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Review Series

GLP-1 receptor agonist (GLP-1RA) medications have transformed the treatment of type 2 diabetes (T2D) and obesity, with robust evidence for cardiovascular and renal benefits. Nevertheless, GLP-1RA therapy is associated with a pattern of adverse events affecting their safety and tolerability. Here, we delineate mechanisms potentially leading to adverse responses to GLP-1RAs, describe the impact of side effects on treatment persistence, discuss potential mitigation strategies, and identify areas requiring further studies. Concerns that GLP-1RAs raise the risk for acute pancreatitis and pancreatic cancer have been dispelled by long-term clinical trials. However, GLP-1RAs may confer an increased risk for thyroid cancer. Sight-threatening eye complications resulting from rapid reductions in glycemia may be avoided by retinal screening and ophthalmologic treatment before GLP-1RA initiation. The slowing of gastric emptying with GLP-1RA treatment increases the propensity for retained gastric contents, which could increase the risk of aspiration during upper gastrointestinal endoscopy or general anesthesia. These risks may, however, be elevated in individuals with long-standing T2D even in the absence of GLP-1RA treatment. Improved pharmacovigilance and a more standardized, quantitative assessment of adverse events in clinical trials, particularly in the assessment of gastrointestinal symptoms, would facilitate definition of the benefit-risk relationship for individual medications and indications.

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The science of safety: adverse effects of GLP-1 receptor agonists as glucose-lowering and obesity medications

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GLP-1 receptor agonist (GLP-1RA) medications have transformed the treatment of type 2 diabetes (T2D) and obesity, with robust evidence for cardiovascular and renal benefits. Nevertheless, GLP-1RA therapy is associated with a pattern of adverse events affecting their safety and tolerability. Here, we delineate mechanisms potentially leading to adverse responses to GLP-1RAs, describe the impact of side effects on treatment persistence, discuss potential mitigation strategies, and identify areas requiring further studies. Concerns that GLP-1RAs raise the risk for acute pancreatitis and pancreatic cancer have been dispelled by long-term clinical trials. However, GLP-1RAs may confer an increased risk for thyroid cancer. Sight-threatening eye complications resulting from rapid reductions in glycemia may be avoided by retinal screening and ophthalmologic treatment before GLP-1RA initiation. The slowing of gastric emptying with GLP-1RA treatment increases the propensity for retained gastric contents, which could increase the risk of aspiration during upper gastrointestinal endoscopy or general anesthesia. These risks may, however, be elevated in individuals with long-standing T2D even in the absence of GLP-1RA treatment. Improved pharmacovigilance and a more standardized, quantitative assessment of adverse events in clinical trials, particularly in the assessment of gastrointestinal symptoms, would facilitate definition of the benefit-risk relationship for individual medications and indications.

Among the two incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), the latter has been established as having therapeutic potential for reducing elevated plasma glucose (1, 2) and body weight (3), while the former has been unable to either stimulate insulin secretion (1) or lower plasma glucose effectively in type 2 diabetes (T2D) (4). Therefore, GLP-1 became the parent compound for the development of GLP-1 receptor agonists (GLP-1RAs) (5–7). GLP-1 acts through a class 2 member of the G-coupled protein C receptor family seven-transmembrane receptor (GLP-1R) (8), which is mainly expressed in pancreatic islets, the brain, and the gastrointestinal (GI) tract (9–12), and less prominently in the kidney and eyes (11–13). This class of drugs is now used widely, with beneficial

GLP-1R-mediated effects on body weight and glycemic control, as well as their cardio-renal complications (7, 14). The stimulation of GLP-1R, however, may also elicit adverse events. The focus of this Review is on adverse events associated with the treatment with selective GLP-1RAs, or with the dual-targeted GIP receptor agonist (GIPRA)/GLP-1RA tirzepatide, the overall treatment uptake, adherence, and persistence of which have been suboptimal. We discuss adverse events of specific interest observed with these therapies (and their potential underlying mechanisms), including GI side effects, psychiatric, ocular, thyroid, biliary, and pancreatic complications (Table 1).

GI side effects

A recent systematic review of 39 randomized controlled trials of GLP-1RAs showed a class effect of increased risks of nausea, vomiting, diarrhea and constipation compared with placebo (15) in individuals without diabetes. For the newer-generation therapies there was increased risk of nausea compared with placebo: semaglutide relative risk (RR) 2.95 (95% CI 2.61–3.32), tirzepatide RR 2.90 (95% CI 2–4.19), and orforglipron RR 4.77 (95% CI 2.02–11.31). In another systematic review that included individuals with T2D from 38 phase III or IV placebo-controlled randomized controlled trials with GLP-1RA-based therapy (16), nausea was reported in 19.3% of participants with active treatment versus 6.5% with placebo, and vomiting was reported in 7.6% of participants versus 2% with placebo. The odds ratios (vs. placebo treatment) for nausea and vomiting were similar for various compounds/preparations of GLP-1RA-based medications,

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Table 1. Summary of GLP-1RA-associated side effects and strategies to mitigate

Adverse event category	Causal relationship?	Incidence/prevalence	GLP-1Rs involved	Prevention possible?	Commentary/interpretation
Nausea, vomiting, diarrhea, constipation	Yes	High (15%–45%)	Area postrema, brainstem	Tolerance possible with slow dose escalation	Important reason for discontinuation of treatment
Acute pancreatitis	No	Low, not increased	No	Not necessary	Relationship suspected because of typical abdominal symptoms and serum lipase elevation
Cholelithiasis	Probable	+45%	Smooth muscles, autonomous nervous system	Cholecystectomy for symptomatic gallstones	Treatment as per standard of care
Any malignant neoplasm	No	Not increased	No	No	No residual risk
Medullary thyroid carcinoma	Yes	Very low	On proliferating C cells	Avoid GLP-1RA treatment in individuals at risk	At-risk status (personal/family history or MEN2 is a contraindication)
Follicular/papillary thyroid carcinoma	Probable	Low	On some (not all) follicular-derived cells	No established strategy available	Unclear if screening for thyroid nodules would be beneficial
Diabetic retinopathy	Yes	Low, depending on preexisting retinopathy	On β cells (pancreas, stimulating insulin secretion)	Treatment of proliferative retinopathy as per guidelines	Avoid aggressive glucose lowering in the presence of untreated proliferative retinopathy
Non-arteritic ischemic optic neuropathy	Unclear	Very low	Unclear	No established strategy available	May be related to rapid lowering of glucose concentrations
Suicidal ideation	Questionable	Very low	Unclear	No established strategy available	In contrast, prevention of depression has been reported with GLP-1RA use
Reduced muscle mass	Yes	High, but prevalence of functional impairments unknown	Hypothalamus, brainstem	Resistance training, protein-rich diet	Individuals at risk for sarcopenia need to be identified

while intended effect sizes (glycemic control and body weight reduction) varied widely (Table 2). More elaborate dose escalation regimens were associated with greater efficacy,

