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EFFECTIVENESS OF SEMAGLUTIDE IN OBESITY TREATMENT AND THE ROLE OF LIFESTYLE INTERVENTIONS

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ABSTRACT

Background: Obesity is a global epidemic, affecting ~13% of adults and driving type 2 diabetes, cardiovascular disease, and other comorbidities (World Health Organization, 2021). In Europe and the U.S., prevalence reaches 30–40%, with >20% in Poland (Gajewska & Harton, 2023). Lifestyle interventions alone often fail to ensure durable results, creating demand for adjunctive pharmacotherapy.
Aim: To review obesity epidemiology and evaluate once-weekly semaglutide 2.4 mg regarding mechanism, efficacy, safety, and synergy with lifestyle changes.
Materials and Methods: Narrative review of publications (2018–2025) from PubMed, Google Scholar, and other databases on obesity, GLP-1 analogs, and lifestyle trials. STEP program data, meta-analyses, and guidelines were included.
Results: Risk factors include genetics, aging, sedentary lifestyle, and poor diet. Semaglutide, a GLP-1 receptor agonist, enhances insulin secretion, delays gastric emptying, and reduces appetite (Papakonstantinou et al., 2024). In STEP Phase 3 trials, semaglutide 2.4 mg weekly produced ~15% mean weight loss over 68 weeks, versus ~2–5% with placebo (Wilding et al., 2021) (Davies et al., 2021). About 69–79% achieved ≥10% loss, over half ≥15% (Davies et al., 2021). Safety was consistent with GLP-1 class, dominated by mild-to-moderate gastrointestinal events (Davies et al., 2021). Lifestyle modification alone yields 5–10% reduction, but in STEP 3, semaglutide plus intensive behavioral therapy achieved 16.0% versus 5.7% with lifestyle alone (Wadden et al., 2021). Continued lifestyle support is crucial to maintain outcomes and limit post-withdrawal regain.
Conclusions: Semaglutide represents a breakthrough in obesity pharmacotherapy, approaching bariatric surgery efficacy in some patients. Optimal outcomes occur with integration of diet, activity, and education. Future dual/triple agonists may enhance efficacy, but issues of cost, access, and adherence persist. Broad, equitable availability is essential for public health.

KEYWORDS

Obesity, GLP-1 Receptor Agonist, Semaglutide, Weight Loss, Lifestyle Intervention, Pharmacotherapy

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1. Introduction

Obesity is a highly prevalent, chronic disease that has been increasing at an alarming rate worldwide. According to the World Health Organization (WHO), in 2016 over 650 million adults (13% of adults globally) were obese, and by 2025 the global obesity prevalence is projected to reach 18% in men and 21% in women(World Health Organization, 2021). Many countries have witnessed a dramatic rise in obesity over the past few decades. For example, the United States saw adult obesity prevalence climb from ~30% in 2000 to about 42% by 2017–2018, and similar trends have been observed across Europe (World Health Organization, 2021). In Poland, more than 65% of adults now have overweight or obesity, including roughly 1 in 4 adults (around 23–25%) classified as obese(Gajewska & Harton, 2023). This epidemiologic shift has serious implications, as excessive body weight is closely linked to a range of adverse health outcomes.

1.1. Background and Health Consequences of Obesity: Obesity's impact on health is profound and multi-systemic. Adiposity, especially when centralized viscerally, drives up cardiometabolic risk. Individuals with obesity are at significantly elevated risk for developing type 2 diabetes mellitus (the risk is several-fold higher compared to normal-weight individuals), hypertension, dyslipidemia, and atherosclerotic cardiovascular diseases (e.g. coronary heart disease and stroke)(World Health Organization, 2021). Obesity is also associated with a higher likelihood of certain cancers (such as colorectal, postmenopausal breast, endometrial, and others) and contributes to conditions like non-alcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, and depression (World Health Organization, 2021). The result is a substantial burden of

morbidity, impaired quality of life, and increased mortality in populations with obesity. Epidemiological data indicate that even a 5–10% weight reduction can yield meaningful improvements in blood pressure, glycemic control, lipid profiles, and other risk factors, underlining the importance of effective obesity treatment (World Health Organization, 2021). Given these stakes, obesity is now recognized as a chronic disease requiring long-term management rather than a simple lifestyle issue.

1.2. Need for Effective Obesity Treatment: Lifestyle modification is the first-line approach for weight management. A caloric deficit through dietary change and an increase in physical activity can induce modest weight loss and associated metabolic benefits. However, in practice, lifestyle interventions often result in only limited weight loss (on the order of 5–8% of body weight) that may be difficult to sustain over the long term (Davies et al., 2021). Biological adaptations to weight loss—including increased hunger hormones, reduced energy expenditure, and changes in nutrient partitioning—tend to favor weight regain, making obesity a”relapsing” condition in many cases (Davies et al., 2021)(Sumithran et al., 2011). As a consequence, there has been growing interest in adjunctive therapies that can help patients achieve greater and more durable weight loss. Pharmacotherapy for obesity, historically, has been limited by modest efficacy and safety issues, but recent advances have produced a new class of medications with markedly improved outcomes (Davies et al., 2021). Among these, glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as especially promising.

1.3. Introduction to GLP-1 and Semaglutide: GLP-1 is an incretin hormone released from the gut in response to nutrient ingestion. It enhances glucose-dependent insulin secretion and signals satiety to the brain. As such, GLP-1 receptor agonists were originally developed to treat type 2 diabetes, leveraging their ability to improve glycemic control. Patients on GLP-1 agonists were observed to lose weight, an effect related to reduced appetite and energy intake. Semaglutide is a potent, long-acting GLP-1 receptor agonist (approximately 94% homologous to human GLP-1) designed for once-weekly administration(Papakonstantinou et al., 2024). It was first approved for type 2 diabetes at lower doses (up to 1.0 mg weekly, under the brand Ozempic®) and demonstrated cardiovascular benefits in diabetic patients at high cardiovascular risk. Given its robust effect on body weight, semaglutide was subsequently studied at a higher dose (2.4 mg weekly) for chronic weight management in non-diabetic individuals. In 2021, semaglutide 2.4 mg (branded as Wegovy®) was approved by the U.S. FDA and later by the EMA and other agencies as an adjunct to a reduced-calorie diet and increased physical activity for adults with obesity (body mass index ≥30) or overweight (BMI ≥27) with at least one weight-related comorbidity. This marked a significant milestone in obesity therapy, as clinical trial results suggested weight loss outcomes far exceeding those of previous medications (Wilding et al., 2021) (Davies et al., 2021).

Semaglutide’s mechanism of action in obesity treatment extends beyond glucose control. By activating GLP-1 receptors in multiple tissues (pancreas, gastrointestinal tract, brain), semaglutide influences metabolic and neurohormonal pathways that regulate body weight. A key site of action is the hypothalamus in the brain, which is the control center for appetite and energy expenditure. Semaglutide readily crosses the blood–brain barrier and activates GLP-1 receptors on anorexigenic pro-opiomelanocortin (POMC) neurons while inhibiting orexigenic neuropeptide Y/AgRP neurons in the arcuate nucleus(Papakonstantinou et al., 2024). This shifts the balance towards satiety: patients on semaglutide report reduced hunger and fewer food cravings, increased fullness during meals, and an overall lower desire to eat. Functionally, these central effects translate into a significant reduction in daily caloric intake.

