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REVIEW

GLP-1 Receptor Agonists: Therapeutic Potential and Emerging Concerns

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Abstract

Purpose of Review The aim of the review is to evaluate the benefits and limitations of GLP-1 receptor agonists, with particular emphasis on adverse effects, unresolved safety issues, and the socioeconomic and ethical aspects of their growing popularity.

Recent Findings Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed the management of type 2 diabetes mellitus (T2DM) and obesity, offering clinically significant improvements in glycemic control, weight reduction, and cardiometabolic outcomes, with additional benefits reported for renal outcomes in patients with chronic kidney disease. Beyond these indications, emerging evidence suggests potential benefits in conditions such as metabolic-associated steatotic liver disease and obesity-related comorbidities including obstructive sleep apnea. Their widespread use, however, has been accompanied by growing attention to side effects, long-term safety concerns, and ethical challenges. Common adverse effects are primarily gastrointestinal and transient, though more severe complications, including gallbladder disease, bowel obstruction, retinopathy, and rare neoplasms, have been reported. Neuropsychiatric symptoms and post-discontinuation weight regain are additional concerns that complicate long-term management. Furthermore, off-label use for cosmetic weight loss has contributed to drug shortages, inequitable access, and increased circulation of counterfeit products, raising serious public health and ethical issues.

Summary Future directions should prioritize robust pharmacovigilance, structured discontinuation protocols, and research into biomarkers of responsiveness. GLP-1 RAs should be repositioned within lifecycle-based, personalized care models, integrating pharmacotherapy with sustainable lifestyle and behavioral interventions. Such an approach will be essential to maximize therapeutic benefit, minimize risk, and ensure equitable use of these powerful yet imperfect agents.

Key Points

GLP-1 receptor agonists are highly effective medicines for treating diabetes and obesity, helping patients lower blood sugar, lose weight, and improve heart and kidney health. However, their growing popularity has also revealed important challenges, including side effects, drug shortages, high costs, and misuse for cosmetic weight loss. To ensure safe and fair use, these treatments should be combined with lifestyle changes and used under medical supervision, with stronger safeguards for long-term safety and equitable access.

Keywords GLP-1 RAs · Semaglutide · Tirzepatide · Obesity · T2DM

Introduction

The discovery of glucagon-like peptide-1 (GLP-1) is largely credited to Svetlana Mojsov, who in 1983 isolated a fragment from the preproglucagon gene capable of stimulating insulin secretion, later recognized as GLP-1 [1]. Although this endogenous hormone showed great promise for treating type 2 diabetes (T2DM) due to its ability to stimulate insulin release in a glucose-dependent manner, its clinical

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utility was initially limited by an extremely short half-life in the human body [1]. A major breakthrough came in the early 1990 s, when John Eng discovered exendin-4, a molecule found in the venom of the Gila monster, which mimicked human GLP-1 but had significantly greater stability [1]. This discovery paved the way for the development of the first GLP-1 analog, exenatide, which was approved by the Food and Drug Administration (FDA) in 2005. Since then, the field has rapidly advanced, culminating in the approval of newer agents such as liraglutide (2014) and semaglutide (2021), which are now among the most widely prescribed drugs in this class (Table 1) [1–3].

Initially, GLP-1 analogs required twice-daily injections, but formulation improvements have allowed for once-daily and even once-weekly administration [4]. These agents are currently registered for the treatment of T2DM and obesity, while only selected incretin-based therapies are indicated for chronic weight management in persons with obesity without diabetes - specifically liraglutide 3.0 mg (Saxenda), semaglutide 2.4 mg (Wegovy), and tirzepatide (Zepbound/Mounjaro, depending on regulatory jurisdiction) [5]. Their mechanism of action is based on mimicking the effects of endogenous GLP-1, an incretin hormone that lowers blood glucose levels without a corresponding increase in hypoglycemia risk [1]. GLP-1 is synthesized in several sites, including neurons in the solitary nucleus, intestinal mucosal L-cells, and pancreatic alpha cells. Upon neuroendocrine stimulation, typically triggered by food intake, GLP-1 is secreted from enteroendocrine L-cells in the distal jejunum, ileum, and colon [6]. Its receptor is expressed in multiple organs, including the pancreas and the central nervous system (CNS), where it plays a critical role in appetite regulation [6]. Synthetic GLP-1 receptor agonists (GLP-1 RAs) are engineered to resemble endogenous GLP-1 but possess structural modifications that confer resistance to degradation by dipeptidyl peptidase IV (DPP4), thereby greatly extending their half-life [1]. Their clinical benefits include enhanced insulin secretion during hyperglycemia, delayed gastric emptying, inhibition of glucagon secretion, and significant weight reduction [4]. These effects have driven enormous commercial success, semaglutide alone generated over $12 billion in global sales by 2022 [1]. Usage of GLP-1 analogs has expanded rapidly. In Australia, the number of users increased tenfold between 2014 and 2022 [7]. A similar trend has been observed in the United States. According to Watanabe et al., Ozempic (semaglutide) use surged from just 569 users in 2019 to over 22,000 by 2022 [8]. While growth was seen across all subgroups, including those with T2DM, cardiovascular disease, and obesity, the rise of semaglutide was particularly pronounced among overweight and obese individuals [8]. However, this popularity has also led to problematic patterns of use. Heavily promoted by celebrities and social media influencers, GLP-1 RAs are increasingly being used off-label for aesthetic weight loss purposes. In particular, the rise of semaglutide, marketed as 'Ozempic', has led to global drug shortages, with some patients resorting to purchasing counterfeit versions through illegal online sources [9]. These shortages have compromised access for patients with T2DM, the population for whom the drugs were originally designed and approved [10]. This dramatic rise in demand, fueled by unrealistic expectations and societal pressures around body image, underscores the urgent need for public education on the appropriate use of GLP-1 RAs. Patients and providers must be aware not only of the therapeutic benefits but also of the potential side effects, risks, and ethical issues surrounding access and misuse. In this review, we aim to critically evaluate the limitations of GLP-1 RAs. We explore their side effects, both common and rare, address the long-term safety concerns that remain unresolved, and consider the economic, ethical, and social dimensions of their rising use. While these drugs have undoubtedly changed the landscape of metabolic medicine, their rapidly expanding use warrants careful evaluation of benefits, risks, and real-world implementation.