GI adverse events not infrequently lead to discontinuation of drug treatment, both in randomized clinical trials (16, 17) and in real-world practice (18, 19). In a systematic review of randomized clinical trials, 6.5% of those using a GLP-1RA discontinued it due to adverse events versus 3.6% of those on placebo (16), but these rates appear to be higher in observational studies where factors associated with discontinuation were an age of 65 years or older and GI adverse events with treatment (21). In the longer-term trials that reported individual adverse event categories associated with discontinuation of drug treatment, nausea was shown to be the leading cause of discontinuation, followed by vomiting and diarrhea, with much lower risks associated with constipation, abdominal discomfort, or pain (Table 3). It is possible that optimizing dose escalation schedules will improve tolerability, and this should be further explored in future studies (20). In a recent phase II trial with subcutaneous semaglutide, when doses were escalated relatively rapidly to 16 mg weekly, participants experienced additional weight loss, but at the expense of more adverse effects (21). However, it should be appreciated that a substantial proportion (>50%) of the participants did not report any GI adverse events, indicating that those individuals may be able to tolerate even higher doses. More individualized approaches to dose escalation may be needed to maximize the therapeutic potential for those who tolerate GLP-1RAs well, and to minimize the frequency and severity of adverse events in those who are more susceptible.

Does GIPR agonism improve GLP-1RA tolerance? Tirzepatide, a coagonist of GIPR and GLP-1R, is characterized by greater efficacy in both glucose lowering and weight loss than can be achieved with current selective GLP-1RAs (16), while having a comparable

adverse event profile. In animal experiments involving shrews (which are able to vomit), GLP-1RAs elicit frequent episodes of vomiting, while GIPRAs do not. Moreover, the GIPRA GIP-085 almost totally prevented vomiting induced by a long-acting GLP-1RA GLP-140 (22). In an exploratory clinical trial, a long-acting GIPRA tended to reduce GI adverse events in response to rapidly escalated liraglutide in healthy individuals (23). In the SURPASS-2 trial, tirzepatide at doses of 5, 10, and 15 mg/week were compared with 1 mg/week semaglutide, and the 5 mg/week tirzepatide dose was found to be only slightly more effective than semaglutide in reducing both HbA_{1c} (−2.01% vs. −1.86%) and body weight (−7.6 vs. −5.7 kg). Under these conditions, overall GI adverse events were, however, only slightly less prevalent with tirzepatide (40.0% vs. 43.0%), with minor differences in favor of tirzepatide for nausea (17.4% vs. 19.2%) and vomiting (5.7% vs. 8.1%), and, less so, diarrhea (13.2% vs. 13.7%) (24). In the systematic review of clinical trials mentioned above, tirzepatide conferred the greatest risk of vomiting, RR 13.23 [95% CI 4.85–36.09], whereas the risks for semaglutide (RR 4.21 [95% CI 3.58–4.95]) and orforglipron (RR 4.43 [95% CI 1.45–13.56]) were similar (15). Moreover, in a recent large cardiovascular outcomes trial (SURPASS-CVOT), numerically higher proportions of participants taking tirzepatide (15 mg weekly) reported nausea, vomiting, and diarrhea compared with those taking the selective GLP-1RA dulaglutide (1.5 mg weekly) (25). Although comparisons between tirzepatide and higher doses of dulaglutide (e.g., 4.5 mg) have yet to be done, these data argue against the concept that GIP coagonism can reduce the risk of GI adverse events. With the advent of dual and triple agonists stimulating additional receptors of gastro-entero-pancreatic peptide hormones with therapeutic potential, there is the possibility of altered adverse event profiles. Table 4 summarizes potential effects of combined stimulation of receptors for GIP, glucagon, amylin, and peptide YY on adverse events.

Table 2. Adverse GI effects of GLP-1RAs related to therapeutic effect sizes in people with T2D

Treatment Compound/ preparation/dose	Adverse events: odds ratio (95% CI) vs. placebo treatment			Intended therapeutic effects (mean, 95% CI; placebo-subtracted)	
	Nausea	Vomiting	Discontinuation due to adverse events	HbA _{1c} reduction (vs. baseline) (%)	Body weight reduction (vs. baseline) (kg)
Liraglutide 1.2 mg/day	2.6 (1.6–4.3)	1.2 (0.5–3.3)	2.6 (1.5–4.6)	–1.3 (1.2–1.4)	–1.6 (1.2–2.1)
Exenatide q.w. 2 mg/week	2.3 (1.1–4.9)	1.7 (0.5–5.9)	1.1 (0.4–2.9)	–0.7 (0.5–0.9)	–0.8 (0.3–1.3)
Dulaglutide 1.5 mg/week	6.9 (4.0–11.7)	21.7 (6.1–91.2)	1.0 (0.5–2.2)	–1.1 (0.9–1.2)	–1.7 (1.2–2.2)
Semaglutide s.c. 1 mg/week	4.5 (2.8–7.6)	4.6 (2.2–9.5)	4.9 (2.2–11.6)	–1.6 (1.4–1.7)	–4.1 (3.5–4.7))
Semaglutide oral 14 mg/day	3.8 (2.7–5.4)	4.1 (2.4–7.2)	3.5 (2.2–5.5)	–1.1 (1.1–1.2)	–3.0 (2.6–3.4)
Tirzepatide 15 mg/week	5.0 (2.5–10.2)	4.6 (1.7–11.4)	3.6 (1.8–8.7)	–1.8 (1.6–2.0)	–9.7 (8.6–0.8)

HbA_{1c}, hemoglobin A_{1c} or glycated hemoglobin; q.w., once weekly; s.c., subcutaneous. Data are from Kang et al. (16).

