gastroenterology insights

Review

GLP-1RA Essentials in Gastroenterology: Side Effect Management, Precautions for Endoscopy and Applications for Gastrointestinal Disease Treatment

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Abstract: Amidst the obesity and type II diabetes mellitus (T2DM) epidemics, glucagon-like peptide-1 receptor agonists (GLP-1RAs) stand out as a promising therapeutic ally, achieving notable success in glycemic control and weight management. While GLP-1RAs' positive clinical outcomes are commendable, they introduce significant gastrointestinal (GI) challenges, emphasizing the pivotal role of gastroenterologists in understanding and managing these implications. Physicians should be vigilant of potential complications if endoscopy is indicated and considered. A protocol coined "The Three E's: Education, Escalation, and Effective Management" is essential as the first defense against GLP-1RA-induced dyspepsia, necessitating routine GI consultations. Awareness and intervention of potential aspiration due to GLP-1RA-induced gastroparesis are vital in clinical management. Furthermore, the evolving recognition of GLP-1RAs' beneficial effects on non-alcoholic steatohepatitis (NASH) suggests gastroenterologists will increasingly prescribe them. Thus, a comprehensive understanding of pharmacological properties and potential GI complications, including the undetermined cancer risk landscape, becomes paramount. This review accentuates the nuances of GLP-1RA therapy from a gastroenterological lens, juxtaposing the therapeutic potential, manageable side effects, and circumstantial challenges, ensuring that GI specialists remain at the forefront of holistic care in obesity and T2DM management.

Keywords: GLP-1RA; gastrointestinal side effects; weight control; T2DM; treatment approach; endoscopy; overweight and obesity; digestive health; drug therapy; NASH

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1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) are synthetic hormones significant in managing T2DM and obesity, offering marked reductions in blood sugar and body weight with a minimal risk of hypoglycemia. As these drugs gain popularity in the U.S. for their "shortcut to fitness" appeal, gastroenterologists must grasp their gastrointestinal effects and broader implications. Prescribing physicians must be well informed about their use, action, dosing, side effects, and management of complications to safely guide patients who are attracted to this weight loss trend. Moreover, given the wide-reaching effects of GLP-1-RAs due to the prevalence of receptors on various organs, they can contribute to weight reduction and increased insulin sensitivity. Still, they may also cause unintended side effects, including nausea and potential undetermined cancer risks. This review provides gastroenterologists with essential insights for managing these effects and ensuring top-tier patient care.

2. Background

GLP-1 is an incretin hormone—a gut peptide secreted following the consumption of nutrients and stimulates insulin secretion in response to hyperglycemia [1]. In patients with T2DM, this incretin effect is markedly reduced; hence, the role that GLP-1RAs play in managing patients with significant insulin resistance is critical. The GLP-1 molecule is secreted as a component of proglucagon from L cells in the distal ileum and colon; the proglucagon is proteolytically cleaved via the action of various prohormone convertase enzymes to form two active peptides, GLP-1 (7,26)-NH2, the most common form, and GLP-1 (7-37) [2,3]. The half-life of GLP-1 is relatively short, reported as approximately two minutes due to the degradative action of a serine aminopeptidase known as dipeptidyl-peptidase-4 (DPP-4) as well as its rapid clearance through the kidneys, a consequence of the GLP-1 molecule's low molecular weight. For this reason, most GLP-1 analogs have been designed to resist the degradative action of DPP-4, specifically: exenatide, liraglutide, and semaglutide [3].

DPP-4 is the subject of several targeted pharmaceutical therapies, known as DPP-4 inhibitors, to prolong the duration of the effect of GLP-1-RAs [3]. The FDA acknowledges several medications in this class, including sitagliptin, saxagliptin, linagliptin, and alogliptin. These medicines are often available as single-ingredient formulations or combined with other diabetes therapies, such as metformin [4]. Initially described as a T-cell surface marker, DPP-4 has been found to exist in a soluble form that persists throughout the gut, liver, lungs, and kidney, as well as peripheral blood, urine, and other body fluids [4].

The GLP-1 receptor exists within multiple organ systems. On the pancreas, activation of GLP-1 receptors induces insulin release while suppressing glucagon; these glucose-dependent responses are significantly associated with low risks for hypoglycemia. Other systems that house GLP-1 receptors include the central nervous system (CNS) and gastrointestinal (GI) tract; stimulation of receptors in these regions produces effects involving reduced appetite and decelerated gastric emptying, resulting in slower glucose absorption [5]. Within the CNS, the hindbrain contains GLP-1-Rs targeted by endogenous and exogenous GLP-1 and analogs to control food intake. Experiments that involved direct injection of GLP-1 into the hindbrain produced acutely reduced food intake, hunger, and cravings and inhibited gastric emptying [6].

Building upon the foundational understanding of GLP-1, its rapid degradation by DPP-4, and the consequential design of resistant GLP-1 analogs and DPP-4 inhibitors, a nuanced exploration into the various GLP-1 receptor agonists (GLP-1RAs) available is critical. Refer to Table 1, which offers a comprehensive overview of several notable GLP-1RAs—highlighting key information regarding their approval, dosing, mechanism of action, clinical studies, and utilization in diverse populations—thereby establishing a thorough context for the ensuing discussion on their detailed applications, considerations, and alternative therapeutic approaches.

Table 1. Overview of GLP-1 agonists: key information, clinical studies, and utilization in various populations.

Drug Name	Approval Date & Use(s)	Dosing and Administration	Key Precautions and Side Effects	Clinical and Post-Marketing	Use in Populations and Conclusion
Albiglutide (Tanzeum/Eperzan) [7,8]	- 2014. - Improves glycemic control in adults with T2DM as an adjunct to diet and exercise. - GlaxoSmithKline (GSK) has discontinued the manufacture and distribution of Eperzan worldwide since July 2018.	- Weekly administration; any time of day; with or without meals. - Starting dose: 30 mg; can increase to 50 mg. - If missed, administer within 3 days.	- Not recommended as first-line therapy or for those with pancreatitis history. - Serious hypersensitivity, thyroid C-cell tumors, hypoglycemia, and renal impairment. - Side effects: URTI, diarrhea, nausea, and injection-site reaction.	- No evidence of macrovascular risk reduction. - Reported adverse reactions: respiratory infections, diarrhea, nausea, injection site reactions, cough, back pain, arthralgia, sinusitis, and influenza.	- Contraindicated in individuals with medullary thyroid carcinoma or MEN syndrome type 2. - Weigh benefits against risks in pregnancy. - Nursing mothers should discontinue nursing or the drug. - No dosage adjustment for renal impairment; monitoring advised.

