

fridays

Semaglutide: Safety, Efficacy, and Delivery Approaches

Whitepaper



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Authors
Sophie Grice (PhD),
Dan Sheridan (PhD)

Executive Summary

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, designed to target key pathways involved in glucose metabolism and appetite regulation. Clinical studies demonstrate that semaglutide is a well-tolerated obesity intervention associated with significant reductions in body weight, often approaching 15% reductions, as well as improvements in waist circumference, body composition, appetite suppression, quality of life, and cardiometabolic risk profiles. At Fridays, our semaglutide products leverage the GLP-1 mechanism to support appetite control through both subcutaneous injection and our liposomal delivery methods that make oral use possible, improving convenience and consistency. The StatRX delivery system, in particular, enables a needle-free option that allows for reliable absorption. Overall, Fridays' semaglutide products provide a safe and effective way to support appetite regulation, metabolic efficiency, healthy weight management, and overall wellness.



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1 Introduction

Recent advancements in metabolic science are reshaping our understanding of weight regulation and transforming the treatment landscape for obesity. Breakthrough therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists demonstrate that targeting hormonal pathways involved in appetite, satiety, and glucose regulation results in significant weight loss¹. These innovations represent a shift away from traditional weight-loss methods towards biology-driven interventions supported by clinical research.

For many individuals, standard weight management strategies such as diet and behavior changes and increased physical activity are not sufficient or sustainable on their own. Metabolic adaptation, increased hunger signals, and reduced energy expenditure frequently limit long-term success². As a result, many who attempt lifestyle-only approaches struggle to achieve long-lasting improvements in weight and metabolic health^{2,3}. More than 40% of U.S. adults met the criteria for obesity in 2022^{1,4}, a condition associated with serious comorbidities, such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, nonalcoholic fatty liver disease, osteoarthritis, sleep apnea, and increased risk of several cancers, contributing to reduced quality of life and increased mortality⁵.

Semaglutide has emerged as one of the most well-studied and promising GLP-1 receptor agonists for weight management. By targeting key pathways involved in appetite regulation and glucose metabolism, semaglutide enables significant and sustained weight loss for many individuals. At Fridays, we translate these scientific advances into accessible solutions through innovative delivery systems, physician-guided dosing, and personalized care, designed for individuals seeking sustainable improvements in health and wellness.

2 Background and History of GLP-1 and Semaglutide

Human and animal experiments beginning in the 1960s showed that oral glucose triggers a stronger insulin response than the same amount of glucose given intravenously, confirming that gut-derived hormones enhance insulin secretion, which is known as the incretin effect⁶. In the 1980s, GLP-1 was identified as an incretin hormone produced from the proglucagon gene⁷. It is secreted by L cells found mainly in the lower part of the small intestine (ileum) and colon after eating and helps the body manage blood sugar levels by stimulating insulin release, reducing glucagon (a hormone that raises blood sugar), slowing how quickly the stomach empties, and increasing satiety⁷. Together, these actions make GLP-1 a powerful regulator of appetite and glucose control⁸.

Natural GLP-1 is broken down rapidly by the enzyme dipeptidyl peptidase-4 (DPP-4) and cleared from the body by the kidneys. Recognizing this limitation led to the development of GLP-1-based therapeutics that can remain active for longer, including GLP-1 receptor agonists and DPP-4 inhibitors⁸. An agonist is a compound that mimics a natural hormone by binding to the same receptor and activating it to produce a biological response. GLP-1 exerts many of its metabolic benefits by binding to GLP-1 receptors, which can be found on insulin-producing pancreatic β -cells, triggering internal signals that promote insulin release when blood glucose levels are elevated⁹.

Semaglutide is a long-acting GLP-1 receptor agonist developed to mimic these natural effects while remaining active in the body for much longer. It was first approved for type 2 diabetes and is now widely used for obesity due to its robust effects on appetite, satiety, and weight reduction.