In the gastrointestinal tract, semaglutide slows gastric emptying – the rate at which food leaves the stomach. By keeping food in the stomach longer, it prolongs the feeling of fullness after eating and blunts the postprandial rise in glucose. Slower nutrient absorption may also modulate gut–brain satiety signaling. Semaglutide’s effects on the pancreas include enhancement of glucose-dependent insulin secretion by pancreatic β-cells and suppression of glucagon release by α-cells(Papakonstantinou et al., 2024). The glucose-dependent nature is important: insulin is increased when blood sugar is high (e.g., after a meal), reducing hyperglycemia, but not during fasting, so the risk of hypoglycemia is low (especially in non-diabetic individuals). Improved insulin and lower glucagon levels promote more stable blood glucose and can indirectly reduce appetite fluctuations linked to glycemic dips. Additionally, semaglutide has been shown to promote β-cell proliferation and survival in preclinical models, suggesting a protective effect on pancreatic function.

Overall, these mechanisms produce a comprehensive metabolic improvement. By inducing negative energy balance (calories consumed < calories expended), semaglutide leads to weight loss that consists primarily of

reductions in fat mass (both visceral and subcutaneous). In clinical studies, semaglutide therapy has also been associated with improvements in cardiometabolic risk markers beyond weight alone. For example, patients typically exhibit reduced systolic blood pressure, lower levels of triglycerides and LDL cholesterol, and improved indicators of glycemic control (even non-diabetics often show lower fasting glucose and HbA1c) (Davies et al., 2021). The weight loss itself likely mediates many of these benefits, but there may be direct GLP-1 effects on tissues like the heart and blood vessels (as hinted by cardiovascular outcome trials in diabetes). It is noteworthy that GLP-1 receptors are present in cardiomyocytes and renal tubules, so ongoing research is examining whether agents like semaglutide have organ-protective effects independent of weight loss.

In summary, semaglutide's mechanism in obesity treatment can be viewed as restoring balance in appetite regulation and energy metabolism. By counteracting the biological drive to eat and facilitating a lower caloric intake, while also possibly enhancing energy expenditure slightly, semaglutide helps patients achieve weight loss that typically would not be attainable through lifestyle changes alone due to counter-regulatory mechanisms. Importantly, semaglutide addresses both hedonic appetite (food cravings, reward) and homeostatic appetite (caloric need) pathways, providing a powerful tool to assist patients in adhering to calorie-reduced diets.

2. Research materials and methods

This article is a narrative literature review synthesizing data from peer-reviewed scientific publications, official reports, and guidelines relevant to obesity epidemiology, pharmacological treatment with GLP-1 receptor agonists, and the role of lifestyle interventions.

The literature search was conducted in PubMed, Scopus, and Google Scholar databases, as well as on official websites of recognized health authorities, including the World Health Organization (WHO), European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), and Polish public health institutions.

The search covered publications from January 2010 to February 2025. Earlier works were also included when they represented seminal studies or provided fundamental background information on the pathophysiology of obesity or GLP-1 receptor agonists.

The following keywords and their combinations were used: *obesity*, *overweight*, *epidemiology*, *GLP-1 receptor agonist*, *semaglutide*, *Wegovy*, *Ozempic*, *STEP trials*, *lifestyle intervention*, *diet*, *physical activity*, *weight loss*, *pharmacotherapy*, *GLP-1RA safety*. Boolean operators (AND, OR) and Medical Subject Headings (MeSH) terms were applied where appropriate.

2.1. Inclusion criteria:

- Randomized controlled trials (RCTs), meta-analyses, systematic reviews, and narrative reviews.
- Clinical guidelines, consensus statements, and official reports from recognized medical societies or public health agencies.
- Observational studies and registry analyses relevant to obesity treatment or epidemiology.
- Publications in English or Polish.

2.2. Exclusion criteria:

- Case reports and small case series unless providing unique mechanistic or safety insights.
- Non-scientific commentaries or opinion pieces without references.

Reference lists of key articles were manually screened to identify additional relevant studies. Data extraction focused on study design, population characteristics, intervention details, clinical outcomes, and safety profiles. The synthesis of evidence was organized into thematic sections: epidemiology of obesity, pharmacological characteristics and mechanism of action of semaglutide, clinical trial evidence, lifestyle intervention strategies, and integration of pharmacotherapy with behavioral modification.

2.3. AI

Artificial intelligence tools were employed in this study solely as assistive instruments under human supervision. They were used for translation of selected sections of the manuscript, refinement of academic English (grammar, style, and clarity), and to improve efficiency in data processing. At no stage did AI replace human judgment — all data interpretation, classification, and formulation of conclusions were performed exclusively by the authors.

3. Results

3.1. Epidemiology of Obesity

Over the last few decades, obesity has evolved into a worldwide public health crisis. The global prevalence of obesity in adults has nearly tripled since 1975. WHO estimates from 2016 indicated that 39% of adults (≈1.9 billion people) were overweight (BMI ≥25), and 13% (≈650 million) were obese (BMI ≥30) (World Health Organization, 2021). This upward trend shows no sign of abating; projections suggest that by 2030 as many as 1 in 5 adults worldwide could have obesity if current patterns persist. Moreover, recent analyses predict that by 2035, over half of the global population will be living with overweight or obesity (World Obesity Federation, 2023). The rise has been especially steep in certain regions. In North America and parts of the Middle East and Oceania, adult obesity prevalence already exceeds 30% (World Health Organization, 2021). Europe has also seen a dramatic increase: between 2000 and 2017, obesity prevalence in many European countries expanded from around 10% into the 20–40% range. The WHO European Regional Obesity Report 2022 highlighted that overweight and obesity now affect nearly 60% of European adults, with obesity rates of 25% or higher in many nations (World Health Organization Regional Office for Europe, 2022). This includes Central and Eastern European countries undergoing lifestyle and dietary transitions.

Poland exemplifies the concerning regional trends. Recent data indicate that more than 65% of Polish adults have above-normal weight, and about 23% are obese, reflecting a sharp rise over previous decades (Gajewska & Harton, 2023). National surveys in Poland show obesity rates climbing in both men and women, with particularly high prevalence among middle-aged and older adults (Gajewska & Harton, 2023). For instance, a large 2019–2020 survey reported that 42.2% of Polish adults were overweight (pre-obese) and 16.4% were obese, meaning nearly 59% had at least excess weight(Gajewska & Harton, 2023). Notably, obesity in Poland (as elsewhere) increases with age: the highest rates are observed in people in their 50s, 60s, and 70s before slightly declining in the very elderly (Gajewska & Harton, 2023). Public health authorities are alarmed by these figures, as they portend increasing burdens of diabetes, cardiovascular disease, and other obesity-linked conditions on healthcare systems.

Several factors are driving the global obesity epidemic. Economic growth and urbanization have led to greater availability of high-calorie processed foods and more sedentary lifestyles in many societies. The nutrition transition—characterized by diets high in sugars, fats, and refined foods—combined with a decline in physical labor and activity, creates a chronic energy surplus for many individuals. Moreover, obesogenic environments (environments that promote food intake and discourage physical activity) and aggressive food marketing contribute to positive energy balance on a population level. The rapid spread of obesity in developing countries alongside persisting undernutrition exemplifies the complexity of malnutrition in all its forms.

