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GLP-1 Receptor Agonists: Emerging Indications, Limitations, and Future Directions

Simran Kaur[1,2*], Liriam Campos Hevia[2,3], Diane Lee[2,3], Haroon Mesdaq[2], Joleen Wong[4], Fatimetou Diallo[5], Shreya Anil[6], Nadia Gharibyar[2], Sarah Gharibyar[2]

[1]Independent Researcher, Red Bluff, USA
[2]New Leaf Peer 2 Peer, LLC, Aurora, USA
[3]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, USA
[4]University of Pittsburgh, Pennsylvania, USA
[5]Capital University, Ohio, USA
[6]Michigan State University, Michigan, USA
Email: *s0skaur1503@gmail.com

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Abstract

Objective: This article outlines the current trajectory of GLP-1 drugs, their future uses, and potential limitations, synthesizing evidence from randomized controlled trials, real-world studies, and emerging clinical literature. **Background:** There are a handful of GLP-1s currently on the US market (Dulaglutide, Liraglutide, Semaglutide, Tirzepatide) with FDA approval to treat diabetes, obesity, and, in some cases, sleep apnea and metabolic steatohepatitis. These therapies differ from earlier glucose-lowering agents by offering additional benefits beyond diabetes, such as improved weight management and cardiometabolic outcomes. As evidence of additional therapeutic effects continues to emerge, research efforts are expanding the potential clinical applications of GLP-1-based therapies. Evidence shows benefits beyond glycemic control, including cardiovascular, renal, and neurologic outcomes. **Results:** Currently, GLP-1s are limited by known side effects (primarily gastrointestinal) and other barriers to access, including cost. Data is limited, especially on long-term use, and new side effects are emerging; there is a need for more research on their use, and new drugs with modified mechanisms/dosage forms may help mitigate safety risks. Several adverse effects appear to be dose-dependent and influenced by patient-specific comorbidities. **Conclusions:** GLP-1s are indicated for treating adults with diabetes/obesity, but are highly effective at preventing their many complications and gaining traction for other therapies (cardio/metabolic, renal, hepatic, and more). Ongoing phase 3 trials and next-generation GLP-1 and dual-agonist therapies may help address current safety and accessibility limitations.

Keywords

Pharmacist Interventions, GLP-1 Receptor Agonists, GLP-1 Medication Management, Medication Access, Side Effects

1. Introduction

GLP-1 receptor agonists make up a class of drugs that include dulaglutide, liraglutide, semaglutide, exenatide, and Tirzepatide [1]. These synthetic peptides regulate glucose by mimicking the effects of GLP-1, a naturally occurring peptide hormone in the gastrointestinal tract [2]. An overview of current GLP-1 drugs in the U.S. is outlined in **Table 1** below.

Table 1. Overview of GLP-1 medications [3].

Drug	Mechanism	Half-life elimination	Administration
Dulaglutide (Trulicity)	GLP-1 agonist	~5 days	Subcutaneous, weekly
Liraglutide (Victoza, Saxenda)	GLP-1 agonist	~13 hours	Subcutaneous, daily/weekly
Semaglutide (Ozempic, Wegovy)	GLP-1 agonist	~1 week	Subcutaneous, weekly
Semaglutide tablets (Rybelsus)	GLP-1 agonist	~1 week	Oral, daily
Tirzepatide (Mounjaro, Zepbound)	Dual-acting GLP-1 agonist and GIP agonist	~5 days	Subcutaneous, weekly

Notably, Tirzepatide acts not only on GLP-1 receptors, but also on glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide, or GIP) receptors [2]. Like the GLP-1 peptide, GIP is an incretin hormone that stimulates glucose-dependent insulin secretion and has been shown to help regulate insulin release and fat metabolism, though it differs slightly in secretion patterns and biological action [4] [5]. For example, Tirzepatide, also known as Zepbound, has been explicitly marketed as a chronic weight management and obstructive sleep apnea therapy to emphasize its metabolic effects and dual action as a GLP-1/GIP agonist [6]. Compared with Mounjaro, Ozempic is marketed more for type 2 diabetes [7]. Overall, the active ingredient for both is Tirzepatide, with the exact mechanism of action and effects; the significant differences are in the marketing approach, clinical focus, and insurance coverage [8].

