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Beyond Semaglutide: The Rise of Multi-Agonist Incretin Therapy in Obesity and Metabolic Disease – A Comprehensive Pharmacological Review

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Abstract: The therapeutic landscape of obesity and type 2 diabetes mellitus has been transformed by the discovery and clinical translation of multi-agonist incretin peptides. Once-weekly semaglutide established glucagon-like peptide-1 (GLP-1) receptor agonism as the benchmark pharmacological intervention, producing approximately 15% body weight reduction. Tirzepatide, the first approved dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor co-agonist, has produced weight reductions exceeding 22%. Retatrutide, a triple agonist of GLP-1, GIP, and glucagon receptors, has demonstrated phase 2 weight reductions approaching 24%, while amylin co-agonist combinations such as cagrilintide–semaglutide (CagriSema) extend the polypharmacological frontier further. This review provides a comprehensive analysis of the molecular pharmacology, receptor biology, clinical trial evidence, and emerging pipeline of multi-agonist incretins. We examine landmark trials including STEP, SURMOUNT, SURPASS, SELECT, FLOW, and the retatrutide and survodutide programs; discuss the expanding indications beyond weight loss in cardiovascular disease, chronic kidney disease, metabolic dysfunction-associated steatohepatitis, and neurodegeneration; and address the unique adverse effect profile including gastrointestinal tolerability, gallbladder disease, pancreatitis surveillance, and emerging concerns regarding sarcopenia and lean mass preservation. The review highlights particular relevance for India, where the projected diabetes burden, obesity prevalence, and cost-access considerations make this drug class strategically important. Future directions include oral peptide and small-molecule incretin agonists, gene therapy approaches, and combination strategies with amylin, glucagon, and other gut hormones.

Keywords: *Amylin; CagriSema; Cagrilintide; GLP-1 Receptor Agonists; Incretin; Mazdutide; Multi-Agonist; Obesity; Retatrutide; Semaglutide; Survodutide; Tirzepatide; Type 2 Diabetes.*

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I. INTRODUCTION

Obesity has emerged as one of the most consequential global health challenges of the twenty-first century, with the World Health Organization estimating that more than 1 billion adults worldwide live with obesity in 2024. India faces a particularly complex epidemiological picture: while approximately 5–6% of urban adults meet World Health Organization criteria for obesity (body mass index ≥30 kg/m²), the prevalence of overweight, abdominal adiposity, and the metabolically obese normal weight phenotype is substantially higher. Coupled with type 2 diabetes mellitus prevalence projected to exceed 100 million Indian adults by 2030, the demand for effective and safe pharmacological obesity therapy has never been greater. [1, 2, 3]

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Until the recent decade, pharmacological options for obesity were limited, broadly disappointing in efficacy, and burdened by adverse effects. Orlistat produced modest weight reductions of 3–5%, while phentermine–topiramate and naltrexone–bupropion offered 5–10% reductions with concerning tolerability profiles. The therapeutic landscape was transformed by the recognition that gut-derived peptide hormones, particularly glucagon-like peptide-1 (GLP-1), could be pharmacologically harnessed to produce sustained, clinically meaningful weight loss with broadly favorable safety. Contemporary consensus guidance on the management of hyperglycemia now positions GLP-1-based therapy centrally within the type 2 diabetes treatment algorithm. [4, 5, 6]

The clinical journey of GLP-1 receptor agonism began with exenatide (twice-daily, then weekly), followed by liraglutide (daily) and, transformatively, once-weekly semaglutide. The Semaglutide Treatment Effect in People with Obesity (STEP) trial program demonstrated mean body weight reductions of approximately 15% over 68 weeks, comparable to the lower range of bariatric surgical outcomes. The recognition that obesity is a chronic, pharmacologically responsive disease has fundamentally reshaped clinical paradigms and unleashed an unprecedented wave of pharmaceutical investment in next-generation incretin therapeutics. [7, 8, 9, 10, 11]

This review provides a comprehensive pharmacological synthesis of multi-agonist incretin therapy. We examine the molecular pharmacology of single, dual, and triple receptor agonism; review landmark clinical trials; discuss pleiotropic effects beyond weight management; address adverse effect profiles and emerging concerns; consider Indian and lower-middle-income country perspectives; and outline future directions including oral and non-peptide approaches.

