



# The Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonist Drugs: A Comprehensive Literature Review

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## Abstract

There is a new class of antihyperglycemic medications called glucagon-like peptide-1 receptor agonists (GLP-1RAs). They work by increasing the effects of insulin on peripheral tissues, decreasing the liver's glucose production, improving satiety through central nervous system action, as well as encouraging appropriate pancreatic cell production and (glucagon) suppression. GLP-1 agonists are a group of drugs used to manage type 2 diabetes mellitus and promote weight reduction. However, they cause several unfavorable side effects such as diarrhea, constipation, nausea, and vomiting, as expected. After extensive research, several clinical studies have found them to be safe for the heart and kidneys. Moreover, patients with a history of pancreatitis are advised to avoid GLP-1RA-based treatments, even though there is insufficient information to determine whether there is a causal relationship.

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## Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), which are a new class of antihyperglycemic medications, increase the effects of insulin on peripheral tissues, decrease the liver's glucose production, improve satiety through central nervous system action (CNS), as well as encourage appropriate pancreatic cell production and (glucagon) suppression. GLP-1RAs are effective in the treatment of type 2 diabetes mellitus (T2DM) and have a positive effect on weight reduction, GLP-1 increases satiety measures and reduces appetite by directly stimulating pro-opiomelanocortin and cocaine and amphetamine regulated transcript POMC/CART neurons while inadvertently decreasing neuropeptide Y (NPY) and agouti-related peptide (AgRP).

A possible treatment strategy for reducing appetite and obesity is the production of gastrointestinal (GI) peptides, which are satiety signals. GLP-1, which functions as a short-term postprandial signal, has long been known to limit food intake. However, the

satiety/satiety circuit that regulates food intake and body weight also involves GLP-1, which is generated in the brain [1].

GLP-1RAs, which have been authorized for the treatment of type 2 diabetes and obesity and include exenatide, dulaglutide, liraglutide, albiglutide, and most recently semaglutide, have emerged as a viable pharmacological approach for lowering calorie intake and body weight.

Patients with T1DM have been evaluated with the GLP-1RAs exenatide and liraglutide, and the published data consistently demonstrate weight loss, decreased total daily insulin needs and a slight improvement in glycemic control. Long-acting analogs have been shown in long-term cardiovascular results studies to reduce the likelihood of cardiovascular disease in addition to the impact of GLP-1 discussed above. Up until now, this effect has only been seen in patients who also had T2DM and cardiovascular risk, but new data suggests that it may also be applicable to people without a history of heart disease. Although the exact mechanism remains unknown, the cardiovascular effects will be crucial in advancing the use of GLP-1

RAs, which are already often suggested as second-line treatments for individuals whose metformin has failed. Treatment with GLP-1RAs for T1DM patients appears to be well tolerated, with rarely noticeable increases in the risk of hypoglycemia. GLP-1RA therapy can assist T1DM patients lose weight, partially improve their glycated hemoglobin (HbA1c) levels, and reduce their insulin doses without significantly increasing their risk of hypoglycemia. Patients with C-peptide who are overweight or cannot achieve their glycemic goals without hypoglycemia responded best to GLP-1 RA therapy [2].

### **T2DM therapy recommendations**

Many people continue to have difficulty with optimal glycemic control. Thus, obtaining different treatment choices is essential. In T2DM patients, once-weekly dulaglutide was found to be superior to metformin as monotherapy, sitagliptin as an addition to metformin and twice-daily exenatide as an addition to metformin and pioglitazone in three phase-3 registration studies. In these studies, dulaglutide's safety profile was similar to that of other GLP-1RA drugs on the market, which are mostly characterized by GI side effects, such as vomiting, nausea, and diarrhea. There has been conflicting evidence linking incretin-based medicines to acute pancreatitis and other pancreatic adverse effects, such as adenocarcinoma. GLP-1 RAs have been linked to increases in pancreatic enzymes.

In addition, according to other research, people with T2D have a greater chance of developing pancreatitis than people in general. Both the European Medicines Agency and the Food and Drug Administration have thoroughly examined data sets relevant to a pancreatic safety signal connected to incretin-based medicines. They concluded that not enough information was provided to establish a causal relationship. Both organizations keep an eye on pancreatic security [3].

