

The Role of Semaglutide in Weight Management: An Analysis of Clinical Studies for Overweight and Obese Adults

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Abstract. Obesity is a mounting global health challenge, and recent advancements in pharmacologic interventions have brought new hope to this complex issue. One such intervention, semaglutide, marketed as Ozempic and Wegovy, has shown promising results in weight management among adults with overweight or obesity. This paper synthesizes findings from key clinical studies to evaluate the efficacy, safety, and long-term impact of semaglutide in weight management. Semaglutide, initially developed for type 2 diabetes management, functions by mimicking the human glucagon-like peptide-1, thereby reducing appetite and food intake. Regulatory bodies in the United States, Europe, the United Kingdom, and Canada have approved its use for weight management at a weekly dose of 2.4 mg, marking a significant step in obesity treatment. Alongside its benefits, the paper also addresses the safety profile and adverse effects associated with semaglutide. While generally well-tolerated, rare but serious adverse effects have been reported, necessitating a careful assessment of risks and benefits in clinical practice. In conclusion, semaglutide presents a significant advancement in the pharmacologic management of obesity. Its ability to induce considerable weight loss, coupled with improvements in cardiovascular and metabolic health, positions it as a promising tool in the arsenal against obesity. Future research should focus on long-term efficacy, safety, and the integration of comprehensive lifestyle interventions to optimize treatment outcomes.

Keywords: Semaglutide; Weight Management; Clinical Studies; Overweight and Obese Adults.

1. Introduction

Obesity represents a significant and growing global health crisis, characterized by excess body weight and associated with numerous comorbidities, including type 2 diabetes, cardiovascular diseases, and various forms of cancer. Traditional approaches to managing obesity have primarily focused on lifestyle interventions, such as diet and exercise, but these have often proved insufficient for sustained weight loss. Consequently, the need for effective pharmacological interventions has become increasingly evident.

In this context, semaglutide, a medication originally developed for type 2 diabetes management, has emerged as a promising tool in the fight against obesity. Marketed under the brand name Ozempic and Wegovy, semaglutide operates by mimicking the human glucagon-like peptide-1 (GLP-1), which regulates appetite and food intake, leading to reduced caloric consumption and weight loss.

1.1. Background on Obesity

Obesity is not just a personal health issue but a growing concern on a global scale. It is a complex condition influenced by a multitude of factors, including genetics, lifestyle choices, environmental factors, and physiological characteristics. The rise in obesity rates worldwide poses significant challenges to healthcare systems due to the increased prevalence of related diseases and the complexity of effective treatment.

Despite numerous strategies and interventions aimed at combating obesity, the condition remains stubbornly prevalent, underscoring the need for more effective treatment options. The limited success of non-pharmacological approaches in achieving and maintaining significant weight loss has led to a growing interest in pharmacological solutions.

1.2. Introduction to Semaglutide (Ozempic/Wegovy) and its Application in Weight Management

Semaglutide was initially developed and approved for the treatment of type 2 diabetes. Its mechanism of action is primarily through mimicking GLP-1, a hormone that increases insulin secretion and reduces glucagon release, thereby lowering blood glucose levels. However, researchers noted that semaglutide also had a significant impact on body weight, prompting further investigation into its potential as a weight management tool.

In 2021, the U.S. Food and Drug Administration (FDA) approved semaglutide for chronic weight management at a dose of 2.4 mg administered as a once-weekly, subcutaneous injection. This approval was based on robust clinical trial data demonstrating the efficacy of semaglutide in weight loss among adults with a body mass index (BMI) of 27 kg/m² or higher [1]. Subsequently, regulatory agencies in the United Kingdom and Europe also approved the drug for weight management, reflecting a growing consensus on its efficacy and safety.

1.3. Scope of the Paper

This paper aims to provide a comprehensive analysis of the role of semaglutide in weight management for overweight and obese adults. It will review and synthesize data from various clinical studies, focusing on the efficacy, safety, and long-term impact of the drug in weight management. By examining semaglutide's effect on body weight, its comparison with other weight management medications, and its influence on cardiovascular health and metabolic outcomes, the paper seeks to present a balanced view of its potential and limitations in the context of obesity treatment.