Generally, GLP-1s are known to delay gastric emptying, modulate appetite, and regulate blood glucose by mimicking the body's natural GLP-1 hormones [1]. Synthetic GLP-1s, such as semaglutide, however, are designed to last in the body for upwards of a week, as shown in **Table 1**, compared to natural GLP-1s, which last only minutes [9].

Currently, GLP-1 drugs are FDA-approved to treat type 2 diabetes, obesity, and in some cases, sleep apnea and metabolic steatohepatitis, but interest in other therapeutic fields is growing [3]. GLP-1s require dose monitoring and a titration schedule to maximize their full effects and to ensure a dose within the patient's tolerability [10]. The 2025 American Diabetes Association (ADA) guidelines recommend GLP-1s to mitigate cardiovascular risk and slow the progression of chronic kidney disease (CKD) in diabetic patients [11]-[13]. The GLP-1 line of therapy depends on the patient's specific conditions and comorbidities. For example, if a patient is obese, has a high ASCVD risk, and has type 2 diabetes, they may benefit from a GLP-1 as a first-line treatment [11]. Metformin remains a foundational first-line recommendation, and many patients continue to take it. For example, if the same patient mentioned previously were initially on Metformin, then a GLP-1 would be considered a second-line therapy according to ADA diabetes guidelines 2025 [11]. While GLP-1s as a drug class are still relatively new to the market, their unexpected demand from a vast patient population has sparked conversation on their possibilities and concerns, as access is limited and the literature is still lacking long-term data. To address these demands, research on additional indications and novel GLP-1 drugs is underway, as outlined in this paper.

2. New Indications

GLP-1s are rapidly evolving into a variety of treatment options beyond type 2 diabetes management. There have been multiple clinical trials evaluating its effects beyond glycemic control and its prospective benefits. GLP-1s were introduced in the early 2000s and continue to expand their scope into various disease management areas, as summarized in **Table 2** [14].

Table 2. Shows an overall timeline of GLP-1 medications and their benefits [14].

Year Released	Agent (Brand/Generic)	Notes
2005	Exenatide (Byetta)	• First GLP-1 RA approved by the FDA for type 2 diabetes. • Subcutaneous injection, twice daily • First, once daily dosing
2010	Liraglutide (Victoza)	• Clinical trials have shown cardiovascular and weight-loss benefits
2014-2017	Exenatide (Bydureon) Dulaglutide (Trulicity) Semaglutide (Ozempic)	• Extended release, longer acting. • Weekly dosing, which improves patient adherence
2021-2023	Semaglutide (Wegovy) Tirzepatide (Mounjaro)	• Clinical trials have shown benefits for obesity and weight management • Ongoing trials have seen benefits for NASH, HFpEF, and, in addition.

2.1. Metabolically-Dysfunctional-Associated Steatohepatitis

Non alcoholic fatty liver disease (NAFLD) is the most prominent liver disease

worldwide, estimated to affect almost a third of adults, partly due to the rise of metabolic syndromes such as diabetes and obesity [15]. The disease is characterized by excess accumulation of hepatic lipids, which can develop inflammation, fibrosis, and complications such as non-alcoholic steatohepatitis (NASH) and cirrhosis of the liver [15]. In August 2025, the FDA granted semaglutide (Wegovy) a new approval for the treatment of metabolic-associated steatohepatitis (MASH) [16]. Previously, the only known effective treatment for NAFLD was weight loss of at least 7% - 10%. In clinical practice, no other pharmacological agents were able to support the lifestyle changes necessary [15].

2.1.1. Sleep Apnea

Obstructive sleep apnea (OSA) is a sleep disorder that disrupts normal breathing during sleep. It impairs the upper airways, causing individuals with the disorder to experience hypopneas and low arterial oxygen saturation [17]. Over time, OSA can lead to significant complications, including neurocognitive changes, hypertension, and systemic inflammation [18] [19]. One important risk factor for OSA is obesity. In fact, obese patients are almost twice as likely to develop OSA compared to adults who are within their normal weight range [20]. Specifically, excessive fat around the neck and upper airway narrows the airway and increases collapsibility during sleep.

