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Advances in Obesity Pharmacotherapy: A Comprehensive Review of Semaglutide

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Abstract: *Obesity is a major global health concern associated with increased risks of type 2 diabetes mellitus, cardiovascular disease, and other metabolic disorders. Alongside lifestyle interventions, pharmacological therapies have become essential for effective and sustained weight management. Semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist originally developed for glycemic control, has recently emerged as a highly effective treatment for obesity.*

This review systematically evaluates clinical evidence on the efficacy, safety, and long-term outcomes of semaglutide in overweight and obese populations. Data from randomized controlled trials, particularly the STEP (Semaglutide Treatment Effect in People with Obesity) program, demonstrate significant and sustained weight reduction, often exceeding 10–15% of baseline body weight, in both diabetic and non-diabetic individuals. These effects are accompanied by improvements in glycemic control, lipid profiles, and cardiovascular risk markers.

Semaglutide promotes weight loss through appetite suppression, delayed gastric emptying, and improved metabolic regulation. It is generally well tolerated, with gastrointestinal symptoms such as nausea, vomiting, and diarrhea being the most commonly reported adverse events, typically mild and transient.

Overall, semaglutide represents a significant advancement in obesity pharmacotherapy, offering substantial and sustained weight loss with additional cardiometabolic benefits. Further studies are needed to evaluate long-term safety, cost-effectiveness, and real-world outcomes across diverse populations.

Keywords: Semaglutide; GLP-1 receptor agonist; Obesity; Weight management; STEP trials; SELECT trial; Cardiovascular outcomes; Systematic review

I. INTRODUCTION

Background:

Obesity is a chronic, multifactorial disease affecting over one billion individuals worldwide and is independently associated with increased risks of type 2 diabetes mellitus (T2DM), cardiovascular disease, dyslipidemia, and premature mortality. In addition to lifestyle interventions, effective pharmacological strategies are essential for sustainable weight management. Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), was initially developed for glycemic control in T2DM but has recently emerged as a transformative therapy for obesity.

In 2021, semaglutide received approval from the U.S. Food and Drug Administration (FDA) for chronic weight management at a dose of 2.4 mg administered once weekly, marking a significant advancement in anti-obesity pharmacotherapy. Its mechanism, involving appetite regulation, delayed gastric emptying, and improved metabolic control, has demonstrated substantial and sustained weight reduction in clinical settings.

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This systematic review consolidates current clinical evidence on the efficacy, cardiovascular benefits, and safety profile of semaglutide in individuals with overweight or obesity, including both diabetic and non-diabetic populations, highlighting its expanding role in modern obesity management.

II. OBJECTIVES

The primary objective of this systematic review is to comprehensively evaluate the clinical efficacy, safety, and cardiometabolic benefits of semaglutide in the management of overweight and obesity. Specifically, the review aims to:

1. **Quantify the magnitude and durability of weight loss** achieved with semaglutide therapy, including the proportion of patients attaining clinically meaningful weight reductions of ≥5%, ≥10%, ≥15%, and ≥20% of baseline body weight over short- and long-term follow-up periods.

2. **Assess cardiometabolic outcomes**, with particular emphasis on improvements in glycemic control (HbA1c), blood pressure, lipid profiles, and the reduction in major adverse cardiovascular events (MACE), thereby evaluating the broader metabolic and cardiovascular benefits of semaglutide beyond weight reduction.

3. **Evaluate the safety profile and tolerability** of semaglutide across diverse patient populations, including individuals with and without type 2 diabetes mellitus (T2DM), by analyzing the incidence, severity, and pattern of adverse events, treatment discontinuation rates, and long-term safety concerns.

Through these objectives, the study seeks to establish semaglutide's overall therapeutic value and its role in contemporary obesity management.

III. METHODS

Search Strategy and Data Sources

A systematic and comprehensive literature search was conducted across major electronic databases, including **PubMed/MEDLINE**, **EMBASE**, and the **Cochrane Central Register of Controlled Trials (CENTRAL)**, from database inception through March 2025. The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and keywords such as *"semaglutide," "GLP-1 receptor agonist," "obesity," "weight loss," "overweight," "cardiovascular outcomes,"* and *"randomized controlled trial."*

In addition, reference lists of relevant articles and previously published meta-analyses were manually screened to identify any additional eligible studies.

IV. ELIGIBILITY CRITERIA

Studies were included based on the following predefined criteria:

- **Study design:** Randomized controlled trials (RCTs)
- **Population:** Adults with
  - Body mass index (BMI) ≥30 kg/m², or
  - BMI ≥27 kg/m² with at least one obesity-related comorbidity (e.g., T2DM, hypertension, dyslipidemia)
- **Intervention:** Subcutaneous or oral semaglutide administered at any approved or investigational dose
- **Comparator:** Placebo or active comparator
- **Outcomes:** Reporting of weight loss and/or cardiometabolic parameters

Studies involving pediatric populations, non-randomized designs, or lacking relevant outcome data were excluded.