Assessment of GI symptoms. In the vast majority of trials, symptoms are evaluated by participant “self-report” that, while simple, has major limitations (26). Firstly, in the absence of a standardized questionnaire providing precise definitions of terms describing individual adverse effects, symptoms are likely to be perceived differently by participants. For example, uncomfortable fullness has the potential to be reported as nausea by one participant, but not another. Therefore, precise definitions, in terms understandable to laypeople, are required. Secondly, with self-reporting of symptoms there may be the expectation of adverse GI side effects (i.e., the nocebo effect). Thirdly, GI symptoms are common in healthy adults, with a greater frequency in individuals with diabetes even if they are not using a GLP-1RA, and these symptoms characteristically fluctuate (27). Therefore, changes in GI symptoms should also be quantified, rather than simply assessing their presence or absence. The ideal subject-reported outcome instrument would employ precise definitions for each symptom and their degree of severity, provide reliable inter-interviewer reproducibility, and be sensitive to the detection of changes in symptoms following initiation of the drug and any subsequent dose changes. In the assessment of treatment outcomes in functional GI disorders such as irritable bowel syndrome (28), the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) have mandated the use of validated questionnaires. We believe that it would be beneficial for a validated instrument to be developed for the evaluation of GI adverse effects in GLP-1RA trials. Table 3 and Supplemental Table 1 represent preliminary examples of the proposed content for such instruments. In the interim, it should be appreciated that several instruments have been used widely in the evaluation of symptoms associated with GI disorders, including the Bowel Disease Questionnaire (BDQ) (29), a comprehensive questionnaire with 71 precisely defined questions. Derived from the BDQ is the Diabetes Bowel Symptom Questionnaire, which also contains items specific for diabetes and its complications (30). Both of these questionnaires, are, however, time-consuming for the participant to complete. Abbreviated instruments include the patient assessment of upper GI symptom severity index (PAGI-SYM) (31), the diabetic gastroparesis symptom severity diary (32), the gastroparesis cardinal symptom index (GCSI) (31), and the Nepean Dyspepsia Index (33). We believe that future trials should adopt such instruments and not rely on participant self-reporting of GI symptoms.

Adverse consequences of motility effects of GLP-1RAs

In one study, the incidence of retained gastric contents in individuals using a GLP-1RA was 56%, compared with 19% for those not using GLP-1RAs (34), although notably there were more individuals with T2D and obesity in the group treated with GLP-1RAs. Supplemental Table 2 summarizes information relating to the risk for retained gastric contents and aspiration in association with upper GI endoscopy.

Three systematic reviews analyzing the risk of retained gastric contents causing premature termination of endoscopy have been published. Baig et al. (35) and Facciorusso et al. (36) reported an increased risk (odds ratios 4.5 and 5.6, respectively) for premature termination among individuals taking GLP-1RAs, while Singh et al. reported an even greater risk (odds ratio 13.9) (37). Importantly, none of these reviews identified an increased risk of aspiration pneumonia. However, it should be appreciated that this severe complication is rare and the risk is also less with endoscopy compared with surgical procedures that require general anesthesia (38). Population-based studies have reported mixed findings on the potential association between GLP-1RA use and aspiration pneumonia (39–44). Furthermore, a systematic review of randomized controlled trials and observational studies also failed to identify an increased risk of aspiration pneumonia in GLP-1RA users, although an increased risk of retained gastric contents was evident (45). In summary, GLP-1RA therapy is clearly associated with a substantially increased risk of retained gastric contents, but there is little evidence to suggest that this translates to an increased incidence of aspiration pneumonia.

Potential risks of retained gastric content and pulmonary aspiration have predictably raised the question as to whether GLP-1RA treatment should be discontinued or modified before procedures associated with such risk. Multi-society consensus guidelines have, in general, recommended an individualized approach toward the decision to withhold GLP-1RA therapy (46). For agents with a long elimination half-life (6, 7), typically used at more than 10 times higher than physiological concentrations, such periods probably would need to be much longer than a week. The maximum duration of any of the few studies in which a good technique has been used to quantify emptying (usually scintigraphy) is 16 weeks, and while the magnitude of the delay in emptying at that time point was not as marked as at 5 weeks, it was substantial in some cases (47). Other strategies have been suggested to reduce the risk of retained gastric

Table 3. GI symptoms and GLP-1RA discontinuation

Symptom	Definition	Can be confused with	Relation to GLP-1RA therapy	Relation to discontinuing GLP-1RA therapy
Eructation/belching	Bringing up gas through the mouth, if repetitive often from “air swallowing”	n.a.	Not often mentioned/unclear	Rare
Gastro-esophageal acid reflux	Gastric acid reaching and sensed in the esophagus	Cardialgia	May be a consequence of delayed gastric emptying	Rare
Feeling full after eating/early satiety	Gastric content is sensed to have reached a point where one does not want to eat any more food	Bloating (gastric/intestinal distension caused by intraluminal gas accumulation)	GLP-1RA therapy increases the feeling of fullness, possibly related to delayed gastric emptying, perhaps also through a direct influence on the CNS	Rare
Loss of appetite	Sensing a reduced drive to start eating, in particular large amounts of food	Nausea	GLP-1RA therapy typically leads to loss of appetite (as part of the mechanism of action leading to reduced food intake and weight loss), most likely by a direct interaction of GLP-1RAs with the brain	Probably not; should be considered a beneficial sensation necessary to elicit body weight reduction
Nausea	Unpleasant feeling attributed to the stomach, as if one may have to vomit if it gets worse (like with motion or sea sickness)	Loss of appetite (e.g., to eat an amount of food that one would previously have considered appropriate)	Nausea is often reported in people taking GLP-1RAs	Nausea is frequently quoted as the reason to discontinue therapy in people taking GLP-1RAs
Vomiting	Sudden, involuntary retrograde emptying of gastric contents through the esophagus, throat and oral cavity, usually accompanied by vegetative symptoms (sweating, pallor, accelerated or slowed heart rate, etc.)	–	Vomiting is often reported in people taking GLP-1RAs	Vomiting is frequently quoted as the reason to discontinue therapy in people taking GLP-1RAs
Meteorism/flatulence	Sensation of too much gas in the lumen (cavity) of the GI tract, or released through the anal sphincter	Fullness refers more to the amount of liquid or solid content sensed in the stomach	Meteorism is rarely mentioned as a symptom prompted by GLP-1RA therapy	Rare
Diarrhea	Frequent discharge of abnormally liquid feces or increased stool frequency (>3/day)	–	Diarrhea is often mentioned as a symptom prompted by GLP-1RA therapy	Diarrhea is frequently quoted as the reason to discontinue therapy in people taking GLP-1RAs
Constipation	Infrequent (<3 times/week) or difficult (requires strain) or hard, dry feces in small pieces	–	Constipation is sometimes mentioned as a symptom prompted by GLP-1RA therapy	Constipation is relatively rarely quoted as the reason to discontinue therapy in people taking GLP-1RAs
Abdominal pain/discomfort	Pain located to the abdomen (epigastrium or elsewhere)	–	Abdominal pain is sometimes mentioned as a symptom prompted by GLP-1RA therapy	Abdominal discomfort or pain are relatively rarely quoted as the reason to discontinue therapy in people taking GLP-1RAs