Furthermore, abdominal fat can reduce lung volume, further blocking normal airflow [20]. Given the obesity epidemic, the prevalence of OSA is expected to increase in the future [21]. The most common treatment for OSA is continuous positive airway pressure (CPAP) [20]. However, many patients are noncompliant with CPAP therapy. One study reported that approximately 46% of patients with OSA did not adhere to CPAP therapy due to limited education on device use, lack of follow-up care, malfunction issues, and financial constraints [22]. GLP-1s are currently being investigated for potential treatment of OSA. One review across multiple studies assessed how GLP-1s affect the apnoea-hypopnoea index (AHI), a key measure of OSA severity. The results showed that GLP-1s can reduce AHI, although the exact mechanism by which they improve OSA symptoms remains unclear [18]. One hypothesis is that GLP-1s exert their effects through weight loss, since obesity contributes to the development and exacerbation of OSA. In contrast, other studies found no significant correlation between changes in AHI and BMI in patients with a BMI above 30, suggesting that GLP-1s may have weight-independent effects on OSA symptoms [23]. The evidence is also inconsistent due to variability in study designs and durations, underscoring the need for further research [18].

In one analysis, patients with OSA who used GLP-1 medications experienced significant reductions in AHI, weight loss, and decreased blood pressure values [24]. Among the participants, obese individuals showed greater improvement, which highlights the relationship between obesity and OSA. Across the therapies examined, Tirzepatide reduced AHI more than liraglutide. This suggests that the specific type of GLP-1 may influence the extent of benefit [24]. In late 2024, the

FDA approved Tirzepatide (Zepbound) as the first GLP-1 for the treatment of moderate to severe OSA in adults [25].

2.1.2. Heart Failure

Heart failure (HF) is a condition in which the heart is unable to pump enough blood to meet the body's metabolic needs, typically due to structural or functional abnormalities [26]. It is classified into four different categories [27]. Overall, it is primarily categorized into heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF), which differ in etiology, treatment response, and prognosis [26]. There are a variety of trials evaluating the effects of GLP-1s in obesity and glycemic control, possibly leading to an overall control of comorbidities such as heart failure. For example, the LEADER trial evaluated the cardiovascular effects of Liraglutide as an add-on therapy in patients with type 2 diabetes [28]. The SURPASS trial assessed the efficacy and safety of Tirzepatide as an adjunct to insulin in patients with uncontrolled type 2 diabetes [29]. The SURMOUNT trial evaluated the effects of Tirzepatide in addition to diet and physical activity on maintaining weight reduction [29]. Lastly, the SUMMIT trial evaluated Tirzapetide as a possible therapy for patients with HFpEF and obesity [30].

GLP-1s were developed to improve glycemic control in diabetes; later, it was discovered that they could also help with weight loss and reduce major adverse cardiovascular events (MACE), especially in people with obesity [26]. In the SELECT trial, once-weekly semaglutide 2.4mg reduced MACE, composite HF (cardiovascular death (CV) or HF hospitalizations), CV death, and all-cause death in patients with and without HF, with consistent benefits in both HFpEF and HFrEF and no increase in serious adverse events [26]. In HFpEF, the STEP-HFpEF trials demonstrated that semaglutide improved symptoms, exercise capacity, inflammatory markers, and weight effects [31].

Small studies of Liraglutide in advanced HFrEF raised concerns about potential harm, including increased HF hospitalizations, leading to caution in that population [30]. However, SELECT results indicate that semaglutide is safe and effective across HF subtypes, potentially expanding its role beyond diabetes into CV risk reduction for patients with obesity, regardless of ejection fraction [26].

Earlier this year, a new development in HF highlighted the role of dual GLP-1/GIP. In the SUMMIT trial, Tirzepatide in patients with HFpEF and obesity significantly reduced the composite endpoint of cardiovascular death or worsening heart failure, with fewer hospitalizations for heart failure, and improved health status and quality of life [32]. This trial demonstrated evidence that GLP-1/GIP therapy can not only improve symptoms but also reduce clinical outcomes, benefiting patients with HFpEF and supporting its potential as a disease-modifying treatment [32].

2.1.3. Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and represents a

growing global health challenge [33]. As a progressive neurodegenerative disease, AD is characterized by memory loss, cognitive decline, and behavioral changes that affect activities of daily living [34]. Pathologically, it involves an accumulation of amyloid-beta plaques and neurofibrillary tangles, synaptic dysfunction, and chronic neuroinflammation [35]. Considered a multipathology disease, its exact cause and available treatments are still under investigation.

