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PHARMACOLOGY OF OBESITY AND METABOLIC DISEASES: CURRENT AND EMERGING ROLES OF GLP-1 RECEPTOR AGONISTS

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ABSTRACT **Background:** Obesity and metabolic syndrome constitute major global public health challenges, substantially increasing cardiovascular, metabolic, and renal morbidity. Lifestyle interventions alone offer limited and often unsustainable long-term benefits, necessitating effective pharmacological approaches. **Objective:** To review established and emerging pharmacological therapies for obesity, with emphasis on glucagon-like peptide-1 (GLP-1) receptor agonists and related incretin-based agents. **Methods:** Recent randomized controlled trials, systematic reviews, and meta-analyses were critically evaluated to assess pharmacological mechanisms, clinical efficacy, safety profiles, global implications, and future therapeutic prospects. **Results:** GLP-1 receptor agonists, dual GIP/GLP-1 receptor agonists, and amylin analogues demonstrate substantial and sustained weight reduction, alongside significant improvements in glycemic control and cardiometabolic risk factors. Semaglutide, tirzepatide, and novel dual and triple agonists dominate contemporary clinical trials, exhibiting superior metabolic efficacy and emerging cardiovascular and renal benefits independent of diabetic status. **Conclusion:** Incretin-based pharmacotherapies represent a paradigm shift in obesity management. Ongoing research into microbiome-based interventions, gene therapy, and drug repurposing offers promising future directions. However, pharmacoeconomic constraints and limited global accessibility continue to shape real-world impact, underscoring the need for equitable and cost-effective treatment strategies. Future policy integration, long-term safety surveillance, and multidisciplinary implementation will determine sustainability, population-level benefit, and successful translation into routine clinical practice worldwide.

KEYWORDS : Obesity, Metabolic syndrome, GLP-1 receptor agonists, GIP dual agonists, Amylin analogues, Cardiovascular, Renal, Microbiome, Gene therapy, Drug repurposing, Pharmacoeconomics

INTRODUCTION

Obesity and metabolic syndrome are among the leading contributors to non-communicable morbidity and mortality worldwide, with a steadily increasing prevalence across all age groups and geographic regions. These conditions substantially elevate the risk of cardiovascular disease, type 2 diabetes mellitus, chronic kidney disease, and premature mortality, thereby imposing a significant burden on global healthcare systems [1,2]. The multifactorial pathophysiology of obesity, involving genetic, neuroendocrine, behavioural, and environmental determinants, complicates both prevention and long-term management.

Lifestyle interventions, including caloric restriction, dietary modification, and increased physical activity, remain the cornerstone of obesity management. However, their long-term effectiveness is frequently limited by poor adherence and compensatory physiological mechanisms that promote weight regain, such as reductions in basal metabolic rate and alterations in appetite-regulating hormones [3]. Consequently, sustained weight loss through lifestyle measures alone is often difficult to achieve, highlighting the need for effective pharmacological therapies.

The development of anti-obesity pharmacotherapy has historically been marked by limited success. Earlier agents, including sympathomimetic appetite suppressants, serotonergic modulators, and gastrointestinal lipase inhibitors, demonstrated modest efficacy and were frequently associated with adverse cardiovascular, psychiatric, or gastrointestinal effects, leading to restricted use or regulatory withdrawal [4,5]. These limitations underscored the need for safer and more effective therapeutic targets grounded in a deeper understanding of metabolic regulation.

A paradigm shift in obesity pharmacotherapy emerged with the introduction of incretin-based therapies, particularly glucagon-like peptide-1 (GLP-1) receptor agonists. Initially developed for glycaemic control in type 2 diabetes mellitus, these agents were subsequently shown to induce clinically meaningful and sustained weight loss by enhancing satiety, reducing caloric intake, and modulating central appetite pathways [6]. Importantly, beyond weight reduction, GLP-1 receptor agonists demonstrated favourable effects on cardiovascular risk factors, renal outcomes, and overall metabolic health.

In recent years, landmark randomized controlled trials published in high-impact journals such as the *New England Journal of Medicine* and *The Lancet* have highlighted the efficacy of semaglutide, tirzepatide, and other dual incretin agonists in achieving substantial weight reduction, often exceeding 15–20% of baseline body weight [7–9]. These findings have generated intense global interest and accelerated clinical research into next-generation metabolic therapies, positioning incretin-based agents at the forefront of modern obesity management.

Against this background, understanding the pharmacological evolution of obesity treatment-from earlier therapeutic failures to current successes-is essential for contextualizing emerging strategies and identifying future research priorities.