2.1. Semaglutide Mechanism of Action

Semaglutide is a 31-amino acid synthetic peptide that mimics the body's natural GLP-1 hormone and acts as a GLP-1 receptor agonist¹⁰. It is engineered to last much longer in the body compared to natural GLP-1, with small structural changes that make it more resistant to breakdown by DPP-4 and enhance reversible binding to albumin (a common blood protein)^{10,11}. This slows the clearance of semaglutide, supporting once-weekly dosing.

By activating GLP-1 receptors, semaglutide lowers blood glucose in a glucose-dependent manner by stimulating insulin secretion from pancreatic β -cells and reducing glucagon secretion from α -cells, thereby improving fasting and after-meal glucose control¹⁰. When glucose is low, these effects are reduced, which helps limit inappropriate insulin stimulation¹⁰.

Semaglutide also supports weight loss by affecting the gut and brain¹⁰. It can cause a delay in gastric emptying and reduce appetite by increasing satiety and decreasing hunger, cravings, and overall energy intake, leading to reduced food consumption and weight loss over time¹⁰ (Fig. 1).

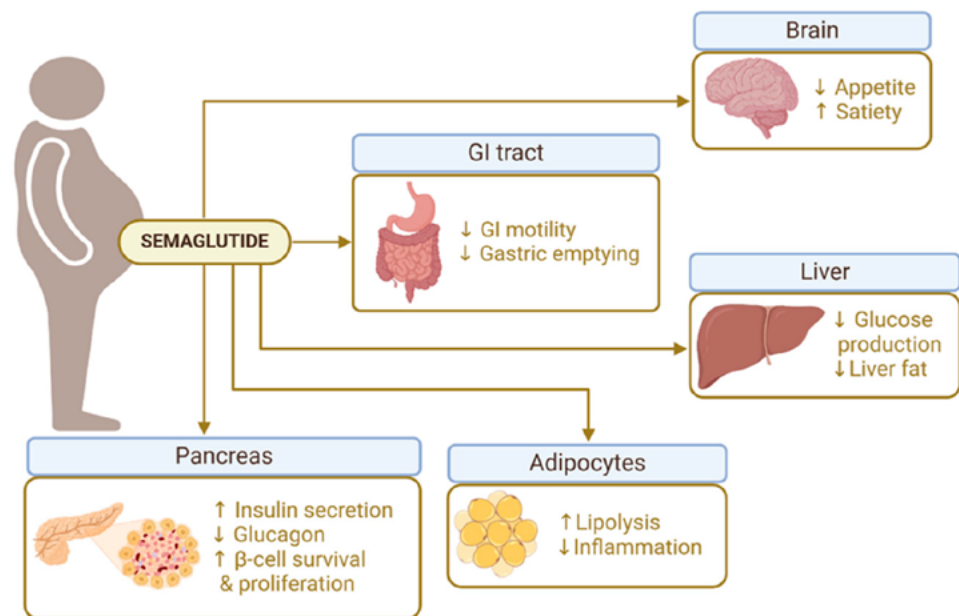


Figure 1. Mechanism of semaglutide for the management of obesity. Image from Salvador et al., 2025¹. Image used under Creative Commons License.

2.2. Pharmacokinetics of Semaglutide

When semaglutide is delivered via subcutaneous injection, it is absorbed slowly into the bloodstream and reaches its peak levels over the first few days¹². As semaglutide binds strongly to blood proteins, it remains in circulation for long periods, allowing for steady exposure and convenient once-weekly dosing¹³. It typically takes four to five weeks of weekly injections to reach stable, steady-state levels in the body¹².

Semaglutide can also be taken orally, although natural GLP-1-based molecules are usually broken down quickly and absorbed poorly. To overcome this, oral semaglutide is combined with an absorption enhancer that helps it pass through the stomach lining¹². Even with this support, only a small amount of the oral dose is absorbed, and food or large amounts of water can reduce how well it enters the bloodstream¹³.

Once absorbed, semaglutide has a relatively small volume of distribution and stays mostly within the bloodstream. Semaglutide has a long half-life of about one week, meaning it stays in the body for several weeks after the last dose. It is eliminated slowly as metabolites through both urine and feces¹³.

