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# Assessing the Clinical Efficacy and Safety of Semaglutide: A Comprehensive Study

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***Abstract***

*Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), has emerged as a versatile therapeutic agent with significant potential in managing a range of diseases. Extensive research has demonstrated its efficacy in treating obesity, type 1 and type 2 diabetes, and even neurodegenerative disorders like Parkinson's disease. This comprehensive review examines the principal outcomes derived from clinical trials that incorporate semaglutide alongside other GLP-1 agonists, with particular emphasis on the mechanisms underlying semaglutide's action, its effects on weight reduction, its safety profile, and its wider health ramifications. Activation of GLP-1 receptors increases incretin activity, resulting in increased insulin secretion and improved insulin sensitivity; consequently, postprandial and fasting glucose levels will reduce, making it a valuable drug in the management of diabetes. Moreover, semaglutide promotes weight loss by reducing caloric intake and slowing gastric motility. This two-fold act contributes to its efficiency in addressing obesity, a mounting worldwide health alarm. Importantly, the drug has been shown to have a favorable cardiovascular risk profile, with no increased risk of cardiovascular events. In conclusion, semaglutide's promising therapeutic potential extends beyond diabetes management. Its ability to address obesity and explore potential applications in neurodegenerative diseases positions it as a valuable treatment option for a wide range of patients. As exploration remains to uncover its full potential, semaglutide is composed to make a substantial influence on health care.*

**Keywords:** Obesity, type 2 diabetes, weight loss, cardiovascular disease, semaglutide

## INTRODUCTION

The global struggle with obesity persists, impacting nearly triple the population compared to 1975 [1]. In America, over 70 percent of the public struggles with overweight issues. Among them, over a third of adults and 20% of adolescents are clinically overweight. The surge in obesity rates transcends international borders, affecting most industrialized nations over recent decades [2]. Cardiovascular diseases rank as a leading cause of female mortality in both established and emerging countries [3]. Simultaneously, type 2 diabetes emerges as a significant global health concern. Conventional treatments for combating obesity, such as lifestyle adjustments involving diet and exercise regimens, often fall short of achieving sustainable weight loss [4].

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Exploring alternative approaches becomes imperative to address the prevention and reversal of obesity for enhanced well-being worldwide. This pressing need underscores the demand for effective pharmaceutical interventions against this public health crisis [5]. Economically, obesity exacts a substantial toll on society by surpassing $100 billion annually in healthcare costs within the United States alone [6]. Furthermore, it exacerbates conditions like type 2 diabetes and

 

cardiovascular diseases while escalating cancer risks. Managing various illnesses becomes more challenging due to complications arising from obesity, notably evident during events like the COVID-19 pandemic [7]. Environmental determinants significantly contribute to the escalation of global obesity incidence by enabling greater availability of calorically dense foods and diminishing levels of physical activity [8]. Obesity not only reduces life expectancy by 5–20 years depending on severity but also elevates the prevalence of multiple disorders across different bodily systems [9].

Semaglutide, available under brands like Ozempic and Wegovy, mimics human glucagon-like peptide-1 (GLP-1), regulating hunger signals that lead to decreased calorie intake and subsequent weight loss. Extensive clinical trials have confirmed semaglutide's therapeutic efficacy in treating obesity-related disorders [10]. Notable among these trials is the PIONEER program examining oral semaglutide's safety and effectiveness as an antidiabetic agent – showcasing improved glycemic control and weight reduction compared to placebos or other diabetes medications [11]. Concurrently, the STEP program evaluated semaglutide solely for its weight-loss potential – demonstrating superior outcomes over placebos in reducing body weight and enhancing waist circumference among obese patients [12].

A variety of GLP-1 receptor agonists are currently accessible for the management of patients with type 2 diabetes mellitus. The pharmacological agents that have received authorization for therapeutic application encompass semaglutide, exenatide, exenatide-LAR, liraglutide, lixisenatide, albiglutide, and dulaglutide. According to their pharmacokinetic and pharmacodynamic characteristics, these agents are generally categorized as either short-acting GLP-1 receptor agonists (namely, exenatide and lixisenatide) or long-acting GLP-1 receptor agonists (which include semaglutide, exenatide-LAR, liraglutide, albiglutide, and dulaglutide). The principal distinction between these two classifications lies in the fact that, when administered in accordance with their designated dosing regimens, short-acting agonists experience significant variability in the plasma concentrations of the active component, whereas long-acting agonists maintain a more stable and sustained effect on the GLP-1 receptor [13].