GI symptom definitions and potential for confusion as reported by people with T2D or clinical obesity treated with GLP-1RAs and the dual GIPR/GLP-1R coagonist tirzepatide.

contents. First, it has been observed that individuals on GLP-1RAs undergoing both endoscopy and colonoscopy had a much lower risk of retained gastric contents, suggesting that a prolonged period on a clear liquid diet may reduce this risk (48). Second, intravenous erythromycin (200 mg), which has been shown to abolish the slowing of gastric emptying by acute intravenous GLP-1 infusion (49), may represent a treatment for individuals identified at having retained gastric content via ultrasonography (50).

Central and peripheral mechanisms underlying GI symptoms. Nausea, vomiting, and diarrhea in association with GLP-1RA treatment are often referred to as GI adverse events, implying that they predominantly represent the expression of an altered GI functional state. Indeed, GLP-1R agonism slows gastric emptying (51, 52) and suppresses small intestinal motility (53). However, an alternative explanation, albeit not mutually exclusive, is direct interaction of GLP-1RAs with GLP-1R in brain regions such as the brainstem

(area postrema, nucleus tractus solitarii), which are not protected by the blood-brain barrier, and are typically involved in medication-induced nausea (chemosensitive area) (54–56). Peripheral GLP-1/GLP-1RAs may also interact with the CNS indirectly by GLP-1R expressed on vagal afferent fibers, signaling via nodose ganglia (57) to the nucleus tractus solitarii within the brainstem. The nucleus tractus solitarii projects to multiple regions of the CNS involved in the regulation of appetite, including the hypothalamus, ventral tegmental area, lateral parabrachial nucleus, and nucleus accumbens (58, 59). Preclinical studies also indicate that tanycytes, specialized glial cells within the CNS, may facilitate the transportation of peripheral GLP-1RAs, such as semaglutide, into the CNS, bypassing the blood-brain barrier to access appetite-regulating hypothalamic regions such as the arcuate nucleus (60, 61). Importantly, there are central pathways that result in a reduction in energy intake without the induction of nausea (62). The mechanisms

Table 4. Mechanisms underlying GI side effects

Gastro-entero-pancreatic peptide hormone	Mechanisms suggesting therapeutic potential	Cardiovascular	GI	CNS/autonomous nervous system	Clinical implications
GLP-1	Insulin ↑ (129) Glucagon ↓ (129) Appetite ↓ (3) Energy intake ↓ (3)	Heart rate ↑ (130)	Gastric emptying ↓ (131), intestinal motility ↓ (53), diarrhea, constipation, abdominal discomfort/pain	Nausea (16, 17), vomiting (16, 17), diarrhea (?) (16, 17)	Thyroid C cell proliferation in rodents (71), thyroid carcinoma (78), limited GI tolerability, potential risk for (medullary) thyroid carcinoma
GIP	Insulin ↑ (129), energy intake ↓ (evidence only for rodents) (132)	Heart rate ↑ (133), blood pressure ↑ (133)	None described	Antiemetic effects in animals (22)	Potential improvement in GI tolerability in combination with GLP-1RA
Glucagon	Energy expenditure ↑ (134, 135), appetite ↓ (135), energy intake ↓	Heart rate ↑ (136), blood pressure ↑ (137), myocardial oxygen consumption ↑ (136)	Gastric peristalsis ↓ (138), intestinal motility ↓↓ (139)	Nausea	Potential worsening of GI tolerability in combination with GLP-1RA
Amylin	Appetite ↓ (140, 141), energy intake ↓ (140, 141)	Gastric emptying ↓ (142, 143)	Nausea, constipation with cagrilintide (144) and pramlintide (145)	Calcium ↓, parathyroid hormone ↑ (stimulation of calcitonin receptor) (146, 147)	Potential worsening of GI tolerability in combination with GLP-1RA, hypocalcemia (?)
Peptide YY	Preserved pancreatic islet function after gastric bypass (148, 149)	No information available	Gastric emptying ↓ (150), intestinal motility/ peristalsis ↓ (151)	Nausea, vomiting with PYY analog Y14 (152)	Potential worsening of GI tolerability in combination with GLP-1RA

Potential mechanisms leading to adverse events when stimulating receptors of gastro-entero-pancreatic peptide hormones with therapeutic potential for the treatment of T2D and clinical obesity (as part of combinations or dual therapy together with GLP-1RA) and their consequences.

underlying the effect of GLP-1RAs on GI motility and symptoms like nausea and vomiting are summarized in Figure 1.

