [90]. Another retrospective analysis of 35,183 subjects noted 4-fold greater rates of aborting esophagogastroduodenoscopy (EGD) procedures ($P<0.0001$) and a doubling of the need to repeat EGD testing ($P=0.0001$) while a different study of 32,275 subjects observed that EGD procedures were aborted in 0.6% on GLP-1RAs versus 0.1% not on GLP-1RAs ($P<0.01$) [91, 92]. A large Cochrane database analyzed 39 studies comprising 1.2 million subjects reported that interruption of EGD procedures was increased (OR 3.22, 95% CI 1.65-6.29) as were needs to repeat EGD testing (OR 2.16, 95% CI 1.14-4.11) [93]. Most recently, a systematic review of 20 studies of 207,708 subjects (including 23,366 on GLP-1RAs) observed increases in gastric retention (OR 5.57, 95% CI 4.07-7.62) and rates of aborted EGDs (OR 4.90, 95% CI 2.94-8.18) [94].

Investigators have attempted to define risk factors for GLP-1RA induced gastric food retention in individuals undergoing endoscopy. In 205 individuals with diabetes undergoing EGD, 5.4% of GLP-RA users versus 0.5% of non-users exhibited retained gastric contents ($P=0.004$) [95]. Notably, all 14 individuals whose procedures were aborted were diabetic. In a study of over 200 individuals with diabetes undergoing EGD, GLP-1RA users with A1c elevations exhibited a 36% increased risk of retained gastric contents per each 1% incremental increase in A1c [96]. In another retrospective investigation of 1438 individuals undergoing

EGD, tirzepatide was associated with the highest incidence of food retention, while exenatide had the lowest rate [97]. In this study, factors that protected against retained food included higher age (OR 0.96, 95% CI 0.93-0.99) and same day colonoscopy (OR 0.18, 95% CI 0.06-0.58) while A1c levels, BMI, and sex did not influence food retention.

Despite concerns about the influence of GLP-1RA induced gastric food retention on the safety of endoscopy, most but not all studies indicate the risk of pulmonary aspiration is low. One small study documented the need for emergency endotracheal intubation in 5 individuals on GLP-1RAs compared to one control individual undergoing EGD, however only one case of aspiration was observed [98]. In a systematic review of 24 studies, there was no increase in aspiration on (4.8 cases per 10,000) versus not on (4.6 per 10,000) GLP-1RAs [99]. In another study, no meaningful increase in aspiration risk was observed (OR 1.26, 95% CI 0.86–1.87) [90]. In an analysis of a national claims database comparing GLP-1RAs to DDP-4 inhibitors, relative risks of aspiration (0.67, 95% CI 0.25-0.75), pneumonia (1.07, 95% CI 0.62-1.86), and respiratory failure (0.75, 95% CI 0.38-1.48) were not higher on GLP-1RAs [100]. A retrospective cohort analysis of more than 130 million diabetics within the US did not identify increased risks of aspiration/penumonitis or 30 day mortality on these agents [101]. Likewise, no increase in aspiration risk was noted in the recent systematic review of 23,366 individuals on GLP-1RAs (OR 1.75, 95% CI 0.64-4.77) [94]. However, the Cochrane analysis of 39 studies comprising 1.2 million participants described previously did calculate significant increases in pulmonary aspiration (OR 2.29, 95% CI1.36-3.87) (Figure 3) [93].

Based on these data, the American Society of Anesthesiologists released a consensus opinion in 2023 that recommended holding long-acting GLP-1RAs for 1 week before invasive procedures [102]. However a study of 62 individuals who discontinued GLP-1RAs for 7 or more

days observed residual gastric food residue in 35 (62%) suggesting this recommendation may have limited validity [103]. It has been proposed that to eliminate risks of food retention would necessitate discontinuing GLP-1RA therapy for 5 drug half lives, which would be about 5 weeks for semaglutide and tirzepatide [89]. Others advocate no change in standard fasting recommendations prior to endoscopy due to the low aspiration risk [104]. The American Gastroenterological Association published a Rapid Clinical Practice Update in 2024 which advised avoiding solids for 8 hours and liquids for 2 hours in individuals on GLP-1RAs who are asymptomatic from an upper GI standpoint [105]. Some experts disagree with this recommendation, given the poor relation of gastroparesis symptoms to gastric emptying delays [89]. Straightforward measures such as a 24-hour clear liquid diet with or without prokinetic medication treatment may reduce procedural risks without interrupting GLP-1RA dosing [90]. In one study, preprocedure clear liquid diets reduced the prevalence of gastric food retention from 10% to 1.5% [106].

