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Obesity: A Persistent Puzzle-Unveiling Past Missteps and Future Promise in Drug Discovery

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Abstract

Since obesity is a chronic, multifaceted, and heterogeneous disease influenced by genetic, biological, and environmental factors, it is imperative to approach obesity with an included and complete treatment strategy. Obesity is one of the resulting causes of morbidity and mortality worldwide, and its incidence is increasing globally. Despite significant advancements in the treatment of obesity-related conditions such as high blood pressure, type 2 diabetes, and high cholesterol, treating obesity itself remains a challenging undertaking. Many antiobesity medications (AOMs) don't work as prescribed, leading to insufficient weight loss and safety concerns. This review investigates the evolution of AOM, highlighting past successes and failings to shed light on contemporary problems. Recent advances, particularly in understanding the molecular dialogue between the gut and brain, offer prospective avenues for the next generation of AOMs. These might hold the key to safely and effectively accomplishing substantial, long-term weight loss.

السمنة: لغز مستمر ـ كشف الأخطاء الماضية والوعد المستقبلي في اكتشاف الأدوية

سرى لطيف الخفاجي،محمد فنوخ العوادي

الخلاصة

السمنة مرض مزمن متعدد الأوجه وغير متجانس يتأثر بالعوامل الوراثية والبيولوجية والبيئية. لذلك، من الضروري معالجة السمنة باستراتيجية شاملة ومتكاملة. تعد السمنة أحد الأسباب الرئيسية للإصابة بالأمراض والوفاة في جميع أنحاء العالم، وتزداد معدلات الإصابة بها على مستوى العالم. وعلى الرغم من التقدم الكبير في علاج الأمراض المرتبطة بالسمنة مثل ارتفاع ضغط الدم والسكري من النوع الثاني وارتفاع الكوليسترول، إلا أن علاج السمنة نفسها لا يزال تحديًا كبيرًا. لا تعمل العديد من أدوية مكافحة السمنة كما هو مقرر مما يؤدي إلى فقدان الوزن غير الكافي ومخاوف تتعلق بالسلامة. تبحث هذه الورقة تطور أدوية مكافحة السمنة مع تسليط الضوء على النجاحات والفشل في الماضي لإلقاء الضوء على المشاكل المعاصرة. تقدم التطورات الحديثة ولا سيما في فهم الحوار الجزيئي بين الأمعاء والدماغ، مسارات واعدة للجيل القادم من أدوية مكافحة السمنة لتحقيق فقدان الوزن بشكل كبير وطويل الأمد بأمان وفعالية.

1. Introduction

One of today's most significant problems in healthcare is controlling excess body fat (Bauer et al. 2014; A et al. 2017). Over two-thirds of Americans suffer from excess body weight, with over one-third of adults and 20% of adolescents obese. Since 1975, the prevalence of obesity has nearly tripled worldwide. Obesity raises the risk of dying from cancers of different organs of the body (Calle et al. 2003; Calle 2007; Berrington de Gonzalez et al. 2010). It also increases the occurrence of disorders, including diabetes type 2 T2D) (Can and Can 2018) and cardiovascular diseases (CVD) (Powell-Wiley et al. 2021). The ongoing COVID-19 pandemic has clearly shown that it makes managing several illnesses more difficult and increases the likelihood of unfavorable results. Individuals with a body mass index (BMI) ranging from 30 to 34.9 kg/m^{-2} are at a higher risk of mortality overall compared to those of average mass. This risk increases to about 40% when the BMI exceeds 40 kg/m^{-2}, and ultimately reaches 100%. Obesity is associated with a worse prognosis for several malignant diseases (Calle et al. 2003; Calle 2007), and it is believed that 4–9% of all cancer cases are related to extra body fat (Arnold et al. 2016). Depending on the severity of the additional weight, how long it has been present, and whether or not concurrent conditions have emerged, obesity is linked to a shortened life expectancy by 2.4 years (Abdelaal et al. 2017; Ward et al.2022) Regarding psychological, neurological, respiratory, gastrointestinal, renal, musculoskeletal, and endocrine problems, obesity raises the risk early in life (Salama A. 2023). The following factors may exacerbate weight gain: lack of sleep (McNeil et al. 2024), circadian disruption (McNeil et al. 2024), long-term stress (Ajoolabady et al. 2022), and usage of psychiatric and anti-epileptic medications. Both genetic and environmental variables significantly influence the variance in BMI (Williams and Periasamy 2020; Sørensen et al. 2022). With a roughly 40–70% heritability estimate (Bray et al. 2016), the genetic component of BMI is similar to that described for Tourette syndrome (58–77%) (Davis et al. 2013), 66 percent psoriasis (Grjibovski et al. 2007), cardiovascular disease (34–53%) Breast cancer (25–56%) (Grjibovski et al. 2007; Mbemi et al. 2020)**.** The widespread notion that a lack of self-control leads to obesity is becoming less stigmatized as obesity is now recognized as a chronic, degenerative disease (Bray et al. 2017; Burki 2021).This furthermore offers the structure for medical professionals and insurance providers to set up programs to manage obesity, encourages funding for scientific and clinical research, and pushes drug manufacturers to provide body weight management plans. The main justification for treating obesity as a chronic illness rather than a risk factor is the pathophysiology specific to obesity, which both causes and defends excess fat development, together with physiological processes that impede calorie loss and promote weight (Blüher 2019). Biological system changes may be the reason behavioral interventions don't work for long-term weight loss. The best way to manage obesity is with medicine and/or surgical procedures, being the most successful. Environmental and behavioral treatments have a modest level of efficacy. Improved laparoscopic methods extend life expectancy and improve blood circulation, sugar level, and lipid regulation, but they cannot fully address global medical needs. The search for antiobesity drugs (AOMs) has been challenging due to social and technological challenges. Over the past 20 years, rational drug development efforts have been limited, with problems such as increased suicide risk, drug dependence, and cardiovascular consequences. (Farooqi 2014). As a result, some medications (Phentermine, amfepramone, and cathin hydrochloride) are only advised for short-term use because of their propensity for addiction or the formation of tachyphylaxis. (Farooqi 2014; Lucchetta et al. 2017a) However, Phentermine is still a commonly prescribed long-term AOM since actual study data has not shown it to have

unfavorable effects on the heart Table 1. Recent advancements in glucagon-like peptide one receptor GLP1R agonists, like semaglutide 2.4mg, fuel optimism for effective medication-based obesity treatment. This FDA-approved drug, combined with lifestyle changes like diet and exercise, gives adults who are obese or overweight and have a weight-related condition encouraging outcomes for long-term control of their weight. Now that liraglutide of 3 mg was approved by the FDA in 2020 for treating obesity in teens aged 12 to 17, and in 2014 for managing adult obesity, this is the second GLP1R agonist approved for body weight management. Most weight-loss drugs, apart from semaglutide 2.4mg (Davies et al. 2021; Rubino et al. 2021;Wilding et al. 2021; Wadden et al. 2021), deliver modest results (less than 10% weight loss on average). Even then, only a few people can achieve and keep off this level of weight loss without experiencing significant side effects. Without the possibility of misuse, tachyphylaxis, or other negative consequences that have previously dogged this sector, Reduced risk of Hypertension and other diseases, along with a notable and sustainable reduction in excess weight, are the goals of an optimal AOM (Jin et al. 2023). This article reviews the history of drug therapy for obesity, contemporary problems, and recent advancements in developing AOMs. CVD, cardiovascular disease; DNP, 2,4-dinitrophenol; ER, extended-release; GLP1R, glucagon-like peptide one receptor; SR, sustained release.