Table 1 Overview of approved GLP-1 receptor agonists

Agent	Year Approved	Indications	Dosing frequency	Route
Exenatide	2005 (Byetta) 2017 (Bydureon)	-T2DM in adults (Byetta) -T2DM in adults and pediatric patients aged 10 years or older	- twice daily - once a week	Subcutaneous (both)
Liraglutide	−2010 (Victoza) −2014 (Saxenda)	- T2DM in adults and pediatric patients aged 10 years or older - Obesity	- once a day - once a day	Subcutaneous (Both)
Dulaglutide	2014 (Trulicity)	T2DM	Once a week	Subcutaneous
Semaglutide	−2017(Ozempic) −2019(Rybelsus) −2021 (Wegovy)	-T2DM in adults - T2DM in adults, obesity - T2DM, obesity (only Wegovy)	-once a week - once a day - once a week	Subcutaneous Oral Subcutaneous
Tirzepatide	−2022 (Mounjaro) −2023 (Zepbound)	-T2DM in adults -Obesity	- once a week (both)	Subcutaneous (both)

T2DM, Type 2 diabetes mellitus

Efficacy and Therapeutic Benefits

GLP-1 Receptor Agonists

GLP-1 RAs are approved for the treatment of both T2DM and obesity, and emerging evidence suggests they may also play a promising role in the management of metabolic associated steatotic liver disease (MASLD), now recognized as the most prevalent chronic liver disease worldwide [11, 12]. The first GLP-1 RA approved for obesity or overweight with comorbidities was liraglutide in 2014, followed by semaglutide in 2021 [13]. Liraglutide (1.8 mg/day) has shown significant effects on body composition [14]. In a study by Silver et al., ≥5% weight loss was achieved in 22% of participants ($P=0.02$), accompanied by a 2.2% reduction in fat-to-lean mass ratio ($P=0.02$) and a 4.8% decrease in visceral adipose tissue ($P=0.04$) [14]. Beyond glycemic control and weight reduction, GLP-1 RAs demonstrate organ-protective effects. Notably, large cardiovascular outcome trials have demonstrated that GLP-1 RAs significantly reduce major adverse cardiovascular events, particularly in patients with established cardiovascular disease or high cardiometabolic risk [15]. In the SELECT trial, Lincoff et al. reported that the primary cardiovascular endpoint occurred in 569 of 8,803 patients (6.5%) in the semaglutide group compared with 701 of 8,801 patients (8.0%) in the placebo group ($P<0.001$) [15]. Among individuals with preexisting cardiovascular disease and overweight or obesity, but without diabetes, once-weekly subcutaneous semaglutide 2.4 mg was superior to placebo in reducing the incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke over a mean follow-up of 39.8 months [15]. In patients with T2DM and chronic kidney disease, semaglutide was associated with an 18% lower risk of major adverse cardiovascular events and slowed the annual decline in estimated glomerular filtration rate (eGFR) compared to placebo (-1.16 mL/min/1.73 m²; $P<0.001$) [16]. In MASLD patients with coexisting T2DM, 52 weeks of semaglutide therapy resulted in at least a one-grade reduction in hepatic steatosis on ultrasound and decreased expression of alpha-smooth muscle actin, a marker of hepatic fibrogenesis [11]. Additionally, semaglutide improved lipid profiles and reduced liver inflammation markers [11]. In addition, emerging evidence suggests that GLP-1 RAs may improve outcomes in patients with heart failure with preserved ejection fraction, likely mediated by weight reduction and improved cardiometabolic status [17]. Moreover, cardiovascular outcome data indicate that GLP-1 RA therapy reduces major adverse cardiovascular events (MACE) in patients with obesity both with T2DM and without T2DM; notably, semaglutide 2.4 mg reduced MACE by 20% in individuals with established cardiovascular disease and overweight/obesity but no diabetes [15]. Interestingly, GLP-1 RAs have also been explored as a potential therapeutic option for obstructive sleep apnea (OSA), a prevalent sleep disorder characterized by recurrent upper airway obstruction and intermittent breathing disturbances during sleep [18]. In a recent meta-analysis including three randomized controlled trials evaluating GLP-1 RAs for OSA in adults with obesity (BMI≥30 kg/m²), Kow et al. reported that GLP-1 RA therapy was associated with a significant reduction in the apnea–hypopnea index compared with placebo [18]. Similarly, emerging clinical evidence suggests that GLP-1 RAs may improve pain and physical function in patients with knee osteoarthritis and could potentially reduce the risk of knee osteoarthritis development, likely through weight reduction and downstream metabolic effects [19, 20]. However, the current body of evidence remains limited, and further well-designed studies are needed to confirm these benefits and clarify underlying mechanisms.