These objective findings underscore semaglutide's vast promise as an intervention solution for individuals struggling with excessive weight gain despite traditional methods proving inadequate. This review aggregates essential findings derived from clinical investigations regarding semaglutide and additional GLP-1 agonists, with a particular focus on semaglutide, detailing its mechanisms of action, effects on weight reduction outcomes, safety parameters, as well as other relevant health factors—providing a concise yet thorough overview that substantiates its therapeutic efficacy in addressing obesity-related disorders.

 

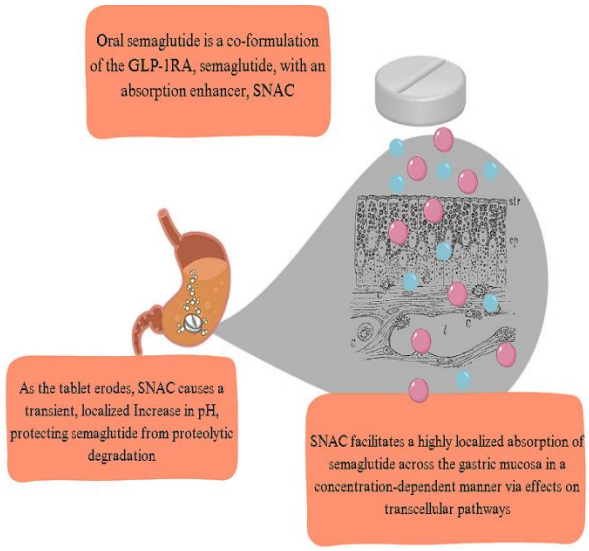


**Figure 1.** Mechanism of semaglutide in gastric mucous.

## MECHANISM OF SEMAGLUTIDE IN THE GASTRIC SYSTEM

Semaglutide activates GLP-1 receptors, thus enhancing incretin activity. Various pathways are accountable for decreasing postprandial and fasting glucose levels, such as elevated insulin secretion (dependent on glucose levels), suppressing glucagon release, and inhibiting hepatic gluconeogenesis. The beneficial proinsulin: insulin ratio exhibited by semaglutide implies an increase in insulin production and enhancement of β-cell functional capacity. Furthermore, there is evidence of enhanced insulin sensitivity, likely stemming from an overall reduction in body weight. Additionally, semaglutide promotes weight loss by decreasing caloric intake and slowing gastric motility (Figures 1–2) [10, 14].

## MECHANISM OF SEMAGLUTIDE IN SEVERAL BODY SYSTEMS

Semaglutide engages with and stimulates the GLP-1 receptor located in the pancreas, eliciting the secretion of insulin from pancreatic islet cells. Consequently, there is an enhancement in glycaemic regulation through the elevation of insulin levels and reduction of blood glucose levels. The deceleration of gastric emptying induced by semaglutide results in a decreased pace of food passage from the stomach, ultimately contributing to diminished food consumption and appetite, thus facilitating weight reduction. By impeding glucagon release, semaglutide suppresses hepatic gluconeogenesis, thereby curtailing the liver's capacity to generate glucose and leading to a decline in postprandial and fasting glucose levels. Through its influence on the central nervous system, semaglutide diminishes appetite, consequently reducing food intake and promoting weight loss. Regarding cardiovascular function, semaglutide is believed to confer benefits by potentially retarding the progression of atherosclerosis and reducing intestinal permeability, factors that could mitigate the likelihood of heart disease [10, 15].

 

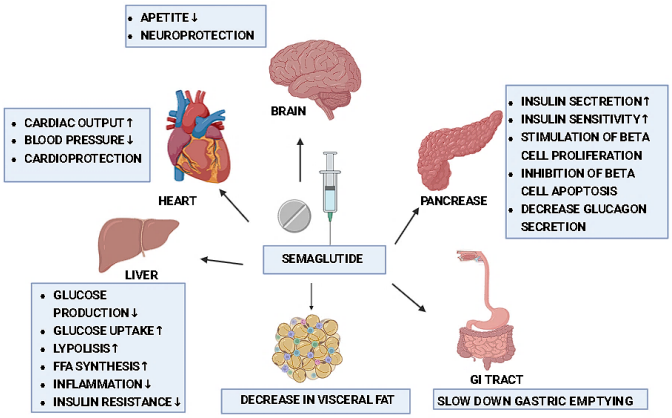


**Figure 2.** Semaglutide mechanism of action and possible benefits for patients with non-alcoholic liver disease, metabolically related liver disease, and other illnesses

## CLINICAL BACKGROUND AND REGULATORY STATUS OF SEMAGLUTIDE

### Role of Semaglutide in Weight Loss

The findings from the meta-analysis of six controlled randomized trials indicate that weekly subcutaneous injection of 2.4mg semaglutide resulted in significant reductions in body weight (11.80%), body mass index (4.5 kg/m2), and waist circumference (9.5 cm). Additionally, a higher proportion of individuals achieved weight loss exceeding 5%, 10%, 15%, and 20% after undergoing this intervention, regardless of various factors like trial setup, accompanying treatments, participants' demographics, or study duration. [16].

