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Novel Pharmacological Advancements in Obesity Management. The Era of Incretins and their analogs.

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ABSTRACT

Obesity has evolved into a global health crisis, characterized as a chronic, relapsing multi-factorial disease with profound clinical and socioeconomic implications. Traditional lifestyle interventions often fail to achieve sustained weight loss due to metabolic adaptation, necessitating advanced pharmacological strategies. This review examines the rapidly evolving landscape of next-generation anti-obesity medications, focusing on the pharmacological mechanisms, clinical efficacy, and safety profiles of novel injectable and oral therapies. A comprehensive analysis was conducted on recent Phase I-III clinical trials involving GLP-1, GIP, and Glucagon receptor agonists, as well as amylin-based analogues. The transition from mono-agonists to multi-receptor poly-agonists marks a paradigm shift in obesity management. Triple agonists like Retatrutide have demonstrated "bariatric-level" weight loss exceeding 28% over 68 weeks, while novel molecules like MariTide offer prolonged dosing intervals. Simultaneously, the development of oral small-molecule agonists (e.g., Orforglipron, VK2735) and high-dose oral peptides (Semaglutide 50 mg) enhance the potent, food-independent, injectables alternatives. Beyond weight reduction, these agents exhibit significant pleiotropic benefits, including cardiovascular protection, improved glycemic control, and the resolution of hepatic steatosis. However, challenges such as gastrointestinal intolerance, the risk of weight regain following cessation, and rare idiosyncratic liver signals in small molecules remain critical considerations. Next-generation anti-obesity medications represent a

therapeutic revolution, bridging the gap between behavioral modification and surgical intervention. While they are not universal panaceas, their integration into a holistic, chronic-care model offers a realistic pathway to mitigating the global obesity epidemic and its associated comorbidities.

Introduction

Obesity is no longer viewed only as a "lifestyle choice" or a lack of willpower. It is now recognized as a complex, chronic, and relapsing disease that stands as one of the most pressing health challenges of our time. Far from being a simple matter of overeating, it is driven by a deep-seated interplay between our genetic blueprint, our modern environment, and a dysregulated neuroendocrine system that traps the body in a cycle of persistent positive energy balance[1]. According to the World Health Organization, this is a crisis of staggering proportions: more than one billion people worldwide are now living with obesity, a number that has more than doubled in adults and quadrupled in adolescents since 1990[2]. Crucially, this epidemic has broken past the borders of high-income Western nations, now placing an immense burden on low- and middle-income countries where healthcare systems are often least equipped to handle its long-term complications[2,3]. Clinically defined by a Body Mass Index (BMI) exceeding 30 K/m^2, a definition that may require broadening to include organ or tissue dysfunction, obesity serves as a major factor for a range of comorbidities[4]. These include Type 2 Diabetes Mellitus (T2DM), hypertension, dyslipidemia, obstructive sleep apnea, and a significantly heightened risk for various malignancies, including colorectal and breast cancer[5,6].

The pathophysiology of obesity has been recently investigated, revealing an increasing number of critical signal transduction pathways. Among these, the MAPK (Mitogen-activated protein kinases), PI3K/AKT (Phosphatidylinositol 3-kinase), JAK/STAT (Janus kinase / signal transducer and activator of transcription), and Wnt/β-catenin signaling pathways have been closely implicated in the development of obesity. Understanding these molecular mechanisms has paved the way for more effective, targeted, and precise therapeutic strategies[5]. The systemic low-grade inflammation associated with excess adipose tissue further accelerates cardiovascular aging, placing an immense burden on global healthcare infrastructures and reducing quality-adjusted life years (QALYs) across all demographics[7,8].

Traditional therapeutic strategies, which focus primarily on intensive lifestyle modifications, such as caloric restriction, increased physical activity, and cessation of harmful habits like tobacco and excessive alcohol consumption, remain the core of management. However, clinical evidence consistently demonstrates that for the vast majority of patients, lifestyle intervention alone is not sufficient to achieve and maintain significant weight loss due to strong compensatory starvation signals and metabolic adaptation[9,10]. Historically, the pharmacological landscape was limited by safety concerns and modest efficacy, often leaving a therapeutic gap between behavioral therapy and invasive bariatric surgery. The necessity for medical supervision in treating obesity is now indisputable, as the condition requires a chronic care model similar to that of hypertension or diabetes. This has necessitated the development of highly targeted agents that can modulate central appetite centers and peripheral metabolic pathways without the off-target cardiovascular or psychiatric side effects that plagued earlier generations of anti-obesity medications (AOMs)[11,12].

