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Pharmacological and Non-Pharmacological Interventions for the Treatment of Obesity: A Review of Guidelines and Clinical Trials (2020–2025)

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ABSTRACT

Background. Obesity is a long-term, relapsing condition that necessitates lifelong treatment. The years 2020 through 2025 signify a paradigm shift in obesity medicine with the departure from behavior-centric models towards neurohormonal interventions, led by the approval of high-efficacy incretin-based therapies.

Aim of the study. To review current clinical practice guidelines and pivotal randomized controlled trials (RCTs) published between January 1, 2020 and January 1, 2025, regarding the efficacy, safety, and cardiovascular outcomes of pharmacological and non-pharmacological treatments.

Material and Methods. A comprehensive search of the literature was conducted in PubMed/MEDLINE, Embase, and Cochrane Library databases covering the period from January 1, 2020 to January 1, 2025. The review focused on Phase 3 RCTs, meta-analyses, and consensus guidelines from major medical societies (ADA, EASO, AACE, ASMBS). Key search terms included obesity, GLP-1 receptor agonists, semaglutide, tirzepatide and lifestyle intervention.

Result. Lifestyle treatment (Medical Nutrition Therapy and physical activity) continues to be the cornerstone of therapy but is associated with limited long-term effectiveness as monotherapy due to metabolic adaptation. In stark contrast, new pharmacologic therapies have transformed the standards of care. Semaglutide 2.4 mg (STEP trials) demonstrated a mean weight loss of 14.9%, while tirzepatide (SURMOUNT trials) achieved up to 20.9% mean weight loss, with more than 30% of patients achieving results comparable to bariatric surgery. The SELECT trial (2023) further demonstrated that GLP-1 receptor agonists decreased MACE by 20% in patients with obesity and established cardiovascular disease.

Conclusions. Multimodal treatment is required for modern obesity care. Although lifestyle modification remains an essential component of metabolic care, next-generation pharmacotherapy is increasingly recommended for patients with a BMI ≥30 kg/m² (or ≥27

kg/m² with comorbidities) to address physiological set points. There is a growing body of evidence supporting the notion that obesity is a chronic disease requiring lifelong management to prevent weight regain.

Keywords: obesity, GLP-1, tirzepatide, semaglutide, lifestyle intervention, cardiovascular outcomes

1. Introduction

Obesity is prevalent globally and leads to many diseases, thus it is considered the largest public health problem of this century. It is predicted that by 2025, around 20% of the world's adult population would have obesity, leading to a heavy burden on healthcare systems due to obesity-related comorbidities including type 2 diabetes, cardiovascular disease, and certain cancers.

In the past, clinical treatment of obesity was based primarily on lifestyle changes and behavioral therapy. However, lifestyle changes alone are generally not enough. This failure to maintain weight loss is not because patients do not comply with their instructions, but due to potent counter-regulatory neurohormonal mechanisms - popularly described as the "metabolic set-point"- that fight weight loss by promoting hunger and suppressing energy expenditure [1, 2, 3, 4].

Therefore, the period of 2020–2025 is a pivot point in obesity medicine, dubbed by many as the "Incretin Era." Availability of high-efficacy Glucagon-like Peptide-1 (GLP-1) receptor agonists and dual GIP/GLP-1 agonists, approaching the efficacy of metabolic surgery options, has revolutionized the therapeutic armamentarium available to clinicians. Meanwhile, the COVID-19 pandemic fueled further recognition of obesity not merely as a risk factor but as a significant, chronic, pro-inflammatory disease state that markedly exacerbates infectious mortality [5].

This review intends to consolidate critical evidence available from January 2020 through January 2025. It highlights the limitations of lifestyle monotherapy versus the efficacy of pharmacological agents and reviews the latest clinical practice guidelines by key international societies, including the American Diabetes Association (ADA), the European Association for the Study of Obesity (EASO), the American Association of Clinical Endocrinology (AACE), and the Endocrine Society [6, 7, 8].