Obesity As A Pharmacological Target: Past Failures And Present Success

Obesity represents a complex pharmacological target due to its multifaceted neurohormonal regulation of appetite, energy expenditure, and adipose tissue biology. Early pharmacological approaches primarily focused on appetite suppression or inhibition of nutrient absorption, often without addressing underlying metabolic dysregulation. Sympathomimetic agents such as phentermine and diethylpropion promoted short-term weight loss through central appetite suppression but were associated with cardiovascular

stimulation and potential abuse liability [4]. Similarly, serotonergic agents, including fenfluramine and lorcaserin, were withdrawn due to safety concerns related to valvular heart disease and malignancy risk, respectively [5].

The limited efficacy and safety concerns of these earlier therapies constrained their long-term clinical utility and highlighted the need for mechanisms that more closely aligned with physiological regulation of energy balance. The emergence of incretin-based therapies marked a turning point by targeting endogenous hormonal pathways involved in glucose homeostasis and appetite control. GLP-1 receptor agonists, such as liraglutide and semaglutide, demonstrated not only superior weight loss efficacy but also favourable cardiometabolic profiles, thereby redefining therapeutic expectations in obesity management [6,7].

More recently, dual GIP/GLP-1 receptor agonists, particularly tirzepatide, have further advanced the field by exploiting synergistic incretin pathways, resulting in greater and more sustained weight reduction compared with GLP-1 monotherapy [8,9]. These developments signify a transition from modest, short-term weight control to disease-modifying pharmacological strategies with broader metabolic and cardiovascular benefits.

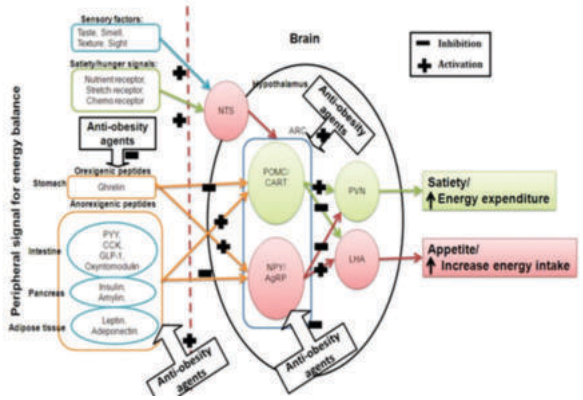

Fig 1: Mechanism Of Action

GLP-1 Receptor Agonists

GLP-1 receptor agonists mimic the incretin hormone GLP-1, enhancing glucose-dependent insulin secretion, suppressing glucagon, slowing gastric emptying, and promoting satiety via central mechanisms. These agents reduce food intake while minimizing hypoglycemia risk. In addition to peripheral metabolic actions, GLP-1 receptor agonists exert central effects by modulating hypothalamic and mesolimbic reward pathways, thereby reducing hedonic eating and food-related reward behavior.

- Agents: Exenatide, liraglutide, dulaglutide, semaglutide, oral semaglutide.
- Clinical Evidence: Semaglutide (once-weekly) produces >15% average body weight loss in Phase III trials, with robust glycemic and metabolic improvement.
- Oral semaglutide represents a significant advance by improving patient adherence and expanding accessibility to non-injectable incretin therapy.

GIP/GLP-1 Dual and Triple Agonists

Tirzepatide activates both GIP and GLP-1 receptors, leading to synergistic enhancement of insulin secretion and suppression of appetite. GIP receptor activation may enhance adipose tissue insulin sensitivity and mitigate gastrointestinal intolerance associated with GLP-1 monotherapy, contributing to improved tolerability and efficacy. However, long-term cardiovascular safety and durability of weight loss with triple agonists remain under active investigation. The SURPASS program[6,7] reports mean weight loss up to 18–22% in obesity and diabetic populations, with superior metabolic outcomes versus GLP-1 monotherapy.

Future Prospects: Survodutide (GLP-1/glucagon dual agonist), triple agonists targeting multiple incretin and metabolic pathways are in early clinical development.

Amylin Analogues

Amylin is co-secreted with insulin, augmenting satiety and reducing caloric intake by modulating gastric emptying and central appetite circuits. Pramlintide (injectable) and cagrilintide (phase II) offer additional, complementary weight reduction.

Combination therapy: GLP-1 RA + amylin analogues may yield additive/synergistic results.

The requirement for injectable administration and gastrointestinal intolerance remain key barriers to the widespread use of amylin analogues as monotherapy.

