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SEMAGLUTIDE FOR WEIGHT REDUCTION: A COMPARATIVE ANALYSIS WITH OTHER PHARMACOLOGICAL TREATMENTS

Marta Handzel *(Corresponding Author, Email: zuza.handzel@gmail.com)*
Pomeranian Medical University in Szczecin, Szczecin, Poland
ORCID ID: 0009-0004-0348-0051

Julia Czerniewska
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0009-3769-8047

Klaudia Jurkowska
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0003-0205-6999

Julia Mądrzak
Faculty of Medicine, Kazimierz Pułaski University of Radom, Radom, Poland
ORCID ID: 0009-0007-3387-9225

Olga Endler
Faculty of Medicine, Poznan University of Medical Sciences, Poznan, Poland
ORCID ID: 0009-0002-0256-9965

Mikołaj Dybicz
Faculty of Medicine, Poznan University of Medical Sciences, Poznan, Poland
ORCID ID: 0009-0001-7270-7625

Marianna Ciastoń
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0001-9458-7097

Magdalena Filuk
Collegium Medicum in Bydgoszcz, Bydgoszcz, Kujawsko-Pomorskie, Poland
ORCID ID: 0009-0004-6969-7173

Jakub Fidelus
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0006-6889-8509

Dominika Dutkiewicz
Independent Public Health Care Centre of the Ministry of the Interior and Administration in Gdańsk, Poland
ORCID ID: 0009-0006-2035-8079

ABSTRACT

Obesity is a chronic, complex disease linked to major illness and death. Related conditions include heart disease, type 2 diabetes, and cancer. Its global prevalence has soared, demonstrating the need for treatments beyond lifestyle change. Pharmacotherapy is essential, particularly for people unable to maintain weight loss through behavioural interventions. This review evaluates the efficacy and safety of glucagon-like peptide-1 (GLP-1) receptor agonists, specifically semaglutide and liraglutide. These are assessed against established anti-obesity drugs, including orlistat and phentermine. A structured search was carried out across PubMed, Scopus, and Google Scholar. Priority was given to randomised controlled trials, meta-analyses, and large observational studies published from 2010 to 2025. Key clinical trial programmes, such as STEP, SUSTAIN, LEADER, SELECT, and SURMOUNT, were critically reviewed. Semaglutide shows superior efficacy. Mean weight reductions often exceed 10–15%. These reductions are linked to considerable improvements in glycaemic and cardiometabolic parameters. Liraglutide provides modest weight loss but has proven cardiovascular benefits. Orlistat and phentermine have lower efficacy. They also have tolerability issues and limited long-term use. Despite their strengths, GLP-1 receptor agonists cause gastrointestinal side effects, high cost, and have limited long-term safety data. GLP-1 receptor agonists represent a major advance, making obesity treatment more targeted. Future studies ought to focus on long-term outcomes, accessibility, and improving the tolerability and affordability of therapy.

