Pharmacological Management of Obesity: An Evidence-Based Review of Emerging Anti-Obesity Drugs and Their Clinical Applications

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DOI: https://doi.org/10.51244/IJRSI.2026.1307000300

Received: 05 August 2026; Accepted: 10 August 2026; Published: 15 August 2026

ABSTRACT

Obesity is now recognized as a chronic, relapsing neurohormonal disease rather than a failure of willpower, yet effective pharmacological treatment has only recently become available. The last decade has witnessed a revolution driven by gut-derived incretin hormones. This review provides a comprehensive overview of emerging anti-obesity drugs, from molecular mechanism to clinical application and future outlook. Semaglutide and tirzepatide exert their effects through central appetite regulation, delayed gastric emptying, and improved insulin sensitivity. In clinical trials, they have achieved unprecedented weight loss of up to 20.9%, with a substantial proportion of patients reaching ≥15% reduction in body weight. Importantly, cardiovascular outcome data now support a role for these drugs in risk reduction, with semaglutide showing significant reductions in MACE in high-risk patients with obesity. The safety profile is favorable, dominated by mild to moderate nausea and gastrointestinal symptoms that wane over time. Despite efficacy, major challenges persist. Treatment costs exceed $1000 per month in many regions, access is inequitable, and discontinuation leads to regain of approximately two-thirds of lost weight within one year. Novel agents in development aim to address these gaps. Oral GLP-1 receptor agonists and triple agonists targeting GIP, GLP-1, and glucagon receptors promise greater convenience and efficacy. Concurrently, advances in AI and digital biomarkers may enable precision prescribing and proactive dose adjustment. Ultimately, the integration of these new pharmacotherapies with lifestyle intervention and behavioral support represents the future standard of care for obesity.

Keywords: Semaglutide and tirzepatide, Gastrointestinal, GIP, GLP-1, Pharmacotherapies

INTRODUCTION

Obesity has emerged as one of the most pressing public health challenges of the 21st century, affecting over 1 billion people worldwide and contributing to more than 4 million deaths annually (WHO, 2024). Far beyond a disorder of energy balance, obesity is now recognized as a chronic, relapsing, neurohormonal disease that drives insulin resistance, dyslipidemia, hypertension, cardiovascular disease, and several cancers (Powell-Wiley et al., 2021). The economic burden is equally staggering, with obesity-related healthcare costs exceeding $2 trillion globally per year (Tremmel et al., 2017). For decades, the management of obesity relied predominantly on lifestyle modification, with pharmacotherapy playing a marginal role. Early anti-obesity drugs such as phentermine, orlistat, and lorcaserin produced only modest weight loss of 5–10% and were limited by safety concerns or poor tolerability (Khera et al., 2016).

Consequently, pharmacological treatment was underutilized, and clinical guidelines prioritized diet, exercise, and bariatric surgery as the mainstays of care. This landscape has been fundamentally transformed in the last 3 years by the advent of incretin-based therapies. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as semaglutide and dual GIP/GLP-1 receptor agonists like tirzepatide have demonstrated unprecedented mean weight reductions of 15–21% in phase 3 trials (Wilding et al., 2021; Jastreboff et al., 2022). Beyond weight loss, the SELECT trial established that semaglutide reduces major adverse cardiovascular events by 20% in patients

with obesity and established cardiovascular disease, repositioning these agents as cardiometabolic therapies (Lincoff et al., 2023).

The FDA and EMA have responded with accelerated approvals, and clinical uptake has surged worldwide. Despite this progress, critical gaps persist in the literature. Existing reviews tend to focus on a single drug class or trial, with no comprehensive synthesis that maps the entire therapeutic continuum from mechanism to long-term outcomes (Singh et al., 2023). Most publications emphasize efficacy endpoints such as percent weight loss, but provide limited guidance on real-world implementation, cost-effectiveness, and management of weight regain after discontinuation (Rubino et al., 2023). The majority of trial data are derived from high-income, predominantly Caucasian populations, raising concerns about generalizability to diverse ethnic groups and resource-limited settings including India and other LMICs where the obesity burden is rising fastest (Misra et al., 2022).

Additionally, the role of emerging agents such as oral GLP-1 RAs, triple GIP/GLP-1/glucagon agonists, and AI-driven precision dosing remains poorly defined in current reviews. Given these lacunae, there is an urgent need for an updated, evidence-based review that critically evaluates emerging anti-obesity pharmacotherapies across mechanisms, clinical efficacy, cardiovascular outcomes, safety, and implementation challenges. This review aims to address that gap by providing a clinically oriented synthesis of current data, identifying barriers to equitable access, and outlining future directions for integrating pharmacotherapy into comprehensive obesity management.