The recent paradigm shift in the pharmacology of obesity is defined by the emergence of incretin-based therapies, which have revolutionized our expectations for non-surgical weight loss. By lever-

aging the physiological roles of Glucagon-Like Peptide-1 (GLP-1), Glucose-dependent Insulinotropic Polypeptide (GIP), and Glucagon receptor (GCGR) these newer agents mimic endogenous hormones to enhance satiety, delay gastric emptying, and improve insulin sensitivity. These medications, originally developed for the management of T2DM, have demonstrated "bariatric-level" weight loss in large-scale clinical trials (such as the STEP and SURMOUNT programs)[13,14]. This pharmacological evolution marks a transition from simple appetite suppression to a more sophisticated metabolic reprogramming. As we move toward a precision medicine approach, understanding the pharmacological nuances, safety profiles, and long-term metabolic benefits of these poly-agonists is crucial for clinicians aiming to mitigate the global trajectory of obesity-related morbidity and mortality.

The primary objective of this review is to evaluate the clinical efficacy and pharmacological mechanisms of the newest generation of AOMs. Specifically, this paper will analyze the transition from mono-agonists to dual and triple-receptor agonists, discussing their impact on weight reduction and glycemic control. Furthermore, we aim to examine the safety data regarding their long-term use and explore their potential role in preventing cardiovascular outcomes. By synthesizing the latest evidence from recent clinical trials, this work seeks to provide a comprehensive framework for the integration of these novel agents into the modern therapeutic algorithm for obesity and metabolic syndrome.

Pharmacological Mechanisms and Therapeutic Actions of Next-Generation Anti-Obesity Agents

Incretin Mimetics and Multi-Receptor Synergies

The pharmacological landscape of obesity has been fundamentally transformed by the advent of incretin-based therapies over the last two decades. Glucagon-like peptide-1 (GLP-1) is a gut-derived hormone secreted from the L-cells of the distal ileum and colon in response to nutrient ingestion[15]. Recent evidence emphasizes the extensive benefits of using GLP-1 receptor agonists (GLP-1RAs) in treating a broad spectrum of conditions, including obesity, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), neurodegenerative disorders, and various forms of cancer[16]. As a potent insulinotropic agent, GLP-1 enhances glucose-dependent insulin secretion while simultaneously suppressing glucagon release from pancreatic alpha cells. However, its anti-obesity efficacy is primarily mediated through two distinct pathways: the central nervous system (CNS) and the gastrointestinal tract[5,17,18]. Centrally, GLP-1RAs act on the arcuate nucleus of the hypothalamus and the hindbrain to suppress eating[19]. By modulating pro-opiomelanocortin (POMC) neurons and inhibiting neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons, these agents induce profound satiety and reduce "food noise" or hedonic cravings. Peripherally, GLP-1RAs delay gastric emptying, which prolongs postprandial fullness and blunts glycemic spikes[18,19].

The evolution from mono-agonist to multi-receptor strategies represents a significant leap in pharmacological potency. The current pipeline focuses on combining GLP-1RAs with other entero-pancreatic hormones that offer complementary or synergistic potential, such as GIP, glucagon, and amylin[20]. This twincretin approach, exemplified by Tirzepatide, allows for supra-physiological weight loss. While GIP was historically considered diabetogenic due to its glucagonotropic effects, modern research suggests that GIPR agonism acts synergistically with GLP-1 to enhance energy expenditure and improve tolerability[21]. In the CNS, GIP receptors are expressed in areas that regulate energy balance. Their activation appears to buffer the nausea often associated with high-dose GLP-1RA while augmenting anorexigenic signals [20, 21].