Dual GLP-1/GIP Receptor Agonist: Tirzepatide

Tirzepatide, approved in 2023 for obesity, represents a distinct pharmacological class as a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist [3]. The efficacy of tirzepatide in weight management and prevention of T2DM was demonstrated in the phase 3 SURMOUNT-1 trial, which enrolled 2,539 adults with obesity and prediabetes [21]. After 176 weeks of treatment, patients receiving tirzepatide experienced mean weight reductions of -12.3% (5 mg), -18.7% (10 mg), and −19.7% (15 mg), all significantly greater than placebo ($P<0.001$) [21]. Furthermore, the incidence of progression to T2DM was significantly lower in the treatment group (1.3%) compared to placebo (13.3%) ($P<0.001$) [21]. Interestingly, owing to its dual incretin mechanism, tirzepatide appears to exert favorable effects on cardiovascular risk factors, including blood pressure, lipid parameters, and markers of chronic inflammation, although evidence on its direct effects in heart failure populations is still evolving [22]. Packer et al. reported that in 731 patients with heart failure, an ejection fraction of at least 50%, and a body-mass index of at least 30, tirzepatide reduced the risk of a composite endpoint of cardiovascular death or worsening heart failure compared with placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity [23]. In addition, the SURPASS-CVOT trial, which randomized 13,299 patients, compared tirzepatide with dulaglutide in individuals with T2DM and atherosclerotic cardiovascular disease and demonstrated that tirzepatide was noninferior to dulaglutide for the composite outcome of cardiovascular death, myocardial infarction, or stroke [24]. Tirzepatide has also shown renal benefits: in a

post hoc analysis of the SURPASS-4 randomized clinical trial, tirzepatide reduced albuminuria, improved total eGFR slopes, and nearly halved the risk of a prespecified composite kidney endpoint [25]. Notably, Malhotra et al., in two phase 3, double-blind, randomized, controlled trials involving adults with moderate-to-severe obstructive sleep apnea and obesity, reported that tirzepatide produced significant improvements across all prespecified key secondary endpoints compared with placebo [26].

Despite the demonstrated therapeutic efficacy of both GLP-1 receptor agonists and dual incretin therapies, their expanding use has brought increasing attention to their adverse effect profile, long-term safety considerations, and real-world limitations.

Adverse Effects and Limitations

Increasing use of GLP-1 RAs has brought attention to a broad spectrum of adverse effects. While most reported side effects are gastrointestinal and mild in severity, more serious and rare complications have also been described. Although early studies raised concerns regarding pancreatic and neoplastic risks, recent evidence supports a generally favorable safety profile for clinically approved GLP-1 RAs [27]. Nevertheless, it remains essential to comprehensively outline both common and severe adverse effects to support informed clinical decision-making and enhance patient safety.

Common Adverse Effects

Gastrointestinal symptoms are the most frequently reported side effects across all GLP-1 RAs. These symptoms are mechanistically consistent with peripheral slowing of gastric emptying and alterations in gut motility, as well as central appetite and nausea pathways that are activated alongside satiety signaling. In the STEP 1 trial, approximately 74% of patients using semaglutide experienced nausea, vomiting, diarrhea, or constipation, mostly within the first 20 weeks of therapy [28]. These symptoms were generally transient and mild to moderate in severity, rarely leading to treatment discontinuation [28]. The European Medicines Agency (EMA) lists gastrointestinal disturbances, weight loss-related events, and diabetic retinopathy as common adverse effects of subcutaneous semaglutide [29]. Dysaesthesia, a tingling or mild skin sensation, has been reported in 2.1–5.2% of patients on oral semaglutide at 25–50 mg doses [30]. The overall incidence of gastrointestinal side effects was comparable between oral semaglutide 20 mg and subcutaneous semaglutide 1 mg (56% vs. 54%, respectively). However, vomiting (16% vs. 9%) and diarrhea (20% vs. 14%) were slightly more frequent with the oral formulation, which may partly explain the higher treatment discontinuation rate observed in the oral group (27%) compared to the subcutaneous group (14%) [31]. Liraglutide demonstrates a similar safety profile. In clinical trials, 94% of adverse events were mild or moderate, predominantly gastrointestinal in nature [32]. Treatment discontinuation occurred in 6.4% of patients, significantly higher than in the placebo group (0.7%; $P<0.05$), with nausea being most prevalent in the initial 4–8 weeks [33, 34]. In non-diabetic individuals treated with 3.0 mg liraglutide for obesity, nausea was significantly more frequent than in placebo recipients [35]. Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, is also associated with gastrointestinal side effects. Between 78.9% and 81.8% of patients in the SURMOUNT-1 trial reported at least one adverse event, mostly during dose escalation, and generally of mild to moderate intensity [21]. Another study reported gastrointestinal side effect rates of 39.05%, 45.57%, and 49.25% for tirzepatide at 5 mg, 10 mg, and 15 mg, respectively [36]. Interestingly, nausea (13.27–24.08%), diarrhea (13.19–20.79%), and vomiting (5.67–13.98%) increased with dose [36]. Although these adverse effects are generally mild and self-limiting, their high frequency can affect patient adherence and quality of life. More importantly, beyond these commonly reported symptoms, a range of less frequent but potentially serious adverse effects has been identified and warrants careful consideration.

Although these adverse effects are often mild and self-limiting, proactive management can improve adherence and tolerability. Practical strategies include gradual meal-size reduction, avoidance of high-fat meals, maintaining hydration, and early treatment of constipation [37, 38]. In patients with persistent nausea or vomiting, short-term antiemetic therapy may be appropriate, and clinicians should consider monitoring for dehydration, electrolyte imbalance, and renal function deterioration in vulnerable individuals [37].