II. PHYSIOLOGY OF THE ENTEROENDOCRINE SYSTEM

- *Glucagon-Like Peptide-1*

GLP-1 is a 30/31 amino acid peptide hormone secreted by enteroendocrine L-cells, predominantly in the distal ileum and colon, in response to nutrient ingestion. It is derived from post-translational processing of the proglucagon gene, which is differentially cleaved in α-cells of pancreatic islets (yielding glucagon) and in intestinal L-cells (yielding GLP-1, GLP-2, glicentin, and oxyntomodulin). The native peptide has a half-life of only 1–2 minutes due to rapid degradation by dipeptidyl peptidase-4 (DPP-4) and renal clearance, requiring molecular engineering for pharmacological use. [12, 13, 14]

GLP-1 receptors are class B G-protein-coupled receptors expressed on pancreatic β-cells (where they potentiate glucose-dependent insulin secretion), pancreatic α-cells (where they suppress glucagon), gastric smooth muscle (slowing emptying), arcuate hypothalamic neurons (reducing food intake), the area postrema (mediating nausea and satiety), and additional sites including cardiovascular, renal, and central nervous system tissues. This anatomical distribution underlies the metabolic, cardiovascular, and neuroprotective effects observed clinically. [15]

- *Glucose-Dependent Insulinotropic Polypeptide*

GIP, originally termed gastric inhibitory polypeptide, is a 42-amino acid peptide secreted by K-cells of the proximal duodenum and jejunum in response to fat and carbohydrate ingestion. Unlike GLP-1, GIP exhibits both insulinotropic and glucagonotropic activity, the latter being relevant in the context of hypoglycemia. GIP receptors are expressed on β-cells, adipocytes, osteoblasts, and central nervous system tissues. The metabolic role of GIP has been controversial: native GIP promotes adipogenesis and, in healthy individuals, accounts for approximately two-thirds of the incretin effect, while in established type 2 diabetes its insulinotropic effect is paradoxically diminished. [16, 17]

The biological rationale for combining GLP-1 and GIP receptor agonism rests on three observations: (i) GIP signaling restores normal insulinotropic activity when accompanying GLP-1 agonism, (ii) GIP receptor activation in adipose tissue increases lipid buffering capacity and may improve insulin sensitivity, and (iii) central GIP signaling, particularly in the hypothalamus and the area postrema, appears to attenuate GLP-1-induced nausea while augmenting satiety. [18]

- *Glucagon*

Glucagon, also derived from proglucagon, is the canonical counter-regulatory hormone elevating blood glucose through hepatic glycogenolysis and gluconeogenesis. The therapeutic rationale for glucagon receptor agonism in obesity initially seems counterintuitive given diabetic concerns. However, glucagon also stimulates energy expenditure, lipolysis, and hepatic fatty acid oxidation; controlled infusion studies of glucagon combined with GLP-1 confirm reductions in food intake and increases in resting energy expenditure without deleterious glycemic excursions. When co-administered with GLP-1 and GIP agonism, the glycemic effects of glucagon are blunted while its lipolytic and thermogenic effects are preserved, producing additive weight loss and substantial hepatic lipid clearance. This pharmacological synergy is the principle underlying triple-agonist development. [19]

- *Amylin*

Amylin (islet amyloid polypeptide) is a 37-amino acid peptide co-secreted with insulin from pancreatic β-cells. It acts on amylin receptors in the area postrema to delay gastric emptying, suppress postprandial glucagon, and induce satiety. Pramlintide, a stable amylin analog, has been approved for use in insulin-treated diabetes but limited by hypoglycemia risk. Long-acting amylin analogs such as cagrilintide have been developed specifically for chronic obesity therapy, with engineered tolerability and weekly dosing.

- *Other Gut Hormones in Development*

Additional enteroendocrine peptides under pharmaceutical investigation include peptide YY (PYY), oxyntomodulin, cholecystokinin (CCK), and ghrelin antagonists. PYY 3-36 produces satiety through Y2 receptor signaling in the hypothalamus; oxyntomodulin, a natural dual

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GLP-1/glucagon agonist, has inspired several engineered analogs; and ghrelin antagonism remains an active discovery target despite multiple clinical disappointments.