Adding a third layer of complexity is the inclusion of Glucagon Receptor (GCGR) agonist in triple-agonist frameworks, such as Retatrutide. While glucagon traditionally increases blood glucose via hepatic glycogenolysis, its role in weight loss is centered on increasing metabolic rate and hepatic lipid oxidation[16,22,23]. To prevent the hyperglycemic potential of glucagon, these agents are balanced with potent GLP-1 and GIP components[22]. This triad creates a

powerful metabolic synergy, where GLP-1 and GIP reduce caloric intake while glucagon increases energy expenditure[23]. Furthermore, amylin analogues, such as Cagrilintide, are emerging as critical adjuncts. Amylin, which is co-secreted with insulin, is a vital target for achieving quality weight loss by focusing on fat reduction while protecting lean muscle mass. It primarily regulates meal size and slows gastric emptying through pathways distinct from incretins, often with less nausea[24].

The Oral Revolution

A pivotal frontier in obesity pharmacology is the transition from subcutaneous injectables to potent, patient-friendly oral formulations. This breakthrough was initially made possible by the use of permeation enhancers like SNAC (sodium salcaprozate), which locally raises gastric pH to shield the peptide from degradation while facilitating its transcellular absorption[25]. However, the next generation of small-molecule, non-peptide GLP-1RA represents an even greater leap forward. Unlike their peptide counterparts, these small molecules do not require complex absorption enhancers, are not susceptible to enzymatic digestion, and offer significantly higher oral bioavailability, making them far more versatile.

This shift toward oral administration is not merely a matter of convenience. It is a necessity in the strategic for managing obesity at the population level. While subcutaneous injections are undeniably very effective, they often face obstacles like low patient compliance and adherence due to needle phobia, which, depending on the patient profile, can limit their widespread use in primary care settings[26].

Oral agents, by contrast, allow for easier dose titration and seamless integration into daily routines, fostering broader acceptance across diverse cultural and socioeconomic groups. From a manufacturing and logistical standpoint, small-molecule orals are also far more efficient to produce and scale, avoiding the complex cold-chain requirements of biologics. This pharmacological evolution is mirrored in the market's explosive growth, with financial experts projecting that the global anti-obesity market will soar past $150 billion by the early 2030s[27].

Pleiotropic Effects and Systemic Clinical Benefits

The true therapeutic impact of these newer agents extends far beyond the numbers on a scale. Their multi-organ mechanisms of action yield profound pleiotropic benefits that address metabolic syndrome as a whole, rather than just adipose tissue mass. Cardiovascular protection is perhaps the most well-documented of these advantages[17,28]. By dampening systemic inflammation, refining lipid profiles, and inducing modest yet critical reductions in systolic blood pressure, GLP-1R and dual agonists have significantly lowered the incidence of Major Adverse Cardiovascular Events (MACE). Evidence suggests these agents may exert direct anti-atherosclerotic effects on the vascular endothelium while simultaneously reducing harmful myocardial fat accumulation.

Furthermore, the influence of these therapies on Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is transformative. By reducing hepatic lipogenesis and stimulating fatty acid oxidation, through the synergistic GIP and Glucagon pathways, these drugs can drastically reduce liver fat fraction and even show potential in reversing fibrosis[29]. Beyond metabolic markers, the mechanical and metabolic relief provided by significant weight loss, paired with central effects on respiratory drive, has proven these medications to be highly effective in reducing the severity of Obstructive Sleep Apnea (OSA), offering patients a path to better sleep and improved overall quality of life [30].

Comparative Analysis of Novel Anti-Obesity Agents: Clinical Trials and Efficacy Data

The clinical development pipeline for AOMs has expanded exponentially, transitioning from simple mono-agonists to complex multi-receptor poly-agonists. This chapter categorizes these emerging therapies into injectable and oral formulations, analyzing their Phase I-III clinical trial results, safety profiles, and metabolic outcomes.

Next-Generation Injectable Therapies

While first-generation GLP-1RAs such as subcutaneous Semaglutide provided the proof-of-concept for significant weight loss (mean weight loss of 20.7% at 72 weeks), the current research landscape is dominated by multi-functional molecules that target synergistic metabolic pathways. These agents aim not only for superior weight reduction (often exceeding 25% of total body weight) but also for improved preservation of lean muscle mass and extended dosing intervals to enhance patient compliance[31].