Severe Adverse Effects

Ocular complications, including blurred vision, visual impairment, and diabetic retinopathy, potentially influenced by genetic susceptibility, have been linked to semaglutide and lixisenatide in the FDA Adverse Event Reporting System [39]. In this context, non-arteritic anterior ischemic optic neuropathy (NAION) warrants particular attention. NAION is a rare ischemic optic neuropathy and one of the most common causes of acute painless vision loss in older adults, with an estimated background incidence of approximately 2–10 cases per 100,000 persons per year [40]. In a large retrospective cohort study, Hathaway et al. reported a higher cumulative incidence of NAION over 36 months

among patients prescribed semaglutide compared with non-GLP-1 RA comparators, both in individuals with T2DM (8.9% vs. 1.8%) and in those with overweight or obesity (6.7% vs. 0.8%) [41]. Given the observational design, these findings indicate an association rather than causality. Potential mechanisms remain speculative and may involve impaired optic nerve head perfusion, autonomic effects on vascular tone, and rapid metabolic shifts in high-risk individuals. Rapid glycemic improvement is hypothesized to precipitate retinopathy by outpacing retinal adaptation, though long-term control is likely protective [31]. The clinical relevance of this signal is being evaluated in the ongoing FOCUS trial, a long-term study designed to assess diabetic retinopathy outcomes in patients treated with semaglutide [42]. Results are anticipated in 2026, and should provide more definitive evidence regarding whether semaglutide is associated with retinopathy progression beyond the effect of rapid glycemic improvement [42]. Serious gastrointestinal and hepatic events have also been reported. In the STEP 1 trial, 7% of semaglutide users discontinued treatment due to adverse events. Gallbladder disorders, such as cholelithiasis, were more frequent in the semaglutide group (2.6%) than in placebo (1.2%) [28]. A population study by Sodhi et al. involving 16 million individuals found higher risks of pancreatitis, bowel obstruction, and gastroparesis with semaglutide or liraglutide compared to bupropion-naltrexone, although no significant association with biliary disease was found [43]. Conversely, He L et al. reported increased risks of gallbladder disease (relative risk (RR) 1.27), acute cholecystitis (RR 1.36), and cholelithiasis (RR 2.29) with prolonged or high-dose liraglutide use [44]. A meta-analysis by Gong et al. indicated that tirzepatide increases the risk of gallbladder and biliary disease (RR 1.52), particularly cholelithiasis (RR 1.67), though no dose-dependency was observed [45]. Observational data suggest an association between GLP-1 RA use and intestinal obstruction compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors, although causality cannot be inferred from retrospective designs. One large-scale study reported a hospitalization rate of 1.9 per 1,000 person-years for GLP-1 RA users vs. 1.1 for SGLT-2 inhibitors [46]. This risk increased over time (hazard ratio up to 3.48 after 1.6 years) [46]. However, a meta-analysis found no significant overall increase in bowel obstruction risk across GLP-1 RAs (odds ratio (OR) 1.95; 95% confidence interval (CI) 0.43–8.79), though liraglutide specifically was associated with a higher risk (OR 3.0; 95% CI 2.03–4.45) [47]. Interestingly, because GLP-1 RAs delay gastric emptying, there has been concern that their use before anesthesia or procedural sedation could increase the risk of pulmonary aspiration. The American Society of Anesthesiologists (ASA) issued consensus guidance recommending withholding daily GLP-1 RAs on the day of elective procedures and weekly formulations for one week prior; however, subsequent multi-society guidance emphasized individualized risk assessment and stated that most patients can continue GLP-1 RAs before elective surgery [48, 49]. Notably, a systematic review found no consistent increase in aspiration or pneumonia risk associated with GLP-1 RA use for elective surgery or upper endoscopy [50]. Preventive strategies recommended in perioperative guidance include assessing for high-risk features, considering a 24-hour liquid diet in higher-risk patients, use of point-of-care gastric ultrasound when available, and anesthesia plan modification when aspiration risk is judged to be elevated [49]. Concerns have long existed about pancreatitis, especially in the context of rapid weight loss or gallbladder dysfunction. Although mechanisms such as pancreatic duct blockage or inflammation were proposed, most recent evidence suggests that semaglutide does not significantly increase the risk of acute pancreatitis in patients with or without T2DM [51]. Notably, most large-scale studies have not shown an overall increased cancer risk with GLP-1 RAs. A cohort study by Wang et al. showed that semaglutide use was associated with a reduced risk of pancreatic (hazard ratio (HR) 0.41), gallbladder (HR 0.35), and kidney cancer (HR 0.76) compared to insulin [52]. However, when compared to metformin, GLP-1 RAs were linked to a higher incidence of kidney cancer (HR 1.54), suggesting that patient background and comparator therapy are important considerations [52]. Laboratory data also suggest caution in patients with GLP-1 receptor-expressing neuroendocrine tumors, as these drugs may promote tumor growth [53]. Findings on medullary thyroid cancer (MTC) remain inconclusive. A French nationwide study reported an increased risk of thyroid cancer (adjusted HR 1.58), including MTC (adjusted HR 1.78), whereas a Korean study found no such association [54, 55]. Overall, these findings should be interpreted as mixed observational associations and selected safety signals rather than definitive causal evidence, and ongoing long-term surveillance is warranted. Finally, dermatological reactions, ranging from alopecia to severe immune-mediated skin disorders such as angioedema, have also been observed, occasionally requiring immunosuppressive treatment [56]. Taken together, while severe adverse events are relatively rare, they span multiple organ systems and can carry significant clinical consequences. As the use of GLP-1 RAs expands to broader populations, ongoing surveillance and individualized risk assessment remain critical to ensure their safe and responsible use. To further illustrate the spectrum and frequency of adverse events, Table 2 provides a comparative overview of side effects reported across different GLP-1 RAs as listed by the EMA.

