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REVIEW

Anti-obesity drugs: comprehensive review and emerging therapies

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Abstract

Obesity, an epidemic of modern world lifestyle, has a substantial negative impact on both health and the economy. Traditional weight management strategies, such as dietary modifications and lifestyle changes, are often inadequate for long-term weight control, warranting the immediate intervention of pharmaceutical assistance. This review article evaluates the status of presently approved anti-obesity medications like lipase inhibitors, incretin-based medicines, dual agonists, and melanocortin receptor agonists for their adverse events, alongside novel therapeutic candidates under clinical investigation. The article comprises the impacts of these medications on energy balance, appetite regulation, and metabolic health in the assessment of their mechanisms of action, efficacy, safety profiles and their therapeutic potential with respect to obesity phenotypes. This review article also sheds light on recent promising advancements in anti-obesity innovative therapies such as neuromedin U receptor agonists, amylin/calcitonin dual agonists, and a non-peptide oral GLP-1 receptor agonist. Key future research strategies and directions include the development of multi-targeted and combination therapies were also discussed.

Keywords: Obesity phenotypes · Lipase inhibitors · Incretin hormones · Combination therapies · 5HT2C receptor · Melanocortin 4 receptor · Neuromedin U receptor-2

Introduction

Obesity: A growing global threat

Obesity is termed as excess or abnormal fat, which could pose a hazard to health. It is now a major public health issue in the twentieth century [1]. In the 1990s, the World Health Organisation (WHO) developed a classification system based on BMI, which categorises people into groups such as underweight, normal weight, overweight, and obese [2]. The body mass index (BMI) is the standard utilized in measuring obesity in humans [3]. It determines the relationship between body weight and height by dividing weight (kg) by height squared (m^2) [2]. The range of 25–29.9 kg/m^2 is considered to be overweight, while more than 30 kg/m^2 is termed as obese [4]. According to estimations by the World Health Organization, currently, 800 million people across the world suffers from obesity. This staggering figure ranges across every age group, from children and preteens to adults, regardless of gender, race, or social classes. The issue is not only rampant in industrialized countries but also a significant problem in developing nations as well [5]. Obesity has myriad impacts that go beyond personal health. Many chronic diseases had obesity as an important risk factor, which put a heavy burden on healthcare systems globally [6]. Obesity victims are prone to have a higher risk of developing type 2 diabetes, the condition where the body is unable to produce enough or use the insulin produced to maintain blood glucose levels within normal ranges. Moreover, obesity is among the worldwide causes of death and

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also contributes to several cases of cardiovascular diseases. Some of these include peripheral artery disease, heart disease, and stroke. Obesity also correlates with metabolic syndromes, non-alcoholic fatty liver disease, and chronic kidney disease [7]. It is also widely acknowledged that obesity and some types of cancer, including breast, colon, and endometrium are associated [8]. Moreover, obesity has been found to be associated with several mental health conditions, such as anxiety and depression, in addition to sleep apnoea (Fig. 1) [9]. The high expense of treating obesity-related illnesses puts a strain on healthcare resources and lowers a country's overall economic productivity also resulting from diminished or decreased human capital and productivity [10]. Therefore, a multifaceted strategy including lifestyle changes, public health campaigns, and maybe the use of anti-obesity medications as part of an all-encompassing weight management programme is needed to effectively combat the worldwide obesity epidemic. The cornerstones of managing obesity continue to be healthy diet and frequent physical activity, but for certain people in a population, these measures may not be enough on their own [11].

Necessity for anti-obesity drugs

Any obesity treatment program always begins with a change in lifestyle. Treatment for obesity must include both a reasonable exercise program and a better diet [11]. Nevertheless, cumulative data indicate that most patients are unable to maintain such lifestyle, and over half of the weight lost was gained back within two years, despite randomised trials showing an increase in weight of over 8% in the first year. When lifestyle changes are insufficient to help patients lose weight, anti-obesity medications are produced as a last resort [12]. Anti-obesity medications (AOM) are recommended

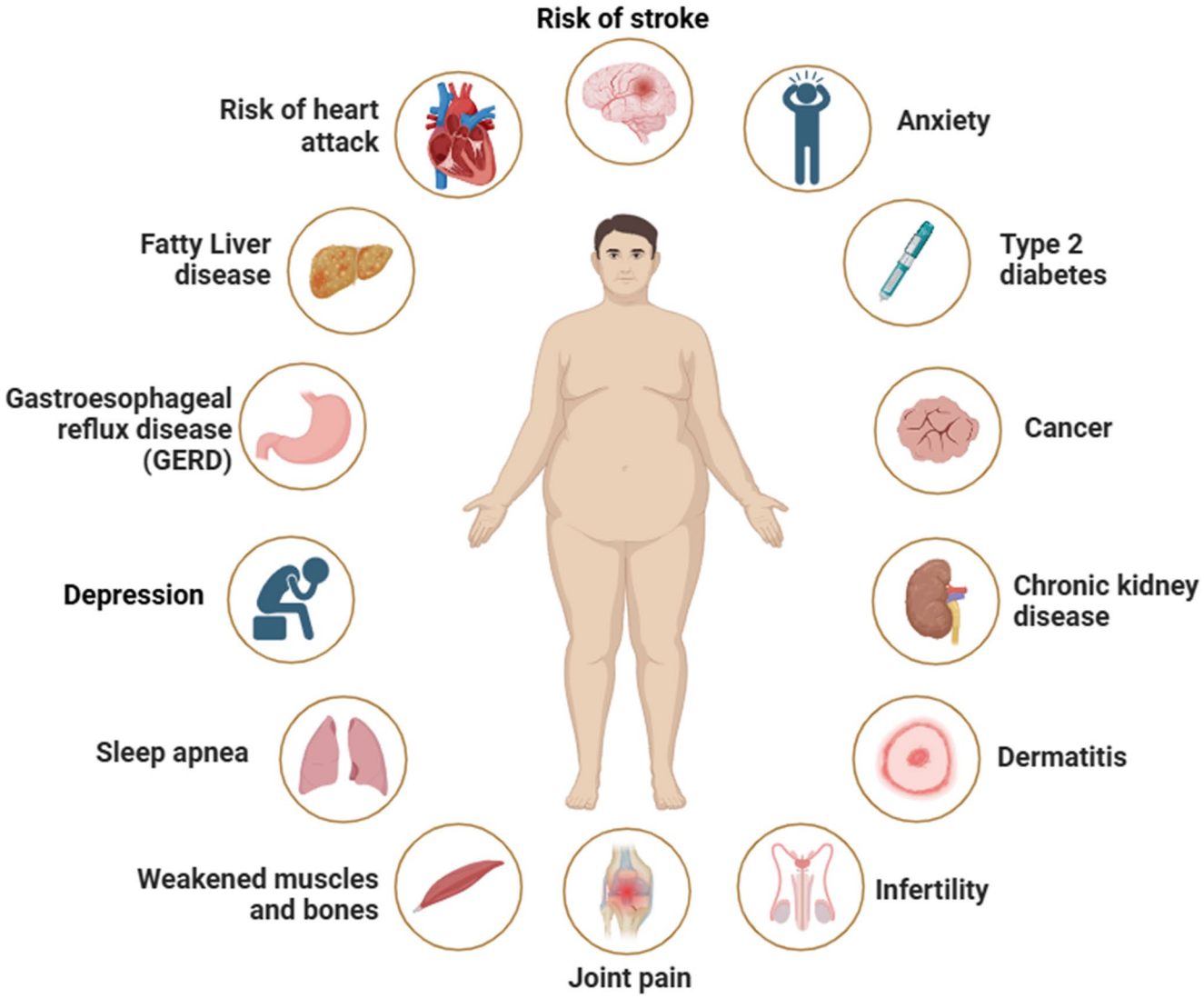

Fig. 1 Impacts of obesity on health

for those who have a BMI of at least 30 kg/m^2 or is at least 27 kg/m^2 and there are one or more co-morbidities. Nevertheless, the history of anti-obesity medications was characterised by the failure of several ones due to major side effects, such as cardiovascular events, dependence, suicidality and addiction risk, and most recently, cancer, following its broad usage in the market [13]. As a result, the European Medicines Agency (EMA) and the Food Drug Administration (FDA) reformed their regulatory approval requirements for AOM, emphasising the importance of cardiovascular and central nervous system safety in particular [13].

This article's objectives are to evaluate obesity pharmacologic management, offer an algorithm for treating excess weight, and outline prospective medications that are available or are presently being researched.

Mechanisms of obesity

A multifaceted interaction of hereditary, behavioural and environmental factors results in obesity [14]. The primary cause of obesity is the chronic variance between energy intake and energy expenditure leading to an increase in adipose tissue mass in the body. A clear association exists between the growth of fat, persistent low-grade systemic inflammation and the production of reactive oxygen species (ROS), which leads to pathological events associated with ROS [15]. It has been discovered that reactive oxygen species (ROS) influence hypothalamic neurones, which regulate appetite and satiety, in many ways, which contribute to the regulation of body weight [16]. Based on the observations from genome-wide association studies, obesity may also be caused by genetic components, as over 140 genetic chromosomal areas have been linked to obesity. Fat storage and metabolism can be impacted by genetics and hormone abnormalities can be resulted in obesity. The CNS has enriched gene expression linked to both BMI and overall adiposity [17]. The distribution of adipose tissue affects the secretion rates and effects of hormones and adipokines. Some obese individuals experience a low-grade systemic inflammatory state as a result of their adipocytes and macrophages secreting excessive amounts of proinflammatory adipokines [18]. As obesity is a multifaceted disease, it can be classified into four phenotypes based on the underlying cause of excessive fat or calorie intake as shown in Table 1. The four main phenotypes are: [1] emotional hunger (hedonic eating and reward dysfunction); [2] hungry gut (abnormal satiation); [3] hungry brain (abnormal satiety signalling); and [4] slow burn (reduced calorie expenditure or adaptive thermogenesis). When various approaches like behavioural, pharmaceutical, and lifestyle therapies are paired with phenotype, they may enable more individualised and successful therapy methodologies that may improve clinical outcomes [19].

Table 1 Obesity phenotypes

Phenotype	Cause
Emotional hunger	Anxiety, depression and emotional imbalance leads to eating and reward signalling dysfunction.
Hungry gut	Rapid gastric emptying leads to excessive food and calorie intake.
Hungry brain	Abnormal gut–brain axis and satiety signalling leads to high intake of calories.
Slow burn	Reduced calorie expenditure and sedentary lifestyle.

Currently available therapies for obesity

A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science for publications from 2000 to 2025. The search combined the following terms: "anti-obesity drugs," "obesity pharmacotherapy," "GLP-1 receptor agonists," "incretins," "novel obesity therapies," "obesity phenotypes," and "tailored obesity medicine." Inclusion was restricted to peer-reviewed articles published in English. To supplement the database results, we traced citations from identified articles and manually sifted through the reference sections of relevant review papers.

Losing weight still primarily involves changing one's lifestyle. Modest weight loss (about 5–10%) with lifestyle modifications can lower the risk of diseases linked to obesity [20]. But most of the people fail to maintain the lifestyle and resulted in rebound of the obesity. Patient, who are obese and have a BMI of ≥ 40 or between 35 and 40 with a comorbid condition which could be improved by losing weight, can only be recommended for surgical treatment like bariatric surgery [21]. Surgery is unlikely to be a widely accepted treatment for the majority of obese people due to its high cost, complications, and postoperative follow-up. Therefore, anti-obesity medications appear to be required in the treatment of obesity.