Retatrutide (LY3437943) represents the pinnacle of current injectable pharmacology. As a triple agonist, it targets the GLP-1, GIP, and GCG receptors. The inclusion of glucagon agonist is particularly revolutionary, as it increases resting energy expenditure and promotes hepatic lipid metabolism, counteracting the metabolic adaptation often seen during caloric restriction[32]. In a landmark Phase III trial (RIUMPH-4), Retatrutide demonstrated unprecedented efficacy. Patients receiving the highest dose (12 mg) achieved a mean weight reduction of 28.7% (compared to a 2.1% weight loss in the placebo cohort) by 68 weeks[33]. Beyond weight loss, Retatrutide showed significant metabolic improvements: glycated hemoglobin (HbA1c) levels decreased by up to 2.0%. Furthermore, the trial indicated secondary benefits in knee osteoarthritis pain scores and cardiovascular markers, including a significant reduction in systolic blood pressure and LDL cholesterol.

UBT251, originally developed by The United Laboratories and now co-developed by Novo Nordisk following an exclusive licensing agreement for territories outside China, is a potent triple GLP-1/GIP/glucagon receptor agonist. In a Phase II trial conducted in China, the compound demonstrated a dose-dependent weight loss reaching up to 19.7% at the highest dose after only 24 weeks of treatment, compared to 9.8% in lower-dose cohorts[34]. This molecule is specifically engineered to maximize energy expenditure through glucagon activation while leveraging the synergistic effects of GLP-1 and GIP on satiety and metabolic regulation. Following these robust results, Novo Nordisk has initiated Phase II clinical trials in North America, positioning UBT251 as a strategic contender to challenge the weight-loss benchmarks set by other triple-agonist therapies.

CT-388 by Roche, following its acquisition of Carmot Therapeutics, is a dual GLP-1/GIP agonist that recently reported a statistically significant placebo-adjusted weight loss of 22.5% at 48 weeks in Phase II trials using the highest 24 mg dose. This once-weekly subcutaneous injection demonstrated high potency without reaching a weight loss plateau, leading to a remarkable resolution of obesity (BMI <30 kg/m^2) in 54% of participants compared to only 13% in the placebo group. Designed to challenge the dominance of Tirzepatide in the twincretin market, CT-388 maintained a safety and tolerability profile generally consistent with its drug class, with no new or unexpected safety signals reported[35].

Amgen's MariTide (Maridebart cafraglutide or formerly AMG 133) introduces a unique "bispecific" mechanism that deviates from the conventional GIP seen in Tirzepatide. MariTide acts as a GLP-1 receptor agonist but a GIP receptor antagonist. This approach is based on genetic data suggesting that GIP receptor inhibition may protect against obesity[36]. Phase I data revealed a rapid weight loss of 14.5% in just 12 weeks at the highest dose, while Phase II trials demonstrated weight loss of up to 20% at 52 weeks. However, the most distinguishing feature of MariTide is its pharmacokinetic durability. Clinical data showed that 150 days after the last dose, patients maintained approximately 11% of their weight loss, suggesting that MariTide may allow for monthly or even quarterly dosing schedules, significantly reducing the treatment burden associated with weekly injections. Consequently, Amgen is already designing Phase III trials with a strategic focus on long-term weight maintenance and optimized dosing intervals[37].

Petrelintide is a long-acting injectable amylin analogue also targets calcitonin receptors to enhance metabolic signaling. It is being co-developed and co-commercialized for people living with overweight and obesity under collaboration between Roche and Zealand Pharma. Phase Ib (ZUPREME-1) results demonstrated a 10.7% weight loss over 42 weeks

versus 1.7% with placebo (p-value<0.001), with a remarkably favorable safety profile and high patient tolerability[38].

Amycretin by Novo Nordisk is a novel co-agonist of GLP-1 and Amylin being developed in both subcutaneous and oral formulations to maximize the synergy between peripheral glucose regulation and central satiety. In the Phase III trial involving patients with T2DM, the injectable formulation demonstrated a statistically significant weight loss of up to 24.3% at 36 weeks, alongside substantial glycemic control. Specifically, amycretin led to significant reductions in HbA1c, with up to 89.1% of participants achieving levels below 7%. These findings position amycretin as a critical component of Novo Nordisk's next-generation metabolic portfolio, offering a dual-action oral alternative to traditional injectable treatments[39,40].

