An Overview of Semaglutide: Effectiveness, Side Effects, and Cost

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Abstract

More than two out of every five people in the United States have obesity (National Institute of Diabetes and Digestive and Kidney Diseases, 2021), and by 2030, approximately half of the U.S. population will have obesity (Finkelstein et al., 2012). Obesity and type 2 diabetes are significant global health challenges, each associated with serious conditions such as cardiovascular disease, hypertension, and other metabolic disorders. As rates of obesity continue to rise, effective treatments are essential to address this growing concern. One such intervention gaining national attention is semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist. Semaglutide was originally developed to manage type 2 diabetes but has also been effective in promoting weight loss, leading to its FDA approval as Wegovy for chronic weight management in 2021. This medication mimics the body's natural GLP-1 hormone to reduce appetite and slow digestion. This paper aims to provide a comprehensive analysis of semaglutide, including its effectiveness and side effects, its role as a GLP-1 receptor agonist in managing diabetes and weight loss, and the long-term challenges associated with its use.

Section 1: The Effectiveness and Side Effects of Semaglutides

Semaglutide has emerged as one of the most effective treatments for obesity available today. Its effectiveness has been expressed in multiple studies, particularly the SUSTAIN and STEP clinical trials, which reported average weight reductions of up to 15% over two years, a percentage far more effective than the results of other weight loss medications (Singh, 2023). For comparison, other commonly used drugs, such as liraglutide or orlistat, achieve an average of only 5–8% weight loss under similar conditions. For semaglutide, on the other hand, a meta-analysis of four large trials involving over 3,600 participants displayed these findings, showing users losing 11.85% of their body weight compared to minimal reductions in placebo groups (Tan et al., 2022). Additionally, over 50% of participants on semaglutide achieved at least a 10% reduction in body weight, while only 5% of placebo users reached this milestone, displaying its efficacy.

Semaglutide achieves its effects by targeting key brain regions involved in appetite control. Specifically, it stimulates receptors in the hypothalamus, reducing hunger and expressing a feeling of fullness after eating. Additionally, it slows gastric emptying, which keeps food in the stomach for longer periods and reduces the urge to eat (Palana et al., 2024). These combined mechanisms help patients reduce calorie intake consistently over time, making semaglutide an applicable tool for long-term weight management, especially when combined with lifestyle changes.

However, this treatment comes with challenges. Gastrointestinal (GI) side effects are the most frequently reported symptoms, including nausea, diarrhea, constipation, and vomiting. These symptoms are often more severe during the early weeks of treatment, although some patients report continuous discomfort. Studies indicate semaglutide users are approximately 1.59 times more likely to experience GI issues compared to placebo groups, with 1 in 10

participants discontinuing treatment due to these side effects (Tan et al., 2022). Additionally, 30-40% of users report nausea during the first few weeks, though this typically subsides over time.

While these side effects can deter patients from using semaglutides, experts have found methods to alleviate such gastrointestinal discomfort. A study conducted by Gorgojo-Martínez et al., which includes an array of individuals such as endocrinologists, nephrologists, primary care physicians, cardiologists, and more experts, suggests multiple methods for alleviating these symptoms. Among these methods are eating smaller portions of food slowly, maintaining a low-fat diet, getting constant fresh air, and eating specific foods or drinks (Gorgojo-Martínez et al., 2022). Through the implementation of these methods, the GI issues that may result from semaglutide intake can be reduced or even prevented.

