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Review Article

Modern pharmacotherapy of obesity: molecular mechanisms, clinical efficacy and future therapeutic directions

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ABSTRACT

Obesity is now recognized as a chronic, relapsing, neuroendocrine disease characterised by dysregulation of appetite, impaired energy homeostasis and complex metabolic disturbances. Traditional lifestyle interventions, although foundational, often fail to achieve durable weight reduction because of adaptive biological mechanisms that favour weight regain. Over the past two decades, pharmacotherapy has evolved from modestly effective agents such as orlistat and sympathomimetics to highly potent incretin-based and multi-hormonal peptide therapies capable of inducing double-digit percentage weight loss. This narrative review summarizes contemporary anti-obesity pharmacotherapy with emphasis on molecular mechanisms, pivotal clinical trial data and future therapeutic directions. Literature was identified using PubMed, Scopus and Embase with search terms including "obesity pharmacotherapy", "orlistat", "phentermine", "liraglutide", "semaglutide", "tirzepatide", "cagrilintide" and "retatrutide". Classical agents such as orlistat, phentermine–topiramate and naltrexone–bupropion typically achieve 3–10% weight loss but are limited by tolerability and safety concerns. GLP-1 receptor agonists (liraglutide and semaglutide) provide substantially greater weight reduction with clinically meaningful improvements in cardiometabolic risk factors. Dual GIP/GLP-1 receptor agonists such as tirzepatide have demonstrated unprecedented efficacy, with up to 22.5% mean weight loss in the SURMOUNT trials. Emerging agents including cagrilintide (amylin analogue) and triple agonists such as retatrutide (GIP/GLP-1/glucagon) are poised to redefine pharmacological obesity treatment. Modern pharmacotherapy for obesity therefore spans a spectrum from older agents with modest efficacy to next-generation multi-agonist peptides approaching bariatric surgery–level outcomes. Rational, individualised drug selection based on comorbidities, tolerability and accessibility will be central to optimising long-term outcomes.

Keywords: Obesity, Pharmacotherapy, GLP-1 receptor agonists, Tirzepatide, Semaglutide, Incretin, Amylin analogue, Dual agonists

INTRODUCTION

Obesity has evolved from being perceived as a behavioural or lifestyle-related condition to being recognised as a chronic, relapsing, biologically defended disease of energy regulation, with far-reaching clinical and societal consequences. By 2025, more than 650 million adults globally are living with obesity, with prevalence accelerating not only in high-income nations but also across low- and middle-income countries, including India.[1] This epidemiological transition has reinforced a critical shift in understanding: obesity is not a failure of individual willpower, but a disorder drivenby neuroendocrine dysregulation, maladaptive

metabolic signalling and altered central reward processing.[2]

In routine clinical practice, obesity functions as a dominant upstream driver of morbidity rather than a passive comorbidity. It substantially increases the lifetime risk of type 2 diabetes mellitus, hypertension, dyslipidaemia, atherosclerotic cardiovascular disease, metabolic dysfunction–associated steatotic liver disease, obstructive sleep apnoea, osteoarthritis and several malignancies.[1-11] Importantly, contemporary interventional data consistently demonstrate that even modest, sustained weight reduction of 5–10% yields disproportionate metabolic benefits, including improvements in glycaemic control, blood pressure, lipid parameters and systemic inflammation.[5,6] These observations validate obesity itself as a primary therapeutic target, rather than merely a risk modifier.

Physiologically, body weight is regulated by a tightly integrated neuroendocrine network centred within the hypothalamus, particularly the arcuate nucleus, which integrates peripheral signals from adipose tissue, pancreatic islets and the gastrointestinal tract.[2] Anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic neuropeptide-Y/agouti-related peptide (NPY/AgRP) neurons dynamically respond to hormonal cues such as leptin, insulin, ghrelin, peptide-YY and incretins.[2] In individuals with obesity, this system undergoes pathological recalibration. Leptin and insulin resistance, impaired gut–brain signalling and hypothalamic inflammation establish a higher biologically defended body weight, rendering sustained weight loss biologically difficult and strongly predisposing to weight regain after initial success.[13]

Beyond homeostatic regulation, feeding behaviour is also shaped by hedonic mechanisms involving the mesolimbic dopamine system. Chronic exposure to highly palatable, energy-dense foods alters reward sensitivity, reinforcing compulsive eating patterns and weakening satiety signalling.[2-14] From clinical experience, this interaction between metabolic drive and reward circuitry explains the marked inter-individual variability observed in both lifestyle and pharmacological weight-loss responses.