CagriSema by Novo Nordisk is a fixed-dose combination of semaglutide and cagrilintide (GLP-1 and amylin analogue respectively) designed to leverage the synergistic effects of two distinct hormonal pathways[41]. Phase III data from the REIMAGINE 2 trial in adults with T2DM demonstrated encouraging results, with CagriSema achieving superior weight loss of 14.2% and a 1.91%-point reduction in HbA1c at 68 weeks compared to semaglutide alone. In this cohort, 43% of participants achieved a weight loss of ≥15%, while 24% reached the ≥20% threshold. However, despite these robust outcomes and a demonstrated 23.0% weight loss at 84 weeks in the open-label REDEFINE 4 trial, the primary endpoint was not met as the treatment failed to establish non-inferiority compared to high-dose tirzepatide[42]. Despite this clinical outcome, CagriSema continues to show a safety and tolerability profile consistent with its drug class, remaining a significant contender in the landscape of potent injectable metabolic therapies.

Survodutide (also known as BI 456906) by Boehringer Ingelheim and Zealand Pharma is another GLP-1/GCG agonist currently in Phase III trials (SYNCHRONIZE-1, SYNCHRONIZE-2 and SYNCHRONIZE-CVOT). Phase II data showed up to 18.7% weight loss at 46 weeks, with specific emphasis on its anti-fibrotic effects in the liver, positioning it as a potential breakthrough for metabolic-associated steatohepatitis MASH[43].

Pemvidutide by Altimmune is a balanced GLP-1 and glucagon receptor dual agonist whose primary clinical focus extends beyond weight loss to the significant reduction of liver fat content. Preliminary data suggest high effect in patients with concurrent MASLD with the drug being currently evaluated in the Phase IIb IMPACT MASH trial involving approximately 190 subjects [44]. This therapeutic approach is directly linked to obesity management because more than 80% of patients with MASH are overweight or obese, making a treatment option that simultaneously improves fibrosis and promotes weight loss the ideal clinical solution.

The Oral Revolution: Peptide and Non-Peptide GLP-1 Receptor Agonists

The transition from injectable to oral administration represents the "holy grail" of the obesity pharmacology. Historically, oral delivery of large peptides like semaglutide was hindered by gastric degradation and poor bioavailability. However, the development of permeation enhancers and the discovery of potent non-peptide small molecules have overcome these barriers, promising a new era of convenient, high-efficacy therapy.

The approval of oral semaglutide marked a historic milestone as the first-ever pill sanctioned by the FDA for the long-term management of obesity[45]. This breakthrough was further solidified by the OASIS 4 trial, where a daily 25 mg dose of oral semaglutide achieved a 16.6% mean weight loss over 64 weeks. Similarly, the OASIS 1 trial demonstrated a 15.1% reduction with a 50 mg daily dose over 68 weeks, with both results significantly outperforming the placebo groups[45,46]. These findings are transformative, as they demonstrate that oral peptide formulations can now match the weight-loss efficacy of many injectable counterparts. Furthermore, recent indirect comparisons suggest that oral semaglutide may offer superior weight reduction compared to orforglipron, alongside a lower likelihood of patients discontinu-

ing treatment due to side effects[47].

In contrast, recently approved orforglipron represents a different pharmacological approach as a novel, non-peptide small molecule[48]. Unlike semaglutide, orforglipron is not a protein, which means it remains stable against stomach acid and does not require any specific food or water restrictions, allowing patients to take it at any time of day. Long-term clinical data are equally compelling, with extended 72-week results showing sustained weight maintenance and further reductions reaching 12.4%[49,50]. Orforglipron emerges as a leading candidate for global obesity management due to its easy-to-use daily profile and the absence of complex cold-chain logistics.

VK2735 by Viking Therapeutics is a novel oral GLP-1/GIP dual agonist, being developed in both oral and subcutaneous formulations. It is attracting significant attention for its rapid onset of action for the potential treatment of various metabolic disorders such as obesity. In a Phase I study, a 100 mg oral dose led to 8.2% weight loss in just 4 weeks[51]. Subsequent Phase II data showed a reduction up to 12.2% at 13 weeks using a 120 mg dose. Viking is also investigating a maintenance protocol, transitioning patients to a lower 30 mg dose to sustain weight loss after the initial intensive phase [52].