Biliary/pancreatic complications. In a systematic review of 55 double-blinded, placebo-controlled randomized clinical trials, GLP-1RA treatment was associated with an increased risk of cholelithiasis compared with placebo (RR 1.46, 95% CI 1.09–1.97) but not cholecystitis, cholangitis, or pancreatitis (63). This contrasts with case reports of acute pancreatitis with the first approved GLP-1RA, exenatide b.i.d. (64). The case reports of pancreatitis prompted searches of adverse event-reporting databases (65), which indicated a substantially higher risk for acute pancreatitis with GLP-1RA treatment. These searches have been reproduced with almost identical results (66), leading to the definition of acute pancreatitis as an “adverse event of special interest” in clinical trials of GLP-1RAs. The first trial reporting detailed results on adjudicated cases of suspected acute pancreatitis was the LEADER trial comparing liraglutide and placebo in patients with T2D (18 cases in 4668 participants randomized to liraglutide treatment vs. 23 in 4672 with placebo treatment) (67). Because of the suspected association with acute pancreatitis, amylase and lipase were measured throughout this trial (and in other clinical studies). Surprisingly, liraglutide treatment elevated serum amylase and lipase activity in the majority of participants (68), but such elevations did not predict clinical acute pancreatitis. Subsequent meta-analyses of cardiovascular outcomes trials with GLP-1RAs have clearly excluded a causal role for GLP-1RAs in acute pancreatitis (63, 69, 70), while therapy with inhibitors of dipeptidyl peptidase-4 may lead to a minor elevation of this risk (69). In retrospect, the suspicion that GLP-1RAs provoke acute pancreatitis can be traced to the diagnostic criteria used for acute pancreatitis (two out of the following three features: severe upper abdominal pain radiating into the back, elevations in amylase and/or lipase, and typical results of imaging procedures) and that

GLP-1RA therapy induces abdominal symptoms in a large number of patients, as well as elevations in amylase and/or lipase. Careful adjudication of suspected cases was necessary to scrutinize details of the symptomatic presentation, the degree of elevation on pancreatic enzymes, and the diagnostic specificity of imaging data (68). Alarming reports published in 2011 (65) led to widely discussed safety concerns, which transiently limited the use of GLP-1RAs for the treatment of T2D. These events attest to the potential of adverse event-reporting databases for bias when a serious concern has achieved prominence. The quest for robust pharmacovigilance for suspected adverse events with relatively novel drugs remains an important issue, and benefits and risks must be weighed when available evidence is limited.

Thyroid carcinomas

Medullary thyroid carcinoma became a concern because of alerts from animal experiments showing increased calcitonin secretion and growth (hyperplasia, adenomas, and carcinomas) of C cells in rodents following treatment with the long-acting GLP-1RA liraglutide (71). The presence of GLP-1R in the rodent thyroid gland and on rodent C cells had been shown earlier (72, 73). In contrast, in primate and human thyroids, GLP-1R has either not been detected (74) or only found in small fractions of healthy C cells (75), and treatment with liraglutide does not stimulate calcitonin secretion (76). On the other hand, most human medullary thyroid carcinomas and hyperplastic C cells express GLP-1R (75, 77) (Figure 2). Accordingly, a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) represents a contraindication to the use of GLP-1RAs and are exclusion criteria for participation in clinical trials with GLP-1RAs. Recent health insurance data from France are indicative of an elevated risk of medullary thyroid carcinoma in individuals treated with

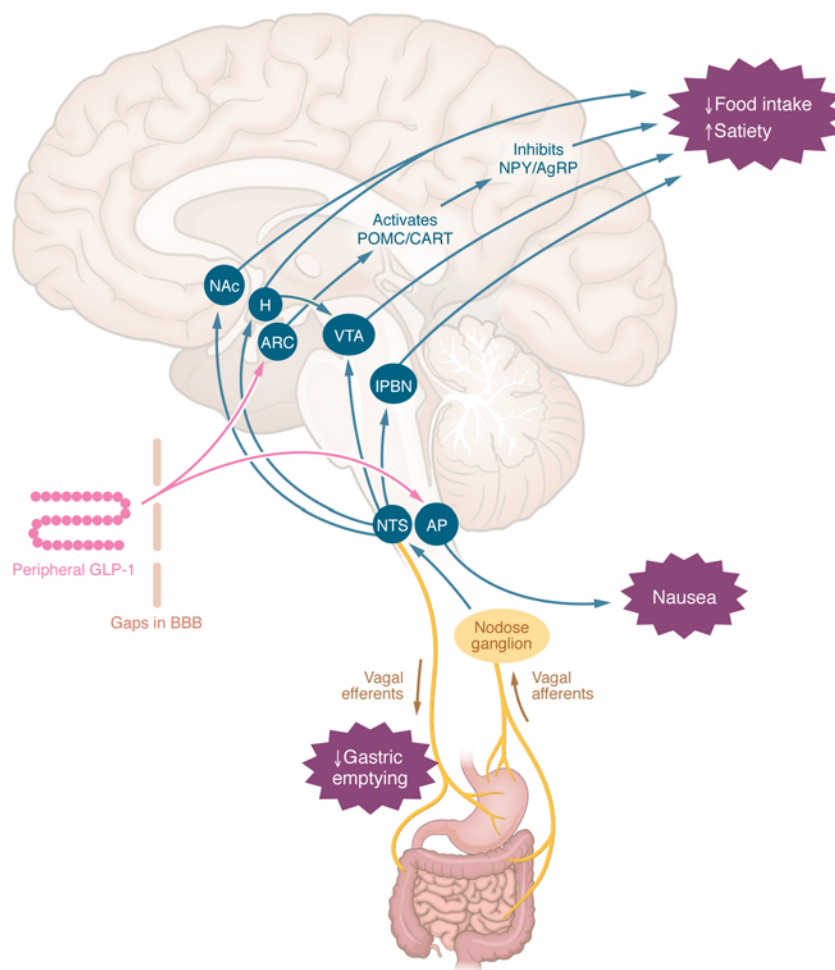


Figure 1. Central mechanisms by which peripheral GLP-1RAs may reduce appetite or induce nausea. Peripheral GLP-1 or GLP-1RAs may interact with appetite-regulating regions of the brain via gaps in the blood-brain barrier (27), via tanycyte uptake (32), or indirectly via the nodose ganglia (29). The effects to slow gastric emptying, induce nausea, and reduce energy intake are independent (34). AgRP, agouti-related peptide; AP, area postrema; ARC, arcuate nucleus; BBB, blood-brain barrier; CART, cocaine- and amphetamine-regulated transcript; H, hypothalamus; IPBN, lateral parabrachial nucleus; NAc, nucleus accumbens; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; POMC, proopiomelanocortin; VTA, ventral tegmental area.