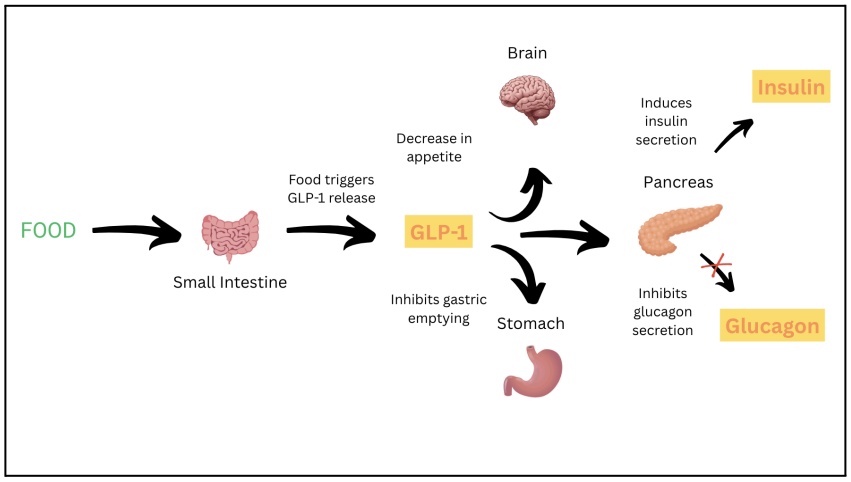
Besides the common GI effects, rare but serious risks have been reported as well, including pancreatitis, gallbladder disease, and in some cases, kidney problems. There are, however, methods to alleviate these symptoms if their rare and negative effects were to occur. For example, the management of pancreatitis in patients treated with semaglutide involves immediate discontinuation of the drug, supportive care including IV fluids and analgesia, and close monitoring for complications. Additionally, a continuation following this period of discontinuation with GLP-1 receptor agonists is generally not recommended due to the potential for recurrence (Chaudhury et al., 2020). A review by Ghusn & Hurtado (2024) found semaglutide users had a 1.6 times greater likelihood of developing gallstones or gallbladder inflammation compared to non-users. Though these risks are uncommon, they display the importance of careful management and proper patient control to minimize harm.

Ultimately, semaglutide offers significant benefits for weight loss but requires individual care plans to address side effects. Additionally, it is worth noting that semaglutide intake should be avoided by specific people, such as pregnant women, those with a history of thyroid cancer, or those with a general hypersensitivity to the treatment. Its success in helping patients achieve significant, sustained weight loss represents a breakthrough in obesity and diabetes treatment. However, ensuring long-term adherence depends on balancing its effectiveness with manageable side effects.

Section 2: Semaglutides as GLP-1 Receptor Agonists for Weight Loss and Diabetes

Semaglutide's ability to ultimately offer these benefits is attributed to its GLP-1 receptor agonist background. Semaglutides, including Ozempic and Wegovy, belong to this class of drugs, which work by mimicking the function of glucagon-like peptide-1, a hormone naturally produced by the gut in response to food.

FIGURE 1
GLP-1 Pharmacological Action and Bodily Route



In the central nervous system, semaglutide acts on GLP-1 receptors located in the hypothalamus, a region of the brain responsible for regulating hunger and energy balance. Activation of these receptors affects neurons that control appetite and satiety, reducing the urge to eat. This action is mediated by second messenger systems, including cyclic AMP (cAMP), which alters neuronal activity to suppress hunger signals.

Semaglutide also assists with dopamine signaling pathways involved in reward-driven eating behavior. This contributes to reduced cravings for higher-calorie foods, further supporting weight loss (Singh, 2023).

One of the key gastrointestinal actions of semaglutide is its ability to delay gastric emptying, which prolongs the time food stays in the stomach. This effect is mediated by GLP-1 receptors in the stomach and duodenum, which slows the rate at which the stomach releases its contents into the small intestine. The long presence of food in the stomach increases feelings of fullness and reduces calorie intake.

Biochemically, this process involves the suppression of gastric motility, the muscular contractions that push food through the digestive tract. By reducing motility, semaglutide contributes to satiety and improved glycemic control, as slower digestion prevents post-meal blood sugar spikes (Ghusn & Hurtado, 2024).

Semaglutide's effects also relate to adipose tissue, where it affects fat storage and energy usage. While the direct mechanisms are still being studied, current research suggests that GLP-1 receptor activation may shift lipid metabolism by reducing the uptake and storage of triglycerides in fat-storing adipocyte cells. This effect helps prevent weight gain and results in healthier fat distribution (Tan et al., 2022).

By activating GLP-1 receptors, semaglutides also help control blood sugar levels by increasing insulin release and decreasing glucagon production, a hormone that raises blood sugar (Palana et al., 2024). For individuals with type 2 diabetes, these combined actions improve glucose control, reducing the risk of issues like neuropathy, retinopathy, and kidney disease.

Semaglutide binds to GLP-1 receptors located mainly on pancreatic beta cells, neurons in the brain, and cells in the gastrointestinal tract. These receptors are part of the G protein-coupled receptor (GPCR) family, which initiates intracellular signaling cascades upon activation. By stimulating these receptors, semaglutide increases insulin secretion from beta cells in response to elevated blood glucose levels. This process, known as glucose-dependent

insulin secretion, ensures that insulin is only released when needed, minimizing the risk of hypoglycemia (Palana et al., 2024).

Additionally, semaglutide suppresses the secretion of glucagon, a hormone released by pancreatic alpha cells that typically raises blood sugar levels by increasing glycogen breakdown in the liver. By inhibiting glucagon release, semaglutide helps maintain lower blood glucose concentrations.