Obesity has emerged as a critical public health issue over the past few decades. Effective prevention and treatment are required. Although bariatric surgery is the most effective medical treatment for morbid obesity-related weight reduction, less drastic measures are still needed. GLP-1RAs, a group of incretin-based medicines, are the most efficient treatment for obesity. By activating the GLP-1 receptor, they raise insulin secretion after meals, and by promoting satiety and delaying stomach emptying through their peripheral and central extra-pancreatic actions, they help in weight reduction. Semaglutide has been shown to have a significant capacity to reduce weight in several phase-3 clinical studies. As a result, it recently became the first long-acting GLP-1 RA to be licensed by and Drug Administration of the United States for the treatment of obesity [4].

## **Indications**

T2DM and, in certain cases, obesity are both treated with GLP-1RAs. Medications in this category include exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, and semaglutide. According to the American Diabetes Association, metformin is still the first-line medication recommended for type 2 diabetes. When adding a GLP-1 analog, patients with atherosclerosis, heart failure, or chronic kidney disease should be considered, as should those who are ineligible for or intolerant of metformin, those whose HbA1c levels are 1.5% or higher than the target, or those who do not reach their target A1c in 3 months [5], [6].

Semaglutide and high-dose liraglutide have also been given food and drug administration approval as pharmacologic therapies for people who are overweight or obese; those with other conditions may be recommended to take these drugs as well. Due to its positive effects on hemoglobin A1c levels and weight loss outcomes in individuals with T1DM, the use of GLP-1 analogs has become a research topic [7].

Evidence with a high level of certainty revealed that GLP-1RA decreased mortality from cardiovascular disease and other causes. Evidence with a moderate degree of certainty to high degree of certainty indicated that GLP-1RA may lower the incidence of fatal or non-fatal myocardial infarction and fatal or non-fatal stroke. GLP-1 RA was the most effective therapy for these two outcomes (fatal or non-fatal myocardial infarction/stroke) according to treatment rankings. Regarding safety outcomes, data with a limited degree of certainty indicated that GLP-1RA could reduce damaging renal function while having no effect on pancreatitis [8].

## **Mechanism of Action**

GLP-1RAs can lower glucose in several ways:

- a. Increase glucose-dependent insulin release from pancreatic b-cells

Increased insulin release is caused by the linking of GLP-1 to its receptor on pancreatic b-cells, which is glucose-dependent. Thus, GLP-1RAs support a level of translation of b-cell's insulin release and secretory capability while also maintaining its insulin reserves [9].

- b. Decrease endogenous glucose production

GLP-1RAs reduce the generation of endogenous glucose. At any glucose level, the a-cells are directly affected, becoming more glucose-sensitive and producing less glucagon. The amount of glucose produced by the liver decreases when glucagon is

suppressed, lowering the need for insulin, and improving glucose management [9].

In addition, through the GLP-1 receptors in the CNS, GLP-1RAs may influence peripheral glucose metabolism [10].

### c. Regulate food intake and energy utilization

Animal studies have shown that GLP-1RAs' central activation of GLP-1 receptors induces brown adipose tissue thermogenesis and white adipose tissue browning, which reduces food consumption and increases energy expenditure. In addition, individuals who received GLP-1RA therapy for a year had higher energy expenditure [11]. However, new animal research findings indicate that these processes may not play a substantial role in weight loss caused by long-term GLP-1RA medication [12].

### d. Delay stomach emptying

GLP-1RAs inhibit penta gastrin, meal-stimulated gastric pH production, and stomach emptying. GLP-1 receptors in the CNS and/or vagal afferent fibers, which comprise the vagus nerve, supply sensory information to the brainstem.

Postprandial glucose absorption is reduced as a result of delayed stomach emptying [13]. Compared to longer-acting GLP-1RAs, rapid-acting GLP-1RAs given with meals had greater effects on stomach emptying and are linked to greater reductions in postprandial glucose absorption [14].

### For weight loss

GLP-1RAs such as liraglutide and semaglutide were initially developed to treat T2DM but has since been found to be effective in lowering blood sugar levels and total body weight [15]. GLP-1 reduces body weight in several ways, including reducing appetite and hunger as well as promoting satiety, leading to lower calorie consumption [9].

GLP-1 increases satiety measures and reduces appetite by directly stimulating POMC/CART neurons while inadvertently decreasing NPY and AgRP [16] (Figure 1).

## Administration Method

The United States allows for the prescription of a wide range of GLP-1 agonist formulations. Due to their poor oral bioavailability, all of these medications were previously administered subcutaneously and through injection. Exenatide, unlike lixisenatide, liraglutide, albiglutide, dulaglutide, and semaglutide, which are all delivered once daily, can be given as a twice-daily or once-weekly injection.