GLP-1RAs versus other glucose-lowering agents (35 cases, hazard ratio [HR] 1.78 [95% CI 1.04–3.05]) (78). A meta-analysis of cardiovascular outcomes trials indicates that spontaneous medullary thyroid carcinomas have been diagnosed in patients receiving GLP-1RA (6 with active vs. 2 with placebo treatment) (79). These findings reinforce the “at-risk” status as a contraindication to GLP-1RA treatment, but given their low incidence, screening measures to facilitate early diagnosis of medullary thyroid carcinomas in GLP-1RA-treated individuals have not been established.

Other histological types of thyroid carcinoma have not been examined as closely because less biological evidence exists for a convincing mechanism of action. GLP-1R has been detected in healthy thyroid cells other than C cells, as well as in some papillary thyroid cancers (75). A case-control study of health insurance data from France indicated an increased risk for thyroid carcinoma with GLP-1RA treatment, with an HR of 1.58 (95% CI 1.27–1.95) (78). In contrast, a Scandinavian cohort study using nationwide cancer registries found no association between GLP-1RA use and thyroid cancer (HR 0.93, 95% CI 0.66–1.31) (80). Further information is

needed before definitive recommendations can be made regarding GLP-1RA treatment in individuals with a family history of other thyroid cancers.

Retinopathy and other vision-related complications

Diabetic retinopathy. Subcutaneous semaglutide treatment led to an increased number of retinopathy complications in the SUSTAIN-6 cardiovascular outcomes trial (81). “Retinopathy complications” were defined as a composite of vitreous hemorrhage, onset of diabetes-related blindness, and a need for treatment with intravitreal injection or retinal photocoagulation, all serious clinical events. In this study, baseline retinopathy status had, perhaps surprisingly, not been assessed, and there were not any systematic follow-up examinations during the trial. Semaglutide predictably resulted in greater reductions in both plasma glucose and HbA_{1c} concentrations than standard-of-care treatment. The observations in SUSTAIN-6 are predictable, given that intensified versus conventional insulin therapy is well known to have the

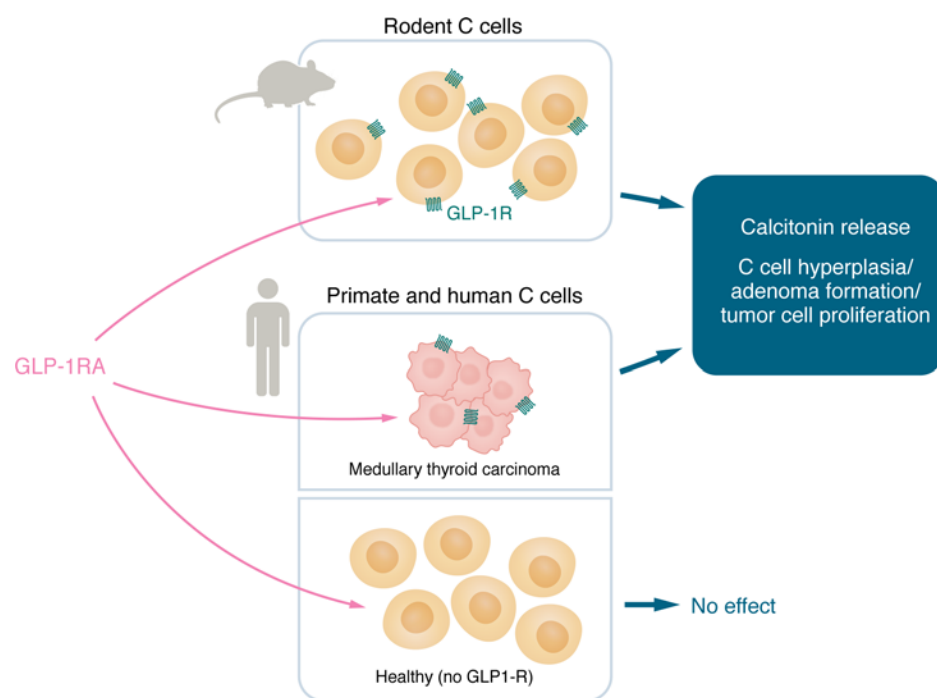


Figure 2. GLP-1Rs and thyroid C cells.

GLP-1Rs are typically expressed in rodent C cells (83). Some GLP-1Rs are expressed in medullary thyroid cancer (85), but there are almost no GLP-1Rs in healthy human/primary C cells (84). Accordingly, there may be an increased risk of medullary thyroid cancer with GLP-1RA use in susceptible individuals, but this may not be the case for healthy individuals.

capacity to precipitate initial worsening of retinopathy in patients with T2D with advanced preexisting retinopathy, as shown in the Diabetes Control and Complications Trial (82). However, in the longer term, retinopathy progression is slowed substantially with the improved glycemic control resulting from intensified insulin treatment (82) (Figure 3). Accordingly, a retrospective analysis of SUSTAIN-6 examined the role of preexisting advanced retinopathy and the induction of rapid reductions in plasma glucose and HbA_{1c} and found retinopathy complications mainly in those with preproliferative or proliferative retinopathy at baseline who experienced a large reduction in HbA_{1c} within 16 weeks after initiation of semaglutide (83). In SUSTAIN 1–5 and SUSTAIN 7, studies in which preexisting diabetic retinopathy and maculopathy were excluded, the rates of retinopathy were comparable across treatment groups (84). The same phenomenon was evident in those receiving other glucose-lowering medications (such as insulin or SGLT-2 inhibitors) as part of the standard of care (82, 85). A prospective trial focusing on the effects of semaglutide on retinopathy progression and complications (FOCUS) is ongoing (ClinicalTrials.gov NCT03811561; reporting in 2027) to further characterize risks and benefits associated with semaglutide treatment in T2D.

