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Research Paper

Pharmacological management of obesity: a comprehensive narrative review of diagnostic classification, incretin-based and legacy drug therapy, and landmark trial evidence

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ABSTRACT

Background: Obesity is officially a chronic relapsing condition and is estimated to affect 890 million adults around the world in 2022. Incretin-based pharmacotherapy has revolutionized the magnitude of weight loss we can achieve in order to modify the disease; thus, pharmacotherapy is now one of the main disease-modifying treatment modalities.
Objective: This narrative review summarizes up-to-date diagnostic classification criteria, comparative pharmacology of the legacy and incretin-based anti-obesity drugs, and evidence from landmark randomized trials that has directed contemporary anti-obesity drug prescribing and management.
Methods: PubMed/MEDLINE, Cochrane Library and ClinicalTrials.gov were used to conduct a structured narrative search of phase 3 randomized, placebo or active-controlled trials of anti-obesity pharmacotherapy, and the most recent World Health Organization (WHO) guidance was identified between 1990 and 2025.
Results: Mean weight loss was 2–4 percentage points less with orlistat compared with placebo and 17–19 percentage points less with tirzepatide 15 mg compared with placebo, which is a 5-fold difference in efficacy across the 6 major drug classes. Cardiovascular outcome benefit was shown in the SELECT trial in 17,604 participants without diabetes, with an HR of 0.80 (95% CI 0.72–0.90). Comparative pharmacology, evidence from trials, safety monitoring, patient selection and an integrated treatment algorithm are introduced.
Conclusions: The age of drugs to promote weight loss of more than 15-20% of body weight has arrived and drugs that affect the incretins offer a new path to sustained weight loss. These therapies cannot be stopped once they are started, and are often used for prolonged periods of time. Access to evidence-based pharmacotherapy is a critical opportunity to better manage obesity and prevent costly cardiometabolic conditions.

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1. INTRODUCTION

The World Health Organization has therefore defined obesity as a chronic, relapsing disease caused by a complex interplay of genetic, neurobiological, behavioral and food and physical-activity environments, not just a result of personal choice [1]. It is estimated that in 2022 there were 2.5 billion adults who were overweight, of which 890 million were obese, an adult obesity prevalence that has more than doubled since 1990, and even faster for adolescents (quadrupling since 1990). Obesity has a causal relationship with type 2 diabetes, hypertension, dyslipidaemia, obstructive sleep apnoea, several cancers, osteoarthritis and cardiac and vascular disease, with even small, sustained weight loss resulting in significant improvements in this wide range of comorbidities [2].

In the modern pharmacological age, obesity treatment was regarded as a relatively small step on the road to lifestyle modification, and approved drugs (orlistat, phentermine-topiramate, naltrexone-bupropion) yielded 3-9 percentage points of weight loss over the placebo. This all changed with the clinical development of glucagon-like peptide-1 (GLP-1) receptor agonists, first approved for type 2 diabetes and then the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor co-agonist tirzepatide, which have yielded mean weight loss of 15–21% of body weight in pivotal trials — an amount that was previously thought to be possible only with bariatric surgery. This change has completely transformed the place of pharmacotherapy in obesity therapy from the secondary step and an addition to the treatment to the primary step and a first line of therapy [3].

1.1 Objectives

The purpose of this review is to: (i) recap existing diagnostic and classification guidelines for overweight and obesity; (ii) outline the comparative molecular pharmacology of the key classes of anti-obesity drugs, ranging from the legacy agents to incretin-based treatments, including cardiovascular outcome data; (iii) summarize and synthesize the landmark randomized trial evidence that guides current prescribing practices; (iv) discuss patient selection criteria and safety monitoring; and (v) propose an integrated treatment algorithm based on current evidence and guidance.

2. RELATED WORK

2.1 Epidemiological Background

WHO Fact Sheet (2024) – obesity is now recognised as a chronic relapsing condition. Pooled analysis at global level from NCD Risk Factor Collaboration (Lancet, 2024) – the obesity prevalence more than doubled since 1990 (more than 890 million adults were affected in 2022).