KEYWORDS

Semaglutide, Liraglutide, Orlistat, Phentermine, Obesity, GLP-1

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1. Introduction

Obesity is now recognised as a chronic, relapsing disease caused by biological, environmental, and behavioural factors. The World Health Organisation defines it as excessive fat that poses a risk to health (GBD 2021 Risk Factor Collaborators, 2024). Clinically, a body mass index (BMI) of 25.0–29.9 kg/m² means overweight. A BMI of ≥30 kg/m² means obesity. Obesity has shifted from a lifestyle-associated disease to a major public health challenge. Between 1990 and 2022, its global prevalence more than doubled to about 16% of adults (GBD 2021 Risk Factor Collaborators, 2024). Urbanisation, less physical activity, and easy access to cheap, unhealthy foods are major drivers. The effects of obesity go beyond excess body weight. These include cardiovascular disease, type 2 diabetes, some cancers, and a shorter life expectancy (Bray & Ryan, 2012; GBD 2021 Risk Factor Collaborators, 2024). Obesity is often thought to be due to an energy imbalance, but its causes are more complex. Hormonal regulators—such as leptin, insulin, ghrelin, and incretins—control energy balance by acting on the hypothalamus and brain reward pathways (Al-Massadi et al., 2019). Genetic predisposition also matters. Mutations can impact appetite and metabolism. For example, deficiencies in the leptin pathway are linked to severe, early-onset obesity (Keith et al., 2006). Environmental and behavioural factors, such as low physical activity and increased consumption of processed foods, interact with biological factors to maintain high energy intake (Keith et al., 2006). Psychological factors also influence the development and persistence of obesity. Binge and stress eating involve neural reward systems that reinforce high-calorie intake (Al-Massadi et al., 2019). Some drugs—glucocorticoids, antipsychotics, and certain antidepressants—also cause weight gain and add complexity (Keith et al., 2006). These factors reveal the limits of simple obesity models and highlight the need for comprehensive treatment. Lifestyle changes, like diet and exercise, are central to obesity management. Long-term success is frequently limited by poor adherence and frequent weight regain. Biological compensation and individual differences drive these complications, demonstrating the need for secondary treatment strategies. Recently, improved understanding of neuroendocrine regulation has changed the field of obesity pharmacotherapy. Older drugs mainly targeted

appetite or nutrient absorption, often with modest results and notable side effects. Newer agents, such as GLP-1 receptor agonists, act on hormonal pathways controlling appetite, satiety, and glucose metabolism (Røder, 2019). These drugs mimic incretin hormones, boost insulin secretion, lower glucagon secretion, slow gastric emptying, and sustain reduced calorie intake. This change denotes a shift to mechanism-based therapy in obesity care. Of current treatments, semaglutide stands out for its long half-life, weekly dosing, and strong effects on weight and metabolism. Other drugs, such as liraglutide, orlistat, and phentermine, remain in use yet differ in their therapeutic effect, safety, and long-term suitability. This review gives a comparative study of GLP-1 receptor agonists, especially semaglutide, versus other obesity medicines, concentrating on direct comparisons of efficacy, safety, and clinical usefulness. The review explains how these aspects differ between semaglutide, other GLP-1 receptor agonists, and alternative obesity treatments. It also considers long-term outcomes and future directions in the treatment of obesity.

2. Methodology

2.1 Search Strategy and Information Sources

A targeted literature search identified studies on obesity drugs with a focus on GLP-1 receptor agonists. Searches in PubMed/MEDLINE, Scopus, and Google Scholar covered publications from January 2010 to January 2025. This period captures the rise and clinical use of GLP-1 drugs and key outcome studies. Searches used keywords and MeSH terms: “obesity,” “GLP-1 receptor agonists,” “semaglutide,” “liraglutide,” “orlistat,” “phentermine,” and “weight loss drugs.” Boolean operators refine searches. Reference lists from reviews and trials supplemented results.

2.2 Study Selection and Eligibility Criteria

Studies were chosen using clear inclusion and exclusion criteria to ensure relevance.

Inclusion criteria:

- Adult populations (≥18 years) with a body mass index (BMI) ≥30 kg/m², or ≥27 kg/m² with at least one obesity-related comorbidity (e.g., hypertension, dyslipidaemia, or type 2 diabetes mellitus)
- Studies evaluating pharmacological interventions approved or in advanced clinical development for chronic weight management were included. This focused on semaglutide, liraglutide, orlistat, and phentermine.
- Randomised controlled trials (RCTs), meta-analyses, and large observational studies
- Studies reporting primary outcomes related to weight loss and/or metabolic parameters
- Publications in English

Exclusion criteria:

- Studies involving paediatric populations
- Case reports, editorials, and narrative reviews without primary data
- Studies lacking clearly defined outcome measures
- Non-English publications

Preference was given to studies with strong methods. This included large samples, longer follow-up, and clear clinical outcomes.