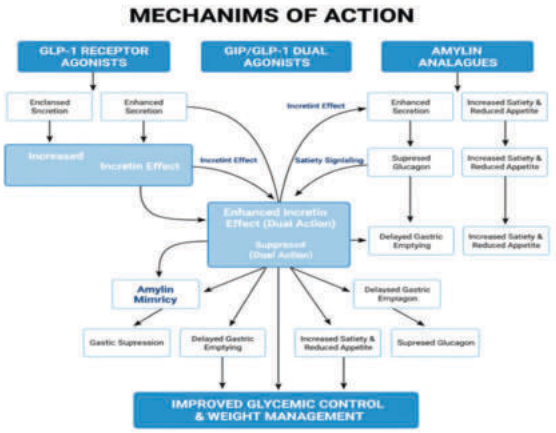

Fig 2: Mechanisms of action for GLP-1, GIP/GLP-1 dual, and amylin analogs.

Clinical Benefits: Metabolic, Cardiovascular, Renal

Metabolic Benefits

- GLP-1 RA and dual agonists produce profound reductions in HbA1c (1–2%), fasting glucose, and insulin resistance, enhancing weight loss and reducing visceral adiposity.
- Amylin analogues further improve postprandial glycemic control and reduce insulin requirements.
- Emerging evidence suggests that incretin-based therapies also reduce hepatic steatosis and inflammation, supporting potential roles in non-alcoholic fatty liver disease (NAFLD) and steatohepatitis[4,10].

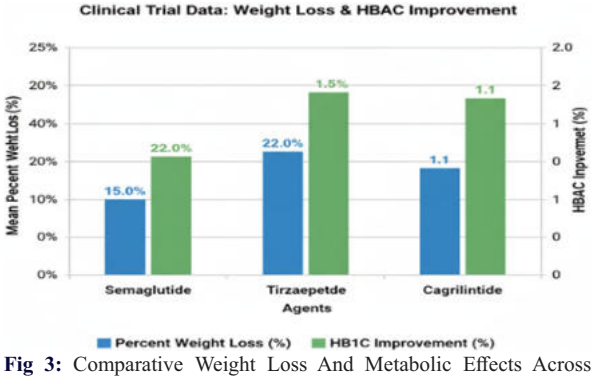

Fig 3: Comparative Weight Loss And Metabolic Effects Across Leading Agents (semaglutide, tirzepatide, cagrilintide)

Cardiovascular Outcomes

- The SELECT Trial (Lancet, 2024) confirmed significant MACE reduction in overweight/obese patients treated with semaglutide independent of diabetic status[11].
- GLP-1 RAs reduce systolic blood pressure, improve lipid profiles, and attenuate atherosclerotic risk, making them favorable for cardiovascular risk mitigation.
- Cardiovascular benefits are likely mediated through weight reduction, blood pressure lowering, anti-inflammatory effects, and direct vascular endothelial actions.

Renal Outcomes

- These drugs reduce macroalbuminuria, slow diabetic nephropathy progression, and improve renal outcomes, extending their benefit beyond glycemic control.
- Notably, renoprotective effects appear to be partially independent of glycaemic control, suggesting direct renal and haemodynamic mechanisms.

Safety Concerns and Long-Term Unknowns

Adverse Effects

- Gastrointestinal: Nausea, vomiting, diarrhea, delayed gastric emptying.
- Pancreatic: Increased risk of pancreatitis (rare; more in predisposing conditions).
- Thyroid C-cell tumors: Seen in rodents but not confirmed in humans; FDA requires ongoing surveillance.

Long-Term Unknowns

- Cancer risk: Recent population cohorts report either neutral or protective associations of GLP-1 RA with malignancies, but surveillance continues.
- Psychiatric and neurocognitive effects: Concerns remain about possible mood disorders and neuroendocrine impacts with long-term use.
- Weight regain: Discontinuation may result in substantial weight rebound, highlighting the need for ongoing therapy and lifestyle support.

Overall, serious adverse events remain uncommon, and the benefit–risk profile of GLP-1 receptor agonists is favorable when appropriately prescribed.

Pharmacoeconomics and Global Accessibility

Cost and Insurance Coverage

- GLP-1 RA are among the most expensive chronic medications, often not covered for obesity unless comorbid diabetes is present.
- Budgetary impact: Global obesity prevalence could make these drugs a significant health system expense.

Real-world studies indicate high discontinuation rates due to cost, gastrointestinal intolerance, and supply limitations, which may attenuate long-term population-level benefits.

Global Access

- Supply chain bottlenecks, low- and middle-income country availability, insurance denials are major limiting factors.
- Policy efforts: Advocating for inclusion on essential medicines lists and broader government reimbursement.