Novel therapies for obesity have been developed and approved at a rapid pace in recent years, providing encouraging options for managing weight. These drugs mostly target particular processes related to energy expenditure, appetite control, and food absorption as shown in Table 2. One class of such drugs are the lipase inhibitors, which inhibits the breakdown of fat in the gastrointestinal tract, leading to the reduction of dietary fat absorption [22]. Another class of drug that has acquired significant attention is the Glucagon like peptide-1 (GLP-1) receptor agonists which acts like the naturally occurring gut hormone GLP-1 which slows gastric emptying, promotes satiety and reduces appetite. These substances have pleiotropic effects that go beyond their well-established effects on weight loss

Table 2 Therapeutically approved anti-obesity drugs

Parameters	Name of the drug							
	Orlistat	Semaglutide	Liraglutide	Tirzepatide	Phentermine/Topiramate	Bupropion/Naltrexone	Setmelanotide	Lorcaserin
Brand Name	Xenical	Ozempic	Saxenda	Mounjaro	Qsymia	Contrave	Imcivree	Belviq
Company name	Roche pharmaceuticals	Novo Nordisk	Novo Nordisk	Eli Lilly	VIVUS	Bausch health	Rhythm pharmaceuticals	Eisai Inc.
FDA approval	1999	2021	2014	2022	2012	2014	2020	2012 (Discontinued in 2020)
Chemical formula	$C_{29}H_{53}NO_5$	$C_{187}H_{291}N_{45}O_{59}$	$C_{172}H_{265}N_{43}O_{51}$	$C_{225}H_{348}N_{48}O_{68}$	$C_{10}H_{15}N$	$C_{13}H_{18}ClNO$	$C_{49}H_{68}N_{18}O_9S_2$	$C_{11}H_{14}ClN$
Molecular weight/Protein weight	495.735 gm/mol	4113.64 gm/mol	3751.26 gm/mol	4810.52 Da	149.2328 gm/mol	239.741 gm/mol	1117.32 gm/mol	195.69 gm/mol
Dosage	120 mg orally	0.25 mg initial dose with 0.5 maintenance dose	0.6 mg subcutaneously	2.5 mg subcutaneously	15–30 mg orally in combination with 92 mg topiramate	360 mg orally	3 mg subcutaneously	10 mg orally
Mechanism of action	Gastrointestinal lipase inhibition which results in inhibition of triglycerides in the intestines	Mimics the actions of endogenous GLP-1 to help with glycaemic management. By acting on the same receptor, it decreases incorrect glucagon release, slows stomach emptying, and increases glucose-dependent insulin secretion.	GLP-1 receptor agonist that reduces body weight by reducing cravings and suppressing hunger and regulate satiety by glucagon production, inhibits insulin secretion, and postpones stomach emptying	Dual agonist for glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)	Mild, reversible monoamine oxidase and serotonin reuptake inhibitor in addition to stimulating the release of dopamine and serotonin from nerve terminals. The subsequent rise in norepinephrine levels in the synaptic cleft stimulates β-2 adrenergic receptors, hence suppressing appetite.	Inhibition of norepinephrine-dopamine reuptake reducing cravings and assisting with attempts to stop smoking.	Melanocortin 4 receptor (MC4R) agonist which When activated, the MC4R pathway decreases hunger and increases energy expenditure.	Serotonin agonist that specifically stimulates serotonin 2 C receptors which suppresses hunger by binding to 5-HT2C receptors in the central nervous system (CNS).
Adverse effects	• Liver injury • Oily/fatty stools • Faecal urgency • Flatus with discharge	• Gastrointestinal side effects • Nausea • Diarrhoea • Abdominal pain • Acute pancreatitis	• Acute pancreatitis • Urine sodium excretion • Impaired left ventricular function • Acute gall bladder or biliary disease	• Hypoglycaemia • Acute pancreatitis • Cholelithiasis • Cholecystitis • Nausea • Diarrhoea • Gastrointestinal side effects	• Constipation • Paraesthesia • Dry mouth • Dysgeusia • Sleeplessness • Nephrolithiasis	• Gastrointestinal adverse events • Cardiovascular adverse events • Sleep disorder • Anxiety • Depression • Constipation • Nausea • Vomiting • Headache	• Hyperpigmentation disorder • Nausea • Vomiting • Sexual arousal problems • Gastrointestinal side effects	• Hypertension • Cognitive decline • Hypoglycaemia • Nasopharyngitis • Upper respiratory tract infection • Valvopathy
References	(23,35,37,38,46)	(27,63,67,68)	(70,75,76)	(83,95,96)	(98,99,106,107)	(108,112,114,115)	(121,122,126)	(132,138,141)

and include anti-inflammatory and anti-oxidative properties that protect the cardiovascular system [23, 24]. Also, GLP-1 receptor agonists improve insulin secretion and glucose control [25, 26]. Furthermore, combination therapies have emerged as a viable option for weight management by regulating multiple mechanisms of appetite regulation and targeting multiple physiological pathways. Compared to monotherapy, these combinations may offer more efficient and sustainable weight loss. Even though these therapies have a lot of promise for improving metabolic health and helping people lose weight, research is still being done to determine their long-term safety and effectiveness.

Lipase inhibitors

Pancreatic lipase converts the fats and oils in meals into subunits like glycerol and fatty acid molecules which are absorbed by body for energy purposes [27]. Since dietary triglycerides (DTG) constitute the primary source of fats, which are responsible for the high energy source and obesity, lipase inhibition is an intriguing strategy to lower lipid absorption [28]. Inhibitors of pancreatic and gastric lipase (PL) can obstruct lipid digestion and absorption in the gastrointestinal tract, potentially facilitating weight loss in accordance with individual dietary habits (Fig. 2). Additionally, limiting lipid intake has been validated as one of the most practical methods to reduce body weight [29]. Orlistat is the only marketed drug for the lipase inhibitor. As the lipase inhibitor decreases the direct calorie intake, it may be effective against all obesity phenotypes.

Orlistat

Orlistat is an effective, selective and irreversible inhibitor of gastric and pancreatic lipases. It possesses a β-lactone ring as a warhead for the active site covalent binding (Fig. 2) [22, 30]. Orlistat works by forming a covalent bond with the serine residue found in the pancreatic and stomach lipases' active sites [31]. It is a synthetic derivative of lipstatin, which is naturally produced by *Streptomyces toxytricini* (Fig. 2) [32]. Orlistat was synthesized to increase the stability of the lipstatin by converting the unsaturated alkyl chain to a saturated chain. Therefore, it is also alternatively called as tetrahydrolipstatin. Orlistat was found to be equally active as lipstatin and favoured due to its stability [22]. Orlistat reduces fat absorption by inhibiting pancreatic and gastric lipases, resulting in a decrease in calorie intake [33]. It can lead to 30% decrease in fat absorption and has slight impact on weight loss primarily depending on the individual diet. It is an oral medication (120 mg) that can be given up to an hour after a meal [34].

The effectiveness of orlistat was assessed in the XENDOS study, which was a prospective, double-blind trial. 3,305 individuals were randomised to three daily doses of either a placebo or orlistat 120 mg in addition to lifestyle modifications. Individuals who participated in the study had normal (79%) or impaired (21%) glucose tolerance, and their BMI was more than 30 kg/m2. The time to onset of type 2 diabetes and change were the primary goals [35]. Among patients receiving orlistat, 52% finished their course of medication, compared to 34% of those receiving

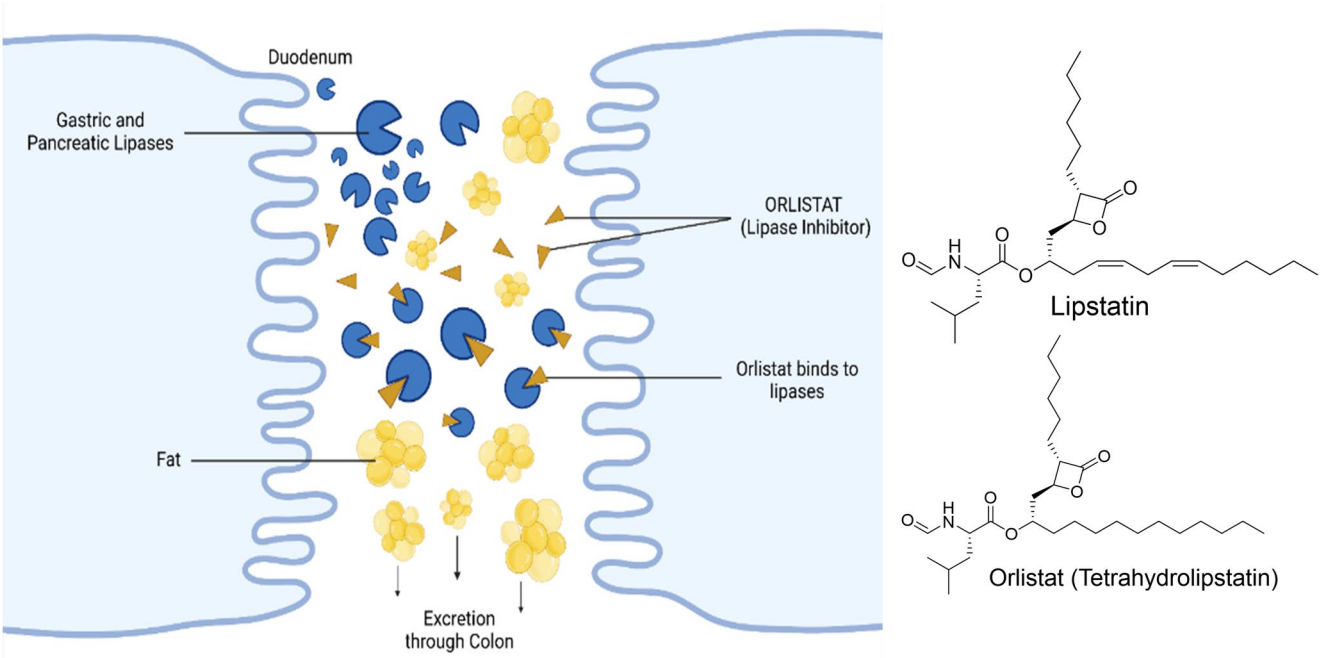

Fig. 2 Mechanism of action of orlistat on gastric and pancreatic lipases

a placebo (P 0.0001). The cumulative incidence of diabetes after four years of treatment was 9.0% with a placebo and 6.2% with orlistat; this represents a 37.3% reduction in risk (P 0.0032). According to exploratory studies, the difference in subjects with IGT explained the preventative impact. After four years, orlistat considerably increased the mean weight loss (5.8 kg vs. 3.0 kg with placebo; $P \sim 0.001$) and comparable in the orlistat groups with impaired (5.7 kg) and normal (5.6 kg) glucose tolerance at baseline. An additional analysis, which maintained the baseline weights of trial participants who discontinued participation, revealed that the orlistat group lost more weight (3.6 kg compared to 1.4 kg; P 0.001) [35].

While frequent use of orlistat leads to minor but unpleasant gastrointestinal side effects, there are also concerns that it may elevate the risk of major hepatic events. In research comprising of 94,695 patients who were administered with orlistat, 988 patients suffered acute liver damage; 653 instances were deemed probable, and 335 cases were verified as definite. An elevated incidence of liver injury was observed in the study with an incidence rate ratio 2.21 (95% confidence interval 1.43 to 3.42) during the first 30 days of treatment, this elevated risk remained until extended use brought it back to baseline levels [36]. Another study showed that gastrointestinal adverse effects were frequently recorded. These included fatty/oily stool, faecal urgency, flatus with discharge, and oily spots. The study also stated that, with only 3–33% of investigator outlined adverse events being published, the reporting of adverse events in trials frequently overstated the harms [37]. It has also been demonstrated that orlistat inhibits the essential detoxification enzyme carboxylesterase-2, which can cause serious harm to the kidneys, pancreas and liver [38].

Additionally, some co-administered drugs can interact with orlistat affecting their effectiveness and absorption. For example, it may decrease the absorption of lipophilic antiepileptics such gabapentin, vigabatrin, valproic acid, and lamotrigine, requiring the amount of antiepileptic drug to be monitored [39]. Additionally, it decreases the absorption of cyclosporine and amiodarone, the latter of which needs at least three hours between delivery and routine cyclosporine level monitoring [40, 41]. Levothyroxine and orlistat should be taken at least 4 h apart because orlistat can bind with levothyroxine in the intestines, lowering plasma levels and possibly causing hypothyroidism [42]. Monitoring coagulation parameters is necessary because the combination of orlistat and warfarin can prolong prothrombin time and INR (International Normalized Ratio) because of decreased absorption of vitamin K [43]. Last but not least, because orlistat reduces the absorption of antiretroviral medications, HIV viral load monitoring is necessary, and if viral levels rise, orlistat may need to be discontinued [44]. Large scale observational studies are required to produce thorough data that will help physicians and regulatory bodies to make well-informed choices regarding the extended use of orlistat for anti-obesity medication [45].