While GLP-1s are primarily used to treat type 2 diabetes and obesity, they have emerged as promising candidates for neuroprotection. GLP-1 receptors are expressed across major brain cell types and can cross the blood-brain barrier [36]. Research suggests that AD disrupts the function of several brain cell populations, including oligodendrocytes and astrocytes. Oligodendrocytes, which myelinate neurons to allow rapid signal conduction, are often reduced in patients with AD, but GLP-1s have been shown to increase oligodendrocyte progenitor cells [36] [37]. Astrocytes usually support neurons by regulating neurotransmitters, providing metabolic energy, and maintaining the blood–brain barrier [38]. In AD, they often become overactive, leading to the release of inflammatory molecules and contributing to neuronal damage. GLP-1 receptor agonists can help shift astrocytes back toward a protective role by reducing inflammation, improving glutamate clearance, and enhancing energy support to neurons [36]. Early clinical studies indicate that agents including semaglutide and liraglutide may reduce amyloid and tau pathology, reduce neuroinflammation, improve synaptic function, and preserve cognitive performance in AD [39]. In one animal model, semaglutide decreased markers of gliosis and phosphorylated tau, thereby improving impaired cognitive function [40]. In another study, liraglutide reduced amyloid plaque burden by approximately 33% and enhanced synaptic plasticity [41]. Both studies used mouse models, but similar research is now being extended to human populations. In 2025, a large U.S. cohort of patients with type 2 diabetes who used semaglutide showed a significantly reduced risk of developing Alzheimer's disease compared with those on other antidiabetic medications such as insulin and metformin [42].

Other clinical trials have shown less consistent findings. In one randomized study of patients with mild AD, participants received either daily subcutaneous liraglutide or a placebo. The results indicate that Liraglutide failed to meet its primary endpoint of improving cerebral glucose metabolism. However, it demonstrated secondary benefits, including less brain volume loss and better composite cognitive scores than placebo [43].

Most trials are of limited duration, and larger, long-term studies, such as the ongoing EVOKE semaglutide trials, will be crucial for determining whether GLP-1s can meaningfully slow or prevent disease progression [44].

2.1.4. Addiction

The mechanistic role of GLP-1s in alcohol use disorder and other substance use disorders is still unclear. A small number of clinical studies have suggested GLP-1s may reduce alcohol intake by modulating the rewarding effect of alcohol or

producing a satiating mechanism consistent with the known impact on nutrient intake [45]. GLP-1s are also hypothesized to suppress seeking behaviors by modulation of stress systems [45]. In a small study of 48 participants with alcohol use disorder, those treated with once-weekly semaglutide drank significantly less alcohol per drinking day than the placebo group, producing initial evidence that semaglutide may reduce some craving and drinking outcomes [46]. More robust clinical trials are necessary to evaluate GLP-1s for alcohol use and other substance use disorders.

2.1.5. Weight Loss & Eating Disorders

Binge-eating disorder (BED) and bulimia nervosa (BN) may lead to obesity and cardiometabolic risk [47]. In obesity, even a 5% - 10% reduction in body weight can improve metabolic and cardiovascular health, reducing risk factors; however, sustaining that loss with lifestyle changes alone may be challenging [48].

GLP-1s contribute to weight management through appetite and gut-brain mechanisms, including slowed gastric emptying and layered gastric sensorimotor function [49]. In a physiologic study of healthy volunteers, Liraglutide administration led to meal-induced gastric adaptations without changes in meal satisfaction, although nausea was observed at high doses [49].

GLP-1s have shown significant clinical benefits for BED; A 2025 systematic review and meta-analysis of 5 studies and about 182 participants found greater weight loss, lower BMI, and waist circumference, and improvement in BED severity, even though it would benefit from a longer trial and more data to have a deeper understanding of the benefits [47].

A 2-year trial of liraglutide 2.4/3.0 mg resulted in significantly greater weight loss compared to orlistat [48]. Unlike GLP-1s, orlistat inhibits gastric and pancreatic lipases in the lumen of the gastrointestinal tract, thereby decreasing systemic fat absorption [50]. The most common adverse events are transient, mild-moderate nausea and vomiting [48]. Overall, GLP-1s can support weight-loss goals that matter for cardiometabolic health, may lessen the severity of BED and BN for some patients, and are being integrated into broader obesity care pathways [47] [51] [52].