2.3 Outcomes of Interest

The primary outcomes assessed in this review included:

- Mean percentage change in body weight from baseline
- Absolute weight loss
- Proportion of participants achieving clinically significant weight reduction (≥5%, ≥10%, and ≥15%)

Secondary outcomes included:

- Glycaemic control, primarily measured by glycated haemoglobin (HbA1c)
- Cardiovascular outcomes, including major adverse cardiovascular events (MACE)
- Safety and tolerability, including incidence of adverse events and treatment discontinuation

2.4 Quality Assessment and Evidence Hierarchy

We prioritised strong evidence, favouring large randomised trials and outcome studies, and paying special attention to key studies that define current knowledge.

Key trials included:

- The STEP programme, evaluating semaglutide in individuals with overweight or obesity (Wilding et al., 2021)
- The SUSTAIN trials, assessing semaglutide in patients with type 2 diabetes mellitus
- The LEADER trial, investigating cardiovascular outcomes associated with liraglutide (Marso et al., 2016)
- The SELECT trial, examining cardiovascular outcomes in individuals with overweight or obesity without diabetes (Lincoff et al., 2023)
- The SURMOUNT programme, evaluating the dual GIP/GLP-1 receptor agonist tirzepatide (Jastreboff et al., 2022)

Study quality was assessed on the basis of methodological rigour. This included randomisation, blinding, sample size, duration of follow-up, and completeness of outcome reporting. Particular attention was given to potential sources of bias. These included attrition bias, selection bias, and shortcomings in external validity.

2.5 Data Extraction and Synthesis

Data extraction focused on key clinical and pharmacological characteristics of each intervention, including mechanism of action, efficacy outcomes, and safety information. For GLP-1 receptor agonists, additional consideration was given to pharmacokinetic properties, such as half-life and dosing frequency, as these factors influence adherence and real-world effectiveness. Given the diversity of study designs, populations, and outcome measures, a qualitative synthesis approach was adopted. This allowed for a structured comparison of pharmacological classes while accounting for differences in trial methodology, including variations in treatment duration, co-interventions, and baseline patient characteristics. Safety data were synthesised with particular emphasis on gastrointestinal adverse effects, serious adverse events (SAEs), and long-term safety considerations, while recognising the need for ongoing pharmacovigilance for emerging therapies.

3. Results

The findings from contemporary clinical trials and systematic reviews provide a detailed comparison of the efficacy and safety of semaglutide and other pharmacological treatments for obesity. Evidence from randomised controlled trials (RCTs), meta-analyses, and large cardiovascular outcome studies consistently presents differences in weight reduction, metabolic outcomes, and tolerability across drug classes (Wilding et al., 2021; Lincoff et al., 2023). Overall, glucagon-like peptide-1 (GLP-1) receptor agonists—particularly semaglutide—are associated with greater weight loss and improved cardiometabolic outcomes compared with older drug agents such as orlistat and phentermine. Across multiple studies, semaglutide has demonstrated higher proportions of participants achieving clinically meaningful weight loss thresholds (≥5%, ≥10%, and ≥15%) alongside improvements in glycaemic control, blood pressure, and lipid profiles (Wilding et al., 2021). Meta-analytic evidence further supports these data. A systematic review by Zheng et al. (2018) reported that semaglutide produced significantly greater reductions in body weight than placebo and other anti-obesity medications, with consistent benefits across several patient populations. These outcomes were accompanied by improvements in cardiometabolic risk factors, including reductions in HbA1c and inflammatory markers. Despite these conclusions, variability in treatment response has been observed. Differences in baseline characteristics, adherence, and the intensity of concurrent lifestyle interventions contribute to heterogeneity in outcomes across trials (Wilding et al., 2021; Lincoff et al., 2023).