Table 1. *Cont.*

Drug Name	Approval Date & Use(s)	Dosing and Administration	Key Precautions and Side Effects	Clinical and Post-Marketing	Use in Populations and Conclusion
Dulaglutide (Trulicity) [9]	- 2014. - Adjunct for glycemic control in adults with T2DM. - Reduces risk of major adverse cardiovascular events in adults with T2DM and cardiovascular disease or risk factors.	- Initiate at 0.75 mg subcutaneously once weekly. - May increase to 1.5 mg, 3 mg, and up to 4.5 mg once weekly with at least 4 weeks between dose increases. - If missed, administer if at least 3 days until the next dose. - Can be taken any time of day, with or without food.	- Not for patients with pancreatitis history or severe gastrointestinal disease. - Contraindicated with medullary thyroid carcinoma or MEN syndrome type 2 history and serious drug hypersensitivity. - Side effects: nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.	- Pancreatitis, hypoglycemia with insulin secretagogues or insulin, serious hypersensitivity, acute kidney injury, and gastrointestinal reactions reported. - Diabetic retinopathy complications seen in cardiovascular outcomes trial.	- Use in pregnancy only if the benefit outweighs fetal risk. - May delay gastric emptying, affecting oral medication absorption.
Exenatide (Byetta/Bydureon) [10]	- 2005. - Improves glycemic control in adults with T2DM as an adjunct to diet and exercise.	- Inject subcutaneously within 60 min before morning and evening meals (or two main meals; at least 6 h apart). - Starting dose: 5 mcg twice daily. - Increase to 10 mcg twice daily after 1 month based on response.	- Not a substitute for insulin; avoid in type 1 diabetes or diabetic ketoacidosis. - Not recommended with insulin. - Not for patients with pancreatitis history or severe GI disease. - Possible side effects: nausea, hypoglycemia, vomiting, diarrhea, jitteriness, dizziness, and headache.	- No established macrovascular risk reduction. - Reports of pancreatitis, hypoglycemia with sulfonylureas, renal issues, hypersensitivity, and increased INR with warfarin.	- Use with caution in moderate renal failure, renal transplantation, and severe GI disease. - Weigh benefits against risks in pregnancy and nursing mothers.
Liraglutide (Victoza, Saxenda) [11,12]	- **Victoza** (2010): Improves glycemic control in adults with T2DM; reduces cardiovascular event risk.	- **Victoza**: 0.6 mg daily, increasing to 1.2 mg and possibly 1.8 mg; once daily, at any time, without regard to meals.	- **Victoza**: Not for type 1 diabetes or diabetic ketoacidosis; contraindications include medullary thyroid carcinoma, MEN syndrome type 2, and serious hypersensitivity. Common side effects: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, and constipation.	- **Victoza**: Risks include thyroid C-cell tumors, pancreatitis, hypoglycemia with insulin, renal impairment, hypersensitivity, and gallbladder disease. - Increased risk of worsening diabetic retinopathy	- **Victoza**: No renal dose adjustment; consider risks in pregnancy; may delay gastric emptying affecting oral medication absorption.

Table 1. *Cont.*

Drug Name	Approval Date & Use(s)	Dosing and Administration	Key Precautions and Side Effects	Clinical and Post-Marketing	Use in Populations and Conclusion
Liraglutide (Victoza, Saxenda) [11,12]	- **Saxenda** (2010): Chronic weight management for adults with obesity or overweight with weight-related comorbidity.	- **Saxenda**: Start at 0.6 mg daily, increasing weekly to 3 mg; once daily, at any time, without regard to meals.	- **Saxenda**: Not for T2DM treatment; contraindications similar to Victoza. Common side effects: nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase.	- **Saxenda**: Risks include thyroid C-cell tumors, pancreatitis, gallbladder disease, hypoglycemia with insulin secretagogues, increased heart rate, and renal impairment.	- **Saxenda**: Contraindicated in pregnancy and nursing; pediatric safety not established; similar effects on gastric emptying.
Lixisenatide (Adlyxin) [13,14]	- 2016. - Adjunct for glycemic control in adults with T2DM.	- Begin with 10 mcg once daily for 14 days, and then increase to 20 mcg once daily. - Administer within one hour before the first meal of the day. - Subcutaneous injection in the abdomen, thigh, or upper arm.	- Avoid in patients with chronic pancreatitis, type 1 diabetes, diabetic ketoacidosis, or gastroparesis. - Hypersensitivity to Adlyxin components possible, including anaphylaxis. - Watch for pancreatitis, hypoglycemia (with sulfonylurea or insulin), acute kidney injury, and immunogenicity. - Common adverse reactions: nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia.	- No demonstrated macrovascular risk reduction with Adlyxin.	- Not for end-stage renal disease patients. - Use in pregnancy only if benefit outweighs fetal risk. - May delay gastric emptying, affecting oral medication absorption. - Oral contraceptives should be taken 1 h before or 11 h after Adlyxin.
Semaglutide (Ozempic/Rybelsus/ Wegovy) [14]	- **Ozempic** (2017): Adjunct for glycemic control in adults with T2DM.	- **Ozempic**: Start at 0.25 mg weekly, and increase to 0.5 mg and possibly to 1 mg. Administer once weekly, at any time, with or without meals.	- **Ozempic**: Avoid as first-line therapy for diet and exercise control failure; not for type 1 diabetes or diabetic ketoacidosis.	- **Ozempic**: Reports of pancreatitis, diabetic retinopathy; no established macrovascular risk reduction.	- **Ozempic**: Women should discontinue 2 months before a planned pregnancy. Monitor for hypoglycemia, acute kidney injury, and hypersensitivity.
	- **Wegovy** (2020): Adjunct for chronic weight management in adults and pediatric patients 12+ with obesity.	- **Wegovy**: For adults, start at 0.25 mg weekly, and increase to 2.4 mg (recommended) or 1.7 mg. Pediatric maintenance dose: 2.4 mg weekly. Administer once weekly, at any time, with or without meals.	- **Wegovy**: Do not use with MTC, MEN2 history, or known semaglutide hypersensitivity. Not for concurrent GLP-1 receptor agonist use.	- **Wegovy**: Reports of pancreatitis, gallbladder disease; not studied in patients with a history of pancreatitis.	- **Wegovy**: Discontinue during pregnancy and 2 months prior due to long half-life. Monitor for hypoglycemia, acute kidney injury, hypersensitivity, diabetic retinopathy complications, increased heart rate, suicidal behavior, and ideation.

3. Exploring the Multifaceted Impact of GLP-1RAs: Beyond Glycemic Control

3.1. Weight Reduction

Compared to placebo, GLP-1-RAs have demonstrated significant reductions in body weight, with studies reporting reductions between 2.1 and 8.4 kg over as many as 56 weeks using liraglutide, semaglutide, or efpeglenatide in various dosages [15–20]. The effects of GLP-1-RAs on body weight reduction have been well established in studies, contributing to their widespread adoption. In addition to the aforementioned effects that GLP-1-RAs have on insulin and glucagon release and modulating appetite through gastroparesis, rodent studies have also postulated a secondary effect of increased energy expenditure. The treatment of rodents with GLP-1-RAs was shown to excite CNS pathways, resulting in activation of brown adipose tissue (BAT), increasing BAT temperature, and increasing energy expenditure to decrease body weight and adiposity; selective knockout of the GLP-1 receptor produced the opposite effect, with resultant increases in body weight and adiposity. However, preclinical studies have confirmed that this mechanism of body weight reduction is secondary to the effects of reduced food intake and inhibited gastric emptying and may not be a clinically significant means of weight loss [6].