In summary, the introduction and background section set the stage for a detailed exploration of semaglutide's role in weight management, highlighting its significance against the backdrop of a global obesity epidemic and the limited effectiveness of existing treatment options.

2. Clinical Background and Regulatory Status of Semaglutide

2.1. Development and Mechanism of Action of Semaglutide

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, represents a significant advancement in pharmacologic options for obesity management. Initially developed for type 2 diabetes (T2D), semaglutide functions by mimicking GLP-1, a hormone that regulates insulin secretion. This mechanism not only aids in glycemic control but also reduces appetite, leading to decreased caloric intake and weight loss. The transition from a diabetes treatment to a weight management solution marks a pivotal shift in the application of this medication.

2.2. Regulatory Approval for Weight Management

The U.S. Food and Drug Administration (FDA) approved semaglutide for chronic weight management in June 2021, under the brand name Wegovy. This approval was a landmark decision, making semaglutide the first GLP-1 agonist approved for obesity management. The decision was based on extensive clinical trials, which reported significant weight loss findings, ranging from 15% to 18% of body weight during the trials [2].

Further validating its efficacy, regulatory agencies in other regions, including the European Medicines Agency and the UK Medicine and Health Products Regulatory Agency, also approved semaglutide for weight management. These approvals were influenced by the medication's demonstrated impact on body weight and its potential in addressing the global obesity epidemic [1].

2.3. Semaglutide in Diabetes Management

Before its recognition as a weight management drug, Ozempic (semaglutide) was approved in December 2017 as an adjunct therapy for glycemic control in adults with T2D. This initial approval was based on its ability to regulate blood glucose levels, an essential factor in diabetes management.

However, its impact on weight loss in diabetic patients hinted at a broader application, setting the stage for its subsequent approval for obesity treatment [2, 3].

2.4. Prescription and Accessibility

As a prescription medication, semaglutide requires approval from a healthcare professional, such as a primary care physician or an endocrinologist. Its administration as a once-weekly, subcutaneous injection makes it a convenient option for chronic weight management, aligning with patient needs for effective and manageable treatment regimens [3].

3. Analysis of Clinical Studies on Semaglutide

The clinical efficacy of semaglutide in weight management has been extensively studied through various clinical trials. These trials have been pivotal in assessing the effectiveness of semaglutide in adults with overweight or obesity. Here are some key findings from these studies:

3.1. Three-Year Study Released on EASD

The study on the long-term effects of Semaglutide (Ozempic/Wegovy) for type 2 diabetes demonstrated significant improvements in blood sugar control and weight loss over a period of three years.

The study retrospectively evaluated 23,442 subjects from the Maccabi diabetes registry who had redeemed at least one prescription for weekly Semaglutide injections between August 2019 and December 2022. Six months after starting treatment, subjects experienced an average reduction in HbA1c (a measure of blood sugar control) by 0.77% (from 7.6% to 6.8%) and an average weight loss of 4.7 kg (from 94.1 kg to 89.7 kg) [4].

The study showed that these effects were sustained for up to three years. For subjects with high adherence to treatment for at least two years, HbA1c was further reduced by 0.76% after 24 months and by 0.43% after 36 months, and body weight was reduced by 6.0 kg after 24 months and 5.8 kg after 36 months.

3.2. FDA Approval for Chronic Weight Management

The U.S. Food and Drug Administration approved Wegovy (semaglutide) injection (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight who have at least one weight-related condition such as high blood pressure, type 2 diabetes, or high cholesterol. This is to be used in conjunction with a reduced-calorie diet and increased physical activity. It is the first drug approved for chronic weight management in adults with general obesity or overweight since 2014. Wegovy is indicated for patients with a BMI of 27 kg/m^2 or greater with at least one weight-related ailment or those with a BMI of 30 kg/m^2 or greater [5].

Wegovy's safety and efficacy were studied in four 68-week trials. These included three randomized, double-blind, placebo-controlled trials and one randomized withdrawal trial. In these studies, more than 2,600 patients received Wegovy for up to 68 weeks, and over 1,500 patients received a placebo. In the largest placebo-controlled trial involving adults without diabetes, individuals receiving Wegovy lost an average of 12.4% of their initial body weight, compared to those receiving placebo. Another trial with adults having type 2 diabetes showed that those receiving Wegovy lost 6.2% of their initial body weight compared to the placebo group [5].