Pathophysiology of Obesity: Rationale for Pharmacotherapy

Obesity is no longer viewed simply as a consequence of excess caloric intake and sedentary behaviour. It is now understood as a complex, chronic, and relapsing neurohormonal disease involving dysregulation of appetite, energy homeostasis, and reward circuitry in the central nervous system (Powell-Wiley et al., 2021). The hypothalamus integrates peripheral signals such as leptin, insulin, ghrelin, and gut-derived incretins to regulate hunger and satiety. In obesity, this signaling becomes resistant and maladaptive, leading to persistent hyperphagia despite adequate energy stores. Furthermore, metabolic adaptation following weight loss results in reduced resting energy expenditure and increased hunger hormones, which explains why lifestyle interventions alone have high failure rates beyond 12 months.

Gut hormones have emerged as critical therapeutic targets. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are secreted post-prandially and act on receptors in the brainstem and hypothalamus to promote satiety, slow gastric emptying, and enhance insulin secretion in a glucose-dependent manner. In individuals with obesity, post-prandial secretion of these incretins is blunted, contributing to impaired satiety and glycemic control. This pathophysiological understanding provides a strong biological rationale for pharmacological augmentation of incretin pathways. Rather than relying solely on willpower, medications that mimic or enhance these hormones can correct the underlying hormonal deficit. This paradigm shift is essential because it reframes obesity as a treatable disease requiring long-term medical management, similar to hypertension or diabetes, rather than an acute behavioral problem (Powell-Wiley et al., 2021).

Historical Perspective and Limitations of Older Anti-Obesity Drugs

For nearly two decades, pharmacotherapy for obesity remained stagnant and clinically underutilized. The available agents included orlistat, phentermine, and combination therapies such as phentermine/topiramate and naltrexone/bupropion. Meta-analyses showed that these drugs produced only modest weight loss, typically in the range of 5–10% of baseline body weight over one year (Khera et al., 2016). While this degree of loss can confer some metabolic benefit, it rarely achieved the ≥15% threshold associated with resolution of type 2 diabetes or meaningful improvement in obstructive sleep apnea. More importantly, safety concerns severely limited their use.

Lorcaserin was withdrawn due to cancer risk and sibutramine because of increased cardiovascular events. Phentermine is approved only for short-term use due to sympathomimetic effects, and topiramate carries risks of cognitive dysfunction and teratogenicity. Orlistat, though safe, is associated with unpleasant gastrointestinal

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

side effects and poor adherence. Consequently, both patients and physicians were reluctant to initiate pharmacotherapy, and clinical guidelines continued to prioritize lifestyle modification and bariatric surgery as the main interventions (Khera et al., 2016).

This created a major treatment gap. With global obesity prevalence exceeding 1 billion people and causing over 4 million deaths annually (World Health Organization, 2024), and lifestyle programs showing <5% sustained success, there was no effective, scalable medical option for the majority of patients. The economic burden is equally staggering, with obesity-related healthcare costs exceeding $2 trillion globally per year (Tremmel et al., 2017). The absence of drugs with durable efficacy meant that obesity was not treated with the same urgency as other chronic diseases.

Emerging Incretin-Based Anti-Obesity Pharmacotherapies

GLP-1 Receptor Agonists

The introduction of high-dose GLP-1 receptor agonists marked the beginning of a new era in obesity treatment. Semaglutide 2.4 mg once weekly was evaluated in the STEP clinical program. In STEP 1, 1961 adults without diabetes achieved a mean weight loss of 14.9% at 68 weeks compared to 2.4% with placebo (Wilding et al., 2021). Nearly 70% of participants lost ≥10% and 32% lost ≥20% of body weight. Weight loss was accompanied by significant reductions in waist circumference, systolic blood pressure, and inflammatory markers. STEP 4 demonstrated that continued treatment is necessary to maintain weight loss, as switching to placebo led to weight regain of 6.9%. STEP 8 showed semaglutide was superior to daily liraglutide 3.0 mg, with 2.4 times greater weight loss (Rubino et al., 2023).

The most transformative data came from SELECT, a cardiovascular outcomes trial in 17,604 adults with obesity and established cardiovascular disease but without diabetes (Lincoff et al., 2023). Over 40 months, semaglutide reduced the risk of major adverse cardiovascular events by 20% compared to placebo, independent of weight loss magnitude. This established GLP-1 RAs as the first anti-obesity drugs with proven cardioprotective effects, fundamentally changing their clinical positioning (Lincoff et al., 2023).

Dual GIP/GLP-1 Receptor Agonists

Tirzepatide is a novel dual agonist of GIP and GLP-1 receptors. The synergistic action is hypothesized to enhance insulin secretion, improve insulin sensitivity, and produce greater central appetite suppression than GLP-1 alone. In SURMOUNT-1, 2539 adults with obesity but without diabetes received tirzepatide 5, 10, or 15 mg weekly (Jastreboff et al., 2022). At 72 weeks, mean weight reductions were 15.0%, 19.5%, and 20.9% respectively, compared to 3.1% with placebo. Over 50% of participants on the highest dose lost ≥20% of body weight, a magnitude previously only seen with bariatric surgery. SURMOUNT-2 in patients with type 2 diabetes also showed ∼15% weight loss and significant HbA1c reduction (Jastreboff et al., 2022). The metabolic benefits extended beyond weight. Tirzepatide improved lipid profiles, blood pressure, and liver enzymes. The FDA approved tirzepatide for chronic weight management in 2023. The magnitude of efficacy has led many experts to consider dual agonists as first-line pharmacotherapy for patients requiring >15% weight loss.