2.2 Legacy Anti-Obesity Drug Trials

XENDOS– orlistat vs. placebo, 3,304 participants, 4 years; ~2-4 percentage point placebo subtracted weight loss CONQUER – phentermine/topiramate showed a weight loss of 10.9% compared to 1.6% for the placebo group. COR-I – naltrexone-bupropion; 5.4% vs. 1.3% weight loss with placebo

2.3 Incretin-Based Drug Trials

[4] Liraglutide 3.0 mg, first incretin-based drug to be approved for chronic weight management treatment STEP 1– semaglutide 2.4 mg; −14.9% vs. −2.4% placebo SURMOUNT-1 TIRZEPATIDE – up to

–20.9% weight loss at 15 mg SURMOUNT-5– head-to-head tirzepatide vs. semaglutide; 20.2% vs. 13.7% Weight Watchers– weight loss intervention, 12,940 participants with overweight/obesity and no diabetes; 25% reduction in weight loss for participants in the intervention group.

2.4 Foundational WHO Guidance

WHO Technical Report Series 894 (2000) – "Obesity: Preventing and Managing the Global Epidemic"

3. METHODOLOGY

This is a narrative review and no original patient data was collected, and no formal meta-analytic pooling was undertaken. A systematic search of PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials and Clinical Trials [5]. gov, was performed with a combination of the terms “obesity,” “weight management,” “GLP-1 receptor agonist,” “tirzepatide,” “semaglutide,” “orlistat,” “phentermine-topiramate,” “naltrexone-bupropion,” and “randomized controlled trial” from January 1990 to mid-2025, in English-language publications. Phase 3, randomized, placebo- or active-controlled trials with a pre-specified body-weight or cardiovascular outcome were prioritized, in addition to current World Health Organization classification and guidance documents. The following percentage weight changes, hazard ratios, confidence intervals and prevalence estimates are direct quotes from the cited primary publications and WHO documents and do not represent a calculation, pooling or simulation by the present authors [6].

This condition is diagnosed using a specific classification known as the Diagnostic Classification of Overweight and Obesity (DCO). Although there are known drawbacks in people with extremely high muscle mass or unusual body shapes, body mass index (BMI) continues to be the most commonly used screening tool for obesity and overweight at population level [7], [8]. The World Health Organization's BMI Classification is shown in Table 1 and Figure 2.