3.1 Semaglutide

Semaglutide is a long-acting GLP-1 receptor agonist with approximately 94% structural homology to endogenous GLP-1 (Lau et al., 2015). Structural modifications confer resistance to degradation by dipeptidyl peptidase-4 (DPP-4) and enable albumin binding, resulting in an extended half-life of approximately one week (Lau et al., 2015). Clinical trials have demonstrated substantial potency in weight reduction. In the STEP 1 trial, participants receiving semaglutide 2.4 mg showed a mean weight reduction of approximately 14.9% over 68 weeks compared with placebo (Wilding et al., 2021). A greater proportion of individuals in the treatment group achieved ≥10% and ≥15% weight loss, indicating consistent attainment of clinically significant

outcomes. The SELECT trial further evaluated cardiovascular outcomes in individuals with overweight or obesity who did not have diabetes. Results presented a reduction in major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (Lincoff et al., 2023). Adverse events associated with semaglutide are predominantly gastrointestinal, including nausea, vomiting, and diarrhoea. These effects are typically dose-dependent and most often occur during treatment initiation (Wilding et al., 2021; Lincoff et al., 2023).

3.2 Liraglutide

Liraglutide is a shorter-acting GLP-1 receptor agonist with a half-life of approximately 10–14 hours, requiring once-daily administration (Marso et al., 2016). Clinical trials have demonstrated moderate efficacy, with average weight reductions of approximately 5–8% (Marso et al., 2016). The LEADER trial assessed cardiovascular outcomes in patients with type 2 diabetes mellitus and demonstrated a reduction in major adverse cardiovascular events, supporting liraglutide's cardioprotective profile (Marso et al., 2016). Adverse effects are similar to those observed with semaglutide, with gastrointestinal symptoms representing the most common events leading to treatment discontinuation.

3.3 Orlistat

Orlistat acts by inhibiting gastrointestinal lipases, reducing dietary fat absorption by approximately 30% (Torgerson et al., 2004). Clinical studies have demonstrated modest efficacy, with average weight loss typically ranging between 3% and 5% of baseline body weight (Torgerson et al., 2004). The XENDOS study reported that long-term use of orlistat, in combination with lifestyle intervention, was associated with reduced incidence of type 2 diabetes (Torgerson et al., 2004). However, high rates of treatment discontinuation have been observed, largely due to gastrointestinal adverse effects such as steatorrhoea and faecal urgency.

3.4 Phentermine

Phentermine is a centrally acting sympathomimetic agent that promotes weight loss by suppressing appetite through noradrenergic pathways (Hendricks & Greenway, 2011). Clinical evidence supports short-term efficacy, with reductions in body weight observed over treatment periods of up to 12 weeks (Hendricks & Greenway, 2011). However, long-term data are limited, and concerns regarding cardiovascular safety restrict its use in patients with pre-existing cardiovascular conditions. As a result, phentermine is generally indicated for short-term management rather than sustained treatment.

3.5 Tirzepatide

Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. Clinical trials have demonstrated substantial weight reduction, with the SURMOUNT-1 trial reporting reductions exceeding 20% over 72 weeks (Jastreboff et al., 2022). In addition to weight loss, tirzepatide has shown improvements in glycaemic control and cardiometabolic risk factors. Gastrointestinal adverse events remain the most frequently reported side effects, similar to those observed with GLP-1 receptor agonists.

3.6 Comparative Outcomes Across Clinical Trials

A more detailed comparison of major clinical trials reveals significant differences in study design, population characteristics, and reported outcomes that influence the interpretation of the effectiveness of medicinal agents. The STEP programme, which evaluated semaglutide 2.4 mg in individuals with overweight or obesity, consistently presented substantial reductions in body weight across multiple populations, including those without diabetes (Wilding et al., 2021). In contrast, earlier GLP-1 receptor agonist trials, such as those included in the LEADER programme, primarily focused on individuals with type 2 diabetes mellitus, where weight loss was a secondary outcome (Marso et al., 2016). This distinction is clinically relevant, as patients with diabetes usually exhibit attenuated weight loss responses due to underlying metabolic variations. As a result, comparisons between semaglutide and liraglutide must account for differences in study populations, baseline glycaemic status, and concomitant therapies. Similarly, trials evaluating orlistat and phentermine frequently differ in duration, with many phentermine studies limited to short-term use, thereby restricting the ability to assess sustained weight loss (Hendricks & Greenway, 2011). The SURMOUNT-1 trial of tirzepatide further expands this landscape by demonstrating weight reductions exceeding 20% in a non-diabetic population, highlighting the potential of dual incretin receptor agonism (Jastreboff et al., 2022). However, differences in trial duration, lifestyle intervention intensity, and participant eligibility criteria must be considered when interpreting these conclusions alongside earlier studies.