Table 2 Comparison of European Medicines Agency listed side effects of GLP-1 RAs

Symptoms	Oral Semaglutide (Rybelsus)	Semaglutide (Wegovy)	Semaglutide (Ozempic)	Tirzepatide (Mounjaro)	Liraglutide (Saxenda)	Dulaglutide (Trulicity)	Lixisenatide (Lyxumia)	Exenatide (Bydureon)	Exenatide (Byetta)
Reference	[57]	[58]	[29]	[59]	[60]	[61]	[62]	[63]	[64]
Immune system disorders									
Hypersensitivity	Uncommon	N/L	Uncommon	Common	N/L	Uncommon	N/L	N/L	N/L
Anaphylactic reaction	Rare	Rare	Rare	Rare	Rare	Rare	Uncommon	Rare	Rare
Angioedema	N/L	Rare	Not known	Rare	N/L	Rare	N/L	Not known	Not known
Nervous system disorders									
Dizziness	Common	Common	Common	Common	Common	N/L	Common	Common	Common
Dysgeusia	Uncommon	Common	Uncommon	Uncommon	Common	N/L	N/L	Uncommon	Uncommon
Dysaesthesiae	Common	Common	N/L	Uncommon	N/L	N/L	N/L	N/L	N/L
Headache	N/L	Very common	N/L	N/L	Very common	N/L	Very common	Common	Common
Somnolence	N/L	N/L	N/L	N/L	N/L	N/L	Common	Uncommon	Uncommon
Gastrointestinal disorders									
Nausea	Very common	Very common	Very common	Very common	Very common	Very common	Very common	Very common	Very common
Diarrhoea	Very common	Very common	Very common	Very common	Very common	Very common	Very common	Very common	Very common
Vomiting	Common	Very common	Common	Very common	Very common	Very common	Very common	Common	Very common
Constipation	Common	Very common	Common	Very common	Very common	Common	N/L	Common	Common
Abdominal distension	Common	Common	Common	Common	Common	Common	N/L	Common	Common
Abdominal pain	Common	Very common	Common	Very common	Common	Very common	N/L	Common	Common
Dyspepsia	Common	Common	Common	Common	Common	Common	Common	Common	Common
Delayed gastric emptying	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Rare	Rare	Uncommon	Uncommon
Gastritis	Common	Common	Common	N/L	Common	N/L	N/L	N/L	N/L
Acute pancreatitis,	Rare	Uncommon	Uncommon	Uncommon	Uncommon	Rare	N/L	N/L	Not known
Gastrooesophageal reflux disease	Common	Common	Common	Common	Common	Common	N/L	Common	Common
Flatulence	Common	Common	Common	Common	Common	Common	N/L	Common	Common
Eructation	Uncommon	Common	Common	Common	Common	Common	N/L	Uncommon	Uncommon
Intestinal obstruction (Nonmechanical intestinal obstruction)	Not known	Not known	Not known	N/L	Not known	Not known	N/L	N/L	Rare
Skin and subcutaneous tissue disorders									
Rash	N/L	N/L	N/L	N/L	Common	N/L	N/L	N/L	Not known
Urticaria/ Pruritus	N/L	N/L	N/L	N/L	Very common	N/L	Uncommon	Common	Common
Hair loss (alopecia)	N/L	Common	N/L	Common	N/L	N/L	Very common	Uncommon	Uncommon
Cutaneous amyloidosis	N/L	N/L	N/L	N/L	Not known	N/L	N/L	N/L	N/L
Hyperhidrosis	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Uncommon	Common
Injection site abscesses and cellulitis	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Not known	N/L
Macular and papular rash	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Not known	N/L

Table 2 (continued)

Symptoms	Oral Semaglutide (Rybelsus)	Semaglutide (Wegovy)	Semaglutide (Ozempic)	Tirzepatide (Mounjaro)	Liraglutide (Saxenda)	Dulaglutide (Trulicity)	Lixisenatide (Lyxumia)	Exenatide (Bydureon)	Exenatide (Byetta)
Hepatobiliary disorders									
Cholelithiasis	Uncommon	Common	Common	Uncommon	Common	Uncommon	Uncommon	N/L	Uncommon
Cholecystitis	N/L	N/L	N/L	Uncommon	Uncommon	Uncommon	Uncommon	N/L	Uncommon
Eye disorders									
Diabetic retinopathy complications	Common	Common	Common	N/L	N/L	N/L	N/L	N/L	N/L
Cardio-vascular									
Increased heart rate	uncommon	Uncommon	Uncommon	N/L	N/L	N/L	N/L	N/L	N/L
Orthostatic hypotension	N/L	Uncommon	N/L	N/L	N/L	N/L	N/L	N/L	N/L
Hypotension	N/L	Uncommon	N/L	Common	N/L	N/L	N/L	N/L	N/L
Psychiatric disorders									
Insomnia	N/L	N/L	N/L	N/L	Common	N/L	N/L	N/L	N/L
Infections and infestations									
Influenza, Upper respiratory tract infection, Cystitis, Viral infections	N/L	N/L	N/L	N/L	N/L	N/L	Common	N/L	N/L
Musculoskeletal system									
Back pain	N/L	N/L	N/L	N/L	N/L	N/L	Common	N/L	N/L
General disorders and administration site conditions									
Injection site reactions	N/L	Common	Uncommon	Common	Common	Uncommon	N/L	Common	uncommon
Fatigue	Common	Very common	Common	Common	Common	Common	N/L	Common	N/L
Malaise	N/L	N/L	N/L	N/L	Uncommon	N/L	N/L	N/L	N/L
Feeling jittery	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Uncommon	Common
Asthenia	N/L	N/L	N/L	N/L	Common	N/L	N/L	Common	Common
Injection site pruritus	N/L	N/L	N/L	N/L	N/L	N/L	Common	Common	N/L
Injection site pain	N/L	N/L	N/L	Uncommon	N/L	N/L	N/L	N/L	N/L
Injection site erythema	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Common	N/L
Metabolism and nutrition disorders									
Hypoglycemia	N/L	N/L	N/L	N/L	Common	N/L	N/L	N/L	N/L
Hypoglycaemia in patients with type 2 diabetes	N/L	Common	N/L	N/L	N/L	N/L	N/L	N/L	N/L
Hypoglycaemia (with insulin)	N/L	N/L	N/L	N/L		N/L	N/L	Common	N/L
Hypoglycaemia (in combination with a sulphonylurea and/or a basal insulin)	Very common	N/L	Very common	Very common	N/L	N/L	Very common	Common	N/L
Hypoglycaemia (in combination with metformin alone)	N/L	N/L	N/L	Uncommon	N/L	N/L	Common	N/L	N/L