III. FIRST-GENERATION GLP-1 MONO-AGONISTS

➢ *Liraglutide*

Liraglutide, a fatty-acid acylated GLP-1 analog with 97% homology to native GLP-1, was the first daily-dosed GLP-1 receptor agonist approved for both type 2 diabetes (Victoza, 1.8 mg/day) and chronic weight management (Saxenda, 3.0 mg/day). The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial established a 13% reduction in major adverse cardiovascular events (MACE) in type 2 diabetes patients with established cardiovascular disease or high cardiovascular risk, providing the first definitive cardiovascular outcome benefit for the GLP-1 class. [20]

In obesity, the SCALE Obesity and Prediabetes trial of liraglutide 3.0 mg in 3,731 adults with body mass index ≥30 kg/m² (or ≥27 with comorbidities) produced mean weight loss of 8.0% compared to 2.6% with placebo at 56 weeks. Liraglutide is also approved for pediatric obesity in adolescents aged 12 years and older following the SCALE Teens trial. [21]

➢ *Semaglutide*

Semaglutide represents a chemical evolution of liraglutide with optimized fatty acid linker chemistry and amino acid substitutions producing a half-life of approximately 1 week, enabling weekly subcutaneous administration; the medicinal-chemistry trajectory connecting these two molecules is now regarded as a landmark in rational peptide design. The SUSTAIN program established its glycemic efficacy in type 2 diabetes, while the STEP program defined its obesity indication. In STEP 1, once-weekly subcutaneous semaglutide 2.4 mg produced mean weight loss of 14.9% versus 2.4% with placebo over 68 weeks in adults with obesity but without diabetes, consolidating its position as a benchmark anti-obesity agent. [7, 22, 23]

The cardiovascular outcomes of semaglutide were established in SUSTAIN-6 (subcutaneous) and PIONEER 6 (oral) in type 2 diabetes patients, both demonstrating non-inferiority versus placebo. The Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) trial extended these findings to non-diabetic obesity, demonstrating a 20% reduction in MACE over a mean follow-up of 39.8 months — a result that fundamentally repositioned obesity therapy as cardiovascular risk reduction. [24, 25, 26]

Additional landmark indications include the Flow Cardiorenal Outcomes in Diabetic Kidney Disease (FLOW) trial demonstrating a 24% reduction in major kidney disease events, and the STEP-HFpEF program demonstrating improvements in symptoms and exercise capacity in heart failure with preserved ejection fraction patients with obesity. [27, 28]

➢ *Oral Semaglutide*

Oral semaglutide (Rybelsus) was made possible by co-formulation with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), an absorption enhancer that increases gastric pH and protects the peptide from proteolytic degradation in the stomach, enabling bioavailability of approximately 0.4–1%. The PIONEER 1–10 trials demonstrated comparable glycemic efficacy to injectable comparators — including direct comparison with subcutaneous liraglutide in PIONEER 4 — while PIONEER 6 demonstrated cardiovascular safety. Oral semaglutide has been studied at higher doses (25 mg and 50 mg) for obesity, with results published in OASIS 1 and OASIS 4 trials demonstrating mean weight reductions of approximately 15% at the 50 mg dose. [29, 30, 31]

IV. TIRZEPATIDE: DUAL GLP-1/GIP RECEPTOR AGONISM

➢ *Molecular Pharmacology*

Tirzepatide is a 39-amino acid synthetic peptide engineered to bind and activate both GLP-1 and GIP receptors. Its structure is based on the native GIP sequence with strategic modifications including a C20 fatty diacid moiety attached via a glutamic acid-aminoethoxyethoxyacetic acid linker at lysine 20, enabling albumin binding and extending half-life to approximately 5 days. The molecule exhibits biased agonism, with relatively greater activation of GIP receptors compared to GLP-1 receptors, distinguishing its pharmacology from balanced dual agonists in development. [32, 33]

➢ *SURPASS Program in Type 2 Diabetes*

The SURPASS clinical trial program established tirzepatide efficacy across the spectrum of type 2 diabetes. SURPASS-1 demonstrated superiority over placebo as monotherapy; SURPASS-2 demonstrated superiority over semaglutide 1.0 mg with greater HbA1c reductions and weight loss; SURPASS-3 demonstrated superiority over insulin degludec when added to metformin; SURPASS-4 demonstrated superiority over insulin glargine in high-cardiovascular-risk patients; and SURPASS-5 demonstrated added benefit over background insulin glargine. Across SURPASS trials, tirzepatide 15 mg produced HbA1c reductions of 1.9–2.4% and weight reductions of 8.5–12.9 kg. [34, 35, 36]