3 Clinical Data Supporting Semaglutide

Semaglutide supplementation is one of the most well-researched GLP-1 agonists to date, with numerous randomized controlled trials and meta-analyses in populations with obesity and type 2 diabetes. Clinical research is ongoing; however, current evidence suggests that semaglutide can produce significant reductions in body weight, enhance body composition, reduce waist circumference, suppress appetite and food cravings, improve eating behavior, and improve quality of life and key cardiometabolic markers^{14–26}.

3.1. Significant Reduction in Body Weight

Multiple meta-analyses and systematic reviews have evaluated the clinical efficacy of semaglutide for weight reduction in overweight or obese populations. In one systematic review and meta-analysis of eight studies involving 4,567 overweight/obese individuals, it was found that compared to placebo, semaglutide induced significant body weight loss, with an average reduction of approximately 10%, in addition to a significant reduction in body mass index (BMI)¹⁴.

An additional systematic review and meta-analysis included six randomized controlled trials involving 3,962 overweight/obese participants who took once-weekly subcutaneous semaglutide (2.4 mg)¹⁵. Compared to placebo, semaglutide produced significant and sustained reductions in body weight, with an average decrease of almost 12% in percentage body weight and significant reductions in absolute body weight and BMI¹⁵.

In terms of the long-term effectiveness of once-weekly subcutaneous semaglutide (2.4 mg) for weight loss in overweight or obese populations, a systematic review and meta-analysis examined four randomized controlled trials involving 3,087 participants with a follow-up of at least 68 weeks¹⁶. Compared with placebo, semaglutide produced a significant and sustained reduction in body weight in the long term¹⁶. On average, participants receiving semaglutide lost 12.1% of body weight, corresponding to approximately 12.3 kg more weight loss than placebo¹⁶. In addition, a much higher proportion of individuals treated with semaglutide achieved a body-weight reduction of at least 20% compared with those receiving placebo¹⁶.

Included in these analyses are the phase III double-blind randomized controlled trials (STEP trials), which provide pivotal evidence for the safety and efficacy of semaglutide in non-diabetic individuals who are overweight or obese. The STEP 1 trial, involving 1,961 participants with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related complication, excluding diabetes, evaluated once-weekly subcutaneous semaglutide (dose-escalated to 2.4 mg) versus placebo over 68 weeks with lifestyle alterations¹⁷. Participants treated with semaglutide experienced a mean body-weight reduction of 14.9%, compared with a 2.4% reduction in the placebo group¹⁷. In absolute terms, the change in body weight from baseline to week 68 was -15.3 kg in the semaglutide group, compared with -2.6 kg in the placebo group¹⁷.

The STEP 5 trial, involving 304 participants with a BMI ≥ 30 kg/m², or ≥ 27 kg/m² with at least one weight-related complication, excluding diabetes, evaluated once-weekly subcutaneous semaglutide (dose-escalated 2.4 mg) versus placebo over 104 weeks with lifestyle alterations¹⁸. Participants receiving semaglutide achieved substantial and sustained weight loss, with a mean reduction in body weight of approximately 15%, compared with a 2.6% reduction in the placebo group¹⁸ (Fig. 2).