Table 2 (continued)

Symptoms	Oral Semaglutide (Rybelsus)	Semaglutide (Wegovy)	Semaglutide (Ozempic)	Tirzepatide (Mounjaro)	Liraglutide (Saxenda)	Dulaglutide (Trulicity)	Lixisenatide (Lyxumia)	Exenatide (Bydureon)	Exenatide (Byetta)
Hypoglycaemia (when used as monotherapy or in combination with metformin plus pioglitazone)	N/L	N/L	N/L		N/L	Common	N/L	N/L	N/L
Hypoglycaemia1 when used with metformin and SGLT2i	N/L	N/L	N/L	Common	N/L	N/L	N/L	N/L	N/L
Hypoglycemia (with sulphonylourea)	N/L	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Very common
Hypoglycaemia (when used in combination with insulin, glimepiride, metformin† or metformin plus glimepiride)	N/L	N/L	N/L	N/L	N/L	Very common	N/L	N/L	Very common
Hypoglycaemia when used with other oral antidiabetic products	Common	N/L	Common	N/L	N/L	N/L	N/L	Very common	N/L
Decreased appetite	Common	N/L	Common	Common	N/L	Common	N/L	common	Common
Dehydration	N/L	N/L	N/L	N/L	Uncommon	Uncommon	N/L	N/L	Uncommon
Other									
Weight decrease	Uncommon	N/L	N/L	Uncommon	N/L	N/L	N/L	N/L	N/L
Drug-induced thrombocytopenia	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Not known	N/L
Feeling jittery	N/L	N/L	N/L	N/L	N/L	N/L	N/L	N/L	N/L
Altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine	N/L	N/L	N/L	N/L	Rare	N/L	N/L	Uncommon	Uncommon

N/L, not listed; SGLT-2, sodium/glucose cotransporter 2

Long-Term Safety Concerns and Unknowns

The long-term safety profile of GLP-1 RAs remains an area of active investigation, particularly in individuals using these agents off-label for weight loss without coexisting T2DM. While their clinical benefits in approved populations are well established, the growing and often inappropriate use of GLP-1 RAs raises concerns about poorly understood or underreported risks in individuals for whom these drugs were not originally intended. For instance, a notable 4-year study of semaglutide revealed a slightly higher incidence of gallbladder complications among treated participants compared to placebo (2.8% vs. 2.3%) [15]. Furthermore, incretin-based therapies, including GLP-1 RAs and dipeptidyl peptidase-4 (DPP-4) inhibitors, have been associated with elevated serum lipase and amylase levels, markers that may reflect subclinical pancreatitis with long-term use [65]. Cardiovascular data on GLP-1 RAs used off-label have produced

mixed results. Liraglutide and semaglutide are known to cause dose-dependent increases in heart rate, up to 3.2 bpm with semaglutide 1.0 mg, likely via autonomic modulation or direct stimulation of sinoatrial node pacemaker cells [66]. This effect may, at least in part, reflect autonomic (including sympathetic/adrenergic) modulation in response to GLP-1 receptor activation. While these modest heart rate increases are generally not associated with adverse cardiovascular outcomes in large cardiovascular and kidney outcome trials, where several GLP-1 RAs demonstrate overall cardiovascular benefit, they may warrant closer monitoring in patients with established heart failure [66]. At the same time, semaglutide 2.4 mg has demonstrated cardioprotective effects in high-risk populations, including a 20% reduction in major adverse cardiovascular events, underscoring the need for careful patient selection and individualized risk assessment [66]. Changes in body composition also warrant attention. While GLP-1 RAs effectively reduce fat mass, several studies have documented concurrent reductions in fat-free mass, including skeletal muscle [67–69]. This risk of muscle loss highlights the need for ongoing body composition monitoring and the implementation of resistance exercise and adequate protein intake. Such precautions may be lacking in individuals using these medications off-label and without medical supervision. Importantly, weight loss, regardless of etiology, is typically accompanied by some reduction in lean mass, and this is not unique to GLP-1 RA therapy. During diet-induced weight loss, approximately 24–28% of weight lost may derive from fat-free mass, whereas combining diet with exercise can reduce this proportion to 11–13% [70]. Larger and more rapid weight loss, such as after bariatric surgery, produces substantial reductions in total body weight, and is also associated with clinically relevant lean mass loss, supporting the importance of adequate protein intake and resistance training to mitigate functional consequences [71]. Therefore, changes in lean mass observed with GLP-1 RAs should be interpreted within the broader context of weight-loss physiology rather than as a drug-specific adverse effect per se, and their clinical relevance should be assessed alongside muscle function measures, which have not been routinely evaluated in many GLP-1 RA trials. Neuropsychiatric outcomes have been reported during GLP-1 RA therapy, but current evidence largely reflects pharmacovigilance signals and observational data rather than causally established adverse reactions. Although weight loss may improve psychological well-being for many, some patients report insomnia, anxiety, depression, and even suicidal ideation while on GLP-1 RAs [72–74]. These symptoms may be exacerbated by underlying psychiatric disorders or glycemic instability, and both the EMA and FDA are currently reviewing the evidence [72, 74]. The EMA initiated a signal review in July 2023 after approximately 150 case reports of suicidal thoughts and self-injury were retrieved across GLP-1 RAs, noting that exposure exceeded 20 million patient-years and that causality was unclear [75]. Following review of non-clinical data, clinical trials, post-marketing surveillance, and real-world evidence studies, the EMA PRAC concluded in April 2024 that the available evidence does not support a causal association between GLP-1 RAs and suicidal or self-injurious thoughts and actions, and that product information updates were not warranted [76]. Nonetheless, given the clinical relevance and limitations of spontaneous reports, clinicians should remain vigilant, particularly in patients with pre-existing psychiatric illness, and should counsel patients to report emergent mood changes or suicidal ideation. Additionally, semaglutide use has been associated with increased rates of erectile dysfunction and testosterone deficiency in otherwise healthy persons without obesity, raising further questions about its long-term impact on mental and sexual health [77]. A particularly challenging aspect of GLP-1 RA therapy is the tendency for significant weight regain after treatment cessation. However, it is important to emphasize that this pattern reflects the chronic, relapsing nature of obesity and is not unique to GLP-1 RAs, as weight regain is commonly observed after discontinuation of many weight-loss interventions. Therefore, post-treatment weight regain should be framed primarily as a manifestation of disease biology rather than a drug-specific adverse event [78]. Studies suggest that this is driven in part by a rebound in appetite, likely linked to reduced GLP-1 signaling in brain regions involved in reward and satiety [72]. In one randomized trial, patients regained approximately two-thirds of the weight they had lost within one year of stopping semaglutide [79]. Similar outcomes were observed in the SURMOUNT-4 trial of tirzepatide, where patients switched to placebo regained a substantial portion of their previously lost weight over the 52-week follow-up [80]. Even when paired with continued diet and exercise, long-term weight maintenance remains elusive for many patients once pharmacotherapy ends [81]. In addition to metabolic and neuropsychiatric effects, GLP-1 RAs can lead to systemic adverse events such as headaches, dizziness, and gallbladder dysfunction, likely due to reduced cholecystokinin-mediated contractility [81]. While GLP-1 RAs hold promise for treating non-alcoholic steatohepatitis, some studies have reported elevated liver enzymes and rare cases of autoimmune hepatitis [65]. Renal effects are similarly complex. Although agents like liraglutide may improve renal markers by reducing inflammation and proteinuria, volume depletion from gastrointestinal side effects can increase the risk of acute kidney injury [81]. Enzyme elevations are also common, with semaglutide increasing serum amylase and lipase by 13% and 22%, respectively, and tirzepatide showing even greater increases [81]. GLP-1