➢ *SURMOUNT Program in Obesity*

The SURMOUNT obesity program established tirzepatide as the most effective approved pharmacotherapy for obesity. SURMOUNT-1, in 2,539 adults with obesity without diabetes, demonstrated mean body weight reductions of 22.5% with tirzepatide 15 mg compared to 2.4% with placebo over 72 weeks. SURMOUNT-2 in type 2 diabetes patients with obesity produced 15.7% weight loss with tirzepatide 15 mg. SURMOUNT-3 demonstrated added benefit with intensive lifestyle intervention, and SURMOUNT-4 demonstrated weight regain upon withdrawal — underscoring the chronic nature of obesity pharmacotherapy. [37, 38, 39, 40]

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The first head-to-head comparison of the two most effective approved agents, SURMOUNT-5, demonstrated significantly greater weight reduction with tirzepatide than with semaglutide 2.4 mg in adults with obesity without diabetes, and analyses extending to diabetes prevention have reinforced the metabolic value of sustained tirzepatide exposure. [41, 42]

Subsequent landmark trials have demonstrated tirzepatide efficacy in sleep apnea (SURMOUNT-OSA), heart failure with preserved ejection fraction (SUMMIT), and metabolic dysfunction-associated steatohepatitis (MASH), establishing the molecule's broad metabolic activity. Cardiovascular outcome data from SURPASS-CVOT are awaited at the time of writing. [43, 44]

V. RETATRUTIDE: TRIPLE GLP-1/GIP/GLUCAGON AGONISM

Retatrutide (LY3437943) is a 39-amino acid peptide engineered as a triple agonist of GLP-1, GIP, and glucagon receptors. The molecule represents the most pharmacologically ambitious incretin to date, integrating three distinct receptor signaling streams to deliver weight loss exceeding any prior pharmacological intervention. In the phase 2 retatrutide obesity trial, 338 adults with obesity received retatrutide doses of 1–12 mg weekly versus placebo. At 48 weeks, mean body weight reductions reached 24.2% with the 12 mg dose compared to 2.1% with placebo, with no efficacy plateau observed at 48 weeks suggesting potential for further reduction with continued treatment. [45, 46]

The mechanism by which glucagon receptor agonism contributes to weight loss in combination involves stimulation of basal metabolic rate, hepatic lipolysis, and lean mass preservation. In retatrutide phase 2, increases in resting energy expenditure and substantial reductions in hepatic fat content (greater than 80% relative reduction) were observed, supporting the molecule's positioning for MASH and other metabolic conditions. Glucagon-induced hyperglycemia, an a priori concern, was effectively countered by the simultaneous GLP-1 and GIP-mediated insulinotropic effects, with HbA1c reductions observed in retatrutide phase 2 diabetes studies comparable to those of tirzepatide. [47]

Retatrutide phase 3 programs (TRIUMPH for obesity and metabolic disease) are ongoing as of 2026, with anticipated regulatory submissions to follow. The development program is examining cardiovascular, renal, and hepatic outcomes in parallel.

VI. AMYLIN CO-AGONISTS AND COMBINATION STRATEGIES

- *Cagrilintide*

Cagrilintide is a long-acting amylin analog engineered for weekly subcutaneous administration. In a phase 2 dose-finding trial, cagrilintide monotherapy at the 4.5 mg dose produced mean weight loss of 10.8% over 26 weeks. The molecule has been positioned not for monotherapy use but rather as a combination partner with semaglutide. [48]

- *CagriSema (Cagrilintide + Semaglutide)*

CagriSema, the fixed-dose combination of cagrilintide 2.4 mg and semaglutide 2.4 mg, has been evaluated in the REDEFINE phase 3 program. In REDEFINE-1, CagriSema produced mean weight loss of 22.7% over 68 weeks compared to 16.1% with semaglutide alone and 11.8% with cagrilintide alone in adults with obesity without diabetes — establishing the additive efficacy of amylin and GLP-1 combination but with somewhat lower-than-expected magnitude that has prompted analytic reflection on protocol design and dose titration patterns. [49, 50]