Table 1. Pharmacological Agents Used In Obesity: Mechanisms, Adverse Effects, Fixed-dose Combinations, And Withdrawal Status

Drug	Category	Mechanism of Action	Important Adverse Effects	Fixed-Dose Combination (FDC)	Withdrawal Status / Remarks
Semaglutide	GLP-1 receptor agonist	Enhances satiety and delays gastric emptying via GLP-1 receptor activation	Gastrointestinal upset, pancreatitis	None	Not withdrawn
Liraglutide	GLP-1 receptor agonist	GLP-1–mediated appetite suppression and satiety	Gastrointestinal upset	None	Not withdrawn
Tirzepatide	Dual GIP/GLP-1 receptor agonist	Activates GIP and GLP-1 receptors, amplifying incretin effects	Gastrointestinal effects, hypoglycaemia	None	Not withdrawn
Phentermine	Appetite suppressant (sympathomimetic)	Noradrenergic stimulation of central appetite pathways	Insomnia, cardiovascular risk	Yes (with Topiramate)	Not withdrawn
Naltrexone / Bupropion	Combination therapy	Modulates reward and appetite via opioid and dopamine/ norepinephrine pathways	Seizures, mood changes	Yes (Contrave®)	Not withdrawn
Orlistat	Lipase inhibitor	Inhibits gastrointestinal lipases, reducing fat absorption	Steatorrhea, fat-soluble vitamin deficiency	None	Not withdrawn
Setmelanotide	MC4 receptor agonist	Activates melanocortin-4 receptor pathway (rare genetic obesity)	Injection-site reactions	None	Not withdrawn
Lorcaserin	Serotonergic agent	5-HT2C receptor agonist, appetite suppression	Increased cancer risk	None	Withdrawn (2021)
Sibutramine	Appetite suppressant	Serotonin and norepinephrine reuptake inhibition	Cardiovascular events	None	Withdrawn (2010)
Rimonabant	CB1 receptor antagonist	Inhibits endocannabinoid appetite regulation pathway	Psychiatric adverse effects	None	Withdrawn (2008)

Future Therapies: Gene Therapy and Microbiome

These clinical and economic considerations underscore the importance of continued innovation in obesity pharmacotherapy, including novel targets, combination strategies, and precision-based approaches.

Gene Therapy

Gene-based interventions represent a highly experimental yet potentially transformative approach to obesity management by targeting fundamental metabolic pathways involved in energy balance, adipogenesis, and appetite regulation **[13,14]**. Emerging strategies employ CRISPR-Cas9 gene editing, viral vector–mediated gene transfer, and enzyme replacement techniques to modulate key regulators of lipid metabolism and mitochondrial function **[15]**. Experimental models involving overexpression of enzymes such as carnitine palmitoyltransferase-1A (CPT1AM) have demonstrated enhanced fatty acid oxidation and resistance to diet-induced obesity, suggesting the possibility of durable or lifelong metabolic benefits **[16]**.

Despite these promising preclinical findings, ethical concerns, off-target genetic effects, long-term safety, and regulatory barriers continue to limit clinical translation **[14,17]**.

Microbiome–Metabolism Links

The gut microbiome has emerged as a critical regulator of host metabolism, influencing adiposity, insulin sensitivity, energy harvest, and systemic inflammation **[18,19]**. Alterations in gut microbial composition and diversity have been consistently associated with obesity and metabolic syndrome **[18]**.

Microbiome-directed interventions, including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT), have demonstrated modest improvements in insulin resistance, inflammatory markers, and body weight in small clinical studies **[20,21]**. Ongoing randomized controlled trials aim to clarify optimal microbial strains, dosing strategies, and long-term efficacy **[22]**.

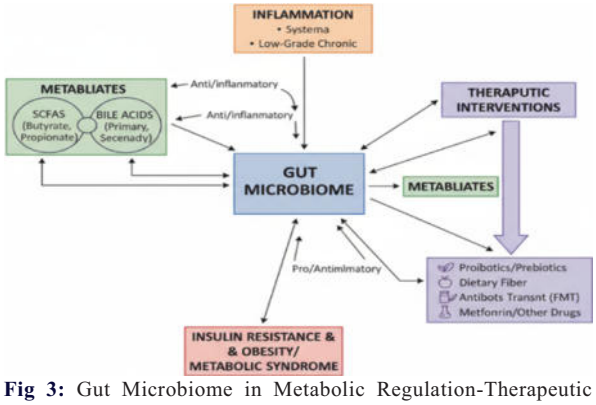

Fig 3: Gut Microbiome in Metabolic Regulation-Therapeutic Interventions

Drug Repurposing And Combination Therapies

GLP-1 receptor agonists, initially developed for glycaemic control in type 2 diabetes mellitus, are increasingly being investigated for therapeutic roles in non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), neurodegenerative disorders such