RAs represent a powerful and promising tool for metabolic disease management. However, their long-term safety, particularly in off-label use, demands a cautious, individualized approach. Clinical benefits must be carefully weighed against the potential for adverse outcomes, and treatment should be paired with ongoing monitoring, patient education, and a structured plan for sustainable lifestyle change.

Equity, Cost, and Ethical Concerns

While GLP-1 RAs have demonstrated substantial clinical benefits in the treatment of T2DM and obesity, their use is accompanied by significant financial costs [82]. This has raised concerns about their overall cost-effectiveness, equitable access, and ethical prescribing practices, particularly as their indications expand beyond T2DM into obesity and metabolic-related conditions. Numerous studies have attempted to assess the balance between clinical efficacy and economic burden. In a study by DeKoven et al., involving 234 patients treated with liraglutide and 182 with exenatide, pharmacy costs were significantly higher for liraglutide ($2,002 vs. $1,799; $P<0.001$). However, a greater proportion of patients on liraglutide achieved HbA1c levels below 7%, suggesting superior glycemic control and clinical efficacy despite the increased cost [83]. A more recent cost-effectiveness analysis compared tirzepatide (at 5 mg, 10 mg, and 15 mg doses) to semaglutide. While tirzepatide was associated with improved survival and clinical outcomes, it also incurred higher medical expenses [84]. The incremental cost-effectiveness ratios (ICER) were $75,803, $58,908, and $48,785 per quality-adjusted life year (QALY) gained for the 5 mg, 10 mg, and 15 mg doses, respectively, indicating a dose-dependent increase in cost-effectiveness [84]. When compared with insulin, GLP-1 RAs generally result in higher medication and outpatient costs. However, these are often offset by a reduced need for emergency visits and hospitalizations due to better glycemic control and a lower incidence of hypoglycemia [85]. Still, GLP-1 RAs are generally less cost-effective than older oral antidiabetic agents such as dipeptidyl peptidase-4 inhibitors, sulfonylureas, or thiazolidinediones [86]. In obesity management, semaglutide (1 mg) has emerged as the most cost-effective among GLP-1 RAs, with an ICER of $135,467 per QALY [82]. Despite this, GLP-1 RAs remain a less cost-effective strategy for obesity alone compared to their use in diabetes management [82]. Nonetheless, the development of oral formulations and generally favorable safety profiles contribute to their growing appeal in clinical practice [82]. Beyond cost-effectiveness, substantial disparities in access to GLP-1 RAs are influenced by socioeconomic status, education, and insurance coverage. A Swedish cohort study of 16,436 individuals found that higher income, higher educational attainment, and male sex were significantly associated with off-label use of GLP-1 RAs [87]. The growing role of private online health platforms has further complicated prescribing practices. Some of these digital dispensaries have been implicated in inappropriate or non-guideline-based prescriptions, which can exacerbate access disparities and compromise patient safety [87]. Health insurance coverage is another critical determinant of access. Variability in co-pays, coverage limitations, and prior authorization requirements can significantly restrict availability, especially in countries like the United States where insurance systems are fragmented and often inadequate [88, 89]. Access is even more limited in low- and middle-income countries, where high drug prices and under-resourced healthcare systems make GLP-1 RAs largely inaccessible to the majority of patients, regardless of clinical need [90]. A further issue complicating equitable access is the global shortage of GLP-1 RAs. As societal stigma around obesity decreases and public interest in pharmacological weight loss increases, driven in part by media influence, demand has surged. Since 2022, Europe has faced intermittent shortages of semaglutide (Ozempic), liraglutide (Saxenda, Victoza), and dulaglutide (Trulicity) [91]. This high demand has led not only to restricted availability for patients with legitimate clinical indications, but also to the emergence of counterfeit products sold through unauthorized channels, raising serious safety concerns [91]. This trend also raises ethical concerns, as individuals without medical indications increasingly access these therapies for aesthetic or non-therapeutic purposes, potentially at the expense of patients with chronic disease [92]. In response, the EMA and the Heads of Medicines Agencies, through the Medicines Shortages and Safety Steering Group, have issued targeted recommendations to manage and mitigate the impact of these shortages (Table 3) [91].