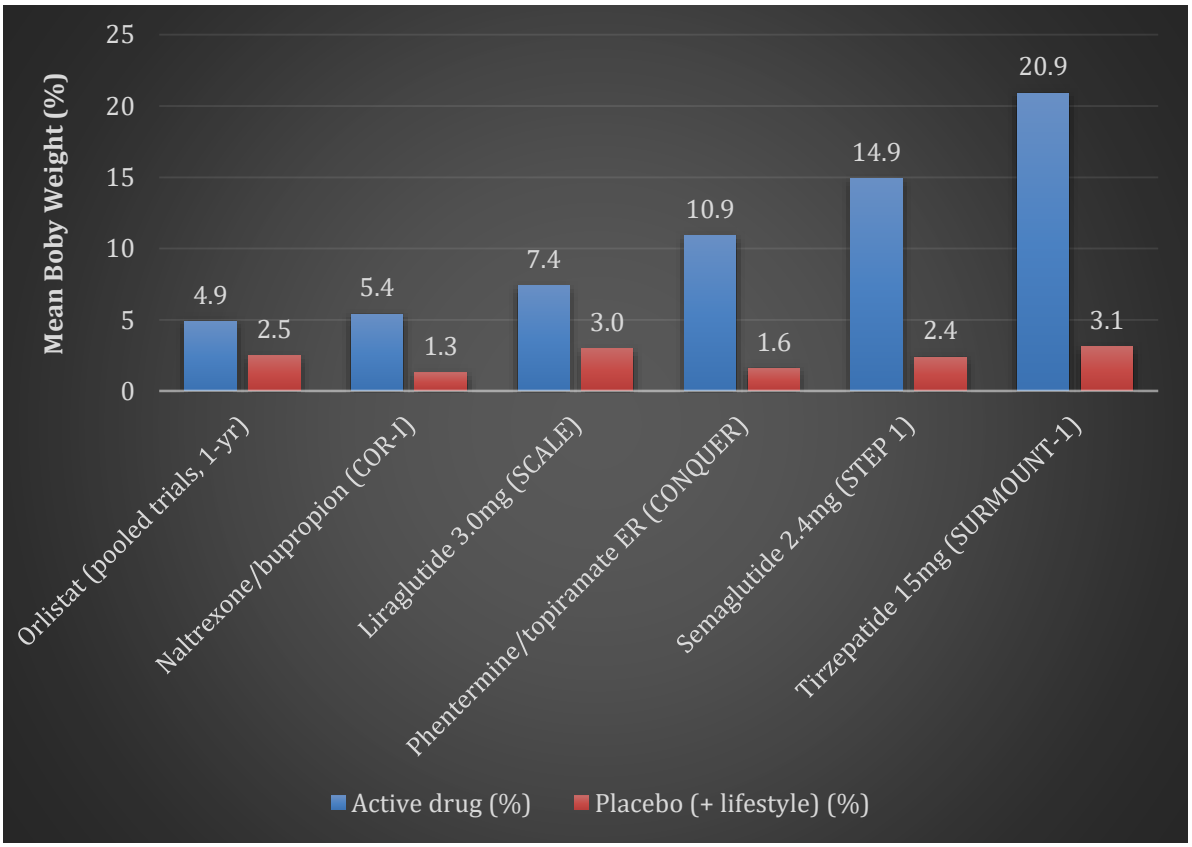

Figure 1. Mean Percentage Body Weight Loss with Approved Anti-Obesity Pharmacotherapy in Landmark Randomized Trials

Table 1. World Health Organization Body Mass Index Classification

Category	BMI (Kg/M^2)
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obesity Class I	30.0–34.9
Obesity Class II	35.0–39.9
Obesity Class III (severe)	≥40.0

Values shown as magnitude of weight loss (%), not signed change. Trial durations and populations differ (see Table 3); cross-trial comparison should be interpreted with the caveats discussed in the Limitations section.

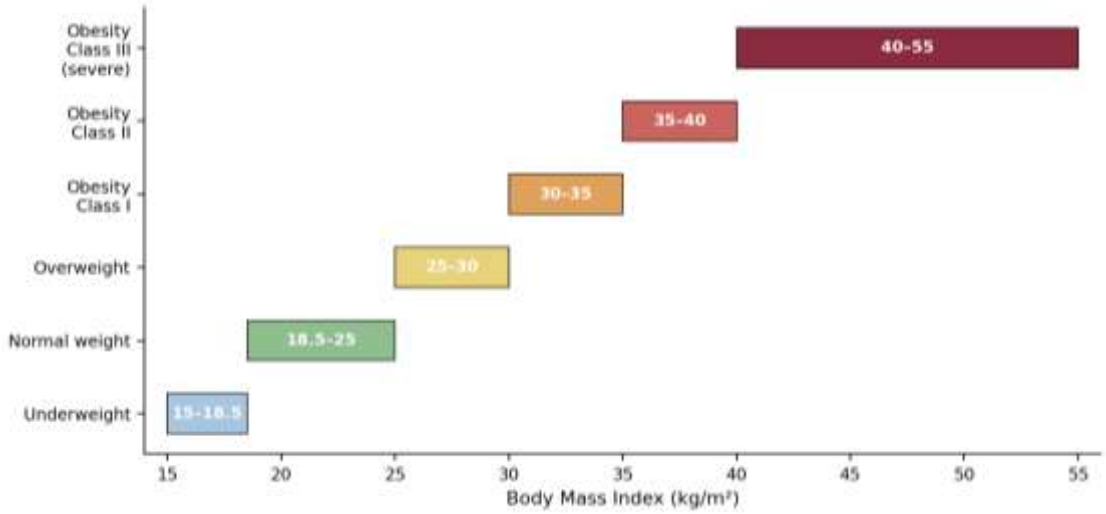

Figure 2. WHO Body Mass Index Classification

3.1 Global Epidemiology

The burden of overweight and obesity at the global level for each age group as of 2022 is presented in Figure 3, based on the latest WHO and NCD Risk Factor Collaboration pooled analyses [9].