Non-arteritic anterior ischemic optic neuropathy. Non-arteritic anterior ischemic optic neuropathy (NAION) is a potential, but rare cause of blindness among adults (86). The pathophysiology of this condition is incompletely understood but thought to be related to hypoperfusion of the optic nerve head leading to edema and infarction of optic nerve fibers (87, 88). Hathaway et al. reported in a cohort study ($n = 16,827$) that there was a higher risk of NAION in individuals prescribed semaglutide (HR 4.28) (89). Cai et al. subsequently confirmed this association in a large multicenter database study of 37.1 million adults, but the incidence was low at 14.5 per 100,000 person-years among semaglutide users, and there was only a modest increase in risk attributable to semaglutide (90). Grausland et al.

in a 5-year longitudinal cohort study found a stronger association, reporting that semaglutide exposure more than doubled the risk of NAION (91). Fung et al. specifically examined those older than 65 years with T2D and also found an association between semaglutide and NAION (HR 1.39, 95% CI 1.13–1.72) (92). None of these studies have been able to establish causality, and complicated T2D and hypertension are known risk factors for NAION (93). The association may, therefore, reflect the higher presence of risk factors in semaglutide users rather than an effect of semaglutide. Furthermore, some studies have not found any increase in the risk of NAION in individuals using semaglutide or other GLP-1RAs (94, 95). Dedicated, prospective studies are required to confirm or refute this association, to clarify causality, and to determine whether there is a class effect with all GLP-1RAs. The mechanism(s) by which GLP-1RAs would cause NAION is also unclear, particularly as GLP-1RAs are associated with neuroprotective properties and reductions in ischemic risk (96), but it has been hypothesized to be related, like the exacerbation of retinopathy, to rapid improvements in glycemic control (Figure 3).

Potential psychiatric complications GLP-1R agonism

Chronic diseases, including diabetes and obesity, are risk factors for depression and suicidal ideation (97). Furthermore, treatment of T2D and obesity with metabolic surgery, which results in increased GLP-1 secretion (98), has been associated with an increased risk of suicide and self-harm (99), hinting to a potential causal relationship. Along those lines, Kornelius et al. reported a three-fold higher risk of major depression, and a doubled risk for anxiety and suicidal behavior in a large ($n = 11,683,623$) retrospective study of GLP-1RA users utilizing the TrinetX database (100). However, another systematic review by Chen et al. (101) found the opposite; GLP-1RA use was associated with a reduction in depression, suggesting that GLP-1RA could potentially be considered an antidepressant therapy. In two

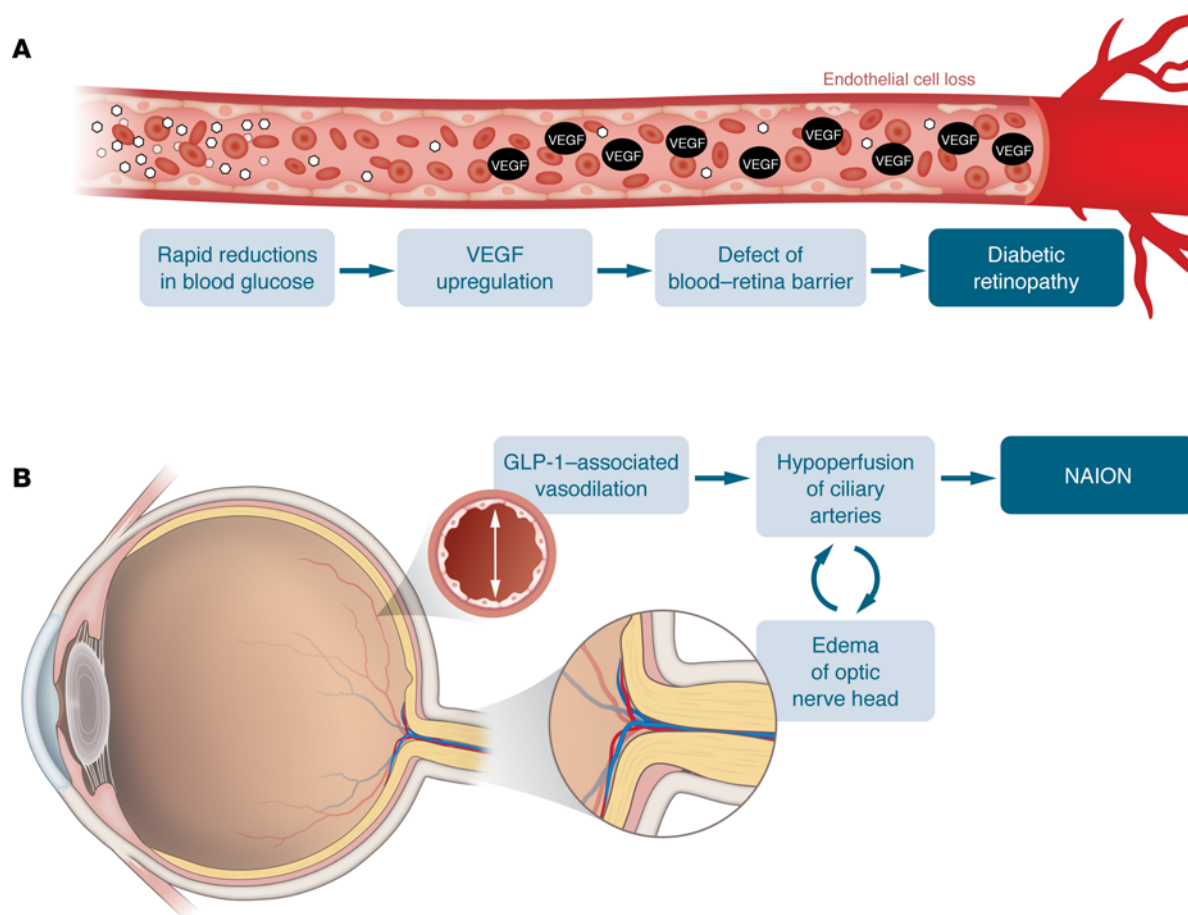


Figure 3. Hypothesized mechanisms for ocular complications associated with GLP-1RA therapy. In the eye, rapid reductions in glycemia due to GLP-1RA use may lead to the progression of diabetic retinopathy (A) or NAION (B). Figure based on Chou et al. (95) and Abdeen and le Roux (98).

recent systematic reviews and meta-analyses, no link between GLP-1RA use (for obesity and/or T2D) and increased suicidal ideation was identified, but there was substantial heterogeneity between studies, particularly regarding the definition of suicidal ideation (102, 103). Furthermore, many of these were pharmacovigilance studies, and the outcome of suicidal ideation was inconsistently documented (104). The best designed study to date is a systematic review of 80 randomized clinical trials involving 107,860 participants, which found no association with GLP-1RA treatment and serious psychiatric adverse effects: major depression, suicide, or psychosis (105). Furthermore, GLP-1RA therapy was associated with an improvement in mental health-related quality of life (105). Accordingly, recent systematic reviews have provided substantial reassurance regarding the psychiatric safety profile of GLP-1RAs.