Petrelintide, a next-generation amylin analog developed by Zealand Pharma, is being developed both as a monotherapy and in combination with GLP-1 agonists. Phase 2 results have shown mean weight loss of 8.6% over 16 weeks with petrelintide monotherapy, supporting further development. [51]

VII. EMERGING DUAL AND TRIPLE AGONISTS

- *Survodutide (BI 456906)*

Survodutide is a dual GLP-1/glucagon receptor agonist developed by Boehringer Ingelheim. Phase 2 data in 387 adults with obesity demonstrated mean weight reduction of 19% with the 4.8 mg dose over 46 weeks. The molecule has also shown remarkable efficacy in MASH, with phase 2 results demonstrating MASH resolution without worsening of fibrosis in over 80% of patients at the highest dose, leading to phase 3 LIVERAGE and LIVESTONE programs in MASH. [52, 53]

- *Mazdutide (IBI362)*

Mazdutide is a dual GLP-1/glucagon agonist developed by Innovent Biologics for the Chinese market and beyond. The DREAMS program has demonstrated phase 3 weight reductions of approximately 14% in Chinese adults with obesity, and the molecule received Chinese NMPA approval in 2024. Mazdutide represents an important development in incretin pharmacology pricing accessibility for Asian markets. [54]

- *Cotadutide*

Cotadutide (MEDI0382), a dual GLP-1/glucagon agonist developed by AstraZeneca, demonstrated favorable phase 2 results in MASH and chronic kidney disease but was discontinued from obesity development in favor of other portfolio priorities. The molecule's clinical data nonetheless contributed to the broader understanding of dual-agonist pharmacology. [55]

- *Efinopegdutide and Other Candidates*

Efinopegdutide (MK-6024) is a dual GLP-1/glucagon agonist in development by Merck for MASH. Ecnoglutide, a GLP-1 mono-agonist developed by Sciwind Biosciences, is in advanced clinical development in China. Additional candidates including pemvidutide, JNJ-65436795, and several preclinical multi-agonists continue to expand the pharmacological space.

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VIII. EXPANDING INDICATIONS BEYOND WEIGHT LOSS

➢ *Cardiovascular Disease*

Cardiovascular outcomes data for GLP-1 receptor agonists have evolved from non-inferiority to definitive superiority, supported by an increasingly well-characterized vascular biology that includes endothelial, anti-inflammatory, and direct myocardial effects. LEADER, SUSTAIN-6, REWIND (dulaglutide), PIONEER 6, AMPLITUDE-O (efpeglenatide), and SELECT collectively demonstrate consistent MACE reduction. Meta-analyses indicate approximately 14% reduction in MACE, with effects on stroke (-17%), cardiovascular death (-12%), and all-cause mortality (-12%). The SELECT trial extended these findings to non-diabetic obesity, fundamentally changing cardiovascular prevention paradigms. [26, 56, 57]

➢ *Chronic Kidney Disease*

The FLOW trial in 3,533 patients with type 2 diabetes and chronic kidney disease (eGFR 50–75 mL/min/1.73 m² with UACR 300–5000 mg/g, or eGFR 25–50 with UACR 100–5000) demonstrated that semaglutide 1.0 mg weekly produced a 24% reduction in major kidney disease events. This established GLP-1 receptor agonists as nephroprotective agents, complementing SGLT2 inhibitor effects. [27]

➢ *Metabolic Dysfunction-Associated Steatohepatitis*

GLP-1 agonists, dual GLP-1/glucagon agonists, and triple agonists have all demonstrated activity in MASH. Semaglutide 2.4 mg in the ESSENCE trial demonstrated MASH resolution without worsening of fibrosis. Survodutide demonstrated similar effects with greater magnitude. The hepatic effects of glucagon co-agonism appear to drive particularly strong reductions in hepatic fat content, positioning multi-agonists as a potentially transformative class for MASH alongside resmetirom and FGF21 analogs. [58, 59]

➢ *Neurodegenerative Disease*

GLP-1 receptors are expressed on neurons in regions vulnerable to neurodegeneration, including the substantia nigra, hippocampus, and cortex. The Exenatide-PD trial demonstrated motor improvements in Parkinson's disease, and the LixiPark trial of lixisenatide produced positive motor outcomes. The EVOKE program is evaluating semaglutide in Alzheimer's disease, with results anticipated in coming years. These investigations position GLP-1 agonists as potentially the first disease-modifying neurodegenerative agents from a metabolic class. [60]

➢ *Substance Use Disorders*

Observational data and preliminary clinical trials suggest that GLP-1 receptor agonists may reduce alcohol consumption, opioid use, nicotine craving, and gambling behaviors, potentially mediated through dopaminergic reward circuit modulation. Definitive randomized trials in alcohol use disorder and other addiction indications are ongoing.