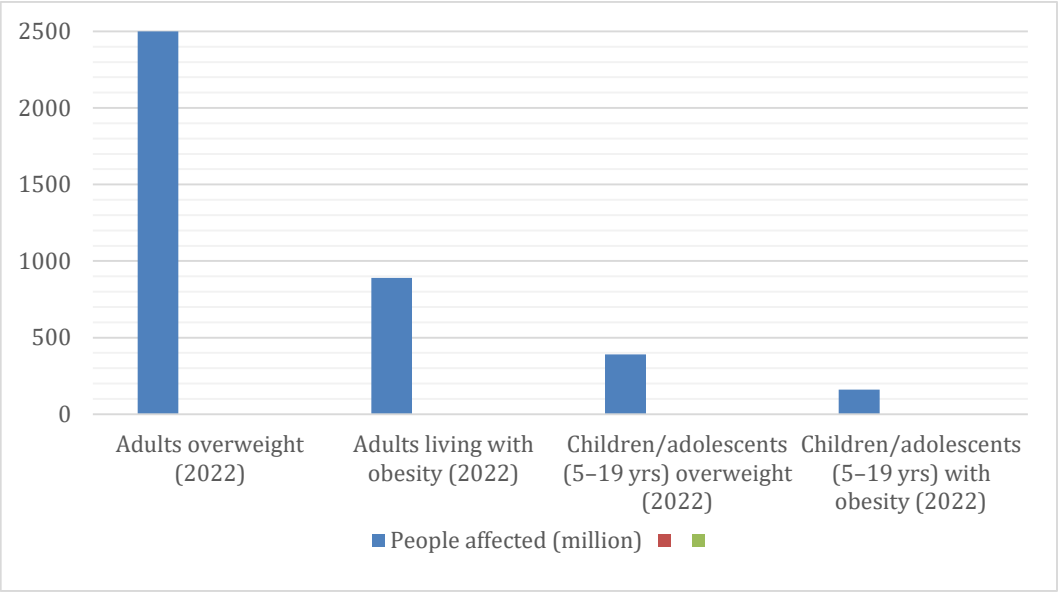

Figure 3. Global Burden of Overweight and Obesity, 2022

This is not evenly distributed and is being seen more and more in LMICs in the process of nutritional transition, exacerbating the challenge of equitable access to the more effective [10], but much more expensive, incretin-based pharmacotherapies mentioned below.

3.2 The Pharmacology of Antioxidant Drug Classes

3.2.1 The Incretin System as a Pharmacological Target

The incretin hormones GLP-1 and GIP, released from intestinal L-cells and K-cells after food ingestions, respectively, exert central appetite-suppressing and peripheral metabolic effects, both by stimulating specific receptors in hypothalamus/brainstem, and in peripheral tissues such as the pancreas, stomach, and adipose tissue. Figure 4 shows this pathway and compares the path of action of two drugs that are in development to treat obesity: semaglutide, a selective GLP-1 receptor agonist and tirzepatide, a dual receptor agonist for GLP-1 and GIP, which is thought to achieve more weight loss due to complementary, but not fully overlapping, receptor distribution in regions of the brain involved in appetite regulation [11].

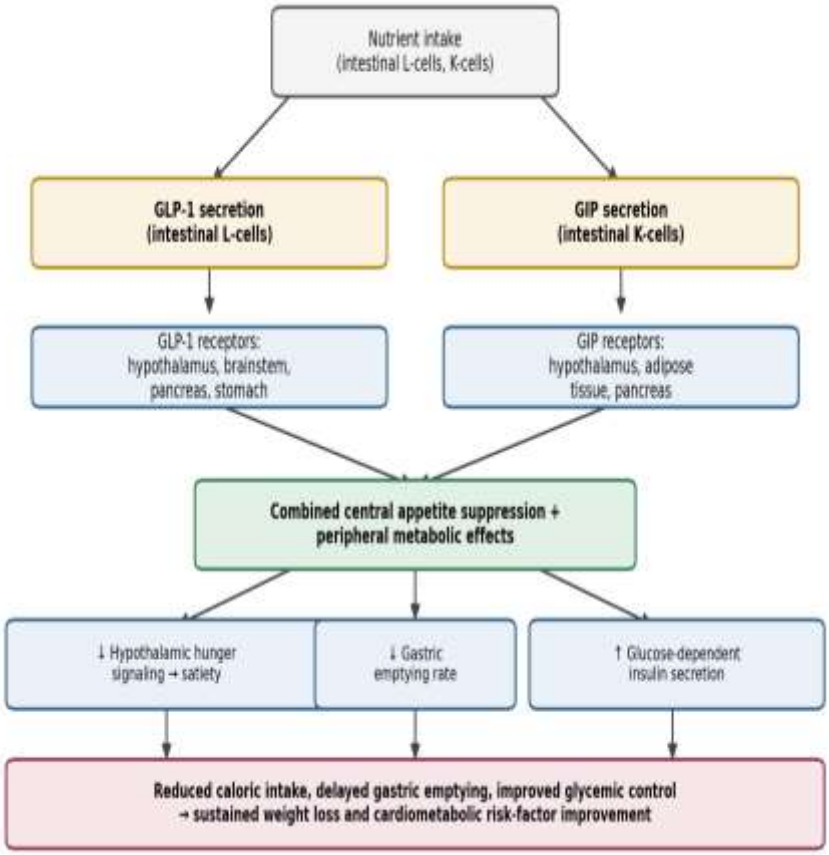

Figure 4. The Incretin (GLP-1/GIP) System and Its Role in Appetite Regulation and Weight Loss Pharmacotherapy