These findings demonstrate the effectiveness of Wegovy in aiding weight loss and managing chronic weight conditions in adults with obesity or overweight, especially when combined with a healthy diet and increased physical activity.

3.3. The STEP 5 trial in Two Years

Conducted from October 2018 to February 2019, the trial involved 304 participants. Most were female and white, with a mean age of 47.3 years and a mean BMI of 38.5 kg/m^2 [6].

Weight Loss Results (see in Fig. 1): The average weight loss in the Semaglutide group was 15.2% from baseline to week 104, compared to a 2.6% loss in the placebo group. Over 75% of participants in the Semaglutide group achieved more than 5% weight loss, and a significant number lost over 10%, 15%, or even 20% of their baseline weight [6].

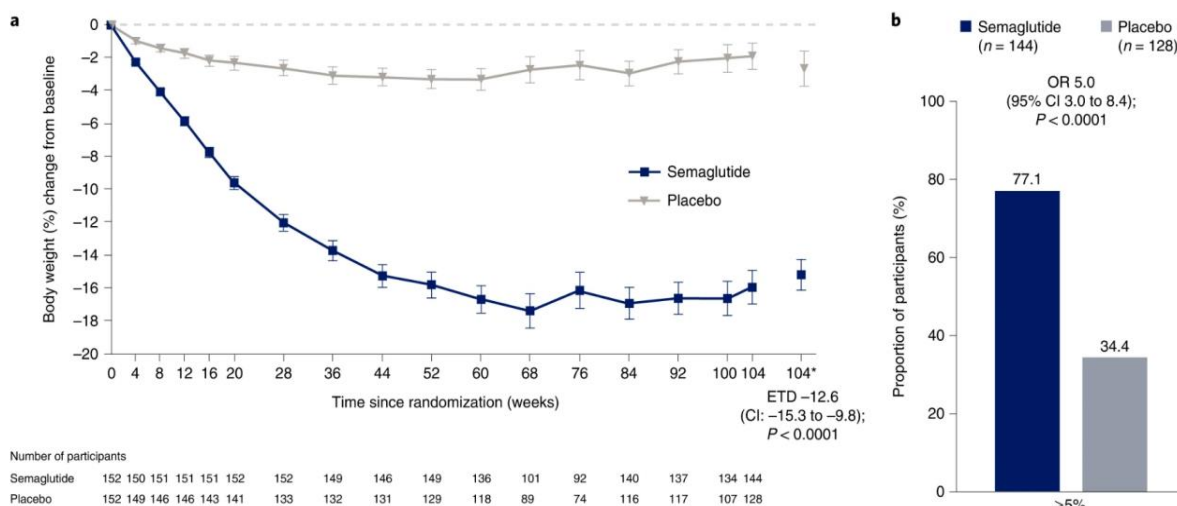


Fig. 1 Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial [6].

The study concluded that substantial weight loss achieved with Semaglutide in earlier trials could be maintained for up to 104 weeks. The mean weight loss of about 15% at week 104 with Semaglutide was greater than weight loss reported in similar trials with other weight management pharmacotherapies.

3.4. Other Studies

In addition to the STEP 5 trial, there are several other significant Semaglutide-related studies, such as STEP 4 Randomized Clinical Trial [7], comparison with Liraglutide Trial [8], comparison with Placebo over 68 Weeks [9], etc..

The results from these clinical trials have been consistently positive. These studies collectively highlight the long-term effectiveness and safety of Semaglutide in reducing weight and managing obesity or overweight conditions. A comprehensive review of various studies also corroborated these findings.

4. Efficacy and Safety of Semaglutide in Long-Term Weight Management

4.1. Long-term Effects of Semaglutide on Weight Management

The STEP 5 trial is instrumental in assessing the long-term efficacy of semaglutide. This phase 3, randomized, double-blind, placebo-controlled trial represents the most extended study on semaglutide for weight management to date. The trial, conducted over two years, focused on adults with obesity or overweight with at least one weight-related comorbidity, without diabetes. Its co-primary endpoints were the percentage change in body weight and the achievement of weight loss of $\geq 5\%$ at week 104 [10, 11].