1.1.Control of Body Mass

The need to maintain body fat has probably been a driving force behind human evolution in response to environmental pressures for survival. This acquired benefit has become a liability with growing industrialization and easy access to high-fat foods. In a remarkably narrow range, our bodies use both peripheral and central systems to defend body weight and fend off a wide range of threats, from hunger to chronic overfeeding. Rarely more than a 20% change in body weight is linked to even the less carefully monitored long-term effects. The brain controls appetite and the body's energy metabolism, and it contains the majority of the gene products and pathways linked to obesity in many different gene studies (Collen et al. 2023; Neurology and 2021 2021) Fig.1. However, as past studies have repeatedly demonstrated, selectively targeting cellular circuits is necessary to directly manipulate the central nervous system (CNS) signaling pathways. This remains a technological challenge. Medications would likely need to target energy intake and consumption for the best chance of success with weight loss. However, changing the core "survival" processes is a difficult task that has resulted in removing numerous AOMs Table 1. The difficulty is striking a balance between increasing psychological significance and promotig a healthy metabolism, all while maintaining safety and tolerability. Although the late stage treatment candidates hold more promise, existing medications only achieve a small portion of the intended performance. (O'Neil et al. 2018a; Kushner et al. 2020) Better information of hunger and energy use has allowed AOMs to be constructed, with the fast weight loss following bariatric surgery providing a model for AOMs to come. **The AOM's past**. Antiobesity medications often reduce appetite, prevent fat absorption, or boost the production of heat and calorie burning Fig.2.

Table 1: The Past of Antiobesity Medications

Drug	Company	FDA Approval	Possible adverse effects	Ref
Mitochondrial uncoupler				
DNP	Stanford University	1933–1938 (USA)	treatment ≥52 weeks Hyperthermia, tachycardia, fever, tachypnoea, death	(Müller et al., 2018)
Sympathomimetic				
Diethylpropion/afepramone	Merrell National Drug	1959–present (EU)	Nausea, constipation, insomnia, headache, tension and irritation, seizures	(Müller et al., 2018)
Methamphetamine	Abbott Laboratories	1947–1979 (USA)	Nigh risk for abusiveness and addiction	(Müller et al., 2018)
Phentermine	Teva Pharmaceuticals	1959–present (USA, only for short-term use)	Palpitations, elevated blood pressure	(Antel & Hebebra, 2012)
Cathine (nor-pseudoephedrine	Riemser Pharma	1975–present (EU, only for short-term use)	Tachycardia, increase in blood pressure, restlessness, sleep disorder, depression	(Hauner et al., 2017)
Phenmetrazine	Ciba-Geigy Corp	1956–present (USA	Nausea, diarrhea, dry mouth	(Müller et al., 2018)
Fenfluramine and dexfenfluramine	Wyeth Ayerst	1973–1997 (USA	Cardiac valvular insufficiency and pulmonary hypertension.	(Carvajal et al., 2000)
Sibutramine	Abbott Laboratories	1997–2010 (USA, EU)	Non-fatal myocardial infarction and stroke (in individuals with pre-existing CVD)	(James et al., 2010)
Polypharmacy				
Rainbow pills	Clark & Clark and others	1961–1968 (USA)	Insomnia, palpitations, anxiety, increase in heart rate and blood pressure, death	(Müller et al., 2018)
CB1 receptor blocker				
Rimonabant	Sanofi SA	2006–2009	Depression, suicidal ideation	(Van Gaal et al., 2008)
Pancreatic lipase inhibitor				
Orlistat	Roche Pharmaceuticals	1999–present (USA, EU)	Liver injury, gastrointestinal symptoms	(Nelson & Miles, 2005)
5-HT2C serotonin agonist				
Lorcaserin	Arena Pharmaceuticals	Eisai 2012–2020 (USA)	Depression, suicidal ideation, palpitations, gastrointestinal symptoms, increased cancer risk	(Smith et al., 2010)
Sympathomimetic/anticonvulsant				
Phentermine/topiramate ER (with titration)	Vivus	2012–present (USA)	Depression, suicidal ideation, cardiovascular events, memory loss, birth defects	(Garvey et al.; Lei et al., 2021)
Opioid receptor antagonist/dopamine and noradrenaline reuptake inhibitor				

Naltrexone SR/bupropion SR (with titration)	Orexigen Therapeutics Inc.	2014–present (USA, EU	Seizures, palpitations, transient blood pressure elevations	(Carbone et al., 2021)
GLP1R agonists				
Liraglutide	Novo Nordisk	2014–present (USA, EU)	Nausea/vomiting, diarrhea, constipation, pancreatitis, gallstones	(Pi-Sunyer et al., 2015)
Semaglutide	Novo Nordisk	2021 (USA)	Nausea/vomiting, diarrhea, constipation	(Wilding et al., 2021)