3.2.2 Comparative Pharmacology of the Major Drug Classes

Table 2 provides a summary of the mechanism of action, representative agents, and typical efficacy of the major classes of anti-obesity drugs used or recently used clinically. The activity of Orlistat is to block the intestinal uptake of fats from the diet by about 30% by blocking gastric and pancreatic lipases. The combination of phentermine and topiramate is a sympathomimetic appetite suppressant and an anticonvulsant with incompletely known central appetite-suppressing effects [12]. Naltrexone-bupropion is a combination drug that blocks opioid receptors and increases the levels of the neurotransmitters dopamine and norepinephrine to inhibit the circuits in the hypothalamus that regulate appetite and the mesolimbic reward pathway that is involved in hedonic eating. Liraglutide 3.0mg is a once-daily GLP-1

receptor agonist which was the first incretin-based agent to be approved specifically for chronic weight management, and has since been outperformed by once weekly 2.4mg of semaglutide and tirzepatide [13].

Table 2. Comparative Pharmacology of Major Anti-Obesity Drug Classes

Drug Class	Representative Agent	Mechanism of Action	Typical Placebo-Subtracted Weight Loss	Principal Adverse Effects
Lipase inhibitor	Orlistat	Inhibits gastric/pancreatic lipase, reducing intestinal fat absorption by ~30%	2–4 percentage points	Steatorrhea, fecal urgency/incontinence, fat-soluble vitamin malabsorption
Sympathomimetic /anticonvulsant combination	Phentermine-topiramate ER	Appetite suppression via noradrenergic (phentermine) and GABAergic/carbonic-anhydrase (topiramate) mechanisms	7–9 percentage points	Insomnia, dry mouth, paresthesia, teratogenicity (topiramate), contraindicated in cardiovascular disease
Opioid antagonist/antidepressant combination	Naltrexone-bupropion SR	Modulates hypothalamic POMC neurons and mesolimbic reward pathway	4–5 percentage points	Nausea, headache, insomnia, contraindicated with uncontrolled hypertension or seizure disorder
GLP-1 receptor agonist (daily)	Liraglutide 3.0 mg	Selective GLP-1 receptor agonism	4–5 percentage points	Nausea, vomiting, diarrhea (dose-dependent); rare pancreatitis
GLP-1 receptor agonist (weekly)	Semaglutide 2.4 mg	Selective GLP-1 receptor agonism, long-acting formulation	12–13 percentage points	Nausea, vomiting, constipation, gallbladder disease
Dual GIP/GLP-1 receptor co-agonist	Tirzepatide (5–15 mg)	Combined GIP and GLP-1 receptor agonism	13–18 percentage points (dose-dependent)	Nausea, vomiting, diarrhea; generally dose-dependent and transient

4. RESULTS AND DISCUSSION

4.1 Landmark Randomized Trial Evidence

4.1.1 Orlistat — XENDOS, a Long-Term Legacy Agent Trial

[14] In the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial, 3,304 people with obesity were randomly assigned to orlistat or placebo, for 4 years, plus lifestyle changes [15]. In the main orlistat efficacy trials, pooled analyses of the main trials show that orlistat led to a percentage weight loss of about 2–4 percentage points above that observed with placebo at 1 year, with or without orlistat.

4.1.2 Conquer Trial: Phentermine-Topiramate

The CONQUER trial compared the efficacy of phentermine-topiramate extended-release to placebo in a randomized trial of patients with obesity and ≥2 weight-related comorbidities. Among the largest effect sizes reported for a non-incretin-based agent was mean weight loss of 10.9% after 1 year vs 1.6% with placebo, at the highest approved dose (15 mg/92 mg) [16].

4.1.3 Naltrexone-Bupropion — The COR-I Trial

[17] The mean weight loss for the COR-I (Contrave Obesity Research-I) trial was 5.4% in the naltrexone-bupropion sustained-release group after 56 weeks, compared with 1.3% in the placebo group, which means that this combination is a moderately effective agent with a different profile of adverse effects than the sympathomimetic or incretin-based agents.