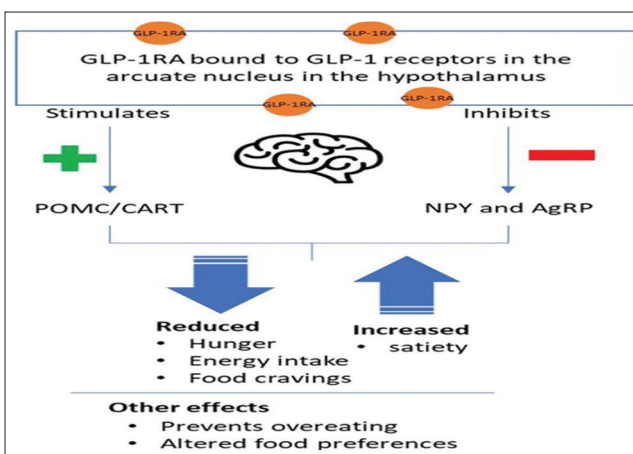


Figure 1. GLP-1's effects on the CNS [17].

### Short-acting GLP-1RAs

#### Exenatide

Exenatide's initial dose is 5 mcg subq twice daily, given within an hour of the day's two main meals and at least 6 h apart. After 4 weeks, the dose is increased as tolerated to 10 mcg subq twice daily if glycemic goals are not met [18].

#### Lixisenatide

Lixisenatide's starting dosage is 10 mcg subq once daily, given 1 h before any meal. After 2 weeks, the dose is increased to 20 mcg subq once daily or as tolerated [19].

### Long-acting GLP-1RAs

#### Dulaglutide

Dulaglutide's initial dosage is 0.75 mg subq once weekly. If glycemic goals are not attained after 4 weeks, increase the dose as tolerated every 4 weeks as follows: 1.5 mg subq once weekly, 3 mg subq once weekly, and then 4.5 mg subq once weekly [20].

## Semaglutide

- Subq formulation: The initial dosage is 0.25 mg subq once a week for 4 weeks, then, it is increased to 0.5 mg subq once a week. If the patient's glycemic objectives have not been achieved after at least 4 weeks, the dosage is increased as tolerated every 4 weeks as follows: 1 mg subq once per week and then 2 mg subq once per week [21].
- Oral formulation: While fasting, take no more than 4 ounces of plain water at least 30 min before breakfast or any oral medications. The

initial dosage is 3 mg once daily for 30 days, then increased to 7 mg once daily. Increase the dosage as tolerated to 14 mg once daily if glycemic targets are not met after 30 days on the 7 mg dose [22].

decreased dosages [35]. If gallstones are suspected, a careful clinical follow-up is required. In addition, practitioners must be aware that persons taking GLP-1RAs for weight control have a greater incidence of cholelithiasis (gallstones), which can occur with rapid weight loss [33].

## Side Effects and Toxicity

GLP-1 agonists are a group of drugs used to manage T2DM and promote weight reduction. However, they cause several unfavorable side effects such as diarrhea, constipation, nausea, and vomiting, as expected. In addition, individuals at risk for thyroid cancer and pancreatitis should proceed with caution if they experience injection-site reactions because they can affect the endocrine system, resulting in hypoglycemia [23], [24].

### GI

The majority of GLP-1RAs' adverse effects (mainly GI symptoms such as nausea and vomiting) are transient, mild to moderate in severity, and frequently occur during initial administration and therapy up-titration [25]. Other GI side effects such as constipation, which lasts more than other side effects, may not endure [26]. The adverse effects on the digestive system are dose-dependent and most likely class effects [27]. Higher dosages and quick-acting medications are associated with more frequent adverse effects. Diarrhea, however, occurs more frequently with long-acting medications [28].

According to previous studies, the following approach should be observed: (a) patients should be informed about the possibility of GI side effects as well as strategies for reducing their severity, and (b) the appropriate dosage must be gradually increased [29].

Transient nausea is the most prevalent side effect of GLP-1 [30]. Obesity studies seem to indicate that constipation is more common than T2DM [31]. Nausea is more typical during the first few weeks of therapy; it usually gets better after that [32]. Compared to the number of people who feel sick, much smaller proportion vomit. Long-acting GLP-1RAs also appear to be better tolerated as the vomiting frequency decreases over time. In addition, GLP-1 prescription agonists should be cautiously administered to individuals with severe GI diseases due to the increased risk of adverse GI symptoms [33]. Nausea, vomiting, and diarrhea are the most frequent side effects of GLP-1 agonists and may cause acute kidney injury due to volume constriction [34].