3.7 Subgroup Analyses and Heterogeneity of Response

Subgroup analyses across major trials indicate that treatment response is not uniform and is determined by numerous patient-related factors. Baseline body weight, presence of comorbidities, sex, and adherence to lifestyle interventions all contribute to variability in outcomes. For example, data from the STEP trials suggest that subjects with higher baseline BMI tend to achieve greater absolute weight loss, although relative percentage reductions stay consistent across groups (Wilding et al., 2021). Sex-based differences have also been observed, with some studies reporting slightly greater weight reduction in female participants, although the underlying mechanisms remain unclear. Additionally, type 2 diabetes mellitus is associated with a reduced weight-loss response to GLP-1 receptor agonists, likely due to altered insulin dynamics and metabolic adaptation (Marso et al., 2016). Adherence represents an additional critical determinant of treatment efficacy. Trials incorporating structured lifestyle interventions, frequent follow-up, and patient education tend to show higher weight-loss outcomes than real-world clinical data. This highlights the relevance of considering trial conditions when translating findings into clinical practice.

3.8 Cardiometabolic Outcomes Outside Weight Loss

In addition to weight reduction, GLP-1 receptor agonists show considerable effects on cardiometabolic parameters. Improvements in glycaemic control, as measured by reductions in HbA1c, are consistently seen across both diabetic and non-diabetic populations (Wilding et al., 2021). Furthermore, reductions in systolic blood pressure and improvements in lipid profiles—including decreases in low-density lipoprotein cholesterol—have been reported. The SELECT trial provides particularly important evidence regarding cardiovascular outcomes in individuals without diabetes, showing a reduction in major adverse cardiovascular events (Lincoff et al., 2023). These results indicate that the benefits of GLP-1 receptor agonists exceed glucose regulation and weight loss, supporting their role inside broader cardiometabolic risk reduction.

3.9 Safety Profiles and Discontinuation Rates

A more detailed analysis of safety data indicates that adverse event profiles differ across pharmacological classes and may considerably impact long-term adherence. Gastrointestinal adverse effects are the most commonly reported side effects associated with GLP-1 receptor agonists, with nausea occurring in a substantial proportion of participants during dose escalation phases (Wilding et al., 2021). Discontinuation rates due to adverse events vary across trials but remain clinically significant. In the SELECT trial, a considerable proportion of participants discontinued treatment permanently, mainly due to gastrointestinal intolerance (Lincoff et al., 2023). These findings show the importance of gradual dose titration and patient education in clinical practice. In contrast, orlistat is associated with predictable gastrointestinal effects related to fat malabsorption, which often result in poor adherence (Torgerson et al., 2004). Phentermine, while generally well tolerated in the short term, carries cardiovascular risks, including elevated heart rate and blood pressure (Hendricks & Greenway, 2011).

3.10 Comparative Evidence for Non-Semaglutide Pharmacotherapies

While GLP-1 receptor agonists such as semaglutide currently dominate obesity pharmacotherapy due to their superior efficacy, alternative agents—including liraglutide, orlistat, and phentermine—remain clinically relevant, particularly when GLP-1-based therapies are inaccessible, contraindicated, or not tolerated. Comparative evaluation of these agents highlights significant differences in mechanisms of action, durability of effect, and applicability in clinical practice.