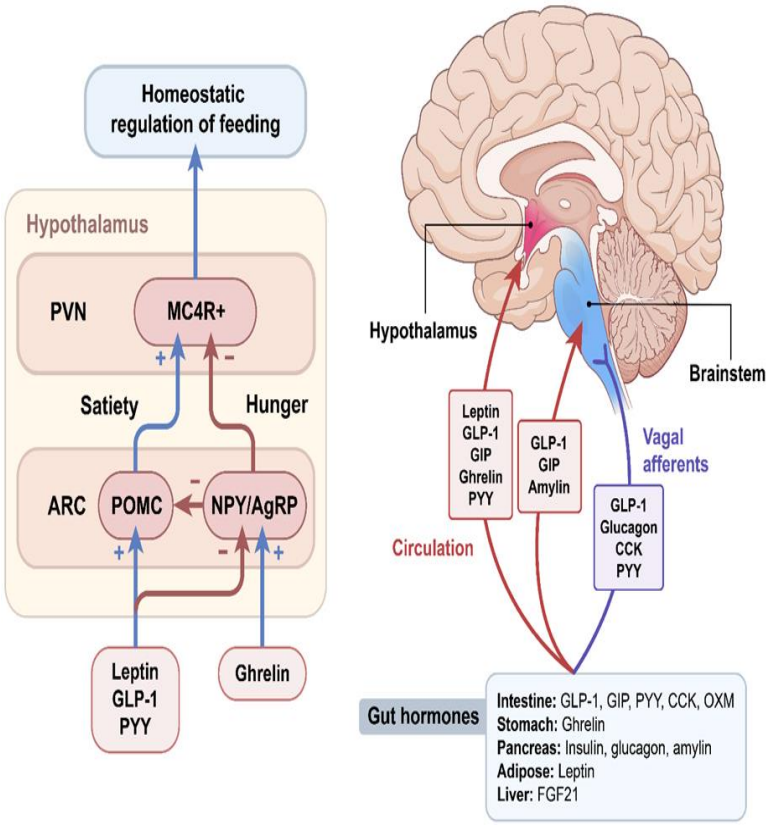

Figure 1: Control of food intake by the gut and brain. By influencing integrated neuronal circuits in the hypothalamus and brainstem, several peripheral hormones, including gut hormones, control how much food is consumed. Anorexic neurons that produce pro-opiomelanocortin (POMC) and appetite-inducing neurons that co-express agouti-related peptides (AgRP) and neuropeptide Y (NPY) are part of the hypothalamic melanocortin system, which serves as a major hub for the regulation of homeostatic food intake. The vagus nerve afferents that go to the nucleus tractus solitaries in the hindbrain or the circulation that reaches the brainstem's region postrema and the median eminence of the hypothalamus serve as the pathways via which gut-brain communication occurs. ARC, arcuate nucleus, cholecystokinin, FGF21, fibroblast growth factor 21, GIP, glucose-dependent insulinotropic polypeptide, GLP-1, glucagon-like peptide-1, MC4R, melanocortin 4 receptor, OXM, oxyntomodulin, PVN, paraventricular nucleus, and PYY, peptide tyrosine tyrosine. (Roh and Choi 2023)

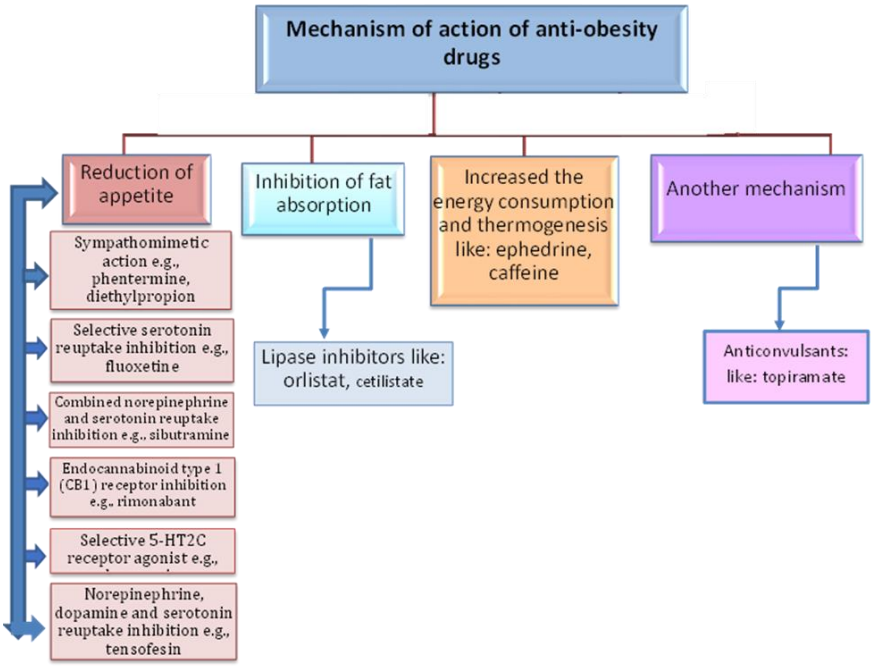

Figure 2: Mechanism of Action of Antiobesity Agents.

Drug treatment for obesity has a convoluted and dramatic past, marked by the withdrawal of promising medications because of safety concerns (Müller et al. 2018a). Over the past century, several medication combinations (rainbow pills) that had been approved by regulators but were quickly withdrawn because of dangerous side effects have been used to treat obesity. These include the usage of several centrally acting sympathomimetics, including Phentermine, cathine, and diethylpropion, which are still prevalent. Drugs such as mitochondrial uncouplers (Müller et al. 2018a), sympathomimetics (Lucchetta et al. 2017b; Müller et al. 2018a), lipase inhibitors (Kumar and Chauhan 2021), cannabinoid receptor antagonists (Després et al. 2005; Van Gaal et al. 2005; Pi-Sunyer et al. 2006), serotonergic agonists (Ditschuneit et al. 1996; Smith et al. 2010; Khera et al. 2016), and an expanding family of gastrointestinal-derived peptides (Davies et al. 2021b), (Müller et al. 2018a) have all been studied to obesity. When weight loss increases, several significant acute or long-term side effects follow (Table1). The recently approved GLP1R agonist semaglutide 2.4 mg, with one notable exception, decreased the body's mass after 17 months of administration by −14.9% as opposed to −2.4% in individuals receiving a placebo who were obese or overweight but did not have diabetes in phase III clinical trials. AOMs control energy balance through central or peripheral pathways (Cawley and Meyerhoefer 2012 and Yanovski 2021; Wen et al. 2022), such as Orlistat, which lowers dietary fat absorption. They also modulate serotonergic, noradrenergic, or dopaminergic action to enhance satiety. Some AOMs raise energy expenditure by promoting lipolysis or thermogenesis (Müller et al. 2018a), like Phentermine and other sympathomimetic drugs, which stimulate β-adrenergic receptors and raise norepinephrine levels. Topiramate and Phentermine modulate GABAergic neurotransmission (Antel and Hebebrand 2012), affecting energy metabolism and potentially promoting thermogenesis despite potential vasoconstriction and elevated sympathetic tone (Walter et al.

2014). Despite AOMs' failures, licensed medications like Orlistat, naltrexone/bupropion, liraglutide, and semaglutide are available for obesity management and behavioral changes. Bupropion, an opioid antagonist, blocks opioid receptors in the hypothalamus, stimulating feeding. When combined with naltrexone, it reduces food intake and may increase blood pressure in hypertension patients (Carbone et al. 2021), but no adverse cardiovascular events were found. (Nissen et al. 2016). Liraglutide, a GLP1-based AOM, was licensed for adult obesity treatment in 2014 and 2020 for weight management in obese adolescents. It was previously used for T2D. The LEADER trial showed decreased adverse cardiovascular events. (Nissen et al. 2016) Constipation, vomiting, diarrhea, and nausea are the most frequent gastrointestinal adverse events reported by patients receiving subcutaneous liraglutide 1.8 mg (Pi-Sunyer et al. 2015). Compared to placebo controls, semaglutide, approved by the FDA more recently, reduces body mass to around 15% after 17 months of administration (at a dose of 2.4 mg). While the usual side effects of GLP1—mainly nausea, vomiting, diarrhea, and constipation—remain prevalent, the medication is generally well-tolerated (Wilding et al. 2021a).