The resultant abatement in food intake and the inherent incretin effects of GLP-1-RAs lead to a decrease in blood glucose. However, different formulations of GLP-1 analogs will exhibit varying degrees of fasting blood glucose and postprandial hyperglycemia. Results have shown that shorter-acting GLP-1-RAs generally have a half-life of 2–5 h and have relatively modest decreases in fasting blood glucose with relatively substantial decreases in postprandial hyperglycemia. In contrast, longer-acting GLP-1-RAs have half-lives of 12 h and produce relatively substantial decreases in fasting blood glucose with relatively modest reductions in postprandial hyperglycemia; both types of GLP-1-RAs were equally efficacious in reducing body weight by 2–5 kg on average. Long-acting GLP-1-RAs appear to act identically to endogenous GLP-1 by decreasing body weight through its action on the CNS, while short-acting GLP-1RAs primarily exert blood glucose control via the inhibition of gastric motility to delay glucose absorption, consequently moderating the release of postprandial insulin [3].

Thus, GLP-1RAs demonstrate flexibility in various treatment strategies, asserting their utility as integral to individualizing weight loss and hyperglycemia management. Recent findings suggest that in overweight and obese adults, a combination of GLP-1-RAs and phentermine-topiramate are the best drugs to reduce body weight, with semaglutide being the most effective [3].

3.2. Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have recently increased in prevalence, most likely secondary to the increase in T2DM and metabolic syndrome. As insulin resistance is a primary driver in the development of NAFLD and NASH, applying GLP-1-RA therapy to increase insulin sensitivity is vital in decreasing steatosis and improving liver histology, ameliorating the pathogenesis of these diseases [3].

Studies on the acute use of exenatide and other GLP-1-Ras reveal that treatment reduces hepatic glucose production in healthy individuals and overall decreases de novo lipogenesis within hepatic tissue, the liberation of free fatty acids through lipolysis, and toxic metabolites derived from triglycerides [3]. In a double-blind, randomized, placebo-controlled trial, fourteen patients were randomized to 1.8 mg liraglutide or placebo for 12 weeks. The patients had a definitive diagnosis of NASH on a liver biopsy within six months of the study and were between 18 and 70 years old. The study's results showed that treatment with liraglutide was associated with improved metabolic dysfunction, insulin resistance, and lipotoxicity. Throughout the study, several biochemical parameters were assessed, including liver biochemistry, inflammatory markers, hepatic and systemic insulin sensitivity, lipolysis, hepatic de novo lipogenesis, and hepatic steatosis—all of which showed improvement following the administration of liraglutide [21]. The 12-week study concluded that treatment with liraglutide successfully resolved problems associated with metabolic dysfunction, insulin resistance, and lipotoxicity related to the development of NASH, with great potential for modifying the disease course. Detailed insights from this and related trials have been summarized in Table 2, which comprehensively compares outcomes and metrics studied across various clinical trials focusing on GLP-1Ras and their role in NAFLD and NASH [22].

Another randomized trial compared treatment with 3 mg liraglutide with a supervised program of dieting and moderate-intensity aerobic exercise in obese patients with NAFLD diagnosed using MRI and without any other causes of hepatic steatosis. After 26 weeks of treatment, both groups presented with significant and similar reductions in weight, liver fat fractions, and liver stiffness, as well as serum C-reactive protein, alanine aminotransferase, and aspartate aminotransferase. The comparable effects of liraglutide to a structured lifestyle modification program illustrate its efficacy in tempering the liver pathologies associated with NAFLD; a combination of both liraglutide and exercise results in enhanced maintenance of weight loss, abdominal fat, and inflammatory markers than either treatment alone [23,24].

However, while GLP-1-Ras have been shown to reduce liver steatosis through their actions on body mass effectively, GLP-1-Rs have thus far not been identified on key cells implicated in the generation of liver fibrosis, namely hepatocytes, Kupffer cells, and hepatic stellate cells [24]. In patients with NAFLD, the hallmark mechanism that drives disease development is de novo lipogenesis within the liver. The primary enzyme controlling this process is ATP citrate lyase (ACLY). In mouse studies, ACLY inhibitors such as bempedoic acid reduced liver steatosis, hepatocellular ballooning, lobular inflammation, and liver fibrosis. This antifibrotic effect appears to result from active suppression of lipogenesis and inhibition of transforming growth factor-beta (TGF-beta)-induced proliferation and activation by bempedoic acid. Furthermore, bempedoic acid produced marked antifibrotic effects independent of reductions in steatosis in select strains of mice with NASH without obesity or insulin resistance. Considering these results, the experiments imply that the therapeutic effects of ACLY inhibitors and GLP-1-Ras are independent and distinct [24].

Table 2. Effects of GLP-1Ras on hepatic outcomes in NASH and T2DM patients.

Year & Study Author	Participants & Condition	Type of Study	Drug & Outcomes
2009; Jendle et al. [25]	314 T2DM patients, 18–80 years, BMI $\leq$ 40 kg/m^2 (LEAD-2), $\leq$45 kg/m^2 (LEAD-3), HbA1c 7.0–11.0%	Randomized, double-blind, and parallel-group trials (LEAD-2 and LEAD-3), where the reduction in fat mass and hepatic steatosis was a primary outcome.	Liraglutide 1.8 mg/metformin: Significant increase in liver-to-spleen attenuation ratio, indicating reduced hepatic steatosis.
2015; Tang et al. [26]	35 T2DM patients inadequately controlled on metformin monotherapy or combination	Randomized study; insulin vs. liraglutide effects on liver fat were the primary outcome.	Insulin: Improved glycated hemoglobin (7.9% to 7.2%, p = 0.005), decreased liver MRI-PDFF (13.8% to 10.6%, p = 0.005), liver volume, and total liver fat index (304.4 vs. 209.3%·mL, p = 0.01). Liraglutide: Improved glycated hemoglobin (7.6% to 6.7%, p < 0.001), no significant change in liver MRI-PDFF, liver volume, or liver fat index.
2015; Eguchi et al. [27]	27 subjects with NASH and glucose intolerance, post lifestyle modification intervention.	Prospective, uncontrolled study; the impact on histological findings in NASH was a primary outcome.	After 24 weeks of liraglutide treatment at 0.9 mg/body per day, 19 subjects showed significant improvements in body mass index, visceral fat accumulation, aminotransferases, and glucose abnormalities. Six subjects who continued liraglutide for 96 weeks showed a decrease in histological inflammation as determined by NASH activity score and stage as determined by Brunt classification without significant adverse events.
2016; Armstrong et al. [28]	52 overweight patients with clinical evidence of non-alcoholic steatohepatitis.	Multicentre, double-blinded, randomized, placebo-controlled phase 2 trial; resolution of non-alcoholic steatohepatitis without worsening in fibrosis was a primary outcome.	1.8 mg daily of liraglutide led to a resolution of definite non-alcoholic steatohepatitis in 39% of patients, compared with 9% in the placebo group (relative risk 4.3 [95% CI 1.0–17.7]; p = 0.019). A total of 2 (9%) of 23 patients in the liraglutide group versus 8 (36%) of 22 patients in the placebo group had fibrosis progression. Adverse events were mostly mild to moderate, with gastrointestinal disorders being more common in the liraglutide group.