Included Studies and Clinical Trial Programs

Key large-scale and high-quality RCTs included in this review comprise:

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- The **STEP (Semaglutide Treatment Effect in People with Obesity) program (STEP 1–8)**, evaluating subcutaneous semaglutide in diverse populations
- The **SELECT trial**, assessing cardiovascular outcomes in overweight/obese individuals without diabetes
- The **OASIS 1 trial**, examining the efficacy of oral semaglutide for weight management
- Supporting **systematic reviews and meta-analyses** to strengthen evidence synthesis

Sr. No.	Authors	Year	Title of Paper	Journal	Study Type	Population	Key Findings
1	Davies MJ et al.	2017	Semaglutide as a therapeutic option for type 2 diabetes	The Lancet Diabetes & Endocrinology	Review	T2DM patients	Demonstrated strong glycemic control and weight reduction potential
2	Marso SP et al.	2016	Semaglutide and cardiovascular outcomes in patients with T2DM	New England Journal of Medicine	RCT (SUSTAIN-6)	T2DM patients	Reduced cardiovascular risk and improved metabolic profile
3	Wilding JPH et al.	2021	Once-weekly semaglutide in adults with overweight or obesity (STEP 1)	New England Journal of Medicine	RCT	Non-diabetic obese adults	~14.9% mean weight loss; significant improvement vs placebo
4	Davies M et al.	2021	Semaglutide 2.4 mg in adults with overweight/obesity and T2DM (STEP 2)	The Lancet	RCT	Obese + T2DM	~9.6% weight loss; improved glycemic control
5	Wadden TA et al.	2021	Effect of subcutaneous semaglutide as adjunct to lifestyle intervention (STEP 3)	JAMA	RCT	Obese adults	Enhanced weight loss with lifestyle + drug
6	Rubino D et al.	2021	Effect of continued weekly semaglutide vs withdrawal (STEP 4)	JAMA	RCT	Obese adults	Sustained weight loss; regain after discontinuation
7	Kushner RF et al.	2020	Clinical utility of semaglutide for weight management	Obesity Science & Practice	Review	Obese population	Highlighted effectiveness and safety profile
8	Blundell J et al.	2017	Effects of semaglutide on appetite and energy intake	Diabetes, Obesity and Metabolism	Clinical Study	Obese individuals	Reduced appetite and caloric intake
9	O'Neil PM et al.	2018	Efficacy and safety of semaglutide vs placebo for weight loss	The Lancet	RCT	Non-diabetic obese adults	Significant dose-dependent weight loss
10	Wharton	2022	Semaglutide for the	Diabetes,	Review	General	Confirmed

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	S et al.		treatment of obesity: a review	Metabolic Syndrome and Obesity		obese population	superior efficacy over other anti-obesity drugs

IV. OUTCOME MEASURES

Primary Outcomes

- Percentage change in total body weight from baseline
- Proportion of participants achieving:
  - ≥5% weight loss
  - ≥10% weight loss
  - ≥15% weight loss
  - ≥20% weight loss

Secondary Outcomes

- Changes in anthropometric measures: BMI and waist circumference
- Glycemic parameters: HbA1c and fasting plasma glucose
- Cardiovascular risk factors:
  - Systolic and diastolic blood pressure
  - Lipid profile (LDL, HDL, triglycerides)
- Incidence of major adverse cardiovascular events (MACE)
- Safety outcomes: adverse events, serious adverse events, and treatment discontinuation rates

Quality Assessment and Risk of Bias

The methodological quality of included studies was rigorously evaluated using the **Cochrane Risk of Bias 2 (RoB 2) tool**, which assesses potential bias across domains such as randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.

Data Synthesis and Reporting

Data were systematically extracted and synthesized qualitatively, with quantitative findings summarized where appropriate. The review adhered strictly to the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** guidelines to ensure transparency, reproducibility, and methodological rigor.

V. RESULTS

Across the STEP clinical trial program and supporting meta-analyses, semaglutide 2.4 mg administered once weekly demonstrated consistently superior weight reduction compared with placebo. In the pivotal STEP 1 trial (n = 1,961; duration: 68 weeks), participants without diabetes achieved a mean weight loss of 14.9% with semaglutide versus 2.4% with placebo (treatment difference: −12.4 percentage points; 95% CI: −13.4 to −11.5; $p < 0.001$). Notably, 86.4% of participants receiving semaglutide achieved ≥5% weight loss.