1.2.The Difficulties Facing The Progress of Aoms

1.2.1. Variability in Patient Groups

Obesity is a multifactorial illness with rare cases of monogenetic aetiology (Neurology and 2021 and more prevalent cases of multifaceted origin for neurobehavioral, hormonal, and biochemical causes. (Li et al. 2015; Chatterjee and Davies 2018; Udler et al. 2018; Ahlqvist et al. 2018; Xue et al. 2022). Almost every chromosome has quantitative trait loci and obesity-related risk factors (Fall and Ingelsson 2014; Bouchard 2020; Meier 2012). There may yet be more variables that predispose to obesity due to epigenetic processes (Hoggart et al. 2014; Huypens et al. 2016). It is crucial to do further scientific research to understand epigenetic, inherited, and ambient risk factors better since they may influence each person's response to specific pharmacotherapies and explain variations in BMI (Melvin et al. 2018). Over 10% of highly obese children have rare genetic abnormalities (Aykut et al. 2020), including loss-of-function mutations in genes encoding pro-opiomelanocortin (Langdon 1999)76], melanocortin receptors(MC4R) (Trevellin et al. 2021; Le Collen et al. 2023), leptin receptors, and leptin (Mazen et al. 2023), with obesity-associated gene mutations and fat mass being prevalent polygenic risk factors. A comprehensive understanding of metabolic and genetic characterization, disease etiology, and drug action mechanisms could improve patient care and advance the next generation of AOMs. The success of different mechanisms in obesity treatment remains uncertain.

1.2.2. A Consideration of Neuroendocrine Systems

In the hypothalamus and other brain areas, several peripherally derived endocrine variables work in concert to control appetite by influencing particular neurocircuits (Friedman 2003; Friedman 2004; Friedman 2009) (Figure 1). This strictly regulated system is vital to its existence. Still, because it gradually protects against undernutrition and negative energy balance, it has become a significant barrier to attaining appreciable body weight loss (Kraschnewski et al. 2010; MacLean et al. 2011; Leibel et al. 2015). The most likely reason for this phenomenon is that weight loss causes a drop in peripheral adiposity signals, such as insulin and leptin, and extended fasting increases susceptibility to and production of orexigenic neuropeptides in the hindbrain and hypothalamus. The chronic rise of insulin and leptin causes sensitivity and impairs the responsiveness of this homeostatic system, which is another barrier in the drug therapy of weight loss (Kumar et al. 2020)85]. A noteworthy observation that bolsters this viewpoint is that leptin

replacement is essentially useless in more prevalent polygenetic types of obesity but exhibits exceptional efficiency in reducing the weight of the body in those inherent leptin insufficiencies (Gibson et al. 2004; Von Schnurbein et al. 2013).

1.2.3. Effects on Body Weight

Research indicates a strong relationship between mammals and rodents regarding the ability of different drugs to reduce body weight. Meta-analyses confirm animal models to predict the effects of naltrexone/bupropion on humans (Tak and Lee 2021a). Incretin-based therapy with peptides like exendin 4, liraglutide, semaglutide, and tirzepatide lowers body weight in rodents (Coskun et al. 2018; Gabery et al. 2020a) and human (Berrington de Gonzalez et al. 2010; Frias et al. 2018; O'Neil et al. 2018). However, body mass is reduced in patients with diabetes, possibly due to insulin resistance and chronic hyperglycemia (Davies et al. 2021c; Wadden et al. 2021; Wilding et al. 2021b; Rubino et al. 2021b). Weight loss effects in rodents are generally more effective than in humans, but their effectiveness is historically lower. Mice have higher mass-specific energy expenditure and brown adipose tissue (Tschöp et al. 2012), making them more susceptible to drugs affecting energy expenditure. This makes them more susceptible to pharmacological inhibition of food intake.

1.2.4. Metabolizing Lipids and Glucose

A five to ten percent reduction in body weight can result in a medically significant improvement in blood pressure, serum triglycerides, HDL cholesterol, HbA1c, and blood pressure. Additional weight loss gradually amplifies these cardiometabolic improvements (Wing et al. 2011). Improved sensitivity to insulin and reduced hepatic and abdominal fat deposition are linked to even slight weight reduction., and improved β-cell activity. Certain AOMs can obtain additional benefits to cardiometabolic outcomes through their direct improvement of glycaemic management.

Specifically, GLP1R and GIPR agonists raise blood sugar levels by increasing insulin secretion (Müller et al. 2019) and slowing the rate at which glucose enters the bloodstream by delaying stomach emptying (MO Goodarzi 2018). Following a year of treatment with liraglutide (Khera et al. 2018), phentermine/topiramate, Orlistat, and naltrexone/bupropion, a large-scale meta-analysis that included 29,018 individuals revealed modest to moderate improvements in glucose metabolism. Along with low to somewhat enhanced LDL cholesterol, all of these medications—aside from Orlistat—also boosted HDL cholesterol (Khera et al. 2018) Recently, in a 26-week placebo-controlled study II research, trizepatide significantly reduced fasting blood glucose, lipids, and HbA1c while showing superior efficacy to dulaglutide (Frias et al. 2018a). Tirzepatide reduced HbA1c, fasting glucose, and body weight more effectively than a 1 mg dose of semaglutide in phase III clinical studies, regardless of the tested doses. (Frías et al. 2021). Tirzepatide therapy reduced HbA1c in 29-51% of patients compared to semaglutide 1 mg and helped patients lose weight in 15%-40% of cases. The agonist PF-05231023 decreases body weight and enhances metabolism through the action of fibroblast growth factor 21 (FGF21) agonists. PF-05231023 improved the metabolism of lipids in people considerably, although it did not significantly improve blood sugar (Talukdar et al. 2016). Although less specific, the effect on body weight is less than observed in preclinical studies or compared to incretin-based therapy. It has not yet been proven that longer trials or higher doses can result in clinically meaningful weight loss or better glucose metabolism, similar to what is seen in rats. Nonetheless, it is noteworthy when the pharmacological profile seen in preclinical research has become regrettably different in a clinical investigation.

1.3.Safety

The following generation of AOMs must consider human diversity while posing safety and toxicity concerns. Early research is influenced by commercial factors, which results in the underrepresentation of specific patient populations. Clinical studies do not include patients with extreme obesity or younger ages; instead, they concentrate on large, middle-aged patients with typical severity. Pharmacotherapy for weight loss places safety on reaching the maximum amount of weight lost, then modifies lifestyle and continues therapy with AOMs to lower the risk of escalated therapy. CVD is the leading cause of obesity-related deaths (Di Angelantonio et al. 2016). Hence, weight loss interventions should be the main priority. Pharmacotherapy, however, can have a variety of effects; some can improve cardiovascular health, while others can make it worse. Abuse hazards increase because of the cosmetic attractiveness of weight loss. The purpose of the SELECT study is to evaluate these results (Ryan et al. 2020). Amphetamines release norepinephrine, increasing heart rate, blood pressure, and cardiac contractility. Misuse can lead to tachycardia, dysrhythmias, and chest discomfort, leading to its discontinuation in the 1940s. (Mladěnka et al. 2018).