Although GLP-1s are currently used to treat obesity and weight loss, with additional research suggesting benefits in treating binge eating disorder, one concern with the use of GLP-1s is the potential for exacerbation or development of eating disorder symptoms and psychopathology [51].

3. Emerging Side Effects

3.1. Current Side Effects

GLP-1 use is often limited by its adverse effects, most notably gastrointestinal effects such as diarrhea, nausea, vomiting, and constipation [53]. Studies have found increased risks of biliary disease, pancreatitis, bowel obstruction, and gastroparesis in patients taking GLP-1s for diabetes and obesity, with around 27 extra cases

per 10,000 treated persons experiencing higher risk. However, it is also worth noting that these patients may have had a higher baseline risk for these events to begin with [54]. Immunogenic effects, such as antibody formation, may also occur; however, these did not appear to affect efficacy or safety [55]. The FDA has required boxed warning labels for GLP-1s due to the risk of thyroid C-cell tumors. However, evidence is conflicting on the causative effect of GLP-1s on thyroid malignancies [56]. The FDA released a safety update warning in 2024 regarding reports of suicidal thoughts or actions in patients taking GLP-1s. However, preliminary evidence does not point to a causative effect [3].

3.1.1. Diabetes Ketoacidosis (DKA)

Diabetes ketoacidosis (DKA) is a complication associated with uncontrolled diabetes mellitus, affecting about a third of T2D patients. During DKA, the body lacks sufficient insulin to use glucose for energy, so it resorts to burning fat. This produces ketones, causing higher blood sugar and symptoms like nausea, vomiting, and abdominal pain [57]. It is the first clinical manifestation in patients with T1D. Still, it is more difficult to improve latent autoimmune diabetes in adults (LADA) patients, who are often misdiagnosed with T2D.

DKA is an emerging side effect of GLP-1, as case studies highlighting LADA patients who presented with gastrointestinal adverse reactions after use have recently been brought to attention. The case studies highlight the lack of studies on the side effects of GLP-1s in patients with LADA, as GLP-1 lacks evidence-based support in this patient population [58]. Scientists have hypothesized that gastrointestinal side effects may predispose patients to DKA, particularly when combined with energy restriction [59]. Other patients have been diagnosed with euglycemic diabetic ketoacidosis (EDKA), which presents similarly to DKA but without the abnormal glucose levels [59]. This was increased, particularly when used in conjunction with other glucose-lowering agents, such as SGLT2 inhibitors, a class for which EDKA is already a known and labeled risk [59]. Additional reports describe EDKA occurring in patients on GLP-1 therapy who were previously stable on treatment, including one case of an individual with an 8-year history of type 2 diabetes who developed EDKA after adding a low-carbohydrate diet [59]. This challenging condition was complex for physicians to treat, as the patient was diagnosed with type 2 diabetes for 8 years and had adherence to his medication, but only changed his diet to become low-carbohydrate [59].

Overall, the association of DKA with GLP-1s appears to occur when insulin is reduced or discontinued [60]. As GLP-1s do not suppress insulin secretion, they instead enhance glucose dependence [55] [58]. As previously mentioned, DKA is more commonly seen in patients on GLP-1 and in combination therapy with an SGLT-2 inhibitor [60].

However, there have also been reports of non-diabetic patients experiencing euglycemic ketoacidosis (EKA) while using GLP-1s, alarmingly escalating the range of patients in whom this side effect is present [61]. EKA is a common side effect characterized by euglycemia, metabolic acidosis, and ketonemia [62]. The

increased use of GLP-1s reflects an increasing incidence of EKA, which can be life-threatening [61].

3.1.2. Dental Effects

GLP-1s have been linked to various oral health concerns, including tooth decay, enamel erosion, and oral sensitivity [62]. These effects are thought to result from gastrointestinal side effects such as nausea, vomiting, and reflux, which repeatedly expose enamel to acidic conditions [62]. Delayed gastric emptying may further prolong reflux episodes and increase risk [63]. Xerostomia, or dry mouth, has also been reported in case studies and may be associated with appetite suppression and decreased oral intake [62].

At the same time, GLP-1s may provide protective benefits for oral health. Improved glycemic control reduces the risk of diabetes-related periodontal disease, while preclinical studies suggest GLP-1 therapies can promote osteogenic differentiation of periodontal ligament stem cells and decrease alveolar bone loss [64] [65]. Animal studies further show that GLP-1 signaling supports salivary gland function, where reduced activity was associated with apoptosis and impaired secretion [66].