High-Risk Groups and Disparities: Obesity does not affect all segments of the population equally; certain groups are at higher risk due to genetic, behavioral, or socioeconomic factors. **Age:** Middle-aged and older adults tend to have the highest obesity rates. Basal metabolic rate decreases with age, and age-related sarcopenia (loss of muscle mass) can lower energy expenditure, making weight gain more likely if diet is not adjusted. In Poland, for example, obesity prevalence peaks in the 55–74 age range for both sexes (Gajewska & Harton, 2023). **Sex:** In many regions, women have slightly higher obesity prevalence than men, though this varies by country. In Europe overall, ~30% of women vs 27% of men are obese, whereas in the U.S. the gap is larger (about 40% of women vs 35% of men). Biological factors (e.g. hormonal influences on fat distribution) and sociocultural factors (e.g. differences in work patterns or health behaviors) may contribute. **Family history and genetics:** Individuals with one or both parents obese are at much higher risk of obesity, reflecting both genetic predisposition and shared family lifestyle. Dozens of genetic loci (e.g. FTO, MC4R) have been identified that modestly increase obesity susceptibility, and rare genetic disorders can cause severe obesity from childhood. These genetic factors often interact with environmental influences—our modern environment effectively"pulls the trigger" on genetic susceptibility. **Lifestyle and behavior:** People with sedentary lifestyles and chronically high caloric intake are obviously at elevated risk. Diets rich in ultra-processed foods, sugar-sweetened beverages, and large portion sizes promote weight gain. Physical inactivity, whether due to occupation (desk jobs), urban living (reliance on cars, screen time), or personal habits, contributes to an energy surplus. In contrast, higher levels of regular physical activity are protective and aid in weight regulation. **Socioeconomic status (SES):** There is an inverse relationship between SES and obesity in many high-income countries—obesity is more prevalent in lower-income, less-educated populations (especially among women). This is often attributed to factors like limited access to healthy foods (healthy options can be more expensive or less available in disadvantaged areas), lower health literacy, chronic stress,

and fewer opportunities for exercise. In Poland, surveys have found that women with higher education have significantly lower obesity rates than those with only primary education (Gajewska & Harton, 2023). **Urban vs rural:** Interestingly, rural populations in some countries now have equal or higher obesity rates compared to urban residents (Gajewska & Harton, 2023). Reduced physical labor in rural settings and increased penetration of processed foods might be narrowing the gap that historically showed urban lifestyles as more obesogenic.

Childhood obesity deserves mention as well, since it portends adult obesity. Globally, over 340 million children and adolescents (ages 5–19) were overweight or obese in 2016 (World Health Organization, 2021). The WHO European COSI survey found about 29% of children 7–9 years old had excess weight in 2019, and 12% were obese (Gajewska & Harton, 2023). Pediatric obesity tracks strongly into adulthood; an overweight child is far more likely to become an obese adult than a normal-weight child. Thus, preventing obesity early in life is critical to curbing the overall epidemic.

In summary, the epidemiology of obesity underscores that this is a widespread and worsening problem, affecting diverse populations with certain groups at particular risk. These trends form the backdrop against which enhanced treatment strategies, including effective medications like semaglutide, have become urgently needed. Before turning to treatment modalities, we will delve deeper into semaglutide's profile as a new therapy in obesity management.

3.2. Semaglutide as a Therapy in Obesity

Mechanism of Action and Metabolic Effects: Semaglutide is a GLP-1 receptor agonist that exerts multiple physiological actions beneficial for weight reduction and metabolic health. By binding to GLP-1 receptors throughout the body, semaglutide effectively amplifies the effects of endogenous GLP-1 hormone. A key site of action is the hypothalamus in the brain, which is the control center for appetite and energy expenditure. Semaglutide readily crosses the blood–brain barrier and activates GLP-1 receptors on anorexigenic POMC neurons while inhibiting orexigenic neuropeptide Y/AgRP neurons in the arcuate nucleus (Papakonstantinou et al., 2024). This shifts the balance towards satiety: patients on semaglutide report reduced hunger and fewer food cravings, increased fullness during meals, and an overall lower desire to eat. Functionally, these central effects translate into a significant reduction in daily caloric intake.

In the gastrointestinal tract, semaglutide slows gastric emptying – the rate at which food leaves the stomach. By keeping food in the stomach longer, it prolongs the feeling of fullness after eating and blunts the postprandial rise in glucose. Slower nutrient absorption may also modulate gut–brain satiety signaling. Semaglutide's effects on the pancreas include enhancement of glucose-dependent insulin secretion by pancreatic β-cells and suppression of glucagon release by α-cells (Papakonstantinou et al., 2024). The glucose-dependent nature is important: insulin is increased when blood sugar is high (e.g., after a meal), reducing hyperglycemia, but not during fasting, so the risk of hypoglycemia is low (especially in non-diabetic individuals). Improved insulin and lower glucagon levels promote more stable blood glucose and can indirectly reduce appetite fluctuations linked to glycemic dips. Additionally, semaglutide has been shown to promote β-cell proliferation and survival in preclinical models, suggesting a protective effect on pancreatic function.

Overall, these mechanisms produce a comprehensive metabolic improvement. By inducing negative energy balance (calories consumed < calories expended), semaglutide leads to weight loss that consists primarily of reductions in fat mass (both visceral and subcutaneous). In clinical studies, semaglutide therapy has also been associated with improvements in cardiometabolic risk markers beyond weight alone. For example, patients typically exhibit reduced systolic blood pressure, lower levels of triglycerides and LDL cholesterol, and improved indicators of glycemic control (even non-diabetics often show lower fasting glucose and HbA1c) (Davies et al., 2021). The weight loss itself likely mediates many of these benefits, but there may be direct GLP-1 effects on tissues like the heart and blood vessels (as hinted by cardiovascular outcome trials in diabetes). It is noteworthy that GLP-1 receptors are present in cardiomyocytes and renal tubules, so ongoing research is examining whether agents like semaglutide have organ-protective effects independent of weight loss.

Pharmacologically, semaglutide is formulated as a long-acting agent. Its peptide structure was modified by acylation (attachment of a C-18 fatty acid chain) and amino acid substitutions, which confer strong binding to albumin and resistance to degradation by the DPP-4 enzyme (Papakonstantinou et al., 2024). As a result, semaglutide's half-life in circulation is ~1 week, supporting once-weekly dosing. This is a significant convenience advantage over the earlier GLP-1 agonist for obesity, liraglutide, which requires daily injections. Semaglutide for obesity (2.4 mg dose) is administered subcutaneously via a prefilled pen injector. Patients initiate therapy at a low dose (0.25 mg weekly) and escalate gradually (0.5 mg, 1.0 mg, etc., at roughly 4-week

intervals) to reach 2.4 mg weekly over about 16–20 weeks. This titration mitigates side effects, particularly gastrointestinal ones.

In summary, semaglutide's mechanism in obesity treatment can be viewed as restoring balance in appetite regulation and energy metabolism. By counteracting the biological drive to eat and facilitating a lower caloric intake, while also possibly enhancing energy expenditure slightly, semaglutide helps patients achieve weight loss that typically would not be attainable through lifestyle changes alone due to counter-regulatory mechanisms. Importantly, semaglutide addresses both hedonic appetite (food cravings, reward) and homeostatic appetite (caloric need) pathways, providing a powerful tool to assist patients in adhering to calorie-reduced diets.