Some centers are adopting on-site gastric ultrasound in the endoscopy suite to detect gastric food residue and quantify its volume prior to EGD or surgery (Figure 4) [107]. In one study of 20 subjects, 90% of individuals on semaglutide exhibited retained solids on ultrasound after 8 hours of fasting versus 20% of controls (P=0.005) [108]. This method has been employed to alter anesthesia plans to reduce the risk of aspiration. Artificial intelligence methods have been developed to enhance this capability [109].

Although risks of GLP-1RA use during EGD have been highlighted in the literature, GLP-1RAs may actually be beneficial in reducing complications in some endoscopic and surgical settings. In a systematic review of 14 studies of 2143 subjects, glucose levels were lower, needs for rescue insulin administration were less, and periprocedure hypoglycemia was

not increased in individuals taking GLP-1RAs [110]. In a different report, postoperative needs for antiemetics were reduced among individuals on GLP-1RAs [101].

6. Conclusions

Including GLP-1RAs into mainstream treatment of type 2 diabetes, obesity, metabolic liver disease, and other off-label indications has ushered in a new era of metabolic therapeutics. GLP-1RAs demonstrate efficacy in improving glycemic control, promoting weight loss, and reducing adverse cardiovascular events. However, their widespread adoption reveals a growing need for gastroenterologists to understand their complex impacts on GI physiology and symptoms.

GLP-1RAs exert multifactorial effects on gut functions which, while central to their therapeutic efficacy, also contribute to a spectrum of GI symptoms and other adverse events. GI consequences of GLP-1RA use may be influenced by comorbid factors including diabetes-related autonomic neuropathy, poor glycemic control, or concurrent use of medications with side effects that overlap with those caused by GLP-1RAs. Challenges lie in identifying individuals most susceptible to these adverse effects, followed by initiating treatments that preserve benefits of GLP-1RA therapy while mitigating the burden of GI symptoms. Proposed therapeutic options include GLP-1RA dose titration, dietary counseling, and judicious use of pharmacotherapies targeting individual symptoms while enabling continuation of GLP-1RAs. Gastroenterologists should consider implications of GLP-1RA use when planning endoscopic testing, given the risks of gastric food retention and possible pulmonary aspiration. Although evidence does not support

prolonged GLP-1RA discontinuation for most individuals prior to EGD, recommendations including a 24 hour clear liquid diet can permit safe endoscopic evaluation in most cases.

7. Expert opinion

When GLP-1RAs were initially introduced into clinical care, the breadth and severity of GI functional and symptom complications of therapy with these agents were poorly understood. As a consequence of investigations presented in this review, a robust knowledge base is now available to facilitate diagnosis of disturbances of transit as well as pancreaticobiliary disease and to suggest treatment approaches to ameliorate these abnormalities. Furthermore, expert guidelines have been generated for anesthesia guidelines for individuals on these medications.

However, much of the literature describing GI consequences of GLP-1RA use relies on articles with study design limitations and incompletely quantitative outcome measures. Although study data from industry-sponsored randomized controlled trials provide detailed information on outcomes supporting GLP-1RA benefits including glycemic control and weight reduction, their enumeration of GI symptoms including nausea, vomiting, abdominal pain, and bowel disturbances, the timing of when these adverse events present, and the impact of these symptoms on quality of life, psychosocial functioning, healthcare resource use and the ability to continue GLP-1RA use are less meticulous. Other investigations included in this review present data from case series or from hospitalization or claims reports which also provide incomplete details.