➢ *Polycystic Ovary Syndrome and Reproductive Health*

GLP-1 agonists have shown promise in polycystic ovary syndrome (PCOS) for weight management, menstrual regulation, and fertility outcomes. Concerns regarding effects during pregnancy and the recommended wash-out period before conception are areas of active investigation.

IX. ADVERSE EFFECTS AND SAFETY CONSIDERATIONS

➢ *Gastrointestinal Tolerability*

Nausea, vomiting, diarrhea, and constipation are the most common adverse effects across the incretin class, occurring in 30–70% of patients depending on titration speed and dose. Most cases are mild to moderate and improve with continued therapy, but discontinuation rates due to gastrointestinal events range from 5–15%. Step-up dose titration over 12–20 weeks substantially mitigates these effects. [61]

➢ *Gallbladder Disease and Pancreatitis*

Meta-analyses have demonstrated a modest but real increase in gallbladder events (cholelithiasis, cholecystitis) with GLP-1 receptor agonists, with risk ratios of approximately 1.3–1.5. The mechanism likely involves delayed gallbladder emptying. Acute pancreatitis was an early concern with the class but multiple large observational and trial datasets have failed to demonstrate a significant signal, and current evidence does not support contraindication in patients with prior pancreatitis history alone. [62]

➢ *Sarcopenia and Body Composition*

An emerging concern with high-magnitude weight loss is the proportional loss of lean mass, with reports indicating that 20–40% of total weight loss with incretin therapy is from lean tissue. The clinical significance of this lean mass loss in older or sarcopenic populations is under investigation, with concerns regarding falls, frailty, and functional decline. Glucagon co-agonism (as in retatrutide) appears to preserve lean mass to a greater degree than GLP-1 monotherapy, supporting potential advantages of triple-agonist therapy in older adults. [63]

➢ *Medullary Thyroid Carcinoma and C-Cell Hyperplasia*

GLP-1 receptor agonists are contraindicated in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2). This restriction is based on rodent C-cell tumor findings; human data have not demonstrated increased thyroid cancer risk in long-term cohorts. The relevance of rodent findings to human pharmacology remains debated.

➢ *Suicide and Mental Health*

A regulatory signal of suicidal ideation associated with GLP-1 agonist use prompted FDA and EMA review in 2023–2024. Subsequent large-scale pharmacovigilance analyses have not demonstrated a causal relationship, with the European Medicines Agency concluding no causal link in 2024. However, clinicians should remain attentive to mental health monitoring in patients receiving these agents.

➢ *Diabetic Retinopathy*

An early signal of worsening diabetic retinopathy with semaglutide in SUSTAIN-6 prompted ongoing investigation. The FOCUS trial is examining retinopathy outcomes

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specifically. Current guidance recommends ophthalmologic monitoring in patients with pre-existing diabetic retinopathy initiating GLP-1 therapy with rapid HbA1c reduction.

X. INDIAN AND LOWER-MIDDLE-INCOME COUNTRY PERSPECTIVES

India's metabolic disease burden — including approximately 100 million people with diabetes and a similar number with prediabetes, and a rising obesity prevalence particularly in urban areas — creates substantial demand for effective pharmacotherapy. However, several factors complicate the integration of incretin therapy into Indian healthcare: (i) cost — the monthly retail cost of branded semaglutide and tirzepatide in India ranges from ₹15,000–25,000, well beyond the reach of most patients; (ii) cold-chain logistics for injectable peptides in tier-2 and tier-3 cities; (iii) cultural and dietary factors influencing tolerability and adherence; and (iv) the South Asian metabolic phenotype characterized by central adiposity, early β-cell failure, and lean MASH. [64, 65]