Incretin hormones receptor agonists

The more increase in insulin secretion after the meal ingestion as compared to the intravenous glucose administration is termed as the incretin effect [46]. The hormone responsible for the incretin effect are termed as the incretin hormones. The two known incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released through gut and exert the insulinotropic effect by binding with their receptor like GLP-1 Receptor and GIP receptor, a GPCR family receptors, respectively (Fig. 3) [47]. Incretin hormones regulate islet hormone secretion, glucose concentrations, lipid metabolism, gastrointestinal motility, appetite and body weight, and immunological function [48]. Increase secretion of incretin hormones decreases hunger, food intake, and increases the satiety effect. These critical role of incretin in energy homeostasis make them legitimate target for the anti-obesity drugs [49]. These agents also have pleiotropic effects that go beyond just helping people lose weight. They offer cardioprotective properties by reducing blood pressure, enhancing lipid profiles, improving endothelial function, and preventing major adverse cardiovascular events (MACE) [24]. Additionally, GLP-1 receptor agonists have anti-inflammatory and antioxidative qualities that decreases the long-term low-grade inflammation linked to insulin resistance and obesity [23]. Two GLP-1R agonists like semaglutide and liraglutide, and one dual agonist of GLP-1R and GIP receptor, tirzepatide, were approved by authorities for anti-obesity medication. Their various biological functions make them effective in all four obesity phenotypes.

Glucagon-like peptide-1 (GLP-1) receptor agonists

GLP-1, a 30-amino acid incretin peptide hormone, is secreted in response to food intake by intestinal epithelial endocrine L-cells [50]. GLP-1 stimulates insulin secretion in a glucose-dependent manner by activating its specific glucagon like peptide-1 receptor, a family of G-protein coupled receptor, primarily found on pancreatic β-cells, thus promoting glucose uptake and facilitating glycaemic management [51]. Additionally, GLP-1 suppresses glucagon release from the pancreas. Therefore, the incretin effect contributes significantly to postprandial insulin secretion and, consequently, to both human and animal glucose tolerance [52]. These myriad actions of GLP-1 peptide analogues greatly legitimate them as target for diabetes and obesity [53].

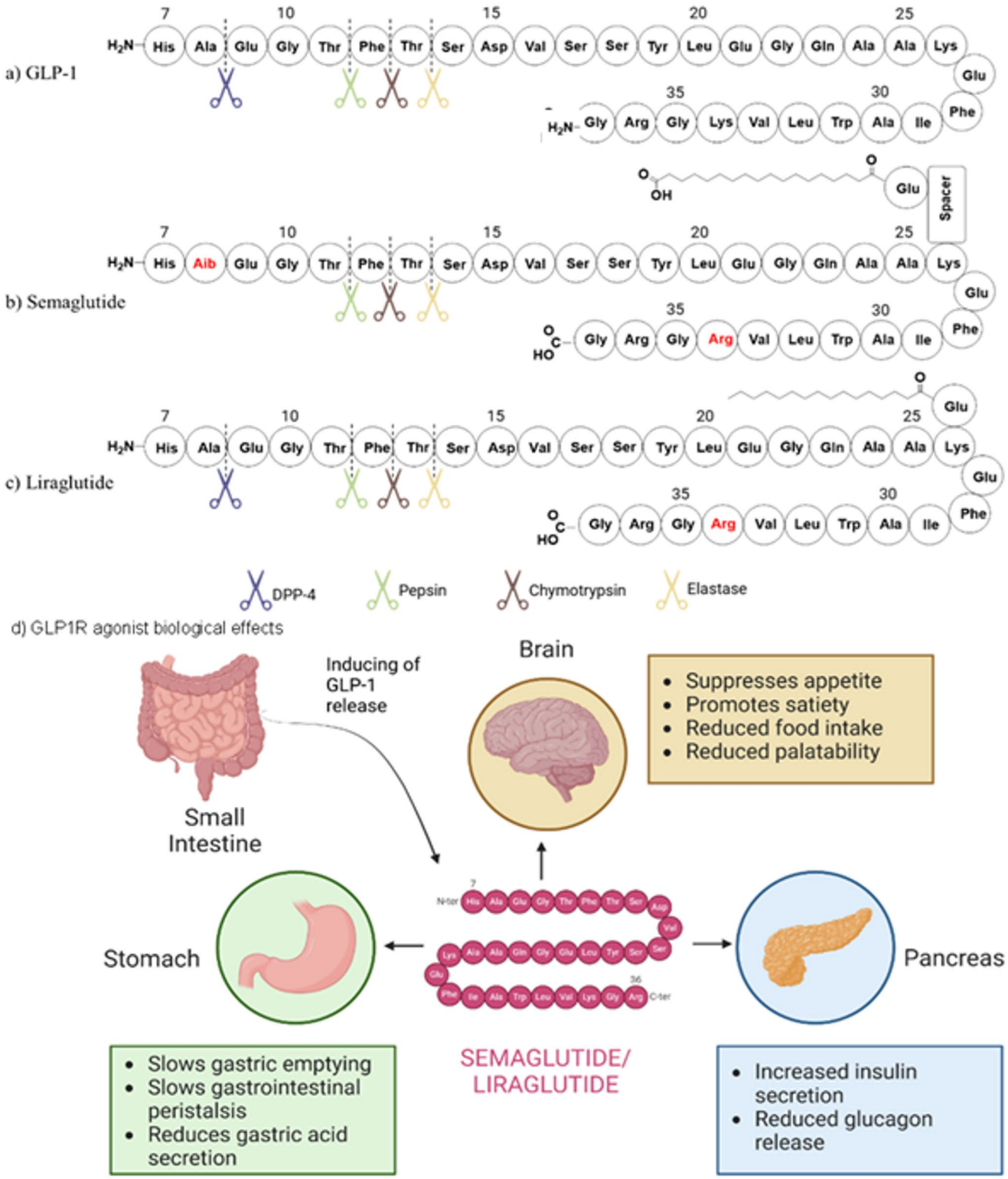

Fig. 3 Amino acid sequence of GLP1R agonists like GLP-1, Semaglutide, and Liraglutide with their modifications, peptidase-prone digestion sites, and biological effects

Circulating GLP-1 is rapidly inactivated by the serum protease dipeptidyl peptidase-4 (DPP-IV), which cleaves the two N-terminal amino acids [54, 55]. Oral administration of GLP-1 is vulnerable to digestive proteases, such as pepsin, trypsin, chymotrypsin, and elastase, thereby presenting a considerable obstacle to oral administration (Fig. 3) [55]. Well-studied techniques for the development of peptide therapies such as integration of non-natural amino acids to protect against proteolytic degradation at vulnerable locations, along with lipidation to improve reversible binding to serum proteins to reduce renal clearance were explored for GLP-1 analogue development [56]. The lipidation method had been used for the liraglutide to increase the half-life time. While lipidation and substitution with unnatural amino acid had been employed for semaglutide to improve its half-life [57]. Structure-activity relationship using alanine scanning of GLP-1 has demonstrated that His1, Gly10, Phe12, Thr13, Asp15, Ser17, and the C-terminal half of GLP-1 are crucial for its biological activity [58, 59].

Semaglutide Semaglutide is a human GLP-1 analogue with 94% resemblance to normal human GLP-1 [25, 60]. In contrast to GLP-1, semaglutide's amino acid sequence includes acylated lysine at position 26, arginine at position 34 (Fig. 3b) [61]. The fatty acid chain is linked to lysine via glutamic acid increases the peptide half-life time by binding to albumin protein. The incorporation of diaminoisobutyric acid (Aib) at the DPP4 susceptible Ala8 increases the peptide stability to proteases. These Modifications enable improved stability and once-weekly dosing. It functions by activating GLP-1 receptors present in the gastrointestinal tract, brain and pancreas. After activation of GLP-1 receptors, semaglutide lowers blood glucose levels by stimulating glucose-dependent insulin secretion [62]. By acting on the same receptor, it decreases incorrect glucagon release, slows stomach emptying, and increases glucose-dependent insulin secretion. Semaglutide also increases insulin secretion in both the first and second phases [26]. Injectable semaglutide has been shown in multiple trials to lower major adverse cardiovascular events in people with type 2 diabetes, hence protecting against cardiovascular (CV) risk. Semaglutide's advantages for CV are supported by strong preclinical data that it affects atherosclerosis [63].

The effectiveness and safety of subcutaneously administered semaglutide at a dose of 2.4 mg once weekly was assessed as part of the Semaglutide Treatment Effect in People with Obesity (STEP) program. Adults who were overweight or obese, with or without issues connected to their weight, were included in this experiment. The study aimed at assessing the impacts of semaglutide when taken in combination with lifestyle changes to reduce body weight and achieve other associated objectives. In this case, semaglutide and a placebo were tested in the above 68-week experiment [64]. This research was a double-blind, randomised experiment to determine whether semaglutide actually works in obesity treatment. This study comprised the whole population of individuals aged ≥ 30 years, inclusive, 27 in those with ≥ 1 weight-related disease. In addition to lifestyle counselling, participants were randomized to receive either placebo or weekly 2.4 mg subcutaneous semaglutide. The primary objectives of this study were percentage change in body weight and percentage of participants who lost at least 5% of the initial body weight. Whether the participants finished the entire 68 weeks of treatment or received additional treatments, the review aimed at addressing the efficacy of treatment [64]. The study postulates that semaglutide greatly outdid a placebo in promoting physical functioning, lowering cardiometabolic risk factors, as well as improving weight loss [65]. Individuals administered with semaglutide experienced an average loss of 14.9% in body weight, whereas participants on a placebo lost an average of 2.4%. More patients in the semaglutide group lost clinically significant weight [64].

Long-term safety and tolerability of semaglutide in clinical use have emerged as concerns. The majority of side effects attributed to GLP-1R agonists were gastrointestinal in nature, including nausea, vomiting, diarrhoea, and abdominal pain. Moreover, use of GLP-1RAs is associated with increased risk for thyroid cancer and acute pancreatitis [66]. Another study compared adverse event profiles of the injection routes of semaglutide, which include both subcutaneous and oral routes. The researchers noted that oral administration poses a higher threat of gastrointestinal adverse events and accelerates the onset of adverse reactions as opposed to subcutaneous administration, which was likely to cause endocrine adverse events [67].

Liraglutide Liraglutide is a GLP-1 analogue with 97% resembles to native GLP-1. Compared to GLP-1, liraglutide consist of lysine26 connected to glutamic acid by isopeptide bond. This glutamic acid is further modified by a 16-carbon palmitic acid side chain (Fig. 3c) [61]. This fatty acid side chain improves the stability against DPP4 degradation, reduces the renal clearance, and prolonged the half-life by forming a hydrophobic interaction with albumin. Liraglutide have been investigated for the treatment of obesity in patients with and without type 2 diabetes since it was discovered that it causes significant and long-lasting weight loss [68]. Liraglutide is a GLP-1 receptor agonist that reduces body weight by reducing cravings and suppressing hunger, and regulates satiety by glucagon production, increases insulin secretion, and postpones stomach emptying (Fig. 3d) [69]. Additionally, ligarglutide seems to have positive

effects on plasmalipids and lipoproteins by lowering total cholesterol, triglycerides, and LDL cholesterol while simultaneously raising HDL cholesterol. Liraglutide's favourable effects on a number of metabolic pathways could delay atherosclerosis and perhaps lower cardiovascular risk [70, 71]. Studies have demonstrated that, in patients with type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), liraglutide significantly lowers carotid intima-media thickness (IMT), a surrogate marker of subclinical atherosclerosis, regardless of changes in body weight or glycaemic parameters. This research shows that it may help improve vascular health, particularly in high-risk groups like people with non-alcoholic fatty liver disease (NAFLD), who are more likely to experience cardiovascular problems and accelerated atherosclerosis [72].