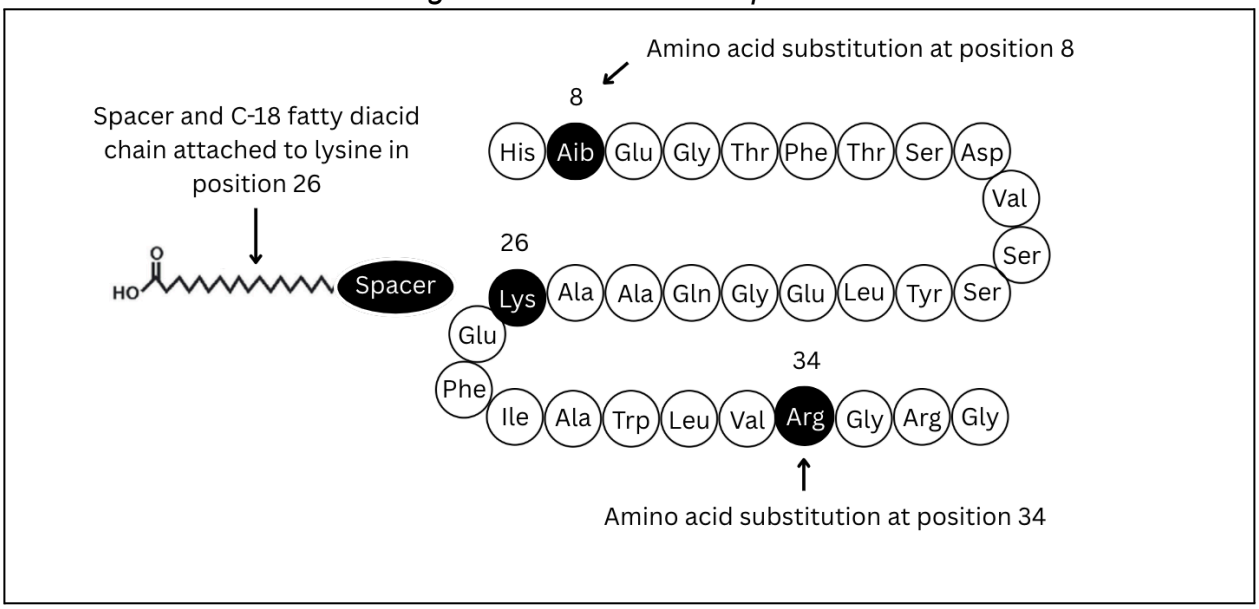
Besides glucose regulation, semaglutide has effects that contribute to its therapeutic benefits. It improves endothelial function by reducing oxidative stress and inflammation in blood vessels. This effect is thought to occur through signaling pathways involving nitric oxide, which helps maintain vascular health. These mechanisms explain why semaglutide has been associated with reduced cardiovascular risk in patients with obesity and type 2 diabetes. (Palana et al., 2024).

Semaglutide is a modified version of human GLP-1 designed to prevent rapid degradation by dipeptidyl peptidase-4 (DPP-4), an enzyme that quickly breaks down normal GLP-1. This modification significantly increases its lifespan, allowing for once-weekly dosing. After completing its biological actions, semaglutide is metabolized by enzymes and excreted primarily through the kidneys (Singh, 2023).

The biochemical mechanisms of semaglutide provide insight into both its ability to promote weight loss and manage type 2 diabetes. By increasing insulin secretion, reducing glucagon release, slowing gastric emptying, and assisting appetite-regulating pathways, semaglutide addresses the primary causes of these conditions. Its actions on GLP-1 receptors ensure that its effects are both efficient and biologically reasonable, minimizing risks and maximizing benefits. This understanding displays its value as a significant treatment in modern medicine.

FIGURE 2

The Molecular Action of Semaglutide on GLP-1 Receptors



Section 3: Comparing Cost-Effectiveness Among GLP-1 Agonists

Semaglutide's efficacy, benefits, and biological background, all of which have now been explained, are key elements when discussing the positive influence the treatment has on obesity and diabetes management. However, one key factor still must be considered: cost. When evaluating cost-effectiveness among GLP-1 receptor agonists, semaglutide often stands out due to its greater success in managing type 2 diabetes and promoting substantial weight loss. Its ability to address both conditions simultaneously can lead to reduced healthcare costs over time by decreasing additional costs and even side effects associated with other treatments for obesity and diabetes, such as cardiovascular disease and kidney damage. However, the high cost of semaglutides, which can exceed $1,000 per month without insurance, raises questions about their long-term patient and financial accessibility.