Liraglutide, a daily GLP-1 receptor agonist, shares its mechanism of action with semaglutide but differs in pharmacokinetic properties and clinical efficacy. Its shorter half-life of approximately 10 to 14 hours necessitates daily administration, which may reduce long-term adherence compared to once-weekly formulations (Marso et al., 2016). Liraglutide consistently induces weight loss of 5 to 8 percent, although this effect is more modest and less durable than that observed with semaglutide in large-scale trials. Nevertheless, liraglutide remains clinically relevant due to its established cardiovascular benefits, as demonstrated in the LEADER trial, which reported reductions in major adverse cardiovascular events among high-risk patients with type 2 diabetes mellitus (Marso et al., 2016). This dual-benefit profile positions liraglutide as a valuable option for patients prioritising cardiovascular risk reduction alongside moderate weight management.

Orlistat utilises a distinct pharmacological approach by targeting gastrointestinal fat absorption rather than central appetite regulation. It inhibits pancreatic and gastric lipases, thereby reducing dietary fat absorption by approximately 30 percent (Torgerson et al., 2004). Despite this mechanism, orlistat's clinical

utility is constrained by modest efficacy, with average weight loss typically limited to 3 to 5 percent of baseline body weight. Its adverse effect profile, including steatorrhoea, faecal urgency, and gastrointestinal discomfort, significantly impairs adherence and long-term use. Although the XENDOS study demonstrated a reduction in the incidence of type 2 diabetes mellitus during extended follow-up, this benefit must be weighed against high dropout rates and frequent discontinuation due to tolerability issues (Torgerson et al., 2004). As a result, orlistat is generally considered a second-line or adjunctive therapy in current clinical practice.

Phentermine, a sympathomimetic amine, primarily stimulates noradrenergic pathways in the central nervous system, resulting in appetite suppression (Hendricks & Greenway, 2011). Although short-term weight loss of approximately 5 to 10 percent can be achieved, the evidence base is limited by a lack of robust randomised controlled trials beyond 12 weeks of use. This limitation restricts its application to short-duration therapy, often as part of combination regimens. Additionally, concerns regarding cardiovascular stimulation, including elevated heart rate and blood pressure, limit its use in individuals with pre-existing cardiovascular disease or risk factors. Consequently, phentermine is not considered suitable for chronic obesity management in current treatment paradigms.

Tirzepatide is a recent pharmacological innovation that combines GIP and GLP-1 receptor agonism, resulting in synergistic effects on insulin secretion, appetite regulation, and energy balance. Evidence from the SURMOUNT-1 trial demonstrates weight reductions exceeding 20 percent, representing some of the most substantial pharmacological effects reported to date (Jastreboff et al., 2022). Despite these promising results, tirzepatide remains an emerging therapy, with long-term safety, durability of effect, and cardiovascular outcomes still under investigation. Therefore, although it demonstrates superior efficacy in short- to medium-term trials, its role in long-term treatment algorithms continues to be defined.

4. Discussion

The findings of this review highlight substantial advances in the drug-based management of obesity, reflecting advances in understanding neuroendocrine regulation and metabolic disease. The emergence of glucagon-like peptide-1 (GLP-1) receptor agonists—particularly semaglutide—has redefined expectations for pharmacotherapy by achieving levels of weight reduction previously associated primarily with bariatric surgery. These developments demonstrate a shift from modest, symptom-oriented interventions toward therapies targeting the biological mechanisms underlying appetite regulation and energy balance (Røder, 2019).

4.1 Comparative Therapeutic Efficacy

A consistent finding across clinical trials is the superior efficacy of semaglutide compared with both traditional pharmacotherapeutic agents and earlier GLP-1 receptor agonists. Weight reductions exceeding 10–15% represent a clinically meaningful improvement over outcomes observed with orlistat and phentermine, which typically achieve more modest reductions (Torgerson et al., 2004; Hendricks & Greenway, 2011). Liraglutide occupies an intermediate position, providing moderate weight loss together with established cardiovascular benefits (Marso et al., 2016). The introduction of dual incretin receptor agonists, such as tirzepatide, suggests that further improvements in efficacy may be achievable. Clinical trial data demonstrating weight reductions exceeding 20% indicate the potential for pharmacological interventions to approach surgical outcomes (Jastreboff et al., 2022). However, differences between controlled trial environments and routine clinical practice must be considered when interpreting these results.