The results of the STEP 5 trial showed that participants in the semaglutide group achieved a mean weight loss of 15.2% from baseline compared to just 2.6% in the placebo group over 104 weeks. This marked an estimated treatment difference of 12.6 percentage points. Notably, a substantial portion of participants (77.1%) in the semaglutide group achieved weight loss of $\geq 5\%$ from baseline at week 104, highlighting the drug's sustained efficacy over a longer period [11].

4.2. Impact on Cardiometabolic Risk Factors

Besides weight loss, semaglutide demonstrated a significant positive impact on various cardiometabolic risk factors. Semaglutide, sold under the brand name Ozempic, is used to reduce the risk of heart attack and stroke in people with type 2 diabetes and heart disease [12].

The drug was associated with substantial reductions in waist circumference and systolic blood pressure. Improvements were also noted in diastolic blood pressure, glycated hemoglobin (HbA_{1c}) levels, fasting plasma glucose, fasting serum insulin, C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and triglycerides.

A cardiovascular outcomes trials have indicated that Semaglutide reduces the relative risk of major adverse cardiovascular events (MACE) compared with placebo in people with type 2 diabetes and cardiovascular disease (CVD) or at high cardiovascular risk. Specifically, subcutaneous once-weekly Semaglutide 2.4 mg was associated with a 20% reduction in MACE compared with placebo [13].

Another study revealed that weekly treatment with semaglutide reduced the risk of a composite of stroke, heart attack, and death from cardiovascular causes by 20% compared to placebo. In this study, a primary cardiovascular event occurred in 6.5% of the semaglutide group versus 8% in the placebo group. The findings were based on data from about 17,600 participants with preexisting cardiovascular disease and a body mass index of 27 or greater, expanding on prior research that indicated cardioprotective benefits of semaglutide in patients with type 2 diabetes [14].

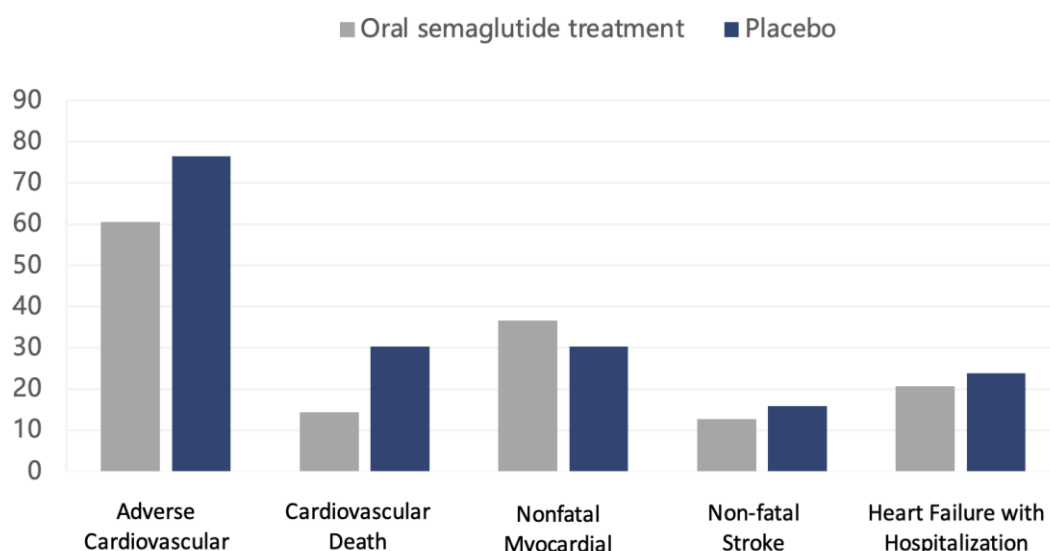


Fig. 2 Number of specific adverse events occurring in the trial [14].

4.3. Semaglutide and Metabolic Outcomes

Semaglutide has also demonstrated significant improvements in various metabolic outcomes. Semaglutide was associated with reduced hunger and food cravings, improved control of eating, and a lower preference for high-fat foods [15]. Preclinical studies indicate that weight loss with Semaglutide results from its effects on glucagon-like peptide 1 receptors, which mediate direct and indirect effects on brain areas involved in regulating appetite, including the hypothalamus and hindbrain. This leads to reduced energy intake [16].