3.3. Clinical Efficacy of Semaglutide for Weight Loss

The efficacy of semaglutide 2.4 mg has been established in the **STEP Phase 3 program (2018–2021)**.

STEP 1: In 1, 961 adults without diabetes, semaglutide produced 14.9% mean weight loss at 68 weeks vs 2.4% with placebo. Notably, 86% achieved ≥5% loss, 69% ≥10%, and 50% ≥15% (Wilding et al., 2021).

STEP 2: In patients with type 2 diabetes, weight loss averaged 9.6% vs 3.4% with placebo, alongside HbA1c reduction of ~1.6% (Davies et al., 2021).

STEP 3: Adding semaglutide to intensive lifestyle therapy yielded 16.0% mean loss vs 5.7% with lifestyle alone. More than 55% achieved ≥15% loss compared to 13% with lifestyle alone (Wadden et al., 2021).

STEP 4: Participants initially lost weight on semaglutide, then were randomized to continue or switch to placebo. Continued therapy maintained ~18% reduction, while discontinuation led to regain, ending at ~6% loss (Davies et al., 2021).

STEP 5: Over 104 weeks, semaglutide sustained 15.2% loss vs 2.6% with placebo, with 77% maintaining ≥5% and 36% ≥20% loss (Garvey et al., 2022).

STEP 8: Head-to-head comparison showed superiority over liraglutide: 15.8% vs 6.4% mean loss (Davies et al., 2021)(Rubino et al., 2022).

Across trials, semaglutide also improved waist circumference, blood pressure (~5 mmHg greater reduction), triglycerides, and quality of life (Davies et al., 2021). Importantly, ~32–36% of patients achieved ≥20% weight loss, a level previously attainable mainly with bariatric surgery (Wilding et al., 2021; Garvey et al., 2022).

Responses vary, and some patients show limited effect despite adherence. Current guidance recommends reassessment after ~3 months on the 2.4 mg dose; <5% loss may define non-response (Garvey et al., 2016).

Table 1. Mean percentage weight loss in STEP clinical trials with once-weekly semaglutide 2.4 mg versus control (placebo ± lifestyle intervention). (Davies et al., 2021)

Trial	Population	Intervention	Comparator	Mean % Weight Loss (Intervention)	Mean % Weight Loss (Comparator)	Duration (weeks)
STEP 1	Adults with obesity (BMI ≥30) or overweight (BMI ≥27 with comorbidity)	Semaglutide 2.4 mg + lifestyle intervention	Placebo + lifestyle intervention	-14.9%	-2.4%	68
STEP 2	Adults with type 2 diabetes and obesity/ overweight	Semaglutide 2.4 mg + lifestyle intervention	Placebo + lifestyle intervention	-9.6%	-3.4%	68
STEP 3	Adults with obesity/ overweight	Semaglutide 2.4 mg + intensive behavioral therapy	Placebo + intensive behavioral therapy	-16.0%	-5.7%	68
STEP 4	Adults with obesity/ overweight (after 20 weeks run-in on semaglutide)	Continued semaglutide 2.4 mg	Placebo	-7.9% (additional)	+6.9% (regain)	48

3.4. Availability and Safety Profile:

Regulatory approval and availability: Semaglutide 2.4 mg (Wegovy®) has been approved in numerous regions including North America, Europe, and other areas for chronic weight management. In the United States, FDA approval came in June 2021, and the medication became available by late 2021. The European Medicines Agency (EMA) also approved semaglutide 2.4 mg in 2021, and countries like the UK, Canada, and Australia have since authorized it. However, availability in practice has been impacted by very high demand and production constraints, resulting in intermittent shortages in some markets. Additionally, access can vary by country due to differences in insurance coverage or reimbursement policies. For instance, as of 2024, semaglutide for obesity was not reimbursed by public health insurance in many European countries, including Poland, unless the patient also has type 2 diabetes. Such policies (often driven by cost concerns and the notion that lifestyle change should suffice) have limited the use of anti-obesity drugs in certain healthcare systems (Lasota et al., 2024). This means that in some countries patients must pay out-of-pocket, making the drug less accessible to lower-income individuals – a significant barrier given the chronic nature of treatment required.

Safety and side effects: Semaglutide's safety profile in obesity trials has been well-characterized and is generally favorable, with no unexpected adverse events emerging beyond those known for the GLP-1 class. The most common side effects are gastrointestinal (GI) symptoms: nausea (which occurs in ~30–40% of patients), vomiting (~10–20%), diarrhea (~20–30%), and constipation. In the STEP trials, about 80% of participants on semaglutide reported at least one GI symptom, versus around 50% on placebo (Davies et al., 2021). These effects are typically transient and mild to moderate in intensity, often occurring during the dose-escalation phase as the body adjusts. They tend to improve over time; for example, nausea usually peaks in the first 8–12 weeks and then subsides in most patients. Adhering to the gradual dose titration schedule and advising patients to eat smaller meals can help manage GI symptoms. Despite the high incidence of GI events, treatment discontinuation rates due to adverse effects were relatively low in trials (ranging from 5% to 8% of semaglutide patients, compared to ~2–4% on placebo) (Davies et al., 2021). The majority of participants were able to tolerate the medication and continue therapy.

No evidence of clinically significant hypoglycemia was seen in non-diabetic trial participants, as expected from the glucose-dependent action of GLP-1 agonists (though diabetic patients on concomitant insulin or sulfonylureas should monitor for low blood sugars). There were no increases in cardiovascular adverse events; on the contrary, heart rate increased slightly (by ~2–3 beats per minute on average with semaglutide), a known class effect whose clinical significance is uncertain (Davies et al., 2021). Gallbladder-related events (e.g. cholelithiasis) were slightly more frequent with semaglutide than placebo in trials (Davies et al., 2021). This is thought to be secondary to rapid weight loss (which can predispose to gallstone formation) rather than a direct drug effect, since weight loss from any cause can increase risk of gallstones. Patients should be counseled to report any symptoms of gallbladder disease. Pancreatitis is a theoretical concern with GLP-1 RAs (due to postmarketing reports in diabetics), but in the STEP trials there was no significant difference in acute pancreatitis cases between semaglutide and placebo groups (Davies et al., 2021). Nonetheless, semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, owing to a rodent finding of thyroid C-cell tumors with GLP-1 analogs. This appears to be a species-specific effect (no signal in humans so far), but caution is exercised as a class warning. Furthermore, there is emerging evidence from the SELECT trial that semaglutide 2.4 mg may reduce the incidence of major cardiovascular events in high-risk patients (this is further discussed under Future Directions), reinforcing its safety and potential benefit profile in those with obesity-related heart disease (Lincoff et al., 2023).