Altogether, the use of GLP-1 RAs is shaped not only by clinical benefit but also by complex interactions between cost, access, prescribing practices, and health policy. To ensure equitable use, further research is needed to better understand how socioeconomic status, insurance type, and national health infrastructure affect access to these increasingly important therapies.

Conclusions and Future Directions

GLP-1 RAs have revolutionized the treatment for T2DM and obesity. Their demonstrated ability to improve glycemic control, induce significant weight loss, and provide protective effects across multiple organ systems marks

Table 3 EMA and the Heads of Medicines Agencies, through the Medicines Shortages and Safety Steering Group recommendations for mitigating GLP-1 RAs shortages

Marketing authorisation holders	Recommendations
	• Seek regulatory approval for promotional activities and pair them with awareness campaigns on responsible use. • Increase manufacturing capacity and implement short-term mitigation. • Involve EMA's SPOC WP and MSSG in decisions affecting supply and availability.
Member States	• Implement and monitor mitigation measures; exchange information via SPOC WP. • Consider controlled distribution at national level in collaboration with marketing authorisation holders. • Develop guidelines (with experts/learned societies) to prioritise patients in need during shortages.
Healthcare professionals	• Prescribe GLP-1 RAs strictly according to approved indications and national guidelines. • Avoid prescribing for cosmetic weight loss (patients without obesity or obesity-related health problems). • Pharmacists should follow dispensing restrictions in their country. • Switch patients to suitable alternatives if medicines are unavailable.
Patients and the public	• Use GLP-1 RAs only with a prescription and under medical supervision. • Be aware of side effects. • Do not purchase GLP-1 RAs from unverified online sources due to risk of falsified products. • Base weight management on diet and physical activity, consulting healthcare professionals for guidance.

EMA, European Medicines Agency; HMA, Heads of Medicines Agencies; MSSG, Medicines Shortages and Safety Steering Group; GLP-1 RAs, Glucagon-Like Peptide-1 Receptor Agonists; SPOC WP, Medicines Shortages Single Point of Contact Working Party

Table 4 Strategic recommendations for optimizing GLP-1 RAs therapy

Long-term safety	Recommendation
	Establish robust post-marketing surveillance and patient registries for monitoring delayed side effects.
Patient selection	Develop personalized profiling tools to identify high-responder, low-risk candidates.
Muscle mass, muscle function, and nutritional status	Standardize body composition and muscle function assessment and encourage adequate protein intake plus resistance training programs.
Mental health and sexual health	Include routine screening for neuropsychiatric symptoms and sexual dysfunction.
Off-label use regulation	Enforce tighter restrictions on aesthetic or non-indicated prescribing.
Access and equity	Improve insurance coverage, lower drug costs, and expand access in low- and middle-income countries.
Public and healthcare professional education	Launch targeted education campaigns for the public and structured training for healthcare professionals to improve prescribing, monitoring, and management of GLP-1 RA therapy and its adverse effects.

GLP-1 RAs, Glucagon-Like Peptide-1 Receptor Agonists

them as one of the most impactful drug classes in contemporary metabolic medicine. However, their rapid uptake, including widespread off-label use for non-medical purposes, has revealed a series of challenges that demand closer attention. While most patients tolerate GLP-1 RAs well, we highlighted a wide range of adverse effects, from common gastrointestinal disturbances to rare but serious complications affecting the pancreas, gallbladder, kidneys, eyes, and mental health. These risks are amplified when medications are used without appropriate clinical oversight, as is increasingly the case in cosmetic or aesthetic applications. Importantly, the problem of post-treatment weight regain, unequal access to therapy, high treatment costs, and drug shortages all contribute to the complexity of implementing GLP-1 RAs safely and equitably on a large scale. A notable gap persists in long-term safety data, particularly for individuals using GLP-1 RAs without formal indications. The lack of structured post-marketing surveillance and insufficient research into long-term quality of life outcomes, including effects on muscle mass, nutrition, and psychological well-being, limit our ability to fully assess the risk-benefit ratio over time. As such, a shift is needed- from viewing GLP-1 RAs as a singular intervention to integrating them within personalized, lifestyle-based care models that are dynamic, ethical, and sustainable. To effectively address these challenges and support optimal patient outcomes, a set of actionable recommendations has been outlined in Table 4.

Future research should prioritize the development of individualized treatment frameworks that incorporate GLP-1 RAs as part of dynamic, long-term care strategies, rather than isolated pharmacologic solutions. This includes exploring biomarkers of responsiveness, intermittent dosing protocols, and adjunctive therapies to support muscle preservation and psychological well-being. Additionally, given the consistent pattern of weight regain after cessation of GLP-1 RAs, future clinical strategies should include structured discontinuation protocols. These might involve pharmacologic tapering, integration of behavioral interventions, and extended follow-up to sustain lifestyle changes and prevent relapse. Such models could be particularly important for patients who respond well to initial treatment but lack access to long-term therapy due to cost or supply constraints.

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