### Role of Semaglutide in the Cardiovascular System

Both SUSTAIN-6 and PIONEER-6 trials have semaglutide demonstrated the favorable impact of semaglutide on reducing cardiovascular risk. The hazard ratio of  for adverse cardiovascular events exhibited a significant advantage over a placebo, suggesting a notable cardiovascular benefit. An analysis conducted post-hoc revealed that semaglutide led to a reduction of approximately 24% in cardiovascular adverse events compared to a placebo. Studies have shown that semaglutide diminishes atherosclerosis in ApoE−/− and LDLr−/− mice by modulating inflammatory pathways. Additionally, existing evidence highlights the cardioprotective properties of GLP-1 agonists through the inhibition of apoptosis in cardiac cells of rats [17–19].

### Role of Semaglutide in the Type1 Diabetes Mellitus

50 type 1 diabetes (T1D) patients who were initially treated with semaglutide and monitored for a year were examined in the study. A control group of 50 computer-matched patients who did not take weight-loss medication over the same period was also included. Concerning age, length of diabetes, and continuous glucose monitor use, a study with 92% non-Hispanic white patients produced the same findings. Baseline glycosylated hemoglobin (HbA1c), total daily insulin dose (TDD), and insulin dose per kilogram body weight did not significantly differ among the semaglutide group. While there was no difference in insulin dose adjustments, time above range (TAR), or time below range (TBR), the semaglutide group did experience larger declines in mean, BMI, body weight, HbA1c, CGM glucose SD, coefficient of variation, and increase in CGM time in range (TIR) relative to the control group [18–23].

### Impact of Semaglutide in the Type-II Diabetes Mellitus (DM)

Semaglutide's beneficial effects in the treatment of type 2 diabetes were demonstrated by sustained decreases in glycated hemoglobin levels, decreased blood glucose levels, and enhanced glycaemic control. These results highlight the value of semaglutide as an additional therapy to improve adults with type 2 diabetes's glycaemic control, which helps with better disease management and metabolic

 

regulation [23, 24].

### Role of Semaglutide in Parkinson's Disease (PD)

Regarding liraglutide's impact on PD patients, a phase II clinical trial that was double-blind, randomized, and double-blind was also carried out. There were 18 placebo subjects and 37 active subjects in this trial. Patients with Parkinson's disease (PD) receiving standard PD medication received subcutaneous injections of liraglutide for 52 weeks. The everyday living of Parkinson's disease patients receiving liraglutide medication was found to have significantly improved in this study. Common side effects were gastrointestinal problems and reactions at the injection site. Although eleven severe side effects were recorded, none of them had anything to do with the study's intervention. Analysis of more parameters is still ongoing [21, 25–28].

## SEMAGLUTIDE SAFETY PROFILE WITH COMMUNAL SIDE EFFECTS AND THOUGHTS

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), has a deep-rooted safety profile in mutually subcutaneous and oral formulations. Communal side effects include gastrointestinal (GI) adverse effects, such as nausea, vomiting, and diarrhea, which are mostly mild and self-limiting. Additionally, semaglutide increases the risk of cholelithiasis (gallstones), but this is generally mild and self-limiting.

Semaglutide is also shown to possess a favorable cardiovascular risk profile. It is not associated with increased risk for cardiovascular events. Patients at risk for deterioration of existing diabetic retinopathy (DRP) should be closely monitored if treated with semaglutide, especially if treated with insulin. Furthermore, there is no increased risk of acute kidney injury (AKI) or pancreatitis, but the risk of pancreatic cancer cannot be ruled out due to the low incidence of this condition.

The pharmacokinetic profile of oral semaglutide is different from that of subcutaneous semaglutide, with lower plasma levels achieved with oral administration. Complex doses of semaglutide are often linked with more frequent GI adverse effects, and a dose appreciation scheme is advised, preliminary with a low dose (3 mg). Post-marketing scrutiny will help to clarify whether the subcutaneous and oral deviations differ in their real-world safety profile.

In comparison to other GLP-1RAs, semaglutide appears to be allied with more frequent nausea and vomiting. However, semaglutide has a significant impact on glucose metabolism, blood pressure, body weight, and cardiovascular endpoints, making it a valuable treatment option for patients with type 2 diabetes. Overall, the safety profile of semaglutide is favorable, with a low risk of severe adverse events and a significant impact on patient outcomes [29–33].