From a clinical monitoring perspective, patients on semaglutide for obesity should have periodic check-ins to assess tolerability, reinforce lifestyle measures, and track weight and metabolic parameters. Liver enzymes and renal function do not appear to be adversely affected on average; in fact, many patients see improvement in fatty liver indices and blood pressure as they lose weight. The early results of the SELECT cardiovascular outcomes trial further indicate that substantial weight reduction via semaglutide can reduce major cardiovascular events in high-risk patients(Lincoff et al., 2023), affirming that treating obesity can modify hard outcomes. Semaglutide's safety profile is consistent with other GLP-1 agonists and deemed acceptable, with gastrointestinal symptoms being the main concern but manageable in most cases. The medication fills a significant gap between lifestyle-only management and invasive bariatric surgery, offering a non-surgical means to achieve substantial weight loss. Next, we consider how best to integrate semaglutide therapy with lifestyle interventions, which remain the foundation of obesity management.

3.5. Lifestyle Interventions in Obesity Management

Lifestyle modification remains the cornerstone of obesity treatment. Core components include dietary changes, physical activity, and behavioral support.

Dietary modification: Sustained caloric deficit is essential. Reducing intake by 500–750 kcal/day yields ~5–10% weight loss over 6 months, sufficient for cardiometabolic benefit. No diet type (low-carb, low-fat, Mediterranean, high-protein) has shown clear long-term superiority; adherence is key (Jensen et al., 2014). High-protein diets help preserve lean mass (Johnston et al., 2014)(Wycherley et al., 2012). Very-low-calorie diets (<800 kcal/day) induce rapid loss but are generally short-term and supervised.

Physical activity: Exercise alone leads to modest weight loss (2–3%), but is critical for fat reduction, fitness, and long-term maintenance (Wycherley et al., 2012). Guidelines recommend ≥150–300 minutes/week of moderate aerobic activity plus resistance training ≥2 days/week (Jensen et al., 2014). Registry data show sustained weight loss correlates with high activity (~2500 kcal/week expenditure) (Wing & Phelan, 2005).

Behavioral strategies: Self-monitoring, stimulus control, goal setting, problem-solving, and cognitive restructuring improve adherence (Jensen et al., 2014). Social support and structured follow-up (e.g., dietitian visits, group programs) enhance outcomes. In *Look AHEAD*, intensive lifestyle achieved 8–10% loss at 6 months, but only ~50% maintained ≥5% loss after 8 years (Look AHEAD Research Group, 2013)(Wadden et al., 2014).

Challenges: Weight regain is common as caloric needs fall with weight loss and biological adaptations promote increased appetite. Medications like semaglutide help counter these mechanisms, but lifestyle change is indispensable to maintain results (Jensen et al., 2014).

In summary, lifestyle interventions yield 5–10% weight reduction and broad health benefits. When combined with semaglutide, they enhance outcomes and help sustain weight loss (Jensen et al., 2014)(Johnston et al., 2014)(Wycherley et al., 2012)(Wing & Phelan, 2005)(Look AHEAD Research Group, 2013)(Wadden et al., 2014).

3.6. Integrating Semaglutide with Lifestyle Interventions

The combination of pharmacotherapy and lifestyle modification is widely regarded as the most effective approach for managing obesity. Semaglutide, as a pharmacological tool, can enhance the results of dietary and physical activity efforts by mitigating biological barriers (like hunger and adaptive thermogenesis) that often limit weight loss from lifestyle alone. Conversely, maintaining healthy eating and exercise habits while on semaglutide can help patients achieve greater absolute weight loss and improve functional outcomes such as fitness and muscle preservation. This section explores the synergy between semaglutide and lifestyle interventions, evidence comparing combined versus single-modality therapy, and practical guidance for clinicians on implementing this integrated strategy.

Synergistic Effects on Weight Loss and Health Outcomes: As highlighted earlier, the STEP 3 trial provides compelling evidence of synergy: semaglutide + intensive lifestyle counseling yielded ~16% weight loss, versus ~5–6% with lifestyle alone over 68 weeks (Wadden et al., 2021). This clearly demonstrates that adding semaglutide approximately tripled the weight loss achieved by lifestyle modification, even when the lifestyle program was robust. Notably, the weight loss seen with combined therapy in STEP 3 (mean 16%) was slightly higher than that seen with semaglutide in STEP 1 (mean ~15%) where lifestyle counseling was more limited, suggesting that lifestyle efforts can still contribute additional benefit on top of the drug's effect (Davies et al., 2021) (Wadden et al., 2021). In practical terms, a patient who might lose 10 kg with diet and exercise alone could potentially lose 25–30 kg with the addition of semaglutide – a difference that could mean moving from still obese to near-normal BMI.

Beyond weight loss magnitude, combined therapy tends to result in faster initial weight loss as well. Patients often see a significant drop in the first 8–12 weeks when starting a low-calorie diet and semaglutide simultaneously. This early success can be very motivating, encouraging continued adherence. There may also be improvements in body composition: while any weight loss will include some lean mass loss, the inclusion of exercise and adequate protein intake alongside semaglutide may help preserve muscle. The drug's appetite suppression helps patients maintain a high-quality diet (e.g. sufficient protein, vegetables) without feeling overly deprived, because total intake is naturally reduced by diminished hunger.

Combined therapy has also shown enhanced metabolic benefits. In an analysis of cardiometabolic risk factors, semaglutide plus lifestyle reduced HbA1c, triglycerides, and C-reactive protein more than lifestyle alone (Wadden et al., 2021). Measures of physical function and patient-reported health status (vitality, daily activity levels) also improve significantly. In obese patients with knee osteoarthritis or limited mobility, the

addition of exercise to weight loss (augmented by semaglutide) can markedly improve joint pain and mobility – weight loss relieves mechanical load on joints, and exercise strengthens muscles and improves range of motion.

A crucial aspect of synergy is in weight-loss maintenance. Continuing lifestyle habits during pharmacotherapy and especially after discontinuation of the drug can help sustain results. For instance, one study (an extension of STEP 1) observed that one year after stopping semaglutide, participants on average regained two-thirds of the weight they had lost during treatment. However, those who adhered better to lifestyle recommendations regained less weight (Wilding et al., 2022). This suggests that while semaglutide powerfully induces weight loss, the long-term outcome still hinges on lifestyle to some degree. A patient who has built strong diet and exercise habits will be more likely to maintain a lower weight if the medication is withdrawn. That being said, given obesity's chronicity, many patients may require long-term pharmacotherapy to prevent regain, similar to how antihypertensives or lipid-lowering drugs are used chronically. Lifestyle interventions remain indispensable as adjuncts in any case.

Combined Therapy vs Pharmacotherapy Alone: What Studies Show: It is ethically and practically challenging to design a trial of"drug alone without lifestyle advice" because standard of care is to always encourage at least some lifestyle change. In all major trials (STEP 1–4), both drug and placebo groups received some form of lifestyle counseling (ranging from brief monthly advice in STEP 1 to intensive therapy in STEP 3). Therefore, we don't have a pure"semaglutide without lifestyle" arm to compare directly. However, we can indirectly glean insights:

From STEP 1 vs STEP 3: In STEP 1, semaglutide with minimal lifestyle support led to ~15% weight loss (Wilding et al., 2021). In STEP 3, semaglutide with intensive lifestyle led to ~16% weight loss (Wadden et al., 2021). These averages are quite close, implying semaglutide can drive substantial weight reduction even without rigorous lifestyle intervention. However, the placebo group in STEP 1 lost only ~2.4%, whereas the placebo (intensive lifestyle) group in STEP 3 lost ~5.7%. This indicates that lifestyle on its own had a significant effect (an extra ~3% weight loss) and that effect was mostly additive when semaglutide was added (since semaglutide's absolute benefit over placebo was slightly smaller in STEP 3: about 10.3 percentage points, versus 12.5 points in STEP 1) (Wilding et al., 2021) (Wadden et al., 2021). In other words, lifestyle contributed a few percentage points of weight loss that semaglutide alone would not have provided.