The purpose of the double-blind, randomised, placebo-controlled BARI-OPTIMISE clinical trial was to assess the safety and effectiveness of liraglutide 3.0 mg once day in patients who had not lost much weight after metabolic surgery. The experiment enrolled adult patients from two hospitals in London, UK, who had undergone surgery and lost at least 20% of their body weight, as well as those who showed subpar nutrient-stimulated glucagon-like peptide-1 (GLP-1) response. Type 1 diabetes, severe mental, gastrointestinal, cardiac, kidney, or metabolic problems, as well as the usage of insulin or other GLP-1 receptor analogues, were important exclusion factors. There was a 4-week follow-up period after the 24-week study period [73]. The primary endpoint, which was examined on an intention-to-treat basis, was the percentage change in body weight from baseline to the conclusion of the 24-week trial period. Changes in physical function, physical activity levels, body composition, and health-related quality of life were among the secondary outcomes. Monitoring biochemical markers, such as liver and kidney function, physical examinations, and adverse event reporting were all part of the safety assessments. The reduction in body weight observed in the liraglutide 3.0 mg group was found to be considerably larger than that of the placebo group. The trial's findings demonstrated liraglutide's potential as an adjuvant medication in this population by showing that it was safe and effective as a weight management intervention for patients who had poor weight reduction outcomes following metabolic surgery [73].

Liraglutide has been linked to a number of adverse events, especially regarding to pancreatic health. According to a clinical research, patients receiving liraglutide have higher serum levels of lipase and amylase, two major indicators for the diagnostics of acute pancreatitis [74, 75]. One study observed, in overweight and obese hypertensive patients with type 2 diabetes, sustained liraglutide administration for three weeks increases urine sodium excretion regardless of changes in atrial natriuretic peptide or blood pressure [76]. There are also some major concerns over the extended use of liraglutide in patients with impaired left ventricular function and chronic heart failure because liraglutide was linked to an increase in heart rate and more serious cardiac adverse events [77]. Liraglutide is also most commonly associated with gastrointestinal symptoms and it can also elevate the risk of acute gall bladder or biliary disease [78].

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) dual agonist

GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) are the two known incretin hormones released from the lower (GLP-1, L cells) and upper (GIP, K cells) guts in response to food ingestion [79]. Both circulating GIP and GLP-1 quickly metabolize into their inactive physiological form by the ubiquitous serum enzyme dipeptidyl peptidase 4 (DPP-4) [80]. While GIP is the principal incretin hormone in healthy individuals and mediates most incretin effects, type 2 diabetes mellitus (T2DM) markedly diminishes the insulin response subsequent to GIP release. Consequently, GIP has always been viewed as an unattractive treatment target for type 2 diabetes. This idea has been shifting in recent years because to reports that glycaemic control can be improved to reverse GIP resistance and restore its efficacy. This information opened the door for the creation of a GIP receptor agonist-based treatment for type 2 diabetes, while also exploring the potential for a GLP-1/GIP receptor agonist combination [81].

Tirzepatide

Tirzepatide is a revolutionary drug that offers a new way to manage type 2 diabetes and obesity. It works as a dual agonist for both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (Fig. 4) [82]. Tirzepatide increases insulin secretion in response to meal ingestion by concurrently activating both GLP-1 and GIP receptors, which effectively lowers postprandial blood glucose levels. It also lowers the generation of glucose in the liver, which helps with overall glycaemic management [83]. In addition to slowing stomach emptying, tirzepatide also helps to further facilitate postprandial glucose management by regulating the rate at which glucose reaches the bloodstream [84]. Tirzepatide not only helps with glucose metabolism but also increases satiety effect and decreases hunger, which results in noticeable weight loss (Fig. 7d) [85]. It has been demonstrated that activating GIP receptors increases insulin sensitivity, which adds another level of effectiveness

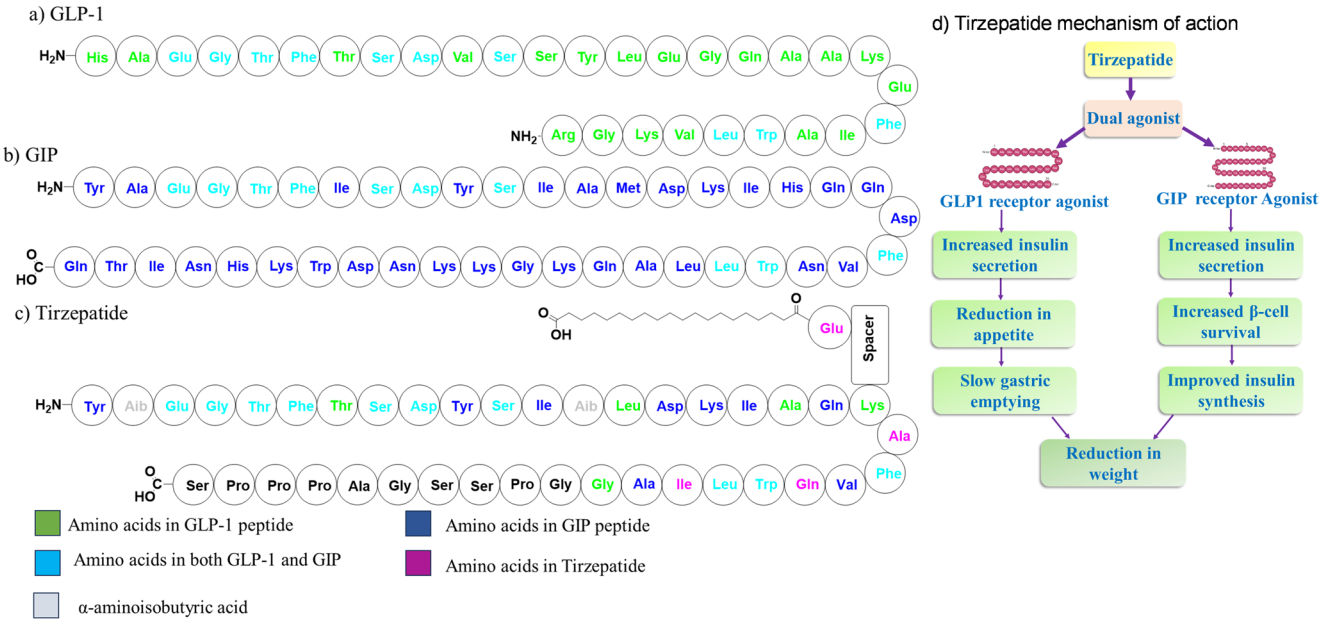

Fig. 4 Primary sequence comparison of incretin hormones with tirzepatide and its dual agonist mechanism

to glucose management [84]. Tirzepatide is a very effective therapy choice for people with type 2 diabetes and obesity because of these combination activities, which significantly improve glycaemic control and help patients lose weight [85]. Significant cardiovascular advantages have also been shown by tirzepatide, including reductions in cardiometabolic risk variables like body weight, blood pressure, and lipid profile in individuals with type 2 diabetes as well as a decrease in severe adverse cardiovascular events [86].

Through multiple major clinical trials, tirzepatide has shown great efficacy and safety in the management of obesity and type 2 diabetes. In patients with insufficient metformin control, tirzepatide and semaglutide were evaluated in the 40-week, randomised, open-label SURPASS-2 trial. With the highest dose resulting in an average HbA1c decrease of 2.30% and a mean weight loss of 11.2 kg, tirzepatide demonstrated greater reductions in HbA1c and body weight [87]. In the 52-week SURPASS-3 trial, tirzepatide and insulin degludec were compared [88]. The results showed that tirzepatide caused higher reductions in body weight and HbA1c, with the maximum dose producing an average reduction of 2.37% in HbA1c and a mean weight loss of 7.5–12.9 kg whereas, insulin degludec increased the body weight by 2.3 kg [89]. Tirzepatide was assessed in the 104-week SURPASS-4 trial in individuals who had an elevated risk of cardiovascular disease. The study showed notable improvements in glycaemic management and weight loss, with the maximum dose resulting in an average HbA1c decrease of 2.59% and a mean weight loss of 7.1–11.7 kg [90]. Additionally, tirzepatide was evaluated for chronic weight management in individuals with obesity in the 72-week SURMOUNT-2 trial. The results showed a mean weight decrease of 14.7% and 79–83% of participants achieved at least a 5% weight reduction [91]. Together, these studies demonstrate tirzepatide's promise as a very successful type 2 diabetes and obesity medication, with notable enhancements in weight loss, glycaemic management, and cardiovascular risk reduction. A multi-centre, randomised, open-label, phase 3b trial called SURMOUNT-5 (NCT05822830) assessed the safety and effectiveness of Zepbound (tirzepatide) in comparison to Wegovy (semaglutide) in people with obesity. In a 1:1 randomisation, 751 participants from the United States and Puerto Rico were assigned to receive either Wegovy (1.7 mg or 2.4 mg) or Zepbound (10 mg or 15 mg) at their highest tolerated dose. The study's main goal was to show that Zepbound outperformed Wegovy in terms of the percentage change in body weight at 72 weeks from baseline. In comparison to Wegovy (semaglutide), Zepbound (tirzepatide) resulted in a 47% larger relative weight reduction, with an average weight loss of 20.2% as opposed to 13.7% with Wegovy [92].

A meta-analysis of ten clinical trial data revealed that dose-dependent gastrointestinal issues were most common adverse event reported. The incidence of GI adverse events was 39% for 5 mg dose, 46% for 10 mg dose and 49% for 15 mg dose [93]. The most common adverse events were diarrhoea and nausea with the duration of these AEs days being 3–4 days, and 1–2 days, respectively [94]. The 10 mg dose was most likely to cause mild hypoglycaemia. Acute pancreatitis, cholelithiasis, cholecystitis, severe hypoglycaemia, and fatal adverse events were uncommon, occurring in < 1% of the cases [93].

Combination therapies

The use of two or more drugs or therapies that target distinct pathways in appetite regulation, metabolism, and fat absorption is known as combination therapy for the treatment of obesity. These methods seek to reduce adverse effects while increasing the effectiveness of weight loss. Obesity is a multifaceted illness influenced by numerous factors. Therefore, combination therapy can address various facets of obesity, including hunger, metabolic processes, and hormone regulation, potentially resulting in more successful weight management [95]. The two-combination therapy phentermine with topiramate and naltrexone with bupropion are available to the patient (Fig. 8). Topiramate works by decreasing appetite via phentermine's stimulant action on the hypothalamus and promoting satiety effect through topiramate's influence on neurotransmitters. Naltrexone/bupropion acts on the brain's reward and appetite regulation centres. Bupropion boosts dopamine and norepinephrine to reduce cravings, while naltrexone blocks opioid receptors to decrease food-related pleasure and reinforce satiety. Theses combination therapies may be more effective for slow burn and emotional hunger phenotypes as they mainly work on the satiety signalling and energy expenditure.

Topiramate and phentermine

Topiramate is a mild carbonic anhydrase inhibitor that is authorised for the treatment of epilepsy, prevention of migraines, and partial-onset and generalized-onset seizures (Fig. 5) [96, 97]. The exact mechanism underlying weight loss is unknown, but it may involve a decrease in lipogenesis, modification of food taste through inhibition of carbonic anhydrase isoenzymes, increased energy expenditure through activation of γ-aminobutyric acid (GABA) receptors, and antagonism of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (Fig. 5) [98, 99]. As an indirect-acting sympathomimetic, phentermine decreases norepinephrine reuptake while simultaneously increasing norepinephrine release from presynaptic vesicles in the lateral hypothalamus (Fig. 5) [97, 100, 101]. Phentermine functions as a mild, reversible monoamine oxidase and serotonin reuptake inhibitor in addition to stimulating the release of dopamine and serotonin from nerve terminals. The subsequent rise in norepinephrine levels in the synaptic cleft stimulates β-2 adrenergic receptors, hence suppressing appetite [101].