Table 2. *Cont.*

Year & Study Author	Participants & Condition	Type of Study	Drug & Outcomes
2016; Dutour et al. [29]	44 obese subjects with T2DM uncontrolled on oral antidiabetic drugs.	Prospective randomized clinical trial; hepatic and epicardial fat reduction was a primary outcome.	Exenatide treatment resulted in significant weight loss (−5.3 ± 0.4 kg; $p = 0.001$ for the difference between groups) and a decrease in epicardial adipose tissue (EAT) (−8.8 ± 2.1%) and hepatic triglyceride content (HTGC) (−23.8 ± 9.5%), compared with the reference treatment (EAT: +1.2 ± 1.6%; HTGC: +12.5 ± 9.6%; $p = 0.003$ and $p = 0.007$, respectively). No significant change in myocardial triglyceride content (MTGC) was observed.
2016; Armstrong et al. [21]	14 NASH patients	Double-blind, randomized, placebo-controlled trial; the effect on insulin sensitivity, hepatic lipid handling, and adipose dysfunction was a primary outcome.	Liraglutide treatment led to a reduction in BMI (−1.9 vs. +0.04 kg/m^2; $p < 0.001$), HbA1c (−0.3 vs. +0.3%; $p < 0.01$), LDL cholesterol (−0.7 vs. +0.05 mmol/L; $p < 0.01$), and ALT (−54 vs. −4.0 U/L; $p < 0.01$). It also increased hepatic insulin sensitivity and decreased endogenous glucose production ($p < 0.05$), increased adipose tissue insulin sensitivity ($p < 0.05$), and inhibited lipolysis and de novo lipogenesis (both $p < 0.05$) in vivo and in primary human hepatocytes.
2017; Seko et al. [30]	15 biopsy-proven NAFLD patients with T2DM refractory to diet intervention.	Retrospective study; the effectiveness of dulaglutide in NAFLD patients with T2DM was the main focus, implying it was a primary outcome.	Dulaglutide (0.75 mg for 12 weeks) significantly reduced body weight, hemoglobin A1c, transaminase activities, total body fat mass, and liver stiffness.
2017; Khoo et al. [23]	Non-diabetic Asian adults with NAFLD; BMI ≥ 30 kg/m^2, mean weight 96.0 ± 16.3 kg	Randomized study; comparing liraglutide and lifestyle intervention on NAFLD was a primary outcome.	Both the liraglutide group (3 mg daily) and the diet/exercise group saw similar and significant weight reductions (−3.5 ± 3.3 kg vs. −3.5 ± 2.1 kg, respectively, $p = 0.72$) and liver fat fraction decreases (−8.9 ± 13.4% vs. −7.2% ± 7.1%, $p = 0.70$). Changes in serum alanine aminotransferase (−42 ± 46 vs. −34 ± 27 U/L, $p = 0.52$) and aspartate aminotransferase (−23 ± 24 vs. −18 ± 15 U/L, $p = 0.53$) were not statistically significant.
2019; Newsome et al. [31]	Subjects with obesity and/or T2DM at risk of NAFLD.	Data from a 104-week cardiovascular outcomes trial and a 52-week weight management trial; effect on alanine aminotransferase (ALT) and high-sensitivity C-reactive protein (hsCRP) as primary outcomes.	In the weight management trial of patients with elevated baseline ALT, semaglutide led to end-of-treatment ALT reductions of 6–21% ($p < 0.05$ for doses ≥0.2 mg/day) and hsCRP reductions of 25–43% vs. placebo ($p < 0.05$ for 0.2 and 0.4 mg/day). Normalization of elevated baseline ALT occurred in 25–46% of weight management trial subjects vs. 18% on placebo. In the cardiovascular outcomes trial, no significant ALT reduction was noted at 0.5 mg/week. A reduction was observed at this dose at week 30 but was not sustained to week 56, while a 9% reduction vs. placebo was seen at 1.0 mg/week ($p = 0.0024$).
2020; Teshome et al. [32]	590 participants with non-alcoholic fatty liver disease (NAFLD).	Systematic review; the study compiled data from randomized controlled trials, single-arm trials, and cohorts.	GLP-1 analogs led to decreased serum transaminases, improved liver histology and insulin resistance, reduced body weight, and normalized liver enzymes. Specifically, ALT, AST, and GGT decreased by 5.5%, 59.5%, 52.8%, and 44.8%, respectively, and there was a reduction in proinflammatory cytokines and an enhancement of protective adipokines noted in some studies.

3.3. Neurodegenerative Applications of GLP-1RAs

GLP-1RAs present promising therapeutic avenues for counteracting neurodegenerative diseases by leveraging endocrine–neural interactions. These receptors, including GLP-1R, GIPR, and GcgR, are intricately woven into various anti-inflammatory pathways and have been shown to alleviate neural degradation and inflammation associated with Alzheimer's and Parkinson's diseases (AD and PD) [33–38]. Notably, GLP-1 and its metabolites have demonstrated improvements in AD and PD pathologies under experimental conditions, with GLP-1A playing a vital role in ameliorating motor and emotional aspects of PD as well as enhancing glucose metabolism in the brain, relevant to AD management [3,33,39,40]. Furthermore, mouse models have showcased GLP-1R activation's potential in improving neuroinflammation, neurogenesis, and synaptic plasticity while also counteracting inflammatory, oxidative, and apoptotic pathways in PD [3]. Despite these promising findings, translating these results to clinical practice requires further investigation in human studies.

3.4. Cardiovascular Implications of GLP-1RAs

Transcending their neural applications, GLP-1RAs render cardiovascular benefits, particularly in the context of T2DM and obesity. Trials spotlight a noteworthy reduction in cardiovascular events with GLP-1RAs, a promise grounded in preclinical and clinical landscapes [6].

Specifically, Albiglutide and Efpeglenatide have demarcated their potential to reduce major adverse cardiovascular events (MACEs) in individuals with T2DM, even while achieving only moderate weight loss [6]. It is imperative to recognize that although preclinical findings affirm the cardioprotective capabilities of GLP-1RA in animals with obesity absent diabetes, a thorough extrapolation to human circumstances, particularly in non-diabetic environments, demands additional scrupulous research [6].

4. GLP-1RA-Associated Side Effects and Potential Concerns

The adverse effects and concerns associated with GLP-1RA therapy encompass a vast spectrum, ranging from gastrointestinal disturbances to potential oncological implications. To encapsulate these varied effects, we present a comprehensive figure detailing the multifaceted ramifications of GLP-1RA use (Figure 1).