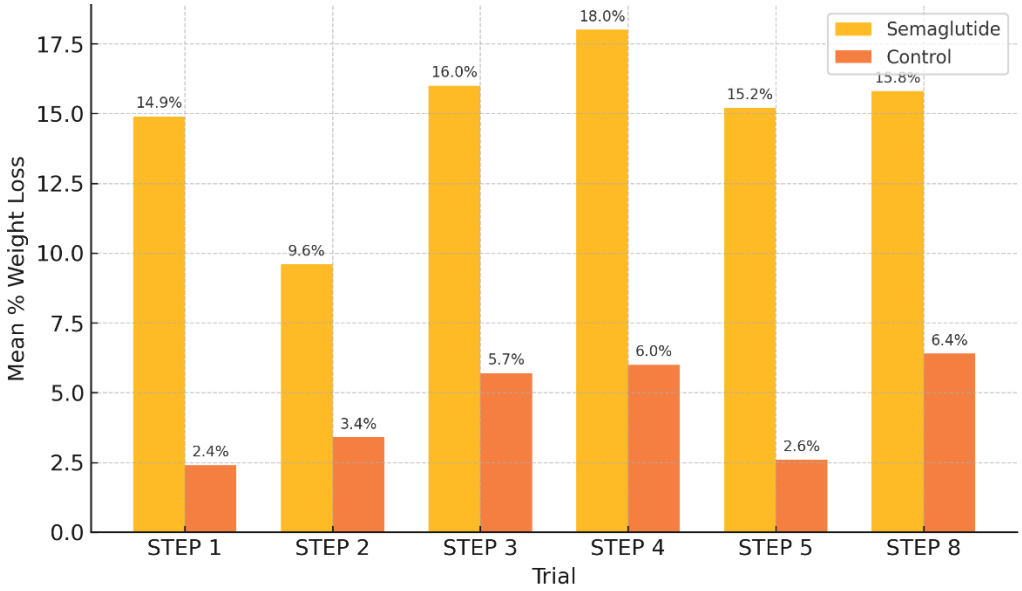

Fig. 1. *Mean percentage weight loss in STEP clinical trials with once-weekly semaglutide 2.4 mg versus control (placebo ± lifestyle intervention) (Wilding et al., 2021), (Davies et al., 2021), (Wadden et al., 2021).*

Other medications data: Previous obesity drug trials (for instance, with orlistat or liraglutide 3.0 mg) have shown that even when patients are on medication, those who adhere to lifestyle recommendations lose more weight than those who rely on the pill or injection alone (Jensen et al., 2014). Medications often make it easier for patients to stick to diets, but if a patient were to take semaglutide and not make any dietary changes

at all (for example, continue eating calorie-dense foods out of habit even without hunger), they would likely still lose some weight, but not as much. Appetite suppression does not automatically guarantee healthy food choices; it simply reduces the drive to eat. Some individuals might take in fewer calories but still consume suboptimal nutrition (e.g. skipping meals and then having calorically dense snacks). Thus, dietary guidance ensures that the caloric deficit is actually realized and that nutrition quality is maintained.

Real-world evidence: Emerging real-world studies of GLP-1 agonists suggest that weight loss outcomes can be more variable outside of clinical trial settings. Patients who engage with multidisciplinary weight management programs in addition to taking semaglutide tend to have greater weight loss than those who receive a prescription with minimal lifestyle follow-up. Real-world cohort data (e.g., retrospective analyses from obesity clinics) indicate ranges of weight loss outcomes, and one of the differentiators is the level of lifestyle support. Those with structured dietitian visits, exercise plans, or behavioral coaching lost a higher percentage of weight on average compared to those without such support (Rodriguez et al., 2024).

Discontinuation and regain: When pharmacotherapy is stopped, what remains is the lifestyle. A patient who has not internalized healthier eating and activity patterns may regain weight rapidly post-medication, as appetite signals return and old habits take over. Conversely, if the patient has adopted a new lifestyle, they might hold on to more of the weight loss. The extension of STEP 1 (off-treatment observation) showed that about 48% of those who had been on semaglutide still maintained ≥5% weight loss a year after stopping, compared to 22% of those who never took semaglutide (Wilding et al., 2022). While this still indicates regain for many, it suggests roughly half managed to keep some weight off – presumably those who persisted with lifestyle changes.

In summary, semaglutide is effective even with minimal lifestyle intervention, but for optimal results, it should not be used as a monotherapy in a behavioral vacuum. Lifestyle interventions amplify weight loss and are critical for effecting health behavior change, while semaglutide pharmacologically enhances the ability to adhere to those lifestyle changes by controlling appetite and cravings.

Practical Recommendations for Combination Therapy: For healthcare providers implementing semaglutide therapy, the following practical points may be considered to integrate lifestyle management:

- **Initiation Phase:** Prior to starting semaglutide, counsel the patient on dietary and activity adjustments so they can begin lifestyle changes concurrently with medication initiation. Some clinics use the lead-in period (while titrating the dose up) to focus on nutrition education – for example, by the time the patient reaches the full dose (which might take ~4 months), they are already following a healthier diet and routine exercise. This pairing often yields significant weight loss even during the titration phase.
- **Nutritional Counseling:** Consider referral to a registered dietitian or a structured weight-loss program. Patients on semaglutide might need guidance on ensuring adequate nutrient intake despite reduced appetite. Emphasize protein and fiber intake to maintain muscle and satiety. Dietitians can tailor meal plans (e.g., Mediterranean or low-carb) that align with patient preferences and accommodate the appetite changes from GLP-1 therapy (patients often feel full faster, so nutrient-dense foods should come first).
- **Managing GI Side Effects through Diet:** Lifestyle measures can also mitigate side effects. For example, patients should avoid large, high-fat meals which can exacerbate nausea when on GLP-1 agonists. Eating smaller, more frequent meals and stopping eating when comfortably full (not forcing portions) are advisable. Staying hydrated and consuming ginger or peppermint tea might alleviate mild nausea. If needed, temporary use of anti-emetic medication (like ondansetron) can be considered in consultation with the physician.
- **Exercise Plan:** Initiate or increase physical activity gradually. With weight coming down and possibly improved energy, patients may find exercise becomes easier over time on semaglutide. Encourage a mix of cardio and resistance training. If the patient is very heavy or has joint pain at baseline, non-impact activities (swimming, cycling, elliptical) can be good starts until some weight is lost. Setting step-count goals (using a pedometer or fitness tracker) is a simple way to increase daily movement.
- **Behavioral Support:** If possible, incorporate regular check-ins with a health coach or behaviorist. Some practices have group medical visits for patients on weight-loss medications, which can be efficient and effective. Alternatively, leveraging digital health tools (text reminders, app-based coaching) can provide ongoing behavioral reinforcement. Cognitive-behavioral strategies should be employed to help patients navigate triggers such as emotional eating or social events involving food. Planning ahead for”high-risk” scenarios (like holidays or travel) is crucial.