2. Material and Methods

A comprehensive literature search was performed using PubMed/MEDLINE, Embase, and the Cochrane Library databases. The search period covered publications from January 1, 2020, to January 1, 2025. The search strategy utilized Medical Subject Headings (MeSH) and keywords combined by Boolean operators: ("Obesity/therapy"[Mesh] or "Anti-Obesity Agents"[Mesh]) and ("GLP-1 Receptor Agonists" or "semaglutide" or "tirzepatide" or "lifestyle intervention") and ("Cardiovascular Diseases"[Mesh] or "weight loss").

The review included studies involving adults (≥18 years) with a BMI ≥30 kg/m² or ≥27 kg/m² with weight-related comorbidities. Priority was given to Phase 3 Randomized Controlled Trials (RCTs) with large sample sizes (N > 500), systematic reviews, meta-analyses, and consensus guidelines. The primary outcomes of interest were percentage body weight change and Major Adverse Cardiovascular Events (MACE). Secondary outcomes included safety, tolerability, and body composition changes. Additional relevant articles were identified by manual screening of the reference lists of the included guidelines.

3. Results

3.1 Non-Pharmacological Interventions: The Foundation Although there has been a shift in focus towards pharmacological treatment, all major clinical guidelines from 2020 to 2025 (ADA, EASO) state that broad lifestyle intervention remains a primary aspect in obesity management. Nevertheless, the therapeutic purpose of such interventions has shifted from being the primary weight loss driver to supporting metabolic health and body composition [9, 10]. Although pharmacological agents are highly effective, dietary supplements for weight loss are still lacking robust evidence for long-term clinical usefulness [11].

3.1.1 Medical Nutrition Therapy (MNT) The traditional concept of a “blanket” dietary prescription is questioned by recent evolutions, highlighting dietary adherence and energy deficit.

- **Macronutrient Composition:** A definitive systematic review and meta-analysis (BMJ, 2020) concluded that low-carbohydrate and low-fat diets result in similar weight loss at 12 months when the energy restriction is the same. This supports a patient-centred approach based on individual preferences to optimise long-term adherence [12].

- **Intermittent Fasting (IF):** IF and Time-Restricted Eating (TRE) gained popularity during the review period. However, a key RCT published in the New England Journal of Medicine (2022) showed that TRE was not superior to daily calorie restriction for weight loss. The authors concluded that the effects of IF are largely a consequence of reduced overall calorie intake, with no independent metabolic effects of timing [13, 14, 15].

3.1.2 Physical Activity The 2020 World Health Organization Guidelines on Physical Activity and Sedentary Behavior recommend 150-300 minutes of moderate-intensity aerobic physical activity per week for health. The concept of treating obesity shifted dramatically in the context of:

- **Weight Loss and Maintenance:** Current evidence suggests that exercise is a poor means of producing acute weight loss (typically associated with <3% reduction due to compensatory physiological responses that increase appetite). Yet, physical activity has been identified as the most robust predictor of successful long-term weight loss maintenance [16].
- **Resistance Training and Body Composition:** The availability of highly effective anti-obesity medications (AOMs) that induce rapid weight loss has heightened the potential for sarcopenia (muscle loss). Newer guidelines explicitly recommend adding resistance training (2–3 sessions per week) to prevent lean muscle mass catabolism and maintain resting metabolic rate [17].

3.2 Pharmacological Management: The New Standard The 2023–2025 updated guidelines reflect a clear divergence from historical algorithms. Drug therapy is not considered a "last-resort" or simply cosmetic intervention, but rather a critical biological therapy line for patients with a BMI ≥30 kg/m² (or ≥27 kg/m² with comorbidities) who fail to achieve metabolic set-points through lifestyle modifications alone.

3.2.1 GLP-1 Receptor Agonists: Semaglutide Semaglutide 2.4 mg (Wegovy), a once-weekly injectable GLP-1 receptor agonist, was the first agent to consistently induce double-digit weight loss in broad populations.

- **Efficacy (The STEP Program):** The pivotal STEP 1 trial (2021) demonstrated that semaglutide 2.4 mg achieved a mean weight loss of 14.9% versus 2.4% with placebo

after 68 weeks [18, 19]. STEP 3 further suggested that semaglutide combined with intensive behavioral therapy could nearly approach the efficacy of the drug alone, cementing the power of the medication [20]. Data from STEP 5 (2022) later confirmed this effect for up to two years, overcoming concerns of rapid tachyphylaxis [21].