Although both risks and benefits have been reported, the long-term dental impact of GLP-1 therapy remains unclear. Further studies are needed to determine whether specific formulations or patient populations are more susceptible to adverse oral effects.

3.1.3. Gastroesophageal Reflux Disease (GERD) via Delayed Gastric Emptying

GLP-1s are also associated with delayed gastric emptying, which is a risk factor for gastroesophageal reflux disease (GERD). Delayed gastric emptying can lead to prolonged stomach distension and increased intragastric pressure, making it easier for stomach contents to escape into the esophagus [67]. GLP-1s cause delayed gastric emptying by suppressing stomach muscle contractions, slowing the passage of food from the stomach to the small intestine [69]. Thus, patients may experience GERD symptoms, such as heartburn. In a study with adults aged 18 years or older with type 2 diabetes initiating GLP-1s, it was seen that the primary outcome was GERD, and the secondary outcome was its complications [68]. Although further studies are needed, this side effect appears to increase the risk in patients taking GLP-1 medications compared to the general population.

3.1.4. Compounded Medication Issues

Specific compounded GLP-1 formulations remain unapproved by the FDA due to concerns associated with compounded medication practices. While the FDA does not approve compounded drugs, federal regulations allow compounding when the medication is FDA-approved and listed on the FDA drug shortage list. This permits compounded versions to be distributed during limited supply [69]. However, the FDA has identified fraudulent compounded semaglutide and Tirzepatide products that were marketed in the U.S during shortages. These products caused

adverse side effects, including redness, swelling, pain, and a red lump that appears at the injection site. There were also associated dosing errors with compounded injectable semaglutide products. This shows that GLP-1s can be used dangerously, and healthcare professionals and providers must be more vigilant when it comes to checking the quality and administration of the proper medications [70].

4. Accessibility and Limitations

Glucagon-like peptide (GLP-1) receptor agonists, with generic names such as semaglutide and tirzepatide, have become the leading treatments for type 2 diabetes and obesity, proving effective in promoting weight loss and substantially improving renal and cardiovascular health [71]. Nevertheless, the high demand, combined with limited supply, has created significant accessibility challenges. The popularity of GLP-1 medications has led to nationwide shortages, making it increasingly difficult for patients with the prescription to obtain their medication [72]. With many challenges intertwined with affordability, patient education, and insurance coverage, these issues highlight the accessibility and limitations of GLP-1 therapy.

When prescribed for type 2 diabetes, GLP-1 drugs are often covered by insurance or Medicaid, but coverage for obesity is frequently ignored [73]. Patients repeatedly face barriers, such as high costs, step therapy, and prior authorizations, which can cause significant delays and sometimes discourage patients from treatment. For patients without insurance or with limited coverage, the monthly cost exceeds $1000, making GLP-1 therapy difficult to access [74]. These administrative and financial hardships highly impact low-income and minority patients, who studies show have high rates of obesity and diabetes but are least likely to gain access to treatment [75].

Minority communities feel the hardship of the high demand and low supply of GLP-1 drugs. Hispanic and Black communities have higher rates of diabetes and obesity, but are less likely to be prescribed medications compared to White Communities [75]. Even when the drug is prescribed, the high cost and low insurance coverage prevent most patients from starting their treatment and, in some cases, continuing to maintain therapy. The shortage of GLP-1 drugs has only added to the already intense problem, sometimes making patients find alternatives that are unsafe and would worsen their health [76]. These challenges show how shortages and financial barriers often leave minority communities carrying the heaviest burden, making it even harder to overcome the already deep inequities in obesity and diabetes care. These challenges have placed a significant burden on underserved communities, making it difficult for them to access the healthcare assistance and support they need.

Beyond supply shortages and financial costs, patients' lack of education about GLP-1 therapy is one of many barriers to accessing treatment. Many patients are unaware of insurance requirements, eligibility criteria, or safe ways to access therapy, leaving them incredibly vulnerable to misinformation or unsafe alternatives. Several patients stop taking GLP-1 medications early because they have unrealistic

expectations about how quickly weight loss will happen [77]. Side effects, dosing schedules, and the importance of lifestyle changes are not always explained, creating barriers to adherence and long-term success. Patient education can be beneficial by setting realistic goals, teaching patients how to manage side effects, and keeping them engaged in their treatment journey [77]. It can help bridge accessibility gaps by ensuring patients understand both the benefits and limitations of GLP-1 therapy.