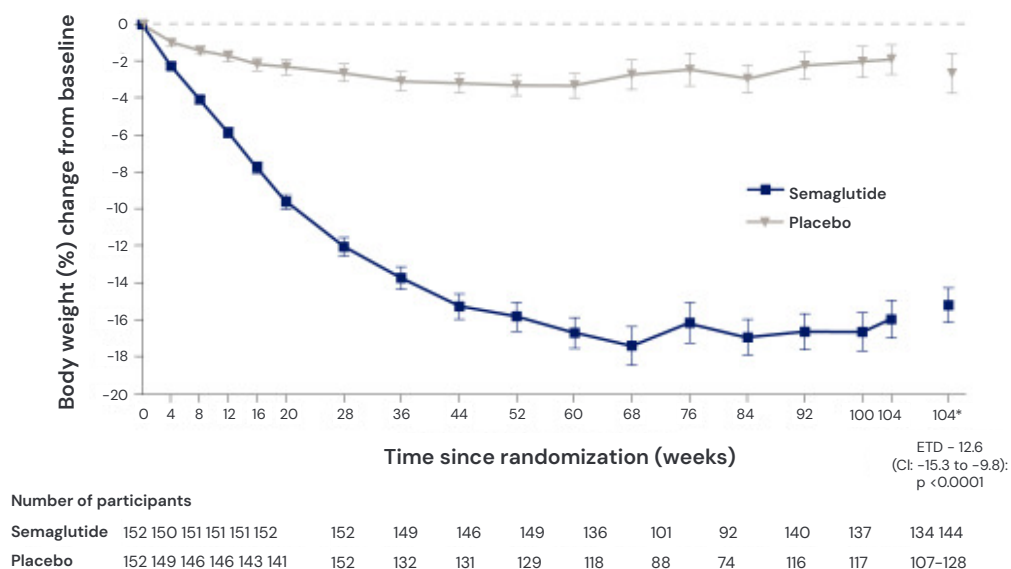


Figure 2. Mean percentage body weight change from baseline over time since randomization for participants in the STEP 5 trial. Adapted from Garvey et al., 2022. Image used under Creative Commons License®.

3.2. Improved Body Composition and Waist Circumference

In the STEP 1 trial, by the end of the study, semaglutide-treated participants saw significant reductions in waist circumference of -13.54 cm compared to -4.13 cm in the placebo-treated group¹⁷. Additionally, in the STEP 5 trial, by week 104, participants who received semaglutide had significant reductions in waist circumference of 14.4 cm compared to 5.2 cm in the placebo group (Fig. 3).

A sub-study of the STEP 1 trial evaluated changes in body composition in a subset of 140 participants (semaglutide, n = 95; placebo, n = 45) selected from the original cohort of 1,961 individuals¹⁹. Participants underwent dual-energy X-ray absorptiometry (DEXA) scans at baseline and at week 68 to assess changes in body composition¹⁹. From baseline to week 68, participants treated with once-weekly subcutaneous semaglutide (2.4 mg) experienced a mean reduction in body weight of -15.0%, total fat mass of -19.3%, and lean body mass of -9.7%, compared with reductions of -3.6% in body weight, with minimal changes in body composition in the placebo group¹⁹. Semaglutide treatment also resulted in a marked reduction in regional visceral fat mass (-27.4%) and an improvement in the lean body mass-to-fat mass ratio¹⁹.