Lifestyle modification remains the foundation of obesity management and confers broad cardiovascular and metabolic benefits. However, long-term follow-up studies consistently demonstrate that diet and physical activity alone rarely achieve durable weight loss at a population level.[8-13] Compensatory reductions in resting energy expenditure, heightened hunger signalling and adaptive hormonal responses counteract weight loss efforts, reinforcing the concept of obesity as a chronic relapsing disease.[12] These biological realities underscore why pharmacotherapy is increasingly necessary not as a short-term adjunct, but as a long-term disease-modifying intervention.

Historically, pharmacological options for obesity were limited to agents targeting fat absorption or central appetite suppression, such as orlistat and sympathomimetic combinations. While these therapies demonstrated proof-of-concept efficacy, weight loss was modest and frequently constrained by tolerability, safety concerns or poor long-term adherence.[3,4] Consequently, pharmacotherapy was often viewed as secondary or temporary. This perspective has changed fundamentally over the past decade.

Advances in incretin biology and peptide engineering have reshaped the therapeutic landscape. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were the first agents to directly counter the neurohormonal drivers of obesity, producing sustained weight loss with consistent improvements in cardiometabolic risk factors.[5,6-16] Importantly, by 2023–2024, large cardiovascular outcome trials began to decisively alter the clinical positioning of these agents.

The SELECT trial demonstrated that semaglutide 2.4 mg significantly reduced major adverse cardiovascular events in individuals with overweight or obesity without diabetes, establishing—for the first time—that pharmacological weight loss can translate into hard cardiovascular outcome benefits independent of glycaemic control.[17] This finding represents a pivotal conceptual shift, reframing obesity pharmacotherapy not merely as cosmetic or metabolic management, but as cardiovascular risk–modifying therapy. In parallel, emerging data from dual-incretin programmes suggest that the magnitude and durability of weight loss may correlate with proportional reductions in cardiometabolic risk, although definitive cardiovascular outcome data for newer agents remain under active evaluation.

More recently, dual and multi-agonist peptides targeting combinations of GLP-1, glucose-dependent insulinotropic polypeptide (GIP), amylin and glucagon receptors have surpassed previous pharmacological efficacy thresholds. Agents such as tirzepatide and retatrutide have demonstrated average weight reductions of 20–25% in clinical trials, approaching outcomes historically achievable only through bariatric surgery.[7-9] These developments raise important clinical and ethical questions regarding treatment sequencing, duration of therapy and the evolving role of metabolic surgery in the era of highly effective pharmacotherapy.[15]

From a contemporary clinical standpoint, this represents a paradigm shift. Pharmacotherapy for obesity has transitioned from a supportive role to a central pillar of evidence-based disease management, with increasing justification for early initiation, long-term continuation and integration into cardiovascular prevention strategies.[10-17]As newer agents continue to emerge and long-term outcome data mature, the boundaries between obesity treatment, diabetes prevention and cardiovascular risk reduction are becoming increasingly blurred.

This narrative review synthesises current and emerging evidence on anti-obesity pharmacotherapy, with emphasis on molecular mechanisms, pivotal clinical trial outcomes and evolving therapeutic strategies that are redefining obesity treatment in 2025 and beyond.

METHODS

A narrative review methodology was adopted to provide a clinically oriented synthesis of contemporary pharmacotherapy for obesity. Relevant literature was identified through systematic searches of PubMed, Scopus, Embase and ClinicalTrials.gov up to the year 2024.[10,11] Search terms included "obesity pharmacotherapy", "anti-obesity drugs", "orlistat", "phentermine–topiramate", "naltrexone–bupropion", "liraglutide 3.0 mg", "semaglutide 2.4 mg", "tirzepatide", "cagrilintide" and "retatrutide".

Priority was given to high-quality evidence sources, including randomised controlled trials, large phase-2 and phase-3 clinical trials, systematic reviews, meta-analyses and major international clinical practice guidelines relevant to obesity management.[3,6,7,10,11]

Non-pharmacological interventions, animal studies without clear clinical applicability and isolated case reports were excluded. As the primary objective was to provide a practical and clinically usable narrative overview rather than a formal systematic review, no quantitative meta-analysis or structured risk-of-bias assessment was undertaken, in keeping with established approaches for narrative reviews.[11-15]