There are other barriers to GLP-1 access, such as patients who are under 12 years old or patients with an aversion to injections. Childhood obesity is a global epidemic, with prevalence increasing with age [78]. Approximately 20% of American children are considered obese, and pediatric obesity rates in the US have more than tripled since 1960 [78]. Given the considerable impact of obesity on the development of future complications, guidelines support treating obesity and its comorbidities without stigma and delay [78]. While evidence does not support the use of weight loss medication in children, pharmacotherapy may be beneficial when behavioral interventions are insufficient [78]. Many weight-loss agents have not been approved for use in pediatric patients, and this treatment gap requires further research. Adherence to diabetes therapy is also often affected when patients are needle-averse or are fearful of injections [79]. GLP-1s are currently approved only for adult patients, and nearly all options on the market today involve injectable therapy.

The accessibility of GLP-1 therapies is shaped by a complex set of limitations: soaring demand and supply constraints, insurance barriers that restrict coverage, affordability disparities that exclude marginalized populations, and gaps in patient education that obstruct safe and effective use. While these drugs hold transformative potential for obesity and diabetes management, addressing these challenges is essential to prevent the deepening of existing health inequities. Comprehensive strategies that expand coverage, reduce cost burdens, stabilize supply, and strengthen patient education are necessary to ensure that GLP-1 therapies fulfill their promise equitably across all communities.

5. Future Directions

Several new therapies are currently in the GLP-1 research pipeline. Orfoglipron, Danuglipron, and CT-996 are oral, non-peptide GLP-1 receptor agonists at varying stages of clinical development [80]. Orfoglipron's 2025 Phase 3 trial results demonstrated promising efficacy in significantly reducing hemoglobin A1c levels over 40 weeks in adults with early type 2 diabetes; however, more long-term safety and efficacy data are needed [81]. Oral dosage forms may help overcome cost and accessibility barriers associated with injectable treatments [80].

GLP-1 therapies currently in late-stage clinical development, or phase 3 trials, include Cagrilintide-Semaglutide, Survodutide, Mazdutide, and Retatrutide, which are all injectable once-weekly therapies with additional mechanisms including amylin, glucagon, and other diverse targets [80].

To address the cost barriers to GLP-1 therapy, strategies include manufacturer

coupons, insurance prior authorizations, and payer-specific coverage models that can reduce patients' out-of-pocket expenses. However, these efforts may stay inconsistent and difficult for some patients to navigate. Expanding standardized insurance coverage and creating support programs will ensure that the cost does not remain the defining obstacle for people in need of treatment.

Improving accessibility also requires a stronger community focus. This means that we can develop culturally tailored education programs, engage marginalized communities, and provide clear communication about the benefits and effects of GLP-1 therapy. By meeting patients where they are, healthcare systems can close the gap between who qualifies for these therapies and who actually receives them.

Healthcare professionals, such as physicians, dentists, and pharmacists, play a huge role in bridging these gaps. Providers can easily advocate for fair coverage policies, help patients navigate prior authorizations, and educate them about managing side effects and realistic weight-loss expectations. Pharmacists, in particular, are well-positioned to support adherence, explain safe use, and connect patients with affordable programs. Altogether, these interventions can reduce cost-related dropouts, minimize side effects, educate patients, and improve positive long-term outcomes.

6. Conclusion

GLP-1-based treatments have produced significant advancements in the treatment of type 2 diabetes and obesity. Their incidental success in other therapeutic areas has garnered widespread attention, and research is underway to expand their indications for use in heart failure, sleep apnea, substance use disorder, Alzheimer's disease, and more. However, the drug class is still relatively new, and several emerging side effects, such as endocrine, gastrointestinal, dental, and other effects, require additional data to ensure safety, especially with long-term use. Current clinical development of GLP-1s aims to enhance safety, efficacy, and accessibility through novel dosage forms and additional mechanisms of action. Despite their current limitations, supporting appropriate access to GLP-1s can produce several therapeutic benefits for many patients and prevent complications from chronic diseases like diabetes, obesity, and more.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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