Pipeline and Future Agents

The pipeline is expanding rapidly to address limitations of injectable peptides. Oral non-peptide GLP-1 receptor agonists such as orforglipron and danuglipron are in late-stage development. Triple agonists targeting GIP, GLP-1, and glucagon receptors are also being tested. Retatrutide demonstrated up to 24% weight loss in phase 2, the highest reported to date. CagriSema, a combination of long-acting amylin analog cagrilintide and semaglutide, is in phase 3. Beyond drugs, AI-driven tools are being tested to predict treatment response and optimize dosing (Singh et al., 2023). These innovations aim to move obesity care toward precision medicine. However, long-term safety data and real-world effectiveness in diverse populations remain key unanswered questions.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

Table 1. Comparison of Approved and Emerging Anti-Obesity Pharmacotherapies

Drug	Dose	Mechanism of Action	Route	Mean % Weight Loss	Key Trial
Semaglutide	2.4 mg weekly	GLP-1 receptor agonist	Subcutaneous	14.9%	STEP 1 (Wilding et al., 2021)
Tirzepatide	15 mg weekly	Dual GIP/GLP-1 receptor agonist	Subcutaneous	20.9%	SURMOUNT-1 (Jastreboff et al., 2022)
Liraglutide	3.0 mg daily	GLP-1 receptor agonist	Subcutaneous	7.4%	SCALE (Khera et al., 2016)
Phentermine/Topiramate ER	15/92 mg daily	Sympathomimetic + GABA modulation	Oral	9.8%	CONQUER (Khera et al., 2016)
Naltrexone/Bupropion	32/360 mg daily	Opioid + DA/NE antagonist	Oral	6.1%	COR (Khera et al., 2016)
Orlistat	120 mg TID	Pancreatic lipase inhibitor	Oral	3.5%	Meta-analysis (Khera et al., 2016)
Retatrutide	12 mg weekly	Triple GIP/GLP-1/Glucagon agonist	Subcutaneous	Up to 24%	Phase 2 (Singh et al., 2023)
Orforglipron	45 mg daily	Non-peptide GLP-1 receptor agonist	Oral	~14%	Phase 3 Ongoing

Note: % Weight Loss = Placebo subtracted. TID = Three times daily. ER = Extended Release

Safety Profile and Implementation Challenges

The safety profile of incretin-based therapies is generally favorable but requires clinical vigilance. The most common adverse events are gastrointestinal: nausea, vomiting, diarrhea, and constipation, occurring in 30–50% of patients during dose escalation. These are usually mild to moderate and decrease over 4–8 weeks. Gallbladder-related disorders and acute pancreatitis have been reported at low rates. The major implementation challenges are systemic. Cost remains the biggest barrier, with monthly prices exceeding $1000 in many countries, and insurance coverage is inconsistent. In LMICs including India, out-of-pocket costs make these drugs inaccessible to most patients, despite the rapidly rising obesity burden in South Asians (Misra et al., 2022). This creates a profound equity issue. Another critical issue is weight regain. Data show that discontinuation of semaglutide or tirzepatide leads to regain of approximately two-thirds of lost weight within one year, accompanied by reversal of metabolic benefits (Rubino et al., 2023). This reinforces that obesity is a chronic disease requiring lifelong therapy. Finally, trial populations have been predominantly White and from high-income countries. Data in South Asians, who develop metabolic complications at lower BMI, are limited, raising questions about generalizability (Misra et al., 2022).

CONCLUSION

The landscape of obesity pharmacotherapy has been transformed by incretin-based medications. This review highlights that obesity is a complex neurohormonal disease, not merely a lifestyle disorder, which provides a strong rationale for targeted pharmacological intervention. Older anti-obesity drugs were limited by modest efficacy and safety concerns, leaving a major treatment gap for over a billion people worldwide. The emergence

of high-dose GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists marks a new era. Clinical trials demonstrate that semaglutide and tirzepatide achieve 15-21% weight loss, with semaglutide also showing significant cardiovascular risk reduction in patients with established CVD. These magnitudes of weight loss were previously only attainable with bariatric surgery. The pipeline of oral GLP-1 RAs, triple agonists, and combination therapies promises even greater efficacy and convenience.

However, several challenges remain. Gastrointestinal adverse effects, though generally mild, require careful dose titration. The high cost of these medications creates profound inequity, particularly in LMICs like India where the obesity burden is rising rapidly among South Asians who develop complications at lower BMI. Weight regains upon discontinuation underscores that obesity requires chronic disease management. Additionally, current trial data lack diversity, limiting generalizability. In conclusion, emerging anti-obesity drugs offer unprecedented clinical potential. To maximize their impact, healthcare systems must address issues of affordability, access, and long-term monitoring. Future research should prioritize real-world effectiveness, safety in diverse populations, and AI-driven precision approaches. Treating obesity with the same rigor as diabetes and hypertension is no longer optional but essential.

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