Indian manufacturers including Biocon, Cipla, Sun Pharma, and Dr. Reddy's are developing biosimilar GLP-1 agonists. Liraglutide biosimilars have entered the Indian market, and semaglutide biosimilars are expected following patent expiration. The Government of India has expressed interest in including GLP-1 agonists in the national essential drugs list for select indications, which would substantially reduce costs through bulk procurement. [66]

Research priorities for the Indian context include: ethnicity-stratified efficacy and dosing studies, real-world cost-effectiveness analyses, integration with Ayurvedic and yoga-based lifestyle interventions, and post-marketing surveillance addressing population-specific adverse effect profiles. The Research Society for the Study of Diabetes in India (RSSDI) and the Indian Society for Bariatric and Metabolic Surgery have begun issuing guidance documents on appropriate use.

XI. FUTURE DIRECTIONS

Several developmental trajectories will define the next decade of incretin pharmacology. First, oral peptide and non-peptide small-molecule GLP-1 receptor agonists are entering late-phase development. Orforglipron (Eli Lilly), danuglipron (Pfizer, discontinued for obesity), and GSBR-1290 (Structure Therapeutics) represent the non-peptide chemotype. The ATTAIN program of orforglipron in obesity has shown phase 2 weight reductions of approximately 14.7%, with phase 3 readouts expected to inform the impact of oral incretin availability.

Second, quad-agonist and higher-order combination peptides incorporating PYY, amylin, oxyntomodulin-like activity, or FGF21-like activity are in preclinical and early clinical development. The conceptual aim is approaching surgical weight loss outcomes (25–35% reduction) through pharmacotherapy alone.

Third, gene therapy approaches including AAV-mediated GLP-1 expression and CRISPR-engineered metabolic targets are advancing in preclinical research, with potential for single-administration durable effects.

Fourth, biomarker-guided personalization including genetic predictors of response (POMC, MC4R variants), gut microbiome stratification, and ethnicity-specific dosing will refine therapeutic decision-making.

Fifth, the regulatory and reimbursement frameworks for chronic obesity therapy must evolve to support indefinite treatment, given the demonstrated weight regain upon discontinuation. Indian regulatory authorities, insurance providers, and public health policymakers will face complex decisions regarding access, cost-effectiveness, and prioritization.

XII. SUMMARY TABLES

Table 1 Approved and Pipeline Incretin Therapeutics

Drug	Type	Route	Dose	Status	Manufacturer
Liraglutide	GLP-1	SC daily	0.6–3.0 mg	Approved (T2D, obesity)	Novo Nordisk
Dulaglutide	GLP-1	SC weekly	0.75–4.5 mg	Approved (T2D)	Eli Lilly
Semaglutide SC	GLP-1	SC weekly	0.25–2.4 mg	Approved (T2D, obesity, CV, CKD)	Novo Nordisk
Semaglutide oral	GLP-1	Oral daily	3–50 mg	Approved (T2D); pending obesity	Novo Nordisk
Tirzepatide	GLP-1/GIP dual	SC weekly	2.5–15 mg	Approved (T2D, obesity, OSA, HFpEF, MASH)	Eli Lilly
Retatrutide	GLP-1/GIP/glucagon triple	SC weekly	Phase 3	Phase 3 TRIUMPH	Eli Lilly
Survodutide	GLP-1/glucagon dual	SC weekly	Phase 3	Phase 3 LIVERAGE/LIVESTONE	Boehringer/Zealand
Mazdutide	GLP-1/glucagon dual	SC weekly	4.5–9 mg	Approved China; phase 3 global	Innovent
CagriSema	GLP-1 + amylin	SC weekly	Fixed-dose	Phase 3 REDEFINE	Novo Nordisk
Petrelintide	Amylin	SC weekly	Phase 2	Phase 2	Zealand

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Orforglipron	Oral non-peptide GLP-1	Oral daily	Phase 3	Phase 3 ATTAIN/ACHIEVE	Eli Lilly