4.1.4 Step 1 — Semaglutide 2.4 mg

The Semaglutide Treatment Effect in People with Obesity (STEP 1) study enrolled 1,961 people with obesity or overweight and at least one weight-related comorbidity who were randomized to receive semaglutide 2.4 mg subcutaneous once weekly with lifestyle intervention or placebo with lifestyle intervention for 68 weeks [18]. Mean weight loss was greater with semaglutide (−14.9%) than with placebo (−2.4%), and 86.4% of the participants who received semaglutide lost at least 5% of their body weight, compared with 31.5% of those who received placebo.

4.1.5 Surmount-1 — Tirzepatide

SURMOUNT-1 enrolled 2,539 adults with obesity or overweight and with at least a weight-related complication at baseline, and randomized them to receive tirzepatide 5 mg, 10 mg, 15 mg, or placebo once a week for 72 weeks. The mean weight change was −15.0% (5 mg), −19.5% (10 mg) and −20.9% (15 mg) versus −3.1% (placebo); the greatest pharmacological effect size reported so far in a placebo-controlled obesity trial with >20% weight loss for more than 50% of patients in the higher-dose groups [19].

4.1.6 Surmount-5 — Head-to-Head Comparison

In the SURMOUNT-5 trial, tirzepatide was directly compared to tirzepatide at the MTDs with semaglutide for 72 weeks in 751 adults with obesity who were not diabetic. Tirzepatide resulted in significantly more weight loss than semaglutide (20.2% vs. 13.7%, $p<0.001$), and caused more weight loss than semaglutide did in terms of waist circumference reduction, representing the first direct comparison between the efficacy of these two incretin-based drugs [20].

4.1.7 Select — Cardiovascular Outcomes Independent of Diabetes

The SELECT trial enrolled 17,604 adults aged 45 years or older, who had a BMI ≥27 kg/m^2 and had established cardiovascular disease, but no diabetes, and randomized them to semaglutide 2.4 mg or placebo. The primary composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) was lower in the semaglutide group compared with the placebo group over a mean follow-up of 34.2 months: 6.5% versus 8.0% (HR 0.80, 95% CI 0.72–0.90, $p<0.001$); this 20% relative risk reduction was the first to be demonstrated in a population defined by obesity and cardiovascular disease, but not by diabetes, and established the role of incretin-based weight loss as a cardiovascular benefit.

4.1.8 Determine and Synthesize Effect Sizes

Figure 1 summarizes the mean percentage weight loss achieved with active drug and placebo across the six trials described above.

Table 3. Landmark Randomized Trials in Anti-Obesity Pharmacotherapy

Trial (Drug)	Year	N	Duration	Population	Primary Outcome	Result
XENDOS (orlistat)	2004	3,304	4 years	Obesity	Body weight change	−5.8 kg vs. −3.0 kg (placebo)
CONQUER (phentermine-topiramate)	2011	2,487	1 year	Obesity + ≥2 comorbidities	Body weight change	−10.9% vs. −1.6% (placebo)
COR-I (naltrexone-bupropion)	2010	1,742	56 weeks	Obesity	Body weight change	−5.4% vs. −1.3% (placebo)
STEP 1 (semaglutide 2.4 mg)	2021	1,961	68 weeks	Obesity/overweight + comorbidity	Body weight change	−14.9% vs. −2.4% (placebo)
SURMOUNT-1 (tirzepatide)	2022	2,539	72 weeks	Obesity/overweight + complication	Body weight change	−20.9% (15 mg) vs. −3.1% (placebo)
SURMOUNT-5 (tirzepatide vs. semaglutide)	2025	751	72 weeks	Obesity, no diabetes	Body weight change	−20.2% vs. −13.7%
SELECT (semaglutide, CV outcomes)	2023	17,604	34.2 months (mean)	Obesity/overweight + established CVD, no diabetes	CV death, MI, or stroke	HR 0.80 (0.72–0.90)

4.1.9 Adverse Effects and Safety Monitoring

Table 4. Safety Profile and Recommended Monitoring for Anti-Obesity Pharmacotherapy