Nevertheless, these studies provide a firm foundation for new investigations with the goal to better understand appropriate surveillance and management of complications of GLP-1RA therapy. Future research should include generation of large multicenter registries comprised of

individuals who can report GLP-1RA adverse events using uniform inclusion criteria, validated symptom survey instruments, and consistent data forms to quantify these diverse impacts of symptoms. Similarly when considering GLP-1RA effects on GI physiology, testing methods should be standardized between centers and for all individual GLP-1RAs. Construction of a prospective GLP-1RA registry would be enriched by including collaborators in gastroenterology, endocrinology, bariatric medicine, and nutrition with the aims of better quantifying the incidence, severity, timing, and duration of GI symptoms across diverse populations on the different GLP-1RAs and identifying clinical and physiologic factors associated with symptom development. This information could help to stratify individuals by risk of GLP-1RA complications to help providers make decisions regarding personalized protocols for GLP-1RA prescription including implementation of reduced dosage protocols. Performance of standardized methodologies of gastric emptying testing in serial fashion over could glean additional insight into the observed tachyphylaxis to GI motility effects of GLP-1RAs. Although tachyphylaxis is often considered a negative adaptation to repeated drug dosing, its development during longitudinal GLP-1RA dosing could be a positive outcome to help reduce adverse GI events with long-term use. Rigorous analyses could determine if such tachyphylaxis occurs similarly among all GLP-1RAs, how quickly and often it occurs, which clinical or demographic factors relate to its development, and if tachyphylaxis is routinely associated with resolution of symptoms including nausea and vomiting.

Another area of research important to pursue would be the definition of evidence-based dietary and medication therapies for GI complications of GLP-1RA treatment. Current management recommendations in these patients describe therapies that are routinely used in related conditions like gastroparesis or DGBIs but have not been tested in individuals on GLP-

1RAs. Recruiting subjects into longitudinal cohort investigations or randomized controlled trials evaluating therapeutic strategies designed to mitigate GLP-1RA adverse events such as modified titration protocols and gut-directed therapies including antiemetics, prokinetics, or constipation medications would inform practical, tolerable models for long-term treatment to transform our approach to one which is more data-driven.

Over the next 5 to 10 years, the emergence of next-generation incretin-based therapies will present new opportunities and challenges. Dual or triple agonist therapies, the first of which is the combined GLP-1RA and GIP agonist tirzepatide, are proposed to provide more effective weight reduction and glycemic control versus agents acting solely on GLP-1 receptors. Combined subcutaneous GLP-1RA and glucagon receptor agonists in testing include mazdutide, survodutide, catadutide, pemvidutide, and JNJ-64565111, while an agent with triple action as agonists for GLP-1, GIP, and glucagon—retatrutide—has been investigated [111]. Small molecular GLP-1RAs in testing like ofroglipon may be better accepted by virtue of their oral administration [84]. It is likely that these agents will exhibit similar side effect profiles as current GLP-1RAs because of their similar mechanisms of action. Lessons learned from the proposed structured investigations of existing GLP-1RAs described above could be adopted to studying these newer agents. By embracing these collaborative, evidence-informed approaches, gastroenterologists will be able to navigate this evolving therapeutic landscape including this expanded range of GLP-1RA therapies, thereby ensuring individual well-being whilc supporting optimal use of this important drug class for its clinical indications.

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** *This paper presents a detailed review of incretin biology and concludes with a comprehensive description of next-generation therapies targeting incretin pathways.*

TABLE LEGENDS

Table 1: Currently available GLP-1RAs are shown along with their dosing frequencies, routes of administration, and drug half-lives.

Table 2: The physiologic targets of GLP-1, effects of GLP-1 receptor activation, and clinical implications of GLP-1 receptor activation are shown.

Table 3: Recommendations from the literature on managing GI side effects of GLP-1RAs are summarized. The entries in this table represent the combined recommendations from several references cited in this article including 81, 87, 88, 89, and 111.

TABLES

Table 1: CLINICALLY AVAILABLE GLP-1 RECEPTOR AGONISTS

AGENT	STRUCTURE/CLASS	DOSING FREQUENCY/ROUTE	HALF-LIFE
Semaglutide	Long-acting human GLP-1 analog modified by fatty acid conjugation and albumin binding	Weekly (subcutaneous) or daily (oral)	~7 days
Liraglutide	Acylated GLP-1 analog	Daily (subcutaneous)	~13 hours
Dulaglutide	GLP-1 analog with fusion to Fc immunoglobulin fragment	Weekly (subcutaneous)	~5 days
Exenatide	Exendin-4 analog	Twice daily (short-acting subcutaneous formulation) or weekly (long-acting extended release formulation)	~2.4 hours for twice daily formulation Longer with extended release formulation
Tirzepatide	Dual GLP-1/GIP receptor agonist	Weekly (subcutaneous)	~5 days