4.2 Adherence and Tolerability

Despite their performance, GLP-1 receptor agonists are associated with tolerability challenges that may limit long-term adherence. Gastrointestinal adverse effects, including nausea and vomiting, are the most frequently reported side effects and represent a primary cause of treatment discontinuation in major trials (Wilding et al., 2021; Lincoff et al., 2023). Although these effects are typically transient and dose-dependent, they call for careful dose escalation and patient counselling to minimise their impact. In contrast, older agents such as orlistat are also limited by adverse effects, particularly gastrointestinal symptoms related to fat malabsorption, which contribute to poor adherence (Torgerson et al., 2004). Phentermine, while generally well tolerated in the short term, generates concerns about cardiovascular stimulation, limiting its long-term use (Hendricks & Greenway, 2011). These findings highlight that tolerability is a key determinant of real-world effectiveness among all pharmacological classes.

4.3 Accessibility and Health Equity

A major limitation of newer therapeutic drugs is their cost and limited accessibility. GLP-1 receptor agonists, particularly semaglutide and tirzepatide, are significantly more expensive than older medications, and access is often restricted by insurance coverage policies. In many healthcare systems, reimbursement is prioritised for patients with type 2 diabetes mellitus rather than obesity alone, despite comparable long-term health risks. This difference brings up critical concerns regarding health equity, as populations with the highest burden of obesity frequently face the greatest barriers to accessing effective treatment. As obesity prevalence continues to rise globally, particularly in low- and middle-income countries, addressing affordability and access will be critical to ensuring the wider public health effect of these therapies.

4.4 Obesity as a Chronic Disease

An important implication of recent clinical evidence is the recognition of obesity as a chronic, relapsing condition demanding sustained management. Data from discontinuation studies establish that cessation of pharmacological therapy is commonly followed by weight regain, reflecting persistent biological mechanisms that regulate body weight (Rubino et al., 2022). This pattern is consistent with other chronic conditions, such as hypertension and type 2 diabetes mellitus, in which ongoing treatment is required to maintain disease control. These findings question the perception of obesity treatment as a short-term intervention and support a model of long-term, individualised management. Pharmacotherapy should therefore be considered as part of a integrated strategy that includes behavioural modification, nutritional support, and, where appropriate, surgical intervention.

4.5 Future Directions in Pharmacotherapy

The rapid development of incretin-based therapies suggests that further advances in obesity pharmacotherapy are likely. Emerging approaches include dual and triple receptor agonists, improved oral formulations, and exact medicine strategies to customize treatment to individual patient characteristics. Future research should prioritise several key areas. Long-term safety data remain limited, particularly regarding rare adverse events and outcomes beyond several years of continuous use. Additionally, further investigation is needed to evaluate the impact of these therapies on all-cause mortality and long-term cardiovascular outcomes across diverse populations. The integration of pharmacotherapy into real-world clinical practice, including adherence patterns and cost-effectiveness, also warrants continued study.

4.6 Limitations

This review has several limitations that should be acknowledged. First, heterogeneity among included studies—including differences in population characteristics, trial duration, and concurrent lifestyle interventions—limits direct comparability across pharmacological agents. Second, the reliance on published literature introduces the potential for publication bias, particularly in the reporting of positive outcomes. Third, long-term data for newer agents, including semaglutide and tirzepatide, remain limited, restricting the ability to fully assess long-term safety and durability of treatment effects.

4.7 Mechanistic Insights and Therapeutic Implications

The superior efficacy of GLP-1 receptor agonists stems from their multifaceted mechanism of action, which targets both peripheral metabolic processes and central appetite regulation. By acting on hypothalamic pathways, these agents reduce hunger and energy intake, while peripheral effects on gastric emptying and insulin secretion further enhance metabolic control (Al-Massadi et al., 2019). This dual mechanism distinguishes incretin-based therapies from older pharmacological agents that primarily target a single pathway. For example, orlistat acts exclusively at the level of the gastrointestinal tract, while phentermine primarily influences central appetite pathways through sympathomimetic activity. The broader physiological impact of GLP-1 receptor agonists may therefore explain their greater clinical efficacy and additional cardiometabolic benefits.