Pathophysiology of obesity relevant to pharmacotherapy

Hypothalamic regulation and leptin resistance

The arcuate nucleus (ARC) of the hypothalamus contains two principal neuronal populations that play a central role in appetite regulation and energy homeostasis: anorexigenic POMC/cocaine- and amphetamine-regulated transcript (CART) neurons and orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons.[2-12] Leptin secreted by adipocytes and insulin released from pancreatic β-cells normally suppress NPY/AgRP neuronal activity while stimulating POMC neurons, thereby promoting satiety and increasing energy expenditure.[2]

In individuals with obesity, leptin resistance develops as a consequence of impaired leptin transport across the blood–brain barrier, post-receptor signalling defects and hypothalamic inflammation.[12,13] This disruption results in persistent activation of orexigenic pathways despite elevated circulating leptin levels, establishing a higher biologically defended body weight and strongly favouring weight regain following weight loss.[12,13]

Reward circuitry and hedonic eating

Beyond homeostatic control, feeding behaviour is strongly influenced by hedonic mechanisms mediated through the mesolimbic dopamine system, particularly the ventral tegmental area and nucleus accumbens.[2] Highly palatable, energy-dense foods evoke robust dopaminergic responses, reinforcing food-seeking behaviour and conditioning reward pathways. In obesity, dysregulation of this reward circuitry contributes to compulsive eating and reduced sensitivity to satiety signals.[12]

Several anti-obesity pharmacological agents exert part of their effect through modulation of central reward pathways, either directly via monoaminergic mechanisms or indirectly through gut–brain hormonal signalling.[4-12] This interaction between homeostatic and hedonic systems partially explains inter-individual variability in treatment response.

Gut hormones and the incretin axis

Gut-derived hormones play a critical role in short- and long-term regulation of appetite and metabolism. Hormones such as glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), ghrelin, cholecystokinin (CCK) and peptide YY (PYY) convey nutrient-related signals from the gastrointestinal tract to central appetite centres.[5,6]

GLP-1 and GIP, collectively referred to as incretins, potentiate glucose-dependent insulin secretion, while GLP-1 additionally suppresses appetite, delays gastric emptying and enhances satiety.[5,6] Targeting this incretin axis has emerged as a cornerstone of modern obesity pharmacotherapy, forming the mechanistic basis for GLP-1 receptor agonists, dual GIP/GLP-1 agonists and emerging multi-agonist peptide therapies.[6-9]

Classical anti-obesity agents

Orlistat

Mechanism of action: Orlistat is a reversible inhibitor of gastric and pancreatic lipases, reducing the hydrolysis and intestinal absorption of dietary triglycerides by approximately 30% at therapeutic doses.[3] By acting peripherally within the gastrointestinal tract, orlistat does not exert central appetite-suppressing effects, distinguishing it from centrally acting anti-obesity agents.

Clinical efficacy: The XENDOS trial demonstrated that orlistat, when combined with lifestyle intervention, produced a mean weight loss of approximately 5–7 kg over 1–2 years and modestly reduced progression to type 2 diabetes mellitus in high-risk individuals.[3] Despite these benefits, the magnitude of weight loss achieved with orlistat is limited when compared with newer pharmacological therapies.

Adverse effects and limitations: Gastrointestinal adverse effects, including steatorrhoea, oily spotting, faecal urgency and flatulence, significantly impair long-term adherence.[3] Chronic use may result in fat-soluble vitamin deficiencies, necessitating supplementation. Overall, orlistat typically produces 3–5% placebo-subtracted weight loss, restricting its role to patients unable to access or tolerate more effective therapies.

Sympathomimetics and phentermine–topiramate

Phentermine is a centrally acting sympathomimetic agent that suppresses appetite through increased synaptic norepinephrine release in hypothalamic appetite centres.[4] While effective for short-term weight loss, its use is restricted in many regions because of concerns regarding cardiovascular effects, insomnia and abuse potential.

Phentermine–topiramate extended-release combines phentermine with topiramate, a drug that modulates γ-aminobutyric acid (GABA) and glutamatergic neurotransmission, enhancing satiety and reducing caloric intake.[4] In large phase-3 trials (EQUIP and CONQUER), high-dose phentermine–topiramate achieved mean weight loss of approximately 8–10% at one year.[4]

However, adverse effects such as paraesthesia, cognitive slowing, mood disturbances and teratogenic risk (orofacial clefts) necessitate careful patient selection, counselling and monitoring, particularly in women of reproductive age.[4]