- **Cardiovascular Outcomes (SELECT Trial):** The SELECT trial (N = 17,604), published in late 2023, is a game changer in obesity medicine. It demonstrated that semaglutide 2.4 mg was linked with a 20% lower risk of major adverse cardiovascular events (MACE: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) among adults with overweight or obesity and established cardiovascular disease but without diabetes [22].

3.2.2 Dual GIP/GLP-1 Receptor Agonists: Tirzepatide Tirzepatide (Zepbound), a once-weekly unimolecular dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, is the first "twincretin" for the management of type 2 diabetes and obesity. The added effect of GIP agonism is believed to synergize with GLP-1 for its effects on satiety and adipose tissue function.

- **Efficacy (The SURMOUNT Program):** In the SURMOUNT-1 trial (2022), the dose of tirzepatide at 15 mg produced 20.9% body weight loss on average over 72 weeks. Impressively, 36.2% of subjects lost ≥25% of their body weight, a figure previously deemed achievable only by bariatric surgery [23]. Analyses showed a significant reduction in the risk of developing type 2 diabetes for those with prediabetes [24], while early meta-analyses point to a positive cardiovascular safety profile [25].
- **Maintenance Effect:** SURMOUNT-4 (2024) emphasizes the disease's chronic nature: participants observed 25.3% total weight loss when continuing tirzepatide for 88 weeks, compared to those who switched to placebo and regained weight, ending with only 9.9% loss [26].

3.2.3 Emerging Therapies and Comparative Synthesis The obesity pharmacotherapy pipeline remains active and fast-growing [27]. Retatrutide, a triple hormone receptor agonist (GLP-1/GIP/Glucagon), has demonstrated Phase 2 preliminary results of ~24% weight loss, potentially superior to currently available agents [28], and a robust reduction in liver fat content in patients with NAFLD [29]. In addition, oral preparations (e.g., Orforglipron, high-dose oral semaglutide) are under late-stage development. The OASIS 1 and PIONEER PLUS studies

show that oral semaglutide (up to 50 mg) has similar efficacy for weight loss as the injectable formulations [30, 31, 32].

Table 1. Comparison of the most important anti-obesity medications (based on RCTs 2020–2025)

Medication	**Mechanism of Action**	**Key Trial**	**Mean Weight Loss (Maximum Dose)**	**Patients Achieving ≥5% Loss**	**Current Status**
Liraglutide	GLP-1 Receptor Agonist	Reference Standard	**~8.0%**	63%	Approved
Semaglutide	GLP-1 Receptor Agonist	STEP 1	**14.9%**	86%	Approved
Tirzepatide	GIP / GLP-1 Receptor Agonist	SURMOUNT-1	**20.9%**	91%	Approved
Retatrutide	GIP / GLP-1 / Glucagon Agonist	Phase 2 (2023)	**24.2%**	100%	Phase 3 Trials

Orforglipron	Oral GLP-1 Receptor Agonist	Phase 2 (2023)	**~14.7%**	75%	Phase 3 Trials

Table 2. Characteristics and Key Outcomes of Pivotal Randomized Controlled Trials Included in the Review (2020–2025)

Study (Year)	**Intervention**	**Duration**	**Primary Outcome (Weight / Cardiovascular)**	**Key Safety and Clinical Observations**
STEP 1(2021)	Semaglutide 2.4 mg	68 weeks	**-14.9%** weight loss vs. -2.4%	Mostly mild-to-moderate gastrointestinal events.
STEP 5(2022)	Semaglutide 2.4 mg	104 weeks	**-15.2%** weight loss vs. -2.6%	Confirmed sustained efficacy over 2 years.
SELECT(2023)	Semaglutide 2.4 mg	33 months	**-20% Cardiovascular Event Risk**	Significant benefit in patients without diabetes.