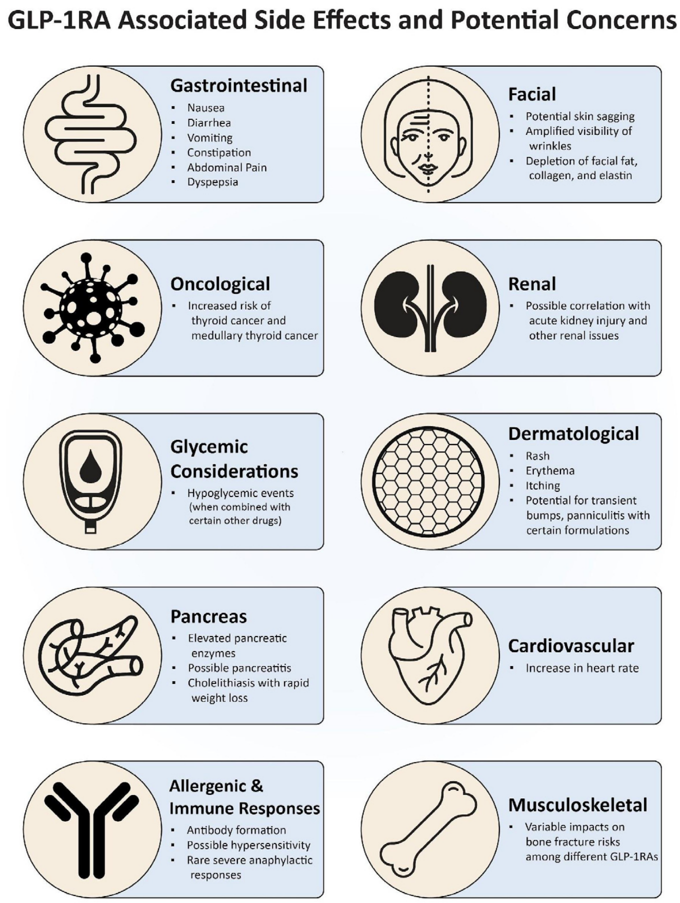

Figure 1. Overview of GLP-1RA-associated side effects and potential concerns. The figure elucidates the various side effects and concerns linked with GLP-1RA administration. Depicted are the primary areas of impact, including gastrointestinal, facial, oncological, renal, glycemic, dermatological, pancreas, cardiovascular, allergenic, and immune responses, and musculoskeletal implications. Each segment details specific conditions or responses that may arise due to GLP-1RA treatment. This comprehensive overview presents a visual summary of the multifaceted interactions of GLP-1RAs within the human body.

4.1. Gastrointestinal Impact of GLP-1 Receptor Agonists

Clinical investigations into GLP-1RAs ubiquitously report gastrointestinal disturbances as a principal side effect, significantly embodying nausea and diarrhea and, to a lesser extent, vomiting, constipation, abdominal pain, and dyspepsia [41–44]. The onset of such side effects predominantly emerges conspicuously during the initiation and up-titration of treatment, demonstrating a potential dose- and class-effect dependency, with nausea disturbing up to 50% of patients [45–47]. The delay in gastric emptying and peaks of the GLP-1 effect with short-acting formulations have been hypothesized as causative agents for the pervasiveness of nausea [48,49]. Notably, gastrointestinal side effects, particularly constipation, may linger despite a general attenuation over time and are seemingly less frequent with long-acting GLP-1RAs [6,47].

Gastrointestinal (GI) disturbances are common adverse effects associated with semaglutide. In phase 3 trials, subcutaneous semaglutide induced nausea in 11.4 to 20%, vomiting in 4 to 11.5%, and diarrhea in 4.5 to 11.3% of patients [50–53]. The incidence of GI disturbances was higher in the SUSTAIN 6 trial, which included older patients with comorbid conditions [53]. For oral semaglutide, the occurrence rates were 5.1 to 23.2% for nausea, 2.9 to 9.9% for vomiting, and 5.1 to 15% for diarrhea during the on-treatment period [54–56]. In a phase 2 trial, the total amount of GI disturbances was similar for oral and subcutaneous semaglutide (56% vs. 54%), with nausea occurring in 34% vs. 32%, vomiting in 16% vs. 9%, and diarrhea in 20% vs. 14% [57]. Higher doses of semaglutide are associated with more frequent GI adverse effects, which has led to the recommendation of a dose escalation scheme starting with a low dose [57]. GI complaints are the primary adverse-event-related cause of drug discontinuation in phase 3 trials, with rates up to 12%. Approximately 10% of patients will discontinue semaglutide because of GI complaints, which may be slightly higher than other GLP-1 analogs [58].

The analysis of GLP-1 dose groups revealed a significant increase in the likelihood of experiencing nausea, vomiting, and diarrhea compared to placebo and conventional treatment (CT). Exenatide 10 µg twice daily (EX10BID) exhibited the highest odds ratio (OR) and incidence for nausea (OR 2.89–6.10, 37.13%) and vomiting (13.13%), significantly surpassing placebo (nausea 9.36%; vomiting 2.01%). A dose–response relationship was observed for nausea and vomiting, with EX10BID posing the highest risk. The risk of both nausea and vomiting decreased for 26 weeks. For diarrhea, all GLP-1 dose groups had a significantly worse impact than placebo and CT, with the highest incidences observed in liraglutide 1.8 mg once daily (LIR1.8, 12.52%), exenatide 2 mg once weekly (EX2QW, 12.09%), and liraglutide 1.2 mg once daily (LIR1.2, 11.94%) [59].

In a study of 1842 patients with T2DM (T2D), participants were divided into three groups to receive different doses of dulaglutide: 1.5 mg, 3.0 mg, and 4.5 mg [60]. The 3.0 mg and 4.5 mg doses were more effective in lowering HbA1c than the 1.5 mg dose. Gastrointestinal (GI)-related symptoms like nausea, diarrhea, and vomiting were the most common treatment-emergent adverse events (TEAEs) [60]. The highest incidence of new-onset GI symptoms occurred within the first two weeks of initiating the 0.75 mg dose, declining by over 50% afterward. Most GI TEAEs were mild, with less than 1% of participants experiencing severe events. Few patients discontinued the study drug due to GI adverse events (1.4% for nausea, 0.7% for vomiting, and 0.7% for diarrhea). Significant interactions were observed between female and male subgroups concerning nausea and diarrhea, with females experiencing higher incidences of nausea across all dose groups and males demonstrating higher incidences of nausea and diarrhea in the 3.0 mg and 4.5 mg groups compared to the 1.5 mg group [61].

Patients experiencing GI disturbances can be counseled to eat slowly with reduced portions per meal, avoid high-fat foods, and consider anti-emetic therapy. However, long-term data are unavailable for the latter [62]. The mechanisms behind nausea/vomiting and diarrhea induced by GLP-1RAs are incompletely understood but may include effects on gastric emptying, the central nervous system, nutrient absorption, and intestinal motility [63–69]. Furthermore, nausea induced by GLP-1RAs is linked to weight loss in some studies, although the relationship is not consistent across all trials [67–69].

4.2. Pancreatic Concerns

GLP-1RAs have insinuated concerns regarding pancreatic integrity. Animal studies and clinical evaluations illustrating elevated pancreatic enzymes have spotlighted potential inflammatory responses and pancreatitis [70–75]. Despite these apprehensions, numerous studies and meta-analyses have contested establishing a direct causative relationship between GLP-1RAs and pancreatitis, presenting a nuanced perspective on its pancreatic safety [76–78].

Concerns about the possible association between GLP-1-RAs and neoplasm emergence have prompted investigators to research the incidence of thyroid and pancreatic neoplasms amongst patients being treated with GLP-1-RAs. A 2011 analysis of FDA databases from 2004 to 2009 found that while both the FDA and EMA assert that concerns of a causal association between incretin-based drugs and pancreatic cancer are inconsistent with current data, thyroid and pancreatic cancer were reported more frequently in patients treated with exenatide than with rosiglitazone [79].

A real-world study by Yang et al. (2022) [4] utilized data from the FDA Adverse Event Reporting System (FAERS) between 2004 and 2021 and found that the proportional reporting ratios (PRRs) for malignant pancreatic neoplasms related to GLP-1-RA therapy were greater than 2. The PRR compares the ratio of neoplasms formed under therapy with GLP-1-RAs with those formed under comparator therapy; PRRs equal to one signify that GLP-1RA-associated neoplasms were reported as frequently as comparator-associated neoplasms.

The study found that in cases with malignant pancreatic neoplasms, about half of these cases were associated with the combination use of GLP-1-RAs with DPP-4 inhibitors; the PRR tended to increase when this combination therapy was utilized. It is proposed that using DPP-4 inhibitors significantly prolongs the half-life of GLP-1-RAs, allowing enhanced β-cell proliferation, inhibiting apoptosis, and increasing the risk of tumor formation.