Table 2 Landmark Cardiovascular and Renal Outcome Trials

Trial	Drug	Population	Primary Outcome	Hazard Ratio
LEADER (2016)	Liraglutide	T2D + high CV risk	MACE	0.87 (P=0.01)
SUSTAIN-6 (2016)	Semaglutide SC	T2D + high CV risk	MACE	0.74 (P<0.001)
PIONEER 6 (2019)	Semaglutide oral	T2D + high CV risk	MACE	0.79 (NS)
REWIND (2019)	Dulaglutide	T2D + CV risk	MACE	0.88 (P=0.026)
AMPLITUDE-O (2021)	Efpeglenatide	T2D + CV risk	MACE	0.73 (P=0.007)
SELECT (2023)	Semaglutide 2.4 mg	Obesity without DM	MACE	0.80 (P<0.001)
FLOW (2024)	Semaglutide 1 mg	T2D + CKD	Kidney + CV death	0.76 (P<0.001)

Table 3 Mean Weight Reductions Across Pivotal Obesity Trials

Trial	Drug	Duration	Active % WL	Placebo % WL
SCALE Obesity (2015)	Liraglutide 3.0 mg	56 wk	-8.0%	-2.6%
STEP 1 (2021)	Semaglutide 2.4 mg	68 wk	-14.9%	-2.4%
STEP 5 (2022)	Semaglutide 2.4 mg	104 wk	-15.2%	-2.6%
SURMOUNT-1 (2022)	Tirzepatide 15 mg	72 wk	-22.5%	-2.4%
SURMOUNT-2 (2023)	Tirzepatide 15 mg in T2D	72 wk	-15.7%	-3.3%
Retatrutide P2 (2023)	Retatrutide 12 mg	48 wk	-24.2%	-2.1%
Survodutide P2 (2024)	Survodutide 4.8 mg	46 wk	-19.0%	-2.0%
REDEFINE-1 (2025)	CagriSema	68 wk	-22.7%	-2.3%

Table 4 Mechanism Comparison of Incretin Pharmacological Targets

Receptor	Net Glycemic Effect	Net Body Weight	Net Hepatic Effect	Net Cardiovascular
GLP-1	↓↓ (glucose-dependent insulin)	↓↓ (satiety, gastric slowing)	↓ (hepatic fat)	↓ MACE
GIP	↓ (insulin secretion)	↓ (CNS satiety; lipid buffering)	Modest ↓	Neutral
Glucagon	↑ (counter-regulatory)	↓↓↓ (lipolysis, EE)	↓↓ (hepatic fat)	Emerging
Amylin	↓ (postprandial glucagon)	↓ (satiety, gastric slowing)	Modest	Not established

Table 5 Approximate Indian Pricing and Access Considerations

Drug	Branded Indian Price (per month)	Indication	Access Pathway
Liraglutide 1.8 mg	₹8,000–12,000	T2D	Direct retail; some insurance
Liraglutide 3.0 mg	₹16,000–22,000	Obesity	Out-of-pocket
Dulaglutide 1.5 mg	₹6,000–9,000	T2D	Retail; some insurance
Semaglutide SC (Ozempic 1 mg)	₹15,000–22,000	T2D	Retail
Semaglutide oral (Rybelsus 14 mg)	₹10,000–14,000	T2D	Retail
Semaglutide SC 2.4 mg (Wegovy)	₹24,000–35,000 (where available)	Obesity	Out-of-pocket
Tirzepatide (Mounjaro 15 mg)	₹22,000–30,000	T2D, obesity	Recent Indian launch

XIII. CONCLUSION

Multi-agonist incretin therapy represents one of the most transformative pharmacological advances of the modern era. From the foundational discoveries of GLP-1 biology in the 1980s to the contemporary phase 3 development of triple-agonist retatrutide and combination amylin-GLP-1 CagriSema, the field has progressed from modest weight reductions to outcomes approaching bariatric surgery. The therapeutic implications extend far beyond obesity to encompass cardiovascular disease, chronic kidney disease, MASH, neurodegeneration, and substance use disorders.

For India and other lower-middle-income countries, the imperative is twofold: ensuring equitable access through biosimilar development and value-based pricing, while generating population-specific evidence to optimize use in the South Asian metabolic phenotype. Pharmacologists, clinicians, regulators, and public health authorities all have critical roles in realizing the potential of this therapeutic revolution.

Pharmacology educators should emphasize multi-agonist incretins as exemplars of rational drug design, the value of integrated metabolic physiology, and the translational continuum from molecular biology to population-level health outcomes.

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