Diethylpropion and Phentermine were created to preserve anorectic activity while less impacting the brain's and heart's reward mechanisms (Paccosi et al. 2020). Clinical trials reveal no adverse effects on heartbeat or arterial pressure. (Tak and Lee 2021b; Zhang et al. 2021a). However, There have been documented instances of rare Postpartum haemorrhage (PPH) and heart valve disease, and their distribution has been stopped. In 1997, fenfluramine and dexfenfluramine were discontinued due to PPH and valvular heart disease risks (Cannistra et al. 1997; Jick et al. 1998); however, sibutramine was taken off the market because it raised the risk of stroke and non-fatal myocardial infarction (MI). (Hayes et al. 2015; Mladěnka et al. 2018). Sibutramine raises blood pressure (Florentin et al. 2008; McAllister et al. 2009), heart arrhythmia, and the heart rate (Florentin et al. 2008; James et al. 2010; Seimon et al. 2015). Naltrexone/bupropion and Orlistat improve blood pressure, while phentermine/topiramate has incredible cardiovascular benefits. (Khera et al. 2018) Liraglutide and semaglutide improve cardiovascular outcomes in T2D patients. Some food intake-reducing drugs did not work in clinical studies due to poor cardiac safety. Often, this was due to variations between species and an absence of preclinical models to use. Animals, like rodents, are less reliable in predicting human cardiovascular safety. The majority of obese people are older, suffering from diabetes and other related conditions, as well as CVD. With such a heterogeneous patient population, the risk of using AOMs is complex to accurately capture preclinically. Trials of cardiovascular outcomes are necessary to assess cardiovascular safety and possibly decrease cardiovascular risk in patients who are obese but do not have significant cardiac risk factors. In these kinds of clinical research, specific characteristics that have together led to medication failure because of harmful cardiac consequences have become apparent. As a result of growing awareness, cardiovascular pharmacology is now given more attention and positive cardiovascular results must be demonstrated so that an AOM can be approved and distributed more widely.

1.4.Innovative Approaches To Treating Obesity.

Despite some setbacks, the scientific community has focused on several noTabletreatment targets: (Arch 2015; Wharton and Serodio 2015; Müller et al. 2018b; Srivastava and Apovian 2018). They display technological advancements in identifying and progressing new medication candidates for human investigation. The primary therapy goal was obesity, and four target areas—growth differentiation factor 15 (GDF15), ghrelin, and mitochondrial

uncouplers were started and progressive. Studies on incretins, particularly GLP1 and amylin, primarily focused on diabetes due to reduced body weight. Late-phase AOM candidates activate GIPR and GLP1R, setting higher performance standards.

1.5.Drug Candidates Related To GLP1

Over the past few decades, increasing biology has advanced, discovering a family of approved GLP1R agonists (Nauck et al. 2021). The development of these drugs was partly prompted by the success of oral DPP4 inhibitors, which increase the levels of endogenous GLP1 and GIP in the bloodstream and enhance glycaemic control without increasing the chances of hypoglycemia. (Gallwitz 2007; Goldsmith et al. 2015; Barboza et al. 2022).

Parenteral administration of active hormone paralogs and synthetic analogues increased the level of circulating medications, leading to better glucose control and an understanding of the intrinsic weight-loss potential of GLP1R agonism. Early clinical trials with GLP1R agonists showed minimal weight loss that was somewhat comparable to that seen with other GI hormones (Huthmacher et al. 2020). It was difficult to determine how much weight loss was due to undesirable local GIT symptoms that reduced appetite because the pharmacological findings were associated with substantial effects on motility in the GI tract. Peptide analogues and dose titrations improved GLP1R agonism treatment, reducing adverse gastrointestinal effects and enhancing metabolic and weight-loss effects Fig.3.

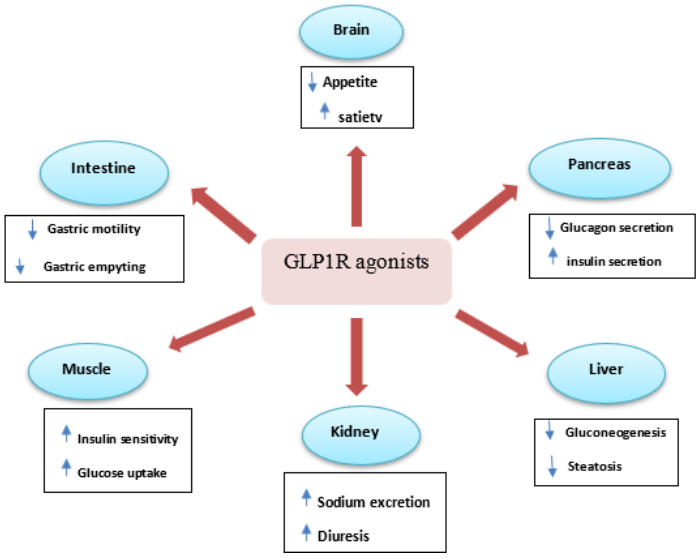

Figure 3: Peripheral and Central Effects of GLP1R Agonists

Liraglutide 3mg, the first GLP1R agonist for obesity treatment, showed a mean weight loss of 8% after a year, potentially improving metabolism and reducing CVD risk. Still, its effectiveness in obesity without T2D remains unclear. (SP et al. 2016; Marso et al. 2020). Semaglutide, a higher dose than T2D treatment, has been allowed for long-term weight control in individuals who are overweight or obese. A phase II trial revealed that the proportion of weight that was lost was twofold[(O'Neil et al. 2018b)], and a phase III clinical trial showed a weight reduction of 14.9% after 68 weeks (Wilding et al. 2021a). Semaglutide, a medication used to treat diabetes and obesity, has been

official by the FDA for weight loss, particularly in patients without diabetes. The FDA has found that semaglutide 2.4mg is more effective than liraglutide 3mg in achieving similar weight reduction. However, whether this is achievable with the new oral form remains to be demonstrated (Buckley et al. 2018). Several other peptides and small-molecule GLP1R agonists are currently in clinical development, including formulations designed for oral administration. Another oral GLP1R agonist (GLPR-NPA) is presently in phase II clinical trials at Eli Lilly (Table2)

1.5.1. GIP-Related Drug Prospects

Because GIPR agonism has a decreased insulinotropic effect in people with T2D, it is not advised for the treatment of obesity or diabetes (Nauck et al. 1993). On the other hand, GLPR antagonistic (Chan et al. 2009; Cavaco et al. 2018) can enhance systemic energy and glucose metabolism by raising central leptin sensitivity (Chan et al. 2009). Preclinical investigations showed better glucose management and body weight reduction with long-acting GLPR agonists. Phase I clinical trials are being conducted to treat T2D with a long-acting GLPR agonist. (Mroz et al.2019; Zhang et al. 2021) (Table 2).