Following the burgeoning trend of amylin-based co-therapies, oral amycretin, developed by Novo Nordisk, represents a pharmacological breakthrough as a long-acting, unimolecular co-agonist of both GLP-1 and amylin receptors. This first-in-class oral peptide leverages the complementary biology of satiety (via amylin) and glucose regulation (via GLP-1) in a single daily pill. Early clinical evidence from a first-in-human, Phase I trial demonstrated that amycretin maintains a safety and tolerability profile consistent with established incretin and amylin-based therapies, with adverse events being predominantly mild-to-moderate and gastrointestinal in nature[53]. Most notably, Phase II data revealed a rapid and significant weight loss trajectory, with participants achieving a 10.1% and 13.1% (50 mg and 100 mg respectively) reduction in body weight at 36 weeks[40].

CT-996 by Genentech/Roche positioned as a best-in-class oral treatment. It is a small-molecule agonist that can be taken regardless of food intake. Early Phase I data showed a remarkable up to 7.3% weight loss in only 4 weeks, outperforming many current competitors in terms of speed[54].

Another highly promising candidate in the small-molecule GLP-1RA pipeline is aleniglipron (formerly GSBR-1290) by Structure Tx. This non-peptide agent has demonstrated significant clinical momentum across its Phase II development program. Initial Phase IIa data reported a robust dose-dependent weight loss of 6.2% to 6.9% at just 12 weeks, which further progressed to 11.3% and 15.3% at 36 weeks for the 120 mg and 240 mg doses, respectively[55]. More recently, topline results from the Phase II ACCESS II Trial highlighted the drug's sustained efficacy over a longer duration. In this 44-week study, once-daily oral aleniglipron achieved a placebo-adjusted mean weight loss of 16.3% at the 180 mg dose and 16.0% at the 240 mg dose[56]. These findings underscore aleniglipron's potential to compete with both injectable and high-dose oral peptide therapies, offering a potent, small-molecule alternative.

AstraZeneca's AZD5004 is an oral, small-molecule GLP-1RA that offers the advantage of food-independent dosing. In early-stage clinical data presented at EASD 2024, a 5.8% mean weight loss was observed in just 4 weeks (Table 1). Following these results, the drug has advanced into the Phase IIb VISTA trial to further evaluate its long-term efficacy and safety as a cornerstone of metabolic care[57].

Limitations, Safety Considerations, and Challenges in Chronic Therapy

While established injectable therapies, such as semaglutide and tirzepatide[14,58], are not analyzed in this review due to their long-standing clinical presence, they serve as the gold reference for comparing the safety and efficacy profiles of emerging agents. Despite the unprecedented efficacy of the latest AOMs, their clinical utility is framed by significant pharmacological and practical limitations. The most pervasive challenges remain the gastrointestinal (GI)

Table 1: Clinical Profile of Emerging Anti-Obesity Agents

Name	Company	Mechanism	Route	Phase	Key Efficacy (Weight Loss)
Semaglutide	Novo Nordisk	GLP-1	Inj.	Approved	13.7% (72 weaks)
Tirzepatide	Eli Lilly	GLP-1 / GIP	Inj.	Approved	20.2% (72 weaks) 25.5% (84 weaks) (& low-calorie diet, exercise)
Retatrutide	Eli Lilly	GLP-1 / GIP / GCG	Inj.	III	28.7% (68 weeks)
UBT251	United Laboratories / Novo Nordisk	GLP-1 / GIP / GCG	Inj.	II	19.7% (24 weaks)
CT-388	Roche/Carmot	GLP-1 / GIP	Inj.	II	22.5% (48 weeks)
MariTide	Amgen	GLP-1 / GIP (Antag)	Inj.	II	20% (52 weeks) - Monthly dose
Petrelintide	Roche/Zealand Pharma	Amylin / Calcitonin	Inj.	II	10.7% (42 weeks)
Amycretin	Novo Nordisk	GLP-1 / Amylin	Inj.	II	24.3% (36 weeks)
CagriSema Semaglutide & Cagrilintide	Novo Nordisk	GLP-1 / Amylin	Inj.	III	23% (84 weeks)
Survodutide	Boehringer Ingelheim Zealand Pharma	GLP-1 / GCG	Inj.	III	18.7% (46 weeks)
Pemvidutide	Altimmune	GLP-1 / GCG	Inj.	II	15.6% (48 weeks)
Semaglutide Oral	Novo Nordisk	GLP-1 (Peptide)	Oral	Approved	15.1% (68 weeks) - 50 mg dose
Orforglipron	Eli Lilly	GLP-1 (Non-peptide, Small Molecule)	Oral	Approved	12.4% (72 weeks) - No food restrictions
VK2735	Viking Therapeutics	GLP-1 / GIP	Oral	II	12.2% (13 weeks)
Amycretin Oral	Novo Nordisk	GLP-1 / Amylin	Oral	I	13,1% (12 weeks) - 100 mg
CT-996	Genentech/Roche	GLP-1 (Small Molecule)	Oral	I	7.3% (4 weeks)