Long-term efficacy was confirmed in the STEP 5 trial (2-year duration), where sustained and clinically meaningful reductions were observed. An updated meta-analysis incorporating STEP 5 reported a significant mean difference in total body weight reduction of −11.80% (95% CI: −12.93 to −10.68; $p < 0.00001$) compared to placebo. Additional improvements included reductions in waist circumference (−9.4 cm), body mass index (−4.5 kg/m²), and absolute body weight (−12.2 kg). Semaglutide also produced favorable effects on cardiometabolic parameters, including lipid profiles, systolic blood pressure, C-reactive protein, and glycaemic indices.

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In the SELECT cardiovascular outcomes trial (n = 17,604; mean follow-up ≈ 40 months), semaglutide significantly reduced the composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke by 20% (hazard ratio [HR]: 0.80; 95% CI: 0.72–0.90; $p < 0.001$) in individuals with overweight or obesity and established cardiovascular disease but without diabetes. A prespecified analysis demonstrated sustained weight reduction over a period of up to four years, with mean decreases of 10.2% in body weight and 7.7 cm in waist circumference compared to placebo.

Further subgroup analysis from SELECT revealed additional benefits in patients with pre-existing heart failure, including reductions in major adverse cardiovascular events (MACE) (HR: 0.72; 95% CI: 0.60–0.87) and the composite heart failure endpoint (HR: 0.79; 95% CI: 0.64–0.98). Moreover, the STEP UP study evaluating a higher dose of semaglutide (7.2 mg once weekly) demonstrated enhanced weight loss outcomes with a favorable risk–benefit profile compared to the standard 2.4 mg dose.

Semaglutide was generally well tolerated across trials. Gastrointestinal adverse events—primarily nausea, diarrhea, constipation, and vomiting—were the most frequently reported, occurring in approximately 74–77% of semaglutide-treated participants compared to 48–52% in placebo groups. These events were typically transient, mild-to-moderate in severity, and manageable with dose escalation strategies. Treatment discontinuation due to adverse events ranged from 4.5% to 16.6%. Serious adverse events, including acute pancreatitis and cholelithiasis, were rare but occurred slightly more frequently in the semaglutide group. No unexpected long-term safety concerns were identified.

VI. CONCLUSION

Semaglutide represents a paradigm shift in the pharmacological management of obesity, demonstrating robust, sustained weight loss and significant cardiometabolic benefits that extend beyond glycaemic control. Evidence from the STEP clinical trial program, the SELECT cardiovascular outcomes trial, and comprehensive meta-analyses establishes semaglutide as the most clinically validated GLP-1 receptor agonist for obesity treatment, offering a dual therapeutic advantage in weight reduction and cardiovascular risk mitigation.

Future research should focus on long-term safety beyond five years, weight regain dynamics following treatment discontinuation, the efficacy and safety of higher dosing regimens, cost-effectiveness analyses, and outcomes in underrepresented populations, including adolescents and diverse ethnic groups.

REFERENCES

1. 1.Davies, Melanie J., et al. “Semaglutide as a Therapeutic Option for Type 2 Diabetes.” *The Lancet Diabetes & Endocrinology*, vol. 5, no. 4, 2017, pp. 275–286.
2. Davies, Melanie, et al. “Semaglutide 2.4 mg Once Weekly in Adults with Overweight or Obesity, and Type 2 Diabetes (STEP 2): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial.” *The Lancet*, vol. 397, no. 10278, 2021, pp. 971–984.
3. Marso, Steven P., et al. “Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.” *New England Journal of Medicine*, vol. 375, no. 19, 2016, pp. 1834–1844.
4. Rubino, Daniela, et al. “Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults with Overweight or Obesity: The STEP 4 Randomized Clinical Trial.” *JAMA*, vol. 325, no. 14, 2021, pp. 1414–1425.
5. Wadden, Thomas A., et al. “Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults with Overweight or Obesity: The STEP 3 Randomized Clinical Trial.” *JAMA*, vol. 325, no. 14, 2021, pp. 1403–1413.

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6. Wilding, John P. H., et al. "Once-Weekly Semaglutide in Adults with Overweight or Obesity." *New England Journal of Medicine*, vol. 384, no. 11, 2021, pp. 989–1002.
7. Kushner, Robert F., et al. "Clinical Utility of Semaglutide for Weight Management in Obesity." *Obesity Science & Practice*, vol. 6, no. 2, 2020, pp. 123–132.
8. O'Neil, Patrick M., et al. "Efficacy and Safety of Semaglutide Compared with Placebo for Weight Loss in Patients without Diabetes: A Randomised, Double-Blind, Controlled Trial." *The Lancet*, vol. 392, no. 10148, 2018, pp. 637–649.
9. Wharton, Sean, et al. "Semaglutide for the Treatment of Obesity: A Review." *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, vol. 15, 2022, pp. 2047–2056.
10. World Health Organization. *Obesity and Overweight*. WHO, 2023, www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.