SURMOUNT-1 (2022)	Tirzepatide 15 mg	72 weeks	**-20.9%** weight loss vs. -3.1%	Highest efficacy among currently approved drugs.
SURMOUNT-4 (2024)	Tirzepatide 15 mg	88 weeks	Continued: **-25.3%** / Discontinued: **-9.9%**	Demonstrates weight regain after stopping treatment.
OASIS 1(2023)	Oral Semaglutide 50 mg	68 weeks	**-15.1%** weight loss vs. -2.4%	Daily oral tablet equivalent to weekly injection.
Retatrutide (2023)	Retatrutide 12 mg	48 weeks	**-24.2%** weight loss vs. -2.1%	Triple-hormone agonist; unprecedented weight loss.

4. Discussion

4.1 The Paradigm Shift: Obesity as a Chronic Disease The theoretical discourse in 2020–2025 is dominated by the unequivocal recognition that obesity is a chronic, relapsing disease and not a short-term behavioral failure. The STEP 4 and SURMOUNT-4 discontinuation studies corroborated this model: stopping GLP-1/GIP treatment uniformly led to a rapid regain of about two-thirds of lost weight within a year [26, 33]. This implies that anti-obesity medication (AOM) functions like antihypertensives or statins-treating pathology only while present in the system-suggesting that treatment may need to be lifelong for many patients.

4.2 Safety and Tolerability Clinical data support the safety profile of incretin-based therapies, but widespread use has raised specific issues prompting clinical vigilance:

- **Gastrointestinal (GI) Events:** Nausea, diarrhea, and vomiting are the most frequent adverse events, observed in >70% of patients during dose titration. Although usually transient, they are the main reason for treatment discontinuation [34].
- **Body Composition and Sarcopenia:** STEP and SURMOUNT DEXA substudies demonstrate that lean tissue (fat-free mass) loss accounts for ∼20–40% of total weight lost. While this ratio is consistent with other caloric restriction methods, the rapid speed of weight loss with new agents is concerning regarding sarcopenic obesity, particularly in the elderly. This underscores the need for simultaneous resistance training prescription [35].
- **Perioperative Aspiration Risk:** In 2023, safety standards were revised. The ASA issued consensus guidance on delaying elective procedures to stop these agents to reduce the risk of pulmonary aspiration related to delayed gastric emptying, following reports of residual gastric content in fasted patients on GLP-1 RAs [36, 37].

4.3 Access and Affordability The massive demand for GLP-1 and dual agonists places healthcare systems under financial pressure. High drug prices could be tempered by cost-effectiveness analyses showing that, despite high upfront costs, the long-term Incremental Cost-Effectiveness Ratio (ICER) improves substantially when considering the reduction in cardiovascular events (as in SELECT) and delayed progression to type 2 diabetes. However, disparities in insurance coverage remain a critical obstacle to uniform care [38, 39].

4.4 Cardiovascular and Systemic Protection The goal of treating obesity is no longer purely cosmetic weight loss, but preventing end-organ damage. This aligns with the 2023 ESC Guidelines on the management of cardiovascular disease in patients with diabetes and obesity, which prioritize agents with proven cardiovascular benefits [40]. The current consensus is to move away from glucocentric or weight-centric targets towards holistic organ protection [34].

5. Conclusion

The treatment of obesity has been radically altered during 2020–2025. Semaglutide and tirzepatide have closed the gap between behavioral interventions and bariatric surgery by providing “bariatric-mimetic” efficacy with a manageable safety profile. A paradigm shift to a multimodal treatment approach is supported by the current evidence:

- **Background:** Lifestyle intervention remains the cornerstone of metabolic health and muscle maintenance, although its limitations as monotherapy for weight maintenance are evident.
- **Escalation:** To address the underlying neurohormonal pathology, pharmacotherapy should be introduced early in eligible patients (BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities).
- **Long-term Objective:** The scope of treatment has shifted from superficial weight reduction to prevention of end-organ damage, demonstrated by the cardiovascular benefits seen in the SELECT trial.
- **Future Directions:** Real-world evidence on long-term safety (>5 years), approaches to reduce lean mass loss, and health economic models to facilitate broad access to these therapies must be the focus of future investigations.

Disclossure

Author Contributions

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