Aleniglipron	Structure Tx	GLP-1	Oral	II	16% (44 weeks)
AZD5004	AstraZeneca	GLP-1	Oral	I	5.8% (4 weeks)

adverse events, which are intrinsically linked to the mechanism of GLP-1 and amylin agonist. Common adverse effects include nausea (28-44%), diarrhea (21-30%), and constipation (11-24%), particularly during the dose-escalation phase[59]. While these are generally transient, they can lead to treatment discontinuation in a subset of the population.

A more complex challenge is the "weight regain" phenomenon observed following drug cessation. Data from withdrawal studies indicate that most patients regain a significant portion of their lost weight within one year of therapy cessation, underscoring the chronic, relapsing nature of obesity. This suggests that AOMs may require indefinite administration, similar to anti-hypertensive or lipid-lowering therapies[60].

Furthermore, as industry pivots toward small-molecule oral agonists, unique safety signals have emerged. Unlike peptide-based drugs, some non-peptide small molecules carry a theoretical risk of idiosyncratic drug-induced liver injury (DILI)[61]. For instance, the experimental oral GLP-1 agonist TERN-601, Danuglipron and earlier prototypes of other small molecules have faced scrutiny due to elevations in hepatic enzymes, which in some cases necessitated the termination of development programs[62,63]. These signals emphasize the need for rigorous, long-term safety monitoring as we move beyond the highly predictable safety profiles of peptide mimetics.

It is imperative to underscore that the pharmacological advancements discussed in this review are not "lifestyle drugs" designed for cosmetic weight loss, but potent medical interventions for a chronic, life-threatening disease. Obesity is a complex pathological state that demands a shift in perspective, from a focus on aesthetics to the mitigation of serious clinical risks. Therefore, these medications must only be administered under strict medical supervision and through shared decision-making between patients and clinicians. Primary care clinicians play a vital role in this process, developing flexible treatment plans that reflect patient preferences and clinical feasibility. AOMs should not be seen as a standalone, effortless solution. Instead, it serves as a powerful adjunct to lifestyle interventions, including nutritional therapy and physical activity. Ultimately, a successful long-term outcome requires an integrated, multidisciplinary approach, one that combines cutting-edge pharmacology with a holistic commitment to improving overall health and quality of life[12,64].

Conclusion

Obesity is fundamentally a chronic, multi-factorial disease, not a failure of willpower or a mere aesthetic concern. Its management necessitates a holistic, medicalized approach that integrates pharmacological intervention with structured lifestyle modifications, including caloric restriction and physical activity. The next generation of GLP-1 receptor agonists and multi-receptor poly-agonists (GIP/GCG/Amylin) marks a genuine revolution in metabolic medicine, offering a powerful tool to reduce the global burden of cardiovascular mortality and metabolic comorbidities.

The evolution from subcutaneous injectables to potent, food-independent oral formulations is expected to transform the therapeutic landscape, making evidence-based obesity care more accessible, affordable, and acceptable to a broader patient population. However, these medications are not simplistic fixes. Their success depends on their integration into a comprehensive care model that prioritizes long-term health, prevents weight regain, and manages the systemic complexities of the disease. As we move toward this new paradigm, the focus of clinical practice must remain on the sustained improvement of quality of life and the mitigation of the severe clinical

consequences associated with the obesity epidemic.

Statements and Declarations

The authors have no competing interests to declare that are relevant to the content of this article.

The authors declare that they have no conflict of interest.

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