Drug Class	Key Adverse Effects	Recommended Monitoring
Orlistat	Steatorrhea, fecal urgency, fat-soluble vitamin deficiency	Consider fat-soluble vitamin supplementation; counsel on low-fat diet to reduce GI effects
Phentermine-topiramate	Insomnia, dry mouth, cognitive effects, teratogenicity	Pregnancy test before initiation and monthly during treatment (topiramate teratogenicity); blood pressure and heart rate
Naltrexone-bupropion	Nausea, headache, insomnia, seizure risk	Blood pressure; avoid in uncontrolled hypertension or seizure disorder history
GLP-1 receptor agonists (liraglutide, semaglutide)	Nausea, vomiting, diarrhea (dose-dependent, usually transient); rare pancreatitis, gallbladder disease	Gradual dose titration; avoid in personal/family history of medullary thyroid carcinoma or MEN2
GIP/GLP-1 co-agonist (tirzepatide)	Nausea, vomiting, diarrhea; generally similar tolerability profile to GLP-1 monotherapy at equivalent titration pace	Gradual dose titration per labeled schedule; same thyroid-malignancy precaution as GLP-1 agents

4.1.10 Patient Selection and Eligibility Criteria

Table 5. Patient Selection Criteria for Pharmacotherapy

Criterion	Threshold
BMI-based eligibility (no comorbidity)	≥30 kg/m^2
BMI-based eligibility (with comorbidity)	≥27 kg/m^2 with ≥1 weight-related comorbidity (hypertension, dyslipidemia, T2DM, obstructive sleep apnea)
Prior lifestyle intervention	Generally expected, though pharmacotherapy may be initiated concurrently with lifestyle intervention rather than strictly sequentially
Early response threshold (typical)	≥5% weight loss by 12–16 weeks to support continuation, per labeling for several agents
Bariatric/metabolic surgery referral threshold	BMI ≥40, or ≥35 with serious obesity-related comorbidity, especially with inadequate pharmacological response
Key contraindications (GLP-1/GIP agents)	Personal/family history of medullary thyroid carcinoma, MEN2 syndrome
Key contraindications (phentermine-topiramate)	Pregnancy, uncontrolled hypertension, hyperthyroidism, glaucoma

4.1.11 Integrated Treatment Algorithm

Figure 5 synthesizes the evidence and selection criteria discussed above into a stepwise pharmacotherapy algorithm.

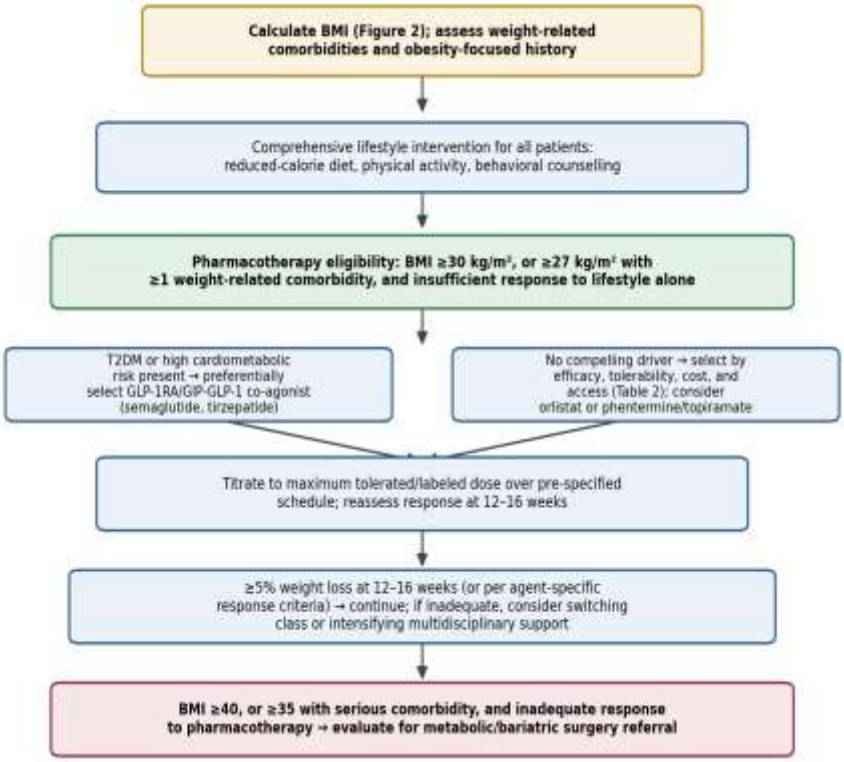

Figure 5. Integrated Treatment Algorithm for Pharmacological Management of Obesity

One key pharmacological principle of this algorithm, and more recently highlighted in modern obesity medicine, is that these drugs are used for the treatment of a chronic disease and do not provide a permanent cure: Similarly, multiple studies, such as the extension of STEP 1 and SURMOUNT-4, have shown that the majority of weight lost when these medications are discontinued is regained within about a year.