GLP-1 and adverse effects in specific populations

Younger individuals. In a meta-analysis of 5 studies evaluating GLP-1RAs in younger individuals with T2D, there was an increased incidence of adverse effects, but withdrawal rates remained low (106). Children and adolescents with obesity are at an increased risk of disordered eating behaviors or eating disorders (107). A small, open-label retrospective cohort study reported reductions in Binge Eating Scale scores for individuals managed with semaglutide (108), but larger trials are needed.

Pregnancy. In animal studies, GLP-1RA exposure was associated with reduced fetal growth, delayed skeletal ossification, and reductions in maternal weight gain and food consumption (109). Therefore, it is not recommended that individuals who are planning pregnancy or currently pregnant use GLP-1RAs. In one relatively small study ($n = 168$), GLP-1RA use was not associated with an increased risk of pregnancy loss or birth defects in humans (110). Larger studies are needed to confirm this, although these would be challenging or infeasible to conduct.

Advanced hepatic disease/hepatic functional impairment. In a population-based study of 467 matched pairs of GLP-1RA users and non-users with T2D and liver cirrhosis, GLP-1RA use was associated with lower risks of death, cardiovascular events, decompensated cirrhosis, hepatic encephalopathy, and liver failure (101). In a cohort study of individuals with T2D and metabolic-associated fatty liver cirrhosis (459 GLP-1RA users), GLP-1RA therapy was associated with reduced risks of hepatic decompensation, portal hypertension, hepatocellular carcinoma, and liver transplantation (111). While these observations are supportive of GLP-1RA use in liver cirrhosis, prospective studies are needed to confirm this. The odds ratio for adverse GI events (e.g., nausea, vomiting, diarrhea, constipation) in individuals with metabolic dysfunction-associated steatotic liver disease using GLP-1RA versus placebo/other diabetes therapy was 4.83 (95% CI 3.36–6.95) (112), which is comparable to the results

summarized in Table 2. There was no increased rate of adverse effects leading to discontinuation of treatment in GLP-1RA users compared with non-GLP-1RA users (112).

Advanced renal disease/severe renal functional impairment. GI adverse effects are more common in individuals with end-stage renal disease using GLP-1RAs (113), as is hypoglycemia in those using concomitant insulin (114). These adverse effects must be weighed against the potential benefits of GLP-1RAs. In a large cohort study of individuals with T2D and stage 5 chronic kidney disease ($n = 27,279$), GLP-1RA use was associated with lower all-cause mortality (HR 0.79; 95% CI 0.63–0.98) and reduced risks of sepsis and infection-related mortality compared with those using dipeptidyl peptidase-4 inhibitors (115). In small studies, GLP-1RAs resulted in modest weight loss in end-stage renal disease and renal transplant recipients (113). Large-scale prospective studies for GLP-1RA use in end-stage renal disease are awaited.

Older individuals. A claims-based database study indicated that the rate of discontinuation of GLP-1RAs in older individuals was high. After 24 months of follow-up, 68.2% of individuals less than 65 years old had discontinued GLP-1RAs, with the proportion rising to 75.3% for those 65–74 years old and 82.6% for those 75 or older (116). Possible reasons for the high rates of discontinuation include cost, variable efficacy, patient preferences, and/or GI adverse effects. However, in a study of weekly dulaglutide, there was a comparable incidence of GI adverse effects in those above and below 65 years of age (117). Another potential risk of relevance to older individuals is bone loss, which was observed with semaglutide (118), although combined treatment with an exercise program may potentially mitigate this risk (119). These “age-related” risks also must be balanced against the cardiovascular risk reduction associated with GLP-1RA use. In a systematic review, three-component Major Adverse Cardiovascular Events (3-p MACE) was reduced, with an HR of 0.86 (95% CI 0.80–0.92) for those over 65 years old, and there was an even more pronounced effect in those over age 75 (HR 0.75, 95% CI 0.61–0.92) (120). Older individuals are also at risk of sarcopenia, as discussed below.

Reduced muscle mass. With weight loss, there is also loss of fat-free mass, which raises concern for the development of sarcopenia. The proportion of total weight loss that was fat-free mass was 39% with semaglutide and 25% with tirzepatide (121). However, there are limitations inherent with this method as a surrogate to evaluating loss of muscle mass (few studies specifically measure muscle mass). For example, with weight reduction, liver mass may decrease, and this would be observed as a reduction in fat-free mass. It is also not known if this loss of fat-free mass is associated with reduced physical functioning. In contrast, a recent study indicated that muscle quality may be improved with tirzepatide therapy, as there is less intramuscular fat infiltration (122). Furthermore, the reduced mechanical load resulting from GLP-1RA-associated weight loss may improve

aspects of physical function, as shown in the STEP 1–4 trials involving semaglutide (123). However, to date there are no studies assessing functional consequences, such as timed sit-to-stand tests. Due to reductions in appetite associated with GLP-1RA therapy, there is also the potential for consumption of dietary protein to be inadequate. Use of protein supplements has not yet been adequately evaluated in individuals on GLP-1RAs, but there is evidence that an exercise program may increase the proportion of fat mass loss, as opposed to loss of fat-free mass (124).

Summary and outlook

A summary of the relative risk of adverse events associated with GLP-1RAs is presented in Table 1. Given the role of GLP-1RAs and other incretin-based medications widely used for the treatment of T2D and obesity, surprisingly little research has been directed at a comprehensive assessment of even the most frequent GI adverse events (125). Based on this suboptimal documentation, potential differences in the risks for such adverse events between compounds/preparations are often not appreciated. Given the vast number of incretin-based medications under development, mainly aiming at higher efficacy in body weight reduction, one may overlook that adherence to, and persistence of, therapy with GLP-1RAs in real-world studies is relatively low (18, 126). Improved methods to assess the adverse events associated with GLP-1RA medications should be introduced. Pharmacovigilance databases have, not surprisingly, been prone to reporting bias, once case reports have alerted the community to potentially important adverse events. For clinical trials, particularly during early development phases where safety and tolerability are the main focus, better tools should facilitate the identification of optimized dose-escalation regimens. Given the large and increasing number of currently developed novel agents within the class of GLP-1RAs (127, 128), it can be anticipated that there will be increasing competition to achieve better tolerability and safety.

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