1.5.2. Polyagonists Based On Incretin

Studies have pharmacologically utilized the idea that mammals regulate energy balance by far more than a single hormone, concurrent with the structural optimization of selective GLP1R and GIPR mono agonists. In that regard, the most notable advancement has been the discovery of poly agonists that simultaneously target the GLP1, GIP, and glucagon receptors. (Day et al. 2009; Finan et al. 2013). The clinical development of several drug candidates has progressed Table 2. Most common methods combine highly effective, complementary GLP1R agonism with either GIP or glucagon receptor (GCGR) agonism unimolecularly. Compared to GLP1R agonists that were pharmacokinetically equivalent, animals with GIPR agonists chemically integrated with GLP1R agonism displayed reduced body weight and metabolic benefits (Coskun et al. 2018 ; Finan et al. 2013). GIP agonism may provide extra metabolic benefits to GLP1 therapy for various reasons, in addition to reducing fat mass and calorie intake via GLP1R-independent mechanisms (Mroz et al. 2019; Zhang et al. 2021b). It has been demonstrated that GIP reverses the emetic effects of GLP1R agonism in musk shrews (Hayes et al. 2021) and that in patients with T2D, GIP's insulinotropic activity is restored at blood glucose levels close to normal. Furthermore, GIP agonism protects against ectopic lipid formation and adipocyte lipid spillover by boosting adipocyte storage capacity (Samms et al.2020). However, the use of GIPR agonists to treat obesity and T2D is controversial. Phase II studies have published results for NN9709 and MAR709, two unimolecular, long-acting GIPR/GLP1R co-agonists. NN9709, intended for intraperitoneal injection daily, demonstrated balanced potency at human GLP1R and GIPR (Frias et al. 2017). When compared to liraglutide, it did not, however, considerably increase body weight. The research emphasizes how central GIPR agonism contributes to weight loss. Tirzepatide, a once-weekly subcutaneous injection, showed significantly superior results in reducing HbA1c and body weight in a phase II trial compared to GLP1R agonists. (Frias et al. 2020) High-dose GIPR/GLP1R co-agonists showed firm glucose control and weight loss in diabetes patients, generating interest and deepening debate on their direct and indirect contribution (DiMarchi 2018; Min and Bain 2021). A phase III trial found that tirzepatide significantly reduces HbA1c and body weight in patients with excess weight. Treating individuals with obesity or overweight diabetes for 40 weeks with this agent similarly lowered HbA1c in T2D, which was verified by a later phase III trial, outperforming semaglutide 1mg in both cases after 40 weeks.

Glucagon agonists and GLP1R agonism co-treatment involve various strategies to reduce body weight, hunger, thermogenesis, and lipolysis while lowering the risk of hyperglycemia. In a 54-week phase IIb research, cotadutide lowered body weight and hepatic fat levels in overweight T2D individuals while improving glucose tolerance (Nahra et al. 2021) The medicine also resulted in a 7% reduction in body weight after four weeks (Kleinert et al. 2017). Multi-agonism therapy is commonly used in preclinical obesity treatment, often in combination with GLP1 agonism. Leptin with pramlintide is one example of a co-therapy. (Chan et al. 2009; Trevaskis et al. 2010; Turek et al. 2010). Salmon calcitonin with exendin 4 (Bello et al. 2010), GLP1 with PYY (Boland et al. 2022), exenatide with CCK (Trevaskis et al. 2015), and liraglutide with setmelanotide (Clemmensen et al. 2015). The enhanced performance of GLP1 co-agonists with GIP or glucagon agonism encourages further research and development of glucagon-like peptides. Based on these data, a single-molecule tri-agonist that exhibits complete and balanced agonism at GLP1R, GIPR, and GCGR is suggested. A promising tri-agonist has been tested in animals and is now being studied in clinical trials (Finan et al. 2015; Tschöp et al. 2016). Combining GLP1 and GIP components in a single molecule reduces the danger of glucagon-induced hyperglycemia, allowing for higher doses to attain weight loss. In 2015, a study found that a GLP1R mono-agonist reduced body mass and plasma cholesterol in DIO mice more effectively than a placebo. Clinical research on a particular tri-agonist, (Finan et al. 2015), has identified a GLP1R/GIPR co-agonist. LY3437943, GGG, and HM15211 are further candidates that demonstrate glycemic effectiveness and weight loss. (Urva et al. 2023). GLP1, glucagon-like peptide; GLP1R; glucagon-like peptide one receptor, GIP, glucose-dependent insulinotropic polypeptide; T2D, Type 2 diabetes ; NASH, nonalcoholic steatohepatitis; OXM, oxyntomodulin.

Table 2: GLP1 and GIP-related drugs

Agent	Company	Development stage	Indications
GLP1/glucagon dual agonists			
Cotadutide (MEDI0382)	AstraZeneca	Phase II	T2D, NASH
BI 456906	Boehringer Ingelheim	Phase II	Obesity, T2D
Efinopegdutide (LAPSGLP/GCG)	Hanmi Pharmaceutical	Phase II	NASH
OXM	Eli Lilly	Phase I	T2D
GIP/GLP1 dual agonists			
Tirzepatide	Eli Lilly	Phase III	Obesity, T2D
GIP/GLP peptide I	Eli Lilly	Phase I	T2D
GIP/GLP peptide II	Eli Lilly	Phase I	T2D
NN9709	Novo Nordisk	Discontinued	Obesity, T2D
GIP/GLP1/glucagon tri-agonists			
HM15211 (LAPS Triple Agonist)	Hanmi Pharmaceutical	Phase II	NASH
GGG tri-agonist	Eli Lilly	Phase I	T2D
NN9423	Novo Nordisk	Discontinued	T2D, Obesity,
GIPR agonists			
GIPR agonist long-acting	Eli Lilly	Phase I	T2D
Efpeglenatide (LAPSExd4 Analog)	Hanmi Pharmaceutical	Phase III	T2D
Rybelsus	Novo Nordisk	Phase III	Obesity
Danuglipron (PF-06882961)	Pfizer	Phase II	Obesity, T2D
GLPR-NPA	Eli Lilly	Phase I	T2D
Glucagon analogue			
HM15136 (LAPS Glucagon Analog)	Hanmi Pharmaceutical	Phase I	Obesity