It has been found that nausea is associated with 6–10% of GLP-1 prescription agonist therapy cessation cases, with 15% of these cases tolerating only

### Cardiovascular

During clinical studies, patients consistently taking GLP-1 prescription agonists had a small but sustained increase in heart rate (2–4 beats/min) [33], [35]. Exenatide and liraglutide have been linked to heart rate increases (1–2 beats/min) [34]. Based on all available evidence, the effects of GLP-1 prescription agonists on heart rate are safe, and patients should not be overly concerned when given these medications [36]. GLP-1RAs have often been discovered to have favorable effects on the heart, lipid profiles, blood pressure, and weight [34].

### Skin reaction

Injection-site responses usually occur, and their severity varies from patient to patient depending on their immunogenicity. Studies have shown that a 10% overall treatment dropout rate is frequently caused by these adverse effects. Those with antibody-positive titers had a higher risk of injection-site reactions, which can progress to allergic reactions or even anaphylactic episodes [37].

### Discontinuation rate

In trials, <10% of patients discontinued GLP-1RA medication due to side effects; however, this rate could be higher in real-world healthcare settings. Adverse event discontinuation rates vary between drugs and studies, but they are typically low. However, a comprehensive analysis found that the majority of individuals discontinued their medication due to adverse effects, primarily GI ones [12]. Negative side effects are more common at higher doses, although they often subside over time. Slow dosage titration can lessen these side effects.

## Contraindication and Precaution

Hypersensitivity and pregnancy are contraindications to the use of GLP-1 agonists. In animal studies, liraglutide enhanced calcitonin production and caused hyperplasia of the thyroid glands, C-cells, and cancers [23]. Moreover, patients with a history of pancreatitis are advised to avoid



GLP-1RA-based treatments, even though there is insufficient information to determine whether there is a causal relationship [38].

The usage of GLP-1RA in pediatric patients has increasing. Liraglutide's recent clearance by the Food and Drug Administration to treat pediatric obesity will probably lead to an increase in the number of prescribed medications written for it. Providers need to be aware of potential adverse effects and alter GLP-1RA dosages accordingly. Professional associations should put more effort toward educating pediatric endocrinology specialists about how to use GLP-1RA correctly and raising their confidence in administering these drugs [39].

## Drug Interactions

Sulfonylureas, also known as glibenclamide, gliclazide, and glipizide among others, are oral hypoglycemic medications used to treat T2DM. In individuals using liraglutide combined with a sulfonylurea, a greater risk of hypoglycemia was seen. To prevent hypoglycemia cases, it is suggested that the dose of sulfonylurea be reduced in half when a patient taking the medication starts taking a GLP-1 agonist. Patients with abdominal obesity who were on insulin improved their glycemic control while taking liraglutide, however with a lower daily dose of the medication and fewer hypoglycemia cases [39].

Exenatide did not adversely alter long-term lipid profiles or statin dose in individuals receiving concurrent statin medication, despite detected changes in lovastatin bioavailability in the pharmacokinetic drug interaction trial. Exenatide a combination does not need changing the statin dose for this reason [40].

A right-shifted and reduced absorption peak was detected in the plasma or serum profiles of atorvastatin, lisinopril, and digoxin following coadministration with liraglutide. The total plasma or serum exposures were very slightly decreased (5–16% decreased AUCs), despite  $t_{max}$  being delayed by up to 2 h and  $C_{max}$  being reduced by 27–38% [41].

## Monitoring

Patients must be monitored for hypoglycemia if a GLP-1 agonist is added to a regimen that already includes a sulfonylurea or long-acting insulin. Furthermore, glycemic indices (A1C, fasting blood glucose) and kidney function must be regularly evaluated in all people with T2DM [23].

## Conclusion

Many studies have proven the effectiveness, efficiency, and safety of GLP-1RA drugs in the treatment of T2DM and obesity; however, despite their efficacy, they have some side effects that must be considered and avoided in cases such as acute pancreatitis. These drugs must only be used with the advice of a physician or pharmacist. In addition, to reduce the occurrence of GLP-1RAs' side effects and ensure optimal intake, patients must be informed of the drugs' potential adverse consequences and be regularly monitored in terms of blood sugar, weight, and kidney functions.

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