In a study involving non-diabetic individuals with obesity or a BMI ≥ 27 kg/m² with comorbidities, the participants in the semaglutide group exhibited significant reductions in waist circumference and systolic blood pressure. Furthermore, 84% of individuals with prediabetes in the semaglutide group achieved normoglycemia by the end of the study. The study also found that semaglutide was associated with reduced fat mass and an increase in the proportion of lean body mass relative to total body mass [17]. In another study, Semaglutide has shown beneficial effects on glucose metabolism, blood pressure, body weight, and cardiovascular health, making it beneficial for diabetic and obese patients. This indicates an overall positive risk/benefit profile for this group of patients [18].

These findings indicate an overall beneficial effect of semaglutide treatment on patient health, extending beyond weight loss to broader metabolic improvements [11].

4.4. Safety Profile and Adverse Effects

While the efficacy of semaglutide in long-term weight management is evident, understanding its safety profile is equally crucial. Despite these benefits, it is crucial to consider the safety and side effects of semaglutide. The main side effects were gastrointestinal disorders, which were more frequent than with glucose-lowering doses of the drug. In the STEP 5 trial, the most frequently reported adverse events were gastrointestinal disorders, such as nausea, diarrhea, vomiting, and constipation. These events were more common in the semaglutide group compared to the placebo group. However, most of these gastrointestinal adverse events were mild-to-moderate and transient, leading to permanent treatment discontinuation in a small percentage of participants [11].

These side effects were transient, typically mild-to-moderate in severity, and mostly resolved without the need for treatment discontinuation. Only 4.5% of participants discontinued treatment due to gastrointestinal symptoms, indicating the safety of high-dose semaglutide for potential long-term use [17].

5. Limitations, Conclusion and Future Perspectives

5.1. Limitations and Future Research Directions

While the results are promising, the study's generalizability is limited due to the predominantly white and female participant demographic. Future research should include more diverse demographics, especially as obesity disproportionately affects minority race/ethnicity groups and those with lower socioeconomic status. The ongoing SELECT trial, involving 17,500 participants, aims to understand semaglutide's effects on cardiovascular morbidity and mortality among individuals with obesity but without diabetes. The potential beneficial effects of high doses of oral semaglutide are also being evaluated, which could be more acceptable to a broader range of patients than the injectable dose [17].

The field of semaglutide for weight management is rapidly evolving. Current research is concentrated on refining dosing strategies and exploring new applications:

1. **Optimal Dosing Regimen:** Ongoing studies are examining the effects of different doses, treatment durations, and combinations with other medications or therapies to establish the most effective and safe use of semaglutide for weight loss.

2. **Combination Therapies:** There is growing interest in combining semaglutide with other weight loss medications or therapies. These combination therapies, targeting various pathways involved in weight regulation, may offer enhanced weight loss outcomes and improved obesity management.

3. **Long-Term Effects:** Long-term studies are crucial for evaluating the sustainability and safety of semaglutide treatment. Research is ongoing to assess the durability of weight loss achieved with semaglutide and monitor potential long-term side effects.

4. **Personalized Medicine:** The concept of personalized medicine is becoming increasingly relevant in weight loss interventions. Researchers are exploring genetic and biomarker profiling to tailor semaglutide treatment based on individual characteristics and metabolic responses [19].

5.2. Conclusion: Semaglutide - A Promising Tool for Obesity Management

Semaglutide has emerged as a significant advancement in the pharmacological treatment of obesity. Its efficacy in inducing weight loss, coupled with positive impacts on cardiovascular health and metabolic outcomes, positions it as a promising option in the arsenal against obesity.

However, the journey of semaglutide is not without challenges. Its long-term effects, optimal dosing, and combination with other therapies remain areas of active research. Personalized approaches to treatment, considering individual patient characteristics and responses, are likely to play a crucial role in the future of obesity management.

As research unfolds, the future of semaglutide as a weight loss tool holds great promise. Ongoing studies and advancements will continue to refine dosing strategies, explore combination therapies, illuminate long-term effects, and pave the way for personalized treatment approaches. These efforts will further enhance the efficacy and safety of semaglutide, offering significant benefits to individuals struggling with obesity and improving their overall health outcomes [19].

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