as Alzheimer disease, and obesity-related malignancies, reflecting their pleiotropic metabolic and anti-inflammatory effects **[6,11,23,24]**. In parallel, combination pharmacotherapy has emerged as a rational strategy to address the multifactorial pathophysiology of obesity. Agents such as sodium–glucose cotransporter-2 (SGLT2) inhibitors, amylin analogues, and non-incretin metabolic drugs are being combined with GLP-1 receptor agonists to achieve synergistic weight loss and improved cardiometabolic outcomes **[25]**.

Comparative Table: Mechanisms and Clinical Effects

Drug/Modality	Mechanism	Clinical Effects	Standout Benefits
GLP-1 RA (Semaglutide)	GLP-1R activation	Weight loss, glycemia	MACE reduction, renal benefit
GIP/GLP-1 RA (Tirzepatide)	Dual incretin activation	Greater weight loss	Superior glycemic control
Amylin Analogs	Promotes satiety	Weight/food intake ↓	GI tolerability
Survodutide	GLP-1/glucagon RA	Promising in trials	Fat mass reduction
Microbiome therapies	Gut flora re-balancing	Insulin sensitivity	Low adverse event rate

Opportunities, Challenges, and Research Gaps

Opportunities

- Expansion into cardiovascular, renal protection, and weight management for high-risk patients.
- Combination therapies, personalized protocols, and long-term metabolic resetting.

Challenges

- Drug tolerability: GI side effects remain the most common limiting factor in dose escalation/maintenance.
- Safety: Need for further research on possible rare adverse events.
- Cost: Necessity to balance efficacy with economic sustainability for health systems.

Research Gaps

- Optimal duration, combinations, and sequencing of agents for lifelong obesity management.
- Long-term cardiovascular and oncologic safety.
- Expanding agents' use for pediatric and severe obesity cases.
- Improving real-world data collection, especially in underrepresented groups and global populations.

DISCUSSION

The emergence of incretin-based pharmacotherapies has fundamentally altered the therapeutic landscape of obesity, shifting clinical goals from modest weight reduction to comprehensive cardiometabolic risk modification. Unlike earlier anti-obesity agents that primarily targeted appetite suppression or nutrient absorption, contemporary therapies exert multifaceted effects on energy balance, glucose homeostasis, and systemic inflammation. This broader physiological impact supports their role not only in weight management but also in reducing obesity-related morbidity and mortality.

A notable strength of GLP-1 receptor agonists and dual incretin therapies is the consistency of efficacy observed across diverse populations, including individuals with and without diabetes. The demonstration of cardiovascular and renal benefits independent of glycaemic control suggests disease-modifying potential, reinforcing obesity as a chronic metabolic condition requiring long-term pharmacological intervention rather than short-term symptomatic treatment. However, the necessity for sustained therapy raises important questions regarding long-term adherence, safety, and economic feasibility.

Combination pharmacotherapy represents a promising strategy to enhance efficacy while mitigating dose-limiting adverse effects. Rational combinations targeting complementary metabolic pathways may enable lower individual drug doses, improved tolerability, and more durable weight loss. Nevertheless, the absence of long-term comparative studies limits definitive conclusions regarding optimal drug combinations, sequencing, and treatment duration. Additionally, the heterogeneity of obesity phenotypes underscores the need for precision-based approaches incorporating genetic, metabolic, and behavioural determinants.

Despite compelling clinical trial data, real-world implementation remains constrained by high costs, limited insurance coverage, and global disparities in access. These factors may exacerbate existing health inequities, particularly in low- and middle-income countries. Future research must therefore extend beyond efficacy to address implementation science, health economics, and population-level outcomes. Large-scale real-world studies and long-term registries will be essential to define sustainable treatment models and inform evidence-based policy decisions.

CONCLUSION

GLP-1 receptor agonists, dual incretin mimetics, and next-generation metabolic drugs have irrevocably transformed the management of obesity and metabolic syndrome. While major advances are already in clinical practice, exciting future prospects—including microbiome therapies, gene editing, and multidrug combinations—hold promise for lifelong obesity control and risk reduction. Addressing safety, cost, and accessibility will be critical for delivering benefits at population scale.

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