4.8 Real-World Effectiveness vs Clinical Trial Efficacy

A critical consideration in interpreting the available evidence is the difference between efficacy observed in controlled clinical trials and effectiveness in real-world clinical settings. Clinical trials often involve highly selected populations, structured follow-up, and intensive lifestyle support, all of which contribute to optimal outcomes. In contrast, real-world patients may have lower adherence, fewer resources, and more complex comorbidities. Emerging real-world data suggest that while GLP-1 receptor agonists remain effective outside trial settings, the magnitude of weight loss may be lower than in controlled studies. This discrepancy underscores the importance of integrating pharmacotherapy with behavioural and clinical support to maximise outcomes.

4.9 Economic Considerations and Cost-Effectiveness

The cost of GLP-1 receptor agonists represents a major barrier to widespread adoption. While these therapies offer substantial clinical benefits, their high prices limit access, particularly in healthcare systems with limited reimbursement policies. Cost-effectiveness analyses suggest that the long-term reduction in obesity-related complications may offset initial treatment costs; however, these benefits are dependent on sustained treatment adherence and long-term outcomes. From a public health perspective, improving affordability and access to effective pharmacotherapy is essential for addressing the global burden of obesity. Policy-level interventions, including expanded insurance coverage and pricing strategies, may play a critical role in facilitating access.

4.10 Integration with Multimodal Treatment Approaches

Pharmacotherapy should not be considered in isolation but rather as part of a comprehensive, multidisciplinary approach to obesity management. Combining pharmacological treatment with dietary modification, physical activity, and psychological support has been shown to improve outcomes compared with any single intervention alone. In certain cases, pharmacotherapy may also serve as a bridge to bariatric surgery or as an adjunct to enhance post-surgical weight maintenance. The integration of these approaches highlights the need for personalised treatment strategies that account for individual patient characteristics, preferences, and comorbidities.

4.11 Ethical and Social Considerations

The increasing use of pharmacotherapy for obesity raises important ethical and societal considerations. Issues related to the medicalisation of obesity, access disparities, and the potential for off-label use must be carefully addressed. Additionally, stigma associated with both obesity and its treatment may influence patient willingness to seek or adhere to therapy. Healthcare providers must therefore adopt a patient-centred approach that emphasises education, shared decision-making, and reduction of stigma.

5. Conclusions

This review demonstrates that pharmacological management of obesity has advanced substantially with the development of incretin-based therapies. Among currently available agents, semaglutide provides the most consistent and clinically meaningful weight reduction, alongside improvements in glycaemic control and cardiovascular outcomes (Wilding et al., 2021; Lincoff et al., 2023). These findings support its role as a leading therapeutic option for individuals who do not achieve adequate results through lifestyle modification alone. While liraglutide remains an important alternative with established cardiovascular benefits, its efficacy in weight reduction is comparatively modest (Marso et al., 2016). In contrast, traditional agents such as orlistat and phentermine are limited by lower effectiveness, tolerability concerns, and, in the case of phentermine, restrictions on long-term use (Torgerson et al., 2004; Hendricks & Greenway, 2011). Emerging therapies, including dual incretin receptor agonists such as tirzepatide, show promising results but require further evaluation to establish long-term safety and cardiovascular outcomes (Jastreboff et al., 2022). The evidence also reinforces the understanding of obesity as a chronic, relapsing condition that requires sustained management. Pharmacotherapy should therefore be integrated into a comprehensive, patient-centred approach that includes behavioural, nutritional, and, where appropriate, surgical interventions. However, significant challenges remain, particularly regarding treatment accessibility, cost, and long-term safety monitoring.

Future progress in obesity pharmacotherapy will depend on improving affordability, expanding access, and generating robust long-term data to guide clinical decision-making. Continued research into combination therapies and personalised treatment strategies may further enhance outcomes and help address the global burden of obesity.

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