A once-daily combination of phentermine and an extended-release (ER) formulation of topiramate (PHEN/TPM ER) has been approved for chronic weight management in obese (body mass index.

[BMI] ~ 30 kg/m2) or overweight (BMI 27 and < 30 kg/m2) individuals with weight-related comorbidities [102]. Its effectiveness and safety in managing weight have been assessed in multiple clinical trials with phentermine/topiramate (PHEN/TPM). One noteworthy study examined the effect of the combination on obese adolescents over a 56-week period using randomised, double-blind, placebo-controlled methodology. Three groups of participants were assigned: mid-dose PHEN/TPM (7.5 mg/46 mg), top-dose PHEN/TPM (15 mg/92 mg), and placebo. The mean percent change in body mass index (BMI) from baseline to week 56

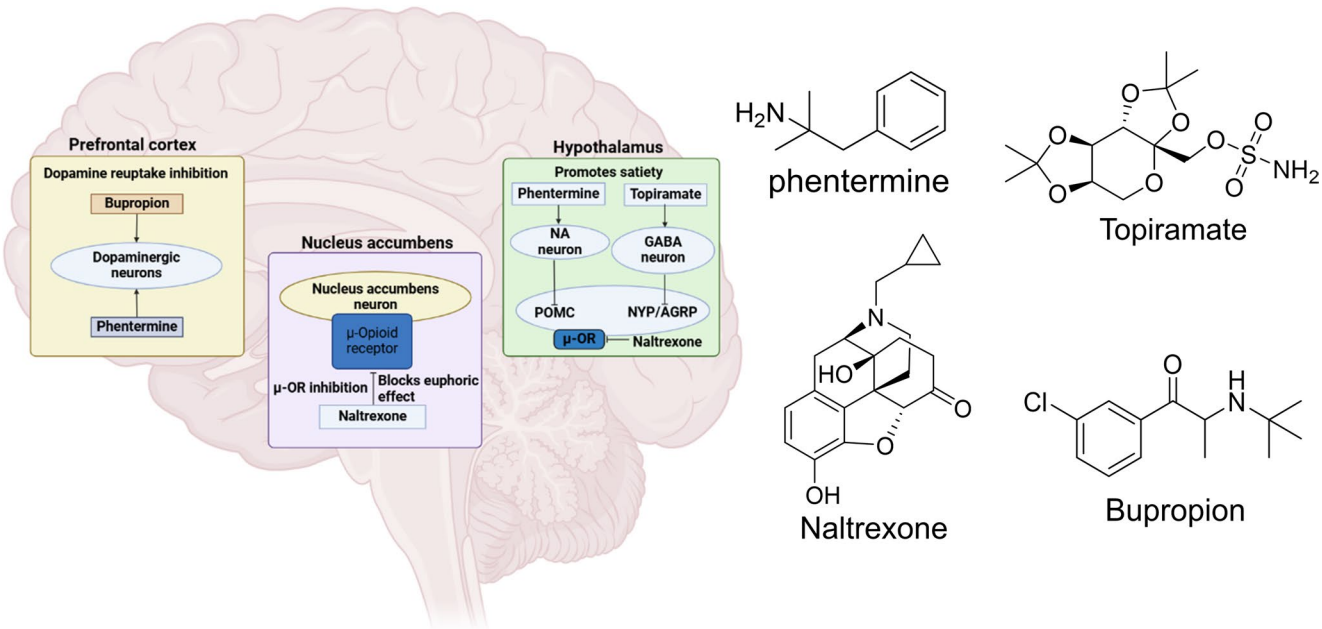

Fig. 5 Mechanism of action of various combination drugs

was the main outcome [103]. In comparison to the placebo group, the mid-dose and top-dose groups' BMIs were significantly lower, according to the data. More specifically, the BMI decreased by 10.44% points in the top-dose group and 8.11% points in the mid-dose group1. Improvements in high-density lipoprotein cholesterol (HDL-C) and triglyceride levels were also noted in the PHEN/TPM groups [103].

The most frequent adverse events with any dose of phentermine/topiramate were constipation, paraesthesia, and dry mouth occurring in 10% of the patients and the 15/92 mg dose caused dysgeusia, sleeplessness and dizziness in over 10% of the patients [104]. Phentermine/topiramate is mostly well-tolerated but sometimes may lead to increased incidence of nephrolithiasis [105]. This combination therapy may be more effective for slow burn and emotional hunger phenotype patience.

Naltrexone and bupropion

A combination of naltrexone and bupropion is used for long-term weight control [106]. Naltrexone is frequently used μ-opioid receptor antagonist to treat alcoholism and opioid addiction [107]. μ- opioid receptors, which are present in the brain, body, and immune system cells and govern a wide range of functions, are predominantly agonists of endorphins. In addition to their strong analgesic effects, endorphins, which are agonists of the body's opioid receptors, also play a role in reward-centric and homeostasis-restoring behaviours [108]. It is possible that naltrexone decreases food intake by inhibiting the action of β-endorphin at the μ-opioid receptor and by blocking pro-opiomelanocortin (POMC) neurones from autoinhibiting (Fig. 5). Oral bioavailability of naltrexone ranges from 5 to 40% during its initial metabolism. Both the 6-β-naltrexol metabolite and primal naltrexone are active forms [109]. As a multifaceted antidepressant, bupropion is well-known for its added advantages in reducing cravings and assisting with attempts to stop smoking. It works by regulating the amounts of certain neurotransmitters in the brain, namely dopamine and norepinephrine [107]. Specifically, bupropion is an inhibitor of norepinephrine-dopamine reuptake, whereas naltrexone is an antagonist of opioid receptors. By altering the reward pathways and appetite regulation of the central nervous system (CNS), this dual mechanism is thought to improve weight reduction [110].

The safety and efficacy of oral extended-release bupropion (450 mg daily) and extended-release injectable naltrexone (380 mg every three weeks) in treating people with moderate to severe methamphetamine use disorder were assessed in a multisite, double-blind, two-stage, placebo-controlled trial using a sequential parallel comparison design. In the initial phase, subjects were randomised in a 0.26:0.74 ratio to receive a matching placebo or the naltrexone-bupropion combination for a duration of 6 weeks. In stage 2, non-responders in the stage 1 placebo group were again randomised to receive the active medication or a placebo for a further six weeks. Twice a week, urine samples were taken in order to track methamphetamine usage. The primary objective was to ensure that at least three of the four urine samples obtained at the conclusion of either stage was methamphetamine-negative. The weighted average of responses from both phases, comparing the active treatment group to the placebo group, was used to calculate the overall treatment impact. 403 people in total were enrolled in stage 1, and 225 people in stage 2. In the first phase, responses were seen in 10 out of 294 people (3.4%) in the placebo group and 18 out of 109 participants (16.5%) in the naltrexone-bupropion group. In the second phase, responses were seen in 2 out of 111 individuals (1.8%) in the placebo group and 13 out of 114 people (11.4%) in the naltrexone-bupropion group. With a weighted average response of 13.6% for the naltrexone-bupropion group and 2.5% for the placebo group over the course of both stages, there was an overall 11.1% point treatment effect (Wald z-test statistic, 4.53; $P < 0.001$) [111].

In a clinical trial involving patients with a history of cardiovascular disease, it was discovered that naltrexone/bupropion is associated to a higher frequency of gastrointestinal and central nervous system adverse events, even if it may lower the risk of major adverse cardiovascular events [112]. In another study comparing the baseline characteristics and comorbidities of patients receiving either placebo or naltrexone/bupropion, it was observed that the most common adverse events associated with the naltrexone/bupropion group, compared with the placebo group, were sleep disorders, anxiety, and depression [113]. The most frequent adverse events associated with naltrexone/bupropion are constipation, nausea, vomiting and headache [106].

Melanocortin 4 receptor agonist

Melanocortin 4 receptor is a G-protein-coupled receptor mainly found in the hypothalamus and is an important component of the leptin-melanocortin system which regulates food intake and metabolic homeostasis [114]. Adipocytes, or fat cells, secrete the hormone leptin, which reduces food intake by binding to the hypothalamic leptin receptors (LEPR) and signalling satiety (Fig. 6) [115]. Under physiological conditions, melanocortin peptides like α-melanocyte-stimulating hormone (α-MSH), which bind to MC4R stabilise the receptor in an active conformation leading to decrease food intake and increase intracellular calcium through [116]. When MC4R is activated, it mainly links to the Gs protein, which causes adenylyl cyclase to

be activated and cyclic adenosine monophosphate (cAMP) levels to rise [117]. Protein kinase A (PKA), which is stimulated by elevated cAMP, phosphorylates downstream substrates that alter neural excitability and decrease appetite [118]. Since MC4R activation decreases appetite and raises energy expenditure, it is a very attractive target for the treatment of slow burn and emotional hunger phenotype.

Setmelanotide

Setmelanotide is a cyclic octapeptide through a disulfide bond possessing a similar central binding motif as α-MSH to bind the MC4R receptor. The cyclic nature and two D amino acids contribute to its stability by increasing peptidase resistance and decreasing metabolism (Fig. 6). Setmelanotide, a melanocortin 4 receptor (MC4R) agonist, has been demonstrated to significantly reduce body weight and food intake in individuals with genetic obesity associated with either leptin receptor deficiency or proopiomelanocortin (POMC) insufficiency [119]. When activated, the MC4R pathway decreases hunger and increases energy expenditure, which is important for leading a negative energy balance [120]. Setmelanotide primarily binds to and activates the MC4R in the lateral hypothalamic area and the paraventricular nucleus of the hypothalamus, two regions implicated in appetite regulation [121].

Setmelanotide was evaluated in a multi-centre phase-3 trial conducted on patients aged 6 years and older with obesity due to Bardet-Biedl syndrome (BBS). After 14-week double-blind period, participants were randomized in a 1:1 ratio to receive either up to 3 mg of setmelanotide subcutaneously or placebo. Thereafter, they were treated with open-label setmelanotide for 52 weeks. The primary endpoint of the study was, patients 12 years or older achieve at-least 10% weight loss after 52 weeks. The primary endpoint was achieved by 32.3% of patients with BBS aged 12 or older (95% Confidence interval, 16.7%, 51.4%; $p = 0.0006$). The setmelanotide group experienced a mean change in body weight of -2.4%, whereas, the placebo group experienced a mean change of -0.3% (difference, -2.1%; 95% CI, -4.6% to 0.4%; $p = 0.052$). The study concluded that setmelanotide considerably reduced weight and hunger in individuals with BBS, identifying it as the first licensed treatment for obesity in this population [122].

In a pooled study of patients suffering from proopiomelanocortin/proprotein convertase subtilisin/kexin type 1 (POMC/PCSK1) or LEPR deficiency the incidence of adverse events associated with setmelanotide was evaluated. The study found that setmelanotide caused hyperpigmentation disorders probably due to peripheral melanocyte's off-target activation of melanocortin receptors, also it can also cause injection site reactions, nausea, vomiting and problems with sexual arousal [123, 124]. Setmelanotide is also associated with gastrointestinal side effects [124].