4.1.12 Discussion

The evidence presented in this trial review shows that over the past two decades or so, the potential weight loss effects of drugs have risen by about 5-fold, from 2–4% on orlistat to 17–19% placebo-subtracted on tirzepatide 15 mg. The effect of this degree of change is not incremental, but rather brings mean weight loss to levels that were formerly seen after specific bariatric surgeries, and now takes an active role in the overall treatment strategy for severe obesity (Figure 5) along with the elimination of the traditional efficacy gap between medical and surgical treatment.

The findings of SELECT trial are particularly relevant to the pharmacology and the clinical results of incretins, namely that the benefit of incretin-based weight loss is not limited to measures of glycemia or body parameters, but is true for major adverse cardiovascular events, which until now have only been seen in diabetes-specific trials with GLP-1 receptor agonists. This discovery provides a justification for thinking about using a semaglutide for appropriate patients with obesity and cardiovascular disease, regardless of their diabetes status, and applies the same individualized risk: benefit and access considerations as are used with any other long-term medication. The SURMOUNT-1 trial and the direct-to-head SURMOUNT-5 trial demonstrated that tirzepatide therapy resulted in greater weight loss compared to GLP-1 monotherapy, which may be explained by the mechanistic distinction between GLP-1 monotherapy and dual GIP/GLP-1 co-agonism (Figure 4) and suggests multi-receptor incretin co-agonism as a potential therapeutic pathway for developing incretin drugs in the future.

4.1.13 Limitations

This is a narrative rather than a systematic review and no formal meta-analytic pooling or risk of-bias assessment were done. It is important to note that the weight loss percentages are not directly comparable among trials (Table 3 and Figure 1) as the trials varied in duration (56 weeks to 4 years), in population, and in the intensity of the background lifestyle interventions provided, and that these estimates are trial-specific, and should not be interpreted as an efficacy ranking directly between the two agents in this review—the SURMOUNT-5 head-to-head trial is the only direct comparative evidence available between two agents included in this review. The long-term (more than 2-4 years) safety and efficacy data of the incretin-based agents are still less than that of the more established agents like orlistat, which has an extended safety profile of more than 10 years. Incretin based therapy medications were not included in this pharmacological review, as they are significantly more expensive than legacy therapy drugs in most health systems, and the role of the psychosocial and weight-stigma aspects of obesity management went beyond the scope of this review.

5. CONCLUSION

In the past decade, pharmacological obesity treatments have evolved from the old-fashioned agents that achieve only several percent weight loss to drugs with incretin activity that can bring about a mean weight loss of 15-20%, of which the dual GIP/GLP-1 co-agonist tirzepatide is currently the most effective approved treatment and semaglutide is also shown to reduce cardiovascular events independent of its diabetogenic activity. Obesity pharmacotherapy should be approached and managed as a chronic disease treatment, with the expectation that it will need to be used consistently to maintain its effects and should be viewed as part of a multi-specialty approach to obesity intervention (including lifestyle intervention, drug selection based on comorbidities, and surgical referral, if appropriate). Access to this rapidly changing pharmacological "armamentarium" is one of the greatest opportunities for improving equitable and affordable access to care today in the field of chronic disease prevention and management.

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Authors Contribution Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Mosrur Ahmed	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	

C: **C**onceptualisation
M: **M**ethodology
So: **So**ftware
Va : **Va**lidation
Fo: **Fo**rmal analysis
I: **I**nvestigation
R: **R**esources
D: **D**ata Curation
O: Writing-**O**riginal Draft
E: Writing-Review & **E**diting
Vi: **Vi**sualisation
Su: **Su**pervision
P: **P**roject administration
Fu: **F**unding acquisition

Conflict of Interest Statement

The authors declare no conflict of interest regarding the publication of this article.

Informed Consent

Not applicable. This article is a narrative review based on previously published studies and does not involve any experiments on human participants.

Ethical Approval

Not applicable. Ethical approval was not required for this study as it is a narrative review of existing literature and does not involve human or animal subjects.

Data Availability

Data sharing does not apply to this article as no new data were generated or analysed during the current study.

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