Table 2: SUMMARY OF KEY PHYSIOLOGIC EFFECTS OF GLP-1 RECEPTOR ACTIVATION

PHYSIOLOGIC TARGET	EFFECT OF GLP-1 RECEPTOR ACTIVATION	CLINICAL IMPLICATION
Pancreatic β-cells	Enhances glucose-dependent insulin secretion	Supports glycemic control with low risk of hypoglycemia
Pancreatic α-cells	Suppresses glucagon secretion	Reduces hepatic glucose output
Stomach and Proximal GI Tract	Delays gastric emptying via vagal efferents and increased pyloric tone	May improve postprandial glycemia but exacerbate symptoms in
Hypothalamus & Brainstem	Promotes satiety; reduces appetite	Contributes to weight loss and early satiety
Area Postrema & Nucleus Tractus Solitarius	Activates central emetic centers	Associated with nausea and vomiting; relevant in dose titration
Vagal Afferents	Mediates gut-brain signaling, including GI discomfort and fullness	May contribute to bloating, early satiety, or visceral hypersensitivity

Table 3: MANAGEMENT OF GI SIDE EFFECTS OF GLP-1RA THERAPY FROM EXPERT CONSENSUS

Eating Habits	Meal Composition	Treat Nausea and Vomiting	Treat Diarrhea	Treat Constipation
Eat slowly Eat only if hungry and stop when satisfied No lying down after eating Not too active after eating No meals near bedtime	Small, frequent meals Low fat, low fiber, low residue intake Clear drinks Water rich foods Boiled oven-baked, or griddle-cooked foods	Eat crackers, ginger-based drinks Generous hydration Avoid strong smells Antiemetic agents Prokinetic medications Neuromodulators	Probiotics Antidiarrheals Reduce metformin dose (if on this agent)	Increase activity Increase water intake Increase fiber intake Stool softeners Gentle laxatives Prescription constipation products

FIGURE LEGENDS

Figure 1: The physiologic actions of GLP-1RAs on the gastrointestinal tract are shown. From Reference 89. Reproduced with permission from The Lancet Gastroenterology & Hepatology (Elsevier) where permission was acquired.

Figure 2: Individual rates of gastric emptying (T1/2 of solids) in individuals with obesity are shown at baseline and after 5 and 16 weeks of treatment with liraglutide. Overall, there was no change in gastric emptying in 28 subjects, persistent gastric emptying delay at 5 and 16 weeks in 20 individuals, and initial delay in gastric emptying at 5 weeks followed by tachyphylaxis in 19 participants. From Reference 44. Reproduced with permission from Obesity (Silver Spring) (John Wiley and Sons) where permission was acquired.

Figure 3: This Cochrane database analysis of 39 studies comprising 1.2 million subjects observed an increase in pulmonary aspiration on GLP-1RAs in those undergoing EGD. From Reference 93. Reproduced with permission from Digestive and Liver Disease (Elsevier) where permission was acquired.

Figure 4: These images are from gastric ultrasound examinations in relation to different stomach contents including an empty antrum (A), an antrum distended with liquids (B), a greatly distended antrum with thick liquids and solids (C), and an antrum with recently ingested solids (D). From Reference 107.

ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
DGBI	Disorder of gut-brain interaction
DPP-4	Dipeptidyl peptidase-4
EGD	Esophagogastroduodenoscopy
FAERS	Food and Drug Administrtion Adverse Event Reporting System
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HR	Hazard ratio
IBS	Irritable bowel syndrome
NIH	National Institutes of Health
OR	Odds ratio
ROR	Reporting odds ratio