4.3. Concern for Thyroid Neoplasms

While studying the incidence of pancreatic neoplasms, Yang et al. (2022) found that the PRRs for benign and malignant thyroid neoplasms associated with GLP-1-RAs were greater than three and five, respectively.

Proposed explanations for this apparent increase in PRR for thyroid neoplasms obfuscate the strength of the association between GLP-1-RA therapy and neoplasm formation. Amongst patients with thyroid neoplasms, Synthroid was the second most common combined drug identified, suggesting that these patients were being treated for hypothyroidism. A 2020 meta-analysis reported that hypothyroidism was associated with a higher risk of thyroid cancer within the first 10 years of follow-up. In addition, the International Agency for Research on Cancer (IARC) found that increased screening for thyroid cancer has directly resulted in an increased incidence of thyroid cancer across 25 countries. This is further compounded by the FDA's issue of a warning that GLP-1-RA use may increase the risk of medullary thyroid cancer, causing reporters to attribute more thyroid cancers to GLP-1-RA use and patients undergoing GLP-1-RA treatment to proactively seek thyroid ultrasounds, resulting in increased detection of thyroid neoplasms [4].

Meanwhile, the PRR for other neoplasms, including respiratory and mediastinal, breast, most male and female reproductive, bone and skin soft tissue, nervous system, ocular, and hematologic, was less than 1 [4].

4.4. Cardiovascular Implications

In the cardiovascular domain, GLP-1RAs have not denoted an elevation in cardiovascular events; nevertheless, a subtle but potentially clinically pertinent augmentation in heart rate has been associated with their administration [80–84]. Selected GLP-1RAs, including exenatide, liraglutide, and albiglutide, have not manifested significant alterations in the QTc interval, offering a degree of cardiovascular reassurance [85].

4.5. Endocrinological and Glycemic Considerations

GLP-1RAs, when co-administered with metformin, do not exacerbate clinically relevant hypoglycemic events [86–88]. Contrastingly, their combination with sulphonylurea or insulin reveals a noticeable increment in hypoglycemic incidences, attributed to the potential uncoupling of GLP-1's insulinotropic effect from its glucose dependence [89–91]. This underscores the advisability of modulating sulphonylurea or insulin dosages upon GLP-1RA initiation [92].

4.6. Allergenic and Immune Responses

Diverging into the immunogenic milieu, GLP-1RAs and synthetic peptides can engender antibody formation, presenting a spectrum of immunogenicity [93–97]. Despite the perceivable risk of hypersensitivity, re-exposure to agents such as exenatide did not elevate hypersensitivity occurrences [98]. Although rare, severe anaphylactic responses have been documented in post-marketing, stipulating prudent monitoring and management of hypersensitivity phenomena [93–95].

4.7. Musculoskeletal Implications

A notable dichotomy exists between various GLP-1RAs regarding skeletal impacts, where liraglutide demonstrates a risk reduction for bone fractures, whereas exenatide evidences an elevation in such risk [99]. Comparatively, studies involving exenatide twice daily and insulin glargine once daily exhibited no substantial modulation in bone mineral density or select serum markers [100].

4.8. Dermatological Implications

GLP-1 receptor agonists (GLP-1RAs) manifest dermatological side effects predominantly at injection sites, with common occurrences of rash, erythema, and itching, particularly with long-acting formulations [93,96,97,100]. Exenatide once weekly has been associated with the emergence of small, transient bumps, while isolated reports connect it with panniculitis and other dermatological issues like hyperhidrosis, alopecia, and certain rashes [93,100,101].

4.9. Renal Concerns

The intersection between GLP-1RAs, notably exenatide, and renal functionality has been scrutinized, with correlations drawn to acute kidney injury, often propelled by side effects like nausea, vomiting, and dehydration [102,103]. Detailed renal examinations have unearthed ischemic glomeruli and diabetic nephropathy [104], with other potential contributors being GLP-1-induced natriuresis and diminished renal perfusion [105]. Nevertheless, contrasting analyses have deemed renal issues as seldom and not distinctively divergent from comparators [106,107]. Practitioners must heed acute renal failure risks, especially in volume contraction scenarios [102].

4.10. Facial Implications

The exploration of GLP-1 receptor agonists, notably Ozempic, reveals an intriguing yet often under-discussed aesthetic concern known as the "Ozempic face." This phenomenon manifests as a marked, gaunt appearance of the face, resulting from a swift depletion of facial fat, collagen, and elastin, amplifying the visibility of wrinkles and auguring skin sag [108]. Not universally documented in clinical trials, this accelerated facial aging confronts plastic surgeons with a unique challenge, necessitating specialized approaches to mitigate these potent aesthetic and potentially psychological changes amidst the enduring popularity of the medication [109]. Offering solutions that span from minimally invasive fillers to more substantial surgical interventions, surgeons must also navigate the intricacies of nutritional aspects and their influence on pre- and post-operative recovery [110]. Thus, it becomes imperative for facial plastic surgeons to immerse themselves in the particulars of Ozempic and related semaglutide products, considering their aesthetic repercussions and perioperative considerations while transparently communicating potential side effects to those contemplating their use.

4.11. Implications of Overdose

Overdose with GLP-1RAs, while documented, typically precipitates symptoms like nausea, vomiting, and abdominal pain without hypoglycemia, even in cases of substantial overdose [111–113]. Therapeutic intervention in these instances leans predominantly towards supportive care.

5. Management of Gastrointestinal Adverse Events: "The Three E's"

The side effects induced by initiating treatment with GLP-1-RAs can be seen as a considerable barrier to those struggling to meet their health goals, which are refractory to other treatment modalities, such as lifestyle modification. The most commonly cited methodology for managing side effects is individualized and gradual dose-escalation of the medication; a more gradual dose escalation is recommended to reduce the frequency of gastrointestinal adverse events. However, if side effects arise during the dose escalation, a delay in up-titration should be considered [6,114,115].

A proposed approach designed by Wharton et al. (2022) identified evidence of several strategies of side effect management in clinical practice gathered from real-world studies on GLP-1-RA adverse event mitigation described as "The Three E's: Education and explanation, escalation to an appropriate dose, and effective management of GI side effects" [47].

The first step involves counseling eligible patients on the potential side effects of GLP-1-RAs and providing appropriate reassurance that such effects typically subside following gradual dose escalation. Modifiable patient behaviors should be made clear, such as reducing meal portion sizes; mindfulness to stop eating when feeling full; resisting eating when not hungry; avoiding foods that are high in fat or spicy; and a moderation of alcohol intake and other carbonated beverages. Importantly, prescribing physicians should discuss regular bowel habits with their patients to establish any current GI disorders (e.g., constipation, diarrhea) as a baseline, particularly in patients who are overweight or obese, as GI disorders will commonly be present within these populations. Prompt resolution of these existing GI disorders should be executed before initiating GLP-1-RA therapy. For patients with more severe pre-existing GI diseases, such as gastroparesis, GLP-1-RAs should be avoided.

As previously described, gradual dose escalation is recommended as a standard of practice when beginning therapy with GLP-1-RAs to reduce the risk of encountering adverse GI effects. While clinical trials with this drug class have followed rigid titration regimens to assess the drugs' efficacy appropriately, clinical practice should follow more individualized and patient-centered dose escalation in response to the severity and frequency of GI symptoms within the first few weeks of treatment. The prescribing physician's goal in tempering adverse effects should be to communicate closely with their patients to balance effective weight loss while dispensing a tolerable dose.