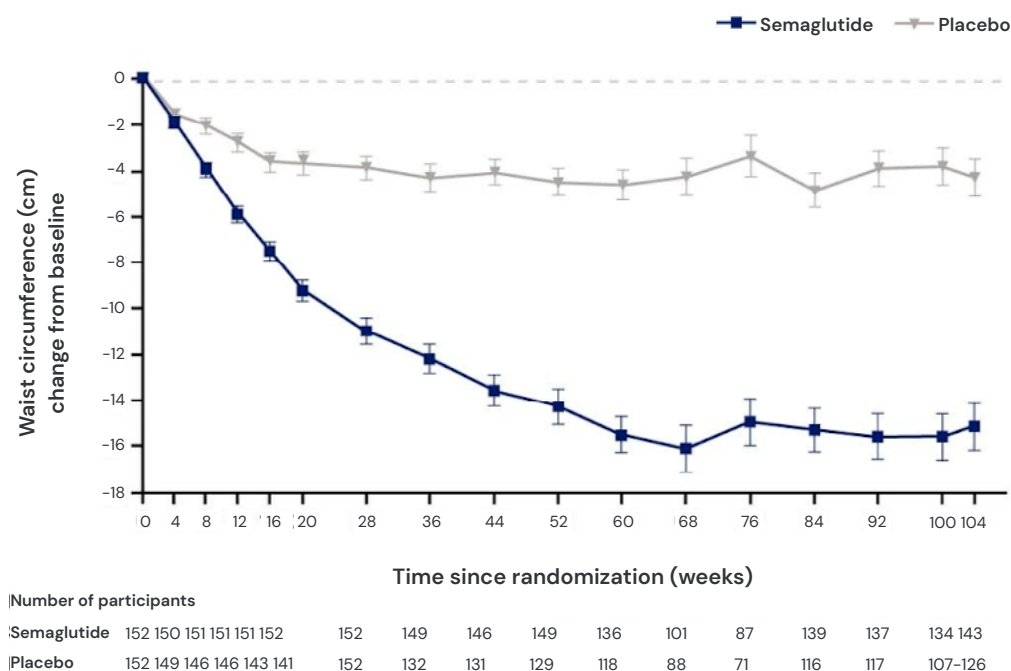


Figure 3. Mean change in waist circumference from baseline over time since randomization for participants in the STEP 5 trial. Adapted from Garvey et al., 2022. Image used under Creative Commons License[®].

3.3. Appetite Suppression and Improved Eating Behavior

Clinical studies have shown that semaglutide significantly reduces appetite and energy intake and improves eating behaviors, which are key mechanisms underlying its weight-loss effects. In a randomized controlled trial involving participants with obesity, 30 individuals who received once-weekly semaglutide (1 mg) for 12 weeks exhibited a 24% reduction in total ad libitum daily energy intake compared with the placebo group²⁰. Semaglutide was also associated with less hunger and food cravings, better control of eating, and a low preference for high-fat foods²⁰.

Additionally, a double-blind, parallel-group trial was conducted in 72 adults with obesity, which examined the effects of once-weekly subcutaneous semaglutide (dose-escalated to 2.4 mg) over 20 weeks²¹. Compared to placebo, semaglutide resulted in a 35% reduction in ad libitum energy intake during a standardized meal²¹. Participants who received semaglutide also reported reduced hunger and prospective food consumption, in addition to increased feelings of fullness and satiety²¹. Questionnaire assessments indicated improved control of eating and fewer or weaker food cravings in the semaglutide group²¹.

In an analysis from the STEP 5 trial, a subgroup of 174 participants completed a questionnaire assessing appetite, cravings, and eating behavior²². Compared to the placebo-treated group, those who received semaglutide had significant improvements in craving control, reduced cravings for savory and sweet foods, increased positive mood, and improved control of eating²².

Notably, in a double-blind randomized controlled study involving 61 participants with obesity, oral semaglutide (dose-escalated to 50 mg) administered over 20 weeks significantly reduced hunger, increased feelings of fullness and satiety, and was associated with fewer food cravings and improved control of eating compared to placebo²³.

3.4. Enhanced Metabolic and Overall Health

In an analysis of weight-related and health-related quality of life, with a focus on physical functioning, using data from the STEP 1–4 trials, semaglutide demonstrated significant improvements in physical functioning compared to placebo, particularly in the STEP 1, 2, and 4 trials²⁴.

Additionally, the large, multicenter randomized controlled trial (SELECT trial) evaluated whether once-weekly subcutaneous semaglutide (2.4 mg) could reduce cardiovascular risk in 17,604 overweight/obese participants without diabetes who had preexisting cardiovascular disease²⁵. Cardiovascular events occurred in 6.5% of participants receiving semaglutide and 8.0% of those receiving placebo, with a reduced risk of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 20%²⁵.

An additional analysis of data from the STEP 1 and STEP 4 trials examining cardiometabolic risk factors found that semaglutide was associated with greater reductions in systolic and diastolic blood pressure, fasting plasma glucose, fasting insulin, and lipid levels compared to placebo²⁶. Participants treated with semaglutide also demonstrated reduced use of antihypertensive and lipid-lowering medications relative to those receiving the placebo²⁶.

Notably, in the STEP 5 trial, by week 104, participants who received semaglutide demonstrated significant reductions in systolic blood pressure compared to placebo¹⁸ (Fig. 4). In addition, semaglutide demonstrated improvements in diastolic blood pressure, glycated hemoglobin (HbA1c), fasting glucose, fasting serum insulin, C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and triglycerides compared to placebo¹⁸.