- **Patient Education and Expectations:** It is important to stress to patients that semaglutide is an adjunct, not a replacement for healthy habits. The medication will do some of the"heavy lifting" by controlling appetite, but long-term success still hinges on lifestyle. Set realistic expectations: while many will lose significant weight, individual results vary. If a patient loses, say, 10% instead of 20%, that is still a very meaningful improvement in health; clinicians should reinforce any progress and not let patients become discouraged by comparisons to trial averages or others' results. Emphasize non-scale victories too (e.g., better blood sugar control, improved stamina, looser-fitting clothes) to keep motivation high.
- **Monitoring and Follow-up:** Typically, patients are seen monthly during dose escalation, then every 2–3 months once on a stable dose. At each visit, review their food and activity logs (if available), discuss challenges, and adjust recommendations. Weigh-ins and possibly body composition analysis can be done to track progress. Celebrate milestones (like 5% and 10% weight loss) as these are significant health achievement points. If weight plateaus, troubleshoot potential causes: dietary adherence issues, medication adherence, emerging hunger (rare if still on drug), or simply physiological adaptation. Possibly intensify lifestyle efforts or consider whether the patient might benefit from adjunctive therapies (e.g., addressing contributors like untreated sleep apnea or medications that cause weight gain).
- **Long-term Planning:** Obesity is chronic; discuss with patients the potential need for long-term semaglutide use. Currently, evidence suggests that stopping often leads to regain. So, if the drug is well-tolerated and effective, most patients should plan to continue it to maintain the weight loss (just as one would continue hypertension medication to maintain blood pressure control). However, continuing emphasis on lifestyle is essential both to maximize current health and to prepare patients in case they ever have to stop the drug (due to access issues or side effects). Additionally, weight maintenance phases should focus on solidifying habits—transitioning from a calorie deficit to weight maintenance means learning to adjust food intake to a new equilibrium, which often requires continued monitoring and support.
- **Multidisciplinary Approach:** Ideally, obesity management is done via a team—physician or NP, dietitian, exercise physiologist or physiotherapist, and psychologist or counselor. If such a team is available, semaglutide can be one component of a holistic program. If not, the prescribing clinician should at least coordinate referrals or recommend resources (e.g., encourage the patient to join a local fitness group or an online weight management community) to enhance support.

In practice, patients on semaglutide often report that they"feel in control" of their eating for the first time in a long time. This presents a window of opportunity to help them re-learn healthy eating behaviors without the constant biological drive to overconsume. They can establish appropriate portion sizes and meal patterns while the medication suppresses the usual urges. Over time, the hope is that these behaviors become ingrained habits. Some patients even note changes in food preferences (possibly due to effects on reward pathways): for instance, finding very sweet or greasy foods less appealing. Providers can encourage these shifts, helping patients focus on whole, unprocessed foods which not only aid weight control but improve overall nutrition.

To conclude, the integration of semaglutide with lifestyle interventions is a best-practice approach that leverages the strengths of both: pharmacotherapy provides the physiological assist, while lifestyle change addresses the behavioral and environmental determinants of obesity. Together, they produce greater weight loss and health benefits than either alone. This comprehensive strategy also aligns with the concept of obesity as a chronic condition requiring long-term multifaceted management.

4. Discussion

This review underscores the transformative impact of semaglutide in obesity treatment, demonstrating approximately 15% average weight loss with pharmacotherapy, especially when combined with intensive lifestyle interventions. These findings situate semaglutide's efficacy on par with (or even exceeding) more invasive approaches like metabolic surgery in some cases, and highlight the drug's potential to significantly improve obesity-related outcomes. Below, we address the broader implications of these results, examine emerging obesity therapies on the horizon, and consider the challenges in integrating these advances into clinical practice and public health strategies.

4.1. Emerging Pharmacotherapies and Novel Approaches

Following the success of semaglutide, multi-receptor agonists have emerged. Tirzepatide, a dual GLP-1/GIP agonist, produced 16–22% mean weight loss over 72 weeks in SURMOUNT-1, surpassing semaglutide and approaching bariatric surgery outcomes (Jastreboff et al., 2022). Retatrutide, a triple GLP-1/GIP/glucagon

agonist, achieved 23–24% loss at 48 weeks in Phase 2 trials (Jastreboff et al., 2023). Another approach combines semaglutide with the long-acting amylin analog cagrilintide; the fixed weekly formulation”CagriSema” is now in Phase 3 studies (Enebo et al., 2021)(Lau et al., 2021). High-dose oral semaglutide (50 mg daily) has shown weight reductions comparable to injectable 2.4 mg weekly, potentially improving accessibility and patient acceptance (Knop et al., 2023). Other investigational strategies include MC4R agonists (e.g., setmelanotide) for rare monogenic obesity (Clément et al., 2022), agents enhancing energy expenditure (mitochondrial uncouplers), microbiome-directed therapies, and early-stage gene therapy, though most remain experimental. Non-pharmacological innovations such as endoscopic balloons, endoscopic sleeve gastroplasty, and vagal nerve blockade devices are also being developed as less invasive alternatives to bariatric surgery (Jastreboff et al., 2023). In summary, dual and triple agonists (tirzepatide, retatrutide) and combination approaches (CagriSema) represent the most promising next-generation therapies, with efficacy exceeding semaglutide. Oral formulations and endoscopic devices may further expand access, while novel biological targets continue to shape future research (Jastreboff et al., 2022), (Jastreboff et al., 2023), (Knop et al., 2023) , (Enebo et al., 2021), (Clément et al., 2022), (Lau et al., 2021), (Aronne et al., 2025).

4.2. Stigma and Perception

The advent of effective drugs has sparked some debate and stigma in public discourse. There’s concern that viewing obesity as treatable by medication could either reduce the focus on healthy lifestyles (the misconception of a”quick fix”) or conversely that those who use medication might be seen as taking the”easy way out.” Itis important to combat these narratives with facts: obesity is a disease with physiological underpinnings, and treating it with medication is as valid as treating hypertension or any other chronic disease. Also, medication is used in conjunction with lifestyle changes, not in lieu of them. Overcoming weight bias in society and among healthcare providers will facilitate more people getting the help they need without shame (Rubino et al., 2020)(Puhl & Heuer, 2010).

4.3. Long-Term Safety and Outcomes

While GLP-1 RAs have a good safety profile and actually show cardiovascular benefits in diabetics, they are still relatively new for life-long use in a broad population. Ongoing studies like SELECT have been crucial – and indeed SELECT recently showed a ~20% reduction in major adverse cardiovascular events in non-diabetic people with obesity on semaglutide (Lincoff et al., 2023), a very encouraging sign that weight loss via medication translates to improved”hard” outcomes. However, we need to monitor other long-term effects: e.g. does sustained GLP-1 stimulation affect pancreatitis risk over decades, or medullary thyroid cancer risk (likely very low if any, but surveillance will tell), or mental health (some patients report transient mood changes or that GI side effects affect quality of life). The initial data are reassuring, and the benefits (including possibly reduced heart failure risk and less need for joint replacements if weight stays down) likely far outweigh potential risks. But as these drugs will be used by millions, rare side effects might emerge and will need vigilance.