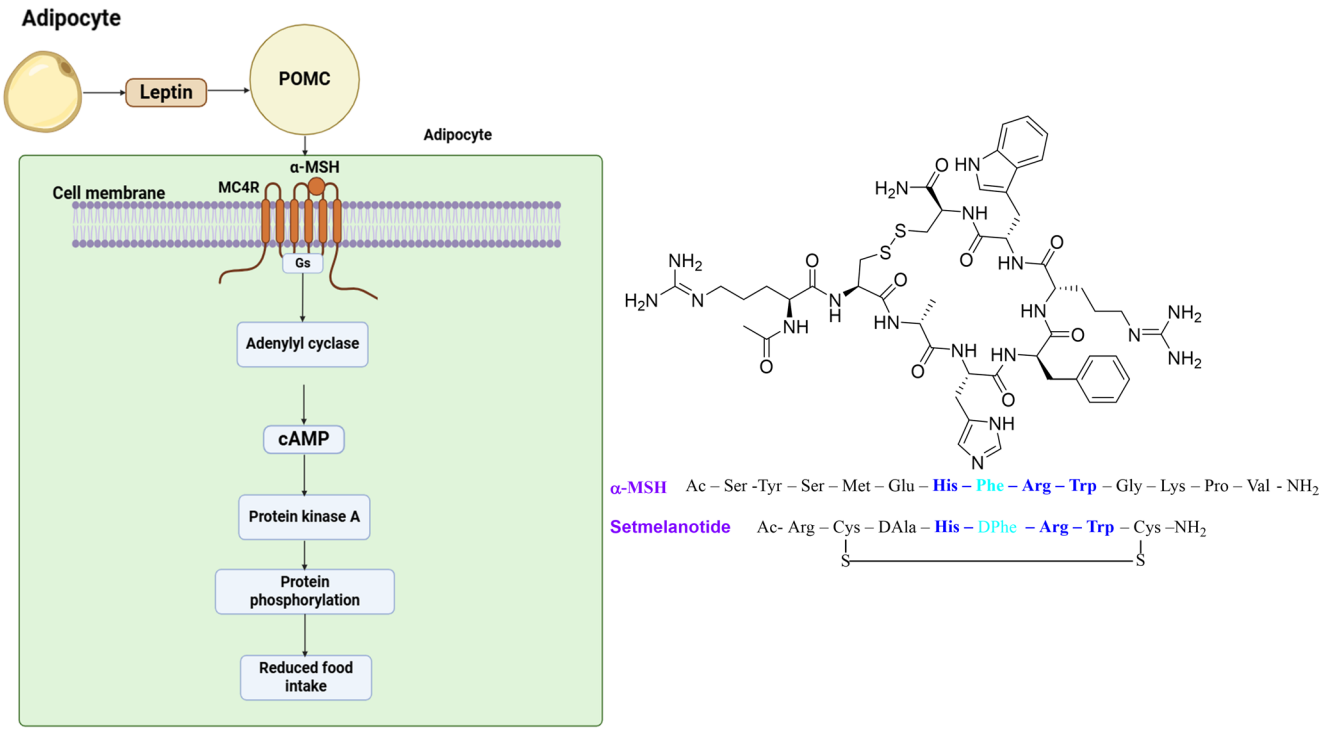

Fig. 6 Leptin released by the adipocyte stimulate the POMC to release α-MSH (alpha-melanocyte-stimulating hormone). MC4R activated by α-MSH reduces appetite and increases energy expenditure, and helping regulate body weight

5HT2C receptor agonists

5-Hydroxy tryptamine (Serotonin) exerts its satiety effect primarily through the 5HT2C receptor located in hypothalamus. 5-HT2C receptor agonists regulate appetite and energy balance via central serotonergic pathways, which is a key factor in the management of obesity (Fig. 7) [125]. The hypothalamic 5-HT2C receptors, specifically those located in the pro-opiomelanocortin (POMC) neurones of the arcuate nucleus of the hypothalamus, are the primary site of action for these agonists [126]. By binding to melanocortin-4 receptors (MC4R) in the paraventricular nucleus, α-melanocyte-stimulating hormone (α-MSH) is released which reduces food intake and increases satiety. 5-HT2C receptor agonists are prospective anti-obesity drugs because of this mechanism, which efficiently reduces excessive calorie consumption [127]. These medications have also been demonstrated to enhance metabolic parameters, such as insulin sensitivity and glucose homeostasis, which are frequently compromised in obesity [128]. Selective 5-HT2C receptor agonists improve safety profiles by reducing off-target effects, as contrast to earlier serotonergic weight-loss medications that impacted several serotonin receptors and resulted in cardiovascular problems [129].

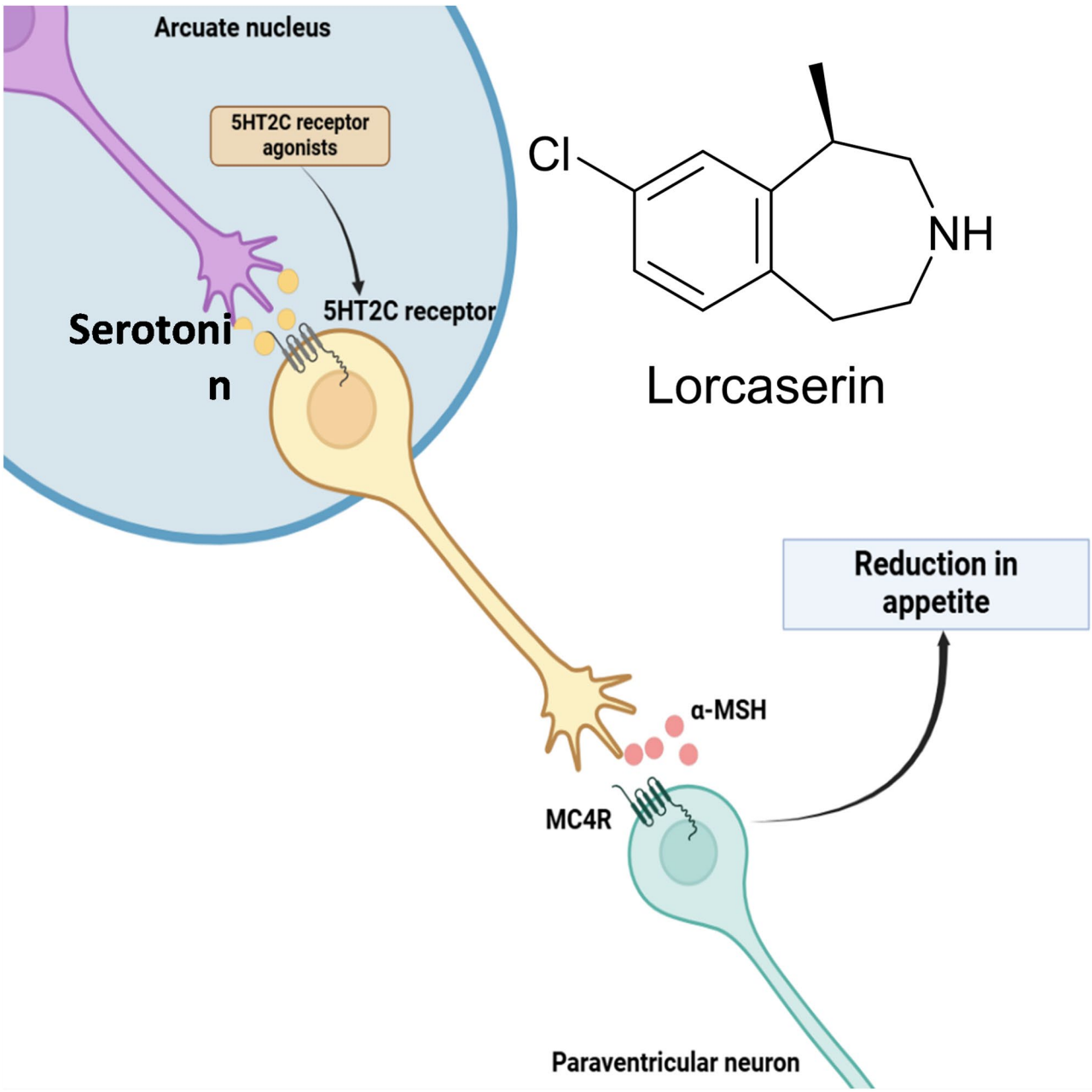

Fig. 7 Mechanism of action of 5HT2C receptor agonists. 5-HT2C receptor agonists decrease appetite by activating the serotonin pathway

Lorcaserin

Lorcaserin is a 3-benzazepine derivative (Fig. 7). When cancer signs were found in animal experiments, lorcaserin was first rejected in October 2010. Following further investigation and reassessment of cardiovascular safety and toxicology data, lorcaserin was finally accepted, and the FDA authorised in June 2012 [130, 131]. In 2016, an extended-release, once-daily form of lorcaserin was authorised based on a food-effect study and one crucial bioequivalence [132]. In early 2020, lorcaserin was discontinued from the market due to long-term research that suggested it raised the risk of cancer [133]. The FDA asked Belviq XR (lorcaserin) manufacturer, Eisai Inc. to voluntarily withdraw it from the market [134]. Lorcaserin is a serotonin agonist that specifically stimulates serotonin 2 C receptors [135]. By binding to 5-HT2C receptors in the central nervous system (CNS), particularly the hypothalamus, lorcaserin reduces appetite. α-MSH (α-melanocortin-stimulating hormone) is released when the drug activates 5-HT2C receptors on pro-opiomelanocortin (POMC) neurones in the arcuate nucleus. By interacting with melanocortin-4 receptors in the paraventricular nucleus, this reduces appetite [136].

To evaluate the efficacy of lorcaserin participants in a large-scale trial with 12,000 overweight or obese patients who had numerous cardiovascular risk factors or atherosclerotic cardiovascular disease were randomly assigned to receive a placebo or lorcaserin (10 mg twice day). After a year, 38.7% of patients in the lorcaserin group lost at least 5% of their body weight, whereas 17.4% in the placebo group did the same. This suggests that lorcaserin has a significant advantage. Furthermore, lorcaserin-using patients exhibited modest improvements in cardiac risk markers such cholesterol levels, heart rate, blood pressure, and glycaemic management. The rate of major cardiovascular events was comparable in the lorcaserin and placebo groups throughout a median follow-up period of 3.3 years (2.0% per year vs. 2.1% per year). Additionally comparable was the rate of protracted major cardiovascular events (4.1% annually versus 4.2% annually). Although the groups' adverse effects were mostly comparable, the lorcaserin group experienced a greater incidence of significant hypoglycaemia (13 vs. 4, $P = 0.04$). When compared to a placebo, lorcaserin was successful in promoting long-term weight loss in a high-risk group without raising the incidence of significant cardiovascular events [137].

The adverse events that were most frequently associated with lorcaserin included dizziness, headaches, back pain, nausea, vomiting, diarrhoea, constipation, exhaustion, upper respiratory tract infections, and urinary tract infections [130]. Lorcaserin also significantly increases moderate or higher mitral regurgitation, according to the FDA Medical Review [138]. Hypertension, cognitive decline, hypoglycaemia, nasopharyngitis, upper respiratory tract infections and valvulopathy are also some of the adverse events associated with lorcaserin [139].

Potential therapies and drug targets for obesity currently under trials

The prevalence of obesity is constantly increasing globally which necessitates the development of novel therapeutic strategies along with the existing interventions to address the complex nature of obesity influenced by genetic, behavioural and environmental factors [14]. Therefore, innovative approaches for treatment of obesity are required to enhance efficacy and patient outcomes. The combination therapies are more attractive as they can show effect at a lower concentration than individual drugs and more effective by targeting the different targets.

Amylin/calcitonin receptor dual agonists

KBP-089, KBP-088, KBP-042, KBP-336 and cagrilintide are dual amylin and calcitonin receptor agonists (DACRAs) which induces the activation of both the amylin receptors and the calcitonin receptors (Fig. 8) [140]. The 37-amino acid peptide amylin features an amidated c-terminus and an intramolecular disulphide bridge that joins cysteine residues at positions 2 and 7 [141, 142]. The role of amylin as a satiety signal is well established, and it works directly by activating amylin signals in nucleus of solitary tract and area postrema of the brain [143]. Calcitonin is a 32-amino acid peptide hormone that exerts effect through calcitonin receptors and it primarily targets bones and kidneys promoting calcium excretion and inhibiting osteoclast activity [144]. DACRAs combine these effects and its dual mechanism results in significant weight loss, improved glucose tolerance and enhanced metabolic health (Fig. 8) [143]. DACRAs effects include the lower food intake, slow gastric emptying, and increased satiety, which resulted in effectiveness against emotional hunger, hungry gut, and hungry brain phenotypes.