Lastly, a stepwise and severity-based approach should be applied to patients who complain of GI symptoms encountered following the initiation of their GLP-1-RA treatment. For patients experiencing upper GI side effects of short duration or mild severity, patient counseling on modifying dietary behaviors, as mentioned above, may be considered. Clinical and real-world studies show that patients with overweight or obese body habitus commonly experience constipation as a side effect of GLP-1-RAs and should be consulted on increasing fiber and water intake; supplemental pharmaceutical interventions such as stool softeners may be considered. Close monitoring of these effects is advised, as worsening symptoms may warrant dose de-escalation of dosing.

In response to patients who report GI side effects that are persistent or severe, dose escalation should be postponed. Before pursuing other actions, clinicians should reconsider the source of these GI symptoms and create a differential diagnosis of other conditions that may be responsible for the patient's presentation. While assessing a patient's presentation of worsening or new onset severe symptoms, if acute pancreatitis is suspected, GLP-1-RA therapy should be immediately halted, and standard clinical management of pancreatitis should be performed—upon confirmation of pancreatitis, GLP-1-RAs should not be reinitiated. A reassessment of the patient's history, including the concomitant use of any other prescription or non-prescription medicines, is prudent. Metformin use simultaneous with GLP-1-RA therapy has been reported to be associated with an increased risk of GI adverse effects in patients with T2DM.

Following appropriate management of alternative conditions, alternative strategies to mollify adverse GI effects may include dose adjustment or the transition to alternative GLP-1-RAs. When GI symptoms are encountered and dose escalation is paused, the up-titration may be resumed once the patient reaches a dose that the patient can tolerate. Further dose escalation is recommended to occur slower than previously attempted. Physicians and patients should be aware that the time for titration to full maintenance dosages may be longer than initially recommended at the start of treatment. Real-world studies using liraglutide to address obesity found that the median time to the 3 mg maintenance dose was nearly 50 days, contrasting with the 28-day recommended prescribing information.

If patients initiating treatment with a GLP-1-RA find extraordinary difficulty in tolerating very low doses of their medication, treatment may be stopped, and a trial with an alternative GLP-1-RA may be attempted as the tolerability profile between numerous GLP-1-RAs varies. Reinitiation with alternative GLP-1-RAs should be performed following a resolution of any adverse effects—the time for resolution of adverse effects following termination of GLP-1-RA therapy can vary between 1 and 2 days and 1 and 2 weeks [47].

To provide a structured and visually accessible guide through the nuanced and pivotal stages of managing GLP-1RA therapy-related gastrointestinal side effects, refer to Figure 2. This figure, through a strategically segmented flowchart, elucidates a systematic approach across three essential phases: A. Education and Explanation; B. Escalation to an Appropriate Dose; and C. Effective Management of GI Side Effects, providing healthcare providers with an actionable and adaptive tool for informed decision-making in the clinical setting.

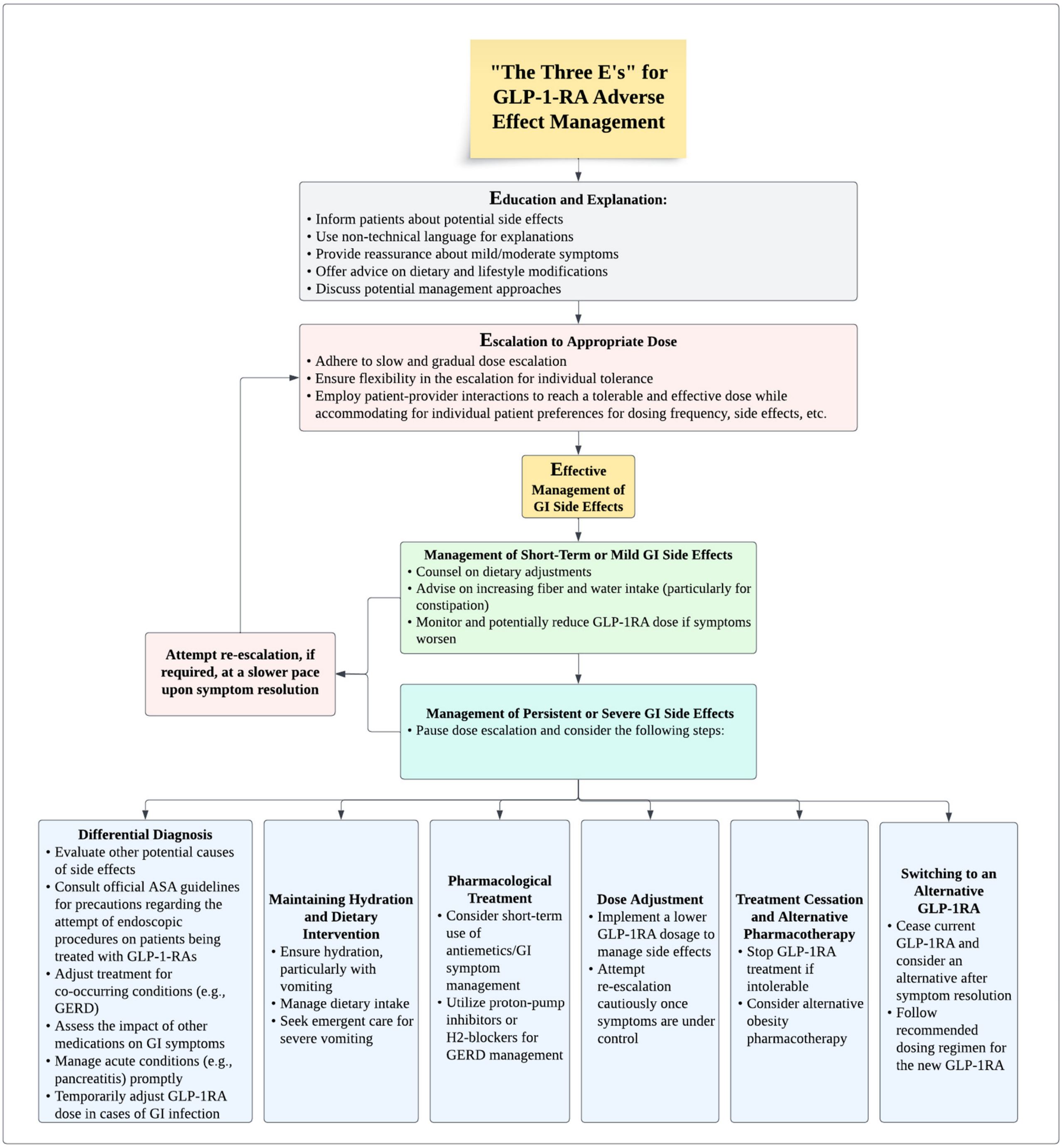

Figure 2. Navigating GLP-1RA therapy-related GI side effect management. This flowchart delineates a strategic approach to managing gastrointestinal (GI) side effects during GLP-1RA therapy, segmented into three pivotal phases: **A. Education and Explanation**, focusing on preemptive patient education regarding potential side effects and lifestyle adaptations; **B. Escalation to an Appropriate Dose**, emphasizing a gradual and tailored dose escalation with persistent patient monitoring; and **C. Effective Management of GI Side Effects**, which addresses both short-term/mild and persistent/severe GI side effects through various strategies, such as dietary intervention, pharmacological treatment, and potential GLP-1RA dosing modifications. This structured yet adaptable guide aims to enhance healthcare providers' decision-making by prioritizing patient safety and therapeutic efficacy amidst GI side effect management challenges in GLP-1RA therapy.