## SAFETY PROFILES OF FURTHER GLP-1 AGONISTS IN CLINICAL TRIALS

### Exenatide

Exenatide, which is offered in both immediate-release (administered bi-daily) and extended-release (administered weekly) formulations, is frequently linked to gastrointestinal adverse effects, including nausea, emesis, and diarrhea. Reactions at the injection site occur more commonly with the extended-release variant. Notable severe adverse events encompass infrequent instances of acute pancreatitis and potential renal impairment, particularly among individuals with pre-existing renal conditions. The safety profile suggests that it is a tolerable pharmacological agent with manageable adverse effects in the majority of patients [34].

### Liraglutide

Liraglutide, administered on a daily basis, exhibits a safety profile that is comparable to that of other GLP-1 receptor agonists, with the most frequently reported adverse effects being nausea, vomiting, and diarrhea. There are rare instances in which it has been associated with thyroid C-cell tumors in rodent studies; however, the implications of these findings for human subjects remain

 

inadequately defined. The occurrence of pancreatitis continues to be a potential hazard. Furthermore, its cardiovascular safety profile and endorsement for weight management—marketed under the brand name Saxenda—offer supplementary advantages, rendering it a preferential choice among specific patient demographics [35].

**Dulaglutide**

Dulaglutide, classified as a weekly GLP-1 receptor agonist, has exhibited a commendable safety profile, with gastrointestinal manifestations, such as nausea and diarrhea emerging as the most prevalent adverse effects. While serious adverse events, including pancreatitis, are infrequent, they remain a potential risk. The cardiovascular safety of dulaglutide was robustly affirmed in the REWIND trial, underscoring its advantages for patients at elevated cardiovascular risk. Dulaglutide is regarded as a secure and efficacious therapeutic option, particularly for individuals necessitating the convenience of once-weekly administration [36].

**Future Perspectives**

Accessibility concerns need to be addressed, especially for patients who are unstable or lack insurance, to guarantee the broad use of semaglutide. Negotiating lower rates, putting in place patient support programs, pushing for more insurance coverage, and looking into alternate funding sources are among the strategies. Stakeholders in healthcare can encourage broader use of semaglutide, enhance patient outcomes, and lessen the burden of chronic conditions like diabetes.

Semaglutide can be used in a mixture with other drugs to address metabolic health concerns and increase therapy efficacy. These treatments work in concert by focusing on different physiological circuits. Tolerability, safety, and interactions must all be carefully considered, though. Research and clinical trials are mandatory to detect the best patient populations and combinations.

The prospective applications of other GLP-1 receptor agonists are directed towards their utilization beyond the realms of type 2 diabetes and obesity, extending to pathologies, such as non-alcoholic steatohepatitis (NASH), cardiovascular ailments, and neurodegenerative diseases. Innovations, including dual or triple agonists, are anticipated to offer enhanced therapeutic efficacy, while developments in delivery mechanisms, encompassing oral formulations and transdermal patches, seek to augment patient convenience. Strategies emphasizing personalized medicine and initiatives aimed at cost reduction will further extend the therapeutic scope of these agents, positioning them as integral components in the management of metabolic and chronic disorders. Further study is needed to determine the long-term consequences of semaglutide use, especially regarding weight maintenance after stopping the medication. Following therapy, weight control is influenced by several factors, such as metabolic adjustments, lifestyle changes, and possible rebound effects. Future research ought to maximize long-term results and investigate if the advantages of semaglutide therapy are sustainable. This will support people in making long-lasting health gains and assist healthcare practitioners in making treatment decisions.

**Limitations**

A relatively new medication for managing weight is semaglutide. Most of the research focuses on usage for a few years or less. More research is required to determine the long-term safety impact of factors like cardiovascular health and cancer risk. Certain people should not use semaglutide. The consumption of this medication is contraindicated in individuals possessing a medical history of pancreatitis, medullary thyroid carcinoma, or marked hypersensitivity reactions to the constituents of semaglutide [37, 38].

 

## CONCLUSIONS

Semaglutide is a medicinal drug that is versatile and has a wide range of uses in treating obesity, type 1, and type II Diabetes, and maybe neurodegenerative illnesses like Parkinson's disease. Its effectiveness in enhancing glycaemic control, encouraging weight loss, and maybe having neuroprotective benefits underlines its therapeutic relevance and shows how it can potentially meet unmet medical needs in a variety of patient populations. To fully exploit the therapeutic potential of semaglutide and enhance patient outcomes across various disease states, more studies are necessary to clarify its mechanisms of action, optimize dosage schedules, and investigate new therapeutic indications.

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