To evaluate the effectiveness of DACRAs animal studies were conducted by Nordic Biosciences. The study aimed to evaluate the metabolic effects of cagrilintide and KBP-336. The tests were carried out on diet-induced obese Sprague Dawley rats which underwent acute and chronic studies. In the acute studies the rats were assigned to treatment groups as per body weight with each group consisting of 7–8 rats and for the CTX-1/calcium study, there were 3–8 rats per group. The rats were fasted the night before, after that they were subcutaneously injected with the test compound. After

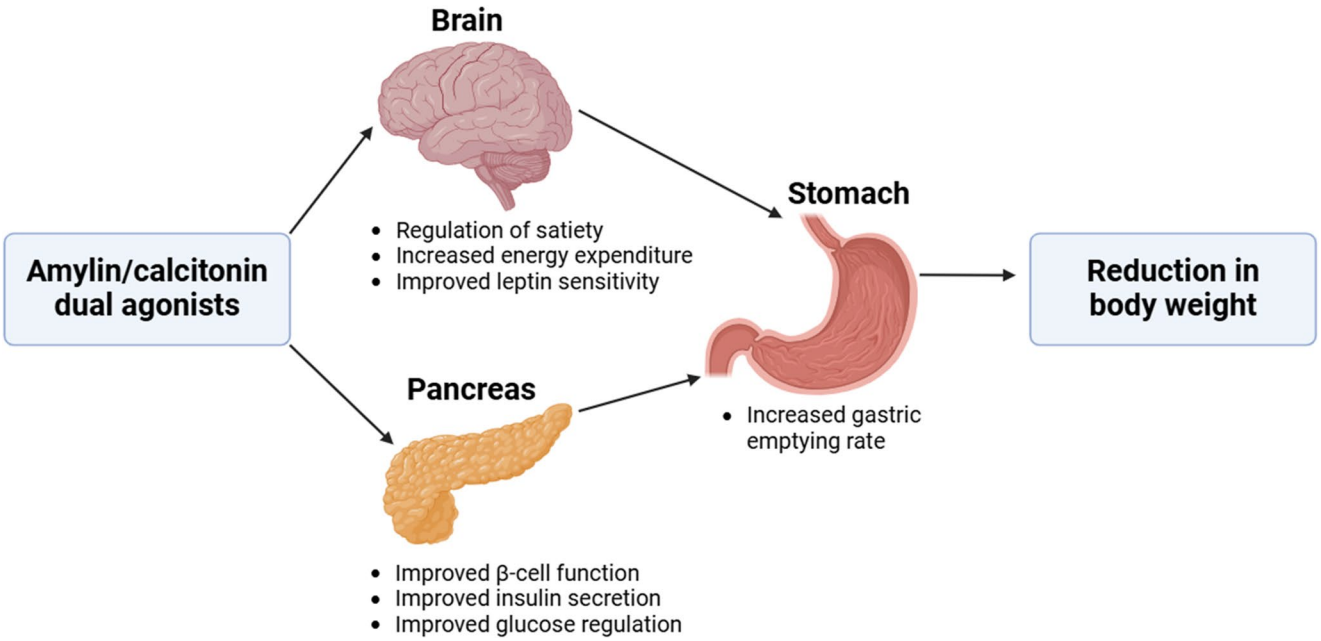

Fig. 8 Mechanism of action of amylin/calcitonin dual agonists. DACRAs modulate brain and pancreas to regulate satiety and energy metabolism, insulin secretion and increases the gastric emptying time

the administration of the test compound, the food intake and body weight of the subjects were recorded at 6, 24, 48, 72 h. Blood samples were withdrawn at 6, 24, and 48 h post injection to measure serum CTX-1 levels. The studies found that both KBP-336 and cagrilintide reduced food intake and weight as compared to control groups. Additionally, the study discovered that cagrilintide significantly decreased body weight in comparison to KBP-336 whereas KBP-336 was found to be superior in improving the glycaemic status than cagrilintide [145].

KBP-089's effects on body weight, glucose balance, and the accumulation of fatty acids in muscle and liver tissue was characterized. When administered subcutaneously to rats which were fed a high-fat diet, KBP-089 caused a dose-dependent and long-lasting weight loss of almost 17% at the maximum dose (2.5 µg/kg), along with a decrease in the size of the fat depot and lipid buildup in the liver and muscle tissue. Additionally, KBP-089 enhanced insulin action and improved glucose homeostasis in Zucker Diabetic Fatty rats, outperforming weight-matched controls that were just given calorie restriction. Notably, food choice tests showed that KBP-089-treated rats showed a significant decrease in total caloric intake and a shift towards greater chow consumption, indicating possible impacts on hedonic eating behaviours, whereas control rats consumed 74% of their calories from chocolate. These results demonstrate the weight-independent metabolic advantages of KBP-089, so confirming its potential as a novel treatment for metabolic diseases and obesity [140].

Neuromedin U receptor-2 agonist

Neuromedin, a group of structurally conserved bioactive neuropeptides with pleiotropic functions, were first isolated from the spinal cord of porcine [146–148]. Neuromedin peptides are divided in four sub-groups based on their physiological roles (i) bombesin-like (NMB and NMC) (ii) assinin-like (NMK and NML), (iii) neurotensin-like (NMN) peptides (iv) NMU group (NMU and NMS) [149]. Neuromedin peptide with potent rat uterus contraction ability is called as NMU (U stand for uterus) peptide [150]. An isoform of NMU isolated from the suprachiasmatic nucleus of rat brain (SCN) coined as Neuromedin S (S stands for suprachiasmatic nucleus) [151]. Both NMU and NMS exert their function through the G protein-coupled receptors (GPCRs), neuromedin U receptor1 (NMUR1) and neuromedin U receptor 2 (NMUR2) [152]. NMU and NMS have identical C-terminal heptapeptide sequence (FLFRPRN-NH2), which is inserted in binding pocket of the receptor [153]. NMU or its related peptide, neuromedin S (NMS) activates the G-protein coupled receptors (GPCRs) it initiates intracellular signalling pathway which regulates energy expenditure and appetite [148]. It has been observed through study that mostly NMUR1 is located in peripheral tissues like Adipose tissue, genitourinary system, placenta, spleen, adrenal cortex, heart, lung, trachea, mammary gland, bone marrow, peripheral lymphocytes, and pancreas while NMUR2 is mainly distributed in CNS particularly in cerebral cortex, spinal cord, thalamus, medulla oblongata,

substantia nigra, hippocampus, hypothalamus, and pontine reticular formation [154].

To investigate its biological activity, NMU was directly administered to various hypothalamus nuclei. The researchers observed the diminished hunger and weight reduction [155]. The extensive distribution of NMUR-2 in the hypothalamus renders it a significant target for anti-obesity medications. It has been observed that removal of NMUR2 gene in mice leads to increase hunger, elevated weight, and reduced metabolic activity. The silencing of NMUR2 in the paraventricular nucleus of the hypothalamus enhances binge-type eating, elevates intake of a high-fat diet, and promotes weight gain. Recent studies indicate that NMU given to the paraventricular nucleus of the hypothalamus reduces both consumption and desire for a high-fat diet (Fig. 9) [156]. The stimulation of NMUR2 demonstrates potential therapeutic benefits for obesity treatment. Animal study of the two small molecule NMUR2 agonist NY0116 and NY0128 shad shown to decrease the food intake, reduced the body weight and cholesterol [157].

The role of neuromedin U (NMU) in regulating food consumption and behaviours associated with alcohol in rodents by means of specific brain regions was investigated. The study involved a combination of molecular analyses, behavioural assays, and targeted brain region manipulations to investigate the effects of neuromedin U (NMU). The anterior ventral tegmental region (aVTA), laterodorsal tegmental area (LDTg), and nucleus accumbens (NAc) shell were the main points of interest. These areas in the brain process the impact of alcohol on behaviour. Given the significance of these regions in regulating alcohol use disorder (AUD), NMU signalling in these areas were evaluated. The expression of NMU and its receptor NMUR2 in the dorsal striatum along with NAc of high vs. low alcohol consuming rats were also investigated [148, 158]. To gain a deeper comprehension of the role of NMU in reward-related behaviours, the study investigated the brain regions involved in the injection of chow and palatable peanut butter. It was observed that administering the rats with NMU into the NAc shell, but not in the aVTA and LDTg, reduced the consumption of peanut butter, and inhibited the locomotor stimulation and memory retrieval linked to acute alcohol exposure [148]. Additionally, the consumption of alcohol in rats administered with NMU in the NAc shell was reduced. In the dorsal striatum, heavy alcohol-consuming rats showed higher NMU and lower NMUR2 expression on a molecular level in contrast to low alcohol-consuming rats. Interestingly, when NMU was administered into the aVTA and LDTg instead of the NAc shell, it specifically decreased chow intake; these areas were found to be the new locations for NMU's anorexigenic effects [148]. Overall, the study showed that alcohol related behaviours and food intake are significantly regulated by NMU signalling in specific brain regions, which present therapeutic properties for the treatment of alcohol use disorder (AUD) and obesity [148]. This class of drug may be more effective for slow burn and emotional hunger obesity phenotypes.

Sodium glucose co-transporter 2 inhibitors

Sodium glucose co-transporter 2 inhibitors are anti-diabetic medications which have long-lasting effects on body weight and glycaemic levels [159]. By preventing the kidney's proximal tubule from reabsorbing glucose from urine, these medications increase the excretion of glucose in urine (Fig. 17). Calorie excretion rises when plasma glucose levels rise because the amount of resulting glucosuria is related to plasma glucose over threshold. This suggests that SGLT2 inhibitors may be more effective helping people with type 2 diabetes to lose weight [160]. Furthermore, dapagliflozin, canagliflozin, empagliflozin, and other SGLT2 inhibitors have long-lasting impacts on weight and blood glucose. SGLT2 inhibitors have been shown to consistently reduce body weight in a number of type 2 diabetes patients, whether used alone or in conjunction with other hypoglycaemic medications [161]. As this class of drug increases the glucose excretion, it may be effective against all obesity phenotypes.

To evaluate the effectiveness of dapagliflozin, 50 Japanese patients with type 2 diabetes (T2DM) who were uncontrolled and had an average age of 56.1 years, a mean body mass index (BMI) of 27.1 kg/m2, and an average HbA1c of 7.9% were treated for six months with either non-SGLT2i medications or dapagliflozin (5 mg/day). The results showed that both treatment groups experienced considerable drops in body weight, BMI, and HbA1c; however, there were no discernible variations in the groups' HbA1c reductions. Without changing skeletal muscle mass, dapagliflozin therapy resulted in notable decreases in body weight and overall fat mass. Furthermore, there was no discernible difference in the groups' changes in soft lean mass and skeletal muscle mass. The psoas muscle index was not considerably reduced by dapagliflozin, and the absolute reductions in this index were similar in the two groups [162].