1.5.3. Leptin, Leptin Sensitizers and MC4 Agonists

The multifunctional enzyme lipoprotein lipase breaks down fats and lipids, breaks fats into lipids and glycerol, improves the absorption of fats, and keeps the gallbladder functioning. Lipase plays a significant role in the development of obesity due to its favourable absorption and degradation of fat. Body fat builds up from the dispersion of hydrolyzed triglycerides because lipase can remove triglycerides from circulation and promote fat absorption. Orlistat and Cetilistat, two lipase inhibitor medications, were developed to help obese patients lose weight because of the hereditary function of lipase. Cetilistat has not yet received FDA approval in the US. However, Orilstate was approved as an over-the-counter medication in 2007 for individuals who were obese and wanted to reduce weight, while cetilistat was licensed in Japan in 2013 (Tak and Lee 2021c). Orlistat is a naturally occurring lipoprotein lipase from *Streptomyces toxytricini* that inhibits lipoprotein lipase naturally. It works by binding to serine residues of active sites, preventing fat hydrolysis, lowering fat absorption, and lowering the risk of T2D. By improving blood pressure and aiding in reducing body weight, Orlistat works through the GI tract to decrease the risk of T2D (Tak and Lee 2021c). For patients with diabetes mellitus, Orlistat does not contribute to a reduction in obesity despite being beneficial in those with prediabetes. This uncertainty generated the development of a new medication; the cause of this is unknown. Cetilistat is an oral benzoxazinone lipase inhibitor that is highly lipophilic. Although Cetilistat has not yet received FDA approval, it has demonstrated encouraging outcomes in a clinical trial and maybe a secure and reliable weight-loss medication. According to a 12-week randomly selected placebo-controlled research, cetilistat significantly reduced body weight and other obesity-related indicators in patients who have excess fat (Kopelman et al. 2007). In a second phase trial, obese individuals with T2D who were also on glucophage were randomized to receive one of three doses of cetilistat (40, 80, or 120 mg) or a placebo for 12 weeks. The outcomes demonstrated that compared to a placebo, cetilistat 80 or 120 mg significantly improved blood sugar control and decreased body weight (Kopelman et al. 2010). Compared to Orlistat, cetilistat exhibited fewer GI adverse effects (Kopelman et al. 2010). It's unclear why there is this disparity. While the methods of action of cetilistat and Orlistat are similar, their distinct chemical structures may impact how they interact with fat in the intestine. Some disadvantages of cetilistat can include impaired absorption of vitamins and minerals that require fat for absorption. In obese patients, cetilistat effectively lowers total serum cholesterol, low-density lipoprotein cholesterol, and glycosylated hemoglobin, or HbA1c, in obese diabetics (Kosmalski et al. 2023). For the best weight-loss results, cetilistat and Orlistat should be used with a low-calorie, low-fat diet Table3. Metreleptin, approved by the FDA and EMA in 2014 and 2018, treats lipodystrophy and normalizes metabolic and neuroendocrine alterations in individuals with congenital leptin deficiency and anorexia nervosa. Leptin supplementation is effective in individuals with congenital leptin deficiency but struggle to lower body weight under common polygenetic obesity conditions. Additionally, the formation of antibodies against metreleptin is a barrier to its clinical application, even if it is not associated with decreased efficacy or safety. (Tschöp et al.2012) Unless remarkably advised for congenital or acquired widespread lipodystrophy, leptin is not the best pharmacological target for treating obesity. Over the past 30 years, MC4R agonists have been shown to decrease body weight and food intake in experimental DIO animals, but they also cross-stimulate MC1, MC3, and MC5 receptors. MC4R activation can raise blood pressure and heart rate and induce sexual arousal in males. (Sharma et al. 2019)

Clinically tested MC4R agonists were discontinuated for weight loss or adverse effects. Rhythm Pharmaceuticals developed setmelanotide, a structurally related MC4R agonist, which showed profound weight loss in humans with congenital deficiency of POMC or LEPR without significant adverse effects in phase III clinical trials. (Clément et al. 2020). FDA approved setmelanotide in 2020 for obesity treatment in POMC, PCSK1, or LEPR deficiency patients. Future studies should investigate polygenetic obesity and Prader-Willi syndrome, where the primary obesity source is not melanocortin-related. Preclinical evidence of improved leptin sensitivity has also been demonstrated after co-therapy with other agents (Müller et al. 2012; Clemmensen et al. 2014). Additionally, it has been shown that plant-derived small molecules such as celastrol (Liu et al. 2015) and withaferin A (Lee et al. 2016) reduce body weight by increasing leptin sensitivities. T2D, Type 2 diabetes, POMC, Pro-opiomelanocortin; PCSK1; prohormone convertase1, LEPR; leptin receptor.

Table 3: Leptin, Leptin Sensitizers And MC4R Agonists

Drug	Company	Stage	Indications, FDA approval
Withaferin A	Academic, non-commercial	Phase I	Obesity, T2D
Celastrol	Academic, non-commercial	Preclinical	Obesity, T2D
Cetilistat	Alizyme and Takeda Pharmaceuticals	Phase II	Obesity
Metreleptin,	Amylin Pharmaceuticals	Discontinued	Leptin deficiency in patients with lipodystrophy
setmelanotide	Rhythm Pharmaceuticals	Phase III	obesity treatment in POMC, PCSK1, or LEPR deficiency patients

1.5.4. Targeted Mitochondrial Uncouplers

2,4-Dinitrophenol (DNP) is one example of a mitochondrial uncoupler that can enhance mitochondrial ineffectiveness, which reduces the rate of metabolism and generation of ATP. These uncouplers, such as UCP1, are found in brown and beige adipocytes and can be induced by chemicals like cholesterol and T3. However, DNP was prohibited from usage in medicine because of side effects and fatalities, ((Müller et al. 2018b), but continues to be used by bodybuilders and others. Mitochondrial uncouplers can be cytotoxic at high concentrations but at doses not toxic; they have the power to prevent cells from dying. (Demine et al. 2019) Treating conditions, including hypertriglyceridemia, insulin resistance, hepatic steatosis, and diabetes, may be possible with the development of safer uncoupling agents for patients. (Perry et al. 2015). The mitochondria-specific protonophore uncoupler BAM15 raises energy expenditure and reduces body fat mass without changing BMI or dietary intake (Axelrod et al. 2020). It boosts insulin sensitivity and increases food absorption, insulin action, and the activity of mitochondria. However, it's too early to determine if BAM 15 or similar approaches promote medicinal safety for complications associated with overweight. A growing body of research has focused on targeting macrophage-inhibiting cytokine 1 (MIC1; also known as GDF15) in the war against overweight. GDF15 is a divergent member of the converting growth factor-β (TGFβ) superfamily (Hale et al. 2021).. In terms of physiology, GDF15 is expressed at modest levels in various tissues; nevertheless, its expression rises in response to or in correlation with inflammation, metabolic diseases, cancer, tissue damage, and

CVD (Assadi et al. 2020; Hale et al. 2021). Additionally, it has been suggested that GDF15 functions as a cytokine that reduces inflammation in the heart. (Rochette et al. 2021). Obese animals and primates with obesity from diet exhibit reduced body weight following exogenous infusion of rDNA-derived GDF15 and analogs, indicating a potential homeostatic function in energy homeostasis. (Mullican et al. 2017; Hale et al. 2021)

GDF15 was recently demonstrated to physiologically regulate body weight and energy homeostasis through receptor activation, principally via appetite suppression.