6. Safety and Tolerability of GLP-1RAs

In the therapeutic landscape, GLP-1RAs are positioned as notable agents with efficacy in diverse medical conditions, given their direct impact on metabolic and potentially neurodegenerative pathways. Nevertheless, a thorough understanding of their safety and tolerability is quintessential to optimizing their therapeutic utility.

GLP-1RAs extend a commendable safety profile concerning the risk of hypoglycemia, even in non-diabetic cohorts, attributed to their inherent glucose-dependent mechanism of action [17,116–119]. However, a panorama of gastrointestinal side effects, including nausea, vomiting, and diarrhea, is a recognizable companion of GLP-1RA therapy, albeit their typically mild-to-moderate and transient nature, ensuring these agents are generally well-tolerated [20,120,121].

A 2011 randomized clinical trial compared the weight and cardiometabolic effects experienced by patients who received either once-weekly semaglutide or placebo for 68 weeks. The study's results revealed that 52 weeks after termination of treatment with semaglutide, patients experienced a regain of 11.6% of their original weight, compared to only 1.9% in the placebo group. However, patients on semaglutide still recorded a net weight loss of 5.6% of their original weight. In addition, blood sugar, cholesterol, and inflammatory marker measures remained improved following semaglutide treatment for 120 weeks after treatment cessation [122].

Tran et al. (2018) studied the effects of liraglutide therapy and withdrawal of therapy on β-cell functioning and glucose tolerance. It was found that following a 48-week treatment with liraglutide and a 2-week washout period, 57.7% of patients treated with liraglutide reverted to a statistically significant decline in β-cell functioning and higher 2 h blood glucose compared with patients in the placebo group. The study highlights the need for further study to understand the effects of GLP-1-RA therapy on glucoregulatory mechanisms and the long-term sustainability of these medications in patients with advanced β-cell dysfunction [123].

While GLP-1RAs have a generally favorable safety and tolerability profile, judicious evaluation and management strategies are essential to navigate specific scenarios and mitigate associated risks, ensuring optimal patient care. This synthesis of current knowledge affirms the necessity for ongoing research to further delineate the safety boundaries and guidelines for GLP-1RA use in diverse clinical contexts.

Official Statements Regarding Endoscopic Procedure Precautions

Venturing into more specialized considerations, the American Association for the Study of Liver Disease (AASLD) has harbored concerns regarding the potential association between GLP-1RAs and safety issues pertinent to sedation and endoscopy. The use of this drug class has been shown to be associated with increased gastric residue in esophagogastrodudenoscopy due to delayed gastric emptying, potentially affecting parameters such as procedure duration and diagnostic accuracy [124]. The anecdotal correlation of GLP-1RAs with an enhanced risk of gastroparesis is underscored as being dose-dependent and a class-effect phenomenon. However, the AASLD conscientiously notes the scarcity or absence of data concerning the relative risk of complications from aspiration, emphasizing the necessity for further exploration into the implications of discontinuing therapy before upper gastrointestinal endoscopy [125].

Additionally, the recommendations from the American Society of Anesthesiologists (ASA) delineate that for patients on daily-dosed GLP-1RAs, cessation of the medication on the day of a procedure is prudent; for those on a weekly regimen, withholding the medication the week prior is ideal. Engagement with the prescriber for potential bridging therapy is advisable to navigate the risks of hyperglycemia during the withholding period. Furthermore, ASA guidelines advocate a delay when severe symptoms manifest on the day of the procedure. Procedures can commence if patients are without symptoms and have adhered to medication withholding guidelines. Conversely, if patients necessitating endoscopy have not adhered to medication withholding instructions and no symptoms are apparent, practitioners are advised to exercise "full-stomach precaution" (indicative of high aspiration risk). Utilization of stomach ultrasounds to guide further action may be considered [126].

7. Alternative Non-GLP-1-RA Approaches to Weight Loss

Non-pharmacological modalities for addressing weight loss exist alongside drugs such as GLP-1-RAs. The FDA has approved medical devices such as Plenity to approach weight loss via mechanical means instead of hormonal. Plenity is a unique nonsurgical device for weight management in overweight and obese adults (tested on participants with a body mass index of 27 to 40 kg/m^2) in conjunction with diet and exercise.

Plenity, approved by the FDA in April 2019, is a novel, oral, nonsystemic, superabsorbent hydrogel developed to treat overweight patients and those with obesity. The gel is contained within a capsule and is comprised of naturally occurring building blocks. A type of modified cellulose cross-links with citric acid to form a three-dimensional matrix. When the device is ingested and the capsule dissolves, the hydrogel particles release and expand to occupy nearly a quarter of the patient's stomach volume when maximally hydrated. The gel mixes with ingested food within the stomach and small intestine to induce a feeling of satiety. Plenity is available in capsule form, but it is not considered a drug because it is not absorbed by the body. Rather, the hydro-gel capsule releases gel particles that absorb water, expanding significantly in size and signaling satiety without being absorbed. As the formed product travels throughout the small intestine, it maintains its mechanical properties until degradation by enzymes housed within the large intestine. Upon degradation, the colon releases and resorbs water while the cellulose is excreted within feces. For these reasons, Plenity is considered a medical device rather than a drug, leading to a different threshold for approval.

Plenity is currently indicated for patients with a BMI of at least 27 kg/m^2 without comorbidities and does not have any restrictions on the duration of therapy. Contraindications to Plenity include a history of GERD, gastric ulcers, or gastrointestinal structures either due to chronic diseases such as Crohn's disease or prior gastrointestinal surgeries that may have altered motility throughout the GI tract. The product is also cautioned against use by patients who are pregnant or allergic to any of its ingredients [127].

8. Conclusions

GLP-1 receptor agonists (GLP-1-RAs) offer promising avenues for combating obesity and type 2 diabetes mellitus (T2DM), owing to their accessibility and low hypoglycemic risk. Despite their broad-reaching effects across multiple organ systems, concerns persist regarding upper gastrointestinal side effects and their potential link to certain cancers. This review outlines the uses and side effects of GLP-1-RAs, emphasizing the need for caution in prescribing, particularly for patients undergoing sedation procedures or at risk for thyroid and pancreatic cancers. While acknowledging these risks, the significant potential for ameliorating weight gain and hyperglycemia underscores the importance of considering GLP-1-RAs in pharmaceutical treatment strategies.

This comprehensive review recognizes several limitations in regard to the selection of cited literature and the limitations of the data obtained from the literature. Primarily, reliance on studies that themselves are reviews introduces the risk of compounding biases and interpretations. Additionally, the inclusion of relatively dated articles may overlook recent advancements and nuanced understandings in the field. Moreover, the reliance on in vitro studies without corresponding human trials raises questions about the direct applicability of findings to clinical settings, potentially limiting the generalizability of conclusions to real-world contexts. These constraints underscore the necessity for cautious interpretation and the need for further empirical investigations to consolidate and validate the insights gleaned from the review.

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