Long-term monitoring of individuals suffering from type 2 diabetes was conducted in two studies assessing canagliflozin. During a 52-week core phase and a 52-week extension, 1,450 patients between the ages of 18 and 80 received either glimepiride or canagliflozin (100 or 300 mg) as an adjuvant to metformin in Study 1. During a 26-week core phase and a 78-week extension, 714 individuals between the ages of 55 and 80 were administered with canagliflozin (100 or 300 mg) or a placebo in addition to their current anti-hyperglycemic medication. Changes in body weight, body

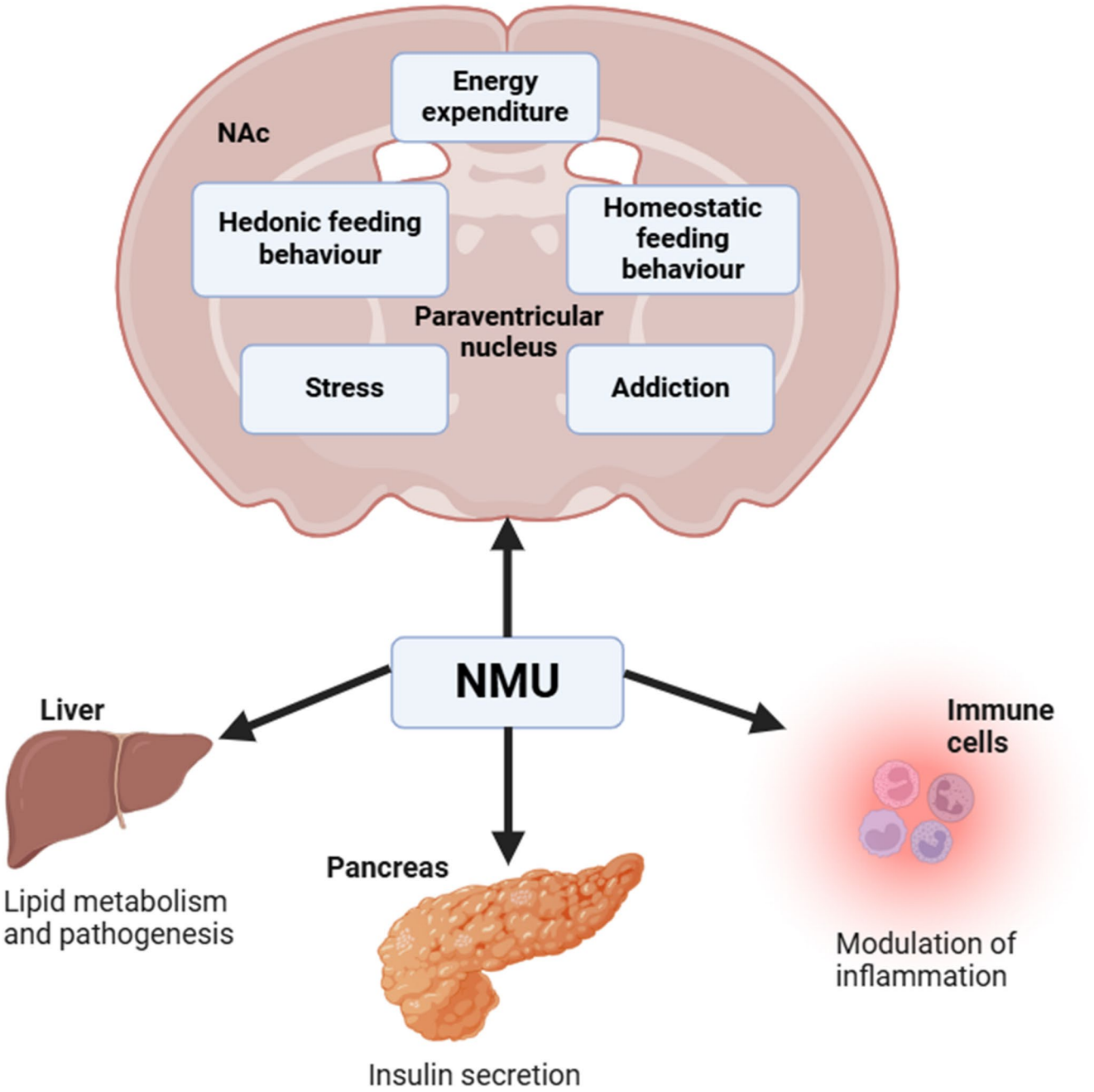

Fig. 9 Mechanism of action of NMU receptors. NMU lowers appetite and raises energy expenditure by binding to NMUR2 receptors in the hypothalamus, namely in the paraventricular nucleus (PVN)

mass index (BMI), waist circumference, and body composition were assessed in both investigations. In comparison to glimepiride or a placebo, the results demonstrated that canagliflozin 100 and 300 mg produced long-lasting weight loss for a period of 104 weeks. Compared to the comparators, more patients lost weight at all and lost minimum 5% of their body weight while taking canagliflozin. Canagliflozin was found to significantly lower waist circumference and BMI, with a significant amount of weight loss attributable to decreased fat mass [163].

Over the course of 12 and 24 weeks, researchers evaluated the impact of empagliflozin on a number of body composition metrics in individuals with type-2 diabetes mellitus. 3,300 individuals were enrolled in the study; 823 were in cohort 1 (12 weeks) and 2,477 were in cohort 2 (24 weeks). Using analysis of covariance, weight, waist circumference, visceral adiposity index, central obesity index, and predicted

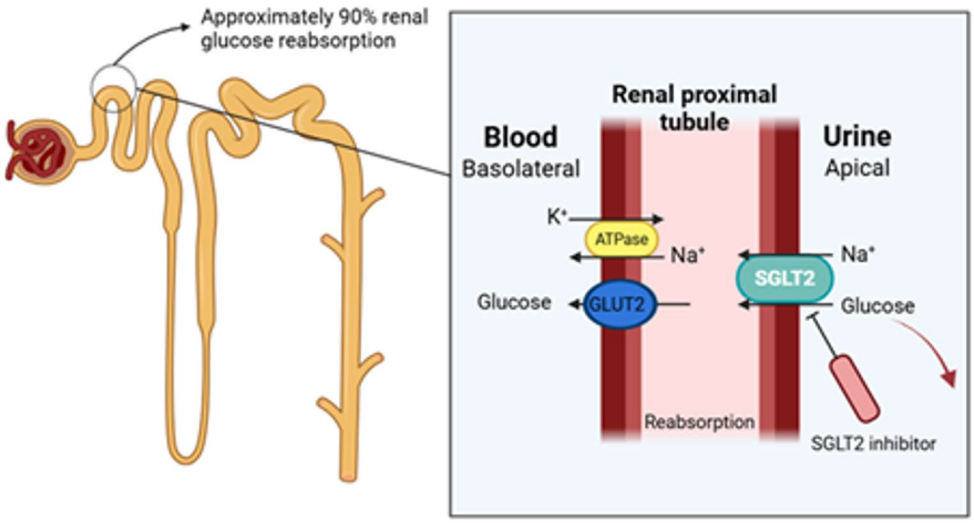

Fig. 10 Mechanism of action of Sodium glucose co-transporter 2 (SGLT2) inhibitors. SGLT2 inhibitors lower blood glucose by inhibiting glucose reabsorption and encouraging its excretion in urine

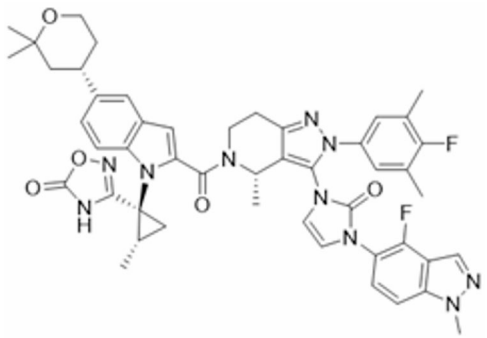

Fig. 11 Structure of orforglipron. Orforglipron is a small non-peptide molecule binds to GLP1R

total body fat changes were assessed while taking baseline waist circumference, age, and sex into account. The results demonstrated that, in both cohorts, empagliflozin significantly decreased weight, waist circumference, and adiposity indices when compared to the placebo group. In comparison to the placebo group, the study discovered that participants in the empagliflozin group had significant reduction in their body weight (about 1.8 kg), waist circumference (1.3 cm), and central obesity index. However, the visceral adiposity index showed modest but inconsistent outcomes in terms of statistical significance, and reductions in total body fat were not significant. Overall, weight, waist circumference, and central obesity all showed discernible reductions with empagliflozin [164].

GLP-1 receptor small molecule agonist: Orforglipron

To improve patient compliance and expand the accessibility to GLP-1 therapy, orally administered small molecules are an attractive research target. Small molecule Orforglipron, was developed as an alternative to semaglutide and liraglutide (Fig. 11). A once-daily oral, non-peptide GLP-1 receptor, agonist called orforglipron is being developed for treatment of type 2 diabetes and help people lose weight. Compared to peptide GLP-1 receptor agonists, orforglipron may provide less receptor desensitization due to its strong pharmacologic profile, which primarily affects cyclic AMP (cAMP) signalling rather than β-arrestin recruitment [165]. Orforglipron enables the GLP-1 receptors, which improves glycaemic control and helps in weight loss by slowing stomach emptying and promoting satiety, as well as by increasing release of insulin in response to meals and suppressing glucagon secretion [166].

The effectiveness of orforglipron on obese adults or overweight individuals with at least one weight-related complication, excluding those with diabetes, was evaluated in a phase-2 randomized double-blind trial where researchers assessed the effects of orforglipron. For 36 weeks, individuals were randomised to be administered with either a placebo or one of four dosages of orforglipron (12, 24, 36, or 45 mg) every day. The percent variance in body weight at week 26 served as the primary metric, while a secondary evaluation was conducted at week 36. The 272 people's mean initial body weight was 108.7 kg, and their mean BMI was 37.9. By week 26, the group administered with orforglipron had lost a large amount of weight, ranging from 8.6% to 12.6%, whereas the placebo group had lost only 2.0%. At week 36, the orforglipron group lost between 9.4% and 14.7% of their body weight, compared to 2.3% for the placebo group. Remarkably, by week 36, 46% to 75% of orforglipron users had lost at least 10% of their body weight, while the placebo group had lost 9%. Orforglipron also improved a number of cardiometabolic and weight-related metrics [165].

Mild to moderate gastrointestinal complications were the most frequent adverse events, occurring mostly during dose escalation and causing 10% to 17% of patients to stop taking the medication. Orforglipron successfully encouraged

weight loss in the trial group, and its overall safety profile was comparable to that of other GLP-1 receptor agonists [165].

Future scope and conclusion

Semaglutide, liraglutide, and tirzepatide, incretin-based treatments, are particularly effective in patients with obesity and associated cardiometabolic risk factors, given their substantial weight loss effects and pleiotropic advantages on cardiovascular, inflammatory, and metabolic parameters. Patients with visceral obesity, type 2 diabetes, or insulin resistance are particularly well-suited for these medications [24]. Although it necessitates rigorous dietary adherence and may be constrained by gastrointestinal side effects, orlistat may be better for people looking for a non-systemic drug or those who are contraindicated for centrally acting treatments [32]. Centrally acting drugs that suppress appetite and regulate cravings, such as lorcaserin (where available) and naltrexone/bupropion, may be perfect for people who have emotional eating disorders or dopaminergic reward dysregulation [167]. In patients who require more drastic weight loss, phentermine/topiramate is frequently investigated due to its synergistic appetite suppression and metabolic enhancement; nevertheless, its use may be restricted by tolerance or contraindications in cardiovascular risk individuals [168]. The use of the melanocortin-4 receptor (MC4R) agonist setmelanotide for uncommon hereditary types of obesity, like POMC or LEPR deficiency, highlights the importance of precision medication and genomic screening in some patient groups [169].

GLP-1 receptor agonists are most likely to play a bigger role in treatment of obesity in the future. For example, among patients with body mass index 30 or higher, once weekly dose of semaglutide has been accounted for a 12.4% decrease in weight in comparison to placebo. This is a significant improvement over alternative obesity therapy. Although anti-obesity medications are not currently covered under healthcare insurance, if governmental measures to change this are successful, their integration into healthcare insurance can be influenced through policy changes [170]. Moreover, as the field of treatment of obesity is changing, the need for personalized treatment approaches grows. When a single agent pharmacotherapy approach is insufficient to provide long-lasting, clinically significant weight loss due to the various neuroendocrine mechanisms governing hunger and body weight, dual agonists or triple agonists agents are being developed to overcome such redundancies which will target multiple pathways simultaneously [171]. More research is needed for the development of orally absorbed small molecules for the incretin receptor agonist due to its patient compliance as compared to peptide analogues. The NMUR2 agonist alone or in combination would provide the more potential therapeutic way to tackle the obesity pandemic. There has also been a growing interest in traditional medicine in treatment of obesity in addition to the pharmacological advancements, such as the Traditional Chinese medicine-derived polysaccharides (TCMPs) for their antioxidant, anticancer, anti-inflammatory and anti-diabetic properties [172]. A combination of modern medication along with traditional herbal drugs also needs to be explored for the benefit of the patients. The complex interaction study of the effect of microbiota on obesity will certainly reshape the anti-obesity medication course. In conclusion, the development of potent pharmaceutical agents, the use of precision medicine, microbiota study, herbal medicines, and the investigation of conventional treatments will define the future of anti-obesity therapies.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Confilict of interests The authors declare no competing interests.

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