Receptor α-like (GFRAL) (Mullican et al. 2017) of the GDNF family. Particular research has proposed that the anorectic action of GDF15 is mediated by emetic neurocircuitry engagement and nausea induction ((Borner et al. 2020; Borner et al. 2020), although not all investigations have supported this theory. That being said, its depletion causes an increase in body weight (Tsai et al. 2018). However, overexpression of GDF15 has an opposing impact. (Tsai et al. 2018). Carefully evaluating long-term research exhibiting long-term effectiveness that is sufficiently free from side effects, including nausea/vomiting, carcinogenicity, and slender body mass loss, is necessary. In the end, When it comes to managing weight reduction, only human studies can determine whether GDF15 analogs will be safe and effective (Benichou et al. 2023; Hale et al. 2020) Table4 . T2D, Type 2 diabetes ; NASH, nonalcoholic steatohepatitis

Table 4: Targeted Mitochondrial Uncouplers as Aoms

Drug	Company	Stage	Indications, FDA approval
BAM15	Continuum Biosciences	preclinical	Obesity, NASH
GDF15	Novo Nordisk	Phase I	Obesity, NASH
LY-3463251 (GDF15 agonist)	Lilly	Phase I	Obesity, T2D

1.5.5. Tyrosine Peptide Tyrosine

The NPY family includes peptide tyrosine (PYY), secreted by intestinal L cells as PYY1–36 in addition to GLP1. Following the release, DPP-IV quickly cleaves PYY1-36 into its primary active form, $PYY_{3–36}$, a potent agonist of the type 2 NPY receptor (Y2R). This receptor is highly expressed in peripheral sympathetic and parasympathetic neurons and various CNS regions, such as the brainstem (Kang et al. 2023) cortical, and limbic areas. (Table 5) PYY_{3-36} lowers dietary intake and weight loss in rodents (Vrang et al. 2006; Keire et al. 2010), and humans (Schmidt et al. 2014), at least, and Y2R is abundantly expressed on NPY neurons of the ARC in the hypothalamus (Alonso 2022). This is partly due to the effective silencing of NPY neurons, which causes POMC neurons to become indirectly activated. (Alonso 2022) Other systems, such as the brainstem, cortical and subcortical areas, may also promote $PYY_{3–36}$'s control of appetite, such as the brainstem, cortical and subcortical areas, GABAergic and glutamatergic neurons, and the mesolimbic dopaminergic system, which Y2R activates. In addition to controlling dietary intake, PYY_{3-36} substantially impacts memory, learning, central data processing, other domains, and behavioral responsiveness to dopamine-stimulating drugs (Kang et al. 2023) These effects support the significance of dopaminergic pathways in mesolimbic brain regions. $PYY_{3-36's}$ capacity to reduce food intake in both people and animals has prompted the creation of PYY_{3-36} analogs intended to treat obesity (Poulsen et al. 2021). Accordingly, several long-acting $PYY_{3–36}$ analogs (NNC0165-1875 and NN9748) have effectively finished phase I

trials for the treatment of obesity; in addition, NNC0165-1875 is currently being assessed in a phase II combined study with semaglutide. Furthermore, a phase I trial using a PYY analog for treating T2D was launched by Lilly Research Laboratories. T2D, Type 2 diabetes; PYY, peptide tyrosine tyrosine; Y2R, neuropeptide Y receptor type 2.

Table 5: Tyrosine Peptide Tyrosine Agents

Agent	Company	Development stage	Indications
Y2R agonists			
PYY analogue	Eli Lilly	Phase I	T2D
NN9748 (NN9747)	Novo Nordisk	Phase I	Obesity, T2D
NNC0165-1875+semaglutide	Novo Nordisk	Phase II	Obesity, T2D

1.6.Perspectives and Potential Paths

The rise in obesity has accelerated the pursuit of AOMs, molecular understanding of appetite homeostasis, and the development of incretins for T2D. A 20% or higher drop in fat mass could be achievable, but it's essential to consider the difficulty of achieving this reduction in patients with higher initial weight. GLP1R agonism is a promising new approach to weight loss, but its full efficacy and sustained use in diverse populations remain unexplored. The primary focus is on its synergy with GLP1. Semaglutide and liraglutide are potent and selective GLP1R agonists, providing sustained drug plasma concentrations. However, the difference in body weight lowering between the two agents is not due to extended time action but rather molecular basis. The study indicates increased activity in central weight control locations (Gabery et al. 2020b); however, more molecular knowledge might result in better GLP1R agonists or other medications acting independently at similar sites. Clinical results with tirzepatide have sparked interest in GIP-based dual agonists, but our understanding of obesity remains limited in determining in vivo efficacy mechanisms. The mechanism behind tirzepatide's increased efficacy compared to dulaglutide is yet to be fully understood. Still, recent research indicates that loss of GIPR in the CNS makes mice resist GIP-induced weight reduction, suggesting control of energy balance. The primary strategies and target regions of GIP synergy with GLP1 are unclear, and preclinical data supporting GIPR antagonistic therapy to treat obesity are particularly noteworthy. These ambiguities and inquiries will finally have an answer. Clinical results and constraints in converting animal and in vitro pharmacology to human research impact the future of discoveries. Weight loss of 0.5 kg per week remains suitable with high-dose semaglutide and tirzepatide, raising questions about the following priorities and skills. Studies on weight loss have been underpowered, failing to document efficacy. The primary objective is to maintain weight loss rates for individuals with chronic obesity despite the challenges of a finite period.

Longitudinal studies are crucial for assessing the effectiveness of glucagon-based tri-agonists, as they may not be suitable for patients with reduced therapeutic index, especially in the assessment of GLP1–GIPR co-agonists, due to potential adverse effects. GLP1's therapeutic efficacy with GIP raises concerns about semaglutide's combination with other antiobesity medications. Leptin therapy has proven successful in decreasing weight loss after obese mice experienced significant weight reduction. (Müller et al. 2012; Clemmensen et al. 2014; Obradovic et al. 2021). Next-generation multi-omics, developing technologies, and iterative rodent testing must be combined to expedite the following step in safely regulating body weight. Rather than finding clinically successful medication candidates, the

mechanism of action needs to be investigated, and this requires the use of genetic models and altered mice. Clinical situations are challenging due to restricted entry for persons homozygous-deficient in particular biochemical processes, varying obesity nature and treatment response, and limited availability of selective antagonists for pharmacological use. Comparing peptides without biological activity is expensive and time-consuming. Related methods of diagnosis should be employed to finish an overall weight scale to accelerate the development of drugs. This would increase confidence in predicting long-term success, encouraging improved results and experimental clinical research. Finding a correlation between metabolic profile and weight loss tendency could substantially impact the future of obesity-related healthcare.

1.7.Conclusion

The history of pharmaceutical management of obesity has been characterized by issues resulting from patient variability and the limited capacity for translational research provided by animal models. Large-scale, drawn-out clinical trials are expensive and difficult to justify. The recent weight loss of over 10% with tirzepatide and semaglutide is encouraging for future possibilities. In the treatment of obesity, leptin and setmelanotide have also demonstrated promise. Further studies ought to concentrate on other homogeneous forms of the disease and investigate additive pharmacology in larger obesity populations.

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