Naltrexone–bupropion

The fixed-dose combination of naltrexone and bupropion targets the hypothalamic melanocortin system. Bupropion stimulates POMC neurons, while naltrexone blocks endogenous opioid-mediated autoinhibitory feedback, thereby amplifying anorexigenic signalling. Clinical trials demonstrate mean weight loss of approximately 5–8%, with additional benefits on eating behaviour and cravings.[10]

Adverse effects include nausea, headache and insomnia, and bupropion-associated seizure risk limits use in susceptible individuals. The combination is contraindicated in uncontrolled hypertension, seizure disorders and eating disorders.[10]

Overall, classical anti-obesity agents provide modest and variable weight loss and retain a limited role in selected patients, particularly where cost or access restricts the use of newer incretin-based therapies.[3,4-10]

Glp-1 receptor agonists

Liraglutide 3.0 mg

Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist initially developed for the treatment of type 2 diabetes mellitus and subsequently evaluated at higher doses for obesity management. It reduces appetite through central hypothalamic mechanisms, delays gastric emptying and enhances satiety.[5]

The SCALE Obesity and Prediabetes trial demonstrated that liraglutide 3.0 mg once daily produced a mean weight loss of approximately 8% of baseline body weight over 56 weeks, compared with 2.6% with placebo. In addition to weight reduction, liraglutide improved glycaemic control, blood pressure and lipid parameters, highlighting its metabolic benefits.[5]

Gastrointestinal adverse effects, particularly nausea and vomiting during dose escalation, are the most common limitations. Rare concerns include gallbladder disease and pancreatitis, although absolute risks remain low.[5]

Semaglutide 2.4 mg

Semaglutide is a highly potent GLP-1 receptor agonist with a prolonged half-life enabling once-weekly administration. The STEP clinical trial programme evaluated semaglutide 2.4 mg in individuals with overweight or obesity. In STEP-1, semaglutide achieved a mean placebo-subtracted weight loss of approximately 12.4 percentage points, corresponding to a total mean weight reduction of 14.9% at 68 weeks.[6]

A substantial proportion of participants achieved ≥10%, ≥15% and ≥20% weight loss, approaching outcomes previously associated with metabolic surgery in selected populations. Semaglutide also produced significant improvements in glycaemic indices, blood pressure and inflammatory markers.[6-16]

Adverse events are predominantly gastrointestinal and dose-dependent. Concerns regarding thyroid C-cell tumours arise primarily from rodent studies; human relevance remains unproven but warrants ongoing pharmacovigilance.[6]

Dual incretin agonists

Tirzepatide

Tirzepatide is a novel dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, designed to achieve superior metabolic and weight-loss effects compared with GLP-1 receptor agonism alone.[7-15] GIP receptor activation may enhance insulin sensitivity and adipocyte lipid handling, while synergistically amplifying GLP-1–mediated satiety.[15]

In the SURMOUNT-1 trial involving adults with obesity without diabetes, tirzepatide produced mean weight loss ranging from 15% to 21% across doses, with up to 22.5% reduction at the highest dose. Nearly all participants achieved ≥5% weight loss, and a majority achieved ≥20%, outcomes that rival those of bariatric surgery.[7]

The safety profile of tirzepatide is broadly similar to that of GLP-1 receptor agonists, with gastrointestinal events being the most frequent adverse effects. Long-term cardiovascular outcomes and durability of effect are under ongoing investigation.[7-15] These findings position tirzepatide as a landmark advancement in pharmacological obesity management.

Table 1: comparison of anti-obesity drugs.

Drug	Weight loss	Mechanism	Availability	Notes
Orlistat	3–5%	Lipase inhibitor	High	Low cost
Liraglutide	8–10%	GLP-1 RA	Medium	Daily dose
Semaglutide	12–15%	GLP-1 RA	Low	Weekly dose
Tirzepatide	15–22%	Dual agonist	Low	Highest efficacy

Table 2: Dosing and adverse effects.

Drug	Dose	Adverse events	Notes
Orlistat	120 mg TID	GI effects	Low-cost
Liraglutide	3 mg/day	Nausea	Metabolic benefits
Semaglutide	2.4 mg/week	GI symptoms	Highest efficacy

Table 3: Cost in India.