RR	Relative risk
US	United States

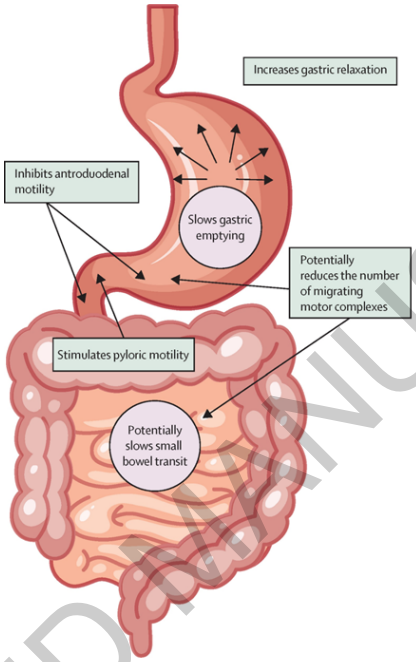

Figure 1

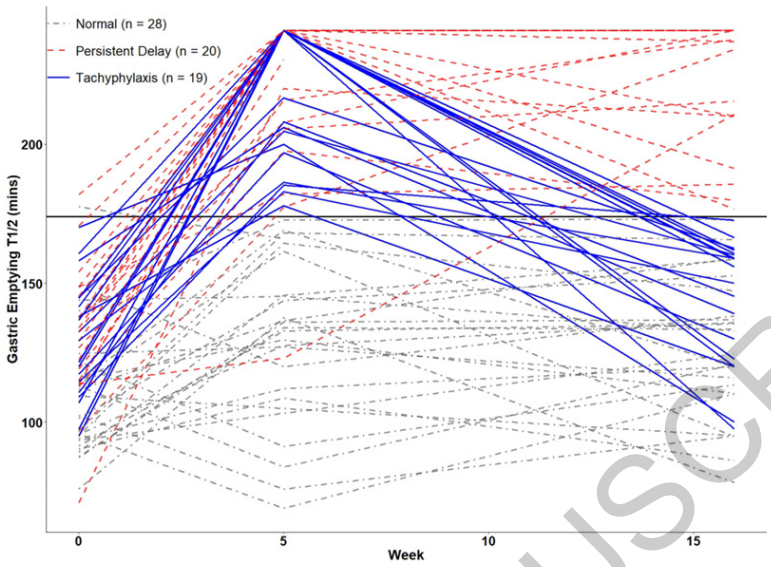

Figure 2

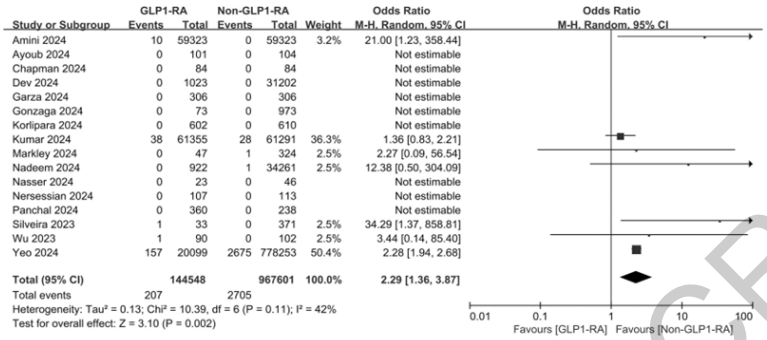

Figure 3

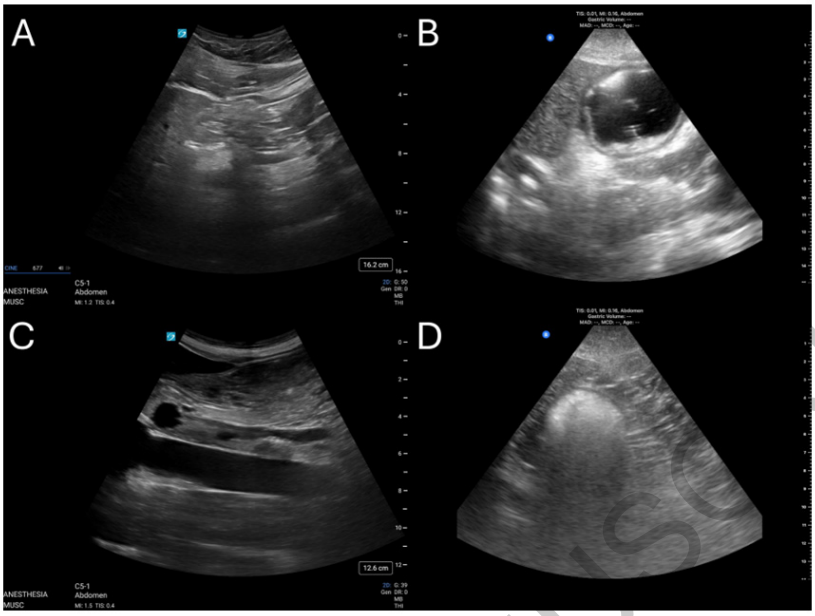

Figure 4