4.4. Complexity of Obesity

Obesity is multifactorial – genetics, environment, behavior, and culture all interplay. Drugs like semaglutide address one major piece (appetite and metabolic efficiency), but they don’t directly fix all drivers (such as stress, food insecurity, or lack of exercise opportunities). Thus, a comprehensive societal approach is still needed: urban planning to encourage physical activity, food policy to promote healthier eating, early childhood interventions, etc. Medications treat individuals effectively, but stemming the global tide of obesity requires upstream prevention too. There’s a risk that people see medications as a panacea and reduce emphasis on population-level measures. The future should ideally incorporate both: wide availability of effective treatment and robust public health strategies for prevention.

Combination Therapy and Sequencing

As multiple anti-obesity medications become available (including existing ones like orlistat, phentermine/topiramate, bupropion/naltrexone, and liraglutide), there is the practical question of how to choose or combine them. Currently, semaglutide or similar GLP-1 RAs are so effective they often render older drugs unnecessary. But in patients who respond suboptimally, combining medications with different mechanisms might yield additional loss (though additive side effects must be considered). For example, could a low-dose phentermine be added to semaglutide for an extra anorectic push? Some clinicians already do this

off-label. Or if semaglutide is not available or contraindicated, using other drugs in combination (even triple therapy) might achieve some success. Research is sparse on multi-drug regimens in obesity, but this may become an area of interest, analogous to hypertension or diabetes where combination therapy is common. The challenge is ensuring safety and obtaining regulatory approval for such uses.

Future Perspectives and Research Directions

Looking ahead, the landscape of obesity management in 5–10 years could be dramatically different. With multiple effective pharmacological options, a chronic disease model will be fully embraced. Physicians might have an"obesity toolbox" akin to the diabetes toolbox, where they choose from GLP-1/GIP agonists, triple agonists, etc., possibly in oral form, and tailor treatments to patient needs, much like different insulins or oral hypoglycemics are used in diabetes. Primary care providers will play a key role in managing obesity medications (not just specialists), so training and guidelines must keep pace.

Research will continue to focus on:

- **Long-term outcomes:** We expect more data on whether treating obesity with medication reduces the incidence of heart attacks, strokes, cancers, and extends life expectancy. SELECT's positive results (Lincoff et al., 2023) set a precedent. Other outcome trials (for tirzepatide and others) are underway or planned.
- **Special populations:** Investigating safety/efficacy in groups like adolescents (the STEP TEENS trial already showed semaglutide's benefit in adolescents with obesity, with ~16% BMI reduction vs <1% for placebo)(Weghuber et al., 2022), older adults (to ensure muscle loss is not problematic), and patients with advanced heart failure or chronic kidney disease (where weight loss might improve outcomes but needs caution).
- **Mechanistic studies:** Understanding precisely how these drugs affect brain reward circuits, whether they alter taste preferences, and how they interplay with gut–brain signaling beyond GLP-1 (maybe they induce other peptides or changes in the microbiome that help weight loss).
- **Preventive use:** Could medications be used short-term in overweight individuals to prevent progression to obesity and metabolic disease? This is a provocative idea – treating overweight like one treats pre-hypertension. Ethical and cost considerations aside, if a safe oral medication existed that caused, say, 5–10% weight loss easily, one could envision it being used more widely as primary prevention in high-risk individuals.
- **Weight regain solutions:** If a patient does regain weight after stopping a GLP-1 RA, what's the best approach? Restart the same drug, or switch to another? Are there ways to consolidate weight loss so that regain is less likely (perhaps a maintenance-phase lower dose, or periodic"booster" courses)? These questions will be answered as we gather more real-world experience.
- **Integration with devices/surgery:** For patients with severe obesity, combinations of therapies might yield the best results. There's interest in using medications as adjuncts to bariatric surgery – e.g., pre-surgery to reduce operative risk via initial weight loss, or post-surgery if weight regain occurs years later. Conversely, endoscopic therapies could be used in combination with drugs to avoid surgery altogether. Optimal integration strategies will evolve.

Finally, from a public health perspective: If the majority of individuals with obesity could get to a healthier weight through safe long-term medication, the impact on rates of diabetes, cardiovascular disease, and even some cancers could be profound. However, achieving this at scale requires solving the cost/access dilemma – ensuring that these treatments are affordable and accessible to all who need them, not just the privileged few. Policymakers will need to grapple with how to fund and prioritize obesity treatment as part of routine healthcare. Meanwhile, efforts to improve diet and physical activity environments must continue, since medications treat the person but not the social determinants of obesity.

5. Conclusions

Semaglutide 2.4 mg once weekly constitutes a major advance in the pharmacotherapy of obesity, delivering clinically meaningful and durable weight loss that, in many cases, approaches the outcomes of bariatric surgery. Across the STEP clinical trials, treatment resulted in average reductions of ~15% of baseline body weight, with the majority of patients achieving ≥10% loss and substantial improvements in glycaemic control, lipid profile, blood pressure, and markers of inflammation. These effects translate into reduced cardiometabolic risk and improved physical function and quality of life.

The greatest and most sustained benefits are achieved when semaglutide is integrated into a comprehensive obesity management strategy that includes dietary modification, increased physical activity, and structured behavioural support. Such combination therapy addresses both the physiological drivers of excess weight and the behavioural/environmental determinants, enhancing adherence, preserving lean mass, and supporting long-term weight maintenance. Conversely, discontinuation of pharmacotherapy is frequently associated with partial weight regain, underscoring the chronic, relapsing nature of obesity and the need for ongoing management.

Future developments—including dual and triple incretin receptor agonists—may surpass current efficacy benchmarks, but challenges such as treatment cost, equitable access, and patient adherence must be addressed to maximise population-level benefits. From a public health perspective, broad availability of effective pharmacotherapy alongside preventive and lifestyle-oriented measures should be prioritised to reduce the global burden of obesity-related morbidity and mortality. Semaglutide thus represents not only a therapeutic breakthrough for individuals, but also a pivotal tool in reshaping long-term obesity care paradigms.

6. Disclosure

6.1. Author's Contribution

Conceptualization: Filip Bracichowicz.; methodology:Igor Winogrodzki.; formal analysis: Patryk Kowalczyk, Kamil Nowak.; investigation: Bartłomiej Trzciński.; resources: Oliwia Guguła.; data curation: Alicja Stryczek-Schlusche.; writing – original draft preparation: Filip Bracichowicz.; writing – review and editing: Aleksandra Gęsińska, Aleksandra Magdalena Furczyńska.; visualization: Hanna Paszkiewicz.; supervision: Filip Bracichowicz; project administration: Filip Bracichowicz. All authors have read and agreed to the published version of the manuscript.

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6.3. Institutional Review Board Statement

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6.4. Informed Consent Statement

Not applicable.

6.5. Data Availability Statement

Not applicable.

6.6. Conflicts of Interest

Author Filip Bracichowicz reports having attended a scientific conference with expenses covered by Novo Nordisk, a manufacturer of Ozempic® and Wegovy® discussed in this manuscript. The author received no other financial support from this company. The remaining authors declare no conflicts of interest.

6.7. Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the author used ChatGPT (OpenAI) for the purpose of translating some sections from Polish to English and refining the language/style. After using this tool, the author reviewed and edited the content as needed and accepts full responsibility for the substantive content of the publication.

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