Drug	Cost/month	Affordability
Orlistat	₹800–1200	Affordable
Liraglutide	₹11,000–18,000	High
Semaglutide	₹16,000–22,000	Very high
Tirzepatide	Not launched	Very high

Emerging peptide therapies

Cagrilintide

Cagrilintide is a long-acting analogue of amylin, a hormone co-secreted with insulin by pancreatic β-cells. Amylin reduces food intake by delaying gastric emptying and promoting satiety through actions on brainstem and hypothalamic pathways. In phase-2 trials, once-weekly cagrilintide produced dose-dependent weight loss of approximately 6–10%.[8]

Combination therapy with semaglutide has demonstrated additive or synergistic effects, suggested complementary mechanisms and highlighted the potential of multi-hormonal strategies.[8]

Retatrutide and triple-agonist strategies

Retatrutide is a triple agonist targeting GIP, GLP-1 and glucagon receptors. While GLP-1 and GIP suppress appetite and enhance insulin secretion, glucagon receptor activation increases energy expenditure and promotes lipid oxidation. In a phase-2 trial, Retatrutide achieved up to 24% mean weight loss at 48 weeks, approaching or exceeding the lower range of bariatric surgery outcomes.[9]

Further multi-agonist peptides targeting combinations of incretins, glucagon and amylin are under active development.[9-15] These agents represent the cutting edge of obesity pharmacotherapy and may fundamentally reshape future treatment paradigms.

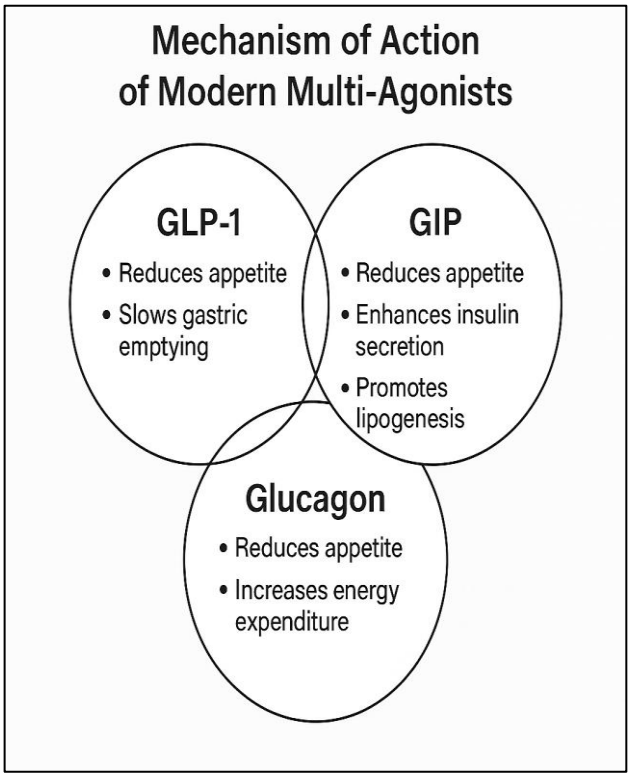

Figure 1: Mechanism of modern multi-agonists.