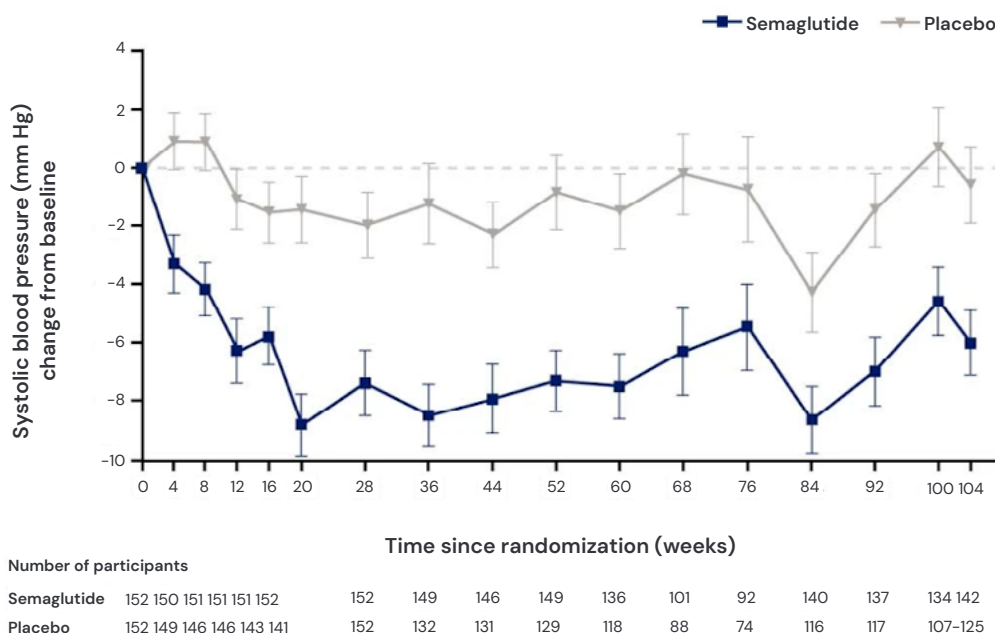


Figure 4. Mean change in systolic blood pressure from baseline over time since randomization for participants in the STEP 5 trial. Adapted from Garvey et al., 2022. Image used under Creative Commons License[®].

4 Safety and Dosing

For weight management, semaglutide is typically administered between 0.25 mg and 2.4 mg as a once-weekly subcutaneous injection, usually with gradual dose escalation to improve tolerability¹⁸. Oral semaglutide is typically administered at 3 mg once daily, then escalating to 7 mg to 14 mg¹². Clinical trial data indicate that semaglutide is generally well-tolerated, with most adverse events being mild to moderate and occurring during the initial dose escalation period²⁷.

The most commonly reported side effects are gastrointestinal, including nausea, diarrhea, vomiting, and constipation²⁷. In a phase IIIb randomized controlled study, the safety and efficacy of higher-dose semaglutide (7.2 mg) were evaluated, demonstrating that increased doses may be more efficacious in terms of weight loss but are associated with a higher incidence of gastrointestinal adverse events²⁸. Gastrointestinal events were reported in 70.8% of participants receiving semaglutide 7.2 mg, compared with 61.2% of those receiving the 2.4 mg dose²⁸.

Other side effects include injection-site reactions and a low risk of mild hypoglycemia, particularly when semaglutide is used in combination with other glucose-lowering agents²⁹. Rare adverse effects include pancreatitis and gallbladder-related disorders such as cholelithiasis and cholecystitis²⁹. Concurrent use of semaglutide with other GLP-1 receptor agonists is not recommended due to overlapping mechanisms of action and an increased risk of adverse effects.

5 Fridays' Semaglutide

Fridays focuses on safety, education, and accessibility, helping individuals explore physician-guided wellness options that may support healthy weight management. With transparent pricing and personalized care, Fridays makes advanced therapies approachable and convenient from home.