Currently, patients pay for semaglutides through various means, including private insurance plans, Medicare, and manufacturer-sponsored patient assistance programs. According to a 2024 Pharmaceutical Access Report, about 70% of major U.S. insurance providers cover semaglutide under certain conditions, primarily for type 2 diabetes management, though coverage for weight-loss indications is less insured. For the uninsured, or those with limited coverage, costs can range from $850 to $1,300 per month depending on dosage and administration method. (Montero et al., 2024)

Semaglutide has demonstrated far better efficiency compared to older GLP-1 receptor agonists like liraglutide. Additionally, semaglutide provides better glycemic control, helping patients achieve significant reductions in HbA1c levels. This greater efficiency translates into long-term health benefits, potentially reducing hospitalizations and expensive medical treatments associated with obesity and diabetes problems.

A cost-effectiveness analysis published in the Journal of Managed Care + Specialty Pharmacy calculated that semaglutide could reduce annual healthcare costs by approximately $2,500 per patient by lowering the incidence of obesity-related complications. Moreover, the drug has been associated with a 25% reduction in cardiovascular events, which are among the most costly consequences of diabetes and obesity to manage (Journal of Managed Care + Specialty Pharmacy, 2022).

Oral doses and methods of semaglutide, which are now entering the market, could provide a more affordable alternative. By eliminating the need for injectable devices, these methods may lower production and distribution costs, making the treatment more accessible to a broader range of patients.

While semaglutide remains a leader in the GLP-1 agonist class, newer therapies like tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, are emerging as competitors. Tirzepatide has shown impressive results in clinical trials, with weight reductions of up to 20%, surpassing semaglutide in some studies. However, its cost-effectiveness is still being evaluated and it remains less widely available and studied as semaglutide.

Semaglutide is also frequently compared to bariatric surgery, an effective intervention for severe obesity. While bariatric surgery can lead to greater weight loss, it comes with higher costs, longer recovery periods, and potential problems. Semaglutide offers a less invasive alternative with comparable weight-loss outcomes for certain patients, making it an appealing option for those who do not prefer surgery or who prefer non-surgical interventions (Ghusn & Hurtado, 2024).

One challenge with semaglutide's cost-effectiveness is the necessity of long-term use. Studies show that patients often regain weight after discontinuing the medication, with up to 70% of lost weight returning within a year (Tan et al., 2022). This portrays the importance of sustained therapy, which can increase overall treatment costs. To address this issue, some healthcare providers advocate being on semaglutide as well as having proper lifestyle changes, such as dietary changes and regular physical activity, to maximize its benefits and reduce dependence on medication alone.

The eventual introduction of semaglutide competitors could significantly lower costs. As patents expire, competition from generic brands is expected to make the drug more affordable, potentially expanding it to more populations. Until then, affordability remains a key issue, with many patients relying on insurance coverage or patient assistance programs to access treatment.

Furthermore, semaglutide has the potential to alleviate the financial burden of obesity and diabetes on healthcare systems. These conditions are some of the most expensive to manage, costing billions annually in the United States alone. By preventing consequences such as heart attacks, strokes, and kidney failure, semaglutide could reduce hospital admissions and improve overall public health outcomes. However, achieving these benefits requires addressing current issues to access, particularly for uninsured populations.

Conclusion

Semaglutide demonstrates clinically significant efficacy, though its accessibility remains constrained by economic barriers. While its higher cost is a challenge, its long-term health benefits can justify this cost for many patients. Moving forward, the availability of oral methods, generic versions, and newer competitors like tirzepatide will shape the image of GLP-1 agonist therapies. Addressing affordability and improving access will be critical for maximizing semaglutide's potential to change obesity and diabetes management on both an individual and global level.

Public health systems could see long-term benefits through decreased rates of cardiovascular disease, kidney failure, and other obesity-related complications, which currently impose significant economic and social burdens. In turn, semaglutide's success has energized the pharmaceutical industry, fueling a new wave of investment into GLP-1 receptor agonists and related metabolic therapies. Competitors such as tirzepatide are rapidly emerging, and the push for more convenient oral formulations and eventual generic versions may increase global accessibility over time.

Ultimately, semaglutide is not only a powerful medicinal agent but also a leader in the future of chronic disease management, particularly for obesity and type 2 diabetes, where science, innovation, and the realm of public health converge for a better future of individual lifestyle.

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