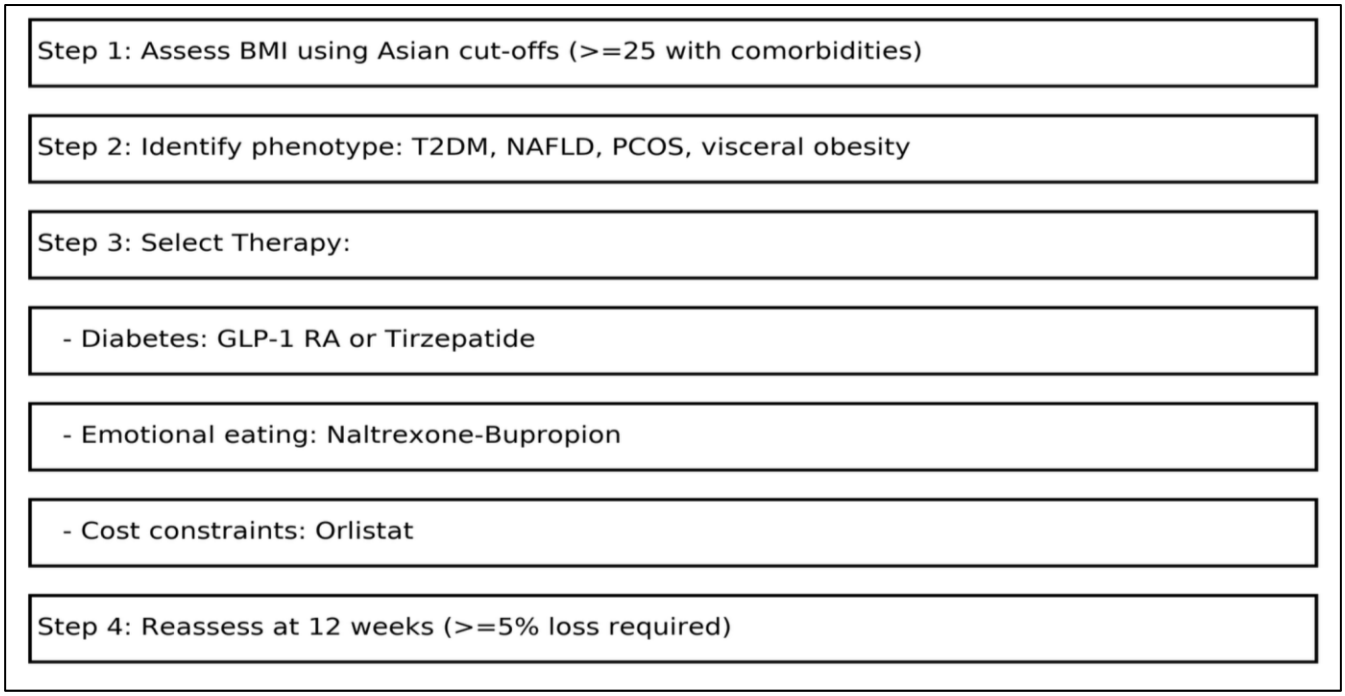

Figure 2: Clinical decision algorithm.

DISCUSSION

The pharmacological management of obesity has evolved from symptomatic appetite suppressants and peripheral lipase inhibitors to rationally designed peptide-based therapies targeting key neuroendocrine pathways regulating energy balance.[14,15] Classical agents such as orlistat, phentermine–topiramate and naltrexone–bupropion continue to have a role in selected patients, particularly where cost, accessibility or contraindications limit the use of modern injectable therapies.[3,4,10] However, their modest efficacy—typically resulting in 3–10% mean weight loss—limits their impact when compared with newer pharmacological options.[3,4]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), particularly semaglutide 2.4 mg, have demonstrated substantial and clinically meaningful weight reduction alongside consistent improvements in glycaemic control, blood pressure and other cardiometabolic risk factors.[5,6,16] Consequently, these agents are increasingly recommended as first-line pharmacological therapy for obesity in international clinical practice guidelines, especially in individuals with type 2 diabetes mellitus or established cardiovascular risk.[10,11]

The emergence of dual and triple incretin-based agonists represents a further paradigm shift. Agents such as tirzepatide and Retatrutide have exceeded previous pharmacological efficacy thresholds, achieving mean weight reductions of 20–25% in clinical trials.[7-9] These outcomes approach those traditionally associated with bariatric surgery and raise important questions regarding the future positioning of pharmacological versus surgical interventions in obesity management.[14] Nevertheless, long-term safety, durability of weight loss, optimal treatment duration and cost-effectiveness remain critical areas for ongoing investigation.[7-15]

Several practical considerations influence the clinical use of modern anti-obesity pharmacotherapy. Patient selection based on body mass index, comorbidities, previous weight-loss attempts and individual risk profiles is essential.^10 Route of administration remains an important determinant of acceptance, as most highly effective agents are injectable.[6,7] Cost and access pose substantial barriers in low- and middle-income countries, including India, where classical oral agents may remain more feasible for a large proportion of patients.[11] Finally, given the chronic nature of obesity, long-term treatment and maintenance strategies must be planned from initiation, as discontinuation of therapy is commonly associated with weight regain.[12,13]

In both Indian and global contexts, optimal obesity management requires integration of pharmacotherapy into multidisciplinary care models incorporating dietary modification, physical activity, behavioural interventions and, when appropriate, bariatric procedures.[11] Such an approach is essential to maximise long-term efficacy and sustainability of treatment outcomes.

CONCLUSION

Obesity is a chronic, biologically defended disease that requires sustained, multimodal management strategies. The pharmacotherapeutic landscape has advanced rapidly, with modern incretin-based and multi-agonist therapies

achieving levels of weight loss and metabolic improvement previously attainable only through bariatric surgery. GLP-1 receptor agonists such as liraglutide and semaglutide, dual GIP/GLP-1 agonists such as tirzepatide and emerging multi-agonist peptides including Cagrilintide-based combinations and Retatrutide represent a new era in obesity treatment.

Clinicians must develop familiarity with the mechanisms of action, clinical evidence, safety profiles and practical considerations of these therapies to deploy them effectively. Future research should focus on long-term outcomes, comparative effectiveness, optimal sequencing of therapies and strategies to improve affordability and access in resource-constrained settings.

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