Semaglutide Subcutaneous Injection: Direct delivery of semaglutide into adipose tissue, where it is gradually absorbed into systemic circulation, providing steady exposure and reducing the need for clinical supervision.

Semaglutide StatRX Sublingual Delivery: A cutting-edge delivery system now enables semaglutide to be taken sublingually, encapsulating semaglutide for potentially enhanced absorption and therapeutic effects. The StatRX delivery system, available exclusively at Fridays, enables easy and reliable delivery of semaglutide through the sublingual pathway, without the need for needles.

5.1. Semaglutide Microdosing

Standard clinical administration of subcutaneous semaglutide typically starts with 0.25 mg weekly, gradually escalating to a maintenance dose. This approach highlights the value of lower-dose exposure in supporting tolerability and long-term adherence. Clinical trial data indicate that semaglutide is generally well-tolerated at 0.25 mg to 2.4 mg, with most adverse events usually occurring during the primary period of dose escalation. Therefore, maintaining treatment at lower doses for longer periods may be beneficial in reducing the likelihood of adverse events.

In a randomized, double-blind phase II trial in individuals with obesity without diabetes, participants who received low daily doses of 0.05 mg or 0.1 mg of semaglutide achieved significant weight reductions of 6.0% to 8.6% over 52 weeks compared to placebo, despite receiving substantially lower doses than those used in other clinical studies³⁰. All semaglutide doses were generally well tolerated, with the most common adverse events being dose-related gastrointestinal symptoms, primarily nausea³⁰. These findings suggest that microdosed semaglutide retains biological efficacy and may represent a viable strategy for individuals who are sensitive to higher doses or who prioritize tolerability over maximal weight loss. Further clinical trials are currently underway to establish the safety and efficacy of microdosed semaglutide through oral and subcutaneous delivery³¹.

Microdosing strategies may also offer several other potential benefits. In individuals undergoing multiple treatment or lifestyle changes, initiating therapy at lower doses may improve tolerability and allow for closer monitoring of treatment response³². Microdosing may also be useful during planned treatment interruptions, where gradual and controlled reintroduction of semaglutide could minimize adverse effects while maintaining therapeutic momentum³².

While formal clinical evidence specific to semaglutide microdosing is still emerging, its potential applications highlight a promising area for further research and clinical innovation, particularly within personalized weight-management strategies.

6 Conclusion

Semaglutide represents a scientifically grounded and clinically supported approach to the management of obesity and related metabolic conditions. By activating the GLP-1 receptor, semaglutide targets key physiological drivers of weight gain, including appetite dysregulation, impaired glucose control, and reduced satiety signaling¹. Extensive clinical evidence demonstrates that semaglutide produces clinically meaningful and sustained reductions in body weight, often approaching 15%, alongside improvements in waist circumference, body composition, appetite control, eating behavior, quality of life, and cardiometabolic risk factors^{14–26}. These studies highlight semaglutide as a potential solution for weight management and also broader metabolic health support.

Across clinical studies, semaglutide has shown a generally well-tolerated safety profile, with most adverse events being mild to moderate and primarily gastrointestinal, occurring most commonly during dose escalation²⁹. Emerging evidence also suggests that lower-dose strategies may retain biological efficacy, highlighting opportunities for more personalized dosing approaches as clinical research continues to evolve³².

As peptide-based therapies traditionally face challenges in delivery and convenience, innovative delivery technologies play a critical role in expanding access and use. Fridays' semaglutide offerings, including subcutaneous injection and the StatRX sublingual delivery system, are designed to support reliable absorption while reducing barriers associated with needles and complex dosing. Combined with physician-guided care and individualized treatment plans, these approaches aim to enhance adherence, flexibility, and patient experience.

Taken together, the current body of evidence supports semaglutide as a safe and effective option for supporting appetite regulation and weight management. With the integration of advanced delivery systems and personalized clinical oversight, Fridays provides a science-backed, patient-centered solution for individuals seeking meaningful improvements in weight management and overall wellness.

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